Reepithelization Speed of Healing after Photorefractive Keratectomy

Ahmed J. Hamoud1, Nebras H. Ghaeb2, Reyadh Ch. Al-Zuhairy3, Ali Zuhair Ridha4*

1Computer Technical Engineering department, College of Information technology, Imam Ja’afar Al-sadiq university, Baghdad, dr.ahmed.jameel@sadiq.edu.iq, Iraq;
2Biomedical Engineering Department, Al-Khawarezmi Engineering College, University of Baghdad, Baghdad, Iraq nebras@kecbu.uobaghdad.edu.iq;
3ministry of Higher Education and Scientific Research, Baghdad, Iraq; reyadhc@yahoo.com;
4mechanical Techniques, Institute of Technology, Middle Technical University, Baghdad, Iraq

ABSTRACT

The Photorefractive Keratectomy (PRK) is one of the refractive surgery that started to be most popular around the globe. This procedure started by mechanical removing of the epithelial layer of the cornea and then laser treatment. The removed layer rebuild after the procedure within more than 48 hours. During the reepithelization the cell density and the concentration of the Epidermal Growth factor (EGF) have interchanged to reach the required level of protection. In the present study, the cell density and the EGF concentration level have been studied. At the first time, by considering a uniform speed of healing of 60 µm/h according to the biological and experimental studies. Then use the data collected to estimate the speed of healing behaviour. Results showed that the average of the maximum speed of the healing is 72.872 µm/h, while the average of the mean speeds of healing reached to 62.516 µm/h which agrees with the biological and practical healing speed of 60 µm/h.

Keywords: Re-epithelization, PRK, Speed of healing, Reaction-diffusion equation.

* Corresponding: alizuhair1979@mtu.edu.iq
Introduction

The Photorefractive Keratectomy (PRK) is the use of some certain laser type to treat the low refraction vision errors (such as the myopia, hyperopia and astigmatism) [1]. This surgical procedure started by physical removing of the first corneal layer (which called the epithelial layer), then use the laser to modify the corneal shape and finally protect the eye with bandage contact lens waiting for the epithelial layer to grow back. Post operatively the patient will wait for days to regrowth the protective epithelial layer. The regrowth or re-epithelization speed have been studied before by many research works.

It was 1990 when Sherratt and Murray [2] started their work together in the field of mathematical modeling of the healing of epidermal wound. The work presented the epidermal cell density, as a function of the wound radius of curvature and time, all which discussed in the reaction–diffusion equation (RDE), which state:

\[
\text{Rate of increase of cell density, } n = \text{Cell migration} + \text{Mitotic generation} \quad (1)
\]

In 1991 Sherratt and Murray [3] back again and modified the simple RDE to a coupled once by adding the concentration of mitosis. The improved mathematical model of wound healing becomes:

\[
\begin{align*}
\text{Rate of variation in cell density, } n & = \text{Migration of cell} + \text{Mitotic generation} - \text{Natural loss} \\
\text{Rate of variation of chemical concentration, } c & = \text{Diffusion of } c + \text{Production of } c - \text{Chemical decay} \\
\end{align*}
\] (2a)

And in differential form:

\[
\begin{align*}
\frac{\delta n}{\delta t} &= D \nabla^2 n + s(c)n(2 - \frac{n}{n_0}) - kn \quad (3a) \\
\frac{\delta c}{\delta t} &= D_c \nabla^2 c + f(n) - \lambda c \\
\end{align*}
\] (3b)

Where \( s(c) \), the logistic regression is a function of chemical concentration, \( k, D \), and \( \lambda \) are positive constants. \( f(n) \) is a biological function.

Based on above differential form many solutions have been suggested for different clinical applications. In ophthalmology, the corneal epithelial mapping attracted at the last five years the researchers, especially, after the presenting of the ocular coherence technology (OCT) system, which have the ability to measure and present the epithelial mapping [4].

Back to equations (3) and customizing them to the corneal epithelial behaviour, Dale et al., [5] proposed an analytical approximation solution verified by numerical scheme calculations. They studied the interaction between the two equations, and they collected also the required constants from different experimental work studies. Their findings guide us to the truth that the epidermal growth factor (EGF) improve the healing rate or the speed of the traveling epithelial wave. The modified differential equations (based on equations (3) and customized for epithelial corneal region) are:

\[
\begin{align*}
\frac{\delta n}{\delta t} &= \nabla.(D_n(c)\nabla n) + s(c)n\left(v - \frac{n}{n_0}\right) - kn \\
\frac{\delta c}{\delta t} &= D_c \nabla^2 c + f(n) - h(c)n - \delta c \\
\end{align*}
\] (4a) (4b)

---

**Fig.1** Research studies regarding the Re-epithelization of cornea.
Ahmed J. Hamoud et al.

Where \(D_c(c)\) is the cell diffusion coefficient, \(h(c)\) cellular degradation, \(v, k, D,\) and \(\lambda\) are positive constants.

