Published in final edited form as:

J Immunol Methods. 2013 November 29; 397(0): 37–46. doi:10.1016/j.jim.2013.08.013.

A computational model of fibroblast and macrophage spatial/temporal dynamics in foreign body reactions

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Abstract

The implantation of medical devices often triggers several immune responses, one kind of which is categorized as foreign body reactions. It is well established that macrophages and many other cells participate in the complex processes of foreign body reactions, and cause severe inflammations and fibrotic capsule formation in surrounding tissues. However, the detailed mechanisms of macrophage responses, recruitment and activation, in foreign body reactions are not totally understood. In the meantime, mathematical models have been proposed to systematically decipher the behavior of this complex system of multiple cells, proteins and biochemical processes in wound healing responses. Based on these early works, this study introduces a mathematical model in two spatial dimensions to investigate the transient behavior of macrophages, fibroblasts and their interactions during the formation of fibrotic tissue. We find that the simulation results are consistent with the experimental observations. These findings support that the model can reveal quantitative insights for studying foreign body reaction processes.

Keywords

Computational model; Foreign body reactions; Spatial and time dynamics; Medical implant; Macrophage; Fibroblast

1. Introduction

Medical devices play an essential role in the advancement of modern medicine. In spite of their increasing importance, almost all medical implants prompt certain degrees of foreign body reactions, including inflammation, infection, fibrosis and coagulation. Foreign body reactions are often started with the accumulation of coagulation products and the release of various inflammatory products around the biomaterial (Kawahara, 1983; Anderson, 2000; Gretzer et al., 2006; Luttikhuisen et al., 2006). The gradient of inflammatory signals leads to the recruitment of macrophages and then fibroblasts surround medical implants (Tang and Eaton, 1995; Malik et al., 2011; Thevenot et al., 2011; Zhou et al., 2011). With the stimulation of the inflammatory mediators, recruited fibroblasts undergo proliferation and then produce procollagens. One of the most potent pro-fibrotic products is transforming growth factor- β (TGF β) (Appling et al., 1989) which can be secreted by activated macrophages (Fujiwara and Kobayashi, 2005) or platelets following coagulation (Streuli et al., 1993). The procollagens can be converted by enzymes into collagens, the dominant

ingredient of the extracellular matrix (ECM) (Goldberg, 1977), while damaged collagen can also be dissolved by collagenase (Stricklin et al., 1978).

It is well established that macrophages play a pivotal role in wound healing models (Dale et al., 1996). Macrophages are highly heterogeneous cells that can rapidly change their function in response to local environmental signals (Murray and Wynn, 2011). In recent years, it has been widely believed that classically activated macrophages and alternatively activated macrophages are two extremes of a spectrum of possible macrophage phenotypes (Mantovani et al., 2002, 2004). During wound healings, macrophages can be classified into three common phenotypes according to the roles they play. Their diversified functions include digesting foreign and debris materials, producing chemotactic signals, and remodeling ECM. However, the roles of various macrophage phenotypes on the dynamics of foreign body reactions are not completely understood.

We have very recently used mathematical models and simulations to determine the interactions between macrophages and fibroblasts during foreign body reactions (Su et al., 2011a,b; Ibragimov et al., 2012). The models are based on kinetics of foreign body reactions in which both macrophages and fibroblasts are two major types of cells in the fibrotic tissues. Interestingly, many processes of foreign body reactions resemble those of wound healing responses. In fact, these basic reactions were considered in a similar modeling study of wound healing and their corresponding key features of kinetics were incorporated in our modeling. There are also reports which incorporated angiogenesis and oxygen level into modeling for wound healing process (Budu-Grajdeanu et al., 2008; Schugart et al., 2008).

Taking advantage of these developments, we introduced a computational model to systematically study the complex dynamics of foreign body reaction processes (Ibragimov et al., 2012). In the model, we focused on the interaction between fibrotic processes and macrophage activations and migrations. We divided macrophages into three phenotypes based on their different functions and provided a modeling study.

In this work, we numerically test this 2-Dimensional computational model in the same physical setting as in an implantation experiment in rats. The computer simulated results are compared with the experimental dataset. Both kinetics trends of cell population distributions in 2-D spaces and experiments/modeling discrepancies are obtained for this comparative study. The modeling results indicate the consistent trend of the cell populations as shown in experimental data and in modeling studies, affirming the value of mathematical modeling in serving as a predictive tool for developing plausible experimental hypotheses.

