The Human Cornea: A New Comprehensive, Biomechanical Structural Model

by

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The main purpose of this study is to theoretically support the new laboratory experiments with biosynthetic materials, trying to replicate the human cornea. It enables to do so by outlining – with a more advanced structural model that is fully supported by experimental data – a fundamental concept that any makers of biosynthetic cornea should always keep in mind: it should faithfully replicate all the features (even the smallest) of a natural human cornea: i.e. sizes, thickness of the layers, shapes, etc., because all the features of a natural human cornea are contributing to a perfect structural distribution of strains and yield stresses both from external forces and from internal sources (i.e. IOP, Intra Ocular Pressure changes inside the anterior chamber).

In section 1 it is being proposed a new, original structural model focusing on the concept of elastic inertia/ellipse, a concept stemming from structural engineering of bridges, that was conceived by Cullman & Ritter at the end of XIX century, which is here being applied for the first time to the structural analysis of the human cornea, leading to the important discovery that the unusual shape of a human cornea’s section (thinner at the central apex, and wider near the limbus) is really the best to assure a constant and uniform distribution of the outside and inside strains on the whole structure.

In section 2, it is underlined the connection between the physiological changes in % of water content, and hydration in corneal membranes, according to the aging, and elasticity/tensile strength. This is a very important - but many times neglected - concept, in the selection of human corneas from donors, and of course in making new biosynthetic corneas. Moreover it is again – as in the first paper in 2012 - emphasized the concept of the reverse “Hall-Petch” tensile strength of the 5 layers in the human cornea, namely the tensile mechanical strength in a crystal lattice is mainly provided by the thinner, outside layers (epithelium + Bowman and Descemet + endothelium layers) rather than by the wider stroma, as it was commonly believed so far in the scientific community.

Some practical applications of mathematical physics concepts, such as the evolution of keratoconus, are also exposed, in order to show the perfect connection between a correct physics model with theory and experimental data.

1) The human cornea as a “watery” multi-layers membrane of collagen crystals floating on the water of the anterior chamber of the eye. Structural analysis according to the elastic ellipse/inertia theory (Cullman & Ritter)

The most important aspect, before starting to conceive a mathematical/physics model of the human cornea, is to clearly understand the main basic features of our cornea, from a structural standpoint.
Our cornea is a series of 5 microscopic layers, having an almost semispherical shape, and whose composition is 80% water molecules, and 20% collagen fibrils and lamellae (in the stroma), plus epithelium/endothelium cells.

This “watery” structure is, in its turn, floating on the liquid of the anterior chamber, and the changes of IOP of water, from a physiological 15 mm. Hg up, are contributing to both stiff the cornea from inside, and to soften the external forces (mainly winking, eye rubbing, etc., but also blows) hitting the corneal membrane.

An important—and very often neglected—feature of the human cornea is the unusual shape of its section, namely an arch whose central apex is narrow (see Dubbelman et al. [1]) around 0.627 mm. thickness, as average, and larger near the limbus, around 0.756 mm. thickness.

Now, as we shall see, this shape is not at all so “by chance”, but such a shape is fundamental to assure the best distribution of the stresses on the whole corneal structure.

To better understand this point, it is necessary to focus on the concept of “ellipse of inertia”, in structural engineering, as conceived by Cullman and Ritter, at the end of XIX century. [2] [3]

Moment of inertia, or polar moment of inertia of a mass, can be defined as the property of distribution of mass in space that is measuring its resistance to rotational acceleration around an axis. (see Wikipedia, [4])

On a basic, “punctiform” approach, we can say that the moment of inertia of a body is:

\[ I = m \, r^2 \]

Where \( m \) is a point mass of a rotating body, and \( r \) is the distance to the rotating axis (according to the Huygens-Steiner theorem).

