ISSN 0974 - 9373

Vol. 14 No.3 (2010) **Journal of International Academy of Physical Sciences** pp. 283-294

Mathematical Model for Wound Healing with Variable Death Rates of Macrophages and TGF-β Factor*

Madhu Jain and G. C. Sharma
Department of Mathematics, Institute of Basics Sciences, Khandari, Agra
E-mail: madhujain@sancharnet.in, gokulchandra@sancharnet.in

Ram Singh
Department of Mathematics, St. John's College, Agra
E-mail: Singh_ram83@yahoo.com

(Received February 20, 2010)

Abstract: Wound healing or healing of burn injuries are characterized by a chronic inflammation phase. The process of healing depends upon oxygen transport towards the wound sites and consequently on the distribution of macrophages phenotypes. This healing process becomes more complicated in a diabetic case in comparison to a normal wound healing. In this investigation, we develop a mathematical model; the governing equations involved are examined by using stability theory for the purpose of predicting the balance of macrophages phenotypes in diabetic wound healing. The model discusses key factors responsible for wound healing in diabetic case. Numerical experiment has been done to predict the effect of the proportion of monocytes that becomes inflammatory macrophages at wound site due to chemical reactions.
Keywords: Mathematical modeling, Wound healing, Macrophages, TGF-β, Diabetes, Stability analysis, Sensitivity analysis.

1. Introduction

Diabetes, also known diabetes mellitus, is the result of the destruction of the insulin producing pancreatic β-cells by the body's own immune system. The pathogenesis of diabetes in humans is difficult to study: currently there are no non-invasive methods to determine the amount of β-cells death in the pancreas; the clinical symptoms of diabetes are not obvious until most of the β-cells have been destroyed. The repairing of tissues is the process in which new tissues replace the damaged or infected ones. The developed model deals with the wound healing in diabetic patients.

*Presented at CONIAPS XI, University of Allahabad, Feb. 20-22, 2010.

A wound healing in diabetic person can take longer time in comparison to a non-diabetic person. When a wound takes place on the human body, some of the blood vessels around that site get cut down and supply of oxygen to that wound site becomes slow. The immune system is comprised of two sub systems, the innate and adaptive immune systems. The innate immune system is responsible for the early response to the infection. The innate immune system remains the same throughout an individual's life time, not improving with exposure to infection. An important cell type in the innate immune system is the macrophage, a large phagocytic cell that clears and digests intra-cellular debris as well as dead and dying cells.

The first stage of wound healing is inflammation stage and in this stage, macrophages are among the first cells that reach to wound site in response to transforming growth factor-β (TGF-β) released by platelets. These macrophages are nothing but differentiated monocytes. These monocytes become inflammatory macrophages, repair macrophages and cytocidal in the presence of different chemicals present at the wound site. The success of a wound healing depends upon the balance between inflammatory and repair macrophages population.

Many researchers have developed different mathematical models in different frameworks for wound healing. Sherrat and Murray[1] studied a mathematical model for the spread of cells across the surface of an epidermal wound. They also suggested that biochemical regulation of mitosis is fundamental to the process, and that a single chemical with a simple regulatory effect can account for the healing of circular epidermal wounds. The homeostasis of glucose, involving the secretion of its controlling hormone insulin by the pancreas in wound healing in diabetic case, has been the object of several mathematical models over the past thirty years[2]. Murray[3] developed a mathematical model to aid the understanding of how events in wound healing are orchestrated to result in wound contraction. Their model provides a predictive means for enhancing or mitigating as is appropriate for managing a particular wound. A reaction-diffusion model for the mechanism involved in the healing of corneal surface wounds was proposed by Dale[4]. The model also focuses on the stimulus for increased mitotic and migratory activity, specifically on the role of epidermal growth factor. A novel model of β -cell mass, insulin, and glucose dynamics, which consists of a system of three nonlinear ordinary differential equations, where glucose and insulin dynamics are fast relative to β -cell mass dynamics has been developed by Topp[5].

