Effect of Age-Related Human Lens Sutures Growth on Its Fluid Dynamics

Ho-Ting D. Wu,1 Louisa A. Howse,1 and Ehsan Vaghefi1,2

1School of Optometry and Vision Sciences, University of Auckland, New Zealand
2Auckland Bioengineering Institute, University of Auckland, New Zealand

Correspondence: Ehsan Vaghefi, Grafton School of Optometry and Vision Science, University of Auckland, 85 Park Road, New Zealand; e.vaghefi@auckland.ac.nz.
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PURPOSE. Age-related nuclear cataract is the opacification of the clear ocular lens due to oxidative damage as we age, and is the leading cause of blindness in the world. A lack of antioxidant supply to the core of ever-growing ocular lens could contribute to the cause of this condition. In this project, a computational model was developed to study the sutural fluid inflow of the aging human lens.

METHODS. Three different SOLIDWORKS computational fluid dynamics models of the human lens (7 years old; 28 years old; 46 years old) were created, based on available literature data. The fluid dynamics of the lens sutures were modelled using the Stokes flow equations, combined with realistic physiological boundary conditions and embedded in COMSOL Multiphysics.

RESULTS. The flow rate, volume, and flow rate per volume of fluid entering the aging lens were examined, and all increased over the 40 years modelled. However, while the volume of the lens grew by ~500% and the flow rate increased by ~400%, the flow rate per volume increased only by very moderate ~38%.

CONCLUSIONS. Here, sutural information from humans of 7 to 46 years of age was obtained. In this modelled age range, an increase of flow rate per volume was observed, albeit at very slow rate. We hypothesize that with even further increasing age (60+ years old), the lens volume growth would outpace its flow rate increases, which would eventually lead to malnutrition of the lens nucleus and onset of cataracts.

Keywords: age-related nuclear cataract, sutural inflow, finite element modelling, lens changes in aging

The visual system allows us to interpret the surrounding environment by processing information, within the visible spectrum. The eye contains two main optical structures, the lens and the cornea, both of which focus light rays onto the retina. The lens is the only optical structure that can fine-tune light onto the retina so that a sharp image is formed. The lens is a transparent, quasi-spherical structure, made up of many fibre cells. These fibre cells are bundled together in layers to form different regions within the lens, namely the outer cortex, the inner cortex, and the core. In order to stay transparent, the lens is avascular. However, the lens cannot rely on passive diffusion alone to provide nutrients and remove wastes from its core as this would be too slow. Instead, the physiological optics homeostasis of the lens is maintained through an active process called the microcirculation system. Briefly, in this system, solutes enter the lens via anterior and posterior poles, predominantly through sutures. These solutes and accompanying water then move extracellularly toward the core of the lens, where at some point, they cross the cell membrane into the cytoplasm of fibre cells. When in intracellular space, the water and solute move outwardly from cell layer to next through a vast network of gap junctions. Then at the surface of the lens, they are pumped out of the lens predominantly at the equator (Fig. 1). As the lens ages, its physiological optic properties change, such as protein: water concentration, overall shape, and known sutural geometry. Specifically, in humans, the lens volume increases with age as new cells are created and added to the bulk of the tissue. One could imagine that a larger lens volume, and increased cell numbers, requires a greater influx of nutrients, such as antioxidants, especially in oldest part of the tissue, which is its nucleus. It then follows that if the aged lens core does not receive sufficient antioxidants, there will be accelerated accumulative oxidative damage to the cells of this region, leading to onset of age-related nuclear cataract.

Hence one natural strategy to delay the onset of cataracts is to increase the influx of nutrients and enhance their access to lens core, to compensate for the aging process. A flow of water and solutes can be increased by increasing its velocity or the surface area of its channel. Hence in an aging lens, enhanced nutrition delivery can only be achieved by a higher extracellular flow velocity and/or a greater sutural surface area. Focusing on the latter component, it has been shown that the sutural structure becomes progressively more complex in primates, which also increases its surface area and volume. In particular, there are four distinct age-groups of sutures patterns throughout the lens, which considerably improves the optical performance of the lens. Throughout the embryonic development, the sutures are "Y" shaped; later, they become star shaped during adolescence. As the lens continues to age, the star-shaped sutures become more...
complicated as new branches are formed. Several different computer models in the form of cylindrical map projections (CMP) and computer aided design (CAD) had been used to describe the process of sutures growth.\(^{10,15}\) However, these models were generic and not representative of true aging process in humans.