Therefore, the displacement of the moment of inertia on a rotating body, can also be expressed in mathematical form, according to the equation of ellipse, namely:

\[ \frac{x^2}{a^2} + \frac{y^2}{b^2} = 1 \]

A further, and more complex (see Bramanti et al.: [5]), way to mathematically describe the moment of inertia on a 3D body \( \Omega \), whose density is: \( \rho(x,y,z) \), and with a distance \( \delta \) of a point with respect to the 3 axes is the following triple integral:

\[ I = \iiint_{\Omega} \delta^2 (x,y,z) \, dx\,dy\,dz, \]

Now, the known equations above can also be used to precisely understand the constant distribution of the external elastic weights and forces applied on an arch iron bridge, as illustrated by Cullman and Ritter.

In order to keep constant (= C) the bending stiffness, namely the forces resting on the arch frame, we can write down as follows the equation of the moment of inertia \( dJ \) (on the arch structure):
Where $E$ is the Young modulus of iron/steel, $dJ$ is the infinitesimal variation of the moment of inertia, and $ds/dx$ is the change of thickness of the arch, in a discretized form (see “On the Theory of Ellipse of Elasticity” p. 588, figure 7) and considering $dx = \Delta x = \text{cost}$.

As the Young modulus of elasticity does not change in a steel bridge, for infinitesimal analysis purpose of stress change, the equation (3) can also be written:

$$dJ \cdot ds/dx = C$$

It is important to underline that any moment of inertia $dJ$ is subject to an equivalent and contrary force: $d\sigma$, which is equal to any outside bending stress on the bridge’s structure.

Therefore, we can write either $dj = -d\sigma$, or better

$$d\sigma = -dJ$$

This means that any bending external stress $d\sigma$ on the bridge’s frame is opposed by an equivalent and contrary moment of inertia $-dJ$.

Moreover, – from a vector standpoint – any force applied on a surface has a double component:

a) a tangential component: $tg$, that is parallel to the surface

b) a normal component: $N$, which is perpendicular to the surface

Therefore, according to the elastic inertia/ellipse theory, any external bending force (stress) $d\sigma (= -dJ)$ is bigger on top of the bridge – and you have bigger tangential and normal components in the modulus of vectors - undergoing the highest strains by the weight of trains, cars and passengers, whereas we have decreasing bending forces from apex to the bases.

However, since the thickness of the bridge is lower at the apex, and it is increasing at the bases, according to the elastic inertia/ellipse theory, the product $d\sigma (= -dJ) \cdot ds/dx$ is always constant ($= C$) in any point of the frame.

This is the first important result we can get: namely an “unusual” structure of an arch bridge: lowest thickness at the apex, and biggest thickness at the 2 bases, is not at all “casual”, but it is important to keep constant on the whole structure (thereby avoiding too many stresses and an overcharge of straining forces on some areas of the frame) the distribution of external stresses.

After this, we can simply transfer the concepts above on the very similar natural structure of the human cornea.

The section of our human cornea is analogous to the arch bridge above.

We have a “narrow” central apex (nearly 83% of the bases near the limbus), and 2 “wider” bases.

The only difference – in respect of the bridge above – is that in our human cornea the central apex is a bit larger, in comparison with the 2 bases of the bridge (where thickness of apex is just 50% of the bases’
thickness), because the Young modulus of elasticity of our cornea is changing on the whole structure, it is lower at the bases (where the structure is “tender” and elastic) and it is a bit bigger at the central apex, where the cornea is stiffening more.

However, Young modulus of the iron bridge is always constant, both on the central apex and at the bases.

Thus, in our human cornea section, there is no need to have a so bigger thickness of the bases, because their elasticity allows a further elongation/expansion near the limbus, as a reaction to the external strains, or to any increase in IOP (Intra Ocular Pressure) from inside.

So, a central apex which is “only” and nearly 83% of corneal thickness near the limbus/bases is enough to keep constant (C) the distribution of stresses on the whole corneal structure, considering the expansion/elongation of the more elastic corneal bases, under strain.

It is important, in order to precisely understand and describe the behavior of stresses/forces on the whole corneal structure, to keep in mind the big difference between the behavior of external and internal stresses on the corneal surface.

