Mathematical Modelling of Immune Response to the Lyme Disease

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Abstract

We seek to understand the bull’s-eye rash pattern in the skin during the early stage of Lyme disease. By considering a PDE model incorporating the classical Keller-Segel chemotaxis term, we create a model not too complicated but is able to produce different spatial patterns. We investigate the effect of different parameters on the skin rash pattern. We present numerical simulation results that illustrate the impact of different parameters. We find that the engulfment rate of macrophages and the infection rate of the macrophage cells are the two key factors that produces different rash patterns. The implication of our result on the disease treatment is also discussed.

Mathematics Subject Classification: 35B36

Keywords: Lyme disease, erythema migrans, chemotaxis, immunology, spatial patterns
1 Introduction

Lyme disease is one of the most common vector-borne disease in North America since it’s first incidence in 1975. It is transmitted to humans by a bite from ticks infected with bacterium *Borrelia burgdorferi*. The spirochetes inhabit in the midgut of the tick. During feeding, the bacteria leaves the midgut and migrate to the salivary glands and then is transported to the dermis of the host via saliva [6, 28]. The tick bite and the presence of the spirochetes in the dermis activate the innate immune response. *Borrelia* is able to induce, not only the production of pro-inflammatory cytokines, but also anti-inflammatory cytokines such as IL-10. In addition, chemokines such as IL-8 and adhesion molecules such as E-selectin, VCAM-1 and ICAM-1 by OspA are expressed in response to *Borrelia* [7, 29]. Together, these molecules direct the recruitment of macrophages and neutrophils, which can eliminate the spirochetes by producing oxygen radicals such as nitric oxide [18, 20]. During this initial stage of Lyme disease, mature macrophages *in vitro* ingest and kill spirochetes avidly and in large numbers. They are the most efficient defense against spirochetes during the initial innate immune response while monocytes are less effective [21]. The release of proinflammatory cytokines by macrophages leads to further recruitment of innate immune cells and T cells to the infected region [26]. This inflammatory cascade causes hyperemia in the capillaries, leading to a distinctive circular rash that is well known characteristic to lyme disease [28]. The rash around the bite site usually occurs around 3 to 30 days after being bitten. This is known as erythema migrans. The rash is often described as looking like a bull’s-eye on a dart board (see Fig. 1(a)). The affected area of skin will be red and the edges may feel slightly raised. Most infections do not produce similar rashes. The exact cause of such distinctive rash remains unclear. One may argue that the motility of the bacterium is the primary cause of this feature (see Fig. 1(b)). It is true that *B. burgdoferi* has an intricate network of periplasmic flagella, and as a result they can disseminate to and interact with host’s extracellular matrix (ECM) components and tissue effectively. They also have a special attribute: spirochetes can swim in a highly viscous, gel-like medium, such as that found in connective tissue, that inhibits the motility of most other bacteria [17, 4]. However, the high motility of *B. burgdorferi* is not the primary cause of this bull’s-eye pattern as we will demonstrate with our mathematical model. Instead, the high rate of phagocytosis is the real reason behind this pattern.

Before we present our mathematical model, we would like to point out that while mature macrophages can ingest spirochetes in large numbers and most of them are killed, there are still cell-associated spirochetes that persist [21]. Instead of engulfing the bacteria as a whole, the arms of the macrophages wrap around the bacteria in many layers. Lysosomes are prevented from degrading
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Figure 1: (a) The bull’s-eye rash during early stage of Lyme disease. Photo Credit: James Gathany. Content Providers(s): CDC/James Gathany. This media comes from the Centers for Disease Control and Prevention’s Public Health Image Library (PHIL), with identification number 9875. (b) Morphology of Borrelia burgdorferi: an anaerobic, motile spirochete with seven to 11 bundled periplasmic flagella set at each end that allow the bacterium to move in low- and high-viscosity media alike, which is related to its high virulence factor. Photo Credit: David Darling.