2. Methods

2.1. Mathematical modeling considerations

The process of foreign body reactions to implants involves interactions of many types of cells and proteins and occurs as a cascade of sequential, parallel and overlapping chemical processes forming a network (Anderson et al., 2008). Immediately before and after implantation, the medical implants are surrounded with a layer of plasma proteins and fibrin clots. Within 8–12 h, large numbers of immune cells, mostly neutrophils and macrophages, are recruited to the implantation sites. By the end of 1 week, medical implants are surrounded with multiple layers of macrophages and some fibroblast-like cells (also called fibrocytes) (Tang and Hu, 2005; Thevenot et al., 2011). The migration of macrophages and fibroblasts is mediated by the gradient sensing mechanism which can be captured in essence by chemotactic equations in the model. Upon reaching the implantation site, recruited cells such as macrophages and fibroblasts continue to release more chemotactic agents to

reinforce the gradient fields and to attract more migrating cells. The implant site contains enzymes that activate latent growth factors and stabilize collagen formations. Similar to collagen formation in dermal wound healing, collagenase is synthesized and secreted by fibroblasts as a zymogen, and once the zymogen is activated by enzymes to become collagenase, collagen degradation and collagen formation occur concurrently in a competitive manner.

Foreign body reactions are multi-time scale processes. In fact, the initiation process happens in a much short period of time in comparing with other processes. Furthermore, in wound healing models, conversions between active and inactive forms of proteins, growth factors usually reach equilibrium quickly. The time scale difference allows us to simplify the model by assuming that the initiation is already accomplished and active/inactive protein, growth factors have already reached balance, thus, we get a reduced system of fewer equations for our foreign body reaction model.

2.2. Modeling: chemical kinetics equations with macrophage phenotypes

Macrophages exhibit remarkable plasticity and can adopt different phenotypes in response to environmental cues (Khallou-Laschet et al., 2010). In Mosser and Edwards (2008), macrophages have been categorized into populations based on three different homeostatic activities — host defense, wound healing and regulation, as have been observed experimentally. The varied responses from three kinds of macrophage cells – classical, inflammatory and regulatory macrophage cells – may affect not only the fibroblast proliferation but also the whole foreign body reaction procedure. We incorporated this important feature into our model which is partially from the mass-action kinetics framework developed by Schugart et al. (2008) but used a simplified model in cell and collagen (or extracellular matrix, ECM) growth to avoid over-complication of our study. We added new kinetics of macrophage reactions into the framework so that we can generally catch the kinetics characteristics of fibroblasts and macrophages and gain more insights on how different macrophage populations regulate the foreign body reaction processes. We aim to find the variations between tissue responses at different population mix of classical, inflammatory and regulatory macrophages during the foreign body fibrotic reaction process.

Before we introduce the mathematical equations, we lay out basic hypotheses of the biological process in foreign body reactions:

- A debris cell population, consisting of foreign body damaged cells, blood clots and other injury-released cells, triggers foreign body reactions.
- A generic growth factor such as vascular endothelial growth factor (VEGF) regulates fibroblasts and macrophages through chemotaxis. The chemoattractant undergoes random motion and its concentration is assumed to grow in proportion to secreting inflammatory macrophages but is suppressed by regulatory macrophages.
- Fibroblast represents a main cell type in secreting collagen/ECM during healing. Its proliferation and collagen synthesis are up-regulated by the chemoattractant gradient field as well as being directly up-regulated by classical macrophages through TGF β .
- Macrophages act in different roles during foreign body reactions according to their phenotypes as classical macrophage, inflammatory macrophage or regulatory macrophage. The proliferation of macrophages is through diffusion and migration up-regulated by the chemotactic gradient field, and cell apoptosis is also assumed.

- Fibroblasts secrete procollagen which is then activated by TGF β into collagen (or ECM). ECM diffusion, fibroblast movement, chemotactic migration, and ECM saturation are factored into a mass-action law.

