Numerical solution of flow resistance in outflow pathway and intravitreal drug delivery in vitrectomised eyes

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NUMERICAL SOLUTION OF FLOW RESISTANCE IN OUTFLOW PATHWAY AND INTRAVITREAL DRUG DELIVERY IN VITRECTOMISED EYES

A Thesis
Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Master of Science

in

Mechanical Engineering

by
Jyoti Kathawate
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ABSTRACT

In this study, numerical computations of the ocular fluid dynamics in a human eye are presented with a perspective of understanding the mechanisms of increased flow resistance. In the present study, the TM is represented as a multilayered-graded porous structure with specific pore size and void fraction. The flow patterns and pressure distribution in anterior chamber are analyzed to delineate key flow mechanism; the shear stresses on the lens, iris and IW of SC are also examined to locate the maximum values. Inside the human eye, the largest pressure drop occurs across JCT and IW of SC. The highest pressure in SC is at the midpoint between two collector channels (CC). The pressure falls near CC, which implies that the IW of SC will experience more pressure difference towards CC, and the canal may show a greater tendency to collapse close to the CC exits. The maximum velocity is found in the vicinity of IW pores. It is also seen that AH velocity funneling out of the IW pores is higher in the region underlying the collector. Analysis is also carried out for glaucomatous condition where the IOP is increased to a high value of 8000 Pa.

The later part of thesis is dedicated to the drug delivery to the posterior segment of the eye. The main objective of this study is to characterize the spatio-temporal evolution of drug distribution following intravitreal injection into a vitreous substitute such as silicone oil and in the case of vitreous liquefaction caused due to aging. Both direct injection of drugs and injection of time-released drugs are studied. The results show that the concentration distribution is highly dependent on the vitreous substitute, diffusion coefficient of the drug and the permeability of the retinal surface. For drugs with high diffusion coefficients, convection plays a small role whereas for the drugs with
low diffusion coefficients and low viscosity vitreous fluids, convection is seen to play a more important role and can lead to high drug concentrations on the retina, which can be potentially toxic. Time-released drug injection is shown to avoid conditions of retinal toxicity.
CHAPTER 1. INTRODUCTION

1.1 Objective

The eye is a complex physiological system controlled by mechanical, biochemical, and neurological factors, which, under normal conditions, maintain stability and regulation of the intra-ocular pressure (IOP). This stability and regulation are essential for the maintenance of the eye’s visual functions and for the nourishment of its tissues. Understanding the details of the ocular fluid flow in the human eye is of interest to ophthalmologists so that they can adapt treatment procedures in case of eye disease. However, many aspects of fluid flow within the eye have not yet been fully examined or quantitatively explained. Many difficulties occur for in-vivo experiments on human eye because of their small size, low velocities, etc., and developing numerical models constitutes an attractive approach to study the human eye.

Figure 1-1: Outflow path of Aqueous Humor in the human eye [1]

As represented in Fig. 1-1, aqueous humor (AH) is formed by secretion and ultra-filtration in the ciliary process, which are highly vascularized ridges projected from the ciliary body towards the posterior chamber. Aqueous humor enters the eye in the
posterior chamber and passes between the lens and iris before entering the anterior chamber through the pupil. The bulk flow rate in the normal eye varies in the range of 2-3 $\mu$L/min \cite{5, 47}. More than 80% leaves through Trabecular Meshwork (TM) into the Schlemm’s canal (SC), which is located in the vicinity of the junction between the iris and the cornea, usually called as iridocorneal angle. The aqueous humor is then led into the venous system, either in aqueous veins or episcleral veins. Another exit pathway for aqueous humor is uveoscleral drainage system, whereby aqueous humor enters the iris root and passes between the muscle bundles in the ciliary body to the choroids and out through the episcleral tissues. This pathway contributes little part of the outflow in rabbit eyes (20 %) but more in monkey eye (35 %), which is neglected in our human eye model for the simplicity.

The blood flow in the iris and the ciliary body maintains the temperature of these tissues at the body temperature (37 °C) \cite{9}. The outer surface of the cornea (0.6 mm thick) \cite{54} is generally maintained at 32-33 °C \cite{9} by the tear film evaporation. The inner corneal surface is at lower temperature, and is only 2-4 °C less than the body temperature because of the thermal resistance provided by the corneal tissues. However, the small temperature difference (2-4 °C) across the anterior chamber is believed to be the dominant mechanism driving the fluid flow in the anterior chamber of the eye.

The outflow network system of the eye consists of a graded porous mesh from the inside of the eye to the outside. Aqueous in the trabecular outflow encounters a series of narrow passages that offers resistance to its flow; first the uveal portion of the TM; then, in succession, the corneoscleral portion of the meshwork; the juxtacanalicular tissue
and the Inner wall (IW) of Schlemm’s canal (SC) from where the aqueous humor is drained into aqueous veins [11,54].

Most of the diseases associated with the eye are consequence of increase in IOP inside the anterior chamber. The blockage of the eye-drainage system raises the IOP to abnormal values, which leads to Glaucoma. It is surprising that, despite many years of research, precise reasons for increase in aqueous outflow resistance is not known, which implies that the fundamental factors controlling the IOP is not still well understood. Recently two main schools of thought have emerged. One states that extra-cellular matrix (ECM) within the JCT is responsible for the bulk outflow resistance [4, 30]. The other states that the cells within the aqueous outflow pathways, most likely the cells of the IW of SC [6, 30], are themselves directly responsible for the aqueous outflow resistance.

The existing numerical models for the flow field inside the eye are incapable of analyzing the influence of the TM-IW resistance on the IOP and AH-flow profile, which is determining factor for all forms of Glaucoma. One of the purposes of this study is to accurately model the TM and the IW of SC in order to obtain the major regions of flow resistance or major sites of pressure drop. In this study, the following cases are presented: (1) JCT as the source of resistance (JCT-R), (2) IW as the source of resistance (IW-R) and (3) IW with distributed pores as the source of resistance (IWP-R). In summary our main goal is to:

- Present a comprehensive three-dimensional flow simulation where the details of the TM are represented as a graded porous structure, and the flow patterns and the pressure distribution in the anterior chamber for different parametric conditions are analyzed to delineate the key flow mechanisms.
• Accurately model the JCT considering that the entire pressure drop occurs in this region due to the aqueous humor particles deposited in the ECM of JCT.

• Accurately model the IW endothelium of SC. IW of SC is modeled in such a way that only 0.2% of its total area is open for the AH to pass through. The hydraulic conductivity of these pores is very high but the hydraulic conductivity of these pores is not reported yet. Funneling effect [15] observed in the IW is also demonstrated.

• Study the effects of increased pressure in the anterior chamber i.e., for the case of Glaucomatous eye where the IOP is greater than 8000 Pa.

The later part of thesis is concentrated on the drug delivery in the Vitrectomised eyes. Currently, the treatment of retinal diseases is limited by the difficulty in delivering effective doses of the drugs to target tissues in the vitreous chamber. Many drugs have a narrow concentration window of effectiveness and may be toxic at higher concentrations [32]. Therefore, the ability to predict local drug concentration is critical for proper drug delivery. An intravitreal injection provides the most direct approach to delivering drugs to the tissues in the vitreous segment, and therapeutic tissue drug levels can be achieved. Intravitreal injections, however, have potential side effects of retinal detachment, hemorrhage, endophthalmitis, and cataract. In many cases, repeated injections are needed to maintain the effective range of drug concentrations for a certain period of time since the half-life of drugs in the vitreous is relatively short. Repeated injections cause patient discomfort and may further lead to complications such as vitreous hemorrhage, infection, and lens or retinal injury. Therefore, an understanding of the transport of different drugs following intravitreal injection is necessary, so that, the most effective utilization results from each injection. In the present study, a time-dependent numerical model for studying
drug transport following intravitreal injection is developed with the goal of understanding the important parameters that play a critical role in the drug distribution.

Previously, the studies carried out by some researchers assumed that the vitreous body was filled with vitreous humor. One of the more recent developments in eye surgery has been the introduction of the surgical procedure called vitrectomy. Trans pars plana vitrectomy (TPPV) is used to treat many different retinal disorders such as proliferative diabetic retinopathy (including vitreous hemorrhage), macular hole formation, intraocular infections (endophthalmitis), etc. In TPPV, the vitreous is removed and replaced with vitreous substitutes similar to the liquid being removed from the eye. Silicone oil, fluoro silicone oil, perfluorocarbon liquid, etc., are the most commonly used vitreous substitutes [41-42]. Retinal tears are often associated with age-related liquefaction and shrinkage of the vitreous body. In these cases, the vitreous substitutes can be used intra-operatively to push a detached retina to its normal position and to restore the volume of the vitreous cavity. When the drug is injected into the vitreous cavity, knowledge of the drug distribution following injection is very important in order to maximize the therapeutic benefits while minimizing damage to tissues due to high local concentration. This is highlighted by a study by Stainer et al. [43] and Hegazy et al. [44] who have shown that the concentration of drug that is non-toxic when injected into a normal eye and is toxic if used to treat a vitrectomised eye. Thus, it can be potentially dangerous to use the knowledge base for a normal eye to treat the vitrectomised eye, and it is important to develop an understanding of the drug transport with vitreous substitutes.

