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# Modelling Week

# Mathematical modelling of wound healing processes

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# Mathematical modelling of wound healing processes

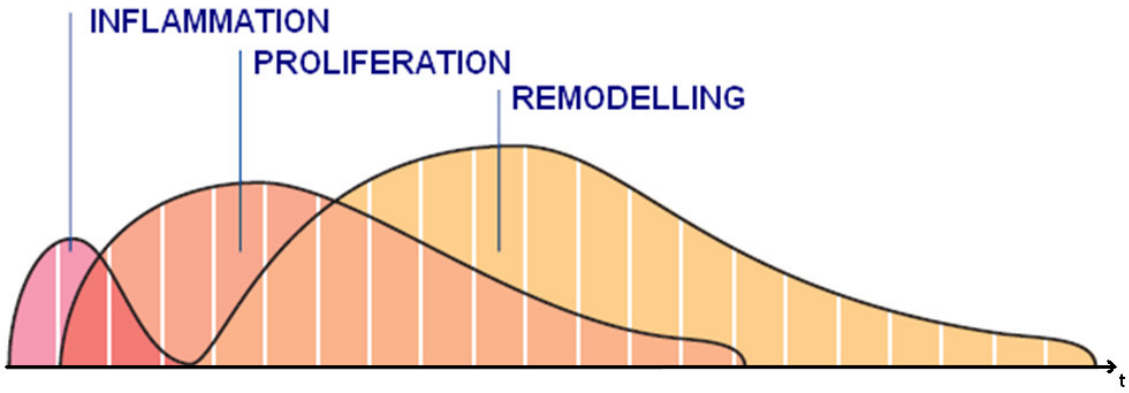
## Abstract

The aim of this analysis is to understand which factors take part in natural wound healing process. To do so, several mathematical models which reproduce this process have been adjusted. Through computer simulations, it is possible to know how the healing time of wounds varies as a function of model parameters. The knowledge of sensitivity to the different factors can help in the search for new treatments which reduce the time of wound healing process.

We have analyzed three reaction-diffusion models adjusted to simulate this process: Sherratt and Murray's model for wound closure, Sherratt, Murray and Maggelakis's model for coupled wound closure and angiogenesis and Olsen's model for wound contraction. Uniformity of wound closure evolution allows us to consider wounds as if they were planar wounds and simplify the problem to one-dimensional case. However, we present some bi-dimensional results too, which illustrates the influence of wound morphology and size in healing time.

## Biological introduction

We can distinguish mainly 3 phases in wound healing process: **Inflammation**, **Proliferation** and **Remodeling**. As it is showed in the next figure this phases overlap in time.




Basically, in inflammation phase, bacteria and debris are phagocytosed and removed. During proliferation phase, the most important events in wound healing process take place and these are the processes we have simulated through mathematical models.

So, the first process we have analyzed is granulation tissue formation and **re-ephitelialization** of the epidermis. We have seen how epithelial cells proliferate in order to provide cover for the new tissue. Simulations have been developed through Sherrat and Murray's model for wound closure.

The second process is named **angiogenesis**, and is related with new blood vessels formation from vascular endothelial cells. In this case, simulations have been developed using other model proposed by Sherratt, Murray and Maggelakis.

Finally, in the process known as **contraction**, the wound is made smaller ('contracted') by the action of two types of cells: fibroblasts and myofibroblasts. The model used to do simulations associated to this process is due to Olsen.

# Sherratt and Murray model for wound closure

## *The model*

To start with, it must be observed that there are growth factors in the body which can stimulate or inhibit cell function during wound healing process. So, the first model, analyzes the closure of epidermal wound for both types of chemical influence separately. The model consists of two conservation equations.
Talking in informal terms, we can see the first equation as a relation established between the rate of increase of cell density on one hand, and cell migration, mitotic generation and natural loss on the other hand.

*Rate of increase of cell density = Cell migration+ Mitotic generation – Natural loss*

According to chemical concentration, we can see the second equation as a quantification of the relation existing between the rate of increase of chemical concentration on one hand, and diffusion chemical substances, production generated by cells and decay of active chemical on the other hand.