We model the fibrotic reactions as follows:

$$\frac{\partial d}{\partial t} = D_0 \nabla^2 d - f_0 M_1 d + \tilde{f}_0 M_3 s \quad (1)$$

$$\frac{\partial c}{\partial t} = D_1 \nabla^2 c + f_1 d + f_2 M_3 - f_3 M_2 c - f_4 c, \quad (2)$$

$$\frac{\partial F}{\partial t} = D_3 \nabla^2 F - \nabla \cdot (\alpha F \nabla c) + a_1 M_1 + a_2 F (1 - F/F_0) - a_3 F, \quad (3)$$

$$\frac{\partial M_i}{\partial t} = D_2 \nabla^2 M_i - \nabla \cdot \left(\alpha H \left(M_0 - \sum_{i=1}^{i=3} M_i \right) M_i \nabla c \right) - a_0 M_i, \quad i=1, 2, 3, \quad (4)$$

$$\frac{\partial E}{\partial t} = D_4 \nabla^2 E + \nabla \cdot \frac{a_4 D_5 E F}{F_0} \nabla F - \frac{a_4 \beta E F}{F_0} H(F_0 - F) \nabla c + a_5 F \left(1 - \frac{E}{E_0} \right). \quad (5)$$

Here, the debris cell population $d = d(x, y, t)$ represents dead tissue or excessive cells following an implantation. We assume that debris cells are digested by M_1 — classical macrophages but the accumulation of M_3 — inflammatory macrophages contributes to the debris during the healing process. The chemoattractant $c = c(x, y, t)$ consists mainly of various forms of TGF β released during the healing. The chemoattractant field is enhanced by the presence of debris cells and inflammatory macrophages, but is inhibited by regulatory macrophages. We assume that cell migration is through diffusion and chemotactic migration. Fibroblast proliferation and collagen synthesis are up-regulated by the chemoattractant gradient field. Thus fibroblast population, $F = F(x, y, t)$, can be approximated by a chemically enhanced logistic growth $F(1 - F/F_0)$ with a carrying capacity F_0 , along with its diffusion in space modeled by $D_3 \nabla^2 F(x, y, t)$, chemotactic migration by $\nabla \cdot (\alpha F \nabla c)$ and its natural decay according to time. The macrophage density, $M(x, y, t)$, is the summation of M_1 — classical macrophages, M_2 — regulatory macrophages, and M_3 — inflammatory macrophages. We assume that they each take on λ_1 , λ_2 , and λ_3 proportion of macrophages, respectively. Each macrophage phenotype may behave differently at different stages of foreign body fibrotic reactions. Our model simplifies the situation in that (a) the proportion of λ_1 , λ_2 , and λ_3 for different phenotypes of macrophages is taken to be fixed; and (b) the total macrophage populations are set to share one common biochemical reaction as their basic biochemical properties are similar. The migration of macrophages at the field is through diffusion and convection along the chemotactic gradient field. The proliferation of macrophages is also up-regulated by the chemoattractant, but their production does reach a limiting value once macrophage population reaches saturation. Macrophage cell apoptosis is also assumed. Finally, fibroblasts secrete procollagens and the product is activated by chemoattractant TGF β s into the collagens or ECM at the quantity $E = E(x, y, t)$. We also incorporate the effects of ECM diffusion, fibroblast movement, chemotactic migration and ECM saturation in mass-action law. Here H is the Heaviside function, and M_0 is the macrophage saturation level.

2.3. Boundary and initial conditions

We simulated the kinetics based on the model under the assumptions that all the functions are defined in the reaction domain which is an annulus $G = \{(r, \theta), L_{in} \leq r \leq L_{out}, 0 \leq \theta < 2\pi\}$, where the inside disk $\{(r, \theta), 0 \leq r \leq L_{in}, 0 \leq \theta < 2\pi\}$ is the location of the implant, and the outside ring $\{(r, \theta), L_{out} \leq r < \infty, 0 \leq \theta < 2\pi\}$ is the normal surrounding tissue. $\{r = L_{in}\}$ represents the inner edge of the wound i.e., the outer edge of the implant. $\{r = L_{out}\}$ represents the outer edge of the wound. Along the outer edge of the wound, it was assumed that the densities of fibroblasts and ECM remain constant at the level of the unwounded state. Along the inner edge of the wound, it was assumed that the densities of debris remain in a wounded state caused by the implant. The densities of the macrophages were assumed to decrease at the boundary of the healthy tissue as the healing process progressed and the flux of the chemoattractant on this boundary was negligible. As shown in Fig. 1, at $r = L_{out}$ the boundary conditions are as follows,

$$F = F_0, \quad M = M_0 e^{-\gamma_2 t}, \quad E = E_0, \quad \frac{\partial c}{\partial r} = 0.$$

