Review article **Allied sciences**

International Journal of Pharma and Bio Sciences

ISSN
0975-6299

AN INVESTIGATION OF MATHEMATICAL MODELS OF DIFFERENT DYNAMICS INVOLVED IN WOUND HEALING PROCESS

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ABSTRACT

Human is the most significant creature on the earth having various complex biological structures. Skin the foremost and important organ of the body with many different functions has always been a center of attraction for a medical scientist. Almost all the functions of the body are managed by the skin. Any disturbance in the body may cause various disturbances in the body. Therefore any wound and its related problems cannot be ignored. Mathematical models of wound healing play an important role to study various complications in biological phenomenon.Theoretical models and wound healing has a close relation to understand whole phenomena of the healing process and activities involved in. Experiments have their limitations on a human being or live organs. Mathematical Models on the basis of experimental facts and figures are competent to obtain results by changing best possible factors without experimental work. The present paper is a review paper on the work done by the researchers. Various mathematical models for the internal and external factors involved in the healing process are discussed. At the end gaps are discussed briefly.

KEYWORDS: ***Mathematical Modelling, Wound Healing, Fibroblast, Temperature***

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Received on: 12.10.2016
Revised and Accepted on : 21-03-2017
DOI: http://dx.doi.org/10.22376/ijpbs.2017.8.2.b484-489

INTRODUCTION

Wound healing has always been a matter of discussion for researchers, medical personnel and clinical trials. Wound healing depends on the health, physiological and pathophysiological condition of the victim. Every human being has a different anatomy[1]. The rate of wound healing is described using the measurement of wound area covered over the time[2]. During the healing process measurement is through by observing wound area. During this process measurement of wound depth and volumes are neglected. These two parameters are rarely measured due to the complex geometry of the wound. The effect of these parameters can be calculated theoretically with the help of suitable Mathematical Model[3]. It is very important to know the anatomy and physiology of wound healing process and factors involved in it before the development of Mathematical Models.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF HUMAN BEING

Humans are able to regulate an average and relatively constant body temperature of 37 °C (±0.5 oC). Temperature variation depends on individual, day timings, the stage of sleep, and various internal changes. Balance in thermoregulation occurs due to production and heat loss mechanisms. The Skin is the most important organ of the human body to regulate the body core temperature [4]. The SST region (skin and subcutaneous region) is structurally divided into three sub-layers viz. epidermis, dermis and hypodermis or subcutaneous layer. The outermost Epidermis layer contains five sub-layers and a network of nerves and no blood vessels. It is nourished by diffusion from the dermis layer. This layer regulates the rate of evaporation which helps in keeping water in the body and taking out the harmful chemicals and pathogens from the skin surface. The dermis lies below the epidermis, contains a number of structures including blood vessels, nerves, hair follicles, smooth muscle, glands and lymphatic tissue, sweat and oil glands, sensory receptors, nerves, blood vessels and hair follicles. The Subcutaneous layer found below the dermis layer. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. The hypodermis has the capacity to contain 50% of body fat. Fat serves as padding and insulation for the body[5].

THE WOUND: PHYSIOLOGY OF WOUND HEALING PROCESS

Any injury accidental or surgical, a split in the epithelial integrity of the skin and punctures of the epidermis, dermis, subcutaneous tissues, fascia, muscles or even bone is known as a wound[6]. Wound healing or wound repair is the body's natural process of regenerating dermal and epidermal tissue. The epidermis (outermost layer) and dermis (inner or deeper layer) exist in steady-state equilibrium; form a protective barrier against the external environment. Once the protective barrier is broken i.e. wound appears. The normal physiologic process of wound healing immediately starts automatically. The entire wound healing process is a set of complex biochemical events and that begins at the moment of injury and can continue for months to years to repair the damaged tissues immediately after the wounding. Successful wound healing requires adequate blood and nutrients to be supplied to the site of damage. The overall health and nutritional status of the patient also influence the outcome of the damaged tissue[5]. There are three phases of wound healing. Each phase is complex, distinct, continuous and overlapping the next [Fig.1 & Fig.2].