A mathematical model, which describes the control of the development and growth of a healing unit, was developed by Maggelakis[6]. Warrender[7] used mathematical modeling and simulation techniques to explore homeostasis of peripheral immune system effectors cells, particularly alveolar macrophages. They also introduced a multi-purpose simulator to study the individual cell responses to local molecular signals and their effects on the population dynamics. In literature several mathematical models of wound-healing have been reported based on the Fisher equation[8, 9, 10] which accounts for constant diffusive migration by random motility in one spatial dimension and proliferation to a carrying capacity, described by logistic growth. The factor that is responsible for the delay in wound healing and inability to provide oxygen to the affected areas has been discussed by Harrison[11]. Sherratt and Waugh[12] put forward a model which offers a possible explanation for diabetic wound healing in terms of the distribution of macrophages phenotypes being altered in the diabetic patient compared to normal wound repair. Watson[13] experimentally measured the depth of burn injuries by conducting an experiment on twenty-seven burn wounds by using an instrument named video microscopy. Denman[14] considered a mathematical model of migrating and proliferating cell type which converts to a quiescent cell type.

The ultradian oscillations of insulin concentration are associated to similar oscillations of the plasma glucose concentration, and they are best seen after meal ingestion, oral glucose intake, continuous enteral nutrition or intravenous glucose infusion[15]. Son[16] developed a model for β-Glucan, a heterogeneous group of glucose polymers, which modulates wound healing via macrophages and are stimulated to release growth factors and cytokines. Liu and Tang[17] proposed a mathematical control system for a simplified regulatory system of blood glucose by taking into account the dynamics of glucose and glycogen in liver and the dynamics of insulin and glucagon receptors at the molecular level.

The wound healing process in a diabetic patient involves cell's migration, mitosis and death. Earlier in this study the death rates were taken as constant linear functions[18]. In our investigation we have attempted to explain the healing process by taking death rates of three variables as exponentially decreasing with time delay, which is a realistic assumption. The rest of the paper is arranged as follows. By stating assumptions and notations, the model description has been given in section 2. Section 3 is devoted to the mathematical analysis of the model based on stability analysis. Numerical illustrations are provided in section 4. Finally, the conclusions are drawn in section 5.

2. Model Description

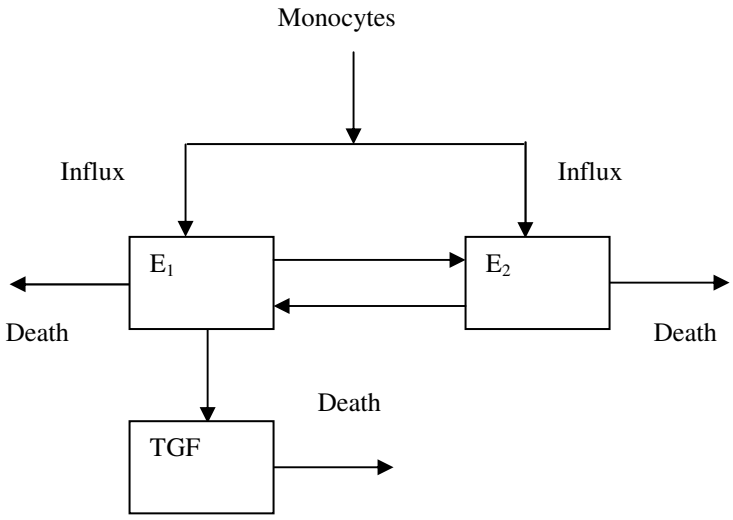


Fig. 1: Structure of the diabetic model.

In the investigation, we develop a mathematical model to predict the effect of monocytes that becomes inflammatory and repair macrophages. The dynamics of wound healing process in a diabetic patient is shown in fig. 1. The model comprises of the variables namely inflammatory macrophages, repair macrophages and transforming growth factor-β (TGF-β). The inflammatory macrophages and repair macrophages are produced by monocytes. The inflammatory macrophages further produce TGF-β cells. Cell populations undergo various stages mitotic division, mutual effects on each other and death process. The delay coupled differential equations have been constructed to explain the concept of wound healing in diabetic patients. In our model, we represent migration of inflammatory macrophages reaches to wound site with TGF-β with the help of function 'K (G)'. Finally the inflammatory macrophages die at the wound site by exponentially decreasing rate. The division of cells is represented by logistic term. The repair macrophages show somewhat similar character as inflammatory as they originated from monocytes. If 'α' is the fraction of monocytes that become inflammatory macrophages then it follows that (1 – α) is the monocyte fraction that becomes repair macrophages, as both macrophage originate from the same source. The cells TGF-β are produced by inflammatory macrophages at constant rate 'm_4' and decay with exponentially decreasing rate β. The idea of incorporation of delay time is

due to the fact that cells arrive at wound site do not die at once, they take some time to die. In the present model, the geometry of wound has not been taken into consideration.