At $r = L_{in}$, the boundary condition includes

$$d = d_0.$$

In all other cases not mentioned above, the following no-flux boundary conditions are used,

$$\frac{\partial F}{\partial r} = \frac{\partial d}{\partial r} = \frac{\partial M}{\partial r} = \frac{\partial E}{\partial r} = \frac{\partial c}{\partial r} = 0 \quad \text{in } L_{in}, \quad \frac{\partial d}{\partial r} = 0 \quad \text{in } L_{out}.$$

The initial values are set at $t = t_0$, and are taken to be a distribution. The formula is

$$\frac{X}{X_0} = \left(\frac{r - L_{in}}{L_{out} - L_{in}} \right)^2 e^{-\left(\frac{L_{out} - r}{\varepsilon(L_{out} - L_{in})} \right)^2},$$

where $X = c, F, M$, or E , and ε is selected such that all the densities are initially near zero away from the wound outer edge. For debris, the initial distribution follows the formula

$$\frac{d}{d_0} = \left(\frac{L_{out} - r}{L_{out} - L_{in}} \right)^2 e^{-\left(\frac{r - L_{in}}{\varepsilon(L_{out} - L_{in})} \right)^2}.$$

2.4. Dimensionless and parameters

Table 1 lists the parameters in both dimensional and dimensionless form. Similar to the method introduced in Schugart et al. (2008), we converted the dimensional parameters to dimensionless units which will be used in the latter simulation study.

In our study, L_{out} is 0.35 cm and L_{in} is 0.1 cm. For the parameters $D_1, f_4, D_2, \alpha, F_0, a_3, \alpha', a_0, D_5, D_3, \beta$, and E_0 , the estimated values were derived from literatures and were handled in the same way introduced in Schugart et al. (2008). For the parameter D_0 , it is expected to be very small because we assume the diffusion rate for debris is lower than the other diffusion rates. Although the precise value was not known, D_0 was chosen to be $1.0E-5$ as its dimensionless value. For f_0 and f_0' , they were chosen so that the debris will be digested with

proper rate according to our experimental results. f_1 , f_2 , and f_3 were chosen so that 1) the healing process should be consistent with the experiment; and 2) their values would be comparable to which introduced in Schugart et al. (2008).

2.5. Experimental data

Experiments on wound healing were performed using a rat subcutaneous implantation model (Dey et al., 2011). The animal experiments were approved by the University of Texas at Arlington Animal Care and Use Committee. Briefly, cylindrical polyethylene catheters (1000 μm in radius and 5 cm in length) were sterilized with multiple washes of 70% ethanol. Then the tubes were implanted in the subcutaneous space on the back of Sprague Dawley rats (~200 g body weight). The incision was then closed with stainless wound clips. After implantation at different periods of time (7 and 28 days), the animals were sacrificed. The implants and surrounding tissue were isolated for histological analyses (Baker et al., 2011; Thevenot et al., 2011). For quantifying the numbers of fibroblasts and macrophages, tissue sections were stained with α -smooth muscle action and MOMA-1 (Santa Cruz Biotech), respectively. The experiment design sketch is presented in Fig. 2 and the experimental results are shown in Fig. 3 and Table 2.

3. Results and discussion

3.1. Simulations and dynamics of the model

In our simulation study, we placed a circular-shaped implant at the center of a reaction domain. Healthy tissue was positioned immediately adjacent to the reaction domain where these normal cell/protein/enzyme values were imposed as boundary conditions. Then, we calculated the densities for macrophages and fibroblasts from area 1 to area 5 on day 7 and day 28, respectively. Because we counted the number of macrophages and fibroblasts from our experimental results which were not the densities that we can only derive from our simulations, we scaled our simulation results by multiplying a factor to fix the simulation result at area 1 on day 7 same to experimental data. Then we multiplied the same scale ratio to the simulation results at other areas on day 7 or day 28. Based on this scale strategy we can observe and compare the trends between simulations and experimental data for the proliferation of macrophages and fibroblasts.

3.2. Macrophage dynamics simulation vs. experimental data

Here, we present the simulation results of macrophages on day 7 and day 28. The graph in Fig. 4(A) shows the macrophages' distribution for five rats while Fig. 4(B) shows the comparison between the simulation and the average of the experimental data on day 7. Similarly, Fig. 5 shows the simulation and the average of the experimental results on day 28.

Furthermore, because we set a time-varying Dirichlet boundary condition for the macrophages, the whole density level of macrophages decreased from day 7 to day 28. This is consistent with what we observed in our experimental data. The distributions of the macrophages in our simulation results are consistent with those derived from the experimental data.

