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Nonlinear DSEK Model: A Novel Mathematical Model that Predicts Stability in Ocular Parameters after Descemet's Stripping Endothelial Keratoplasty

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Abstract. This work comprises of development and analysis of a new mathematical model based on Descemet's Stripping Endothelial Keratoplasty (DSEK). Formulating the nonlinear system of ordinary differential equations to describe changes occuring in ocular parameters during DSEK for scarred cornea, is a unique perspective. In this paper, the formation of the model and the existence of its solution is proved. The stability of DSEK model is discussed by the Jacobian matrix and its eigen values are examined. Also this DSEK model is proved to be uniformly and Lipschitz continuous.

AMS Subject Classification Codes: 11G55; 14M15; 18G35; 55U15
Key Words: Non-linear Differential Equation, Global Stability, Lyapunov Functions, Eigenvalues, Numerical Stability Investigation

1. Introduction

Mathematical models can aid in various real life situations to predict outcomes more swiftly. Mathematics has spread its branches in almost every subject, especially in medical sciences. Mathematical models if provided with the accurate information can do wonders. Since last few years, researchers and mathematicians interested in the areas of medical sciences are contributing their thorough efforts to predict the outcomes of a specific treatment on certain patients beforehand through applications of models. Speaking in brief, everything is being evaluated through mathematical models [4, 5, 6, 9, 10, 14, 18]. Gabriela et al. [8] presented the idea to study eyes mathematically in detail. Many eye related problems, such as the anterior chamber flow, the effects of sclera buckle surgery and the mechanics of retinal detachment and rest of the others have been discussed using concepts of fluid and solid mechanics. A qualitative model of corneal surface smoothing after laser treatment is presented. Results of Laser-Assisted In-Situ Keratomileusis (LASIK) and Photorefractive Keratectomy (PRK) are compared and significant observations and findings are listed [11]. PRK surgery is discussed mathematically by Anna and certain significant results have been extracted from preoperative and postoperative geometry from the corneal topographies [23]. A mathematical model is developed geometrically by Richard et al. to predict the refractive changes only after DSEK [25]. Another simple model of intraocular pressure of eye using concepts of fluid mechanics was developed in the form of an equation that describes the mean curve that is obtained when tomographic tracing is used for externally disturbed eyes [27]. Akman et al. forms a simple mathematical model of a condition of eye i.e. scientifically known as congenital nystagmus which means an unconscious oscillation of eyes due to which patient lacks focus [1]. Results evaluated through Akman et al. model are in waveform. Therefore, it helps ophthalmologists to see behavior of such patients very clearly and can experiment with remedies and treatments via this model. To plot the movement of eye on a 2D plane Oleg et al. presented a two dimensional mathematical model. This model is called Two Dimensional Mathematical Model of Oculomotor Plant [22]. Another model related to retina and a Young's modulus constant has been derived [13]. A revised version of a book in which mathematical models have been discussed for each part of eye such as cornea, lens, anterior chamber etc in ample detail is recommended for interested readers [12].

All situations above either use ordinary or partial differential equations but mathematical models that explain the behavior of eye during some treatment or explaining structure of eye are either geometrical or provide statistical analysis based on population data.

This work is concerned with developing a new mathematical model that describes the change that take place in ocular parameters during DSEK. Function of eye, to produce a clear vision is performed smoothly when its multiple discrete parts work together, just like a sophisticated camera. When a ray of light enters the eye, it first interacts with tear film, which is a transparent crystal clear layer that provides a cover surface to cornea. Cornea is formed of five layers 1) Epithelium 2) Bowman's layer 3) Stroma 4) Descemet's membrane 5) Endothelium see Fig. 1. Among many diseases of eye, the scarring of cornea is common, whether it is due to eye infection, keratoconus, eye herpes, fungal keratitis, growth of eyelashes inward, complications of eye surgery or other conditions. Therefore, light rays entering eye get scattered and the vision of patient is blurred as shown in Fig: 2. DSEK, PRK, LASIK etc can cure scarring of cornea. Also, DSEK can be done for replacement of swollen Endothelium due to some previous surgery. In DSEK, Endothelium layer and Descemet's membrane are removed and a donor's layered tissue is transplanted. As a result of this transplant several parts of the eye near cornea or involved in vision get affected, such as the anterior chamber which is right behind the cornea filled with aqueous fluid. Therefore, when the original cornea layers are replaced and grafted with a new one, a definite change occurs in corneal curvature and refractive index. Based on these assumptions, medical data and standard research findings, this model is constructed.