Notations:

Followings are the notations, which are used to formulate the mathematical model:

E_1 Density of inflammatory macrophages population

E_2 Density of repair macrophages population

G Density of TGF-β

$K(G)$ Proportion of monocytes migration

α Proportion of monocytes that becomes inflammatory macrophage

d_1 Death rate of macrophages

d_2 Death rate of TGF-β

m_1 Proportion of monocytes undergoing mitotic division

m_2 Growth rate of macrophages

m_3 Proportion of effect of $E_1(t)$ on $E_2(t)$

m_4 Proportion of inflammatory macrophages that becomes TGF-β

ω Delay time between monocytes arrival

The differential equations governing the model along with relevant condition are as follows:

$$\frac{dE_1}{dt} = \alpha K(G) + m_1 m_2 E_1\left(1 - m_3\left(E_1 + E_2\right)\right) - E_1 d_1 e^{-d_1(t-\omega)} \tag{2.1}$$

$$\frac{dE_2}{dt} = (1-\alpha)K(G) + m_1 m_2 E_2\left(1 - m_3\left(E_1 + E_2\right)\right) - E_2 d_1 e^{-d_1(t-\omega)} \tag{2.2}$$

$$\frac{dG}{dt} = m_4 E_1 - G\, d_2 (1 - e^{-d_2(t-\omega)}) \tag{2.3}$$

The initial conditions are:

$$E_1(0) = E_{10} > 0, \quad E_2(0) = E_{20} > 0 \text{ and } G(0) = 0 \text{ at } t = 0 \tag{2.4}$$

3. The Analysis

In this section, the mathematical analysis based on population dynamics of the above model has been done. The analysis mainly involves equilibrium points and stability analysis as given below:

3.1 Equilibrium Points

To obtain the equilibrium points, we use equations (2.1)-(2.3).

(1) The equilibrium point $A_1(E_1, E_2, 0)$ is given by

$$E_1 = \frac{d_2 G}{m_4},\ E_2 = \frac{1}{m_3} - \frac{d_2 G}{m_4},\ K = 0$$

(2) The equilibrium point $A_2(E_1, E_2, K)$ is given by

$$E_1 = \frac{d_2 G}{m_4}, E_2 = \frac{(1-\alpha) d_2 G}{\alpha m_4},\ K = \frac{m_1 m_2 d_2 G}{\alpha m_4}\left(\frac{m_3 d_2 G}{\alpha m_4} - 1\right)$$

3.2 The Linear Stability Analysis

We linearize the system of differential equations (1)-(3) by taking followings transformations:

$$\text{(3.1)} \qquad \begin{cases} E_1(t) = E_1 + e_1(t) \\ E_2(t) = E_2 + e_2(t) \\ K(G) = K + k(G) \end{cases}$$

where

$e_1(t)$, $e_2(t)$ and $k(G)$ are small perturbations about the equilibrium points.

3.2.1. Stability analysis about equilibrium point $A_1(E_1, E_2, 0)$:

Using the above transformations given in equations (3.1), we linearize the non-linear system of equations (2.1)-(2.3) about equilibrium point $A_1(E_1, E_2, 0)$ as follows:

The Jacobian matrix J=$[j_{ik}]$ of the linearized system of equations (2.1)-(2.3) at the equilibrium point

$A_1(E_1, E_2, 0)$ is $J\left(\frac{d_2 G}{m_4}, \frac{1}{m_3} - \frac{d_2 G}{m_4}, 0\right)$

$$= \begin{bmatrix} m_1 m_2 m_3 \frac{d_2 G}{m_4} & -m_1 m_2 \frac{d_2 G}{m_4} & \alpha \\ -m_1 m_2 m_3 \left(\frac{1}{m_3} - \frac{d_2 G}{m_4}\right) & m_1 m_2 \left(1 - \frac{2}{m_3} - \frac{2 d_2 G}{m_4}(1 - m_3)\right) & (1-\alpha) \\ m_4 & 0 & -d_2 \end{bmatrix}$$

The characteristic equation about the equilibrium point $A_1(E_1, E_2, 0)$ is given by

$$|J - \lambda I| = 0$$

i.e.