3.3. Fibroblast proliferation simulation versus experimental data

Next we present the simulated fibroblast growth near an implant. The statistical results comparing the model simulation and the experimental data for fibroblasts on day 7 and day 28 are shown in Figs. 6 and 7, respectively. From Figs. 6(B) and 7(B) we can see that, although the simulation results for fibroblasts do not fully agree with the experimental results, the trends of the simulation curves are similar to those derived from the experimental data. We note that in Fig. 7(B), the difference between the two curves is relatively big. This

may be caused by the boundary condition. As mentioned before, we set a constant value for the Dirichlet boundary for fibroblast based on our assumption that the density of fibroblast in healthy tissue is a constant value. This assumption was also applied in Schugart et al. (2008). Area 1 is in the injured region, but closest to the healthy tissue. We observe the simulation result at area 1 on day 7 to be very close to the experimental value at area 1 on day 7. But from our experimental data we noted the fibroblasts increased at area 1 from day 7 to day 28. This difference on boundary may cause the magnified discrepancies in other areas during the evolution, as shown in Fig. 7(B).

Remark: We have observed that there is a discrepancy between the model and experimental data, and this is more significant for fibroblast population than that of macrophage. One plausible reason is the ideal boundary condition that we have imposed for the fibroblast. In Section 2.3, the fibroblast population adjacent to the healthy tissue is assumed to be a constant, whereas the experimental data shows an increased amount of fibroblast along the boundary, partially due to the extra supply from nearby blood vessels' expansion. This discrepancy in boundary conditions explains why the model predicts a lower estimate of fibroblast populations. It is however difficult to account for this blood supply in the system as the mechanism of blood vessels is quite complex.

3.4. Dynamics analysis supports that model can well describe characters of different timing scales temporal kinetics and other qualitative features

In this section we analyze impact of the different phenotypes of macrophages on the dynamics of the process and trends in proliferation of fibroblasts. Macrophages are capable of secreting growth factors which are important in regulating fibro-proliferation. Alternatively activated macrophages overexpress certain extracellular matrix proteins, such as fibronectin, and are believed to be involved in tissue remodeling during wound healing. Human macrophages activated by biomedical polymers in vitro have been shown to stimulate fibroblast activity. Therefore, biomaterial adherent macrophages can help modulate fibrosis and in turn the fibrous capsule which develops around a material following implantation.

3.5. An important feature we found through modeling study is that the compositions of macrophage phenotypes affect both the timing of fibrotic reactions as well as the macrophages presence

We tested temporal dynamics of Eqs. (1)–(5) by assuming that the chemoattractant is instantaneously available. In doing so, we choose parameters in a typical set of parameter as in

Schugart et al. (2008), furthermore, we incorporate a proliferation term for macrophage and fibroblast populations under the influence of c , and neglected all spatial variations. By taking the initial values to be $d = 1$, $c = F = M = E = 0.01$, a few interesting observations (shown in Fig. 8) were obtained through numerical simulations. It can be seen that debris is cleared out much faster when the classical macrophage is taken to be the dominate phenotype in the reaction. Also we see that an inflammatory macrophage dominated reaction leads a much earlier proliferation of growth and fibrotic actions to occur. Furthermore, reactions in which the dominating phenotype was taken to be either classical macrophages or regulatory macrophages both resulted in similar actions, but inflammatory macrophage dominated reactions did display much higher inflammation. In Fig. 8 we observe that there were big differences in chemoattractant if we switched the compositions of macrophage phenotypes especially in inflammatory macrophage dominated case.

We now use the parameter set that is specifically chosen to match this experiment. We observe (in Fig. 9) that with the exception of debris and chemoattractant, the three phenotypes did not cause much difference in reaction alone. In particular, the macrophage total amounts are shown as decreasing in all cases. We predict therefore that the changes in macrophage in our experimental setting of implant inflammatory reactions are mainly due to diffusion and chemotaxis, rather than proliferation. This is a fact that can be further tested in experiments.

4. Discussion

To quantitatively study the processes governing foreign body reactions, we have built a mathematical model with capability to predict the trends of fibroblast and macrophage population distributions, collagen or ECM accumulations by systems of partial differential equations. Our model is built based principally on biochemical mechanisms (mass action laws) and calibrated with experimental data.