Equations (4) have been used as a starting point for the next research studies that deals with the re-epithelization of the corneal layer (see Figure (1)).

Four important disciplines (as shown above) were reflecting the interest of the researchers in studying the corneal re-epithelization process. These disciplines are:

\[\text{a. Mathematical Modelling}\]

Here the solution of equations (4) with different settings of both, initial and boundary condition are discussed. Such solution started with non-dimensional transformation for the equations, boundary and initial conditions, and then set of assumptions and simplifications to solve the equation and find final semi exact solution [5, 6 and 7]. The final results manipulation may need computer numerical scheme solution [5 and 11]. Some solution use the wave theory and their manipulation to solve equations (4) [9, 10, 12 and 14].

\[\text{b. Biological Studies}\]

In such studies the biological behaviour of the cell during the re-epithelization have been considered. How to control the speed through certain corticosteroid and the expected time period for the healing process [8, 11, 13, 26 and 41]. Also, study the cell kinetics during the whole healing process and compare between simulation program and real pathogenesis case studies [12]. The possibility of adding some markers and measure the triggering signal from the stem cell to achieve the optimum healing shape and rate [15, 21].

\[\text{c. Refractive Outcomes}\]

For the patients with low refraction errors the PRK will be the treatment procedure (a safe surgery procedure). In such cases the re-epithelization process will gain back the epithelial layer of about 50 \(\mu\)m which represent an extra power for the patient vision. During the healing period the total thickness fluctuation and the vision outcomes also [13-19, 24, 26, 33-35, 38-40]. In the last few years after the invention of the epithelial mapping which described by the OCT system many ophthalmologist started to use it as an indication for the corneal abnormality such as dryness and keratoconus [23, 24, 27, 29, 31, 32-36, 41, 45 and 46].

\[\text{d. Pharmaceutical Study}\]

Study the normal amount of the EGF during the healing process and the possibility of using some sort of pharmaceutical element to improve the supplied amount to the stem cell [5, 6, 11 and 24]. Possibility of studying the \(\alpha\) and \(\gamma\) – EGF and their interchangeable role during the re-epithelization, with the effect of adding antibodies [11, 15, 24 and 26]. Assessment effective gene and recognize the possibility of gene control to control the final healing shape and rate [43].

\[\text{Mathematical Model}\]

The differential equations (4) have been used here, applying the non-dimensionalize model suggested by Dale [5], and using the following assumptions:

a. The thickness of the epithelium is much smaller than the required length of healing, so the model will be two dimensional form.

b. By considering linear geometry of the wound healing or strip band form with long spatial domain length the equation will be solved in semi-infinite domain of \(-\infty \leq x < TZ\) (Treatment Zone), and the solution will be one dimensional toward the \(x\) direction.

c. The original set of the axis is the wound boarder.

d. The cellular diffusion coefficient change linearly with the EGF concentration value (c).

The new differential form will be:

\[
\frac{\partial n}{\partial t} = \frac{\partial}{\partial x} \left((\alpha c + \beta) \frac{\partial n}{\partial x}\right) + (\alpha_1 c + \beta_1)n(2 - n) - n \tag{5a}
\]

\[
\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + \sigma(2 - 5n) - \frac{\mu c}{\varphi c + \delta} - \delta c \tag{5b}
\]

Where the dimensionless parameters have the following values: \(\alpha = 0.01, \beta = 0.1, \alpha_1 = 0.9, \beta_1 = 0.1, D_c = 25, \sigma = 4000, \mu = 1.37 \times 10^4, \varphi = 3.02, \delta = 110\) and the wound length or the TZ = 8 mm [4, 5, 6 and 7].

The initial and boundary conditions are biologically relevant to the surgical procedure or to the PRK process. Figure (2) shows the center lines, wound center, epithelium boundary and the original point and axis.
The boundary and initial conditions for the solution will be described graphically as shown in Figure (3):

**Fig.2** Important notification on the human eye sketch.

**Fig.3** Initial and Boundary Conditions selected. BEpi = Boundary of Epithelium, WC = Wound Center.

**Proposed Solution**

In the present work a solution for the final equations (5) have been suggested using the Finite Difference (FD) implicit method Crank Nicolson Scheme (CNS). The CNS have the following definitions for the independent variable $u$, first order in time, second order in direction (such as $x$) [16]:

$$\frac{u^{i+1} - u^i}{\Delta t} = \frac{1}{2} \left[ F^{i+1} \left( x, t, u, \frac{\partial^2 u}{\partial x^2} \right) + F^i \left( x, t, u, \frac{\partial^2 u}{\partial x^2} \right) \right]$$  \[6\]