The goal of the present work is to simulate intravitreal drug delivery in the presence of vitreous substitutes. There is limited information available on intravitreal
drug distribution in the normal eye and is based on the studies carried out by Friedrich et al. [36-37], Park et al. [80], Stay et al. [33] and Xu [38]. However, there is no information available on how the drug is transported in the presence of vitreous substitutes that have different transport properties. In the present study, a time-dependent numerical model for studying drug transport following intravitreal injection is developed with the goal of understanding the important parameters that play a critical role in the drug distribution. The concentration distribution of drug is highly dependent on the vitreous substitute, diffusion coefficient of the drug and the permeability of the retinal surface. A parameter of specific interest is the diffusivity of the drug since different drugs are characterized by different scalar diffusivity. So drugs with different diffusion co-efficient i.e., high and low diffusion co-efficient are studied. In the present study, silicon oil is used an intravitreal substitute and drug distribution as a function of time is examined. Both direct injection of drugs and injection of a time released drug distribution are studied.

Another problem associated with the vitreous is the liquefaction of vitreous humor. In humans, aging brings important changes in the rheological characteristics and the nature of the vitreous. From the age of 45-50 years, the volume of the gel-vitreous in the human eyes decreases steadily, and the volume of the liquid-vitreous proportionally increases. This has been observed with slit lamp investigation carried out by Eisner [46] with direct measurement of the liquid vitreous in formalin-fixed eyes. Thus, due to vitreous liquefaction with aging, fluid circulation is expected in the vitreous chamber leading to a reduction of gradients in the drug concentration within the liquefied portion. This will lead to the reduced half life of the drug in the vitreous chamber. Therefore, in
the present study, we have also included water as one of the vitreous fluids in order to compute the drug transport for the case of liquefied vitreous.

1.2 Literature Survey

Computational modeling of complex drainage system of eye and obtaining an insight in the variation of IOP for various pathological conditions is an extremely complicated problem. Several models have been previously reported to explore the temperature distribution and flow mechanism inside the anterior chamber of eye, but these models are limited due to many assumptions and simplifications. These models are focused on analyzing either only the JCT or only the SC, but a complete three-dimensional model with the effect of IW of SC on IOP is still to be addressed.

In 1983, Johnson et al. [5] proposed a mathematical model of Schlemm’s canal to simulate the collapse of the canal and its resistive effect on the aqueous outflow. Their theoretical model is focused on the analysis of two principle sites of resistance, Schlemm’s canal and Inner wall of Schlemm’s canal. In their flow model, the aqueous humor flows from the TM through the inner wall, into the Schlemm’s canal, and along the canal in the circumferential direction, and finally exits through a number of spaced collector channels. They modeled the TM as a series of linear springs that allow the inner wall to deform in proportion to the local pressure drop across it. In their model the inner wall is supported by the meshwork attachment and is flexible in accordance with the pressure changes, while the outer wall is assumed rigid. They concluded that most of the resistance in the aqueous outflow network occurs along the inner wall of the Schlemm’s canal, and Glaucoma is a consequence of the collapse of the Schlemm’s canal alone.
They completely ignored the effect of JCT on the outflow resistance, which is considered by a number of investigators to be most important site of the outflow resistance.

Later Ethier et al. in 1986 [4] developed a model to determine the relation between the resistance of the meshwork with the concentration of the extra-cellular matrix- gel of JCT. They proposed two computational models that could predict the flow resistance of the JCT. In the first model they described the JCT as a porous medium permeated by open spaces (pores) through which AH flows. This model under predicts the resistance of JCT by a factor of 10-100, which suggests that the gel, which fills the open spaces of JCT, may control the resistance of the tissue. In the second model open spaces of the JCT is filled with a GAG gel for predicting the flow resistance of the gel. This model showed that the measured bulk concentration of GAG gel was consistent with gel concentrations needed to account for the estimated resistance of the JCM in-vivo. The entire model is based on the analysis of the effect of gel-concentration on the JCT resistance to outflow, but they did not focus on the flow field and related IOP.

In 1988, Scott [20] presented a mathematical model of human eye based on the bio-heat heat transfer equation for calculating the intra-ocular temperature distribution. They used the Galerkin finite element method for analyzing the sensitivity of the temperature distribution in the unexposed eye to the uncertainties in the parameters investigated, which includes thermal conductivities of the ocular tissues, the heat loss from the anterior corneal surface to the surroundings by convection and evaporation and the convective heat loss from the sclera to the body core. Scott extended this work to calculate the temperature rise experienced by the intra-ocular media when exposed to infrared radiation. The model is used to calculate transient and steady state temperature
distributions for different exposure times and a range of incident irradiances. They did not solve for the intra-ocular flow field, so their analysis of temperature rise is done without inclusion of buoyancy, and therefore the model does not predict realistic temperature rise.

Later in 1992, Johnson et al. [6] proposed a model to explore possible hydrodynamic interactions between JCT and IW pores of the SC. In their study they have considered the JCT and IW of SC as a coupled system to analyze the interaction between these two important sites of outflow resistance. This interaction arises because the pores in the IW endothelium are small and well separated. The flow is non-uniform in JCT and preferentially directed towards the region, which are in vicinity of the pores of IW endothelium, reducing the effective cross-section area available for the flow of aqueous humor. This funneling interaction of the pores markedly increases the effective resistance of the JCT by 30-fold. This increase was not due to the flow resistance of the IW but rather the flow resistance was the result of a decrease in the effective area through which the fluid must flow. They have determined a simple relationship for estimating the magnitude of this effect as a function of the number of the pores and their size. Their work is again limited to the analysis of pores and relation of their resistive effect with respect to the other parts of the drainage system.

Canning et al. [9] solved the flow profile inside the anterior chamber using a simplified three-dimensional computational model and analyzed the deposition of particles leading to the formation of structures inside the eye. Their model show the dominance of buoyancy on the flow field inside the anterior chamber and indicates that only a small temperature difference is required to drive such flows. They analyzed the
deposition of pigment particles on the corneal surface and formation of Krukenberg Spindle; they used the criterion that pigment granules stuck to the ocular tissue if the corneal shear stress at that location is less than a particular value. They estimated the maximum possible size of Hyphema that could be formed at the bottom of the anterior chamber by the sedimentation of erythrocytes in case of ocular trauma or rupture of blood vessel. Depending on the balance of settling force and convective flow they determined how far Hyphema could project upward into the flow before its constituents blood cells are swept away by the flow. The absence of third dimension in their model limits the visualization of real flow field. They did not consider the effect of TM and included lot of simplifications in their model, which restrict their simulations to completely depict the behavior of different particles inside the anterior chamber.

Heys et al. [7] presented a two-dimensional mathematical model of the coupled aqueous humor-iris system that accounts for the passive iris deformation to the iris contour. They modeled the aqueous humor as the Newtonian fluid and iris as linear elastic solid. They solved the resulting coupled equation set by finite element method with mesh motion in response to the iris displacement accomplished by tracking a pseudo-solid overlying the aqueous humor. Their simulation for normal eyes shows that the iris is displaced by the aqueous humor as it circulates through the anterior segment. Their model predicts the iris contour and apparent iris lens contact, which is primarily a function of the aqueous flow rate, the trabecular meshwork permeability, the permeability of the posterior pathway and iris modulus. They modeled the blinking process by applying a normal stress along the cornea. The model prediction of rise in IOP of eye agrees with the experimental measurement on rabbit’s eye, but the shape of the pressure
curve has poor agreement. They also predicted the smallest pressure difference (1Kpa) between the anterior and posterior chamber of eye necessary to achieve the dramatic iris contour observed in case of iris bombe. There are many simplifications in the model due to the absence of the third dimension, symmetry about the center axis and neglecting the buoyancy & gravity effect. The other major limitation of the model is that it includes only a portion of the eye. Due to these simplifications, it is unable to accurately represent the flow process.

Later in 2001, Heys and Barocas [18] have proposed a three-dimensional model with a more realistic geometry of eye in which they have included the iris and posterior chamber. They solved for the buoyancy driven ocular flow inside the posterior and anterior chamber. They released the particles from the tip of the iris and the center of the eye and observed their path inside the anterior chamber. They released few particles evenly spaced on the inner circumference of the iris tip and predicted the formation of Krukenberg Spindle based on the plot of particles residence time at different positions in the coronal plane. Their results show two dark bands in the center of the eye, which represent the location where particles circulated for the longest time. There are two outer bands on the corneal surface which is additional region occupied by the particles for the significant time. They compared these results with the simulations on the eye model with higher temperature gradient across the anterior chamber and found less circulation of particles near to the posterior surface of the cornea for high temperature gradient. Based on these results they suggested that people living in the cooler climate might not develop a spindle as distinct and heavily pigmented as the general population. Although their model is three-dimensional and geometry is more realistic, they have neglected the effect
of TM-resistance on deposition of particles, which play a major role in trapping, or escaping of particles of different traits through TM-pores.