The use of mathematical models in bioengineering study has several advantages. First, our results support that this model can be used to investigate multiple variables and complex interactions in a systematic way, far enriching the experimental results. Second, this model can be modified to simulate different types of inflammatory and fibrotic diseases; these pathological studies are difficult to repeat in controlled experiments. Finally, by further developing mathematical models, we will eventually be able to use it to identify the critical variable and time point in which treatments or interventions can be made to alter fibrotic tissue reactions with favorable outcomes.

Our model was modified from Schugart et al. (2008) so that they share the common characteristic: both of them capture the kinetics of inflammatory cells, fibroblasts, chemoattractant, and ECM, which are the critical factors during the wound healing process. The capillary tips, capillary sprouts, and oxygen concentration that were explicitly used in Schugart's model in order to investigate how the oxygen intensity can affect the healing process. But in our proposed model, we used debris cells instead of the previous three terms because the dead tissue or excessive cells following an implantation are more likely the trigger of a foreign body reaction. In addition, we incorporated three different phenotypes of the macrophages in our model since we focused on the interaction between fibrotic processes and macrophage activations in the proposed model.

In our simulation study, we observed the significant difference in inflammatory responses by macrophages of different phenotypes. When inflammatory dominated responses occur, the chemoattractant and other cell populations proliferate much earlier and at a higher level, while classical macrophages and regulatory macrophages dominated responses show some similarities. But this experiment shows more chemo-tactic phenomenon than proliferation of inflammatory reaction of cells. The spatial distribution and permeability of the cells match well between the experiments and model study, the modeling study can overcome the individual variance between each experimental subject, and present the trend of inflammatory responses.

We note that instead of being constants, the proportions of different macrophage populations, λ s are generally observed to change with time during the healing process. Macrophages are highly heterogeneous cells that can rapidly change their function in response to local environmental signals. As far as we know, there is no biomarker to identify a particular phenotype in experiments. In theory, if we have enough measurement data, we can estimate the time varying λ s. But this will be left to our future work.

At the current stage of our modeling study, the proposed model has its shortcomings. This is expected, as the complexity of the immune response system is not well understood, nor is our model sophisticated enough to include all pathways of the reactions. Nevertheless, the initial step of the modeling efforts did capture the essence of the cell and protein growth in the process, both in temporal dynamics and spatial distributions. We plan to further include other biophysical factors such as cell size, shapes and surface geometry in our future study.

Acknowledgments

This work is supported by the National Institutes of Health grant # 1R01EB007271 for JY, JS, LO and LT, 1R01 EB014404 for LT, and by an NSF GK-12 fellowship (NSF grant # DGE-0841400) for LO. AI is supported by the NSF grants DMS-0813825 and DMS-0908177. We thank Dr. Yajuan Li (Department of Immunology and Internal Medicine, The University of Texas Southwestern Medical Center) for helping us by offering many suggestions on the biological processes.

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Fig. 1. Boundary conditions: At the outer edge 1, 2, 5, and 8, $F = F_0$, $M = M_0 e^{-\gamma_2 t}$, $E = E_0$, and $\frac{\partial r}{\partial c} = 0$, where γ_2 is the decay coefficient at the boundary for macrophages; at the inner edge 3, 4, 7, and 6, $d = d_0$. The axes present dimensionless values.

Fig. 2.
The sketch graph for the experiment design and data collection.

Fig. 3.

The experimental slices with fluorescent dye. For each image, left side is adjacent to the implant. (a) Left column shows that slices obtained from 5 rats have been implanted disks for 7 days. (b) Right column shows that slices obtained from 5 rats have been implanted disks for 28 days.

Fig. 4. Statistical results of simulated data of macrophages as compared with experimental results on day 7. (A) 7th day experimental data (all five rats) plotted together with the average curve; and (B) average experimental data versus the simulated result on day 7.

Fig. 5. Statistical results of simulated data of macrophages as compared with experimental results on day 28. (A) 28th day experimental data (all five rats) plotted together with the average curve; and (B) average experimental data versus the simulated result on day 28.

Fig. 6. Statistical results of simulated data of fibroblast cells as compared with experimental results on day 7. (A) 7th day experimental data (all five rats) plotted together with the average curve; and (B) average experimental data versus the simulated result on day 7.

Fig. 7. Statistical results of simulated data of fibroblast cells as compared with experimental results on day 28. (A) 28th day experimental data (all five rats) plotted together with the average curve; and (B) average experimental data versus the simulated result on day 28.

Fig. 8.