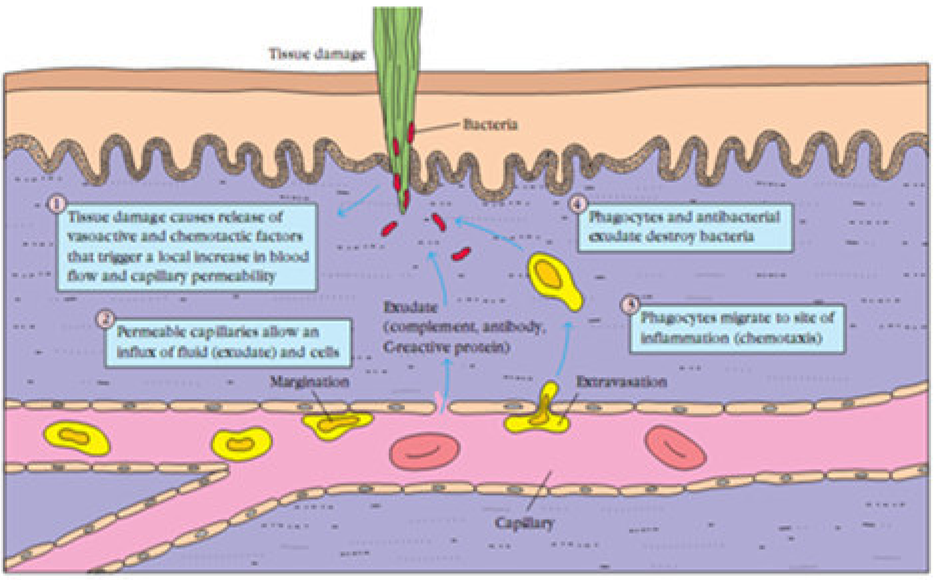

Figure 1
Major biological events take place immediate after wound[25]

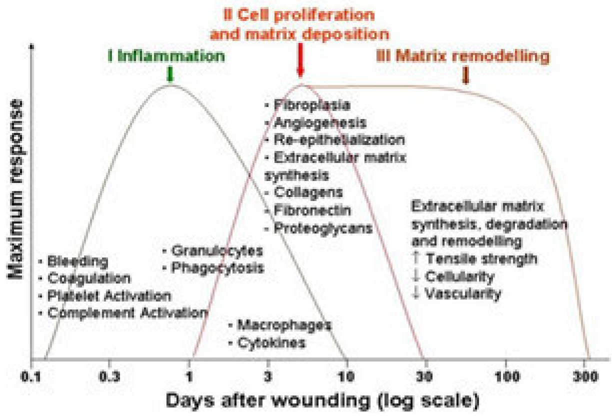

Figure 2
The phases of wound healing process[26]

It is clear from the above figures the healing process is a very complex phenomena and various biological events are involved in it. Several internal and external factors are also responsible for the entire process. In internal factors, the health of the patient, metabolism, blood mass flow rate, tissue density, rate of growth factor etc. and in external factors, surrounding temperature of the wound, the temperature of cleansing material[7], climate, wound bed temperature etc. play an important role in timely healing.

MATHEMATICAL MODELS AND ITS IMPORTANCE IN THE HEALING PROCESS

A theoretical model has a great impact on the complex biology of the wound. Various models of different phases and factors affecting healing process have been developed by researchers time to time.

MODEL 1: A MATHEMATICAL MODEL OF WOUND HEALING AND SUBSEQUENT SCARRING

Tranquillo R. T., Murray J. M. (1992), developed a simple mechanical model of cell traction in wound area by using the partial differential equations. They compared the obtained results with the experiments on rats by McGrath M. H., Simon R. H. (1983). The gaps in the model were identified and studied by Olsen L. Sherratt J. A. et al. (1998). Their study was based on the role of Fibroblast during the healing process. B. D. Cumming (2009) introduced cell model, chemical species model and a six species wound healing model etc. for subsequent scarring.

