MATHEMATICAL MODELS OF WOUND HEALING- AN IMPORTANT BENEFACTION TO MEDICAL SCIENCE

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ABSTRACT

The processes of wound healing, bone regeneration, and problems in tissue engineering have been a dynamic area for mathematical modeling from the last decay. The present model is an application to aim strategies for improved healing presented. In wound healing, the models have particularly focused on the different response in order to improve the healing of the chronic wound. The mathematical models have been applied to design optimal and new treatment strategies for normal and abnormal healing. For the field of tissue engineering, the author focuses on mathematical models that analyse the interplay between cells and their biochemical cues to ensure optimal nutrient transport and maximal tissue growth. Finally, a brief comment on numerical issues arising from simulations of these mathematical models is presented.

Key words: Tissue Engineering, Wound Healing, Numerical Methods, Mathematical Models.

INTRODUCTION:

Mathematics has a great history as a tool for biologists, plays an essential role in understanding biological systems on many different scales like size and time. Biomathematics encompasses the application of mathematical methods to the study of living organisms. Mathematical models not only explain the physiology of human beings but it is very helpful to understand the theoretical aspects. Various mathematical models have been developed by researchers time to time. It is very necessary to understand the all essential factors involved in the process to develop its mathematical model. Present study deals with mathematical model of wound healing. So it is essential to know the facts of healing process.

Skin is the largest organ of the integumentary system plays an important role to maintain the body core temperature (Tb) at 37°C. Any disturbance in the temperature regulation may cause lots of abnormality in the body. Humans are homeotherms, able to maintain an average, relatively constant body temperature of 37 ^{o}C (±0.5 ^{o}C), despite widely ranging environmental temperatures. This temperature varies depending on individual differences, time of day, the stage of sleep, and the ovulatory cycle in women. Thermoregulation is the balance between heat production and heat loss mechanisms that occur to maintain a constant body temperature. Exercise or fever may raise core temperature by up to three degrees, while exposure to cold may lower core temperature by a degree. Beyond these boundaries, the human is susceptible to heat stroke (elevated temperature) or hypothermia, both of which are life threatening conditions. The human autonomic thermoregulatory system consists of a set of temperature sensitive neurons, which senses change in skin and core temperature. A branch of the central nervous system receives, integrates and coordinates afferent sensory information into a thermo effectors response and a set of effectors, through which the body makes the appropriate thermoregulatory response[A. S. Milton, 1990]

Heat is transported from body core to the body surface through skin. Skin is the most important and the largest organ of integumentary system made up of multiple layers. It is the first line of defense, which covers and guards the underlying muscles, bones, ligaments and internal organs. Skin is the interface with the environment, plays an important role in protecting against infectious agents called pathogens and excessive water loss[E. Proksch, 2008]. The SST region (skin and subcutaneous region) is structurally divided into three sub layers viz. epidermis, dermis and hypodermis or subcutaneous layer (Fig. 1).

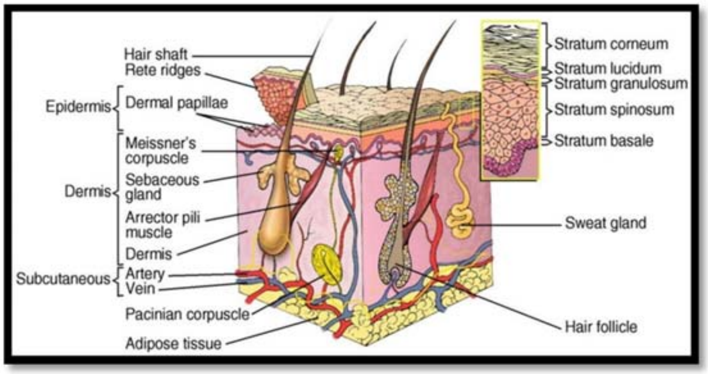


Fig. 1 : Human Skin

Any injury accidental or surgical(Fig.2-3) can be represented as 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. Wound due to surgery is a type of injury in which skin is torn, cut or punctured. It is the blunt force trauma causing contusion and an opening made in the skin or a membrane of the body incidental to a surgical operations or procedures.

