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Full Length Research Paper

Modeling the characteristic effect of phagocytes on wound healing

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Here we use a coupled reaction-diffusion equation to model deep partial thickness wounds in which the interaction of bacteria and normal skin cells is represented by the invasive capacity of bacteria and the phagocytic behavior of normal skin cells. The coupled system is investigated with the assumption that there is a constant consumption rate of bacteria by normal skin cells. The spatially homogenous case is considered obtaining fixed points. Stability analysis was carried out on the steady state solution to determine linear stability. Using biologically appropriate initial conditions numerical solution evolve to form traveling waves and traveling wave analysis was carried out to determine wave velocity. The results of the study reveal that if the wound gets infected, then depending on the model parameters, the wound will either be dominated by bacteria partially healed or totally healed.

Key words: Wound healing, phagocytic, normal skin cell, bacteria.

INTRODUCTION

Clark (1989), Rudolf et al. (1992) and Olsen et al. (1995), describe wound healing as a biochemical phenomenon whose mechanism involves inward movement of the wound edges. If a wound can avoid infection then it can heal normally (Okrinya, 2009). Koerber et al. (2002), maintain that deep partial thickness and full thickness wounds provide a moist nutrient rich environment, which is favorable to bacteria colonization and possible infection. The paper proposes a suitable mathematical model, which investigates the role of quorum sensing by Pseudomonas aeruginosa in burn wounds. Quorum sensing involves diffusion of signalling molecuoles in the wound environment resulting in some losses into the blood supply. If the rate of signaling molecule loss is higher than the rate of diffusion, then the bacteria will go extinct in the wound environment over time. The model considers the balance between signaling molecules production and loss via diffusion and degradation. The paper which discusses the behavior of P. aeruginosa at the pre-virulent stage of burn wound infections provides a useful background to the post infection stage of large wounds. However, the paper does not take into account bacteria invasion of healthy skin tissue and made no mention of how this could affect wound healing.

In Okrinya, 2010, we investigated the interaction between bacteria and normal skin cells in infected wounds. We discussed certain parameters of basic relevance to the biochemistry of wound infection ascertaining their effect on wound healing. The results of the study reveal a partial wound healing due to disseminated infection caused by virulent bacteria present in the wound. We mentioned in our concluding remarks that the interaction between bacteria and normal skin cells may not have been well represented and that further investigation into the problem should include some of the known biology to capture the healing. We have therefore taken further steps to study the wound environment in order to ensure the possibility of wound healing.

Infection can be terminated by both immunological and non-immunological resistance factors. The phagocyte (a type of white blood cell) is a powerful and important means by which the host can defend itself, which operates without delay against the invading bacteria. Specialized phagocytic cells eat up bacteria. The lymph nodes are also sites where the immune response comes into play. The lymphatic system takes invading

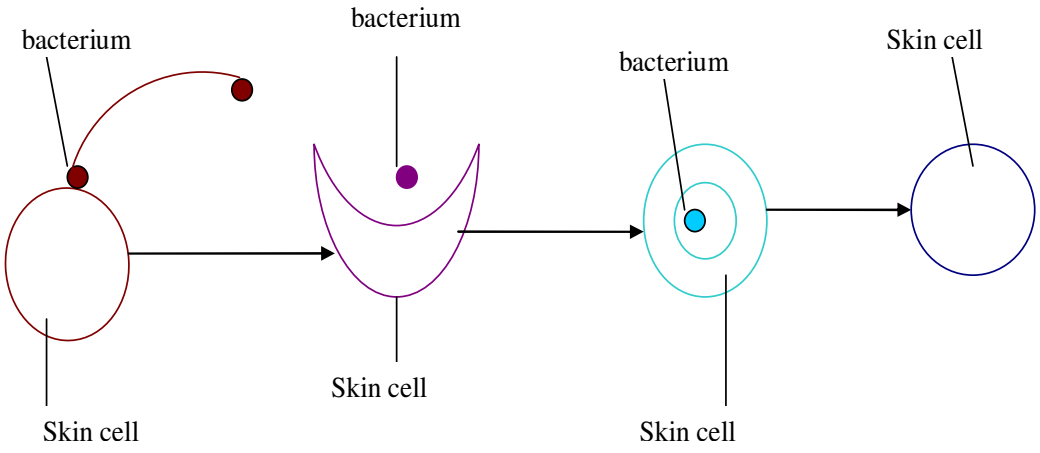

Figure 1. Showing skin cell eating up bacterium.

