A soft tissue injury elicits a well-prescribed wound healing response. The process of wound healing is designed to restore anatomic and functional characteristics of the tissue; however, little progress has been made in improving the wound healing response time or in preventing complications such as fibrosis, infections, and formation of nonhealing wounds. In this paper, we describe a computational model of acute wound healing designed to allow a system-level analysis of the wound healing response using ordinary differential equations (ODEs). As a first step to a more comprehensive model, we have explored the combined effects of bacterial infections, inflammation, and tissue hypoxia on the rate and success of wound healing since these processes are well-known as affecters of healing. As this model matures, it will provide the opportunity to test new mechanisms and novel therapeutics of wound healing strategies in silico.

Despite burgeoning interest in the field of computational biology, work of limited scope has been published on modeling the acute wound. Most of these studies show the difficulties of adequately accounting for the myriad of potential interactions. For example, in their respective works on epidermal wound healing, Stekel et al., Walker et al., and Morel et al. do not attempt to simulate healing by fibroblasts and do not implement inflammatory changes in their models. Dallon et al. constructed an ODE model of collagen deposition focusing on the fibroblasts and their relationship to the underlying extracellular matrix, but do not account for inflammation or repair of underlying tissue damage. Schugart et al. recently published a model of wound angiogenesis as a function of tissue oxygen tension but the model does not specifically address the wound healing process.

Reynolds et al. created an ODE model designed to simulate inflammation and repair on a systemic level in the setting of a systemic insult such as sepsis. We have modified and extended their work to apply it to a local wound. ODEs provide a valuable tool for analysis and prediction of biological systems over time. ODEs model the changes in important physiological variables over time. The equations are derived from a combination of known and hypothesized kinetics of the components of the biological system. In our model, the state variables represent average concentrations of the various dynamic components. Furthermore, parameters are used in the equations to account for static components of the system being modeled. The system is solved numerically and the properties of the system can be explored mathematically. Because these equations are based on biological interactions, ODEs can predict outcomes beyond the range of available data. The most valuable aspect of a mathematical model is the ability to manipulate the variables and parameters, perform experiments in silico, and examine their results. The biological mechanisms of a wide range of potential situations may then be analyzed together with their outcomes. In vitro validation would then follow from in silico experimentation.

METHODS

As a first attempt to capture the dynamics of local wound healing over time, a four-variable system of ODEs was
developed. The variables in this model represent total local tissue (D)amage, (P)athogen level, overall (i(N)flammation, and the concentration of (F)ibroblasts. For each of these variables we used known biological interactions to develop a differential equation that describes the rate of change for the variable. The interactions included in this model are depicted in the model schematic, Figure 1. The fundamentals of the model are based on the observations that tissue damage is increased by inflammation and hypoxia, whereas wounds are repaired by fibroblasts.13–16 Interpreting the interactions in Figure 1, we developed the four variable model, given below in Equations (1)–(4). This model was adapted from the four-variable model created by Reynolds et al., which is included in Appendix A:

\[
\frac{dP}{dt} = P_{growth} \left(1 - \frac{P}{P_\infty}\right) - \frac{k_{mn}N}{\mu_m + k_{mp}P} - k_{pf}f(N; F)P
\]

(1)

\[
\frac{dN}{dt} = s_n R(P, N, D; F) - \mu_n FN - \mu_n N
\]

(2)

\[
\frac{dD}{dt} = k_{dh}f_s(f(N; F)) - \mu_D - \mu_D DF + \beta_D g(O_2) \left(\frac{D^2}{D^2 + x_0^2}\right)
\]

(3)

\[
\frac{dF}{dt} = s_f + \frac{k_{fa}f_s(N + k_{fa}D; F)}{1 + f(N + k_{fa}D; F)} - \mu_F
\]