Fig. 2: Accidental wound

Fig. 3: Surgical Wound

PHYSIOLOGY OF WOUND HEALING PROCESS

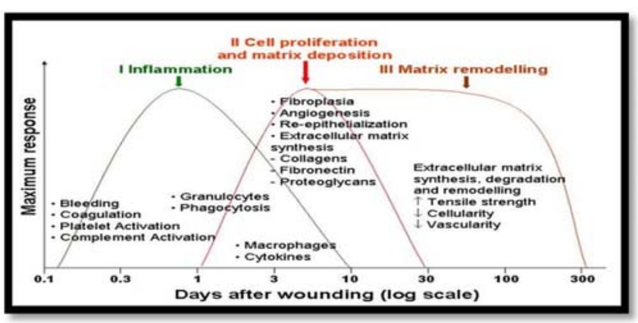


Fig.4: Wound Healing Phases

The phases of wound healing normally progress in a predictable and timely manner. Any disturbance in the phases may cause to either a chronic wound [A. Desmouliere,2005] such as a venous ulcer or pathological scarring such as a keloid scar.

Fig.5: Chronic Ulcer

Fig 6: Kaloid Scar

FACTORS AFFECTING WOUND HEALING

Various intrinsic and external factors affects the wound healing [J. Pfeiffer, 1954], In intrinsic factors role of enzymes, metabolic activities, overall physiology, diabetic conditions etc. whereas in external factors surrounding temperature, diet, stress etc. play important role. It is difficult to manage internal factors but somehow external factors can be managed.

Role of enzymes cannot be neglected in the case of abnormality like wound healing process because the miracle of life would be impossible without enzymes. Enzymes are protein chemicals, which carry a vital energy factor needed for every chemical action, and reaction that occurs in our body. The health of our organs and glands is completely dependent upon our enzyme making abilities [S. O. Brattgard,1978-S. D. Mahanty, 1980], . Proper functioning of the enzymes depend upon two major factors : pH value and temperature.

Out of many intrinsic and extrinsic factors like health, nutrition, temperature, growth factor etc. temperature are one of the most important factors in wound healing process. Like most chemical reactions, the rate of an enzyme-catalyzed reaction increases as the temperature is raised whereas many enzymes are adversely affected by high temperatures. The reaction rate increases with temperature to a maximum level, then declines as temperature increases further.

Level of body temperature has much importance in diagnosis and prognosis in every disease because any disturbance in mechanism of temperature regulatory system can cause lots of complications in natural processing of the body. Body core temperature (T_b) plays an important role and affects all biological processes in human being. The body requires a stable core temperature of 37^{o}C (+0.5 ^{o}C), to maintain cell metabolic activity. Core temperature is the balance between heat gain produced by cell metabolism and heat loss by various mechanisms, including respiration via the lungs and evaporation via the skin. Apart from the core temperature, the measurement of the surface temperature of the human body is also important; in this regard various studies have been done by many investigators. Skin temperature affects the local blood flow [R. Gannon, 2007 & Kathryn Vowden, 2002) and a small rise in temperature can increase metabolic activity and oxygen demand.

Wound healing is body's natural requirement. From wound to healing process every biological and physical activity is very important. Aftereffects of all these activities directly depend on the body core, skin and ambient temperature.

Experimental studies suggested that wounds heal most effectively at normal core temperature (37^{o}C). Wound healing is delayed when temperature falls below normal body core temperature or rise above 42^{o}C [W. McGuinness, et al., 2004]. 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 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, following are very important aspects which have been ignored earlier [27].

- 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.

Temperature of wound bed can be controlled by proper dressing materials and appropriate temperature of cleansing solution [G. Kammerlander, 1999, WANG Cheng-chuan, 1999) 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 as proper wound dressing is necessary to heal, proper rate of evaporation is also 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 be dry and in case of less evaporation wound will be wet all the time. Therefore maintaining a physiological moist environment in treating wound is important[G. Kammerlander, 1999, WANG Cheng-chuan, 1999).

All the above facts suggest that, temperature plays a significant role in wound healing process. Any disturbance in temperature affects the functioning of enzymes, growth factors and ultimately wound bed temperature. This disturbance may be due to the varying atmospheric temperature, rates of evaporation or cleansing solution temperature. This theoretical work has been carried out by studying thermal variations caused at different atmospheric temperatures and different rates of evaporation. This study may be very useful for clinical purposes related to wound healing.

MATHEMATICAL MODELING OF THE PROBLEM

Temperature of tissue, wound bed temperature and surrounding temperature etc. are very important factors for healing process. Wound is assumed after plastic surgery. In third degree burn plastic surgery is the only option to get the new skin.

