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Parameter Search to Find Ranges of Activation and Inhibition of Wound Healing Rate in a Mathematical Model with Introduced Photobiomodulation

Alistair McQueen [1,2] Jacquelyn Dawn Parente[2] Sean McGinty[1] Knut Moeller[2]

[1] University of Glasgow, University Avenue, G12 8QQ, Glasgow, Scotland
[2] Institute for Technical Medicine, Jakob-Kienzle Strasse 17, 78054 Villingen-Schwenningen, Germany
`pjd@hs-furtwangen.de`

Abstract. When light stimulation is used for wound healing therapy, a biphasic dose-response curve is observed, where cells are activated below and inhibited above a treatment dose threshold. Light treatment-dose responses are not yet incorporated into mathematical models of wound healing - yet these relationships would support optimization of wound healing treatment protocols. This work adapts an existing wound healing mathematical model by exploring parameter values and introducing exogenous photobiomodulation treatment inputs for future applications in model-based experimental research. A wound healing mathematical model, created by Sherratt & Murray in 1990, includes proliferation, migration, and activating and inhibitory chemical terms. This model was implemented and discretized by Forward Euler (FE) in time and the Central Difference Method (CDM) in space in 1D. Travelling wave solutions of cell density and chemical concentration were obtained and used to plot wound closure in time and to estimate the wound healing rate. A parameter search was conducted to identify ranges where model simulations resulted in activation, inhibition, saturation, or numeric instability of wound healing. Published results of photobiomodulation treatment-control studies reporting a percentage change in proliferation were used to scale proliferation terms, thus serving as a proxy for light stimulation. Results showed the inhibition model was more sensitive to parameter variation than the activation model. Changes in the cell migration parameter are most sensitive overall. Most model parameters were bounded by saturation or numeric instabilities, while otherwise demonstrating activating and/or inhibitory effects on the rate of wound healing. Light stimulation simulations were consistent with expectations that increasing the proliferation term increased wound healing rate. To support photobiomodulation model-based experimental wound healing research, the model parameter search identified threshold values categorizing activation or inhibition of wound healing rate and this work also adapted a model proliferation term consistent with photobiomodulation biological effects.

Keywords: Mathematical Model, Photobiomodulation, Sensitivity Analysis, Wound Healing

1   Introduction

Mathematical models of wound healing represent coordinated biological processes depending on chemically mediated multi-cellular interactions. Advanced model-based wound healing therapies apply knowledge of these relationships to guide individually optimized treatment protocols [1]. To understand parameter relationships in a wound healing model, we conduct a parameter sensitivity analysis on a species conservation mechanochemical model by Sherratt and Murray [2]. In addition, no existing mathematical models of wound healing incorporate light treatment. Therefore, this work introduces exogenous photobiomodulation treatment inputs to the model.

Eqn. 1 illustrates the change in cell density, with Eqn. 2 demonstrating how the chemical concentration varies with time during the wound healing process. The model's equations are presented below in dimensionless form [2]:

$$\frac{\partial n}{\partial t} = D\nabla^2 n + \left(\frac{2c_m(h-\beta)c}{c_m{}^2 + c^2} + \beta \right) n(2-n) - n, \text{with } \beta = \frac{1 + c_m{}^2 - 2hc_m}{(1-c_m)^2} \quad (1)$$

$$\frac{\partial c}{\partial t} = D_C\nabla^2 c + \delta \left(\frac{n(1+\alpha^2)}{n^2 + \alpha^2} \right) - \delta c, (2)$$

where n is cell density, and c is chemical concentration. In the first term on the right-hand side of Eqn. 1, D portrays cell migration by a diffusive term. Several terms represent cell mitosis: h is the difference in mitosis rates between wounded and unwounded dermis; and c_m is the maximum rate of mitosis, as controlled by the chemical mediator. β is used to group parameters for simplification. The chemical mediator, D_C, represents diffusion, where δ is chemical decay, a first order kinetic parameter. The chemical production term, α, dictates the maximum rate of chemical production.