(4)

where

\[
f_s(V) = \frac{V^6}{x_{dn}^6 + V^6}
\]

\[
f(V, F) = \frac{V}{1 + (F/F_\infty)^2}
\]

\[
R(P, N, D; F) = f(k_{np}P + k_{mp}N + k_{nt}D; F)
\]

\[
g(V) = \frac{-\alpha[1 - \exp((1 + \alpha)(O_{crit} - V))]}{1 + \alpha \exp((1 + \alpha)(O_{crit} - V))}
\]

\[
p_{growth} = \begin{cases} 
  k_{pg} & \text{if } O_2 \geq O_{crit} \\
  k_{pg} + \beta_p \left(1 - \frac{O_2}{O_{crit}}\right) & \text{if } O_2 < O_{crit}
\end{cases}
\]

The difficulties in modeling complex physiologic processes are defining the system variables and representing their interactions mathematically. To address this, we have combined related cell types and signaling process together. As a result, it is not possible to have units on many of the biological quantities. Specifically, because tissue damage is complex and involves many biological markers, it is a difficult quantity to measure. Thus in this model D has no units. Instead, we track the relative changes over time and evaluate healing based on percentage change of damage (D), with a return to under 10% damage considered healed.

**Pathogen equation**

In developing Equation (1), the pathogen equation, we made similar assumptions to those used to develop the pathogen equation in Reynolds et al. We assumed that the pathogen population has a growth rate of \( p_{growth} \), and a carrying capacity of \( P_\infty \) giving rise to the first term of Equation (1). Unlike the Reynolds et al. model we take into account that the pathogen population is increased in low oxygen environments.14 Therefore, \( p_{growth} \) is a function of the oxygen level in the local environment and determined by the function

\[
p_{growth} = \begin{cases} 
  k_{pg} & \text{if } O_2 \geq O_{crit} \\
  k_{pg} + \beta_p \left(1 - \frac{O_2}{O_{crit}}\right) & \text{if } O_2 < O_{crit}
\end{cases}
\]

This relationship between tissue oxygenation levels and bacterial growth is illustrated in Figure 2A with \( O_{crit} \) set to 5, which is equivalent to a transcutaneous oxygen level of 30 mmHg.17,18 If the tissue oxygen level is above the critical value, \( p_{growth} \) is fixed at 0.3. This is because the effects of hyperbaric oxygen on wound healing are not included in this model. However, this function does capture the increase in anaerobic pathogen reproduction that occurs in hypoxic environments. The second term in Equation (1) is directly from the Reynolds et al. model and accounts for local immune mediators that immediately interact with the pathogen, such as defenses and nonspecific antibodies.

Inflammation recruited to the wound is generally thought to contribute to the destruction of pathogens and thereby is assumed to decrease pathogen levels, while causing some degree of tissue damage.2,19–22 The effect of this process on pathogen level is modeled with the third term of Equation (1). We model the depletion of pathogen from an encounter with an inflammatory cell with a term of the form \(-k_{pf}NP\). However, since fibroblasts modulate the inflammatory response by initiating wound repair, \( N \) in this term is replaced with \( f(N; F) \).
The function $f(N; F)$ represents the inhibition of inflammatory cells by fibroblasts. We use the same definition of the function $f(N; F)$ as in Reynolds et al., since we are modeling the down-regulation of the same cell population. Including this inhibition produces the third term of Equation (1): $-k_{pf}f(N; F)P$.

**Inflammation equation**

Inflammatory cells are recruited by pathogens, damaged tissue, and other inflammatory cells and mediators. Incorporating this activation of the inflammatory cells into the model we get the first term of inflammation equation, (2). First we assume that inflammatory cell activation is triggered by the three variables $N$, $D$, and $P$ giving a rate of activation of $R = k_{ap}P + k_{an}N + k_{ad}D$. As in the pathogen equation, Equation (1), we account for the inhibition of inflammation due to the presence of fibroblasts and we replace the basic activation rate with one that includes inhibition of inflammation. Therefore, in Equation (3), we have the term $k_{inf}(f(N; F))$.

The amount of damage that is repaired is proportional to both the current amount of damage and the amount of fibroblasts present. This leads to the term $\mu_dFD$ in the damage equation, Equation (3). Damage is decreased at a faster rate when fibroblast levels are higher. Also we include the term $-\mu_dD$ in Equation (3) to model intrinsic tissue repair.