1) The external strains/stresses of the cornea arise from forces hitting on a relatively small surface on a curve structure (we can say they tend to hit on a “punctual” way)

2) On the contrary, the internal stresses, arise from changes of IOP, according to physical, mental, etc. efforts of our body, or even postural changes, or diseases as glaucoma, etc. causing very often also a change of heart beat and IOP, that could range from 15 mm.Hg, up to 100 mm. Hg and more (see Stamper, Tanaka [6])

But, as the internal changes of IOP are causing also a change of pressure of liquid humor in the anterior chamber, and according to the Pascal law of fluids, as any fluid is transmitting with its whole mass the pressure on it, and with the same intensity to any surrounding solid surface, this means that the internal surface of the cornea, from endothelium to epithelium, is receiving an uniform and equal IOP in any points.

These concepts are very important, because they highlight also a difference in the mathematical description of the internal and external strains on the corneal surface.

With ref. to the external forces/strains, hitting on a curve and almost “punctual” surface - where there is almost no change of Young modulus of elasticity – we can mathematically write down an equation describing precisely their behavior on the whole external surface, as follows:

\[(7) \quad \sigma (\text{or } d\sigma) * ds/dx = C\]

But, in the internal corneal surface, any internal stress/strain \(d \sigma\) from IOP, cannot exactly be compared with the external stresses because, as the IOP from liquid humor’s pressure changes is uniformly and radially distributing on the whole internal surface, this means that – on a vector standpoint – the IOP stress vector \(d \sigma\) is lacking the tangential component \(dtg\), because the latter is always uniform and does not change, as the IOP radial pressure from liquid humor is the same in any points of the internal surface.

Therefore, as the work \(W\) performed by a force \(F\) on a surface, is:
\[ W = \int F^* \Delta s \quad \text{or} \quad W = \int F^* \cos \vartheta \]

And of course the cosine of a 90° tangential component of stress vector is always 0, thus the dσ IOP stress vector is lacking the tangential component, and can be described just as a “scalar”, with only changes in modulus of the normal/radial component.

But this means that the IOP internal radial and uniform stresses from liquid humor, cannot be compared with the external stresses on the corneal surface, as in the eq. (7).

In other words: the net pressure force is given by the vector:

\[ F \text{ (pressure)} = (F_x, F_y, F_z) = -\left(\frac{\partial p}{\partial x}, \frac{\partial p}{\partial y}, \frac{\partial p}{\partial z}\right) \delta x \delta y \delta z = -\nabla p \delta x \delta y \delta z \]

Hence, the net force is only dependent on the gradient of pressure \( \nabla p \) above. “Clearly, a uniform pressure applied to all faces of the parcel [or better: internal surface of cornea N.o.A.] would not introduce any net force” (see PAOC/MIT/edu “Chapter 6: The equation of fluid motion” [7])

However, as any uniform and radial changes in IOP are hitting an internal corneal surface having different values of \( E \) (Young modulus), from bigger numbers (i.e. “stiffer” surface) on the central apex, to smaller (i.e. “tender” surface) numbers near the limbus, at the bases, then we can re-write the equation (7), for the IOP stresses, as follows:

\[ \text{dE} * \frac{\text{ds}}{\text{dx}} = C \]

And now, to see how the corneal surface behaves, in a boundary equilibrium situation, it is sufficient to write the system:

\[ \begin{cases} 
\text{dσ (or – dJ)} * \frac{\text{ds}}{\text{dx}} = C \\
\text{dE} * \frac{\text{ds}}{\text{dx}} = C 
\end{cases} \]

whose simple solution is, clearly:

\[ \text{dσ (or – dJ)} = \text{dE} \]

This formulation is important, because it is the indication that, in the internal surface of human cornea, any stress change is linked to the variation of Young modulus.

Young modulus of elasticity can be written, in an expanded form:

\[ E = \frac{F/A}{l/\Delta l} \]
Where \( F \) is a force/stress laying on an unit Area \((A)\), \( l \) is unit length of a material, and \( \Delta l \) is the elongation of the material under stress. Therefore, there is a reverse relationship: \( \frac{E}{l} = F \), (whenever a constant force/stress is being applied on different materials) between the change of Young modulus and the change of elongation, namely stiffer materials, having higher Young modulus, are displaying lower changes in elongation, according to Hooke’s law.