This paper is organized as follows. In Section 2, DSEK model is established under some assumptions and the existence of its solution is proved. In Section 3, the stability analysis of the proposed DSEK model is investigated. Also equilibrium of the model is discussed. In Section 4, the parameter estimation and numerical simulations are provided. Finally, conclusion of this paper is given.

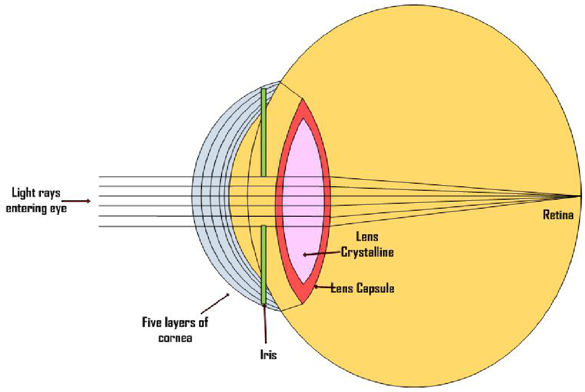

FIGURE 1. Schematic diagram of the eye describing all refractive parts of the eye involved in vision. When a light ray enters the eye it goes straight to the retina due to clear refraction from five layers of cornea.

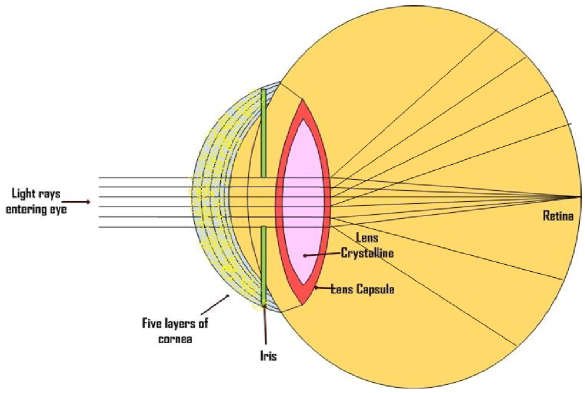

FIGURE 2. Schematic diagram of eye that describes the scarring of the layers of cornea due to some incident or disease.Scarring of cornea layers can be observed in this figure. When light ray enters the eye it gets scattered and does not completely forms image at the retina. This the reason of blurred and hazy vision.

2. FORMULATION OF DSEK MATHEMATICAL MODEL

The model constructed in this paper is based on the relationship among ocular parameters in intraoperative phase. Principles assumed in this work are

- The donor and recipient cornea graft are symmetric around the visual axis.
- The graft thickness variation is symmetrical around the visual axis.
- Age has no effect on central corneal thickness in this case [12, 20].
  Main state variables affected by DSEK are given in Table: 2

TABLE 1. Nomination of Ocular Parameters to Variables.

Name of variable	Symbol
Refractive Index	$p(t)$
Axial length	$q(t)$
Corneal Curvature	$r(t)$
Central Corneal Thickness	$s(t)$

This model will be constructed from the relationship among $p(t), q(t), r(t), s(t)$ state variables and is observed from the following references:

- Central corneal thickness and corneal curvature shows small negative correlation among them i.e. $\frac{r(t)}{s(t)}$ [21].
- Various studies claim connection among axial length and central corneal thickness, but in this model a small positive relation is considered $s(t)q(t)$.
- Anterior chamber depth has opposite behavior to lens thickness whereas anterior chamber depth positively correlates with axial length i.e. $\gamma q(t)$. Central corneal thickness and anterior chamber depth has no effect on each other [21] therefore no relation is considered among them in DSEK.
- Transplanted tissue is of 100-200 microns thick, which is not the normal thickness of natural cornea layer.
- Minimal topographic change is observed after the transplant in corneal curvature [25].
- Also it is a stated fact that only the central part of cornea i.e. $5\,mm$ forms the most important refractive surface, therefore central corneal thickness is considered as state variable $s(t)$ instead of peripheral cornea thickness see Fig. 3.

