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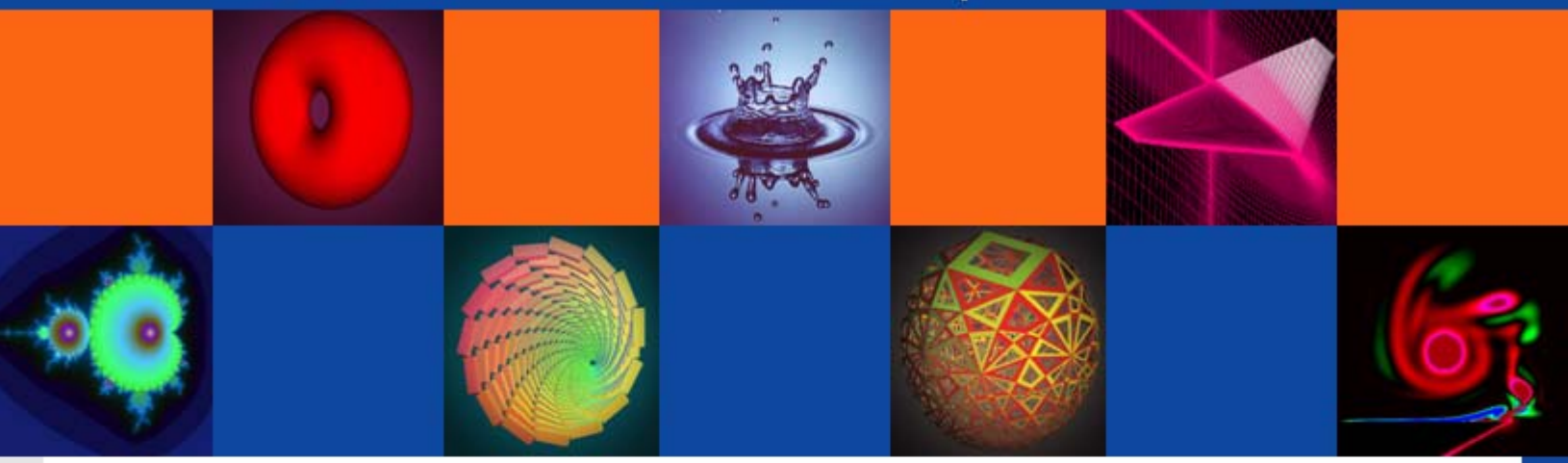

Modeling and Simulation of Foreign Body Reactions to Neural Implants

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Modeling and Simulation of Foreign Body Reactions to Neural Implants

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Abstract. The fibrotic capsulations to neural implant within brains are found to substantially reduce the effectiveness of the devices. While in vitro and in vivo experiments can single out each of the steps in foreign body reaction process leading to the formation of fibrotic tissue surrounding implants, we need the predictive power to analyze the outcome of multiple interactive complex kinetics of various factors and processes and to understand its dynamical behavior during the entire period (up to several months). A mathematical model is constructed to facilitate such a need and to complement experimental work. We report that preliminary simulation results have been consistent with experimental data and the model can provide useful information for future design of implant device.

Keywords: Mathematical Model, fibrosis, medical implants, foreign body reactions

1 Introduction

Mathematical modeling and simulation have been increasingly recognized as a powerful tool for studying signal transduction mechanism and related system biology, by utilizing the large volume of experimental data. In devising novel application of human implants, solely identifying one or one group molecular targets among the complex signaling machinery is not enough. Further, the timing and strength of the signals that carry their information contents need to be assessed quantitatively (Asthagiri and Lauffenburger 2000 [1]). The models that we are presenting, can reveal information content that resides within the signals' dynamics, i.e. the transient interactions rather than simple steady states relations. As an application, the predictive power can determine quantitatively how to influence adherent monocytes, macrophages, and foreign body giant cells to minimize the recruitment of fibroblasts and/or produce matrix metalloproteinases to degrade the fibrotic capsules on the implants.

Despite of the numerous studies in the subject area, there are few realistic and kinetics-based mathematical models. Previous studies had developed models to investigate cell-cell adhesion, the spatial interactions between tumor-associated

macrophages, tumor cells, and normal tissue cells, and the role of macrophages in angiogenesis (Jones 2007 [2] and references therein). To fully account for the network effects of the coagulation and collagen formation, a detailed system consisting of kinetics of all major growth factors, platelet and others were modeled by Kuharsky and Fogelson, 2001 [3], and others. The basic reactions of collagen formations were considered in previous modeling study (Dale et al 1996 [4], Dallon et al 2001 [5]) and their corresponding kinetics were based on a logistics equation for fibroblast proliferation. Their reaction equations were simplified in a certain way that activations rate were linear function. To modify the specific behavior of the phosphoinositide (PI) 3-kinase pathway, Haugh et al 2006 [6] and others had modeled a more realistic activation and proliferation of fibroblast.