The partial differential equation for heat and mass transfer in human body tissues given by Perl is

$$Div(K\ grad\ T) + m_b c_b \left(T_b - T\right) + S = \rho c \frac{\partial T}{\partial t} \tag{1.1}$$

Here 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. Right hand side of eq.(1) shows the storage of heat in tissues. The first two terms of the left hand side represents conduction of heat in the tissues, caused by the temperature gradient and third term is for heat transport between the tissues and microcirculatory blood perfusion. The last term represent heat generation due to metabolism.

The outer surface of the body is exposed to the environment and heat loss at this surface takes place due to conduction, convection, radiation and evaporation. Thus the boundary conditions at the outer surface

$$-K\frac{\partial T}{\partial n} = h(T - T_a) + LE \quad for \quad t > 0 \qquad 1.2$$

Where h heat transfer coefficient, T_a is atmospheric temperature, L and E are respectively, the latent heat and rate of evaporation and $\frac{\partial T}{\partial n}$ is the partial derivatives of T along the normal to the skin surface and for the inner surface

$$T = T_b \quad for \quad t \geq 0 \qquad 1.3$$

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

$$T(x,0) = T_b = 37^{\circ} C \qquad 1.4$$

The values of physiological parameters for unwounded and wounded sites are different from each other. These values are almost negligible in transplanted tissues just after the surgery and they increase gradually with respect to time, causing increase in tissue temperature of human body therefore mathematically it can be written as:

$$K(x,t) = \varsigma(t)\sum_{d=0}^{1}\alpha_d x^d,\ M(x,t) = \psi(t)\sum_{d=0}^{1}\beta_d x^d,\quad S(x,t) = \zeta(t)\sum_{d=0}^{1}\gamma_d x^d \tag{1.5}$$

Here the thickness of SST region is along x axis, therefore, changes in these parameters are the functions of x only. The values for α_d, β_d and γ_d are calculated layer wise.

For normal region **(**tissues of donor site) K, M and S depend on position only.

$$\varsigma(t) = 1,\ \psi(t) = 1 \text{ and } \zeta(t) = 1$$

SOLUTION OF THE PROBLEM :

Above mathematical equations can be solved by using finite element method, finite difference method or any other suitable numerical method by incorporating suitable values of parameters like K, M, S, at different atmospheric temperature and Rate of Evaporation.

NUMERICAL RESULTS AND DISCUSSIONS

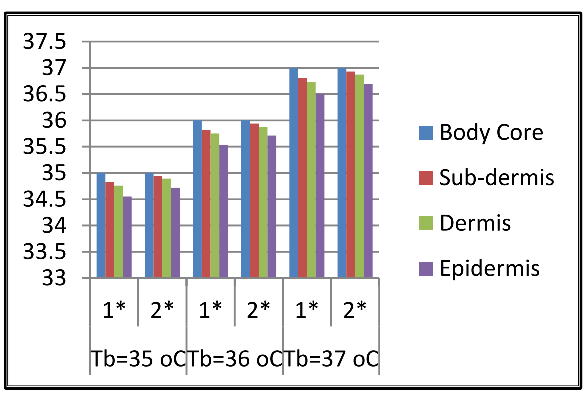
Results have been calculated at E=0, $0.24\text{x}10^{-3}$, $0.48\text{x}10^{-3}$ (gm/ cm^2min) and Surrounding temperature Ta= 0, 15, 23 and 32 (Degree Celsius). It is observed that for the same rates of evaporation the decline in tissue temperature is more at lower atmospheric temperature. This is because more temperature gradient occurs due to low atmospheric temperature. For higher rates of evaporation at the same atmospheric temperature, the fall in tissue temperature of epidermis, dermis and subcutaneous is noted more i.e. at T_a=23°C, the fall in tissue temperature is more for E=$0.48\text{x}10^{-3}$than that of E=0. It shows that the rate of evaporation significantly effects on temperature profile in the region. The results obtained in the model are agreement to the physiological facts.

For Abnormal Region (T_b=37°C)

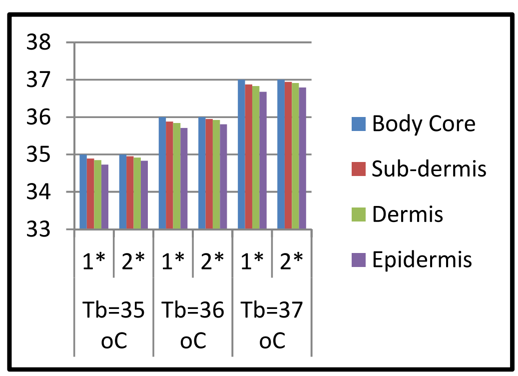
1*: Maximum fall in temperature till 20 min.