the bacteria completely, allowing some bacteria to survive and reproduce intracellularly within the macrophage itself. The ability to survive phagocytosis may be a contributive factor to the virulence of *B. burgdorferi*. However, the internalization mechanisms post-attachment have been understudied. There are still many questions that are unanswered during this internalization process. This internalization may result in host cell damage and may be a mechanism for the bacterium to escape from innate or adaptive host responses or antibiotic treatment [5]. It was reported in [5] that *B. burgdorferi* not only results in an enhanced inflammatory response but also induces apoptosis in monocytes. It is now well known that *B. burgdorferi* can evade the immune system. While the exact mechanism is unknown, several mechanisms have been hypothesized [2]. In a recent paper [22], Naj showed for the first time that uptake of borreliae in phagosomes is critical for their intracellular processing by macrophages. In consequence, interference with Rab22a or Rab5a activity results in increased intracellular survival of spirochetes, pointing to a potential strategy for persistence in the host. Thus it is important to consider those macrophages that are infected with spirochetes. Such internalization may result in host cell damage causing pathology consistent with Lyme borreliosis, or may be a mechanism for them to escape destruction from innate or adaptive immune response. Whether pathogen-induced apoptosis is harmful or beneficial to the host has been a considerable source of debate. Monocytes/macrophages are a major component of cellular infiltrates in *B. burgdorferi*-infected tissues and are believed to be critical for clearance of spirochetes at the site of infection. Apoptosis of macrophages by ingested spirochetes could, therefore, be a parasitic suicide strategy for promoting survival and dissemination of bacteria that
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However, the following questions are still under investigation: (1) Does B. burgdorferi replicate within host cells? (2) Does the B. burgdorferi invasion lead to host cell damage and pathological effects to the host? (3) Is this invasion a temporary event and do they eventually exit the host cells they invade [8]?

The organization of this paper is as follows. In section 2, we introduce our mathematical model that considers spatial effect. In section 3, we analyze the stability of the healthy homogeneous state. In section 4, we provide estimates for parameters used in the numerical simulations. We also discuss the numerical method used in the simulations. Numerical results and observations are presented in section 5. A brief discussion is presented in section 6.

2 The model and preliminaries

Mathematical modeling in immunology started as early as the 1960s. Classical models of immune system began with simple ODE systems, or difference equations, and etc. The ODE models consider the evolution of populations of different immune cells and pathogens without considering the spatial diffusion of these cells. We refer the readers to reference [25] for a review on these models. There are few models that consider the motility and chemotaxis of cells in immune response. One of the earliest PDE models describing immune response was due to Lauffenburger and Keller [16]. In recent years, there are a few spatial-temporal models that investigate the role of immune response in other areas such as tumor cells [3, 23], wound healing [1, 30] and inflammatory response [24]. One of the most recent PDE model of immune response to invading pathogen is due to Su et al [27]. Their model consisted of over 10 equations that models both the innate and adaptive response. Their model further investigated the fact that an increased production of inflammatory cytokines leads to the adaptive response.

Keller and Segel first used partial differential equations to study the interactions of chemotactic cells (slime molds) and a secreted attractant (cAMP)[13, 14]. A typical formulation of the chhemotaxis model is the following system:

\[
\frac{\partial m}{\partial t} = \nabla \cdot (\mu \nabla m) - \nabla \cdot (\chi m \nabla c) + f(m, c), \quad (1)
\]
\[
\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + g(m, c). \quad (2)
\]

Here, \(m\) is the cell density and \(c\) is the chemoattractant concentration. \(\mu > 0\) and \(\chi\) are the cell motility and chemotactic coefficient, respectively. \(\chi > 0\) corresponds to chemoattraction and \(\chi < 0\) corresponds to repulsion. \(f(m, c)\) represents cell proliferation and death. The terms in the dynamics of \(c\) are
random diffusion and production and/or degradation of chemicals, respectively. Since then, many similar models have been used to study a wide variety of systems that involve chemotaxis. We refer the readers to [11] of a review on this subject.