Later in 2003, Kumar et al. [10] carried out numerical simulations on a three-dimensional model for the anterior chamber of rabbit eye to investigate the transport and deposition of particles inside the eye. A geometrical porous-media model for the TM was included in the simulations. The particle simulations for different particle types were performed in a Lagrangian framework using the predicted AH flow field and pressure distribution. Formation of three clinically observed structures, namely KS, Hyphema and Hypopyon, were analyzed by using representative particles (pigmentary cells, erythrocytes and leukocytes) of appropriate size and density. Corneal blood staining or formation of clots on the iris surface, observed clinically for cases with distributed sources of blood cells were also well predicted. Here TM was not modeled as a graded porous filter and moreover the effects of IW endothelium of SC, SC and collector channel were not taken into consideration.

A few recent studies have examined the transport of drugs injected in the vitreous chamber. In 1991, Araie and Maurice [34] measured the distribution contours of fluorescein and fluorescein glucuronide in the rabbit vitreous by freezing the eyeball and sectioning it. In order to estimate the permeability of the retinal-blood barrier, a spherical model was suggested, with the entire surface of the sphere representing the retina. It was assumed that only diffusion occurred in the vitreous humor, and that the transport across the retinal-blood barrier was proportional to the concentration gradient. Fitting the experimental data with this model, they obtained the permeability values of the retinal-blood barrier for different solutes. The concentration profile calculated by this model
would be the same for any cross-section that passes through the center of the sphere, with
the highest concentration in the center and the lowest concentration next to the outer
surface. In a rabbit eye, the center of curvature of the retina is immediately next to the
lens, on the symmetry axis of the vitreous. Qualitatively, the concentration profile
calculated by a spherical model will be correct for the posterior hemisphere of the
vitreous that is behind the center of curvature of the retina. In a spherical geometry, the
concentration profile in the anterior hemisphere will be same as the posterior hemisphere,
because the two hemispheres are the same.

Later in 1992, Yoshida and Kojima [67] suggested another model where the
vitreous was simplified into anterior and posterior sections, and each section was further
divided into eight compartments, each consisting of a thin shell and a separate
permeability was used for the outer surface of each hemisphere. For each section, three
parameters were used to describe the model, inward and outward permeability of the
retinal-blood barrier and the diffusion coefficient of the vitreous humor. Assuming that
rapid movement of the solute occurred by diffusion alone, the concentration within each
compartment is uniform and can be calculated from the Fick’s law. They measured
concentration profile after intravitreous injection and fitted the experimental data to get
the inward and outward permeability. The profile predicted by a model which uses
concentric compartmental shells will always have concentration contours that are parallel
to the retina, because the concentration within each compartmental shell must be uniform.
Because of the simplified geometry, this model can only be applied for a situation when
the concentration contours are parallel to retina.
In 1994, Tojo and Ohtori [35] proposed another model to describe the distribution of the drug in the vitreous humor. They assumed that the vitreous body was a part of a cylinder and the surface was divided into three areas, characterized by the drug-elimination pathways: the retina-choroid membrane, which was represented by the bottom and the curved surface of the cylinder; the lens, which was modeled by the center of the upper surface; and the hyaloid membrane represented by the annular gap between the lens and the retina. They developed a general mathematical model based on Fick’s second law of diffusion describing the pharmacokinetics of the intravitreal injection of dexamethasone sodium m-sulfobenzoate (DMSB). They found that for the drug, the retina-choroid-sclera membrane act as a major route of elimination and also concluded that concentration on the surface of the retina is appreciably affected by the site of injection or the initial distribution profiles.

Friedich et al. [36] used a finite element analysis to solve the mass transfer problem in the vitreous humor of rabbit eye. They assumed that the vitreous was stagnant and the mass transfer occurred by diffusion. Posterior segment of the eye was considered in the model. They studied the effects of different parameters that effect the concentration distribution in the vitreous humor, including the diffusion coefficient of the vitreous humor, the permeability of the retinal-blood barrier, the injection positions. Permeability of different compounds like fluorescein and fluorescein glucuronide through the retina was determined by fitting the model predictions to experimental data.

In a human eye, the lens occupies a smaller portion of the vitreous than in the rabbit eye. The volume of the vitreous humor in the human eye is approximately 4 mL, and the volume of rabbit vitreous is approximately 1.5 mL. Therefore, Friedich et al. [37]
extended their work by considering human eye model. Injections containing an equal mass of drug dissolved in volumes of either 15 µL or 100 µL were compared. They also studied the effects of different parameters that effect the concentration distribution in the vitreous humor, including the diffusion coefficient of the vitreous humor and the different injection positions. Initial position of the drug was assumed to be spherical in shape.

Controlled release of a therapeutic agent from a biodegradable polymeric system presents an improvement to traditional direct-injection treatment strategies that can overcome some of the problems associated with direct drug delivery. Controlled drug delivery systems are designed for long-term administration in which the drug level remains constant, between the desired maximum and minimum level, for an extended period of time. Xu [38] developed a two dimensional convection-diffusion transport model of the drug released from a localized source. The vitreous body was modeled as a porous media and the drug injection site was considered to be cylindrical in shape. Stay et al. [33] developed a three dimensional transport model of the drug following intravitreal injection from a point source. Missel [39] studied bolus injection and drug delivery from intravitreal devices for a rabbit eye model. In all these studies, the convection driven by the pressure drop across the vitreous was taken into account, but with a porous media model for the vitreous. Park et al. [40] developed a three dimensional finite element method to simulate drug transport in the entire rabbit eye following the drug administration by intravitreal injection through a controlled release implant.

1.3 Outline of the Thesis

This first chapter of the present report contained an introduction and literature survey. The introduction part is an outline of the present work, which explains the
problem of interest and the simulations performed in a brief form. The literature survey portion is devoted to present the summary of the previous work done in the field of aqueous humor dynamics and drug delivery to the retina.

The second chapter contains the explanation of anatomy of the eye. It is important to understand the framework of eye, the functioning of its different constituents and the different terminologies used frequently in the context of human eye. This chapter includes all the required details of the eye to understand the present work. This chapter also includes dedicated explanation of the vitrectomy surgery: its causes, current treatment. It also discusses the role of different vitreous substitutes and the classification of vitreous substitutes.

The third chapter is focused on explaining the mathematical and computational model used for the simulations on the eye. The geometry used to represent the ocular tissues and the governing equations, which could predict the ocular fluid dynamics, is explained in detail. Emphasis is given to explain the strategy to accurately model the TM and its interaction with IW of SC. Finally the boundary conditions used on the ocular tissues to properly represent the environmental conditions of eye and numerical procedure used to solve the governing equations is explained. This chapter also includes the results of the simulations performed and the conclusions drawn.

The fourth chapter is devoted on explaining the effects of different methods of drug delivery in the vitrectomised eye. In order to assess the effectiveness of the injected drug, it is critical to know the drug distribution within the eye following injection. This is particularly important when the vitreous medium has been replaced by fluid substitutes since there is little understanding of the transport of drugs in vitreous substitutes. The
main objective of this study is therefore to characterize the drug distribution following intravitreal injection in the vitreous chamber of the human eye with different vitreous substitutes.
CHAPTER 2. ANATOMY OF THE EYE

The eye globe, approximately spherical in shape, is recessed in the pyramidal shaped bony orbit, and it is connected to the brain by optic nerves. The posterior five-sixth of the globe is covered by external white and opaque protective coat, sclera. The remaining anterior one-sixth of the globe consists of a uniquely transparent, convex, protective fibrous structure, the cornea, which is responsible for the refractive incident rays on eye. The limbus marks the transition between the cornea and sclera, Fig. 2-1. The extra-ocular muscles, which originate into the bony orbit and insert into the sclera, are responsible for the directional movement of the globe. The eyelids provide mechanical protection to the globe, and they interrupt and limit the amount of light entering the eye; they harbor the tear secreting glands and distribute the tear fluid over the anterior surface of the globe.

Interposed between the retina and the sclera is vascular tunic of the choroids which primarily supplies nutrients to the retina. Anteriorly, the choroids continue to the
The ciliary body, which is responsible for the formation of intraocular fluid, for providing the distal attachment of the zonular fibers of the crystalline lens, and for harboring the smooth muscles. The ciliary body continues anteriorly as the iris, a diaphragm with a round contractile opening, the pupil. With its variable diameter, the pupil acting like an automatically adjustable aperture of camera allows rays of light to fall on the retina. The choroids, ciliary body and iris together constitute the uvea.

Figure 2-2: Diagrammatic meridional section through the human eye ball [54]

The anterior chamber, an elliptical space between the iris diaphragm and the cornea, acts as a reservoir for a clear, watery fluid, the aqueous humor. In conjunction with the outer fibrous tunic of the eye, the distended, stable dimensions of the globe are maintained largely by the hydro-mechanical properties of this fluid. The aqueous humor is formed continuously by the ciliary processes in the posterior chamber behind the iris.
and flows into the anterior chamber via the pupil; it finally leaves the eye through the intricate system of outflow channels located in the corneoscleral limbus. The resistance encountered during the passage and rate of aqueous humor production is the principal factors determining the level of intraocular pressure. Additionally, this fluid acts as carriers of nutrients, substrates, metabolites and waste products.