On the basis of these observations, the following model has been formed

$$\begin{aligned} p^{'}(t) =& \alpha\frac{r(t)}{s(t)} + \gamma q(t) + \delta \\ q^{'}(t) =& -\delta - \beta\frac{r(t)}{s(t)} - \gamma q(t) - s(t)q(t) \\ r^{'}(t) =& -\beta\frac{r(t)}{s(t)} - q(t) - s(t)p(t) \\ s^{'}(t) =& s(t)p(t) + s(t)q(t) + q(t) \end{aligned} \tag{2.1}$$

constants α, β, γ and δ are used here for balancing system only. Also observe that if $q(t) > 0$ then $s'(t) > 0$ at $t = 0$ in Eq.(2.1). In order to understand the behavior of DSEK mathematical model, let us consider the set Ω and the initial conditions for the system in Eq.(2.1) given by

$$\Omega = \{(p, q, r, s) \mid |p| \leq a, |q| \leq b, |r| \leq c, |s| \leq d\} \tag{2.2}$$

with $p(0) = p_o$, $q(0) = q_o$, $r(0) = r_o$, $s(0) = s_o$ and also for the domain of Ω it is necessary that $a, b, c, d > 0$.

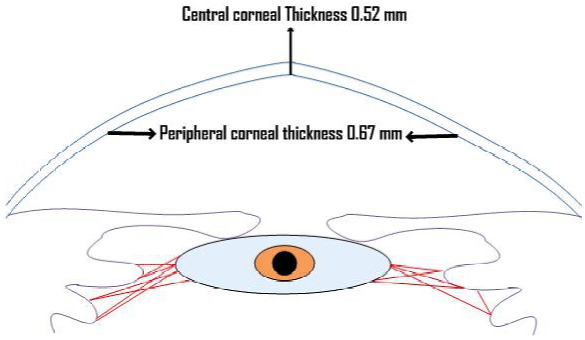

FIGURE 3. Corneal thickness measures differently in central and peripheral regions. Peripheral corneal thickness measures 0.67 mm, whereas, central corneal thickness measures 0.52 mm, which effects refraction activity the most.

Definition 2.1. *Let DSEK mathematical model in Eq.(2.1) can be written as*

$$\frac{dx}{dt} = G(\big(t, x(t)\big) \tag{2.3}$$

$$\frac{dx}{dt} = F(x); \qquad F : D \subset R^n \to R^n \tag{2.4}$$

where F and G both functions are defined to be in $x \in R^n$ and their solution exists for all $t > 0$. If $G(t, x(t)) \to F(x)$ as $x \to \infty$ uniformly for $x \in D$ then system in Eq.(2.2) is said to be asymptotically autonomous with limit system of Eq.(2.3).

In order to prove the stability of DSEK system 2.1, first the existence and uniqueness of the solution will be proved. For this purpose, it will be shown that Eq.(2.3) is closed, bounded and uniformly continuous nonlinear system. Therefore, a theorem is stated below to prove the closed and boundedness of DSEK system 2.1

Theorem 2.1. *All feasible solution $x = x(t) = \Big(p(t), q(t), r(t), s(t)\Big)$ of DSEK model in Eq.(2.1) is bounded and enters the region by $\Omega = \{(p, q, r, s) \mid p \leq a, q \leq b, r \leq c, s \leq d\}$ if and only if $\alpha = 2\beta$ then $F(x)$ is closed and bounded on region Ω.*