*Rate increase chemical concentration =*
*Diffusion + Production by cells - Decay of active chemical.*

In mathematical terms, the reaction-diffusion model is composed of:

- One equation for the cell density per unit area (variable "n")

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} + S(c)(2 - \frac{n}{n^0}) - Kn$$

- One equation for the concentration of the mitosis regulating chemical (c)

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + f(n) - \lambda c$$

In the wounded zone, initial conditions are given by: $n(0) = c(0) = 0$
In the wounded zone, we assume a non-zero cell density ($n^0$) and a non-zero chemical concentration ($c^0$).

Relative to boundary conditions, they are given by:

$$D_n \frac{\partial n}{\partial x}(0,t) = 0 = D_n \frac{\partial n}{\partial x}(L,t)$$
$$D_c \frac{\partial c}{\partial x}(0,t) = 0 = D_c \frac{\partial c}{\partial x}(L,t)$$

We give now a brief description of the terms involved in these equations:

- Derivatives of n with respect to time reflect the increasing rate of "n" and "c" along the time.
- Diffusion coefficients, givens by $D_n$ and $D_c$, quantify speed cells and chemical concentration expansion from the unwounded to the wounded zone.
- In the simulations we have done, we have considered two possibilities. In the first of them, chemical substances activates mitosis process, while in the second case, it inhibits cells proliferation. Although activator and inhibitor substances work together, it's easier to consider both effects separately and the final result can be considered like a good approximation to the phenomenon we have studied.

  These behaviors are controlled by "S" and "f" functions. Sherratt and Murray proposed different expressions for these functions, according to the effect (activator/inhibitor) which is going to be simulated.

  S(c) is responsible for reflecting the chemical control of mitosis while f(n) function reflects the rate of chemical production by epidermal cells. As we will see later, it is important to remark the fact that S function depends on *K* and f function depends on λ.

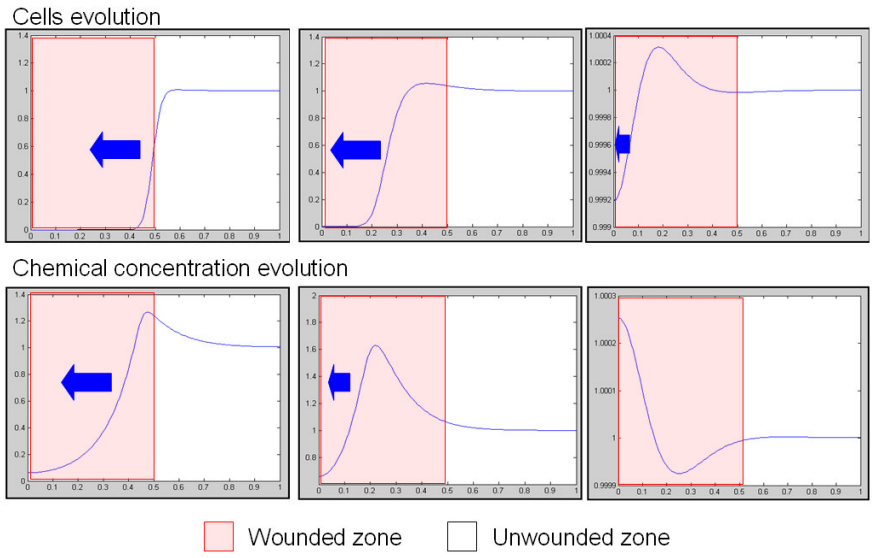
  It is important as well to observe the fact that in the equation associated to cells density variable ("n") there is a function ("s") depending on "c" variable, and that in the equation associated to chemical concentration ("c") there is a function ("f") depending on "n" variable. It causes a feedback loop between cells and chemical factors.
- Cells and chemical life time coefficients, given by the inverse of K and λ terms respectively, allow quantifying how cells and chemical concentration disappear along the time.

## ***Results***

*One-dimensional case*

The results we present now have been obtained using a *matlab* code which solves the system conformed by the reaction-diffusion equations mentioned for different time values. Domain associated to the system has been approximated by a segment of length 1, whose left middle represents the wounded zone (planar wound).

Originally there are no cells in the wounded area (in the segment [0,0.5]). Graphs below show the evolution of the normalized cell density per unit area ($n/n^0$) and the normalized concentration ($c/c^0$) of the mitosis-regulating chemical in the activator case.