The larger posterior chamber of the eye is filled with a transparent, delicate connective tissue gel, and the vitreous humor. The anterior face of the vitreous is hollowed to accommodate the biconvex crystalline lens. The lens, situated behind the iris diaphragm, is supported by suspensory ligaments, also referred to as the zonules that extend between the ciliary body and the lens surface. The lax state of the zonules is imparted by the contraction of the ciliary muscles together with the inherent plasticity of the lens. The lens has the capacity to accommodate to focus outside images clearly to the retina.

2.1 Geometrical Dimensions of the Eyeball

Although the eyeball is referred to as a globe, it is only approximately spherical and consists of segment of two spheres placed one in front of the other. The anterior corneal portion is smaller and more curved than the posterior, has a radius of curvature of about 8 mm, and comprises one-sixth of the surface area of the eye. The cornea is elliptical, with its vertical axis shorter than the horizontal one. The posterior scleral portion is flatter, has a radius of curvature of about 12 mm, and comprises the remaining five-sixths of the ocular surface area.

The anterior and posterior poles are the central points of the corneal and scleral curvatures respectively; the line joining these two poles is the geometric axis. The
external geometric axis is measured from the anterior surface of the cornea to the external surface of the sclera, whereas the internal geometric axis is measured only to the anterior surface of the retina. The three diameters of the globe are the sagittal (anterior-posterior), transverse and vertical.

Histologic sections of the globe can be made in several planes. The meridional plane passes through the anterior and posterior poles of the eye and may be vertical, horizontal or oblique. Sagittal planes lie on either side of the meridional plane and are parallel to it. The equatorial plane is midway between the anterior and posterior poles and is perpendicular to the meridional plane. Sections parallel to the equatorial plane, whether passing anterior or posterior to it, are called transverse, coronal, frontal, or radial planes.

The dimensions of adult human eyes are relatively constant, the average diameters are 24 mm antero-posteriorly (sagittal diameter), 23 mm vertically and 23.5 mm horizontally [54]. The sagittal diameter may vary most, ranging from 21 to 26 mm in normal eyes. With a high degree of axial myopia, the sagittal diameter may be as large as 29 mm; with hypermetropia, it may be as small as 20 mm. The transverse and vertical diameters are less variable with a range of 23 to 25 mm. The circumference of human eye is about 75mm. Overall, the male eye is about 0.5 mm larger than the female eye and the Negro eye is said to be somewhat larger than those of white races. The eye of the newborn is more spherical than the adult eye, and therefore more hypermetropic, with a sagittal diameter of 16 to 17 mm; this increases rapidly in size to 22-23 by three years of age. A further increase of about 1 mm occurs between 3 to 13 years, but thereafter little growth takes place. The eyeball weighs about 7.5 gm, its volume is about 6.5 ml, and its specific gravity varies from 1.002 to 1.009.
2.2 Tunics of the Eyeball

The eyeball, bisected along a meridian, discloses the fundamental architectural plan of the globe, Fig 2-3. The three tunics of the eyeball revealed are the fibrous coat, the uveal tract, and the retina. The external tough fibrous coat is formed by the sclera, which is continuous anteriorly with the cornea and posteriorly with the meningeal covering of the optic nerve. The uveal tract, a highly vascular layer, forms the middle pigmented tunic and is in contact with the sclera. The anterior portion of the uveal tract, the iris, forms a partition subdividing the interior of the eye. The central opening of this diaphragm, the pupil is the aperture of the optical system. The retina forms the whitish, inner tunic of the eyeball and is in contact with the choroid. The nerve fiber layer of the retina continues posteriorly as the optic nerve.

2.2.1 The Fibrous Tunic

The fibrous coat protects the more delicate inner structures and, when distended by the intra-ocular pressure, gives the eyeball its definite shape. Tightly packed collagenous connective-tissue fibers, elastic fibers in much smaller numbers, and
relatively few stroma cells, are the tissue elements that impart strength and resistance to the fibrous coat. Fibrous tunics consist of the following layers:

- **The Sclera**

  The sclera is an opaque, dull white, dense, visco-elastic and resilient outer coat of the eye, which occupies the posterior five-sixth of the globe. In the sclera the tissue elements are arranged into lamellae or broad ribbons which interweave in intricate, strength-increasing patterns. In the most anterior portion of the sclera the fiber bundles run parallel to the limbus; at the equator a meridional course prevails, while crossings of the ribbons at right angles are characteristic of the posterior half. Around the exit of the optic nerve, nasal to the posterior pole, circular fiber-bundles predominate. The thickness of the sclera varies from half a millimeter at the equator to a millimeter or more at the exit of the optic nerve. The outermost layers of the sclera, especially anteriorly, are relatively loosely woven and contain more numerous blood vessels.

- **The Cornea**

![Figure 2-4: Layers of Cornea](image)

Figure 2-4: Layers of Cornea [69]
The cornea consists of a clear, transparent, avascular, visco-elastic tissue with a smooth, convex external surface and a concave internal surface. It occupies one sixth (1.3 cm²) of the total surface area of the fibrous coat of the globe. The main function of the cornea is optical; it forms the principal refracting surface of the dioptic system of the eye. Anteriorly, when the lids are open, the cornea is separated from the air only by the pre-corneal tear film (6-20µm thick), which imparts the characteristic brilliant luster. The tear film is a physiologic secretion that covers the external surface of the corneal epithelium and, strictly speaking, is not an anatomic part of the cornea. It is divisible into three layers. (a) The anterior oily layer, less than 0.5 µm thick, is derived from the sebaceous glands of the lid and caruncle. (b) The middle aqueous layer, 5-18 µm thick, represents the secretion of the lacrimal glands and dissolved proteins. (c) The posterior mucoid layer (0.5 µm thick), rich in glycol-proteins, is derived from the conjunctival goblet cells. By filling minor surface irregularities, the tear film provides a smooth air/cornea interface for refraction of light. The pre-corneal tear film is the main vehicle for the supply of nourishment to the corneal epithelium and for removal of detritus. The movements of the lids replenish the integrity of the tear film and, if the inter-blinking time is prolonged more than half a minute, breaks in the tear film may appear (the so-called tear break-up time). Viewed anteriorly in vivo, the cornea is a meniscus elliptical in shape because of the greater extension of the less transparent limbus above and below it. Therefore, the vertical corneal diameter is smaller than the horizontal diameter (10.6 mm and 11.7 mm respectively in males); in females, each is 0.1 mm smaller. The anterior curvature of the cornea (radius of curvature 7.8 mm) is greater than that of the sclera (radius of curvature 11.5 mm). Nevertheless, the cornea does not protrude much beyond
the scleral surface, because of the flattening of the anterior sclera and peripheral cornea and the sinking effect of the external scleral. In the central or optical zone (approximately 4 mm in diameter), the two surfaces of the cornea are parallel, and the cornea is nearly spherical except for a small amount of astigmatism (the surface is more curved in the vertical than in the horizontal meridian), which gives it a toric form.

Viewed posteriorly, the cornea is circular, with a diameter of 11.7 mm and with an average radius of curvature of 6.5 mm. Measured by optical methods, the cornea in vivo is 0.52 mm thick centrally with little difference between males and females. Towards the periphery, the cornea thickens to 0.97 mm and merges with the conjunctiva, episclera, and sclera. The weight of the freshly excised cornea is approximately 180 mg and the specific gravity is 1.052.

Structurally (Fig. 2-4), the cornea consists of: (1) Epithelial layer with its basement membrane; (2) Stroma with its anterior modified zone of Bowman; (3) Descemet’s membrane, which in fact is the basement membrane of the corneal endothelium; and (4) Endothelium (Mesothelium).

- **The Corneoscleral Junction**

  The limbus is the gray transitional zone between the transparent cornea anteriorly and the opaque, white sclera posteriorly, Fig.2-3. It is here the smaller corneal curvature merges with the greater curvature of the sclera; this region is often referred to as the corneoscleral sulcus. Unlike the circular profile of the posterior corneal periphery, the anterior cornea is horizontally elliptical in shape. The sclera therefore extends forward in the superior and inferior regions in the medial and the lateral aspects. This gives rise to the slightly wider zone of the limbus in the vertical plane (2 mm) than in the horizontal
plane (1.5 mm). The transitional zone of the limbus is composed of both scleral and corneal elements, the contribution of each varying from superficial to deep regions and also in the various sectors around the circumference of the limbus. The limbus can be divided into three separate zones.

The anterior limbus is the part of limbus consisting of the conjunctival epithelium and the stroma that contains the episcleral and subconjunctival vascular plexuses and loose fibrous tissue of the episclera. The mid-limbus consists of compact corneoscleral tissue and traversed by the veins of the deep and intrascleral plexus and by small arterioal channels and nerves. The inner deep limbus contains the trabecular meshwork and Schleim’s canal, as well as related arterial and venous plexuses. The deep limbus contains:

Figure 2-5: Drainage system of eye. (a) SC- Schlemm canal, (b) TM- Trabecular Meshwork, (c) C- Cornea (d) IS- Interscleral vascular channels (e) DM –Descemet’s membrane, (f) SS- Scleral spur, (g) CB- Ciliary body, (h) IR- Iris (From Tripathi and Tripathi [54]).