In this paper, we have used clinical data to create representative computer models of human lens growth and increased complexity of sutural geometry. We then investigated the effects of these changes on water and solute influx rates at different stages of human life. It should be noted that computational modelling of a complex tissue with disruptive geometrical features, like the lens and its sutures, is a step-by-step process. The microcirculation model has been developed and optimized for over decades now, and it still does not include an accurate representation of the sutures. To fully implement the sutures, in this paper the geometry from clinical images has been obtained, representative computer meshes were created, appropriate fluid dynamics equations have been applied, and the sutural model is computationally solved, in isolation. The next step of this research would be to “connect” the computationally stable model of the sutures with the continuum model of microcirculation, through appropriate boundary conditions selection, on both meshes.

By perfecting anatomically and physiologically accurate computational models of the human lens, we can aim to understand and predict the changes of the lens associated with aging, in its geometry, its fluid dynamics and consequently its nutrients influx. This knowledge will be used to increase our understanding of the onset of lenticular pathologies, such as age-related nuclear cataracts, and presbyopia.

**METHODS**

To create a fully functional fluid dynamics model of the human lens, capable of capturing its fluid and solute fluxes, several steps were followed.
design tool of SOLIDWORKS, to visually match the clinical images (Fig. 2).

Geometrical Model of the Lens

The sutural models of different ages had to be embodied in a full model of the lens of the matching age. The overall dimension of the lens was taken from literature and Table 1. It was assumed that the lenses are rotationally symmetric about the visual axis, and the dimensions of the core and the inner cortex can be determined by a ratio to the lens’ overall dimension. The SOLIDWORKS sketch tool was used to create a two-dimensional projection of the core, the inner cortex and the outer cortex, respectively. A revolved structure with these projections with an axis of revolution of 360° were then created to form the solid structures.

It was decided to separate the lens into three different regions of outer cortex, inner cortex, and the core based on the control groups in a study about the lens shape and refractive index distribution in type 1 diabetes. There was no available data for the dimensions of a 7-year-old lens. The lens dimensions were instead determined through interpolation on MATLAB (Mathworks, Natick, MA, USA). Interpolation requires information about the trend on either side of the desired value and the final results are summarized (Table 1) and shown (Fig. 3).

This model was then used to solve the fluid dynamics of the sutures at different stages of human life.

Fluid Dynamics Model of the Sutures

COMSOL Multiphysics (COMSOL, Inc., Palo Alto, CA, USA) was used to model the fluid dynamics of the sutural model that was created in SOLIDWORKS. In the eye, the lens is submerged anteriorly in the aqueous humour in the anterior chamber, and posteriorly in the vitreous humour in the vitreous cavity. The aqueous humour is less viscous than the vitreous humour. To model this phenomenon, the fluid properties and the typical fluid velocity of the aqueous and vitreous humour were used (Table 2). In this instance of applying the boundary conditions, we determined the general inflow velocity magnitude to be 2e-4 and 6e-3 mm/s at the surfaces of the anterior and posterior sutures, respectively. These conditions were applied with a “normal to surface” condition selected within COMSOL Multiphysics programming platform. The modelling software then correctly applied the boundary conditions, with respect to the geometrical structure of the model. Thus, the velocity boundary condition is always normal to the surface and the user did not have to create an explicit set of boundary conditions to supply to the software.

The fluid dynamics of the lens and in turn the sutures can be modelled by a simplified version of the Navier-Stokes equations. It assumed the fluid in the lens is an incompressible Newtonian fluid with a spatially constant viscosity at steady state. The second assumption is that the fluid flow in the lens is a creeping or low-Reynolds number flow with negligible turbulence. From these assumptions, the full Navier-Stokes equations were simplified to the Stokes equations (Equation 1 and Equation 2).

\[ \nabla \cdot \mathbf{u} = 0 \]  
\[ -\nabla p + \mu \nabla^2 \mathbf{u} + \mathbf{f} = 0 \]

Here, \( \mathbf{u} \) is the velocity (m/s), \( p \) is the hydrostatic pressure (N/m²), \( \mu \) is the dynamic viscosity (N · s/m²), and \( \mathbf{f} \) is the body force per unit mass (N/kg) acting on the fluid. The boundary conditions of the bulk fluid movement model were determined from literature. Fluid entered the anterior and posterior lens with velocities of 2 × 10⁻⁴ mm/s and 6 × 10⁻³ mm/s, respectively, which mimics the typical flow velocities in the aqueous and vitreous humour, respectively.