micro-organisms that have penetrated the body surfaces and delivers them directly to phagocytic cells and to the immune system (Mims et al., 1987). The immune cells on the other hand produce antitoxins to fight against bacteria. The mechanism of host tissues response to invading bacteria through non immune cells includes the following:

- Normal skin cells are passive “feeders on bacteria”. Normal skin cells absorb bacteria that come in contact with them through the process of phagocytosis. This is illustrated in Figure 1.
- Host tissue release chemicals, which affect bacteria growth.
- Normal skin cells eat the nutrient from blood supply thereby starving bacteria, which could possibly slow down bacteria growth.

Our previous model on bacteria cum skin cell interaction in deep partial thickness wounds was given as;

$$\frac{\partial N}{\partial t} = D_n \frac{\partial^2 N}{\partial x^2} + r_N N\left(1 - \frac{N}{k_N}\right) - \lambda_N NB \qquad (1)$$

$$\frac{\partial B}{\partial t} = D_b \frac{\partial^2 B}{\partial x^2} + r_B B\left(1 - \frac{B}{k_B}\right) \qquad (2)$$

The method of derivation, the definitions and values of the model parameters are omitted for brevity, but can be obtained in (Okrinya, 2009). Let us consider the case where host tissue feed on bacteria. By assuming a constant consumption rate proportional to the contact rate we will include the term wNB in equation (2) to obtain.

$$\frac{\partial B}{\partial t} = D_b \frac{\partial^2 B}{\partial x^2} + r_B B\left(1 - \frac{B}{k_B}\right) - wNB \qquad (3)$$

After adopting the rescaling

$$N^* = \frac{N}{k_N}, B^* = \frac{\lambda_N}{k_N}, t^* = r_N t, x^* = x\left(\frac{r_N}{D_b}\right)^{\frac{1}{2}}, D = \frac{D_n}{D_b}, a = \frac{r_B}{r_N}, g = \frac{r_N}{\lambda_N k_B}. \qquad (4)$$

We obtain the non-dimensional form of (1) and (3) as

$$\frac{\partial N}{\partial t} = D\frac{\partial^2 N}{\partial x^2} + N(1 - N - B) \qquad (5)$$

$$\frac{\partial B}{\partial t} = \frac{\partial^2 B}{\partial x^2} + aB\left(1 - gB - \frac{w}{a}N\right) \qquad (6)$$

METHODOLOGY

The model is solved using both analytical and numerical methods. Linear stability analysis is carried out by considering a spatially uniform case. For the numerical solution we used MATLAB routine (pdex4pde), an application of finite difference method with a uniform space mesh of 201 points and appropriate step sizes for space and time.

Setting $\frac{\partial^2 N}{\partial x^2}$ and $\frac{\partial^2 B}{\partial x^2}$ to zero equations (5) and (6) reduce to

$$\frac{\partial N}{\partial t} = N(1 - N - B). \qquad (7)$$

$$\frac{\partial B}{\partial t} = aB(1 - gB - \frac{w}{a}N). \qquad (8)$$

The fixed points of the system are (0, 0), (1, 0), $\left(0,\frac{1}{g}\right)$ and $\left(\frac{a(1-g)}{w-ag},\frac{w-a}{w-ag}\right)$. For the fourth fixed points to be physically realistic the parameters must satisfy the following conditions:

If w < a, then w < ag, g > 1.
If w > a, then w > ag, g < 1.