(1) Trabecular Meshwork:

The trabecular meshwork is a triangular-shaped wedge of tissue that encircles the anterior chamber and has its apex located at the peripheral terminus of the Descemet’s
membrane (Schwalbe’s line). From this anterior boundary, the meshwork expands as it bridges the irido-corneal angle of the eye and ends posteriorly by blending with the stroma of the iris, ciliary body, and scleral spur. The scleral spur projects like a shelf into the meshwork at its posterior margin, and serves as a point of insertion for the longitudinal bundle of the ciliary muscle (Fig. 2-5). The trabecular meshwork is composed of a number of superimposed fibrocellular sheets and hence it presents a trabeculated and reticular appearance. It surrounds the eye in an annular shape and forms a three-sided prismatic band. The outermost trabecular sheet borders the tissues of Schlemm's canal; the inner aspect of the trabecular meshwork directly borders on the anterior chamber (Fig. 2-5). For descriptive purposes, the meshwork can be divided into: iris processes or "pectinate" fibers, uveal trabeculae (also called ciliary, ciliocorneal, or uveocorneal trabeculae), corneoscleral (also called sclerocorneal or scleral) trabeculae and juxtacanalicular tissue (JCT). The iris processes are large, wide bands that arise from the anterior surfaces of the iris and join midway in the inner uveal trabeculae.
The uveal (Fig. 2-6) and corneoscleral portions of the trabecular meshwork have an approximately analogous structure. Both are composed of series of trabeculae or beams that delimit a system of aqueous flow channels. At the base, the number of trabecular sheets varies from 12 to 20, but toward the apex they are reduced to 3 to 5 layers. The flow channels become progressively smaller from the uveal to the corneoscleral meshwork. The inner 1-2 layers of uveal sheets closest to the anterior chamber, however, have a round, cord-like, profile and are oriented predominantly in a radial, net-like fashion enclosing large oval, circular, or rhomboidal spaces. The corneoscleral trabeculae are flattened, perforated sheets, the individual layers being 5 to 12 µm thick in the mid region. In man, their number may vary from 8 to 15 layers, measuring from 120 to 150 µm in total thickness. The intra-trabecular spaces vary in size from 25 to 75 µm in the uveal meshwork and from 2 to 20 µm in the outer corneoscleral meshwork. In one of the analysis Grant et al. [70] confirmed that the number and size of these openings are such that the uveal meshwork can be expected to create negligible resistance of flow. Collapse of the trabecular meshwork, as occurs in hypotony, thus reduces the effective area of the openings. The trabecular cells are phagocytic [29]. They are capable of ingesting both endogenous materials such as pigment [29] and hemolyzed erythrocytes and exogenous material such as latex micro-spheres, presumably for the purpose of keeping the trabecular outflow free of potentially obstructive debris.

The JCT, also known as pericanalicular region or cribriform area, intervenes between the first (outermost) corneoscleral trabecular beam and the discontinuous basement membrane of the inner wall of the canal of Schlemm (IW of SC). The thickness of this region varies from 2 to 20 µm. It is believed that the tortuous flow passage from
the JCT accounts for the most of the flow resistance [6] because of its very small pore size approximately 0.1-3.0µm [30] and the presence of the extra-cellular matrix gel in the open spaces. In human eyes studied in vitro by Johnson et al. [71], approximately 50% of 0.18 particles were caught in the trabecular meshwork and especially in the JCT tissue when perfused through this region. Bill et al. [24] further speculated that with increasing age, increased cross linking may occur as part of the process, leading to accumulation of extra-cellular material in the JCT tissue, increased outflow resistance, and ultimately to the development of glaucoma. However, morphologic evidence for such an accumulation, sufficient to generate a significant outflow resistance, is still lacking. The porosity of the meshwork is increased when the trabeculae are separated, as occurs with the contraction of the ciliary muscle and the posterior pull of the scleral spur. Such mechanisms are important in the treatment of glaucoma.

(2) Schlemm’s canal:

The canal of Schlemm (SC) is an annular structure of about 36 mm circumference in the human eye, Fig 2-7. Located in the inner part of the limbus, it is supported on its inner aspect by the trabecular meshwork. Anteriorly, it is bound by the compact scleral tissue; posteriorly, it lies against the main mass of the corneoscleral trabeculae. Laterally, the canal is bordered by the scleral spur and scleral roll, and medially it is limited by the approximation of the first trabecular sheet with the compact corneoscleral tissue of the limbus. The lumen of the canal is usually an elongated, slit-like opening that lies parallel to the corneoscleral trabeculae. Its dimensions vary from eye to eye; in the adult eye, when a single lumen is present, it measures 200-500 µm in the meridional axis and 10 to 25 µm in the opposite axis; it is generally smaller in children. In some instances, the
canal may be triangular in m. shape with the base of the triangle lying against the scleral spur, where it measures 50 µm in width, whereas the apex narrows medially to 5-10 µm. Aqueous humor is drained away from the canal of Schlemm, Fig. 2-7 by the three venous plexuses: the deep intra-scleral, mid-intrascleral, and episcleral and sub-conjunctival. The lumen of the canal is connected to the deep scleral plexus by 25 to 35 collector channels distributed unevenly around the circumference of the canal. The channels are relatively wide when they arise at the canal (diameter, 20-90 µm), but become narrower as they anastomose with the venous channels. The collector channels join the deep scleral plexus, which is made up of fine branches of the anterior ciliary veins. The deep scleral plexus, in turn, is connected to the mid-intrascleral and episcleral plexuses. The mid-intrascleral plexus is formed by a large interconnecting venous network in the limbal sclera; in addition to receiving blood from the deep scleral plexus, it drains the ciliary venous plexus. Posteriorly, the intrascleral plexus drains into the episcleral plexus and finally into the anterior ciliary veins, Fig. 2-7. A few vessels, known as aqueous veins, varying

Figure 2-7: Canal of Schlemm and its communication with collector channels, aqueous veins and intrascleral venous plexus [54]
in number from 2 to 8, arise from the canal of Schlemm and directly join the episcleral plexus. A variable amount of aqueous humor reaches the episcleral veins directly via the aqueous veins. Where an aqueous vein joins a blood vessel, the aqueous humor and blood do not mix immediately, but flow in parallel streams to give a laminated aqueous vein.

![Schematic drawing showing the vacuoles in the IW of SC.](image1)

![Scanning Electron micrographs of the endothelial lining of the wall of SC viewed from the luminal aspect.](image2)

![A vacuole in endothelium lining the inner wall of SC in a control eye.](image3)

![A pore is seen in the vacuole opening both towards the meshwork side and the lumen side.](image4)

Figure 2-8: (a) Schematic drawing showing the vacuoles in the IW of SC, (b) Scanning Electron micrographs of the endothelial lining of the wall of SC viewed from the luminal aspect. Note the spindle shaped appearance of the cells with apical bulges in the central region correspond to the nuclear and macro-vacuolar structures (V), (c) A vacuole in endothelium lining the inner wall of SC in a control eye.(d) A pore is seen in the vacuole opening both towards the meshwork side and the lumen side [22].

A characteristic feature of the IW of SC (Fig. 2-8) is its tendency to form large out-pounchings into SC, called the giant vacuoles. This nomenclature is perhaps misleading, since the giant vacuoles are not intercellular structures, but instead represent deformations of the inner wall endothelial cells that create a small potential space between the extra-cellular material of the JCT and the inner wall of cell. Giant vacuoles
are pressure-sensitive structures in the endothelial lining of Schlemm’s canal. They respond rapidly to changes in the IOP, largely disappearing in <=3min [14] after the IOP is reduced to zero in enucleated eyes. Tripathi [54] suggested that giant vacuoles represent the mechanism of fluid transfer across the endothelial lining of Schlemm’s canal. Changes in IOP are unavoidable in vivo, for example due to normal diurnal variation and/or occasional ocular massage. Changes in IOP significantly affect giant vacuole density, and subject inner wall cells experience variable and transient ‘stretching’ throughout the day. Grierson and Lee [12] showed that as the pressure increases from 8 to 30 mmHg in the rhesus monkey eye, the net area of inner wall cells increases by more than 50% due to giant vacuole out-pounching. This amount of stretching, as shown in Fig. 2-9 (c), is unusual for endothelial cells elsewhere in the body, and in fact stretches of order 50 % cause immediate damage to cultured bovine aortic endothelial cells, as measured by the loss of ability to exclude propidium iodide [28]. It seems likely therefore that the inner wall of SC is somehow adapted to deal with such large deformations.

In an extensive study, Ethier et al. [23], found that there are two distinct kinds of pores present in the IW endothelium namely the Intracellular pores (i.e., passing through the cells) and Paracellular pores (i.e., passing between the cells). There are structures such as endothelial tubules or also called as septae, the purpose of these structures is to prevent the complete collapse of Schlemm’s canal, which would otherwise occur when ever the pressure got too high.