The final term in Equation (3) models the impact of tissue oxygenation $O_2$ level on the rate of change of damage. This impact is described by the function $g(O_2)$ (Figure 2B), which is designed to capture the increase in damage in hypoxic environments and to represent a small healing effect if $O_2$ is larger than the critical value, $O_{crit}$.\cite{17,18}

**Fibroblast equation**

The final equation, Equation (4), models the fibroblast population. We assume in normal skin there is a background source of fibroblasts, $s_f$. This gives rise to a baseline level of circulating fibroblasts, which exist in both pre-wounded tissue and healed tissue.

In response to tissue damage and inflammation, the fibroblast population will increase. The second term in Equation (4) models this growth when inflammation and/or damage are nonzero. The term has the form $\frac{k_{fn}(N+k_{fn}D)}{1+k_{fn}D}$ because we assume that the dependence of the fibroblast population on levels of damage and inflammation is nonlinear. That is, at low levels of inflammation and damage the recruitment of fibroblast is slow, whereas at high levels the process of fibroblast recruitment saturates. As with other terms involving inflammation the process is inhibited using the same function, $f$, so the final form of the term is $k_{inf}(f(N; F))$.

As described above, fibroblasts have an intrinsic death rate, $\mu_f$, and this is modeled by the final term of Equation (4), $-\mu_fF$.

**Simulations**

Our model equations were solved numerically using both the software package XPPAUT\cite{28} (XPPAUT is a freely available software package for solving differential
equations available for download at http://www.math.pitt.edu/~bard/xpp/xpp.html) and several of our own independently developed C++ computer programs. A list of baseline parameters is included in Table 1 for reference. The parameters were derived from experimental values found in the literature or estimated such that the system behaved in a biologically appropriate manner.10,17,18 We performed several in silico experiments to investigate the effects of (i) varying the amount of initial damage, \( D(0) \), and the initial pathogen levels, \( P(0) \), and (ii) varying certain parameters such as the tissue oxygenation level \( O_2 \) and the rate of fibroblast recruitment \( s_f \).

In each experiment, we simulated 2 weeks of the wound healing process (336 hours) after the initial wound insult in order to observe more of the transient effects en route to steady state.29 Two weeks provide an adequate amount of time for normal wounds to heal. The resulting end state of the wound was categorized as one of three types:

- **Healed** if the damage is decreased by 90% within 2 weeks (i.e., for \( D(0)=10 \), damage is \( < 1 \) after 2 weeks);
- **Nonhealing wound** if damage remains higher than 10% of initial damage and pathogen levels decrease to zero (i.e., for \( D(0)=10, \ P(0) > 0 \), damage is \( > 1 \) but pathogens are nonexistent after 2 weeks); and
- **Chronic infection** if both damage and pathogen levels remain at above 10% of their initial levels after 2 weeks (i.e., for \( D(0)=10, \ P(0)=1 \), damage is \( > 1 \) and pathogen is \( > 0.1 \) after 2 weeks).

The nonhealing wounds as defined above correlate clinically to wounds in which there is impaired wound healing, but are not infected.2,3,19,20,30,31 Chronic infections as