Computational results for foreign body reaction processes at different compositions of macrophage phenotypes. λ_1 , λ_2 , and λ_3 are the proportions of macrophages for M_1 — classical macrophages, M_2 — regulatory macrophages, and M_3 — inflammatory macrophages, respectively. The variables are (A) debris, (B) chemoattractant, (C) fibroblast, (D) macrophage, and (E) ECM. Red is at $(\lambda_1, \lambda_2, \lambda_3) = (0.6, 0.2, 0.2)$, blue represents the ratio at $(0.2, 0.6, 0.2)$, and magenta is at the ratio $(0.2, 0.2, 0.6)$.

Fig. 9.

Computational results for foreign body reaction processes at different compositions of macrophage phenotypes. λ_1 , λ_2 , and λ_3 are the proportions of macrophages for M_1 — classical macrophages, M_2 — regulatory macrophages, and M_3 — inflammatory macrophages, respectively. The variables are (A) debris, (B) chemoattractant, (C) fibroblast, (D) macrophage, and (E) ECM. Red is at $(\lambda_1, \lambda_2, \lambda_3) = (0.6, 0.2, 0.2)$, blue represents the ratio at $(0.2, 0.6, 0.2)$, and magenta is at the ratio $(0.2, 0.2, 0.6)$.

Table 1

Table of parameters for differential equations and boundary conditions.

Parameters	Dimensional value	Source	Dimensionless value in our work
L_{out}	0.35 cm	For this study	1
L_{in}	0.10 cm	For this study	0.286
D_0		For this study	$1E-5$
f_0		For this study	1
$f_0^{\sim}$		For this study	1
D_1	$6.9E-2 \text{ cm}^2/\text{day}$	Stokes et al. (1991) and Pettet et al. (1996))	1
f_1		For this study	0.2
f_4	$3.456/\text{day}$	Enholm et al. (1997) and Ristimäki et al. (1998))	2.43
f_2		Schugart et al. (2008))	20
f_3		For this study	18
D_3	$1.47E-5 \text{ cm}^2/\text{day}$	Olsen et al. (1995)	$1.7E-4$
α	$8.64E+6 \text{ cm}^5 \text{ g}^{-1}/\text{day}$	Olsen et al. (1995)	0.1
a_1		For this study	0.4
a_2		Schugart et al. (2008)	0.3
F_0	$1E-3 \text{ g cm}^{-3}$	Olsen et al. (1995)	1
a_3	$1.99E-2/\text{day}$	Hackam and Ford (2002)	$1.404E-2$
D_2		Schugart et al. (2008)	0.015
α'	$8.64E+6 \text{ cm}^5 \text{ g}^{-1}/\text{day}$	Schugart et al. (2008)	0.1
a_0	$0.1728/\text{day}$	Blankson et al. (1999)	0.1215
D_4		Schugart et al. (2008)	$1E-5$
D_5	$1.47E-5 \text{ cm}^2/\text{day}$	Olsen et al. (1995)	$1.7E-4$
a_4		Schugart et al. (2008)	1
β	$8.64E+6 \text{ cm}^5 \text{ g}^{-1}/\text{day}$	Olsen et al. (1995)	0.1
a_5		Schugart et al. (2008)	0.675
E_0	$1E-3 \text{ g cm}^{-3}$	Namy et al. (2004)	1

Table 2

Experimental data of fibroblasts and macrophages.

Area	1		2		3		4		5	
	Fibroblast	Macrophage	Fibroblast	Macrophage	Fibroblast	Macrophage	Fibroblast	Macrophage	Fibroblast	Macrophage
<i>7 days</i>										
#1	50	138	39	124	29	138	17	24	0	0
#2	30	129	29	100	41	51	32	53	0	0
#3	39	80	46	50	29	20	0	0	0	0
#4	27	80	17	59	0	0	0	0	0	0
#5	25	84	18	82	38	60	39	45	0	0
Ave.	34.2	102.2	29.8	83	27.4	53.8	17.6	24.4	0	0
<i>28 days</i>										
#1	28	78	47	38	51	30	42	21	69	18
#2	44	86	65	47	57	10	59	43	54	37
#3	53	80	100	40	50	34	62	18	17	12
#4	32	86	80	56	73	22	49	31	66	20
#5	40	54	74	43	63	30	73	44	51	30
Ave.	39.4	76.8	73.2	44.8	58.8	25.2	57	31.4	51.4	23.4