(3.2) $$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

where

$$a_1 = d_2 - m_1m_2m_3\frac{d_2G}{m_4} - m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right) \Rightarrow a_1 > 0 \; if \; m_2 < 0,$$

$$a_2 = \left(m_1m_2m_3\frac{d_2G}{m_4}\right)\left(m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right)\right) - \left(m_1m_2\frac{d_2G}{m_4}\right)\left(m_1m_2m_3\left(\frac{1}{m_3}-\frac{d_2G}{m_4}\right)\right)$$

$$-d_2\left(\left(\left(m_1m_2m_3\frac{d_2G}{m_4}\right) - \left(\left(m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right)\right)\right)\right)\right) + \alpha m_4$$

$$\Rightarrow a_2 > 0 \; if \; m_1 < 0, \; m_4 < m_3$$

$$a_3 = m_4\left(-m_1m_2\frac{d_2G}{m_4}(1-\alpha) - \alpha\left(m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right)\right)\right)$$

$$+d_2\left\{\left(m_1m_2m_3\frac{d_2G}{m_4}\right)\left(m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right)\right)\right.$$

$$\left.-\left(m_1m_2\frac{d_2G}{m_4}\right)\left(m_1m_2m_3\left(\frac{1}{m_3}-\frac{d_2G}{m_4}\right)\right)\right\}$$

$$\Rightarrow a_3 > 0 \; if \; m_3 < 0$$

Then

$$a_1a_2 - a_3 =$$

$$\left(d_2 - m_1m_2m_3\frac{d_2G}{m_4}\right)\left(m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right)\right)$$

$$-m_4\left(-m_1m_2\frac{d_2G}{m_4}(1-\alpha) - \alpha\left(m_1m_2\left(1+2\left(\frac{d_2G}{m_4}(1+m_3)-\frac{1}{m_3}\right)\right)\right)\right)$$

$$-d_2\left\{\begin{array}{l}\left(m_1m_2m_3\dfrac{d_2G}{m_4}\right)\left(m_1m_2\left(1+2\left(\dfrac{d_2G}{m_4}(1+m_3)-\dfrac{1}{m_3}\right)\right)\right)\\ -\left(m_1m_2\dfrac{d_2G}{m_4}\right)\left(m_1m_2m_3\left(\dfrac{1}{m_3}-\dfrac{d_2G}{m_4}\right)\right)\end{array}\right\}>0$$

It follows from Routh-Hurwitz criteria that system under consideration, is locally asymptotically stable under the conditions stated above at the equilibrium point $A_1(E_1, E_2, 0)$ and unstable otherwise.

3.2.2. Stability analysis about the equilibrium point $A_2(E_1, E_2, K)$

Using the transformation given in equation (4), we obtain the linear system of differential equations corresponding to the non-linear system of differential equations (1)-(3) about the second equilibrium point $A_2(E_1(t), E_2(t), K(G))$ as follows:

$$\frac{de_1(t)}{dt}=\left(m_1m_2-m_1m_2m_3\left(\frac{2d_2G}{m_4}-\frac{(1-\alpha)d_2G}{\alpha m_4}\right)-d_1e^{-d_1(t-\omega)}\right)e_1(t)$$
$$-\left(m_1m_2m_3\frac{d_2G}{m_4}\right)e_2(t)+\alpha k(G) \tag{3.3}$$

$$\frac{de_2(t)}{dt}=\left(m_1m_2m_3\frac{(1-\alpha)d_2G}{\alpha m_4}\right)e_1(t)+\left(m_1m_2-m_1m_2m_3\left(\frac{d_2G}{m_4}-\frac{2(1-\alpha)d_2G}{\alpha m_4}\right)\right)e_2(t)$$
$$-\left(d_1e^{-d_1(t-\omega)}\right)e_2(t)+(1-\alpha)k(G)$$