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**Table 1. Baseline parameter values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_{pm} )</td>
<td>0.6</td>
<td>Rate at which inflammatory cells kill pathogen nonspecifically*</td>
</tr>
<tr>
<td>( k_{pn} )</td>
<td>0.6</td>
<td>Rate at which inflammatory cells kill pathogen by phagocytosis10</td>
</tr>
<tr>
<td>( \mu_p )</td>
<td>0.05</td>
<td>Half-life of activated inflammatory cells10</td>
</tr>
<tr>
<td>( F_{\infty} )</td>
<td>0.30</td>
<td>Maximum fibroblast density*</td>
</tr>
<tr>
<td>( k_{mp} )</td>
<td>0.01</td>
<td>Rate at which nonspecific inflammatory response is exhausted by pathogens*</td>
</tr>
<tr>
<td>( k_{np} )</td>
<td>0.1</td>
<td>Rate of activation of inflammatory cells by pathogens*</td>
</tr>
<tr>
<td>( k_{nd} )</td>
<td>0.015</td>
<td>Rate of activation of inflammatory cells by damaged tissue*</td>
</tr>
<tr>
<td>( s_f )</td>
<td>0.001</td>
<td>Rate of fibroblast recruitment*</td>
</tr>
<tr>
<td>( s_m )</td>
<td>0.005</td>
<td>Rate of inflammatory cell recruitment*</td>
</tr>
<tr>
<td>( k_{mn} )</td>
<td>0.01</td>
<td>Rate of activation of inflammatory cells by activated inflammatory cells*</td>
</tr>
<tr>
<td>( k_{dn} )</td>
<td>0.35</td>
<td>Maximum rate of damage by activated inflammatory cells*</td>
</tr>
<tr>
<td>( k_{sm} )</td>
<td>0.004</td>
<td>Rate of fibroblast recruitment by inflammatory cells*</td>
</tr>
<tr>
<td>( k_{pp} )</td>
<td>0.55</td>
<td>Rate of pathogen growth10</td>
</tr>
<tr>
<td>( s_{mf} )</td>
<td>0.08</td>
<td>Rate of inflammatory cell recruitment*</td>
</tr>
<tr>
<td>( x_{df} )</td>
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<td>Level of inflammatory cells needed to bring damage to half its maximum*</td>
</tr>
<tr>
<td>( k_{ind} )</td>
<td>48</td>
<td>Effectiveness of tissue damage and inflammatory cells to recruit fibroblasts10</td>
</tr>
<tr>
<td>( P_{\infty} )</td>
<td>20</td>
<td>Maximum pathogen density10</td>
</tr>
<tr>
<td>( \mu_{mr} )</td>
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<td>Half-life of inactivated inflammatory cells10</td>
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<tr>
<td>( \mu_d )</td>
<td>0.02</td>
<td>Baseline damage repair rate10</td>
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<tr>
<td>( \mu_f )</td>
<td>0.01</td>
<td>Half-life of the fibroblasts*</td>
</tr>
<tr>
<td>( \mu_m )</td>
<td>0.002</td>
<td>Half-life of non specific inflammation10</td>
</tr>
<tr>
<td>( \mu_{af} )</td>
<td>0.002</td>
<td>Determines the amount of damage healed per unit damage per fibroblast*</td>
</tr>
<tr>
<td>( \mu_{tm} )</td>
<td>0.002</td>
<td>Determines that anti-inflammatory effects of fibroblasts*</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.1</td>
<td>Along with ( \mu_{af} ), determines the amount of damage inflicted by hypoxia*</td>
</tr>
<tr>
<td>( x_{df} )</td>
<td>2</td>
<td>Along with ( \beta_d ), determines the rate of tissue damage caused by hypoxia*</td>
</tr>
<tr>
<td>( \beta_p )</td>
<td>0.3</td>
<td>Along with ( O_2/O_{\text{crit}} ), determines the increase in anaerobic reproduction rate induced by hypoxic conditions*</td>
</tr>
<tr>
<td>( \beta_d )</td>
<td>0.3</td>
<td>Determines the rate of tissue damage caused by hypoxia*</td>
</tr>
<tr>
<td>( O_{\text{crit}} )</td>
<td>5</td>
<td>Critical oxygen level below which wound healing is impaired. Equivalent to a transcutaneous oxygen level of 30 mmHg17,18</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>User defined</td>
<td>Level of tissue oxygenation</td>
</tr>
</tbody>
</table>

*Estimated parameter.
defined above correlate clinically to wounds that are infected and are thereby unable to heal normally.1,3,19,30,31

RESULTS

All simulations started immediately after the wound formation. In the model, this translated to no initial inflammation \( \left( V(0) = 0 \right) \) and to the initial level of fibroblasts at a normal background level \( \left( F(0) = 0.1 \right) \). Initial damage and initial pathogen levels were set to represent different injury scenarios. Unless otherwise specified, all parameter values were set to their baseline values (Table 1).