We can appreciate how the chemical concentration increases with time, stimulating cells proliferation (mitosis process) in the wounded area until it is completely covered.

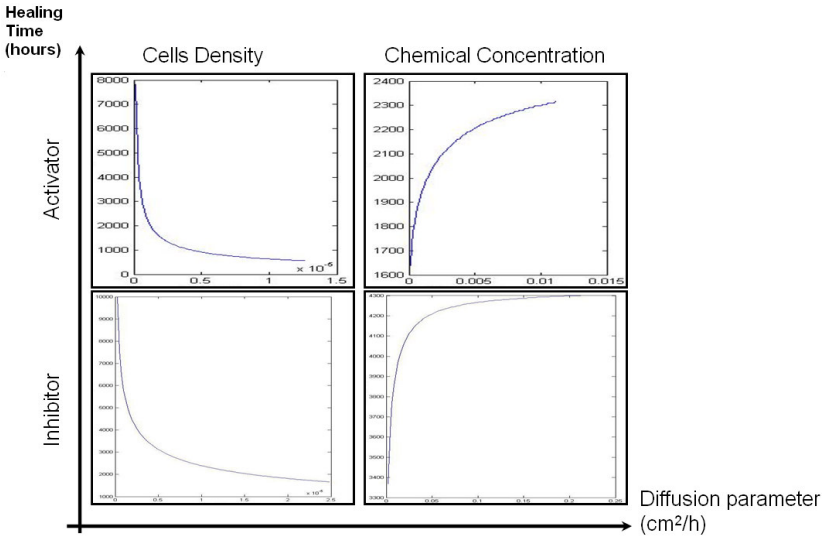
(Note: We have considered that the wound is healed when there is at least an eighty percent of the normal level of cells in the wounded area)

This typical sequence has been reproduced for different values of the model parameters. Our interest focused on quantifying the reduction of the healing time when we modify the value of these parameters. So, the following graphs show healing time on the vertical axis versus diffusion and decay coefficients, comparing results obtained in the activator and inhibitor case.

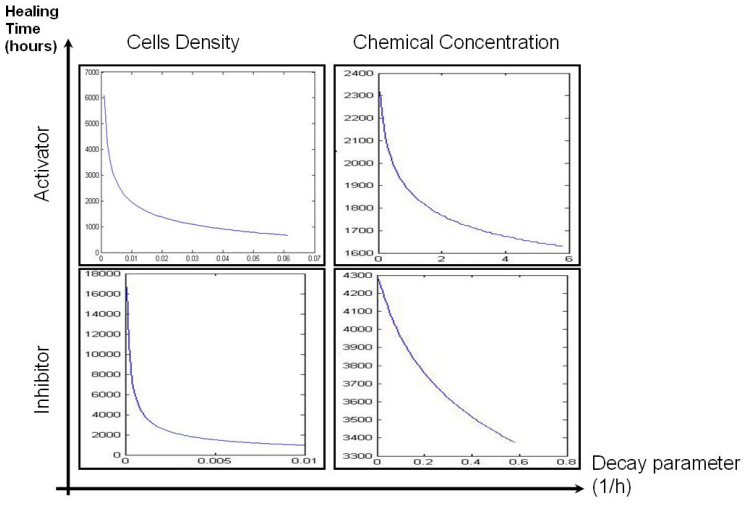
Relative to diffusion parameters, we can appreciate that in both the activator and inhibitor case, the greater the cells diffusion parameter the shorter the healing time. It

seems an expected behavior: when cells proliferation speed increases (responsible for closure the wound), so do the healing time process.

In the case of chemical diffusion parameters is the other way around, the greater the diffusion parameter the longer the healing time.




Relative to decay parameters, we can note that in both the activator and inhibitor case, the greater the decay parameter the shorter the healing time. This fact seems to be rare, because it could appear that when time life decreases, so do wound healing time. However, it can be justified taking into account that "s" and "f" functions depends on decay parameters with opposite sign. So the contribution of these functions to reaction-diffusion system is more relevant that the weight of decay blocks in it.