MODEL 2:A MATHEMATICAL MODEL CELL MATRIX INTERACTION AND ROLE OF FIBROBLAST

Luke Olsen et al. and P. K. Maini and L. Olsen have published various papers on Fibroblast and Extra Cellular Matrix, which are the essential part of the healing process. They focused on the scar formation prediction. In this paper, authors assumed that the movement of fibroblast in 2D and ECM as a continuous variable with the physical properties of collagen fibers, fibroblast cell etc. A macho-chemical model was presented by P. K. MAINI and L. OLSEN (2009) with the help of partial differential equations. Further, they stated that a generic growth factor, concentration c, and ECM, density ρ obey the general conservation equation

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

Where Q is the quantity, the first term on the right-hand side models with the flux J_Q and the second term models production and degradation. They also introduced the fibroblast cell equation by partial differential equations with suitable initial and boundary conditions. The models capture key features of wound contraction, fibroproliferative diseases, wound angiogenesis with clinically testable predictions and treatments.

MODEL 3: MATHEMATICAL MODELS FOR THE GROWTH FACTORS INVOLVED DURING THE HEALING PROCESS

Dallon J. C., Sherratt J. A., Maini P. K. (2001), Wearing H.J., Sherratt J.A. (2002), (Sherratt & Murray, 1991) studied and introduced the model to study the role of growth factors and cytokines. Working of growth factors depends on upon the health of the wounded person. Various growth factors like Platelet Derived Growth Factor (PDGFS), Fibroblast Growth Factors (FGFs) and Granulocyte Macrophage Colony Simulation Factor (GM-CSF) have an important effect on wound healing process (Greenhalgh D.G., 1996). (Vermolen et al., 2006) studied a model, which described the role of the concentration of growth factor at the wound age by suitable partial differential equation

$$\frac{\partial c}{\partial t} - D\,div(grad\,c) + \lambda c = Pf(x,y) \quad for \quad x,y \in \Omega \qquad (1)$$
$$c(x,y) = 0 \quad for \quad (x,y) \in \Gamma \qquad (2)$$
Further
$$F(x,y) = \begin{cases} 1 \; for \;\; x,y \in \Omega 2 \\ 0 \;\; for \;\; x,y \in \Omega 1 \cap \Omega 3 \end{cases} \qquad (3)$$

Where $\Omega 1$, $\Omega 2$ and $\Omega 3$ denote wound itself, active layer and the outer tissue respectively. Boundaries of the domain Γ, D, P and λ are the constant diffusion coefficient, production rate coefficient and delay coefficient of the growth factors. The second and the third term of the equation (1) are growth factor transport and growth factor loss respectively whereas RHS term is for the production of Growth Factor. The model is very useful to predict the healing process on the basis of growth factor concentration for the irregularly shaped wound.

MODEL 4: MATHEMATICAL MODELS FOR EPIDERMAL WOUND

(Sherratt & Murray, 1991) introduced a model of epidermal wound healing. Epidermal wounds are very shallow wound (no bleeding). Healing occurs due to cell movement and increases cell division near the wound edge. The model described as

The rate of increase of cell density = cell movement + Cell Division -Cell Death ….(A)

The equations deal with conservation equation for cell density (n) per unit area. Above equation is helpful to calculate; (i) the relation between relative wound radius vs time (%), (ii) cell density (n) and radius of the wound. But this model was failed to determine results for nonlinear diffusion. Further, they introduced an improved model as follows:

Rate of increase of cell density = cell migration + Mitotic Generation-Natural Death….(B)
Rate of increase of chemical concentration = Diffusion + Production of Cells - Decay of active chemical ……(C)

Mathematically,

$$\frac{\partial n}{\partial t} = D\nabla^2 n + S(c).n.(2-(n/n_0)) - Kn \qquad (B)$$
$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + f(n) - \lambda c \qquad (C)$$

Where, D and D_c are diffusion coefficients for the cell and chemical, n is density per unit area of the mitosis regulating the chemical. n_0 is unwounded cell density. K and λ are positive constant and f(n) is a function of density per unit area of the mitosis. The model deals with the results were obtained for the qualitative form of the function f(n) with the rate of chemical production by the epidermal cell. This model shows the relation between the n and f(n) in terms of rate of chemical production by epidermal cells. This model is very helpful to get the relation between the parameters used in the equations.

