Mathematical and Simulated Modeling of Systemic Effects in a Human Wound Healing Model

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Wound healing is a complex biological process dependent on multiple variables: tissue oxygenation, wound size, contamination, etc. Many of these factors depend on multiple factors themselves. Mechanisms for some interactions between these factors are still unknown, presenting a barrier for scientists intending to model wound healing using an object-based programming approach. Rather than struggling with these gaps in the scientific knowledge base, mathematical models can be constructed which accurately describe and predict the behavior of the system as a whole.

These mathematical models are constructed using systems of ordinary differential equations. A model for human inflammatory response to infection was published by Reynolds et. al in 2006, which was used as the basis for the development of a model of wound healing. It contained a set of four differential equations in which the dependent variables represented levels of pathogen, activated phagocytes, tissue damage, and anti-inflammatory mediators (for example, IL-10).

Differential equations often involve a plethora of constants, and in systems of equations used to model biological systems, many of these are unknown due to lack of experimental data. In order to use the equations the unknown constants are set to be equal to values which yield biologically appropriate behavior.

The current model for wound healing is described by the following set of equations:

$$\frac{dP}{dt} = p_{\text{growth}} P\left(1 - \frac{P}{P_\infty}\right) - \frac{k_{pm} s_m P}{\mu_m + k_{mp} P} - k_{pn} f(N;F) P$$

$$\frac{dN}{dt} = \frac{s_n R(P,N,D;F)}{\mu_{nr} + R(P,N,D;F)} - \mu_n N - \mu_{fn} FN$$

$$\frac{dF}{dt} = s_f + \frac{k_{fn} f(N + k_{fnd} D;F)}{1 + f(N + k_{fnd} D;F)} - \mu_f F$$

$$\frac{dD}{dt} = k_{dn} f_s(f(N;F)) - \mu_d D - \mu_{df} DF + \beta_d \left[\exp\left(\frac{O}{O_{crit}} \ln \alpha \right) - \alpha \right]$$

Where

$$f(V;F) = \frac{V}{1 + (F/F_\infty)^2}$$

$$f_s(V) = \frac{V^6}{x^6{}_{dn} + V^6}$$

$$R(P,N,D;F) = f(k_{np} P + k_{nn} N + k_{nd} D;F)$$

P corresponds to the amount of pathogen present at the wound site, N describes the level of inflammation, F is the number of fibroblasts, D is tissue damage, and O (held constant in the model) is the level of tissue oxygenation. By setting O and watching the other variables change, it is possible to fit the model to realistic situations. For example, if O is set at three times the critical level ($O_{crit} = 5$) then D decays in 145.2 hours. On the other hand, if O is set to be equal to the critical level, D decays to zero in 151.6 hours. If O is less than the critical level, D tends toward a non-zero steady state (indicating that the wound becomes chronic). Inflammation also plateaus when tissue oxygenation is less than the critical level. The tendencies that damage and inflammation have to plateau at non-zero steady states match the behavior of chronic wounds (such as diabetic ulcers in the feet) in which low oxygen levels, high pathogen levels, or other factors send inflammation into a positive feedback loop and thus induce a state of perpetual inflammation.

This summer my research will focus on the addition of the systemic factor, tumor necrosis factor-α (TNF-α) to the model. Adding this factor to the model will increase its usefulness. Before the effects of TNF-α are added to the model, a network map will need to be drawn that explicitly shows the relationships between other factors and TNF-α.

The longstanding goal of this research is to provide an accurate model of wound healing for clinical and experimental use, in which treatments can be chosen based on predicted wound behavior.

References:

1. Menke N, Ward K, Witten T, Bonchev D, Diegelmann R, 2007, Impaired wound healing, *Clinics in Dermatology*, v. 25, p. 19-25.

2. Reynolds A, Rubin J, Clermont G, Day J, Vodovotz Y, Bard E, 2006, A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation, *Journal of Theoretical Biology*, v. 242, p. 220-236.