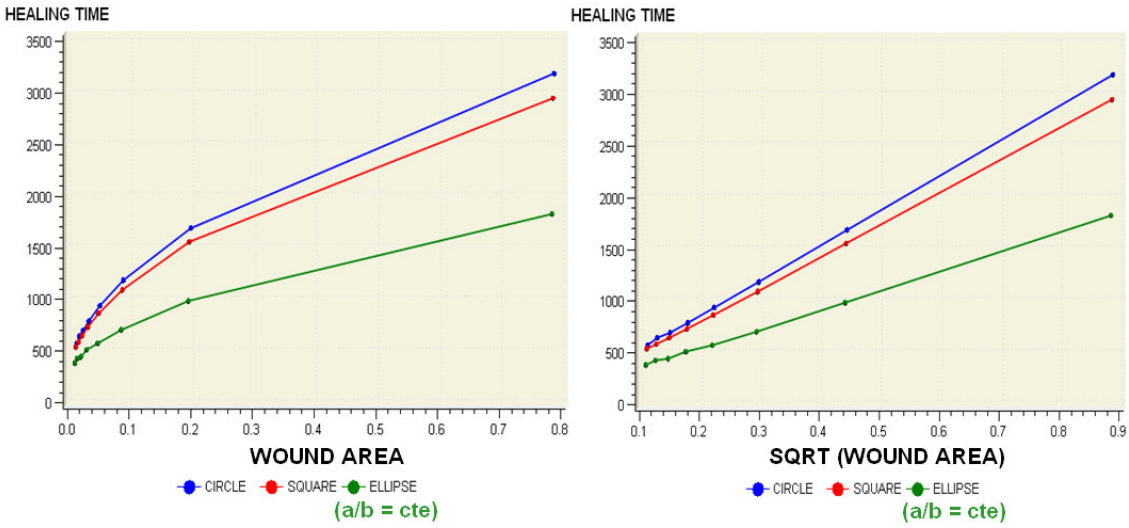
*Bi-dimensional case*

In the bi-dimensional case, we have considered three different geometries associated to wound domain: a circle, a square and an ellipse. Our purpose is to analyze the influence of wound morphology and size in time to healing.

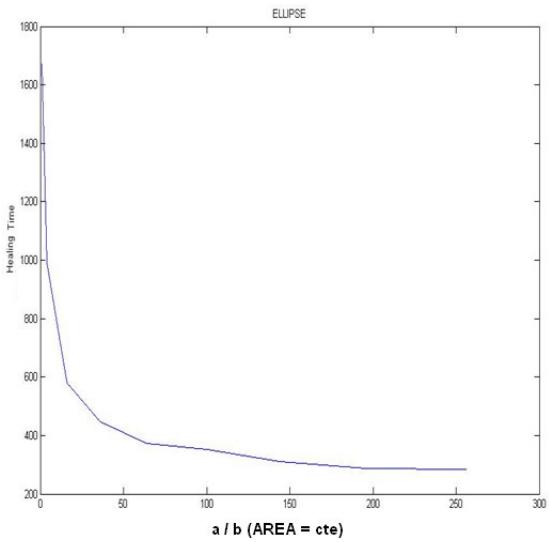
In first place, we have measured the healing time for each of them for different areas (but keeping a common value for the three figures).

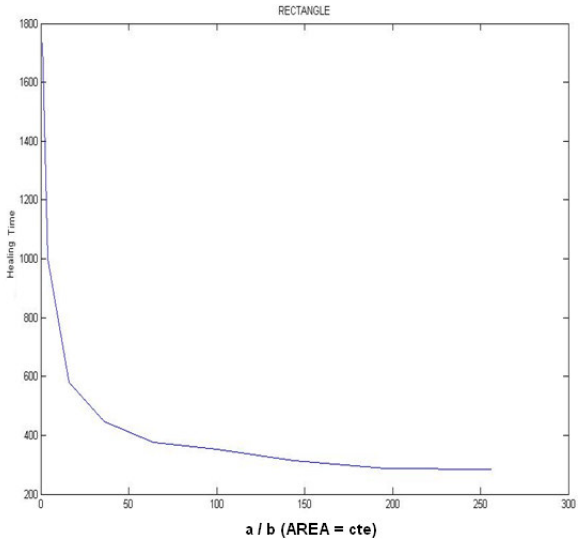
The conclusion we can extract (see graph on the left) is that elliptical domains seem to close faster. It is justified attending to its curvature: "closer wounds close faster".