All vacuoles open towards the meshwork side and some, but not all, are open towards the SC side. The diameter of most openings towards the trabecular side was about 3.5 \( \mu m \) while towards the schlemm’s canal side it was around 1-1.8 \( \mu m \). Bill and
Svendbergh et al. [24], in a meticulous study using SEM found that in human that the IW SC contains 1840 pores/mm². At elevated IOP there are around 20,000 pores in inner wall of SC of human eye but according to Johnson [66] only 13 to 29% of vacuoles have pores on both ends. At higher IOP increase in the number of vacuoles can cause SC to collapse as shown above in Fig. 2-9. Parc et al. [26] found in their experiments that giant vacuoles are preferentially found near collector channels, indicating that aqueous flow across the inner wall is sensitive to downstream pressure. Darryl et. al. [16] cited that the pores in the IW endothelium of SC cause the funneling effect. Flow through JCT is confined to regions near the inner wall pores, forcing a funneling pattern of aqueous flow.
streamlines, as illustrated in the figure above. The reduction in the available area for flow increases the effective outflow resistance.

(3) Scleral spur and scleral roll:

The scleral spur is a firm, fibrous, wedge-shaped ridge or projection from the inner aspect of the anterior sclera and is oriented circumferentially in the inner limbus.

![Diagram of streamlines through JCT](image)

Figure 2-10: An illustration of the streamlines of aqueous flow through the JCT before (A) and after (B) washout [16]

(4) Line of Schwalbe:

A prominent anterior border ring of the trabecular region, called the line of Schwalbe, is seen in only about 15-20% of human eyes. The line of Schwalbe consists of regular collagen fibrils intermixed with elastic fibers, both being oriented parallel to the limbus, somewhat similar to the uveal trabeculae.

2.2.2 The Uveal Tract

The uveal tract forms the pigmented vascular tunic of the eye. It may be divided topographically into three regions: (1) the choroid, (2) the ciliary body and (3) the iris.

- The Choroid

The choroid, a soft, brown vascular tunic, is the posterior part of the uveal tract. The choroid lies between the retina and sclera. It is composed of layers of blood vessels
that nourish the back of the eye. The choroid connects with the ciliary body toward the front of the eye and is attached to edges of the optic nerve at the back of the eye.

- **The Ciliary Body**

  The ciliary body is an anterior continuation of the choroid and of the retina and, as such, is divisible into uveal and neuro-epithelial portions. The ciliary body forms a circumferential, asymmetric girdle, slightly narrower on the nasal side and in the upper part (4.2 to 5.2 mm, respectively) than on the temporal side and lower part (5.5 to 6.3 mm, respectively). One function of the ciliary body is the production of aqueous humor, the clear fluid that fills the front of the eye. It also controls accommodation by changing the shape of the crystalline lens. As the ciliary body contracts, the zonules relaxes. This allows the lens to thicken, increasing the eye's ability to focus up close. When looking at a distant object, the ciliary body relaxes, causing the zonules to contract. The lens becomes thinner, adjusting the eye's focus for distance vision.

- **The Iris**

  The iris is the most anterior portion of the uveal tract and forms a delicate diaphragm between the anterior and posterior chambers of the eye. It has a central aperture called the pupil, which is located slightly nasal from the center and controls the amount of light entering the eye. It also provides communication for the free flow of aqueous humor from the posterior into the anterior chamber. The iris is thickest close to the pupillary zone in the region of the collarette and thinnest (0.5 mm) and weakest at its root, from which it can easily be torn surgically or in contusion injuries (irido-dialysis). The major portion of the iris rests on the anterior surface of the lens. In the absence of
support from the lens, the pupillary plane falls back, the anterior chamber deepens, and the iris becomes tremulous (irido-donesis) during the movements of the eye.

The color of the iris, which varies in different individuals, depends upon the amount of pigment in the stromal cells. The stromal pigmentation increases rapidly during the first year of life, and hence many infants who were born blue-eyed gradually lose the lightness of their irises. An iris devoid of stromal pigmentation, but with a normally pigmented bi-layered epithelium, will also appear blue. In the event of pigment deficiency in the iris epithelium, the red fundal reflex gives the iris a pink color.

The diameter of the iris is about 12 mm. The anterior surface is divided into a central (pupillary) zone and a peripheral (ciliary) zone. The junction of these two zones is marked by the collarette (0.6 mm thick and 1.5 mm from the pupillary margin) and the embryonic location of the minor circulus iridis which gives rise to the embryonic pupillary membrane.

2.2.3 The Retina

The retina is approximately 0.5 mm thick and lines the back of the eye. The optic nerve contains the ganglion cell axons running to the brain and, additionally, incoming blood vessels that open into the retina to vascularize the retinal layers and neurons (Fig. 2-11). A radial section of a portion of the retina reveals that the ganglion cells (the output neurons of the retina) lie innermost in the retina closest to the lens and front of the eye, and the photo-sensors (the rods and cones) lie outermost in the retina against the pigment epithelium and choroid. Light must, therefore, travel through the thickness of the retina before striking and activating the rods and cones (Fig. 2-11). Subsequently the absorption of photons by the visual pigment of the photoreceptors is translated into first a
biochemical message and then an electrical message that can stimulate all the succeeding neurons of the retina. The retinal message concerning the photic input and some preliminary organization of the visual image into several forms of sensation are transmitted to the brain from the spiking discharge pattern of the ganglion cells.

All vertebrate retinas are composed of three layers of nerve cell bodies and two layers of synapses. The outer nuclear layer contains cell bodies of the rods and cones, the inner nuclear layer contains cell bodies of the bipolar, horizontal and amacrine cells and the ganglion cell layer contains cell bodies of ganglion cells and displaced amacrine cells. Dividing these nerve cell layers are two neuropils where synaptic contacts occur. The first area of neuropil is the outer plexiform layer (OPL) where connections between rod and cones, and vertically running bipolar cells and horizontally oriented horizontal cells occur. The second neuropil of the retina, is the inner plexiform layer (IPL), and it functions as a relay station for the vertical-information-carrying nerve cells, the bipolar cells, to connect to ganglion cells. In addition, different varieties of horizontally- and
vertically-directed amacrine cells, somehow interact in further networks to influence and integrate the ganglion cell signals. It is at the culmination of all this neural processing in the inner plexiform layer that the message concerning the visual image is transmitted to the brain along the optic nerve.

2.3 Chambers of the Eyeball

2.3.1 Anterior Chamber

The anterior chamber of the human eye has an approximately ellipsoidal shape. Its boundaries are formed anteriorly by the inner surface of the cornea and peripherally by the inner surfaces of the trabecular meshwork. On the posterior aspect, the chamber is limited by the anterior surface of the iris and the pupillary portion of the anterior lens surface. On the lateral aspect, it ends in the anterior face of the ciliary body, where the anterior and posterior boundaries meet, and where the apex of the angle of the anterior chamber is located. Whereas the corneal endothelium forms a complete covering for the chamber, the anterior surface of the iris, the anterior face of the ciliary body, and the trabecular meshwork do not have a complete cellular covering; the anterior chamber thus communicates directly with the extracellular spaces of these structures.

The size, shape, and depth of the anterior chamber are determined by the curvature of the cornea, the shape of the iris, and the size and position of the lens. Since the plane of the iris is not completely horizontal, because of the forward location of the lens, the pupillary portion of the iris is displaced 0.6 to 1 mm anteriorly with respect to the iris root. This forward displacement of the pupillary plane, however, is smaller in myopic than in hypermetropic eyes. The forward inclination of the iris and the pupillary sphincter produces a ball-valve action, which offers some resistance to flow of aqueous humor.
from the posterior to the anterior chamber. During forceful contraction of the sphincter muscle, the aqueous pressure in the posterior chamber may cause an anterior bowing of the peripheral iris that produces "iris bombe". Pupillary dilatation or iridectomy may reverse this situation.

The diameter of the anterior chamber varies between 11.3 to 12.4 mm and is slightly greater than that of the cornea. Because of the corneal curvature, the chamber is deepest centrally and shallower peripherally near the angle. The diameter of the cornea and the depth of the anterior chamber are related. The chamber depth is slightly greater in males than in females, but in both it decreases with advancing age as the size of the lens increases. As a rule, the anterior chamber is shallower in hypermetropes and deeper in myopes; on average, the central depth measures 3.15 mm (range, 2.6 to 4.4 mm). The depth of the anterior chamber in the two eyes of the same individual is almost equal. The anterior chamber is a reservoir for aqueous humor and, at any given time, contains about 250 µm of this fluid.

The aqueous humor is a clear, colorless watery solution continuously circulated from the posterior chamber of the eye throughout the anterior chamber. The functions of aqueous humor are as follows:

- Carries oxygen and nutrients to the crystalline lens and posterior cornea since these structures have no intrinsic vascular supply.
- Similarly carries away the waste products from the above structures.
- Helps to maintain the shape and internal structural arrangement of the eye by contributing to the intraocular pressure.
• Serves as a mechanism to clear blood, macrophages, and products of inflammation from the anterior segment of the eye.

Figure 2-12: Illustrating the current of aqueous humor from the ciliary body to the canal of Schlemm.