Proof. Given $x = \Big(p(t), q(t), r(t), s(t)\Big)$, then $F(x) = F\Big(p(t), q(t), r(t), s(t)\Big)$. On differentiating it becomes $\frac{dx}{dt} = \frac{d}{dt}(p + q + r + s)$

$$\begin{aligned}\frac{dx}{dt} = \frac{d}{dt}\Big(&\alpha\frac{\int r(t)dt}{s(t)} + \alpha\int\frac{\int r(t)dt}{s(t)^2}dt + \gamma\int q(t)dt + \delta t - \beta\frac{\int r(t)dt}{s(t)} - \\ &\beta\int\frac{\int r(t)dt}{s(t)^2}dt - \int q(t)dt - s(t)\int p(t)dt + \int s'(t)\big(\int p(t)dt\big)dt - \\ &\delta t - \beta\frac{\int r(t)dt}{s(t)} - \beta\int\frac{\int r(t)dt}{s(t)^2}dt - \gamma\int q(t)dt - s(t)\int q(t)dt + \\ &\int s'(t)\big(\int q(t)dt\big)dt + s(t)\int p(t)dt - \int s'(t)\big(p(t)dt\big)dt + \\ &s(t)\int q(t)dt + \int s'(t)\big(\int q(t)dt\big)dt + \int q(t)dt\Big)\end{aligned} \tag{2.5}$$

$$\frac{dx}{dt} = (\alpha - 2\beta)\frac{r(t)}{s(t)} \leq 0 \tag{2.6}$$

Since $\alpha, \beta, \gamma, \delta > 0$, the condition $\alpha = 2\beta$ is proved to be necessary for closed and bounded region. In this case, practically $s(t) \neq 0$ so this rational function is continuous everywhere. If in case let's assume that $s(t) = 0$ then in Eq.(2.6), $\frac{dx}{dt} \to \infty$ and hence a contradiction for this theorem. Therefore it is sufficient and necessary to say $s(t) \neq 0$. Also due to this

$$\frac{d}{dt}(p + q + r + s) = (\alpha - 2\beta)\frac{r(t)}{s(t)} \tag{2.7}$$

It is deduced that Eq.(2.1) is bounded with a condition where $s(t) \neq 0$. □

If explained in terms of real phenomenon this mathematical proof demonstrates that central corneal thickness can never be zero i.e. $s(t) \neq 0$ otherwise the system will be unstable/vision of eyes will get badly effected. Hence this is shown successfully above mathematically.

Lemma 2.1. *DSEK model is uniformly continuous on a bounded region* Ω*.*

Proof. As proved in Theorem 2.1 Eq.(2.1) is closed and bounded hence Eq.(2.1) is uniformly continuous by [2]. □

Lemma 2.2. *DSEK model is Lipschitz continuous.*

Proof. Since Eq.(2.1) is proved to be closed and bounded in theorem 2.1 therefore its Lipschitz function exists [2]. □

Lemma 2.3. *DSEK model has a unique solution.*

Proof. As proved in above theorems that this system is closed, bounded, and uniformly continuous. Also it is Lipschitz continuous [17].
A system has a suitable initial condition $x(t_o) = x_o \in \Omega$ and a unique solution only if F, a nonlinear function is continuously differentiable or Lipschitz continuous. In Eq.(2.1) the used initial time will be $t_o \geq 0$ in the entire space R^n. □

Lemma 2.4. *DSEK system has global solution.*

Proof. System $\frac{dx}{dt} = F(x)$ for $F : I \times \Omega \to R^n$ where $x = p(t) + q(t) + r(t) + s(t)$ has a global solution. Solutions of $p(t)$, $q(t)$, $r(t)$ and $s(t)$ have global solutions therefore all of them show extensions [17]. □

Lemma 2.5. *Lyapunov function exists for DSEK model.*

Proof. Since F is continuous and $F^{'}(x) \leq 0$ so $F(x)$ is a Lyapunov function [26]. □

3. Stability of DSEK Mathematical Model

An important attribute of nonlinear dynamical systems is stability which unveil their behavior at different positions. There are three types of stability systems normally used for nonlinear systems. Orbital stability with respect to its output trajectory, Lyapunov stability discusses the equilibria whereas the third one i.e. structural stability considers the whole system itself [15]. Concepts of Lyapunov stability are being used here to analyze the behavior of system around equilibrium points by finding the Jacobian matrix and then analyzing its eigen values on a hypothetical patient. Stability of every system varies from case to case in dynamical systems. Sometimes oscillations seem normal for a case and stability of that system lies in that wave solutions. In our particular model, stability varies for different cases. Right after transplantation, Eq.(2.1) cannot be stable at once but after few months of surgery, stability can be achieved. Now for stability, let system in Eq.(2.1) be written as