In the graph on the right, we have represented the healing time versus the squared root of the area, which is a magnitude proportional to the radius of the circle, to the side of the square or to the product of length axis in the ellipse case. In this last one, we have kept the ratio between length axis (a / b = 4). The conclusion derived from this graph is that time healing is linearly proportional to this magnitudes.




Finally we have measured the healing time for an elliptical and a rectangular wound, keeping now the area but changing "a over b (a/b) ratio". According to the next graphs we can confirm a result observed in the comparison of elliptical domains respect to circle and rectangular domains: "closer wounds close faster". In fact, the bigger the difference between lengths "a" and "b" ("closer wounds"), the shorter the healing time.


ELLIPSE
Healing Time
1800
1600
1400
1200
1000
800
600
400
200
0
50
100
150
200
250
300
a / b (AREA = cte)


RECTANGLE
Healing Time
1800
1600
1400
1200
1000
800
600
400
200
0
50
100
150
200
250
300
a / b (AREA = cte)

## Sherratt, Murray and Maggelakis's model for coupled wound closure and angiogenesis

### *The model*

During the angiogenesis we have the formation of new blood vessel to provide the wound area with oxygen and nutrients. This process is controlled by a negative feedback mechanism in which the low concentration of oxygen invokes the macrophages at the wound area and these ones issue some factors called macrophages-derived growth factors (MDGF) that cause the proliferation of new capillaries and the deposition of collagen. These new vessels increase the concentration of oxygen and bring it to the cells that are involved in the healing process in the wound area.
We can see that, in order to obtain a successful healing, the concentration of oxygen in the centre of the wound has to be low.
Our model is based on five coupled equations involving the oxygen concentration, the concentration of MGDF, the capillary density, the cell density and the chemical concentration. Each of these equations is a diffusion equation of this form:

*Rate of increase = Diffusion term+ Generation term – Natural loss term*

(except the equation for the capillaries that has not the natural loss term).

Equation for the oxygen concentration: $\frac{\partial c_0}{\partial t} = D_0 \nabla^2 c_0 + \lambda_{0,n} n - \lambda_0 c_0$

Equation for the MDGF: $\frac{\partial c_m}{\partial t} = D_m \nabla^2 c_m + \lambda_{m,0} Q\left(\frac{c_0}{c_\theta}\right) - \lambda_m c_m$

Equation for capillary density: $\frac{\partial n_c}{\partial t} = D_{n,c} \nabla^2 n_c + \lambda_n c_m n_c \left(1 - \frac{n_c}{n_c^0}\right)$

Equation for cell density: $\frac{\partial n}{\partial t} = D_n \nabla^2 n + k\phi_p\left(\frac{c_0}{c_0^0}\right)\hat{s}(c) n\left(2 - \frac{n}{n_0}\right) - kn$

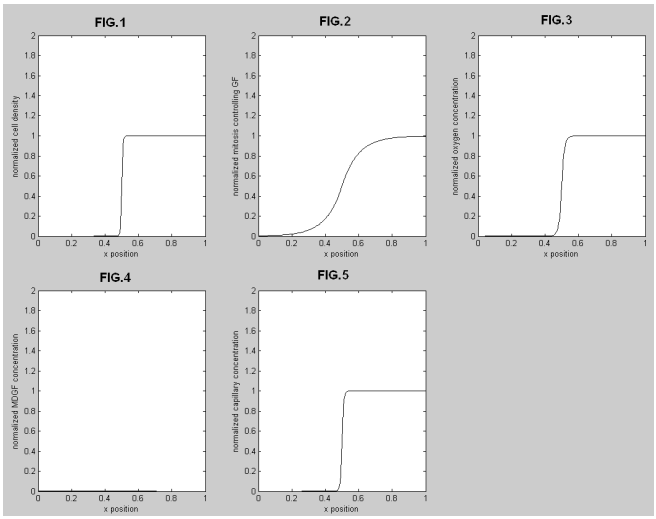
Equation for chemical concentration: $\frac{\partial c}{\partial t} = D_c \nabla^2 c + \lambda \phi_q\left(\frac{c_0}{c_0^0}\right)\hat{f}(n) - \lambda n$