Figure 3 is the baseline simulation and shows normal healing behavior in a small, uncontaminated wound with normal perfusion \( \left( D(0) = 0.2 \right) \) and \( \left( P(0) = 0 \right) \). As expected, this type of wound elicits a brief period of a slightly elevated inflammatory response and an increase in fibroblast level. This scenario results in normal healing of the wound, which is represented by the damage variable decreases to zero within 2 weeks. The solution curves representing damage, inflammation and fibroblasts follow the reported time course for normal wound healing.32,33

The first experiment focused on increasing the initial wound size \( \left( D(0) = 2 \right) \); 10-fold increase from Figure 3) while leaving pathogen levels at zero \( \left( P(0) = 0 \right) \). Figure 4 illustrates the effect of this change on the behavior of the wound. The significantly increased initial wound size, leads to a nonhealed wound at 2 weeks and the damage, fibroblasts, and inflammation all plateau at an elevated level. This correlates clinically to large acute wounds that require prolonged healing times and are at increased risk for developing infections.32,33

Figure 5 shows the impact of tissue oxygenation levels on wound healing behavior by plotting the pathogen and damage levels for three different levels of \( O_2 \). For each level of oxygenation the wound has a moderate initial size and pathogen level \( \left( D(0) = 0.5 \right) \) and \( \left( P(0) = 0.3 \right) \). All parameters except \( O_2 \) were held at their baseline values. If the tissue oxygenation is at the borderline level \( \left( O_2 = O_{2 \text{crit}} = 5.0 \right) \), which leads to chronic infec-

\(\frac{\text{tion}}{\text{to}}\)on, the wound begins to heal after a 2-day transient period during which the amount of tissue damage increases in size as a result of the inflammatory response (Figure 5A and B). Both the damage and inflammation return to zero and the fibroblasts decrease toward their background level by the end of 2 weeks. We also simulated the same wound in a reduced oxygen environment, where \( O_2 \) is below the critical level \( \left( O_{2 \text{crit}} = 4.0 \right) \), which leads to significant impairment in wound healing (Figure 5C and D). The pathogens are successfully removed, but damage persists beyond 2 weeks. Finally, if tissue oxygenation is further lowered \( \left( O_{2} = 2.5 \right) \), both pathogens and damage plateau are at an elevated level, corresponding to chronic infection (Figure 5E and F). These represent the types of nonhealing wounds, both infected and noninfected, seen in patients with vascular insufficiency.2,35

In a third experiment, we investigated the combined effect of tissue oxygenation \( \left( O_2 \right) \) and fibroblast mortality rate \( \left( m_f \right) \) on the wound healing behavior, leaving all other parameters at their baseline values. By increasing the fibroblast mortality rate, we simulated the premature senescence of fibroblasts observed in older patients and diseases such as diabetes mellitus.19,36 Figure 6 illustrates the wound healing behavior for different choices of initial conditions. In Figure 6A, the initial damage and pathogen levels are low \( \left( D(0) = 0.2 \right) \) and \( \left( P(0) = 0.2 \right) \), and the wound always heals within 2 weeks if \( O_2 > O_{2 \text{crit}} \) and fibroblast half life is at baseline \( \left( m_f = 0.01 \right) \). If the mortality rate is increased beyond a critical value \( \left( m_f > 0.14 \right) \), the high mortality of fibroblasts invariably results in a nonhealing wound. In hypoxic environments, we observe nonhealing wounds even when fibroblast mortality is low as a direct result from tissue necrosis. Figure 6B shows the impact of doubling the initial pathogen level \( \left( P(0) = 0.4 \right) \). In this case, both the regions of nonhealing wound and chronic infection become substantially larger.

