Journal of Theoretical Biology 393 (2016) 158–169

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

# Modelling the immune system response to epithelial wound infections

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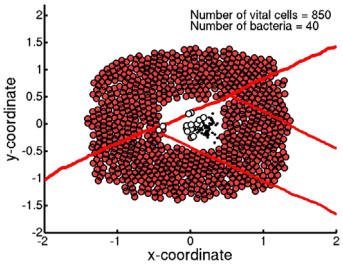
## HIGHLIGHTS

- Cell-based modelling for the immune response system in relation to wound closure.
- Chemotaxis, random walk, cell proliferation, death, engulfment of pathogens.
- Semi-stochastic modelling.
- Long extravenular lifetimes of leukocytes do not enhance the immune system.

## GRAPHICAL ABSTRACT

In this paper, a cell-colony based formalism for the healing of superficial wounds is presented. The paper incorporates the migration, proliferation, and death of constituent cells, in the context of wound healing. The present study considers wound healing under ischemic conditions where a bacterial infection develops, which impairs the motility of the constituent cells. In this work, the performance of the immune response system is incorporated in the sense that migrating white blood cells are modelled which engulf the infectious bacteria. The model is based on both deterministic and stochastic principles. Simulation results are discussed in a biological context and an example is given in the attached figure. In the figure, the red and white cells, respectively, represent the epithelial cells and leukocytes. The latter ones originate from the venules that are represented by the thick red lines (including to parallel branches). Further, the pathogens are represented by the black dots.




## ARTICLE INFO

*Article history:*
Received 8 November 2014
Received in revised form
1 October 2015
Accepted 25 December 2015
Available online 18 January 2016

*Keywords:*
Cell-based modelling
Fundamental solutions
Immune system response

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## 1. Introduction

Under normal clinical circumstances living organisms are attacked by damaging chemicals, pathogens and cells at all times. Therefore, a defense mechanism, referred to as the immune response system, has been developed to protect higher organisms, such as human beings, against toxic doses of hazardous chemicals, pathogens or cells (such as malicious cell mutations that may

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http://dx.doi.org/10.1016/j.jtbi.2015.12.030
0022-5193/

initiate tumors). Hence this immune system is indispensible for the survival of the organism and a disruption of its performance may have a detrimental impact on (the quality of) life (expectancy) of the organism. Many clinical (in-vivo) studies, as well laboratory (in-vitro) experiments, were conducted to unravel the biological mechanisms that determine the performance of the immune system. This allows a better understanding of the role of deficiencies in the immune system, so that one can design treatments to their (partly) removal and increase of life quality and expectancy. Since an increase of understanding of the relations between the various biological parameters and processes involved is aimed at in the clinical studies, a quantitative understanding is crucially important. In order to reach this quantitative understanding, one could employ statistically oriented techniques such as neural networks to reveal the importance of certain parameters on the experimental outcomes. This mathematically sound approach, however, suffers from the lack of physical and biological understanding of the direct quantitative relations between various processes and parameters. Therefore, several mathematical models based on physical principles have been developed to be able to predict the influence of the quantitative relations between the various processes involved on an a priori basis.

The mathematical models developed for wound healing related processes in literature range from a tissue-level treatment in terms of systems of continuum-scale partial differential equations derived on conservation principles, see for instance Sherratt and Murray (1991), Maggelakis (2003), Maggelakis (2004), Gaffney et al. (2002), Olsen et al. (1995), Alarcon et al. (2006), Britton and Chaplain (1993), and Javierre et al. (2009), to cell-based models. Even subcellular processes are dealt with, see for instance Ley et al. (2006) where diffusion through cell membranes is modelled, as well as Karlebach and Shamir (2012) where gene regulatory networks based on an entropy approach for DNA-interactions. The model by Sherratt and Murray (1991) describes a set of reaction–diffusion equations to simulate wound closure without the presence of infections. The closure process refers to the gradual coverage of the wounded area by epithelial cells. In their study, a perturbation analysis is used to describe the solution to the system of partial differential equations. We note that there are many more modelling studies on wound closure. In the studies of Maggelakis (2003), Maggelakis (2004), Alarcon et al. (2006), and Gaffney et al. (2002), the process of angiogenesis is modelled. The process of angiogenesis, which involves the formation of a vascular network within the damaged tissue, is dealt with using systems of partial differential equations for the upscaled parameters that describe the amount of vascularization in terms of densities of endothelial cells or of tips.