We give now a brief description of the terms involved in these equations:

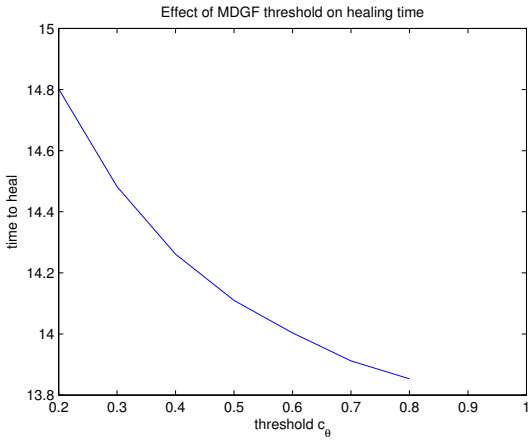
- Derivatives on the left hand reflect the increasing rate of oxygen, MDGF, capillary density, cells density and chemical concentration along the time, respectively
- $D_o$, $D_m$ , $D_{nc}$ , $D_n$ and $D_c$ are the diffusion terms
- $\lambda_{o,n}$ is the rate of oxygen supplied by capillaries
- $\lambda_o$ is the natural decay of oxygen
- The second term on the right hand in the second equation is the MDGF produced when oxygen is low (under the threshold $c_{\square}$)
- $\lambda_m$ is the natural decay of MDGF
- The last term on the right hand in the third equation is the logistic proliferation of capillaries in presence of MDGF
- S and f are the same functions explained in. Sherratt and Murray model for wound closure
- K and λ are again the inverse of cells and chemical life time coefficients
- $\phi_p$ is given by $\phi_i(x) = \frac{x^i}{(1-x)^i + x^i}, i \in \{p, q\}$ and indicates that the wound healing occurs only when oxygen is present, where $p$ and $q$ measure the sensitivity of cell function and chemical production to oxygen.

## ***Results***

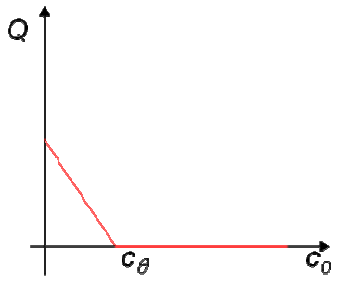
Next graphs are pictures extracted of a matlab movie which represents the solution of the previous equation along the time. It shows how the initial lack of oxygen (fig 3) at the center of the wound invokes the presence of MDGF (fig 4) that raises the capillary density (fig 5) in this zone, thus increasing the oxygen concentration at the center of the wound (again fig 3), resulting in the increase of cell density and chemical factors that regulate mitosis (fig 1 and 2).




Another important result is the influence of the threshold parameter $c_\theta$ on the healing time.




The graph reveals that increasing the threshold $c_\theta$ decreases the healing time, this happens because MDGF is closely related to the $c_\theta$. Indeed, the production of MDGF depends on $Q$, which has this form:




Therefore, if $c_\theta$ is close to zero there is no production of MDGF and healing will not succeed.

## Olsen's model for wound contraction

### *The model*

During the wound healing process, beside the tissue formation models that we have seen, wound contraction, a biomechanical phenomenon that draws the boundaries of the wound inward and consequently makes the wound size smaller, takes place. The wound contraction model according to Olsen's consists of fibroblasts and myofibroblasts that play important roles forming a network along with collagen fibers in the extracellular matrix (ECM). The forces exerting on this network would cause the contraction. During the angiogenesis, the growth factors chemotactically recruit fibroblasts into the wound from adjacent dermis and stimulate these cells to proliferate and to produce growth factors and ECM molecules. Some fibroblasts are also phenotypically converted into myofibroblasts which are contractile cells. While fibroblasts move throughout the wound tissue and exert traction forces on collagen fibers in the ECM, myofibroblasts form the myofibroblast/ECM network whose tension could be transmitted throughout the wound space.