To understand if an advanced therapy might impact wound outcome, we designed an in silico experiment to

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Healing behavior of a small, "clean" wound \( \left( D(0) = 0.2 \right) \), \( \left( P(0) = 0 \right) \). (B) Inflammation peaks within two days after initial insult, and decays to 0 within 2 weeks. (C) Damage steadily decreases, and after two days the amount of wound damage is approximately half its initial amount. (D) Fibroblasts peak three to four days after initial insult, and then return to their baseline value within 2 weeks.}
\end{figure}
investigate the possible impact by varying the rate of fibroblast recruitment ($s_f$), and analyzed the long-term healing behavior. We simulated the first 2 weeks after initial insult for a wound with baseline initial conditions $D(0)=0.5$, $N(0)=0$, $F(0)=0.1$, and $P(0)=0$, for all parameters except fibroblast recruitment ($s_f$). For larger recruitment rates ($s_f > 0.012$), the wound heals within 2 weeks, whereas a nonhealing wound results if recruitment is impaired ($s_f < 0.011$). Increasing $s_f$ i.e., recruiting more fibroblasts, has a strong impact on the overall healing time. For example, if $s_f=0.001$, the wound requires 158.2 hours to shrink to 10% of its original size, as compared with

Figure 4. Nonhealing wound of large initial size and no initial pathogens (D(0)=2, N(0)=0, F(0)=0.1, and P(0)=0). (A) The pathogen level remains at 0 for the duration of the simulation. (B–D) Inflammation, damage, and fibroblast levels plateau at elevated levels, and the wound persists even after 2 weeks.

Figure 5. Transients for pathogen and damage with various O2 values. For all three O2 values the initial conditions used were $D(0)=0.5$, $N(0)=0$, $F(0)=0.1$, and $P(0)=0.3$. (A) and (B) are the pathogen and damage transients, respectively, for a O2 value of 5, which is the value of $O_2_{crit}$. (C) and (D): the pathogen and damage transients, respectively, for a O2 value of 4.0, which results in a nonhealing wound. (E) and (F): the pathogen and damage transients, respectively, for a O2 value of 2.5, which results in a chronic infection.
As a first step toward developing a detailed in silico model of the local and systemic responses to tissue insult, we have modified an ODE model of the acute wound healing response to a soft tissue injury. The model includes factors such as bacterial contamination and tissue oxygenation. Assuming normal conditions, our model predicts the typical progression of healing behavior for a wound. The ODE model was also able to successfully simulate the impairment in wound healing found in a hypoxic wound environment and a contaminated wound. With extremely low levels of oxygen, our model predicts a chronic infection where the wound does not heal and pathogens persist in the wound. Both of these states are well documented clinically.

We also examined the situation of elevated and depressed fibroblast mortality rates. Clinically, instances of elevated fibroblast mortality are seen in diabetic and elderly patients. Here we saw that with high rates of fibroblast mortality the wound cannot heal. Additionally, a scenario of moderately low fibroblast mortality and high initial pathogen levels predicts the state of chronic infection. Finally, we examined the case where fibroblast production is either impaired or enhanced. Impaired fibroblast production results in a nonhealing wound, but under conditions where the production is increased we have wounds that heal at notably faster rates. This provides a framework from which to test a new hypothesis in a living model.

The present study represents only a first step toward developing a detailed mathematical model of acute wound healing. Consequently, there are many opportunities for improving upon our existing model; these include,

- With the exception of time $t$, all quantities are measured in arbitrary units. By expanding the model to include variables that represent specific cell types and mediators one may estimate parameter values and assign physiologically meaningful units.
- In its present form, our model does not incorporate time delays. This prevents the simulation of the time lags inherent in signaling pathways as well as in fibroblast recruitment after the onset of inflammation.
- We did not attempt an exhaustive study of the impact of individual parameters on long-term healing behavior. Although we chose to focus on parameters such as the production and death rates of fibroblasts, it is likely that other parameters have a profound impact on healing.

139.0 hours if $s_f$ is doubled to 0.002 (Figure 7). By doubling $s_f$, the healing time decreases by about 12%. The maximum amount of damage, which accumulated as the wound healed, decreased by 11%. Furthermore, when $s_f=0.002$ the influx of inflammation to the wound site did not elicit more damage than the initial level of $D=0.5$. These experiments correlate to the use of agents such as recombinant platelet-derived growth factor and basic fibroblast growth factor (bFGF). The Akita et al. study reported a 20% decrease in healing time with the use of bFGF, which is on the same order of magnitude as the decrease seen in our model experiment.