By letting $N=\hat{N}+\varepsilon N_2\ell^{\sigma t}$ and $B=\hat{B}+\varepsilon B_2\ell^{\sigma t}$ where $(\hat{N},\hat{B})$ are the fixed points and substituting in equations (7) and (8) we get, after rearranging and dropping terms of $0(\varepsilon^2)$ the expression;

$$\begin{pmatrix} \sigma-\left(1-2\hat{N}-\hat{B}\right) & \hat{N} \\ 0 & \sigma-\left(a-2ag\,\hat{B}-w\,\hat{N}\right) \end{pmatrix}\begin{pmatrix} N_2 \\ B_2 \end{pmatrix}=\begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

Since $(N_2,B_2)\neq(0,0)$, it follows that the determinant of the above matrix must be zero. The fixed points and their stability are given in table 1.

Stability of any of the fixed points depends on the behavior of the parameters w, a and g. When g<1 and w<a, (1, 0) becomes unstable, $\left(\frac{a(1-g)}{w-ag},\frac{w-a}{w-ag}\right)$ is unrealistic and $\left(0,\frac{1}{g}\right)$ becomes stable. Similarly, when w = 0 and g > 1, the point $\left(\frac{a(1-g)}{w-ag},\frac{w-a}{w-ag}\right)$ reduces to $\left(\frac{g-1}{g},\frac{1}{g}\right)$ and becomes stable. These two cases express the stable fixed points of the model (Okrinya,2010). But if w > a and condition 2 is satisfied, then $\left(\frac{a(1-g)}{w-ag},\frac{w-a}{w-ag}\right)$ becomes a stable fixed point signifying an unhealed wound. Table 1 and Figure 2 shows the stable fixed points and their feasible regions.

RESULTS

The non dimensional system is solved using the following two different sets of biologically relevant initial and boundary conditions.

Initial condition 1: N(x,0) = 0, B(x,0) = $\frac{1}{g}$, 0<x<100 and N(x,0) = 1, B(x,0) = 0, x >100.

Boundary condition 1: In the wound (on the left) N = 0, B = $\frac{1}{g}$ and on the right N = 1, B = 0.

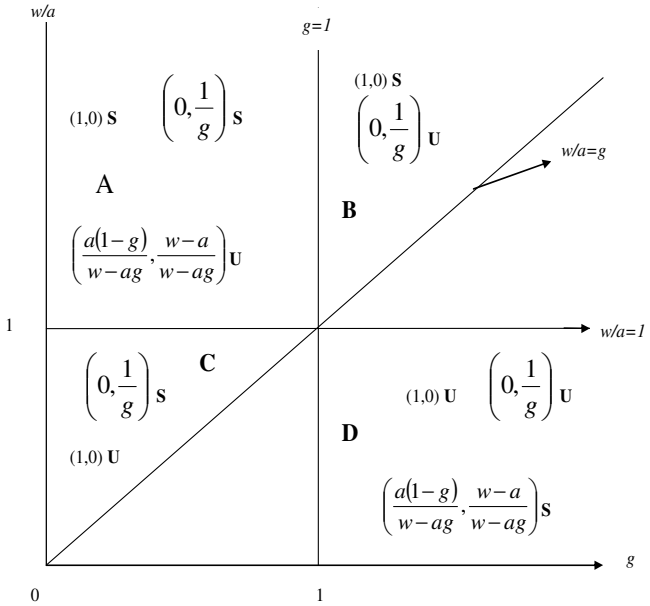

Figure 2. A sketch of w/a against g illustrating stable and unstable fixed points in each region as described in Table 1. (0,0) is unstable in all regions while $\left(\frac{a(1-g)}{w-ag},\frac{w-a}{w-ag}\right)$ is not feasible in regions A and D.

Initial condition 2: N(x, 0) = $\left(\frac{a(1-g)}{w-ag}\right)$, B(x, 0) = $\left(\frac{w-a}{w-ag}\right)$, 0<x<100 and N(x, 0) = 1, B(x, 0) = 0, x>100.

