

AGENT-BASED MODELING OF THE IMMUNE RESPONSE TO IMPLANTED BIOMATERIALS

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Introduction

The implantation of any biomaterial into the body triggers a cascade of inflammation responses collectively referred to as foreign body reaction (FBR) [1]. The FBR starts with the extravasation of blood and ends with the fibrotic encapsulation of the implant, involving different cell populations such as macrophages and fibroblasts. Macrophages are key immune cells which secrete cytokines depending on the stimulus received from the surrounding microenvironment, thus exhibiting a particular phenotype in a continuous spectrum of activation ranging from pro-inflammatory or M1 to pro-healing or M2. This dynamic polarization process has been described by several mathematical models, including agent-based (AB) approaches, which aim to simulate intercellular interactions depending on the spatial position and the state of activation of cells, modeled as mobile agents. In this scenario, our aim is to propose an AB model for simulating the role of the different phenotypes of macrophages and fibroblasts in the FBR induced by the presence of biomaterials at the cellular level.

Methods

We started considering the AB model proposed in [2], where macrophages are stimulated by a pathological pro-inflammatory mediator (PIM) reproducing lipopolysaccharide (LPS), in a 2D grid, following simplified rules. This original scheme was enriched here with the introduction of a “mechanical PIM”, simulating the implanted biomaterial and assumed to be constant at the center of the grid. This mechanical PIM triggers the cellular secretion of chemical PIM and anti-inflammatory mediators (AIM), both representing cytokines. Based on the level of PIM (both mechanical and chemical) and AIM, fibroblasts are subsequently recruited according to specific equations and parameters, to finally form the fibrotic capsule enveloping the implant.

Results

Simulations were run for 36 and 120 hours in MATLAB (MathWorks, Inc.), so as to reproduce acute and chronic responses, respectively. Distributions of the cell populations involved (Figure 1) reveal a localized capsule, mainly formed by M1 and M2 macrophages at 36 hours and by M2 macrophages and fibroblasts from 40 to 120 hours, approximately. By the AB approach we have the access to a large number of kinetic data that can be directly compared to experimental results.

Discussion

Preliminary results highlight that the proposed AB model is suitable for replicating the majority of known phenomena associated with the immune response to biomaterial implantation, with a particular focus on the interaction between macrophages and fibroblasts. Future work will allow us to develop a digital twin of the FBR in small animal models, helping to reduce the number of used animals, the costs of biomaterial discovery and protocols for biocompatibility.

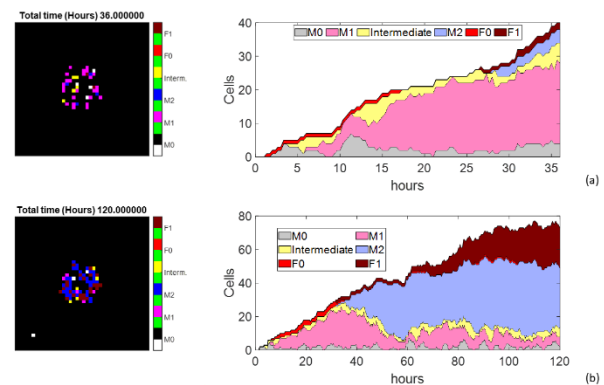


Figure 1: Cell distribution at the single last frame (left side) and overall number of cells counted at each time of the simulation (right side) lasting 36 hours (a) and 120 hours (b).

F1: fibroblasts; F0: fibrocytes; Interm.: intermediate macrophages; M0: non-activated macrophages.

References

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2. S. B. Minucci et al, PLoS ONE, 19:e0270779, 2024.

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