In our model, fibroblasts density, myofibroblasts density, chemical concentration and collagen concentration are modeled based on the fundamental conservation law.

$$\frac{\partial Q}{\partial t} = -\nabla \cdot J_Q + f_Q$$

where $Q = Q(x,t)$ is a space-time dependent quantity, $J_Q$ is the flux of $Q$, $f_Q$ are the kinetic terms. So we have the following equations (the full description for the parameters other than $n$ ,$m$, $c$, $\rho$ could be found in L. Olsen et al. 1995, we will not concentrate on those parameters):

Equation for fibroblasts density: $n(\mathbf{x},t)$

$$\frac{\partial n}{\partial t} = \nabla \cdot \left[ D_n \nabla n - \frac{a_n}{(b_n + c)^2} n \nabla c - n \frac{\partial u}{\partial t} \right] + \left( r_n + \frac{r_{n_{\max}} c}{C_{1/2} + c} \right) n \left( 1 - \frac{n}{K} \right) - \frac{k_{1_{\max}} c}{C_k + c} n + k_2 m - d_n n$$

Equation for myofibroblasts density: $m(\mathbf{x},t)$

$$\frac{\partial m}{\partial t} = \nabla \cdot \left[ -m \frac{\partial u}{\partial t} \right] + \varepsilon_r \left( r_n + \frac{r_{n_{\max}} c}{C_{1/2} + c} \right) m \left( 1 - \frac{m}{K} \right) + \frac{k_{1_{\max}} c}{C_k + c} n + k_2 m - d_m m$$

Equation for chemical concentration: $c(\mathbf{x},t)$

$$\frac{\partial c}{\partial t} = \nabla \cdot \left[ D_c \nabla n - c \frac{\partial u}{\partial t} \right] + \frac{k_c (n + \zeta m)}{\Gamma + c} c - d_c c$$

Equation for collagen concentration: $\rho(\mathbf{x},t)$

$$\frac{\partial \rho}{\partial t} = \nabla \cdot \left[ -\rho \frac{\partial u}{\partial t} \right] + \left( r_\rho + \frac{r_{\rho_{\max}} c}{C_\rho + c} \right) \frac{n + \eta_b m}{R_\rho^2 + \rho^2} - d_\rho (n + \eta_d m) \rho$$

Then the mechanism of contraction is governed by the equation

$$\nabla \cdot (\sigma_{ecm} + \sigma_{cell}) = f_{ext}$$

where $\sigma_{ecm}$ represents ECM viscoelastic behaviour, $\sigma_{cell}$ is the cell traction and $f_{ext}$ are the anchoring. Based on this equation, the displacement could be computed by

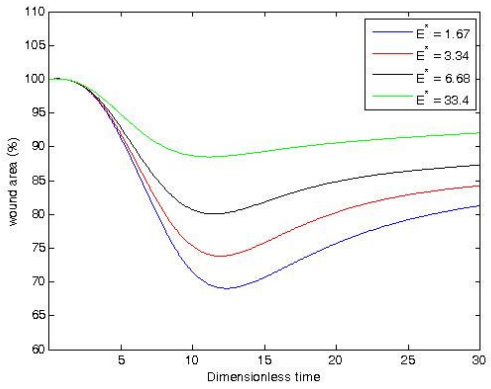
$$\nabla \cdot \left[ \mu_1 \frac{\partial \varepsilon}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} I + \frac{E}{1+\nu} \left( \varepsilon + \frac{\nu}{1-2\nu} \theta I \right) + \tau_0 (1 + \xi m) \frac{n\rho}{R_\tau^2 + \rho^2} I \right] = s \rho u$$

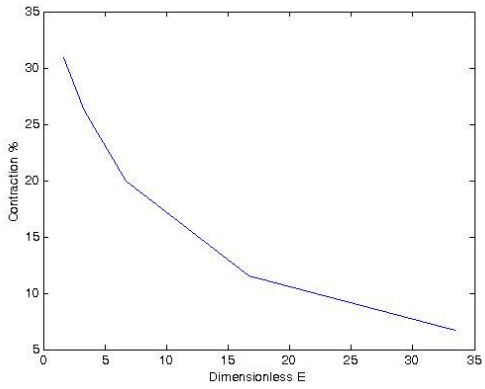
Here we would investigate the influences of three parameters, which are the undamaged skin Young´s modulus $E$, the traction force per cell per unit of collagen density $\tau_0$ and the dermis tethering factor $s$.

## ***Results***

The following results show the influences of the three parameters as we mentioned.