As seen in the Fig. 2-12 the aqueous humor is formed continuously by the epithelial cells of the ciliary processes in the posterior chamber behind the iris and flows into the anterior chamber via the pupil. Aqueous fluid circulates in the anterior chamber by hydrostatic forces, by mechanical means due to ocular and head movements, and by temperature differential between the vascular iris (warm) and the avascular cornea (cooler). The hydro-mechanical property of the aqueous humor is largely responsible for the intraocular pressure and, in conjunction with the fibrous tunics of the eye, provides the stability of the ocular dimensions and of the internal structures of the eye that is essential in the performance of the visual function. Finally, most of the aqueous humor leaves the eye via trabecular meshwork, Schlemm’s canal, the scleral collector channels, the aqueous veins, and the episcleral venous system.

2.3.2 Posterior Chamber

The aqueous humor is secreted by the ciliary bodies in the posterior chamber, which is bound anteriorly by the pigment epithelium of the posterior iris; anterolaterally by the junctional zone of the iris and ciliary body; and anteromedially by the contact of
the iris with the lens. Aqueous humor gains entry into the anterior chamber from the posterior chamber via pupil. The equatorial portion of the lens forms the medial boundary of the posterior chamber. Posteriorly, the anterior face of the vitreous limits it. Laterally, the chamber is bounded by the ciliary body with its processes and valleys, and it may extend back to the point of contact between the anterior face of the vitreous.

2.3.3 Vitreous Cavity

The space between the retina, ciliary body, posterior chamber and lens is filled with a transparent gel (gel vitreous) or a transparent liquid (liquid vitreous) or both. The vitreous, which occupies almost four-fifth of the volume of the globe, is a clear, transparent, avascular, gel-like structure of semi-solid consistency. The gel vitreous portion is a collagen gel in which the water-soluble collagen fibrils are responsible for the gel state. These fibrils are remarkably uniform in diameter (10-20 µm) throughout the animal kingdom. These fibrils are heterotypic in composition; comprising collagen types II, V/XI and IX, though recently even type VI collagen has been identified in the vitreous [75]. They form an almost completely random network. In mammalian vitreous, the glycosaminoglycan (GAG) hyaluronan is a major component that fills the space between the collagen fibrils, but chondroitin sulfate proteoglycans have also been documented [76]. In many species such as cattle, horses, sheep, dogs, cats, rabbits, etc., the entire vitreous space is filled with this gel throughout life. Liquid vitreous is present only in adult eyes of some species (human, rhesus monkey, owl monkey, birds and fishes) and is always contained within the gel vitreous. The framework of the vitreous body changes with age. In humans, aging brings important changes in the rheological characteristics and the nature of the vitreous. From the age of 45-50 years, the volume of the gel-
vitreous in the human eyes decreases steadily, and the volume of the liquid-vitreous proportionally increases. This has been observed with slit lamp investigation carried out by Eisner [46] with direct measurement of the liquid vitreous in formalin-fixed eyes. The associated shrinkage, contraction, and retraction of the vitreous framework may separate it from the inner retinal surface.

The vitreous body in the human eye weighs about 4 gm and its volume is approximately 4 ml; it consists of 99 % water. The specific gravity (1.0053 to 1.0089) is only slightly higher than that of water, and its refractive index (1.334) is slightly lower than that of aqueous humor. Its viscosity is almost twice than that of water, but the osmotic pressure is very close to that of aqueous humor. The vitreous has no blood vessels and derives its nutrition from the surrounding structures like choroids, ciliary body and retina. The vitreous is probably never regenerated [74].

The vitreous, with its transparent but solid character, servers as a stabilizer and shock absorber of any movement or mechanical impact reaching these tissues. The vitreous, as a solid system with visco-elastic qualities, prevents dislocation of the retina, lens and zonules. Vitreous is undoubtedly the most delicate connective tissue structure of the body. Even after fixation, the vitreous body is incapable of maintaining its shape, and the shape of the vitreous cavity, which is spheroidal posteriorly, determines its outline. The large volume of the vitreous body provides support for the intraocular structures including the lens and, in conjunction with the aqueous humor and the fibrous tunics of the eye, helps to maintain the intraocular pressure. The hyaloid membrane, the lens and the retina forms the limiting boundary for the vitreous body. The hyaloid membrane is composed of loosely packed collagen fibers and hyaluronic acid, and spans the gap
between the lens and the ciliary body. Although the hyaloid membrane forms a boundary between the nearly stagnant vitreous and the flowing aqueous humor, it does not form a limiting boundary to the transport of small molecules such as fluorescein. The functions of the vitreous are as follows:

- Vitreous humor has a refractive index of 1.33 and thus contributes to the magnifying power of the eye.
- It acts as a shock absorber, supporting the shape of the eye and the posterior surface of the lens.
- It assists in holding the neural and the pigmented parts of the retina together.
- It allows the circulation of metabolic solutes and nutrients.

2.4 Lens and Zonular Apparatus

The human lens is a transparent, biconvex, elliptical, semi-solid, avascular structure with smooth, shiny surfaces. In infants and children, the lens is soft but the central or nuclear portion becomes firmer with advancing age. The lens is located between the iris and the vitreous, with its anterior central region exposed by the pupil.

![Schematic representation of lens](image)

Figure 2-13: Schematic representation of lens

The posterior surface of the pupillary part of the iris glides over the anterior surface of the lens, Fig. 2-13. In eyes with a narrow anterior chamber angle and shallow anterior chamber, the iris-lens contact may be wider and firmer causing interference with
the passage of the aqueous humor from the posterior to the anterior chamber, and may be a causative factor in angle-closure glaucoma.

Peripherally, the equatorial region of the lens (rounded junction of its anterior and posterior surfaces) projects into the posterior chamber and is separated from the ciliary body by a 0.5 mm wide circumlental space. The lens is supported by a system of zonules (suspensory ligaments) which extend from the ciliary epithelium to a 2.5 mm circular zone around the lens equator; 1.5 mm of this is on the anterior, and 1 mm on the posterior lens surface. When traction is applied, during relaxation of the ciliary muscles, the zonule induces dentate processes on the otherwise smooth, rounded lens equator.

The shape of the human lens in vivo is, to some extent, dependent upon the tension of the suspensory ligament, which in turn, is dependent upon the tone of the ciliary muscle and the inherent elasticity of the lens tissue. The shape of the lens in situ, therefore, differs from that of the excised lens. The lens is almost spherical at birth and flattens markedly during the first two years of life. In adults, the anterior surface is a flattened ellipsoid with an average radius of curvature of 10 mm (range, 8 to 14 mm). The geometric center of this curve constitutes the anterior pole, which is about 3 mm distant from the central posterior corneal surface (i.e., the depth of the anterior chamber). The posterior lens surface is curved more steeply, with an average radius of 6 mm (range, 4.5 to 7.5 mm). At birth, the equatorial diameter is about 6.25 mm and 9 to 10 mm in adult life. The axial (sagittal) diameter, which joins the anterior and posterior poles, varies markedly with age and accommodation. The axial diameter is approximately 3.5 to 4 mm in the newborn and in young children; between the ages of 20 and 50 years, it changes little; in the extremely old, it gradually increases to almost 5 mm. The weight of the lens
also increases with age, with an average of 65 mg at birth, 130 mg by the end of the first year, 204 mg between 40 and 50 years, and 266 mg between 80 and 90 years.

The lens has three main components: the lenticular capsule, the lens epithelium, and the lens cells or fibers constituting the cortical and nuclear zones.

2.5 Vitrectomy

2.5.1 Current Treatment of Posterior Segment Eye Diseases

Vitreous disease is often treated with any related retinal disease. For example, in cases of a severe retinal detachment, or growth of abnormal blood vessels into the eye caused by diabetic retinopathy, it may be necessary to perform a vitrectomy: removal of the vitreous gel and its replacement with an artificial substitute. Vitrectomy may also be performed if the vitreous is clouded by blood or scar tissue [46]. Since changes in the vitreous are the primary cause of retinal detachment, it is clear that ideal techniques to prevent and repair retinal detachment require that we learn how to prevent the vitreous gel from liquefying, shrinking, and tearing the retina in the first place. The most prevalent conditions like diabetic retinopathy and ARMD are usually treated by laser photocoagulation of the affected areas to destroy the stimulus for new vessel formation, although it has the disadvantage of causing possible damage to the retina and surrounding normal areas [52].

Various drugs including steroids, antiproliferative agents, antiviral drugs are used in the treatment of various infective vitreoretinal conditions. The isolation of vitreous caused by the blood–retinal and blood–aqueous barriers creates difficulties for effective drug therapy. Systemic administration is not feasible because only a small percentage of drugs can penetrate the barriers (e.g., chloramphenicol and tetracycline). Thus, the most
common method of drug delivery to the eye is topical. However, this is not suitable for the posterior segment because the drug would need to penetrate the cornea, pass through the anterior segment against the flow of aqueous humor and diffuse throughout the vitreous achieving a very low concentration in the vitreous [45].