Boundary condition 2: In the wound N = $\left(\frac{a(1-g)}{w-ag}\right), B=\left(\frac{w-a}{w-ag}\right)$ and on the right N = 1, B = 0.

Each of the results in Figures 3 to 7 can be fitted into any of the labeled regions. Bacteria will win for all g<1, w/a<1 and some g<1, w/a>1. There is partial healing for all g>1, w/a>1. Healing will occur for all g>1, w/a>1 and some g<1, w/a>1. The behaviour given in Figures 3 and 4 suggests that there is a threshold value $\hat{w}$ such that for w> $\hat{w}$ the wound will heal and for w< $\hat{w}$ the wound will get worse. It is of interest to determine this bifurcation value by looking for the traveling wave solution for g<1. For a wave moving to the right, the equations are given by

$$D\frac{d^2n}{dz^2}+c\frac{dn}{dz}+n(1-n-b)=0 \qquad (9)$$

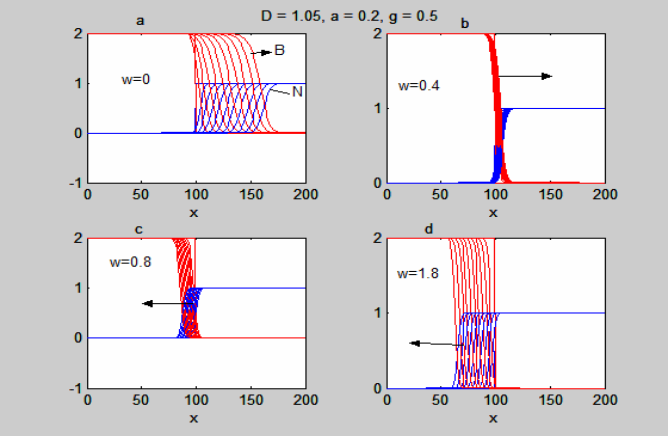

Figure 3. Showing the effect of w on bacteria invasion of host tissue, g<1 case. With g=0.5, a=0.2 and D=1.05, bacteria eat up normal skin tissue when w=0, a situation where normal skin tissue fails to exhibit its phagocytic behaviour. But a continuous increase in w reverses the situation in favor of normal skin cells. Figures a and c show that there is a bifurcation between wound healing and wound getting worse.

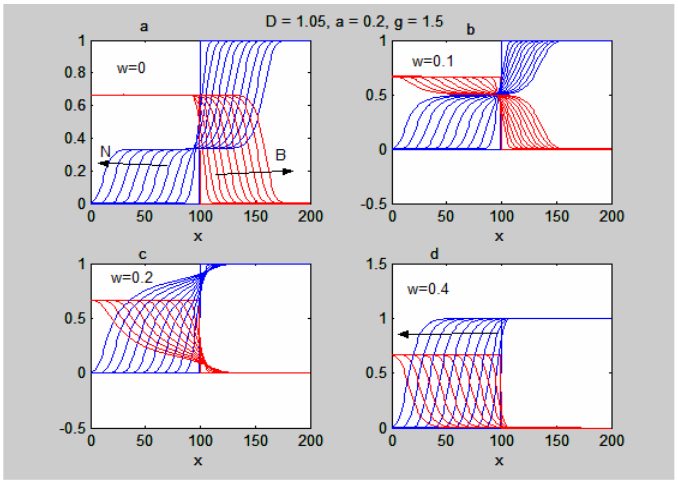

Figure 4. Showing the effect of w on bacteria invasion of host tissue, g>1 case.

$$\frac{d^2b}{dz^2}+c\frac{db}{dz}+ab\left(1-gb-\frac{w}{a}n\right)=0 \qquad (10)$$

Biologically relevant boundary conditions are given in Table 1. So, as $z\to\pm\infty$, we set $n=n^*+\varepsilon n_0\ell^{\alpha z}$ and $b=b^*+\varepsilon b_0\ell^{\alpha z}$ and determine the value of σ for small nonzero (n_0,b_0) leading to the equation.