$$\begin{aligned} f\big(p(t),q(t),r(t),s(t)\big) &= \alpha\frac{r(t)}{s(t)} + \gamma q(t) + \delta \\ g\big(p(t),q(t),r(t),s(t)\big) &= -\delta - \beta\frac{r(t)}{s(t)} - \gamma q(t) - s(t)q(t) \\ h\big(p(t),q(t),r(t),s(t)\big) &= -\beta\frac{r(t)}{s(t)} - q(t) - s(t)p(t) \\ i\big(p(t),q(t),r(t),s(t)\big) &= s(t)p(t) + s(t)q(t) + q(t) \end{aligned} \tag{3.8}$$

Corresponding Jacobian matrix is given as

$$\frac{\partial(f,g,h,i)}{\partial(p,q,r,s)} = \begin{bmatrix} 0 & \gamma & \frac{\alpha}{s(t)} & -\frac{\alpha r(t)}{s(t)^2} \\ 0 & -\gamma - s(t) & -\frac{\beta}{s(t)} & \frac{\beta r(t)}{s(t)^2} - q(t) \\ -s(t) & -1 & -\frac{\beta}{s(t)} & \frac{\beta r(t)}{s(t)^2} - p(t) \\ s(t) & 1 + s(t) & 0 & p(t) + q(t) \end{bmatrix} \tag{3.9}$$

To further analyze the Matrix in Eq.(3.9) we need to find the eigen values and check its stability. Therefore a hypothetical patient data is assumed from medical research papers. Data considered for calculations is closer to real life patient's data.

4. Numerical Simulation of a Hypothetical Case

To verify accuracy of this model, the dataset in Table:2 has been collected from various previously published medical research papers (references given in Table:2). In this regard the most relevant literature was foraged from the most authentic resources in the field of ophthalmology where, the enormous amount of noteworthy articles are being published on daily basis. Articles considered for referencing these parameter values are the ones

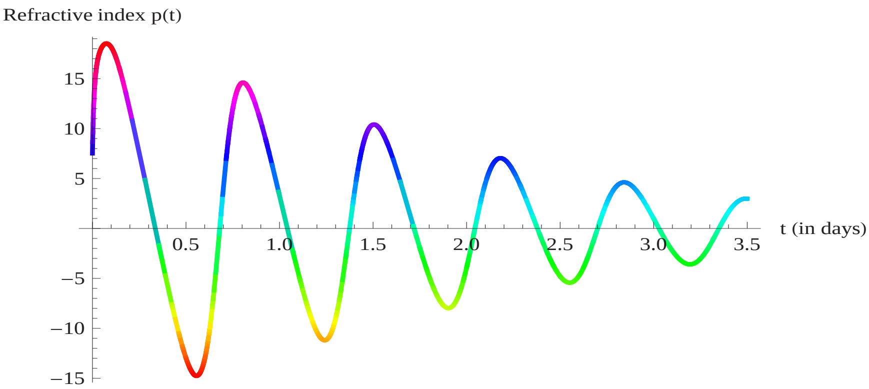

FIGURE 4. This figure depicts the behavior of numerical solution of Refractive index $p(t)$ at the time of surgery which is utterly unstable due to the scarring of cornea. This illustration clearly shows the oscillatory behavior which confirms the instability proved by eigen values.