Alternative treatments for continuum-based models are the cell-based models. Mathematical techniques are either construction of analytic (exact) solutions to the partial differential equations under heavily simplifying circumstances, or finite-element-like techniques to tackle the problem in complicated geometries. Some of the models are very detailed in the sense that they incorporate as many biological aspects as possible, whereas other models are phenomenological, but are capable to reproduce the most important biologically observed trends. A popular approach is the use of cellular automata (or more specifically the cellular Potts models) where cell migration is simulated by Monte-Carlo like techniques by allowing cells to change position over a predefined lattice of positions, see Graner and Glazier (1992) for the pioneering work. Some studies demonstrate a very successful application of this model class to simulate angiogenesis. We refer to the work of Merks, see Merks and Koolwijk (2009), as an example. Another cellular class of models, simulates individual cells in a continuum, where they are subject to hard impingement and contact forces, as well as cell division and cell death. Such models were constructed in many other studies such as Byrne and Drasdo (2009), Drasdo and Höhme (2005), Höhme and Drasdo (2010), Rey and Garcia-Aznar (2013), Neilson et al. (2011), and Cumming et al. (2010). The present work contains a framework where the following cell types are dealt with:

- constituent cells, which are host cells, such as epithelial cells in lungs or in skin;
- pathogens, which are infectious agents that cause disease to the host;
- leukocytes, which are cells that circulate in blood or in other body liquids, and they are involved in battling foreign agents and disease.

Although many cell-based models for processes like wound closure exist in the literature, there is not a cell-based model that combines wound closure with the immune system by combining the migration and proliferation of constituent cells with the infection by pathogens and the clearance of pathogens by leukocytes. The leukocytes clear the pathogens by following the chemical signals released by them, see Segal (2005). Since it is known that the competition between the pathogens and surrounding constituent cells for nutrients and possibly for oxygen (for aerobic pathogens) increases the acidity in the surroundings of the pathogens, the chemotactic signal is used to make the leukocytes migrate towards the pathogens.

In the present study, we consider healing of a wound that is disrupted by a pathogenic infection. Here leukocytes, with diameters ranging between 7 and 50 μm, transmigrate through the venule wall to clear up the pathogens that infect the damaged region. The model that is developed here treats wound closure on a cell-colony level where each constituent cell, being either epithelial cells or fibroblasts, is tracked regarding its migration, division and death. Furthermore, pathogens that infect the colony are taken into account as individual entities that divide and die. Further, they give rise to an increased acidity of the region around them as a result of the competing for nutrients and oxygen with the constituent cells. The leukocytes are modelled as appearing from sites on the venules where they migrate through the tissue region to chase the pathogens. All cell types are modelled as non-deforming soft spheres that exhibit contact forces under hard impingement. Similar approaches can be found in Neilson et al. (2011), Vermolen and Gefen (2012a), Byrne and Drasdo (2009), Vermolen and Gefen (2012b), Groh and Louis (2010), and Rey and Garcia-Aznar (2013). The process of diapedesis, the transmigration of leukocytes through the venule walls is phenomenologically modelled by the probability of appearance of a leukocyte at a certain site of the venule, where the venule is incorporated as a (score of) line(s) in the computational domain. We realize that the actual immune response is very complicated from a biological point of view, where, for the sake of completeness, we describe the biological sequence of this process. The venule wall is relatively porous so that cells are able to transmigrate through it and hence cells are able to leave the venule. This process is also referred to as diapedesis, and it roughly consists of the following sequence, see Hogg (1995), Oda et al. (1992), and Middleton et al. (2002):

1. *Chemo-attraction*: The presence of infectious pathogens make the residing macrophages produce cytokines such as IL-1, TNF$\alpha$ and chemokines. These cytokines make the endothelial cells secrete chemokines that make the leukocytes in the venule migrate towards the venule wall.
2. *Venule wall adhesion*: Once the leukocytes reach the venule walls, they bind to the venule wall, in which they 'roll' over the venule wall surface at the earliest stages and become attached to the venule wall more firmly in the subsequent stages.
3. *Endothelial migration*: The cytoskeleton of the leukocytes is deformed such that the leukocytes can transmigrate through the