Our model consists of four partial differential equations which describes the rate of change of several key cells associated with the innate immune response. The bacteria population is represented by \( B(t, x) \); normal macrophages is represented by \( M(t, x) \); macrophages with bacteria survival is represented by \( M_i(t, x) \); natural killer T cells is represented by \( T(x, t) \).

\[
\frac{\partial B}{\partial t} = D_b \Delta B - \frac{\gamma_b MB}{M} + \frac{\beta}{MB} + \frac{\mu sM_i}{M} \tag{3}
\]

\[
\frac{\partial M}{\partial t} = D_m \Delta M - \nabla \cdot (\chi M \nabla B) + \beta + \frac{\sigma_M B}{MB} - \frac{\gamma_i MB}{M} - \frac{\gamma_m M}{M} \tag{4}
\]

\[
\frac{\partial M_i}{\partial t} = D_i \Delta M_i + \gamma_i MB - \frac{\alpha T M_i}{M_i} - \frac{\mu M_i}{M_i} \tag{5}
\]

\[
\frac{\partial T}{\partial t} = D_T \Delta T + \Lambda + rT \frac{M_i}{a + M_i} - \delta T \tag{6}
\]

The first equation is the rate of change of bacteria population where \( D_b \Delta B \) represents the diffusion of bacteria. \( \sigma_b B \) represents the growth of the bacteria. The last term represents the release of the bacteria after the infected macrophages are killed by natural killer T cells.

The second equation is the rate of change of macrophages where \( D_m \Delta M \) represents the diffusion of macrophages. \( \nabla \cdot (\chi M \nabla B) \) represents the chemotaxis toward the bacteria. \( \beta \) is the recruitment rate from the bloodstream. \( \sigma_M B \) represents the activation of the macrophages. \( \gamma_i MB \) represents the infection of the macrophages. \( \gamma_m M \) is the natural death of macrophages.

The third equation is the rate of change of the infected macrophages with extracellular survival of bacteria. The infected macrophages are necrotized by T cells. The term \( \mu M_i \) is the natural death of infected macrophages.

The last equation is the rate of change of natural killer T cells where \( D_T \Delta T \) is the effective diffusion of T cells. The first term denotes the recruitment rate from the source organs. The second term represents the replication rate of natural killer T cells in the presence of infected macrophages. The last term is the natural death of them.

In an earlier paper by Vig and Wolgemuth, they captured the bull’s eyes pattern through a similar chemotaxis model by considering the populations of macrophages, translocating spirochetes and stationary spirochetes [28]. The
main goal of this work is to understand the impact of the potential intracellular survival of spirochetes along with other factors.

In this paper, we consider the system on the one dimensional interval and assume zero–flux (Neumann) boundary conditions. Boundary conditions can vary considerably for different biological problems, but the zero–flux conditions are a natural choice in many applications. Initial conditions are

\[(B(0, x), M(0, x), M_i(0, x), T(0, x)) = (B_0(x), 0, 0, 0),\]

where \(B_0(x)\) represents the initial concentration of \(B. burgdorferi\).

### 3 Stability of homogeneous states

In this section we analyze the stability of the healthy state consisting of macrophages and T cells:

\[(B_0, M_0, M_{i0}, T_0) = (0, \frac{\beta}{\gamma_m}, 0, \frac{\Lambda}{\delta}).\]

Linearization of the system about this steady state yields

\[
\begin{pmatrix}
\frac{\partial}{\partial t} B \\
\frac{\partial}{\partial t} M \\
\frac{\partial}{\partial t} M_i \\
\frac{\partial}{\partial t} T
\end{pmatrix}
= \begin{pmatrix}
D_b & 0 & 0 & 0 \\
\chi M_0 & D_m & 0 & 0 \\
0 & 0 & D_i & 0 \\
0 & 0 & 0 & D_T
\end{pmatrix}
\begin{pmatrix}
\frac{\partial^2}{\partial x^2} B \\
\frac{\partial^2}{\partial x^2} M \\
\frac{\partial^2}{\partial x^2} M_i \\
\frac{\partial^2}{\partial x^2} T
\end{pmatrix}
+ \begin{pmatrix}
\sigma_b & -\gamma_b M_0 & 0 & \mu s & 0 \\
\sigma_M - \gamma_i M_0 & 0 & -\gamma_m & 0 & 0 \\
\gamma_i M_0 & 0 & -\alpha T_0 & 0 & 0 \\
0 & 0 & 0 & \frac{\sigma}{a} T_0 & 0
\end{pmatrix}
\begin{pmatrix}
B \\
M \\
M_i \\
T
\end{pmatrix}.
\]