MODEL 5: MATHEMATICAL MODEL TO STUDY TISSUE TEMPERATURE OF HUMAN BEING DURING WOUND HEALING

Apart from internal factors, some external factors also play an important role in in healing process. Health and recovery of the wound depend on upon the (i) quality of the dressing material (ii) wound bed temperature (iii) atmospheric temperature (iv) temperature of the cleansing solution etc. Various works have been done in this regard. M. Jain and M. Shakya (2011) studied the temperature distribution in human peripheral tissues during the wound healing process and the obtained results were validated the experimental work done by the E. Villa and (2004) and R. Gannon (2009). Bio-heat equations with suitable conditions were used for the study.

$$Div(K\,grad\,T) + m_b c_b (T_b - T) + S = \rho c \frac{\partial T}{\partial t}$$

Where the effect of metabolic heat generation and blood mass flow are given by the terms S and $m_b c_b(T_b - T)$ respectively. T_b, K, ρ, c, m_b, and c_b are body core temperature, thermal conductivity, density and specific heat of tissue, blood mass flow rate and specific heat of blood respectively.

BOUNDARY CONDITIONS: AT THE OUTER SURFACE

The outer surface of the body is exposed to the environment; heat loss at this surface takes place due to conduction, convection, radiation and evaporation. Therefore, net flux calculated at the normal to the skin surface (A. Jennifer et al., 2009), is

$$-K\frac{\partial T}{\partial n} = h(T - T_a) + LE \quad for \quad t > 0$$

Where h, T_a, L, E, and $\partial T/\partial n$, are heat transfer coefficient, atmospheric temperature, the latent heat, rate of evaporation and the partial derivatives of T along the normal to the skin surface respectively.

AT THE INNER SURFACE

Human body maintains its body core temperature at 37°C, therefore, the boundary condition at inner boundary is

$$T(X,t) = T_h \;\; for \;\; t \geq 0;\; X = (x, y, z)$$

INITIAL CONDITION

The outer surface of the skin is assumed to be insulated at time t=0 hence the initial condition is given by

$$T(\mathrm{X}, 0) = T_b;\;\; \mathrm{X} = (x, y, z)$$

The Model 5, was based on the fact that the basic physiological functioning of normal and wounded tissues during having different from each other. The values of physiological parameters are negligible in tissues just after the wound [19]. With the increase in time, these values will also increase thus the body temperature [20-21]. Experimental studies suggested that wounds heal most effectively at normal core temperature (37°C). Wound healing is delayed when the temperature falls below normal body core temperature or rise above 42°C. A delayed or poorly healing wound may have decreased tensile strength or low collagen accumulation but may eventually heal to normal. Delayed wound healing, especially in the context of stress-induced immune suppression may result in increased infection, scarring, poor esthetic outcome, and poor regenerative potential. In wound healing process, wound bed preparation is the important phase because it creates an optimal wound-healing environment. The body core, skin and ambient temperature play important roles in the preparation of wound bed. The wound bed temperature can be controlled by proper cleansing and dressing of wound time to time. Among the various objectives of wound healing management, the following are very important aspects which have been ignored earlier[22].