The inhibitor model below implements similar fundamental equations as the activator model above; with altered cell proliferation and chemical production terms. Eqns. 3 and 4 describe a chemical inhibitor model in dimensionless form [2]:

$$\frac{\partial n}{\partial t} = D\nabla^2 n + \left(\frac{(h-1)c + h}{2(h-1)c + 1} \right) n(2-n) - n, (3)$$

$$\frac{\partial c}{\partial t} = D_C\nabla^2 c + \delta n - \delta c. (4)$$

The parameters in the inhibitor model have the same characteristics as described within the activator model. Both the activator and inhibitor models employ Dirichlet boundary conditions at the wound centre, equivalent to the unwounded tissue value, and a zero-flux Neumann boundary condition at the wound centre, preventing the movement of cells and chemicals to and from the wound [2].

2   Method and Materials

The model equations were discretized in time by Forward Euler and in space by the Central Difference Method. The algebraic equations progress forward in time when plotting travelling wave solutions; illustrating how both species migrate through the wound space during the healing process. From this, the minimal healing time was devised, allowing for the relative time taken for the wound to close be demonstrated.

A sensitivity analysis was conducted to demonstrate the effect on healing time by, relative to the original healing time (relative healing time), altering individual parameters; providing insight into how the model parameters alter wound healing characteristics. Minimum and maximum parameter values were defined for a fixed mesh size, where the results illustrated behaviour which was numerically unstable or stagnated. Stagnation was defined upon observing a 1% (or less) change in relative heal time after varying the parameter by a single order of magnitude. The total heal time was selected as a marker point for comparison. The extensive sensitivity analysis depicts the change in relative wound healing time to variations of individual parameters within the model, thus providing an initial concept into understanding the effect of light stimulation for wound healing; illustrated through a mathematical model.

After implementing a generic mathematical model portraying wound closure, a simplistic approach into understanding photobiomodulation was addressed in the model. Within the literature, cells proliferation is often noted as a cellular response to light stimulation. Relevant literature was found using the Web of Science (WoS) database, searching for keywords including: 'Light Stimulation', 'LED', 'Wound Healing' and 'Proliferation'. The search was limited to papers published since July 2007. Additionally, most methodologies involving wound healing via light stimulation implement different parameters involving the irradiation of light. Therefore, the fundamental inclusion criteria were to present results from experimental publications which kept irradiation parameters as similar as possible.

The effect of light stimulation was incorporated into the mathematical model by scaling the proliferation term by the percentage increase documented experimentally. This procedure was only applied to the activator model because all experiments documenting positive results to wound healing by the stimulation of red light. Therefore, parameters h and c_m were those primarily effected, illustrating the change in mitosis rate between wounded and unwounded skin and by a chemical mediator, respectively. Five papers in total were used, reporting changes in cell proliferation upon light stimulation, and is documented within Tab. 3 [4, 5, 6, 7, 8].

3   Results

The mathematical models were implemented in 1D to obtain travelling wave solutions to the activator and inhibitor models using original parameter values [2]. The solutions demonstrate cell density and chemical concentration throughout the wound space, and how these levels vary in time. The interval spacing defines the wave speed.

Tables 1 and 2 present parameter sensitivity analysis results for the activator and inhibitor models. Decreased healing time was observed in both models upon decreasing parameters D_C, c_m, and α. However, increasing these values increased the relative heal time. Alternatively, relative heal time increased when decreasing D, δ, and h, while increasing these parameters produced a decreased heal time. Overall, parameter behaviours trends are similar for chemical activator and chemical inhibitor models. Yet, the inhibitor is more sensitive to parameter variation; numerical results tend towards numerical instability, over stagnation. Unstable model results are noted at fixed mesh values, therefore the parameter bounds observed vary upon altering the mesh.

For example, the result of varying parameter h for the activator model is described. Murray and Sherratt used $h = 10$, based upon experimental results [2]. Decreasing h from the original value increased heal time, while increasing the value decreased heal time. A minimum bound at $h = 0.1$ with a relative heal time of 1.24, where the result stagnated. A maximum bound was observed at $h = 100$, with a relative heal time of 0.79, where increasing h beyond this value increased healing time.

Table 1. Sensitivity analysis of activator model (dimensionless results). For each parameter value, the minimum, original [2], and maximum parameter values are shown in bold, below which are the corresponding times to wound closure, relative to the original heal time. At parameter values beyond the limits, the model results were characterized as saturated (S) or numerically unstable (U).