2*: Maximum rise in Temperature after 250 min.

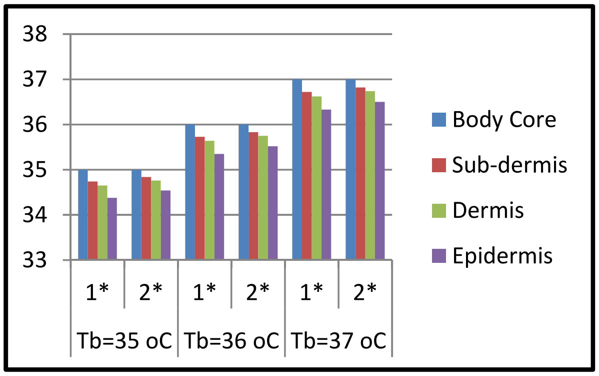
TA= 15°C, E=0



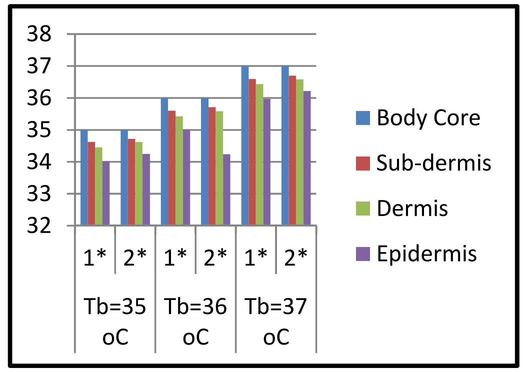
TA= 23°C, E=0



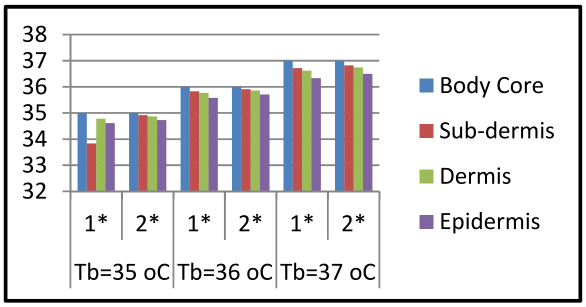
TA= 23^{O}C, E=0.24X10^{-3}



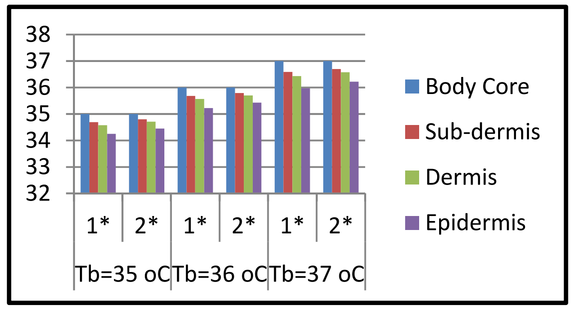
Ta= 23^{o}C, E=0.48x10^{-3}



TA= 33^{o}C, E=0.24x10^{-3}



TA= 33^{o}C, E=0.48x10^{-3}



IMPORTANCE AND FUTURE SCOPE

Mathematical modeling for thermal regulation of human body has great importance in treatment of various diseases because treatment of diseases using thermographic technique known as thermography is popular for detecting thermal asymmetry. Thermograghy needs thermal information and relation among physical and physiological parameters of patient. Temperature information of human body offers the physician an added dimension to the diagnostic picture, detecting neurological and vascular information not available on X-ray. Temperature monitoring is the test of choice for monitoring various diseases like cancer, breast health and changes associated with breast disease. Areas of chronic pain, inflammation, wound healing or disease can be evaluated thermographically to assist the physician with a diagnosis and treatment plan. Detect thermal indicators as they relate to infection, inflammation or fibrocystic disease.

Study of temperature variations during wound healing process has great importance because

- Such mathematical models can be useful to prevent adverse effects of wound.
- Models can be developed for wound healing in hypothermia and hyperthermia cases.
- Wound healing process for different atmospheric temperatures and rates of evaporation can be studied further for more realistic situations.
- Wound healing in diabetic patients is novel idea for research.
- These models can be applied to other situations of engineering and sciences.
- Such models can be further developed to study interesting relationship among various parameters of the body region and understanding the thermal changes occurring in the process.
- This study is helpful in treatment of various diseases, to develop protocols for medical purpose and for evaluation of effectiveness of hyperthermic treatments.
- It will also help in developing more effective devices for temperature measurement. It may

also help in investigations of thermoregulatory mechanisms.

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