- To examine the wound bed temperature reduction resulting from cleansing during dressing changes.
- To examine the association between the time taken to cleanse a wound and the degree of temperature loss.
- To measure the time taken for the wound temperature to return to the pre-procedural temperature.
- The temperature of wound bed can be controlled by proper dressing materials and appropriate temperature of cleansing solution[7,18]. During and after wound dressing following measurements are very important
- Ambient (atmospheric) temperature
- Temperature of the outside of the dressing material (before removal)
- Wound bed temperature immediately after dressing removal
- Wound bed temperature at the completion of cleansing

The role of evaporation has a great importance during the process of healing. Experimentally it is proved that proper wound dressing for an adequate rate of evaporation is very important. The rate of evaporation neither be more nor be less. Both the cases are not suitable for the acute wound because if the rate of evaporation after dressing change is more wound will dry and with less evaporation it will remain wet all the time causing fungal and other infections. Therefore, maintaining a physiological moist environment in treating a wound is important[22-24]. The various temperatures play a significant role in wound healing process. Any disturbance in temperature affects the functioning of enzymes, growth factors and ultimately wound bed temperature[7]. This disturbance may be due to the varying atmospheric temperature, rates of evaporation or cleansing solution temperature.

RESULT AND DISCUSSION

Though wound healing process is well-researched, this area is poorly known. The reason is that all interactions during the healing have not been revealed, as cells interact in a very complicated manner with nonlinear feedback. Such complex feedback mechanisms can be easily addressed by mathematical modeling. The present paper is a review of the mathematical modeling of wound healing process and the role of growth factors, extracellular matrix and fibroblast components and temperature regulation of human tissues during the process of epidermal wound healing. All the models are of partial differential equation type and solved numerical Techniques. Model 1 was a simple mechanical model of cell traction. This model was further refined by B. D. Cumming (2009) for chemical species model and a six species wound healing model etc. for subsequent scarring. In Model 2, K. Maini and L. Olsen (2009), introduced the fibroblast cell equation by using partial differential equations with suitable initial and boundary conditions. The model is used for the predictions and treatments of the complexities during the healing process. Model 3, explains the role of growth factors. They concluded that for timely healing, the functioning of growth factor plays an important role. Model 4 describes the rate of increase of cell density and rate of increase of chemical during the process. Model 5 was developed for the analysis of tissue temperature during the healing process. The result of model 5 had been validated with the conclusion given by E. Villa and Gannon[7,18]. The purpose of the review is to put together all the mathematical models developed by researchers time to time. This effort has been made so that researchers may get the information of few mathematical models with respect to the activities and factors involved in the wound healing process. Mathematical biology is a multi-disciplinary academic research field having a variety of application in biology, medicine, and biotechnology. It helps in the mathematical representation, treatment, and modeling of the biological process with mathematical techniques and tools. Mathematical Biology has a great significance in biological and biotechnology research. In today's era biomedical industry is playing an important role in manufacturing biomedical equipment. These equipment are useful for diagnosis and treatment of various diseases. For this, they need different information including physical and physiological parameters of human beings. This study is helpful in the treatment of various diseases, to develop protocols for medical purpose and for evaluation of the effectiveness of hyperthermic treatments. This will help to convert the biological data to understand the physiology and pathophysiology of a biological process.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Sherratt JA, and Murray JD, Mathematical Analysis of a Basic Model for Epidermal Wound Healing, Journal of Mathematical Biology, 1991, 29(5): 389-404.