By this means each part of the differential equations (5) can be defined according to the followings:

$$u = \frac{1}{2} \left( u^{i+1} + u^i \right)$$  \[7a\]

$$\frac{\partial u}{\partial t} = \frac{u^{i+1} - u^i}{\Delta t}$$  \[7b\]

$$\frac{\partial u}{\partial x} = \frac{1}{4\Delta x} \left( u^{i+1} + u^i + u_{i+1}^j + u_{i-1}^j \right)$$  \[7c\]
Ahmed J. Hamoud et al.

\[
\frac{\partial^2 u}{\partial x^2} = \frac{1}{2(\Delta x)^2} \left( (u_{i+1}^{j+1} - 2u_i^{j+1} + u_{i-1}^{j+1}) + (u_{i+1}^j - 2u_i^j + u_{i-1}^j) \right) \quad (7d)
\]

The simplification and manipulation of the two differential equations, boundary and initial conditions will be done separately and then collect the final results as shown below:

a. One Dimensional Reaction Equation:
From Equation (5a), rearrange the equation to be:

\[
\frac{\partial n}{\partial t} = (\alpha c + \beta) \frac{\partial^2 n}{\partial x^2} + \alpha \frac{\partial n}{\partial x} + (\alpha_1 c + \beta_1) n(2 - n) - n \quad (8)
\]

Equation (8) will be in CNS form:

\[
\frac{n^{j+1i_i} - n^{ji}i_i}{\Delta t} = \frac{1}{2(\Delta x)^2} \left[ \alpha(c_i^{j+1} + c_i^j) + \beta \left( \left( n_{i+1}^{j+1} + n_{i-1}^j \right) - 2(n_i^{j+1} + n_i^j) \right) + \left( n_i^{j+1} - n_i^j \right) \right] + \alpha \left( c_i^{j+1} + c_i^j \right) \quad (9)
\]

b. One Dimensional Diffusion Equation:
From Equation (5b), the CNS form is:

\[
\frac{n^{j+1i_i} - n^{ji}i_i}{\Delta t} = \frac{D_x}{2(\Delta x)^2} \left[ (c_i^{j+1} + c_i^j) - 2(c_i^{j+1} + c_i^j) \right] + \left( c_i^{j+1} + c_i^j \right) \quad (10)
\]

c. Initial Conditions:

\[
n_i^j + n_i^j = c_i^j + c_i^j = 0 \quad \text{for } 0 \leq x < L \quad (11a)
\]

\[
n_i^j(x,0) = n_o \text{ and } c_i^j(x,0) = c_o \quad \text{other than } 0 \leq x < L \quad (11b)
\]

d. Boundary Conditions:

\[
n_i^j(x,0) = n_o \text{ and } c_i^j(x,0) = c_o \quad \text{other than } 0 \leq x < L \quad (12a)
\]

For \( n_o(L,t) = n_o \text{ and } c_o(L,t) = c_o \)

\[
n_i^{j+1} + n_i^j = n_i^{j+1} + n_i^j \text{ and } c_i^{j+1} + c_i^j = c_i^{j+1} + c_i^j \quad (12b)
\]

Results and Discussion

The numerical solution of reaction equation (9) and diffusion equation (10), with their initial and boundary conditions (11 and 12) have been done using the scientific programming language Octave (version 4.4.1).

The solution of above equations have been done for the first step after assuming the wound speed to be constant with a value of 60 \( \mu \)m/h [5]. In this step both the cell density (n) and the variation in concentration (c) are estimated with respect to the direction of healing (from the limbus toward the center of the cornea). In the second step an equation for the speed of the healing will be used to investigate the range and the shape of the wave speed of the healing process. In this time the speed will be studied with respect to the change of both n and c. Where improving the speed of healing will decrease the total time period of the re-epithelization process (time of healing).

Fig.4 cell density for 10 steps of time with 4 hours per each, and through the length from the limbus to the center of healing (center of eye).
**Cell density and concentration**

The change in cell density \( n(x,t) \) is an indication for the cell migration, mitotic activity and natural loss. This is what concerned in equation (2) and related directly to the wound re-epithelization of the corneal tissue. Figure (4), shows the variation of cell density with respect to the direction of healing and time for time period from 4 – 40 hours with ten steps changes.

Figure (5) shows the comparison between the first 4 hours with respect to the others 12, 20, 28 and 36 hours.