**DISCUSSION**

Mathematical models offer a noninvasive intermediary step between animal models and human subject studies that allows hypotheses and therapies to be tested before clinical studies. An in silico model can increase the success rate of clinical trials and aid in designing more appropriate animal studies. These animal or clinical studies would then in turn, validate the model.

**Figure 6.** Long-term wound behavior for various choices of tissue oxygenation $O_2$ and fibroblast mortality ($\mu_f$, $N(0)=0$ and $P(0)=0.1$). (A) A wound with initial damage $D(0)=0.2$ and pathogen level $P(0)=0.2$. Large fibroblast mortality always leads to nonhealing wound. If the fibroblast mortality is lower, then we observe chronic infection in hypoxic environments and healing if tissue oxygenation is appropriately large. (B) If the initial pathogen level is doubled to $P(0)=0.4$, the regions of chronic infection and nonhealing wound are substantially larger, and the wound is unable to heal within 2 weeks time. Simulations were not run for fibroblast half-life values $< 12$ hours (marked by the dashed lines in each plot), since values below this level are typically unseen.

**Figure 7.** Comparison of damage vs. time for different fibroblast recruitment rates ($D(0)=0.5$, $N(0)=0$, $R(0)=0.1$, and $P(0)=0$). The dashed curve is damage transient for the baseline fibroblast recruitment rate, $s_f=0.001$. The solid curve is the damage transient with the same initial conditions and a fibroblast recruitment rate twice baseline, $s_f=0.002$. 

A computational model of acute wound healing

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- We focused on strongly interlinked local factors (inflammation, fibroblast function, and recruitment, bacterial contamination, and tissue oxygenation) with resultant dynamic non-linear behaviors. Factors such as depth and shape of the wound, wound contraction, epithelialization, and angiogenesis have not been addressed.
- We have not included systemic effects on wound healing, for example, nutritional status, age, sex, and underlying comorbidities.

This model shows the use of a systems biology approach to human wound healing. Mathematical models show great potential as a platform for hypothesis generation and experimentation before further refinement in vitro and in vivo. A refined method of computational analysis would decrease overall cost, time, and need for invasive testing. Because our simplified model produces qualitatively reasonable results, we are optimistic that including systemic effects will enhance our understanding of the acute wound-healing process, ultimately leading to improved clinical therapies.

ACKNOWLEDGMENTS

Dr. Menke is the recipient of an NIH NRSA postdoctoral fellowship T32 GM0008695 and Jeffress Memorial Trust Grant.

APPENDIX A

The original equations from Reynolds et al.¹⁰ are

\[
\frac{dP}{dt} = k_{pg}P\left(1 - \frac{P}{P_\infty}\right) - \frac{k_{pm}m_P}{\mu_m + k_{mp}}P - k_pf(N^*)P
\]

\[
\frac{dN^*}{dt} = \frac{s_mR}{\mu_m + R} - \mu_nN^*
\]

\[
\frac{dD}{dt} = k_{df}f_f(f(N^*)) - \mu_dD
\]

\[
\frac{dC_A}{dt} = s_c - \frac{k_{cnf}(N^* + k_{cnd})}{1 + f(N^* + k_{cnd})} - \mu_cC_A
\]

\[
R = f(k_{ap}P + k_{mi}N + k_{ad}D)
\]

\[
f(V, C_A) = \frac{V}{1 + (C_A/C_{A\infty})^2}
\]

\(C_A\) represents the amount of system anti-inflammatory mediator. The parameters \(s_c, k_{cnf}\), and \(k_{cnd}\) correspond to \(S_c, K_{fn}\), and \(K_{fnd}\), respectively. \(N^*\) represents inflammation and all other variables and parameters are represented by the same notation as used in our model.

REFERENCES