A notable difference between this implementation and previous models is that there exists a pressure difference between the anterior and posterior lens. This difference in pressure was calculated by a MATLAB script, which utilised the ratio between the intraocular pressure (IOP) of the anterior

<table>
<thead>
<tr>
<th>Age of Lens, y</th>
<th>Equatorial Length Diameter, mm</th>
<th>Anterior Axial Thickness, mm</th>
<th>Posterior Axial Thickness, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.00</td>
<td>1.10</td>
<td>1.40</td>
</tr>
<tr>
<td>7</td>
<td>7.16</td>
<td>0.98</td>
<td>1.66</td>
</tr>
<tr>
<td>28</td>
<td>9.32</td>
<td>1.04</td>
<td>2.34</td>
</tr>
<tr>
<td>46</td>
<td>9.61</td>
<td>1.57</td>
<td>2.80</td>
</tr>
</tbody>
</table>
high extracellular pressure where intracellular pressure is pressure measurements are available. It was necessary to experimentally measured yet and only intracellular can be seen in Figure 4. The extracellular pressure of the lens is diagrammatic view of the sutural model boundary conditions the centre of the lens is assumed to be 0 mm Hg, a

\[
p_{\text{surf}}(x, y, z) = -p_{\text{surf}} \left( \sqrt{x^2 + y^2 + z^2} \right)^2 + p_{\text{surf}} \quad (3)
\]

Here \( p_{\text{surf}} \) is the pressure of the surface of the lens, \( \sqrt{x^2 + y^2 + z^2} \) is the radius of the lens and \( b \) is the height of the anterior and posterior lens, respectively. The pressure of the centre of the lens is assumed to be 0 mm Hg, a diagrammatic view of the sutural model boundary conditions can be seen in Figure 4. The extracellular pressure of the lens is not experimentally measured yet and only intracellular pressure measurements are available. It was necessary to assume an extracellular pressure gradient, for our sutural model to be solvable. Hence, it was decided to “mirror” the measured intracellular pressure. By “mirror,” we mean low extracellular pressure where intracellular pressure is high, and high extracellular pressure where intracellular pressure is low. Hence, the “mirror” assumption implies a higher extracellular pressure at the surface and lower extracellular pressure at the core of the lens, based on observed “mirrored” intra/extracellular distributions of electrical voltage and solute concentrations.

The 3D geometry of the sutures was discretized to have maximum element size of \( 2.44 \times 10^{-4} \)m, the minimum element size is \( 1.77 \times 10^{-5} \)m, the maximum element growth rate of 1.4, the curvature factor of 0.4, and the resolution of narrow regions of 0.7 (Fig. 4). The particular factors used in the mesh generation were default from COMSOL Multiphysics where the color bar expresses the velocity magnitude throughout the domain of interest (Fig. 5). From these results, it appeared that the velocity of sutural models at varying ages, the velocity of the fluid at two distinct points, one in the anterior and the other in the posterior part of the lens were extracted (Fig. 4). These points were deemed to be of interest, because they are the intersection points where the end of the sutures meet the core of the lens. The positioning of points 1 and 2 at each age stage model and the magnitude of fluid velocity at point 1 and point 2 of the sutural models are listed here (Table 3).

The fluid-flow patterns were produced in the COMSOL Multiphysics where the color bar expresses the velocity magnitude throughout the domain of interest (Fig. 5). In all the patterns, the red areas represented where the fluid was travelling with a faster velocity and blue, slower (Fig. 6).

Using data export function of COMSOL Multiphysics, the effects of aging on sutural fluid dynamics. The velocity magnitude at anterior and posterior surface nodes were first exported from COMSOL Multiphysics, these were subsequently summed to find the total velocity magnitude (\( U \)). The surface area of the sutural outlets were then obtained in COMSOL Multiphysics (A) and the flowrate was calculated by multiplying the total velocity magnitude with the outlet sutural surface area (\( q = UA \)). The total volume of the three lenses were obtained from COMSOL Multiphysics (V). This volume information was then used to calculate the flowrate per volume (\( \dot{q} = q/V \)) (Table 4).

From these results, it appeared that the velocity of sutural fluxes increased with age. Combined with increased surface area of sutures through “branching,” the flowrate is also increased within the sutures. However, the volume of the lens (V) has also increased with aging, which affects the parameter flowrate per volume (\( \dot{q} \)). The age-related changes of these parameters are plotted here (Fig. 6).