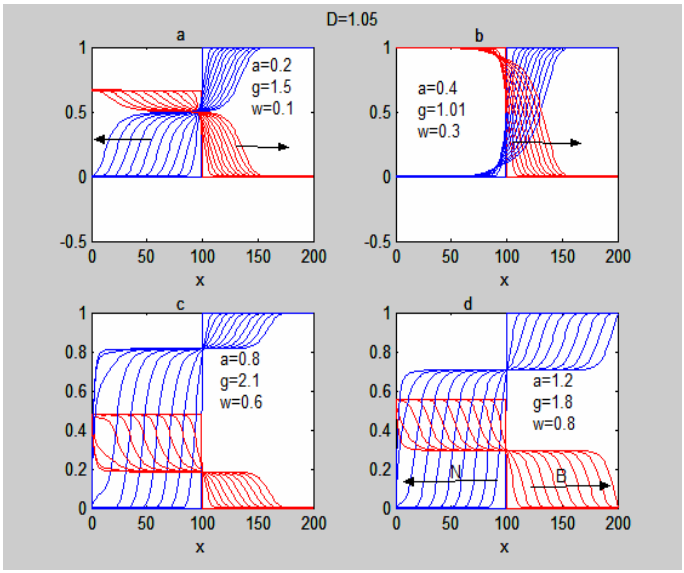

Figure 5. Showing unhealed wounds for g>1, w<a.

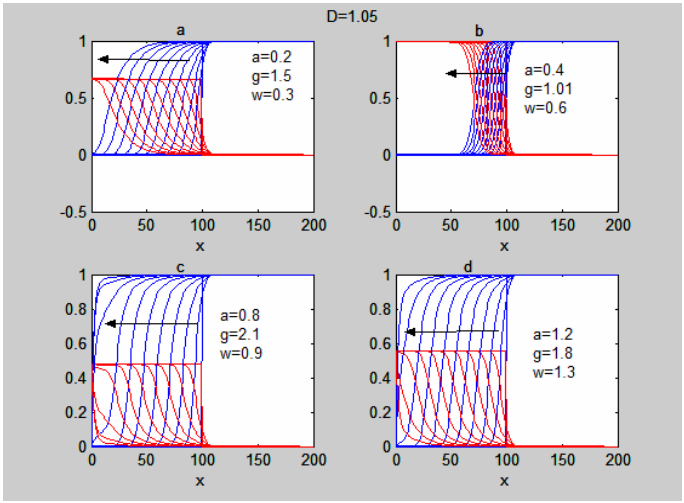

Figure 6. Showing unhealed wounds for g>1, w>a.

$$\begin{vmatrix} D\sigma^2+c\sigma-2n^2-b^*+1 & -n^* \\ -wb^* & \sigma^2+c\sigma+a-2agb^*-wn^* \end{vmatrix}$$
=0.

As $z\to+\infty$, with $(n^*,b^*)=(1,0)$
we get
$(D\sigma^2+c\sigma-1)(\sigma^2+c\sigma+a-w)$ =0, and w=0.2, a=0.3 for w<a. Either 0.3 or 0.2 is used for w=a.

Table 1. Showing stability of fixed points. σ_1 and σ_2 are the first and second Eigenvalues corresponding to each fixed point.

Fixed point	σ_1	σ_2	Description of σ	Nature of stability
(0,0)	*1*	*a*	σ_1 , $\sigma_2 > 0$	unstable
(1,0)	*-1*	*a – w*	$\sigma_1 < 0$ $\sigma_2 < 0$ for $w > a$	Stable for $w > a$, $g < 1$. Unstable otherwise
$\left(0, \frac{1}{g}\right)$	$\left(1 - \frac{1}{g}\right)$	*-a*	$\sigma_1 < 0$ for $g < 1$ $\sigma_2 < 0$	Stable for $g < 1$, $W < a$. Unstable otherwise
$\left(\frac{a(1-g)}{w-ag}, \frac{w-a}{w-ag}\right)$			$\sigma_1 > 0$, $\sigma_2 < 0$, For $g<1$ $\sigma_1, \sigma_2 < 0$ for $g>1$	Stable for $g>1$, $w<a$. Unstable otherwise