Our model will follow the work of Kuharsky and Fogelson, 2001 [3] and that of Dale et al 1996 [4] not only to be inclusive of various growth factors and adherent cells, but also to be realistic in terms of activations and proliferation and migration of cells, similar to Haugh, 2006 [6].

2 Physical Background Of Model

We have selected our mathematical model based on the previous modeling work of Dale et al [4], Kuharsky et al [3] and Haugh [6]. The basic principles of the system are the chemical kinetic equations of the protein-cell and cell-cell reactions. The implant site contains enzymes which activate latent growth factors and also initiate the stabilization of collagen precursors (Miller and Gay 1992 [7]). Similar to other collagen formation such as dermal wound healing, collagenase is synthesized and secreted by fibroblasts as a 'zymogen' (Stricklin et al. 1978 [8]), but collagen degradation cannot occur until the zymogen is activated. These basic reactions were considered in previous study [4,5] and their corresponding kinetics is incorporated in our modeling.

We show below several representative equations of a large system of 69 equations. The active forms of TGF β isoform 1 and isoform 3 $\beta_1(t), \beta_3(t)$ undergo rapid decay and they are also transformed from inactive forms of TGF β, namely $l_1(t), l_3(t)$ under the activation of specific enzyme $e_1(t)$. Use the law of mass action, their relations are:

$$\frac{\partial \beta_1}{\partial t} = k_{12} e_1 l_1 - k_{13} \beta_1 ; \quad (1) \qquad \frac{\partial \beta_3}{\partial t} = k_{14} e_1 l_3 - k_{15} \beta_3 . \quad (2)$$

Now these enzymes $e_1(t), e_2(t), e_3(t)$ are activated by latent forms of TGF β: $l_1(t)$ and $l_3(t)$, latent forms of collagens (i.e. procollagens) $p_1(t)$ and $p_3(t)$ and collagenases $z_1(t)$ and $z_3(t)$ respectively and satisfy their corresponding kinetics

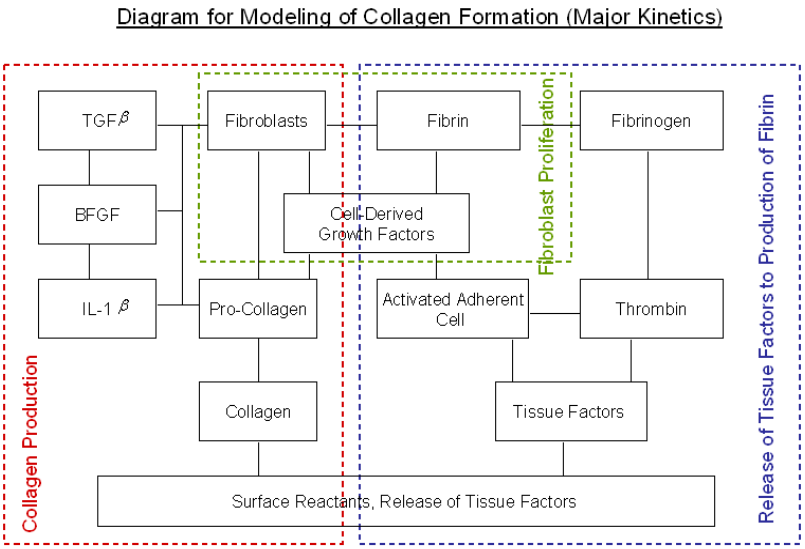
equations. Eventually collagens 1 and collagen 3 fibers are transformed from procollagen 1 and procollagen 3 fibers ($p_1(t)$ and $p_3(t)$ respectively), under the actions of enzymes $e_2(t)$. Collagenases ($s_1(t)$ and $s_3(t)$ respectively) gradually degrade collagen 1 and collagen 3. We use law of mass-action to describe the kinetics

$$\frac{\partial c_1}{\partial t} = k_{28} p_1 e_2 - k_{29} s_1 c_1; \qquad (3) \qquad \frac{\partial c_3}{\partial t} = k_{30} p_3 e_2 - k_{31} s_3 c_3; \qquad (4)$$

Some specific modifications have been made for foreign body reaction process. For example, the activation rate of fibroblast $r = (k_1 + k_2\beta_1 + k_3\beta_3)$ was a simple linear function of $\beta_1(t), \beta_3(t)$ in previous studies [Dale et al 1996]. We have modified fibroblast kinetics according to the limiting activation (Haugh 2006) so that

$$\frac{\partial u}{\partial t} = \frac{c_1(k_1 + k_2\beta_1 + k_3\beta_3)^2}{1 + k_1 + k_2\beta_1 + k_3\beta_3 + (k_1 + k_2\beta_1 + k_3\beta_3)^2} u(1 - \frac{u}{k_0}) - A_4 u. \qquad (5)$$

Shown below are the major components of the kinetics model.