Parameter	Minimum	Original [2]	Maximum
D	-	**0.0005**	-
heal time	increasing	1	decreasing
D_C	**0.0005**	**0.45**	**0.9**
	(S) 0.69	1	1.04 (U)
δ	**0.03**	**30**	**~14900**
	(S) 1.18	1	0.69 (U)
h	**0.1**	**10**	**100**
	(S) 1.24	1	0.79 (-)
c_m	**~5**	**40**	**1000**
	(U) 0.79	1	1.18 (S)
α	**0.0001**	**0.1**	**10**
	(U) 0.70	1	2.49 (S)

Table 2. Sensitivity analysis of inhibitor model (dimensionless results).

Parameter	Minimum	Original [2]	Maximum
D	-	**0.0001**	-
heal time	increasing	1	decreasing
D_C	**~0.4**	**0.85**	**1.7**
	(U) 0.4	1	2.3 (U)
δ	**0.05**	**5**	**~10**
	(S) 1.14	1	0.74 (U)
h	**0.5**	**10**	**10,000**
	(U) 1.37	1	0.9 (U)

Table 3 presents the time taken for the wound to close and travelling wave speed when stimulated by varying doses of red light. The results agree with conclusions drawn from Chaves et. al [3]. A minimum value is observed at 4 J/cm^2, illustrating an overall decrease in wound healing time by 28.00%. For two successive singular increments in dosage, the healing time only reduced by 18.8 and 16.89% respectively. Increasing the dosage to 10 and 16 J/cm^2 illustrates only slight decreases in the healing time by 9.13 and 7.59% respectively. The results represent a positive response, where increases in the proliferation scaling decrease heal time.

Table 3. Scaling the model proliferation term by documented proliferation increase (at various irradiation parameters) decreases healing time. The original parameter values were used [2].

Dose [J/cm^2]	Wavelength [nm]	Proliferation Increase [%]	Closure Time [%]	Travelling wave [mm/h]
Control	-	-	100	2.20×10^{-3}
4 [4]	627	52.0	72.0	3.30×10^{-3}
5 [5]	670	27.5	81.20	2.75×10^{-3}
6 [6]	640	25.0	83.11	2.75×10^{-3}
10 [7]	700	11.6	90.87	2.70×10^{-3}
16 [8]	640	10.0	92.31	2.68×10^{-3}

4   Discussion

The parameter sensitivity analysis demonstrates activating or inhibiting behaviour towards maximum and minimum value bounds, where unstable or stagnant behaviour was observed. The results portrayed the sensitive behaviour of D which, unlike other parameters, is independent of chemical mediators and hence, heavily influences the travelling wave speed and heal time directly.

Altering cellular proliferation parameters, h and c_m of the activator model has opposite effects. Increasing h saw cell density levels fall below the chemical concentration, thus decreasing heal time; with cell density levels increasing above the chemical concentration for increments beyond $h = 100$. Decreasing c_m illustrated stability issues, with interval spacing at the wound centre increasing for decreased values of c_m. Increasing c_m, unlike other parameter variations, saw the chemical concentration increase gradually towards the wound centre, whilst also decreasing the travelling wave speed, possibly explaining why healing time increased.

For chemical mediator parameters, increasing Dc and α increased heal time, while increasing δ decreased heal time. The former two noted decreased levels of chemical concentration when their values were decreased, resulting in an increased heal time. Whereas, increasing δ demonstrated the opposite effect.

An initial approach to incorporating the effects of photobiomodulation into wound healing illustrates the positive effects red light had on relative healing time. Scaling the proliferation term influences c_m and h, which dictate chemical activity and mitosis

rates, respectively. Increasing the scale reduced healing time, which reflects experimental results documenting increased proliferation rates and reduced healing times.

When compared to Arndt-Schulz curve (which portrays bi-phasic cellular activation and inhibition at a threshold dosage [3]) the results do not demonstrate a sharp decrease in cell proliferation. Only doses of 4 J/cm^2 and greater are presented. Thus, the activation increase towards a maximum is not represented. Lastly, the light doses, irradiation parameters, and experimental models are not similar [4, 5, 6, 7, 8].

5   Conclusion

Understanding wound healing mathematical model parameter behaviour aids the development of advanced model-based therapies to modulate wound healing processes. This work identified the numerical behaviour of model parameters and their effects on wound healing time. Additionally, an initial methodology to incorporate photobiomodulation was introduced, to account for documented cellular proliferation responses to red light as a positive influence on decreasing wound closure rate.

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