2. Adam JA, Vermolen FJ, and Barren EV, A Simplified Model for Growth Factor-Induced Healing of Wounds, Mathematical and Computer Modelling, 2006, 44(9): 887–898.
3. Chang AC, Dearman B, Greenwood JE, A Comparison of Wound Area Measurement Techniques: Visitrak Versus Photography. Eplasty. 2011, 11:e18.
4. Guyton AC, Textbook of Medical Physiology, W. B. Saunders Company. ISBN 0-7216-0240-1.
5. Midwood KS, Williams LV and Schwarzbauer JE, Tissue Repair and the Dynamics of the Extracellular Matrix, The International Journal of Biochemistry & Cell Biology, 2004 36(6): 1031–1037
6. MacLellan DG, Chronic Wound management, Professor of Surgery, Canberra Hospital, Canberra.
7. Vella E, Harrison D., McGuiness W., Influence of Dressing Changes on Wound Temperature, Journal of Wound Care, 2004, 13(9): 383 – 385
8. Tranquillo RT., Murray JM., Continuum Model of Fibroblast-Driven Wound Contraction: Inflammation-Mediation. J. Theor. Biol., 1992, 158(2), 135–172.
9. McGrath MH., Simon RH., Wound Geometry And The Kinetics Of Contraction. Plast. Reconstruction. Surg. 1983,72(1); 66–72.
10. Olsen L., Maini PK., Dallon JC., Sherratt JA. Mathematical Modeling Of Anisotropy In Fibrous Connective Tissue, Math. Biosci., 1998, 158(99), 145–170.
11. Cumming BD., D. L. S. Mc. Elwain, Z. Upton A Mathematical Model of Wound Healing And Subsequent Scarring, Journal of The Royal Society Interface. 2010, 7(42); 19-34.
12. Luke Olsen, Philip K. Maini, Jonathan A. Sherratt, and Ben Marchant Simple Modelling of Extracellular Matrix Alignment in Dermal Wound Healing I. Cell Flux Induced Alignment, Journal of Theoretical Medicine. 1998; 1(3), 175 – 192.
13. Maini PK and Olsen L., International Journal of Bifurcation and Chaos, 2002, 12(9),: 2021-2029.
14. Dallon JC., Sherratt JA., Maini PK. Modeling The Effects Of Transforming Growth Factor-B On Extracellular Matrix Alignment In Dermal Wound Repair. Wound Repair Regen. 9, 2001: 278–286.
15. Wearing HJ and Sherratt JA, Keratinocyte Growth Factor Signalling: A Mathematical Model of Dermal-Epidermal Interaction In Epidermal Wound Healing. Mathematical Biosciences, 2000, 165(1):41-62.
16. Greenhalgh DG, The Role of Growth Factors In Wound Healing. J Trauma. 1996, 41(1): 159–167.
17. Jain M. and Shakya M., An Infinite Element Model to Study Temperature Variations during Wound Healing Process After Plastic Surgery. Infinite Dimensional Analysis, Quantum Probability and Related Topics, 2011, 14(2), 209-224.
18. Gannon R., Wound Cleansing: Sterile Water or Saline?, Nurse Times, 2007, 103(9):44-6.
19. Vincent Falanga, E-Book on Cutaneous Wound Healing, Martin Dunitz.
20. Brattgard SO and Severinsson K., Investigations of Pressure, Temperature and Humidity in the Sitting Area in a Wheelchair. In: Asmussen E, Jorgensen K, Editors. Biomechanics VI-B. Baltimore: University Park Press, 1978, 270-3.
21. Mahanty SD. Roemer RB., Thermal Response of Skin to the Application of Localized Pressure. Arch Phys Med Rehabil, 1980, 60(12): 584-90.
22. Wang Cheng-Chuan, Zhi-Biao PU, Hong-Bin LIU et al., Experimental Study on Maintaining Physiological Moist Effect of Moist Exposed Burn Therapy/Moist Exposed Burn Ointment on Treating Burn Wound, The Chinese journal of burns wounds & surface ulcers, 1998, 10(4): 18-20.
23. G. Kammerlander, A. Andriessen, P. Asmussen, Role of the Wet-to-Dry Phase of Cleansing in Preparing the Chronic Wound Bed for Dressing Application, Journal of Wound Care, 2005, 13:1-5.
24. Wang Cheng-Chuan, Zhi-Biao PU, Hong-bin LIU et al., Experimental Study on Moist Burn Therapy/Moist Exposed Burn Ointment on Burn Wound Water Evaporation, The Chinese journal of burns wounds & surface ulcers, 1999,11(1): 1-3.
25. J. Pfeiffer, (1954), Enzymes, the Physics and Chemistry of Life, Simon and Schuster, NY, 171-173.
26. R. Martinek, (1969), Practical Clinical Enzymology, J. Am. Med. Tech., 31: 162.

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We sincerely thank the above reviewers for peer reviewing the manuscript