$$\frac{dk(G)}{dt}=m_4e_1(t)-d_2e^{-d_2(t-\omega)}k(G) \tag{3.4}$$

The Jacobian matrix $J=[j_{ik}]$ of the linearization of equations at the equilibrium point $A_2(E_1, E_2, K(G))$ is obtained as:

$$J(E_1, E_2, K)=\begin{bmatrix}A & B & \alpha\\ C & D & (1-\alpha)\\ m_4 & 0 & H\end{bmatrix} \tag{3.5}$$

where $A=m_1m_2\left(1-\dfrac{m_3(3\alpha-1)d_2G}{m_4\alpha}\right)-d_2(1-d_2(t-\omega))$, $B=-m_1m_2m_3\dfrac{d_2G}{m_4}$

$$C = m_1 m_2 m_3 \frac{(\alpha - 1) d_2 G}{m_4 \alpha}, D = m_1 m_2 \left(1 - \frac{m_3 (2 - \alpha) d_2 G}{m_4 \alpha}\right) - d_1 \left(1 - d_1 (t - \omega)\right)$$

$$H = -d_2 \left(1 - d_2 (t - \omega)\right)$$

The characteristic equation $|J - \lambda I| = 0$ of the above Jacobian matrix (10) yields the characteristic polynomial

$$\lambda^3 + (-D - H - A)\lambda^2 + \left[(D + H)A + DH - BC - \alpha m_4\right]\lambda + \left[(-AD - BC)H - \alpha m_4 D\right] = 0$$

or

$$\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0$$

where

$$a_1 = -(D + H + A), \Rightarrow a_1 > 0 \quad if \quad D < 0, H < 0, A < 0.$$

$$a_2 = \left((D + H)A + DH - BC - \alpha m_4\right) \Rightarrow a_2 > 0$$

$$if \; D < 0, H < 0, A < 0, B < 0, \alpha < 0.$$

$$a_3 = -\left((AD + BC)H + \alpha m_4 D\right) \Rightarrow a_3 > 0 \; if \; C < 0, D < 0.$$

Then

$$a_1 a_2 - a_3 = -(D + H + A)\left((D + H)A + DH - BC - \alpha m_4\right) + \left((AD + BC)H + \alpha m_4 D\right) > 0.$$

It follows from Routh-Hurwitz criteria that system under consideration, is locally asymptotically stable under the conditions stated above and unstable otherwise.

4. Numerical Results

In order to validate the analytical results in our investigation, the sensitivity analysis has been performed to see the effects of variation of parameters on the disease. The numerical results are computed with the help of MATLAB software by fixing different parameters as:

$\alpha = 1$, $d_1 = 0.20$, $d_2 = 5.1$, $m_3 = 0.02$, $m_4 = 0.07$, $\omega = 1.5$.

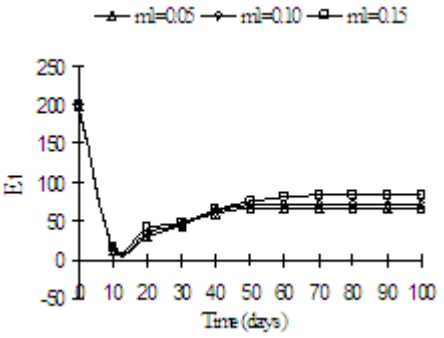
The numerical results have been displayed in figs 2(a-c)-3(a-c). The concentration of three different cells inflammatory macrophages, repair macrophages and TGF factors against the levels of time (t) for different values of 'm_1' has been plotted in figs 2(a-c). From fig. 2(a), it has been observed that the concentration of inflammatory cells initially decreases sharply to a certain level up to near t = 10 and then after it gradually increases but later on attain somewhat constant value with time. Initial sharp decrease may be due to delay time that cells take to reach to wound site. Fig.

2(b) depicts the profile levels of repair macrophages. In this fig., we notice that concentration of cell population slightly decreases initially but there has been an abrupt change in the form of sharp increase in it and reaches up to t = 50 and after that it remains almost constant. The profile shown in fig. 2(c) exhibits the variation of TGF factor against time, it has been seen that in the beginning it remains at very low concentration up to t = 20due to delay production of it from macrophages but at later stage, its concentration significantly increases to wound site which helps in healing.