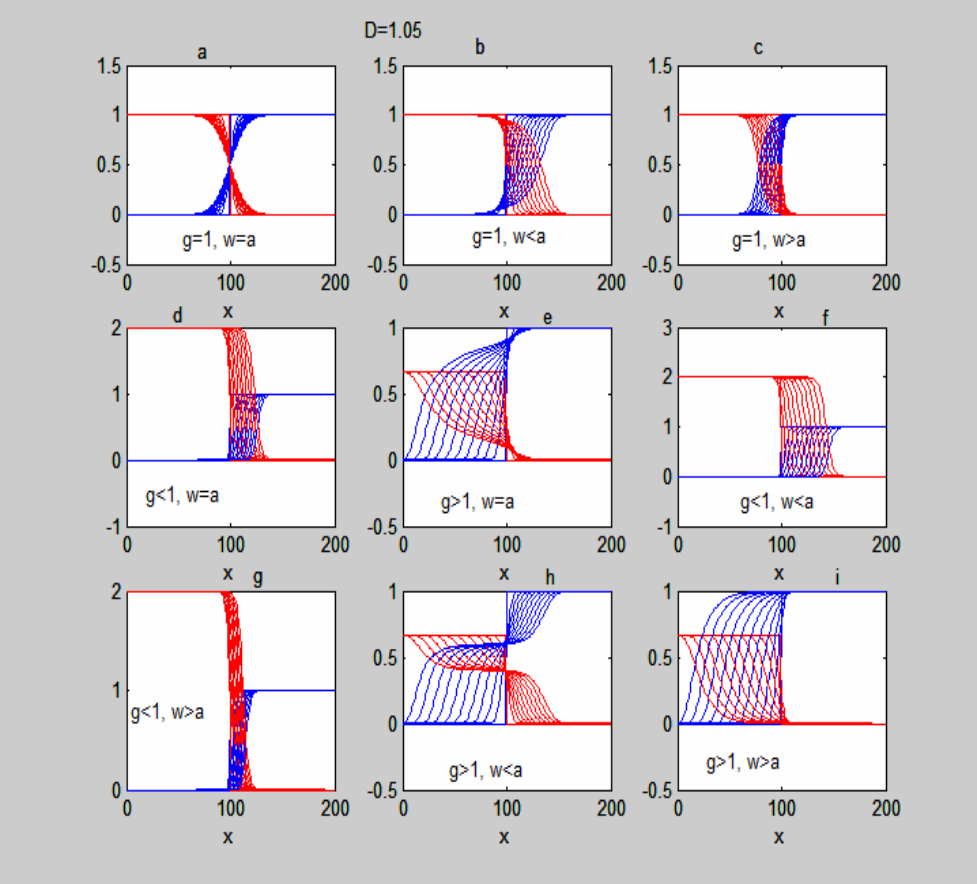

Figure 7. Plots showing the behaviour of the parameters g, w and a in relation to wound healing. There is a bifurcation between wound healing and wound getting worse when g=1 and w=a. For g=1, w>a implies wound healing and w<a results in wound getting worse. Similarly for every g<1, there is a value of a such that w>a involves wound healing and w<a implies wound getting worse. The values used for the simulations are; g=0.5 for g<1 and g=1.5 for g>1. Others are; w=0.3, g=0.2 for w>a.

Giving the values of σ as $-\frac{c}{2D} \pm \frac{\sqrt{c^2+4D}}{2D}$ or $\frac{c}{2} \pm \frac{\sqrt{c^2-4(a-w)}}{2}$.

Similarly, as $z \to -\infty$ where $(n^*, b^*) = \left(0, \frac{1}{g}\right)$, $\sigma = -\frac{c}{2D} \pm \frac{\sqrt{c^2-4D\left(1-\frac{1}{g}\right)}}{2D}$ or $-\frac{c}{2} \pm \frac{\sqrt{c^2+4a}}{2}$.