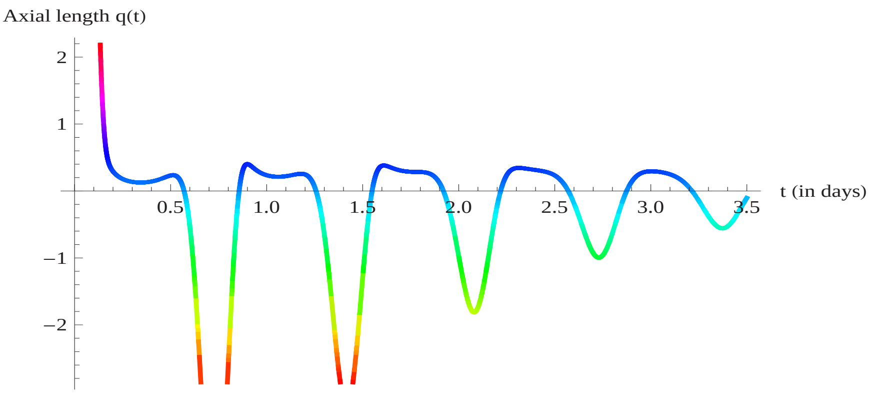

FIGURE 5. Behavior of numerically solved Axial length $q(t)$ is shown here. This depicts the perspective of $q(t)$ at the time of surgery which is utterly unstable due to the scarring of cornea. Graphical illustration depicts the oscillatory behavior which confirms the instability proven by eigen values.

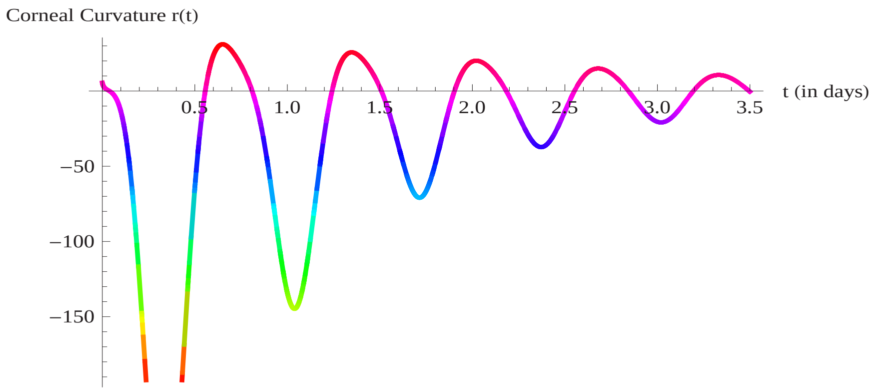

FIGURE 6. Corneal curvature $r(t)$ is calculated numerically and graphically shown here. This depicts the behavior of $r(t)$ at the time of surgery which is utterly unstable due to the scarring of cornea. Graphical illustration depicts the oscillatory behavior which confirms the instability proved by eigen values.

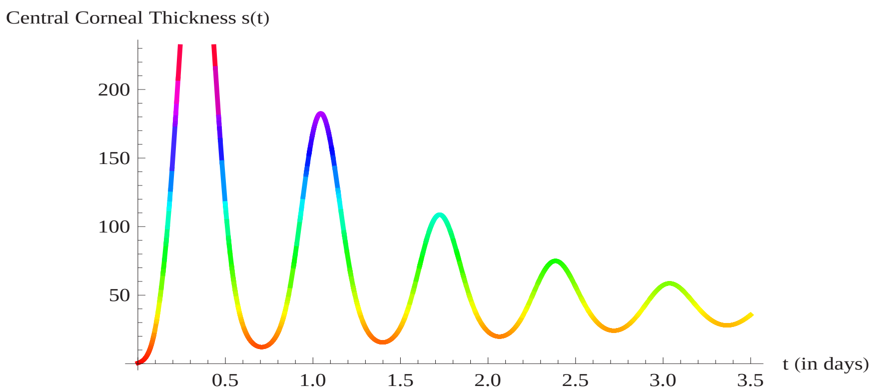

FIGURE 7. Central corneal thickness $s(t)$ is calculated numerically and graphically shown here. This depicts the behavior of $s(t)$ at the time of surgery which is utterly unstable due to the scarring of cornea. Since cornea layers swell due to the irritation of scarring of cornea or disease. Graphical illustration depicts the oscillatory behavior which confirms the unstability proven by eigen values.

that have high clinical importance, accurate surgical techniques and results. Substituting these values from Table:2 in matrix given in Eq.(3.9) and obtain the following characteristic equation

$$3.3651303965598344 \times 10^{-11} - 6058.508488615404\lambda - 3278.358172781065\lambda^2 +$$

TABLE 2. Description of values (assumed/ referenced) for constants and variables.