The Laplacian on a bounded domain \(\Omega\) has a discrete set of eigenfunctions with associated eigenvalues \(-k^2\) that are determined by the shape of the domain and the boundary conditions. In particular, for the one-dimensional domain \(\Omega = [0, L]\) with Neumann boundary conditions, the eigenfunctions are \(\Phi_n(x) = \cos(\frac{n\pi x}{L})\), and the eigenvalues are \(k_n = \frac{n\pi}{L}\). With this substitution, the stability can be determined by the eigenvalues of the following matrix:

\[
\begin{pmatrix}
-k^2 D_b + (\sigma_b - \gamma_b M_0) & 0 & \mu s & 0 \\
k^2 \chi M_0 + \sigma_M - \gamma_i M_0 & -k^2 D_M - \gamma_m & 0 & 0 \\
\gamma_i M_0 & 0 & -k^2 D_i - \alpha T_0 - \mu & 0 \\
0 & 0 & 0 & \frac{\sigma}{a} T_0 & -k^2 D_T - \delta
\end{pmatrix}.
\]

The eigenvalues are given by

\[
\lambda_1 = -k^2 D_M - \gamma_m, \quad \lambda_2 = -k^2 D_T - \delta
\]

and the roots of the following quadratic equation

\[
\lambda^2 + (u + v)\lambda + uv - p = 0,
\]
where
\[ u = k^2 D_b + \gamma_b M_0 - \sigma_b, \quad v = k^2 D_i + \alpha T_0 + \mu, \quad p = \mu s \gamma_i M_0. \]

It is then easy to conclude that the steady state is linearly stable if and only if
\[ u + v > 0, \quad uv - p > 0. \]

It is evident that the two primary factors that can lead to the instability of this healthy steady state are the replication rate of the bacteria and the efficient evasion quantified by the infection rate \( \gamma_i \) and release rate \( \mu s \).

4 Parameter estimates

The motility of \textit{Borrelia burgdorferi} is very complex. Unlike most spirochetes such as \textit{E. coli}, the periplasmic flaga have a skeletal function that affects the entire shape of the cell. As a result, the spirochete swims by generating a backward wave along the length of the cell. In [19], the authors measured the mean crossing speed of \textit{Borrelia burgdorferi} is 1636 \( \mu \)m per minute with a maximum speed of 2800 \( \mu \)m per minute. This is the fastest speed recorded for a spirochete, and upward of two orders of magnitude above the speed of a human neutrophil, the fastest cell in the body. We use Einstein-Smoluchowski equation to deduce the diffusion coefficient formula
\[ D = \frac{1}{2} \lambda v \]
where \( v \) is the average speed and \( \lambda \) is the mean free path. The estimated diffusion coefficient of \textit{Borrelia burgdorferi} is approximately 1 \( cm^2/day \). We note that other bacteria such as \textit{E. coli} has a diffusion coefficient of 0.1-0.3 \( cm^2/day \).

The data in Table 1 are taken in most part from [12, 15, 27] and references therein.