In order to investigate the wave moving to the left we set z = x + ct to obtain the following equations.

$$D\frac{d^2n}{dz^2} - c\frac{dn}{dz} + n(1-n-b) = 0 \quad (11)$$

$$\frac{d^2b}{dz^2} - c\frac{db}{dz} + ab\left(1 - gb - \frac{w}{a}n\right) = 0 \quad (12)$$

With the application of the same conditions we get the eigenvalue σ satisfying

$$\left(D\sigma^2 - c\sigma - 2n^* - b^* + 1\right)\left(\sigma^2 - c\sigma + a - 2ag^*b - wn^*\right) - \left(-wb^*\right)\left(-n^*\right) = 0.$$

Thus as $z \to +\infty$, $\sigma = \frac{c}{2D} \pm \frac{\sqrt{c^2+4D}}{2D}$ or $\frac{c}{2} \pm \frac{\sqrt{c^2-4(a-w)}}{2}$, and as $z \to -\infty$, $\sigma = \frac{c}{2D} \pm \frac{\sqrt{c^2-4D\left(1-\frac{1}{g}\right)}}{2D}$ or $\frac{c}{2} \pm \frac{\sqrt{c^2+4a}}{2}$.

From the results of both wave forms we get for a nonoscillatory solution $c^2 \geq 4(a-w)$ and $c^2 \geq 4D\left(1-\frac{1}{g}\right)$, which gives $c_{\min} = 2\sqrt{a-w}$ and $c_{\min} = 2\sqrt{D\left(1-\frac{1}{g}\right)}$.

Since c must be zero at the point of bifurcation, then we get g =1 and w = a. For $c_{\min} > 0$, only w<a and g>1 will give realistic results.

DISCUSSION

The presence of the parameter w in the model has given a different shape to previous solutions obtained in Okrinya (2010), where g < 1 worsens the wound as bacteria infiltrate normal skin tissue. But the numerical solution to this model shows that a continuous increase in w from low to high values reduces the rate of bacteria infiltration of normal skin tissue. This rate becomes zero at some point and further increases the wave movement in favor of normal skin tissue, leading to healing. This is shown in figure 3, where w increases from 0 to 1.8. Figure 3b in particular suggests that there is a bifurcation between wound healing and wound getting worse. We obtain from the traveling wave solution that such a bifurcation point exists when g = 1 and w = a. Thus, for g < 1 there is a threshold value $\hat{w}$ such that if w> $\hat{w}$ the wound heals and if w< $\hat{w}$ the wound gets worse. Figure 4 illustrates this behavior whereby sufficiently large w, reflecting higher host cell responses terminates the effect of infection. The results in figures 5 and 6 show the effect of w when g > 1. Healing occurs on the left part of the wound while it extends to the right as bacteria invade skin tissue. The parameter g is the ratio of the growth rate of normal skin density to the product of the rate of normal skin loss to bacteria and the carrying capacity of bacteria. So, g < 1 implies domination by bacteria whereas g > 1 expresses normal skin domination. This is represented by the solution since for g < 1 there are more bacteria in the wound and less bacteria for g > 1. An increase in w improves the healing part and reduces the invading effects of bacteria. A lower value of w is required to overcome the effect of bacteria for g > 1 than g < 1. We recall that a is the ratio of the growth rate of bacteria to the growth rate of normal skin tissue. An increase in a, comes from an increase in the linear growth rate of bacteria or a decrease in normal skin tissue growth rate. Therefore, a higher value of a, reduces the effect of w. In fact, $\frac{w}{a}$ is the important parameter that governs the various behaviors. Figure 8 is a sketch of $\frac{w}{a}$ against g and we can see clearly that for g<1, there is a threshold value $\hat{w}$ such that if $\frac{w}{a} > \hat{w}$ the wound heals and if $\frac{w}{a} < \hat{w}$ the wound gets worse. It is important to note that the curve labeled K is not a steady state, but a slowly advancing or receding wave. The only point that seems One important characteristics of our analytical solution is that the rate of healing depends to a great extent on the to be a steady state as resulting from the numerical and