It is interesting to note that, if we integrate the function of Young modulus \( E \), the result is:

\[
\int E \, (dE) = \frac{E^2}{2} + c
\]

Which is a typical exponential function in a parabolic shape, showing that the behavior of changes in Young modulus, in the internal surface of human cornea – as in the protrusion of keratoconus that we shall examine – is following a typical parabolic shape, with vertex of parabolic arch coincident with the apex of conus in keratoconus.

Then, if we examine the behavior of the elongation \( l \), as strictly linked to the change of Young modulus, namely \( l = \frac{1}{E} \), then we can write the eq. (13), as

\[
l^2 = \frac{1}{E^2}
\]

And it is possible to find the same parabolic behavior, examining the experimental apical displacement vs. increase of IOP. (see [8] Anderson K, El Sheikh, Newton: “Application of the Structural Analysis to the Mechanical Behavior of the Cornea”, 2004)

With ref. to the function of the elongation alone (i.e. as not linked to the Young modulus change \( E \)) : \( \frac{1}{l} \), if we integrate, we get:

\[
\int \frac{dl}{l} = \log |l| + c
\]

This is a typical logarithmic function, meaning that the elongation of cornea’s internal surface, as a result of IOP increase, is faster with the first increases of pressure, and then it is rising very slowly.

2). Experimental behavior of keratoconic protrusion, according to the Hall-Petch relationship and the function of Young modulus. Changes of thickness in human cornea, according to aging, % of water content, physiological/pathologic changes of IOP.

It is interesting to find out that the parabolic/exponential eq. (14) above, describing the changes of Young modulus \( E \), along with the Hall-Petch reverse relationship [9] between tensile strength and thickness of the 5 layers of the cornea – according to which the less thick layers are more stronger than stroma, and give a bigger contribute to the mechanical stability of the cornea - are experimentally clearly evidenced, if we take care to the evolution of keratoconus.

Although the aetiology of keratoconus is still far from really having been clarified, many specialists seem to agree that:

“Once initiated, the disease normally develops by progressive dissolution of Bowman’s layer, which lies between the corneal epithelium and stroma. As the two come into contact, cellular and structural changes in the cornea adversely affect its integrity and lead to the bulging and scarring characteristic of the disorder. “ (Epstein A.: “Keratoconus and Related Desorders” 2000 [10])
Description above is important because it emphasizes the major role played by the “thinner” Bowman’s layer, rather than the “wider” stroma (as commonly believed in the scientific community in the past), in the development of keratoconus.

As Bowman’s layer has a major tensile strength than stroma, the dissolution of the former makes the cornea considerably “softer” in the apex than a normal/non pathologic cornea.

Therefore Young modulus of the corneal apex is decreasing, while the elongation increases.

For this reason, the cornea is losing its usual spherical shape, and a protrusion following the eq. (14) above, with a parabolic shape of cone, and vertex at the apex, is taking place, and the typical elongation reaches the peak in the center of apex, where both pressure and weight of liquid humor are bigger than in other areas.

Another experimental evidence of the direct relationship between any changes of IOP, aging, and elongation of the internal surface of the cornea, according to the eq. (12) do (or – dJ) = dE, is provided by Elsheikh, Geraghty, Rama, et al. ([11] “Characterization of age-related variation in corneal biomechanical properties” 2010):

“The stress–strain results show clear stiffening effect associated with increased age. The average increase in material stiffness (as measured by the tangent modulus, E) at a strain of 0.01 ranged between 15 and 20 per cent per decade within the first loading cycle, and between 7 and 11 per cent within the fourth cycle. Increased stiffness could result from age-related changes in corneal microstructure as well as changes in collagen fibril strength. For example, between the ages of 40 and 80, collagen fibril diameters increase (Daxer et al 1998[12]) and collagen centre-to-centre interfibrillar spacings decrease(Malik et al 1992[13]) and this leads to an increase in the fibril volume fraction. Both theoretically (Boote et al 2005[14]) and experimentally (Goh et al 2008[15]) fibril volume fraction has been shown to be directly proportional to the elastic modulus.”