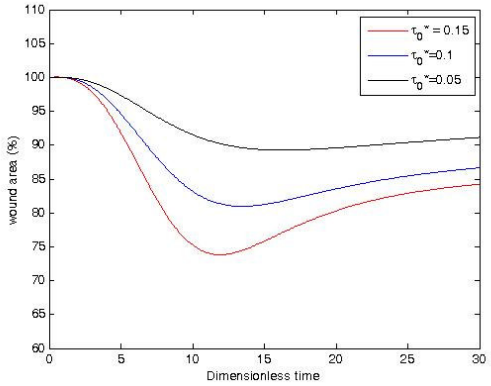
1. The influence of undamaged skin Young´s modulus $E$:

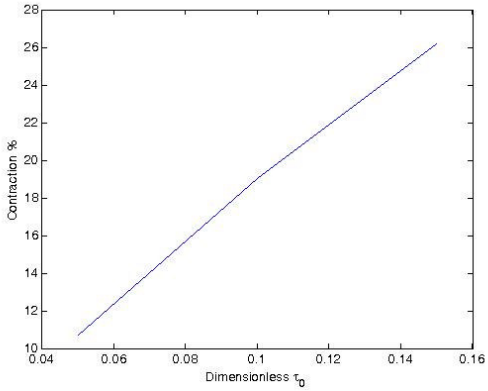


We can see that the stronger the Young's modulus, the less contraction, since the Young's modulus of the undamaged skin affect the forces that resist the contraction.
We also observed that the relationship between the percentage of contraction and the dimensionless E is faster than a linear decreasing.

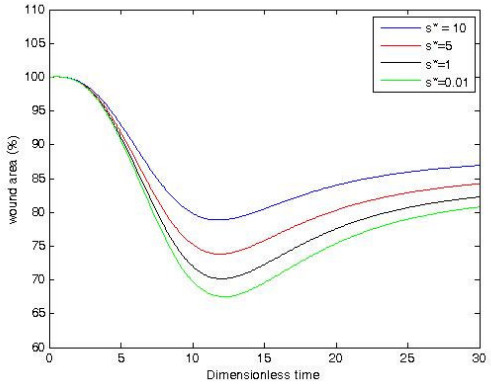
2. The influence of the traction force per cell per unit of collagen density $\tau_0$:

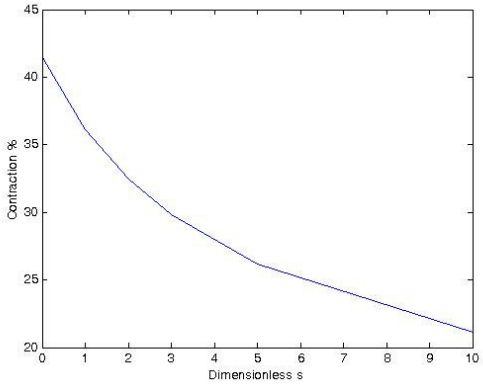



Here the percentage of contraction is proportional to the dimensionless $\tau_0$, since the more the traction force that the myofibroblasts could exert on the collagen, the more efficiently the wound is contracted by the cells.

3. The influence of the dermis tethering factor *s*:




The graphs show that the greater the s, the lower percentage of contraction. This is reasonable since the dermis tethering factor affects the deformability of the wound tissue: the more the tethering, the less deformability. The relationship between the percentage of contraction and the dermis tethering factor is non-linear.

## Conclusions

We'd like to underline the importance of wide applicability of these reaction-diffusion models. Even though the simplest model (model 1) gives a good approximation to the phenomenon which is being simulated, the consideration of additional factors in model 2 and 3 (oxygen concentration, blood vessels growth, differentiating of the types of cells involved in healing wound process, etc) provides a more realistic description of the process which is being simulated.

Particularly interesting are the simulations related to bi-dimensional wounds. It is clearly noticed how the wound decreases its space along the time as the cells cover it and multiply due to the mitosis controlled by chemical concentration. It is especially remarkable to see the influence of the wound geometry along the healing time, giving the expected result (closer wounds, with greater curvature take less time to close)

In our opinion, a natural extension of this analysis would be to consider the influence of the wound thickness or depth and to what extent its three-dimensional structure could have an effect on the healing wound process.