The fundamental equation in our model is the Keller-Segel equation modeling chemotaxis. Numerical simulation of chemotaxis equation is a challenging task. Many different approaches have been proposed in [9]. A successful numerical scheme must address the resolution and computing time of the algorithm. Our method is a pseudo-implicit scheme based on the Crank-Nicolson method. For the discretization of the equation containing chemotaxis term, we use a finite volume approach and Crank-Nicolson Scheme. Even though an explicit scheme can yield high resolution with a small time step, the simulation time is expensive. Moreover, the explicit schemes are not stable. In our numerical simulation, the time step size is primarily determined by the convection equation since the scheme for diffusion equation is unconditionally stable.
Table 1: Parameters used for the numerical simulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Biological Range</th>
<th>Simulation</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_b$</td>
<td>bacteria diffusion rate</td>
<td>1</td>
<td>1</td>
<td>cm$^2$/day</td>
</tr>
<tr>
<td>$D_m$</td>
<td>macrophage diffusion</td>
<td>0.0001 - 0.0006</td>
<td>0.0001</td>
<td>cm$^2$/day</td>
</tr>
<tr>
<td>$D_i$</td>
<td>infected macrophage diffusion</td>
<td>$D_m$</td>
<td>0.0001</td>
<td>cm$^2$/day</td>
</tr>
<tr>
<td>$\sigma_b$</td>
<td>bacteria replication rate</td>
<td>1 - 2</td>
<td>1</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\gamma_b$</td>
<td>bacteria engulfment rate</td>
<td>3 - 5</td>
<td>3</td>
<td>cell$^{-1}$day$^{-1}$</td>
</tr>
<tr>
<td>$\chi$</td>
<td>chemotaxis rate</td>
<td>unknown</td>
<td>1</td>
<td>cm$^2$/day</td>
</tr>
<tr>
<td>$\beta$</td>
<td>macrophage recruitment rate</td>
<td>unknown</td>
<td>0.01</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\sigma_m$</td>
<td>activation rate</td>
<td>1</td>
<td>1</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>recovery rate</td>
<td>unknown</td>
<td>0.01</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\gamma_m$</td>
<td>macrophage death rate</td>
<td>0.003-0.07</td>
<td>0.07</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\gamma_i$</td>
<td>infection rate</td>
<td>unknown</td>
<td>1</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>death of infected macrophage</td>
<td>unknown</td>
<td>0.3</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>T cells recruitment rate</td>
<td>0.1</td>
<td>0.1</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$r$</td>
<td>T cells replication rate</td>
<td>0.02</td>
<td>0.02</td>
<td>day$^{-1}$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>T cells death rate</td>
<td>0.03-0.333</td>
<td>0.1</td>
<td>day$^{-1}$</td>
</tr>
</tbody>
</table>

5 Numerical Results and Observations

In this section, we examine the model by conducting a series of numerical experiments. Our main objective is to identify the factor that leads to the characteristic bull’s-eye rash that is unique during the early stage of Lyme disease. Another objective is to find the correlation between the bacteria survival rate and the rash pattern.

For equation (3), (5) and (6), we use Crank-Nicolson scheme. For equation (4), we use a hybrid finite-volume-finite-difference method. We simulated the system using a 500 point spatial grid for a domain of length 500 for duration $t = 10$. The unit for time in our simulation is 1 day and the unit for length is 1 millimeter. All parameters are as set in the table unless we specify the different data for comparison purpose. The initial data is as follows

$$B(x, 0) = e^{-0.01x^2},$$

and concentrations of all the other cells are set to be zero.

**Observation 1:** Large engulfment rate leads to bull’s-eye rash: for the first simulation, we compare the density of the bacteria for two different engulfment rate $\gamma_b = 3$ and $\gamma_b = 1$ (see Fig. 2). Initially, the bacteria concentration is concave near the infection site. When the engulfment rate is high, the macrophage density quick increase at the center of infection site and the concentration of the bacteria is brought down. This results in a wave front with twin peaks propagating outward. The bacteria density between these two peaks is brought down close to zero. However, when the engulfment rate is low, the bacteria density remains concave resulting in a more homogeneous rash. This result implies that patients with homogenous rash may have a weaker
defense against the bacteria. A stronger dosage of antibiotic and a longer treatment during the early stage of Lyme disease maybe the key to prevent the development of other disease manifestations.

Figure 2: Time evolution of $b$ with parameters given in Table 1. The right picture corresponds to a small engulfment rate $\gamma_b = 1$. Here, the graphs represent plots of $b(x, t)$ with $x$ on vertical axis and time increasing from left to right. The spectral color shows the density of the bacteria. Orange represents higher density and blue represents lower density.

**Observation 2:** Chemotaxis rate does not affect the spreading speed of the bacteria: we compare the spreading of the bacteria with two different chemotaxis rates $\chi = 2$ and $\chi = 10$ (see Fig. 3). In both cases, the edge of bacteria concentration spreads at the same speed. The spreading speeds of the bacteria are around 1 cm in diameter per day. When we compare the concentration of macrophages, we note that for the lower chemotaxis rate, there is a weaker accumulation of macrophages around the infection site.

Figure 3: Time evolution of $b$ with parameters given in Table 1. The top picture corresponds to chemotaxis rate $\chi = 2$. The bottom picture corresponds to a larger chemotaxis rate $\chi = 10$. This comparison shows that the chemotaxis rate of the macrophages does not affect the spreading of the rash.