3 Simulated Collagen Formation Kinetics

The majority of reaction parameters is obtained from literatures (for example, the earlier models by Dale et al 1996**,** Kuharsky and Fogelson 2001 and Haugh 2006,

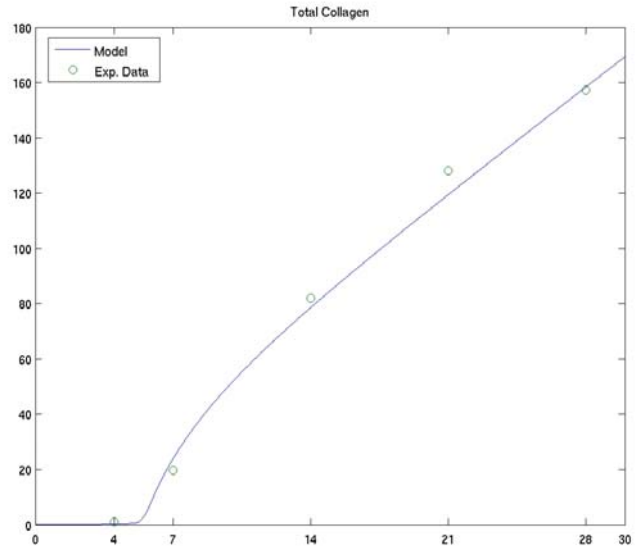


Figure 1. The comparison of Collagen of experimental data (the average value of two samples during a 28-day period, unit: up/cm^2) with a simulated data from the mathematical model.

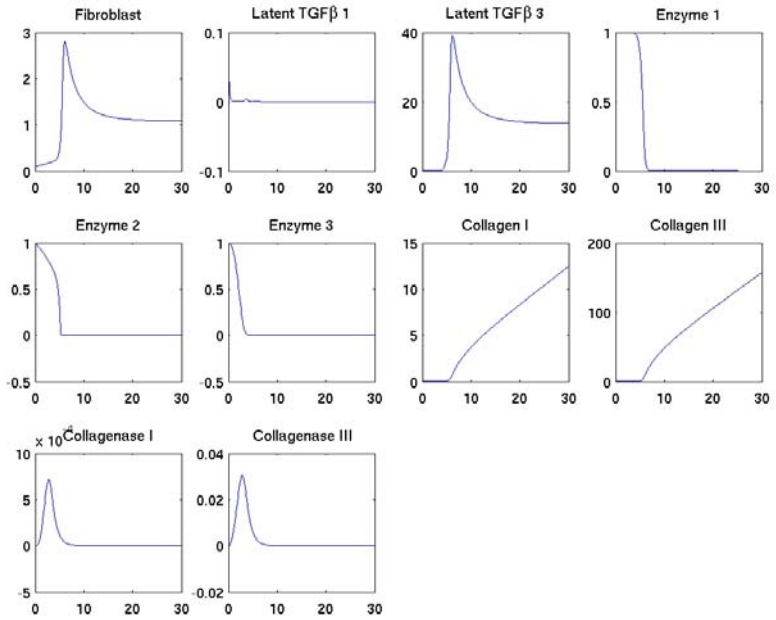


Figure 2. The simulated kinetics dynamics of various variables in collagens, procollagens, collageneses, active and latent isoforms of TGF β etc during first 30 days.

respectively) and some parameter are determined by simulating the systems and comparing with the experiments results.

The numerical code, based on Matlab, can simulate the entire system reactions up to several months. The calculation time is about 2 minutes. We demonstrate the simulated kinetics dynamics of collagen formation process in Figures inserted. We compare the collagen measurements with simulated data from our model for first 30 days in Figure 1. In Figure 2, we depict the kinetics dynamics of various variables in collagens, procollagens, collageneses, active and latent isoforms of TGF β etc.

The code is also capable to systematically test all combinations of parameter values and to find the correct parameters to fit the experimental data. This code can help to find multiple pathways for activate fibroblast proliferation and the collagen formation. Our preliminary date presented here showed the feasibility of our model as a predictive tool for the purpose of studying collagen formation/ or fibrotic reactions to implants.

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