Constants & Variables	Values	Reference
α	100	Assumed
β	50	Calculated
γ	3.32mm	[28]
δ	15 micrometer	Assumed
$p(0)$	45D (7.50 mm approx)	[24]
$q(0)$	24.39mm	[16]
$r(0)$	60D in Flat K=5.63mm	[29]
$s(0)$	0.52mm	Fig. 3

$$68.10384615384615\lambda^3 + \lambda^4 = 0 \tag{4.10}$$

Upon solving Eq.(4.10), the obtained eigen values are -100.21411771528012, -1.7836708943711577, $5.5543875\,2439362 \times 10^{-15}$, 33.89394245580512. Two negative and two positive eigen values shows that the system is unstable. Further numerical simulation of RK4 by using Mathematica 10.0 also be in agreement with our eigen values.

Using initial values and parameters in Table:2, a numerical analysis of this model has been done. On the basis of initial condition the obtained results shows unstable vision and oscillatory behavior. In Fig. 4, 5, 6 and 7, the oscillation is too high in first 24 hours after surgery. But with the passage of time due to the recovery in stitches or worn off swelling in cornea etc it definitely gets better. The results depict that this oscillation reduces in almost 36 hours of surgery. These numerical results exactly matches the results provided in [3, 7]. Gina [7] even suggested that driving is safe after 24-36 hours of DSEK, exact situation can be observed in the numerical results obtained for DSEK model.

Gina [7] researched and stated that complete recovery time is approximately two and a half months or three months maximum if everything goes smoothly after DSEK. Similar pattern can be seen in the numerical solution and graphical illustration of DSEK model. In almost 60 days, healing from surgical effects, the vision does get better and stable. Results of that stable situation through DSEK model can be observed in Fig. 8, 9, 10 and 11.

It should be noted, however, the values obtained for this hypothetical patient do not show perfect vision. It shows that while DSEK improves the vision, it does not resolve the error completely even after surgery. Therefore, ophthalmologists do consider other surgical techniques and treatments according to need of patient to correct their vision back to normal after DSEK if possible [19, 24].

5. CONCLUDING REMARKS

In this paper, a new mathematical model is constructed to critically review the surgical treatment of eye i.e. DSEK in a different perspective. Instead of using geometrical concepts, facts provided about relationships among ocular parameters are used here. This system is uniformly continuous and bounded. Moreover, it is Lipschitz continuous, which guarantees a unique solution. This means for this hypothetical case, there are prospects of successful surgery. Also, the global existence of the solution of this system is proved. In simple words, this work represents or proves that DSEK can be embodied as a system of

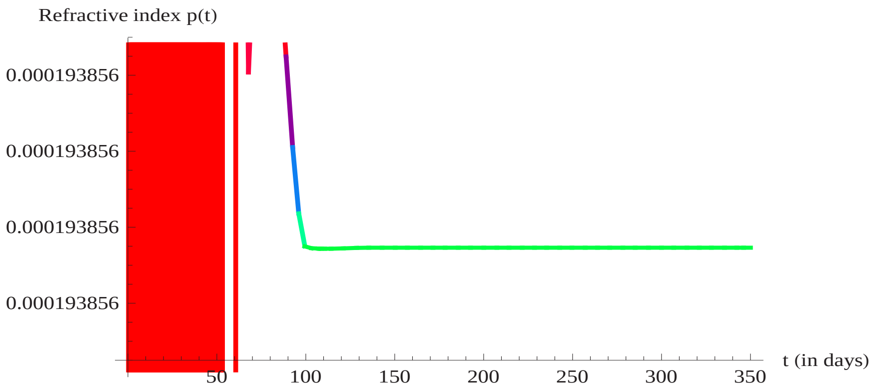

FIGURE 8. In refractive index $p(t)$ almost after 90 days the stability in vision can be observed. The red region shows the recovery period of eye from DSEK. After almost two months a complete recovery can be noticed but after three months results are more feasible.