**Observation 3:** Bacteria diffusion rate $D_b$ clearly affect the spreading speed of bacteria: we compare the spreading speed of the bacteria with $D_b = 1$ and $D_b = 10$. The spreading speed corresponding to the larger diffusion rate is clearly faster (see Fig. 4).
Figure 4: Time evolution of $b$ with parameters given in Table 1 except $\sigma_b = 1$. The top picture corresponds to bacteria diffusion rate $D_b = 1$. The bottom picture corresponds to a larger diffusion rate $D_b = 10$. This comparison clearly shows that the diffusion rate of the bacteria increases the spreading speed of the rash.

**Observation 4:** High intracellular survival rate $\gamma_i$ may lead to homogeneous rash: we compare the profile of the bacterial with $\gamma_i = 0.01$ and $\gamma_i = 1$. Clearly high intracellular survival rate leads to a more homogeneous rash instead of bull’s-eye rash (see Fig. 5). This simulation suggests that an initial homogeneous rash may be an indicator that the bacteria has a higher survival rate which may lead to the persistence of spirochetes in the infected host. This result may imply that for patients with homogeneous rash, a prolonged treatment with antibiotic may be beneficial.

Figure 5: Time evolution of $b$ with parameters given in Table 1 except $\gamma_i = 0.01$ and $\gamma_i = 1$. This shows high infection rate also leads to homogeneous rash.

### 6 Discussion

Over the past two decades, there are many different types of mathematical models that have been developed to stimulate the immune system. The majority of these models are based on ordinary differential equations that are computationally efficient and can describe complex systems elegantly. But many ODE systems failed to capture spatial dynamics that is evident in some
immune response. In this paper, we developed a partial differential equation system with a minimum amount of variables that helps us investigate the key factors causing the hallmark rash of Lyme disease. The motility of \( B.\ burgdorferi \) is 40-100 times faster than neutrophils. It is the most motile immune cells that respond to the infection. The high motility is not only the key factor for the spreading speed of the rash, but also a potential factor that allows the bacteria to evade the immune response. Immune cells such as macrophages which rely on chemotaxis to approach the bacteria may never be able to exactly find them in the position signaled by the chemoattractants such as CCL2.

While the majority of the immune response models are based on the known biology of immune system, all mathematical models of immune response should be considered as aids to understand this complicated process due to the uncertainty of the parameter values. The complex nature of our immune system makes it even harder to the daunting task of collecting and calculating the parameter values. These models are still excellent tools that helps us understand our immune system.

Finally, we would like to remark that there have been other attempts to explain the skin rash. In [10], the authors attempted to explain the Erythema gyratum repens (EGR) using the Belusov-Zhabotinski (BZ) reaction diffusion model. Erythema gyratum repens is a figurate erythema that is believed to be a paraneoplastic process. Its characteristic concentric erythematous bands forming a wood-grain appearance distinguish erythema gyratum repens from other figurate erythema such as Erythema migrans. Among several justifications of this model, the authors argued that the morphology of EGR, the BZ reaction and cAMP waves in slime mould culture show striking similarities[10]. The second reason the authors provided is that the spreading speed of the edge of the rash is too large to be explained using Fickian diffusion. The BZ system may be able to capture some rash pattern that is characteristic to EGR, but the authors did not associate the chemicals in the reaction diffusion system with specific factors during the appearance of a rash.

We may also examine the spatio-temporal distribution of macrophages and bacteria for a double site infection. We use the same algorithm from previous section and consider the following initial density of Borrelia burgdoferi:

\[
b(0, x) = e^{-0.01x^2} + 2e^{-0.01(x-50)^2}.
\]

All the other parameters are the same as in Table 1. Figure 6 shows the spatial-temporal evolution of macrophage and bacteria. Initially, bacteria concentration increases sharply at the infection site. This quickly brings the macrophages into action and its concentration quickly increases at the infection site. By the end of the second day, the bacteria concentration is brought down. By the end of the third day, the bacteria concentration is even lower. By the end of the fourth day, the bacteria concentrations are merged together.
Figure 6: Dynamics of bacteria, macrophages in spatial-temporal space in response to a double site infection. The corresponding time is 1st day, 2nd day, 3rd day, 4th day from top to bottom, respectively.

Over time, the bacteria concentration is low and nearly constant around the two close infection sites.

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