Even more important is the following passage:

The asphericity of both the anterior and posterior corneal surfaces was reported to undergo significant changes with age, leading to a more spherical topography (Lam & Douthwaite 2002[16]) and peripheral thinning (Dubbelman et al 2006 see [1]).

Peripheral thinning related to age, simply means that the more elastic corneal areas near the limbus, undergoing a bigger displacement than the stiffer apex, facing a constant increase of IOP and dσ with age, tend to become thinner, just according to eq. (12).

But it is also important to underline another very important change in human body, with aging, that is normally neglected by the researchers in the ophthalmic/corneal field, and it is the body dehydration, namely the decrease in total body water, with aging, that is progressive, and particularly dramatic between age 60-70 y, both in males and females. (see Schoeller D. “Changes in total body water with age” [17])

This is also important with respect to the cornea, because the decrease of water %, with aging, increases the % content of collagen crystal fibrils/lamellae, and so there is an increase of crystal index, i.e. an hardening of the whole corneal membranes, which is also a further evidence of the Hall-Petch relationship, as applied to the multi-layers crystal lattice of the human cornea.
Experimental evidence of the Hall-Petch relationship validity, according to which thinner corneal membranes such as Bowman and Descemet do contribute to the tensile strength of the whole cornea, more than a much thicker stromal membrane, following a reverse relationship, is provided again by the close examination of the keratoconus disease evolution.

Bowman membrane is less than 2% of the whole cornea (we take an average 560 µ corneal thickness).

If – according to the old common belief in the scientific community – any membranes would contribute to the tensile strength in a directly proportional way to the thickness, then there would be no meaningful contribution by thinner membranes to the stability and tensile strength of the whole structure. Thus, a pathologic dissolution – after the early development of keratoconus disease - of the very thin Bowman membrane would hardly produce something more than negligible consequences (at most a slight unevenness in the round/spherical curvature, i.e. a slight astigmatism).

Conversely, if a reverse “Hall-Petch” relationship between thickness and “hardness”/tensile strength is working, according to the formula: \( \frac{1}{\sqrt{L}} \) (L = thickness), then a Bowman membrane, only 10 µ thick, is contributing to the corneal mechanical stability for \( \frac{1}{\sqrt{10}}/1.275 \) (= total sum of reversed thicknesses of corneal membranes) = 0.31/1.275 = 0.24, namely a relevant 24% (and not only a 2%)

Therefore, pathologic removal/dissolution of Bowman membrane and its contribution, at early stages of keratoconus, very well accounts for the quick and dramatic sinking and parabolic protrusion of the central apex of cornea, so much weakened, and under pressure and weight of liquid humor inside.

And finally, another important (though almost totally neglected) parameter influencing the parabolic protrusion of the weakened corneal apex, is the:

(17)

\[
\text{Coriolis acceleration: } -2 \Omega \cdot u(\text{rot}), \text{ where:} \\
u(\text{rot}) = Dr/Dt
\]

with: \( \Omega = \text{rotation rate}, r = \text{corneal radius (max)}, t = \text{time} \)

It is easy to experimentally find out that Coriolis acceleration of Earth, due to its rotation around its own axis, is another (though not so evident) parameter stressing upon human body and cornea, and overlapping (along with gradient of pressure on the lower central E modulus as in eq. (14)) on the parabolic protrusion of the weakened corneal apex, in keratoconus disease, because if we place water inside a rotating tank, the surface of water is not flat, but it takes on the shape of a parabola, according to eq.:

(18)

\[
h(r) = h(0) + \Omega^2 r^2/2g
\]

where:
h(r) is the height of fluid (or liquid humor), h(0) is the height of fluid in the middle of the tank (or vertex of corneal apex), and g is the gravitational acceleration. (see again “The equation of fluid motion”, p. 180, as above at [7])

Thus, Coriolis acceleration of Earth and Hall-Petch reverse relationship on the weakened corneal frame in keratoconus disease, are two experimental evidences of the quick change from a healthy spherical shape into a pathologic parabolic (“conical”) corneal protrusion of central apex.

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References:


[17] Schoeller D. “Changes in total body water with age” 1989