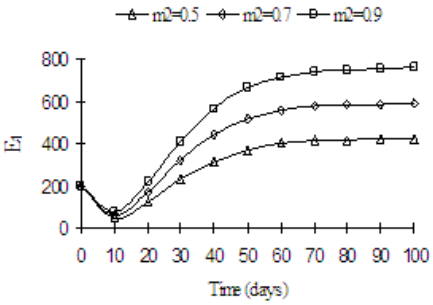
Figs 3(a-c) demonstrate the profiles of the concentration of different cells for different values of 'm_2'. It is noticed from figs 3(a) and 3(b) that the concentration of inflammatory macrophages and TGF factor increase with the increase in the values of 'm_2'. However the concentration of repair macrophages decreases with the increase in the values of 'm_2' as clear from fig. 3(b). As time grows the concentrations of both inflammatory macrophages as well as repair macrophages increase. Based on numerical result, overall, it has been concluded that the factor time delay has been playing a significant role in the healing process.

5. Conclusions

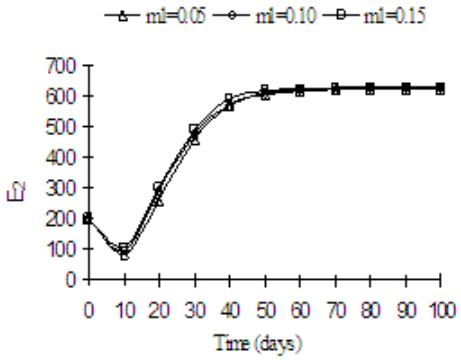
In this investigation, a mathematical model for wound healing in diabetic patients has been developed to understand the mechanism of wound healing process in diabetic cases. We have examined the behavior of the macrophages (inflammatory as well as repair) and transforming growth factor in the wound healing process. The stability analysis provides two equilibrium points: $A_1(E_{1,}E_{2,}0)$ and $A_2(E_1, E_2, K)$. In first point, $K = 0$ which means that there is no migration of TGF factors at wound site at all, which is not possible and this point in our model is unstable. In the second equilibrium point $A_2(E_1, E_2, K)$, 'K' has some definite value showing the cell migration at wound site. Furthermore its stability predicts that the wound healing depends on the migration of TGF factors. The model also reveals that there is an excess of TGF-β in the wound environment, which in turn attracts more monocytes to the wound site, leading to a higher level of inflammatory macrophages. These cells produce more TGF-β, perpetuating this vicious circle of events. The numerical results obtained demonstrate that the density of inflammatory and repair macrophages remain constant with time when the treatment is not provided to the patient. It has also been clear from numerical results that the density of inflammatory and repair macrophages increases with time when the value of mitotic division decreases.



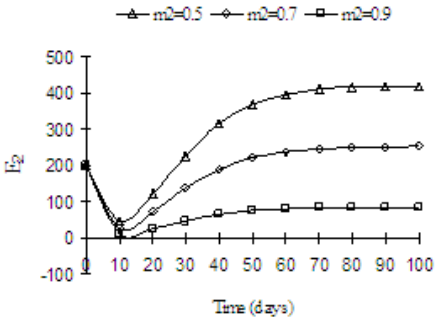
2(a)



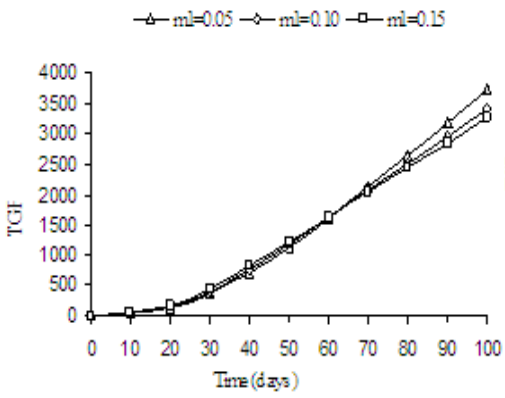
3(a)



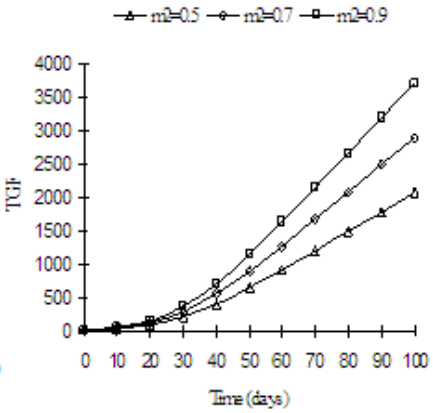
2(b)



3(b)



2(c)



3(c)

Fig. 2: Concentration profile of (a) E_1 (b) E_2 (c) TGF for different value m_1.