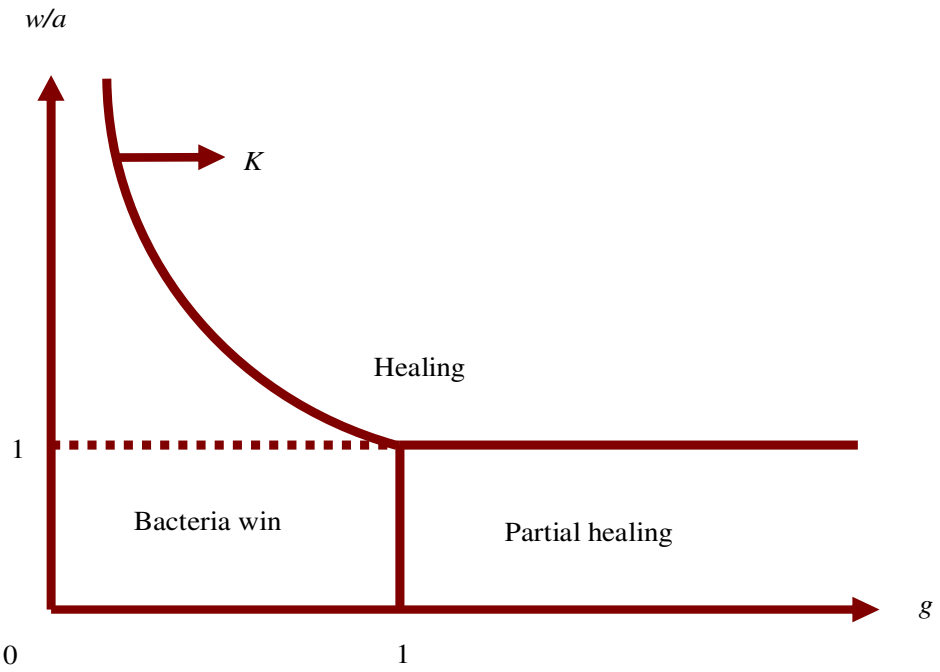

Figure 8. A sketch of w/a against g summarizing the numerical solution.

traveling wave solution is when $\frac{w}{a}=1$ and g = 1. density of bacteria ($\frac{1}{g}$ in the dimensionless terms) in the wound. The traveling wave solutions corroborate the results of the analytical solutions and provide an idea of the speed of healing. The speed of healing of an infected wound can be estimated analytically in terms of the model parameters D, a, g and w. But the traveling wave analysis shows that $c_{\min} > 0$ is only possible where $\frac{w}{a}<1$ and g > 1, implying that we can only get partial healing (see Figure 8). We note that the analysis fails to identify the bifurcation curve K and indeed fails to predict the correct wave speed in a region at least bounded by g<1 and $\frac{w}{a}>1$. In this region the wave speed is not dominated by the tail "pulling" the front along, but by some other selection process. We suggest that a further investigation into this problem should explore other forms of analyses that can explicate the dynamics of the system.

The model does not distinguish between species of bacteria. For those bacteria that have a quorum sensing virulent regulator, the model does not reflect the greater virulence of bacteria in higher density than those at lower density. We recommend that for further studies, this model should be modified to reflect the quorum sensing mechanism. One way of doing this, is by replacing $\lambda_N NB$ in equation (1), with $\lambda_N Nf(B)$ such that when B is small f (B) will be very small and when B is large, f (B) will be very large. Another limitation of the model is that it does not include all aspects of the known biology especially, the effect of the immune system on infection and wound healing and the existing competition between bacteria and host tissue for vital nutrients supplied by the blood stream.

Despite the limitations and the simple nature of the model, it represents a bold attempt to construct a mathematical model that mimics wound healing following infection. The relevance of the model cannot be overemphasized. It is an attempt to solve a problem that poses threat to human life and we believe it will serve as a stepping-stone for further studies.

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