![Cell density for 4 steps (12, 20, 28 and 36 hours) compared with 4 hours, and for the length from the limbus to the center of cornea.](image)

The solution of the first term (cell density) based on the theoretical suggestion that the wound wave speed is constant is the main reason for the differences between the curves in figure (5). Where these differences appears to be significant in the 12 and 28 hours. At the same time cell density reaches the maximum production rate in about the 0.3 and travels towards 0.5 distance starting for the treatment zone (9mm) for the two groups.

The change in chemical concentration of EGF which represent the main drive for the proliferation for epithelial cell, Figure (6) shows the change in concentration \( c(x,t) \) for 40 hours.
Fig. 6 Cell concentration for EGF for 10 steps of time with 4 hours per each, and through the length from the limbus to the center of eye.

Again Figure (7) shows the comparison between the first 4 hours with respect to the 12, 20, 28 and 36 hours.

Fig. 7 Cell concentration of EGF for 4 steps (12, 20, 28 and 36 hours) compared with 4 hours, and for the length from the limbus to the center of eye.
Ahmed J. Hamoud et al.

The cell concentration experimentally and biologically increases with the increase of the time period of healing [5, 7 and 11]. This is agreed with the behaviour of the trend in Figure (7). Approximately the value of 0.6 in length toward the center of the eye have a rapid change of increase more than what happened with the first part of the healing process. Biologically the speed of the healing wave increase rapidly toward the center of healing after spending the first part of mitotic near the stem cell position [12, 15 and 20]. This is why the first part of the trends in figure (7) looks falter than the part after the 0.6 position.

**Speed of healing**

Most of the studies regarding the speed of healing (a) started their modeling from Fisher reaction diffusion equation [2, 5, 10 and 20]. The traveling healing wave solution use the analogy of relative coordinate system to predict the final expected form, which may be expressed as [5]:

\[ a = \frac{2}{\beta + D_c} \sqrt{\beta D_c \left[ 2D_c s \left( \frac{A + \xi}{\delta} \right) - D_c - \delta \beta \right]} \quad (13) \]

Equation (13) has sets of constants that leads to a specific value of healing speed of about 60 \( \mu \text{m/h} \). The modification that have been added hear to equation (13) is to suggest shape of solution that may analogy the trend of solution in both of the cell density and concentration. This suggested analogy predicated from the mathematical interpolation of figures (4 and 6). The new modified shape of the healing speed (a) will be:

\[ a_{mod} = \frac{2}{\beta + D_c} \sqrt{\beta D_c \left[ 2D_c s \left( \frac{A + \xi}{\delta} \right) - D_c - \delta \beta \right]} e^{(n_{oo} + c_{oo})t} \sin (n_{oo} - c_{oo})t \quad (14) \]

Where \( n_{oo} \) and \( c_{oo} \) are the cell density and EGF concentration calculated from above equations (9) and (10), or figures (4 and 6) for the state of constant speed of healing.

Figure (8) shows the healing speed variation with respect the EGF concentration with a time of healing variation from 4 – 40 hours.

![Figure 8](image)

**Fig.8** Speed of healing with respect to the EGF concentration for 10 steps of time.

Figure (9) shows the comparison between the first 4 hours with respect to the 12, 20, 28 and 36 hours.
Fig. 9 Speed of healing with respect the cell concentration of EGF for 4 steps (12, 20, 28 and 36 hours) compared with 4 hours.

It is clear from figure (9) that the increase in EGF concentration level will increase the healing speed. Biologically this is due to increase in diffusion of produced cell. This increase would be happened after the wave of healing reaches close to the center of the corneal surface. The predicted speed of healing would change from 14.690, 32.649, 97.208, 96.658 and 128.150 µm/h for the 4, 12, 20, 28, 36 hours’ time of healing. The average of the ten steps maximum speed of healing is 72.872 µm/h, while the average of the means of the ten steps of times is 62.516 µm/h witch agrees with the biological and practical findings [2, 5, 10 and 20].

This leads to a practical sense that the speed of healing or diffusion rate both are compensate with respect to the position and time to recover the effect reepithelization of the surface of the cornea [17, 23, 29 and 30].

Conclusion

Many chemical and biological parameters are working together to diffuse and control the overall healing process. Specifying these parameters for region of interest (human eye) for certain surgical condition (PRK) help us to study the relationship between the speed of healing, cell density and EGF concertation. The study assigned that specific 60 µm/h to the cell density and EGF concentration, showed these values behaved with respect to both time and position. While the cell density decreases with respect to both time and position, the EGF concentration increase with respect to both. The interchange between the two mechanisms are controlled mechanically by change in speed of diffusion of the mitotic cells that may started from 5 µm/h to about 140 µm/h.
References

Ahmed J. Hamoud et al.