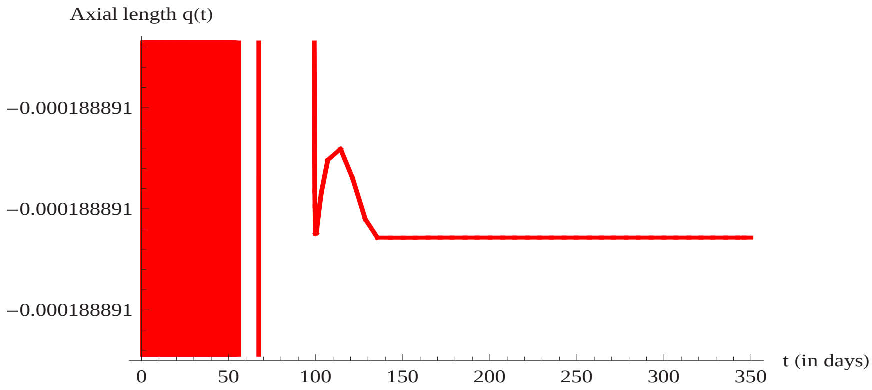

FIGURE 9. In Axial length $q(t)$ as such no huge change occurs. As in this illustration with the passage of time $q(t)$ remains the same.

nonlinear ordinary system of differential equations and it definitely has a global existence since the dynamics of this system does not stop after a specific time, but continues to work endlessly.

Initially, DSEK model suggested the unstable and oscillatory behavior of Refractive Index, Axial Length, Corneal Curvature and Corneal Thickness of eye within 36 hours of DSEK surgery. Which was in complete agreement with the previously published work [3, 7]. Similarly, the graphical illustrations for longer time period shows stability after 50-60 days and complete stability is attained after 90 days and remain stable for life time. These observations are in complete agreement with the results published previously in medical research papers [3, 7].

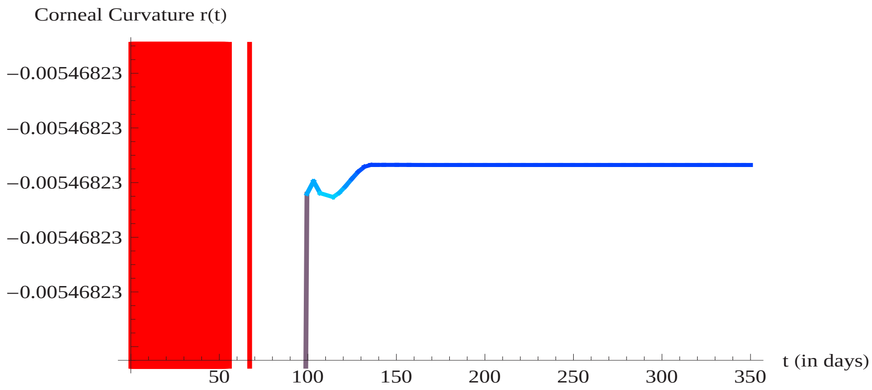

FIGURE 10. In corneal curvature $r(t)$ no huge is observed after few initial days of surgery till when the swelling worn off or stitches gets better.

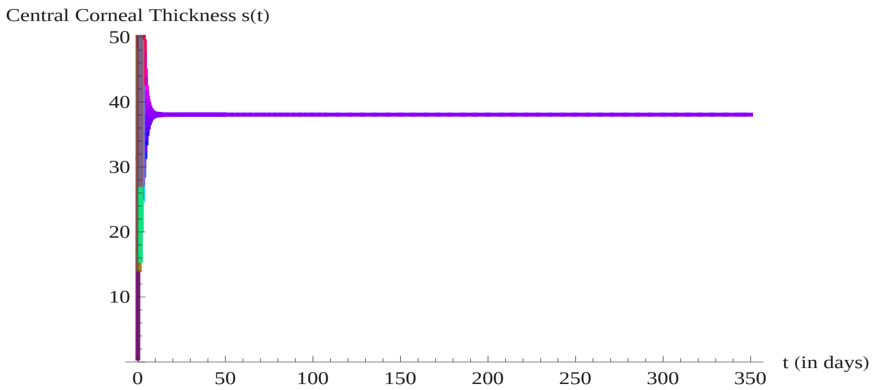

FIGURE 11. After almost three month's of DSEK, the stability can be observed in vision in central corneal thickness $s(t)$.

This method is a simpler technique to analyze the postoperative situation of patients. A numerical case of a hypothetical patient is shown in form of figures to prove the applicability of DSEK system and results are verified by the medical research paper. Such mathematical models can be very helpful for predicting outcomes of the patients beforehand in order to decide whether to opt for surgery or not.

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