It was very interesting to observe (Fig. 6) that flowrate and volume grow at about the same rate. This concludes that the flowrate per volume (\( \dot{q} \)) is relatively constant with aging. In the absence of experimental data, we can only speculate that this observation might have some implication for understanding the process of aging in the human lens.
CONCLUSIONS

The human lens grows by adding new fibre cell layers at the periphery, which results in increase in thickness and diameter with age in a nonlinear fashion.\textsuperscript{11,34–38} This process is accompanied by compaction of fibre cells, especially in the core and inner cortex of the lens, overall flattening of the lens and branching of the originally Y-shaped sutures into *-shape ultrastructure.\textsuperscript{10,39–41} Although complex in nature, the main outcome of this process is for the core of the lens to buried deeper inside the tissue and becoming less accessible by eye’s humours. This in turn translates to reduced supply of nutrients (especially antioxidants) to the lens core with advancing age, accumulated oxidative damage, and ultimately onset of age-related nuclear cataract. However, most humans can live without significant cataract for six decades, and sometimes much longer. We believe that sutures “branching” with age, is an evolutionary compensatory mechanism that could to some extent improves the lens core accessibility.

Here, clinical images of sutural cataract were used to create 3D realistic models of the sutures. These models were then combined with realistic geometries of the lens volume at different ages, based on published measurements. Finally, fluid dynamics of the sutures were modelled using simplified Navier-Stokes equations and published boundary conditions. Overall, an increase in velocity of sutural fluxes was with aging of our model. This increase, combined with larger sutural surface area through “branching” led to higher sutural flowrates, under employed modelling conditions here. However, the flowrate per volume seemed to be relatively constant with age. It should be noted that it is very difficult to choose an average shape and dimension of a human lens, at a certain age. This is due to ethnicity-related eye-shape factor, varying refractive errors, accommodation capacities, and potential presence of cataracts in an age-matched population. Comprehensive clinical ocular and lenticular biometric studies are needed to establish a more representative model of changing human lens and sutures in aging.

Another limitation of this study was that it had to use available sutural cataract data sets, to create a representative

<table>
<thead>
<tr>
<th>Age, y</th>
<th>$\sum U$, m/s</th>
<th>$A$ (m$^2$)</th>
<th>$q$ (m$^3$/s)</th>
<th>$V$ (m$^3$)</th>
<th>$\dot{q}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>986.23</td>
<td>1.44E-05</td>
<td>0.014</td>
<td>7.01E-08</td>
<td>203233.9</td>
</tr>
<tr>
<td>28</td>
<td>1325.07</td>
<td>2.33E-05</td>
<td>0.031</td>
<td>1.52E-07</td>
<td>202325.5</td>
</tr>
<tr>
<td>46</td>
<td>1908.74</td>
<td>3.02E-05</td>
<td>0.058</td>
<td>2.06E-07</td>
<td>279589.3</td>
</tr>
</tbody>
</table>
model of the suture’s geometry. This meant that the oldest lens modelled here was 46 years old. Currently, several imaging modalities are being investigated in our lab to visualize the sutural patterns of healthy lenses. By imaging larger number of participants over a more extended lifetime period, the scope of this project will be expanded and the hypothesis of flowrate per volume decline at later ages can be examined.

The oldest lens in this project was 46 years old. It is known that volume of the lens continues to grow at even older ages. One would expect that the volume growth rate of the lens will eventually outpace its sutural surface area increase. This is due to the fact that volume growth is a function of radius-cube ($r^3$), while sutural surface area increase is related to radius-square ($r^2$). Since the sutural flow rate changes with aging in humans have not been measured experimentally, using the results of our study here, we can speculate that the flowrate per volume might then begin to decline, leading to reduced delivery of antioxidants to the central region of the lens, leading to onset of age-related nuclear cataract.

The presented work here, is an isolated model of the lens sutures, and is not “connected” to a model of the rest of the lens. However, geometrically, the sutural model is the only missing piece of the established microcirculation model. The current form of the microcirculation implementation is a bi-domain continuum model. As the name suggests, the bi-domain model is consisted of two domains, namely the intracellular and extracellular spaces. Each element of the bi-domain continuum model, by design, includes predefined ratios locally varying ratios of intracellular and extracellular spaces of the lens. The bi-domain continuum model then tries to simulate the “net effect” of fluid dynamics of those domains. The bi-domain continuum model is based on the symmetrical nature of the lens. As a result, the asymmetrical structure of the sutures, especially in primates are not currently captured. Hence, the disruptive geometry, fluid dynamics, and age-related changes of sutures of the lens are not currently captured by the bi-domain model. Our current work is a step toward a comprehensive model of the lens microcirculation, by capturing the asymmetrical nature of the lens sutures, and its nonlinear changes with age. We are improving our model toward a comprehensive computational predictive tool, “connecting” the sutural and microcirculation models, so that clinicians could “estimate” an age of cataract onset, based on individual patient data and accurate fluid dynamics modelling.

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References