Figs 3: Concentration profile of (a) E_1 (b) E_2 (c) TGF for different values m_2.

References

1. J. A. Sherratt and J. D. Murray, Models of epidermal wound healing, *Proc. R. Soc. London*, **241 (B)** (1990) 29-36.

2. G. S. Rao, J. S. Bajaj and J. S. Rao, A Mathematical Model for Insulin Kinetics II. Extension of the model to include response to oral glucose administration and application to insulin-dependent diabetes mellitus (IDDM), *J. Theo. Biol*., **142**(1990) 473-483.
3. J. D. Murray and R. T. Tranquillo, Continumm model of fibroblast-driven wound contraction: Inflammation-mediation, *J. Theo. Biol.,* **158** (1992) 135-172.
4. P. D. Dale, J. A. Sherratt and P. K. Maini, The speed of corneal epithelial wound healing, *App. Math. Lett.,* **7** (1994) 11-14.
5. B. Topp, K. Promislow, G. Devries, R. M. Miura and D. T. Finegood, A model of β -Cell mass, insulin, and glucose kinetics: Pathways to diabetes, *J. Theo. Biol*., **206(4)** (2000) 605-619.
6. S. A. Maggelakis, A mathematical model of tissue replacement during epidermal wound healing, *App. Math. Mod*., **27(3)** (2003) 189-196.
7. C. Warrender, S. Forrest and L. Segel, Homeostasis of peripheral immune effectors, *Bull. Math. Biol*., **66** (2004) 1493-1514.
8. P. K. Maini, D. L. S. McElwain and D. Leavesley, Travelling waves in a wound healing assay, *Appl. Math. Lett.,* **17(a)** (2004) 575–580.
9. P. K. Maini, D. L. S. McElwain and D. Leavesley, Travelling wave model to interpret a wound-healing cell migration assay for human peritoneal mesothelial cells, *Tissue Eng.,* **10(b)** (2004) 475–482.
10. U. Savla, L. E. Olson and C. M. Waters, Mathematical modeling of airway epithelial wound closure, *J. Appl. Physiol*., **96** (2004) 566–574.
11. B. S. Harrison, D. Eberil, S. J. Lee, A. Atala and J. J. Yoo, Oxygen producing biomaterials for tissue regeneration, *Biomaterials*, **28**(2007) 4628-4634.
12. H. V. Waugh and J. A. Sherratt, Modeling the effects of treating diabetic wounds with engineered skin substitutes, *W. Rep. Reg.,* **15** (2007) 556-565.
13. S. B. Watson, D. J. McGill, K. Sørensen, I. R. Mackay and I. Taggart, Assessment of burn depth: A prospective, blinded comparison of laser Doppler imaging and video microscopy, *Burn*, **33**(2007) 833-842.
14. P. K. Denman, D. L. S. McElwain and J. Norbury, Analysis of travelling waves associated with the modeling of aerosolised skin grafts, *Bull. Math. Biol*., **69** (2007) 495–523.
15. H. Wang, J. Li and Y. Kuang, Mathematical modeling and qualitative analysis of insulin therapies, *Math. Biosci*., **210(1)** (2007) 17-33.
16. J. H. Son, D. W. Han, H. S. Baek, H. R. Lim, M. H. Lee, Y. I. Woo and J. C. Park, Stimulated TNF-α release in macrophages and enhanced migration of dermal fibroblast by β-glucan, Curr., *App. Phy.,* **7** (2007) e33-e36.
17. W. Liu and F. Tang, Modeling a simplified regulatory system of blood glucose at molecular levels, *J. Theo. Biol*., **252(4)** (2008) 608-620.
18. H. V. Waugh and J. A. Sherratt, Macrophages dynamics in diabetic wound healing, *Bull. Math. Biol*., **68** (2006) 197-207.