Vitreoretinal surgery is employed in later stages of PDR. The treatment of retinal detachment associated with simple retinal breaks except for giant tears employs either scleral buckling or pneumatic retinopexy with the purpose of sealing the retina. Less successful is the repair of tractional retinal detachment, giant tears and other complicated cases that require vitrectomy and the substitution of vitreous with a more permanent tamponade agent [74]. Vitrectomy is a microsurgical procedure in which specialized instruments and techniques are used to repair retinal disorders, many of which were previously considered inoperable. The initial step in this procedure is usually the removal of the vitreous gel through very small (~1.4mm) incisions in the eye wall, hence the name "vitrectomy". The vitreous is removed with a miniature handheld cutting device and replaced with vitreous substitutes, which is similar to the liquid being removed from the eye. A high intensity light source is used to illuminate the inside of the eye while the surgeon works. Although vitrectomy procedures are sometimes performed through
incisions made near the front of the eye, most vitreoretinal surgeons enter the globe through a part of the eye known as the pars plana. Entering the eye through this location avoids damage to the retina and the crystalline lens. This is why the procedure is often referred to as a trans pars plana vitrectomy (TPPV).

2.5.2 Indications for Vitreous Replacement: Posterior Segment Eye Disorders

The prevalence of blindness in developed countries varies from 0.05 to 0.20%, while it is many times higher for Asia (0.75%) and Africa (1.0%). Diabetic retinopathy accounts for 5% to 10% of registered blind in USA and UK while age-related macular degeneration (ARMD) contributes to nearly 30% of blind [74]. Broadly, the posterior segment eye disorders may be vitreous or retinal pathologies. However, both are related as retinal tears can lead to vitreous displacement and vitreous scarring causes retinal detachment.

2.5.2.1 Vitreous Pathologies

- Vitreous hemorrhage: This could be due to injury, diabetes mellitus with retinopathy, hypertension and arteriosclerosis or malignant melanoma of the choroid.

- Degeneration and detachment of the vitreous: Degeneration primarily occurs when the gel structure is disrupted. It may be due to senility, ocular trauma, high myopia, proliferative diabetic retinopathy or chorioretinitis. The liquefied vitreous gains access to the retro-hyaloid space, through a hole in the thinner posterior vitreous cortex and separates the posterior vitreous from the internal limiting membrane of the retina. This causes the collagen meshwork to collapse and move forward, a phenomenon known as posterior vitreous detachment (PVD) [74].
• Vitreous opacities: These are floating bodies which develop in the vitreous humor and which may cause transient opacification or disturbances in vision.

2.5.2.2 Retinal Pathologies

• Retinal detachment: Here, the fragile retina is separated from the underlying epithelium.

• Age-related macular degeneration (ARMD): ARMD is a degenerative condition of the macula. It is the most common cause of vision loss in the United States in those 50 or older, and its prevalence increases with age. ARMD is caused by hardening of the arteries that nourish the retina. This deprives the sensitive retinal tissue of oxygen and nutrients that it needs to function and thrive. As a result, the central vision deteriorates.

• Diabetic retinopathy: This is a major cause of blindness in elderly subjects and develops frequently in longstanding cases of diabetes especially more than 10 years duration [74].

2.5.3 Role of Vitreous Substitutes

The requirements of the vitreous substitutes are as follows:

• In intra-operative procedures such as unfolding of the retinal tears, the removal of subretinal fluid and the floatation and removal of dislocated intraocular lens components.

• Achieving a relatively short-term tamponade effect such as in pneumatic retinopexy.

• As a long term tamponade agent in cases of retinal detachment and in cases of degenerative changes in the vitreous.
• For developing a sustained release system that could maintain therapeutic drug levels in the posterior segment of the eye over long periods [32].

Materials have been used to replace the vitreous throughout the 20th century and the search for an ideal vitreous substitute is ongoing. A major division of the current vitreous substitutes is between those with a short-term tamponade effect as the various gases and those, which promise to act as a longer-term tamponade with one main factor determining the permanence of the tamponade effect being interfacial surface energy. Materials that form an interface with the aqueous environment of the eye can be effective in closing retinal breaks and holding the neural retina in place against the retinal pigment epithelium.

2.5.4 Classification of Vitreous Substitutes

The vitreous substitutes may be classified according to composition or function.

- Classification based on composition

Vitreous substitutes used clinically or experimentally include:

(A) Replacement with natural vitreous

(B) Artificial vitreous substitutes

1. Gases:
   
   (a) Air.

   (b) Perfluorocarbon gases.

2. Liquids:

   (a) Aqueous solutions: water and balanced salt solutions.

   (b) Silicone oil and its derivatives: silicone oil, fluorosilicone oil and silicone-fluorosilicone copolymer.
(c) Perfluorocarbon liquids: Perfluoro-n-octane, perfluorohydrophenanthrene, perfluorotributylamine, perfluorohexyloctane, perfluoropolyether and others.

(d) Semifluorinated alkanes.

3. Gels: These are mainly polymeric materials and can be further grouped as:

(a) Semisynthetic polymers: methylated collagen, sodium hyaluronidate, hyaluronic acid collagen mixture, and sodium carboxymethylcellulose.

(b) Synthetic polymers: poly(1-vinyl-2-pyrrolidinone), polyvinylalcohol, polyacrylamide, poly(glyceryl-methacrylate), poly(2-hydroxyethyl acrylate), poly(methyl acrylamidoglycolate methyl ether).

- **Classification based on function**

  However, perhaps a more convenient way to classify the vitreous substitutes would be according to role they currently play in the treatment of various vitreoretinal pathologies as:

  1. Short intraoperative procedures: gases and perfluorocarbon liquids.
  2. Longer-term retinal tamponade: silicone oil.
  3. Permanent vitreous substitute: no material currently available.

**2.5.5 Different Types of Drug Delivery to Posterior Segment of the Eye**

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the mechanical community. Drug delivery to the posterior segment of the eye is not an easy assignment. The anatomy, physiology, and biochemistry of the eye render this organ exquisitely impervious to foreign substance. It is not uncommon for a drug to have more than one penetration pathway to move from the administration site to
the target site. However, typically, not all the penetration pathways are equally important. The contribution of some pathways may be so small that they are practically non-existent. In other words, the performance of a model will not be significantly affected even though some pathways are removed from the model because they are pharmaco-kinetically unimportant. In order to develop a simple but realistic model, it is essential to have a clear understanding of the contribution of each penetration pathway.

Figure 2-15: Drug delivery alternatives for treating posterior eye diseases. Topical drops (a) must diffuse across the tear film, cornea, iris, ciliary body, and vitreous before reaching the target tissues in the posterior eye, severely diluting the fraction of drug reaching the retina. Systemic drug delivery (b) also has a poor dose–response profile for the retina. Intravitreal injection or implant (c) and transscleral diffusion (d) may increase drug proportions reaching the retina. [32]

Currently, the treatment of retinal diseases is limited by the difficulty in delivering effective doses of the drugs to target tissues in the vitreous chamber. Many drugs have a narrow concentration window of effectiveness and may be toxic at higher concentrations. Therefore the ability to predict local drug concentration is critical for proper drug delivery. Current methods for ocular delivery include topical administration (eye drops), subconjunctival injections, periocular injections, intravitreal injections,
surgical implants, and systemic routes (Fig. 2-15). However, all of these methods have limitations. Therapeutic levels of many drugs may be difficult to achieve in ocular tissues and systemic toxicities are of concern when the oral and intravenous routes of administration are used. Intravitreal injections, periocular injections, and sustained-release implants can be used to achieve therapeutic levels of drugs in ocular tissues, but invasive methods are inherently risky due to the potential for bleeding, infection, retinal detachment, and other local injuries. A typical ophthalmic dropper delivers 30 µl, most of which is rapidly lost through naso-lacrimal drainage immediately after dosing. It has been estimated that typically less than 5% of a topically applied drug penetrates the cornea and reaches intraocular tissues. Eye drops are useful in treating conditions affecting either the exterior surface of the eye or tissues in the front of the eye, but cannot penetrate to the back of the eye for treatment of retinal diseases. The majority of the topically applied drugs enter the eye by passage across the cornea. This is an extremely inefficient process owing largely to the resistance exerted by the corneal epithelium to drug penetration. The corneal epithelium contributes over 90% of the corneal resistance to penetration to the topically applied drug. A measure of the corneal penetration efficiency of drugs is the permeability coefficient. This is generally on the order of 0.1-4.0 E5 cm/s.

An intravitreal injection provides the most direct approach to delivering drugs to the tissues in the vitreous segment, and therapeutic tissue drug levels can be achieved. Intravitreal injections, however, have potential side effects of retinal detachment, hemorrhage, endophthalmitis, and cataract. Further, drugs injected directly into the vitreous are rapidly eliminated. In many cases, repeated injections are needed to maintain the effective range of drug concentrations for a certain period of time since the half-life
of drugs in the vitreous is relatively short. Repeated injections cause patient discomfort and may further lead to complications such as vitreous hemorrhage, infection, and lens or retinal injury. Therefore, an understanding of the transport of different drugs following intravitreal injection is necessary, so that, the most effective utilization results from each injection.
CHAPTER 3. SIMULATIONS OF OUTFLOW PATHWAY OF HUMAN EYE

3.1 Geometrical Model of Anterior chamber of Human Eye

(a) Pictorial representation of outflow path of AH in the human eye [78], (b) Vertical section of the computational grid

In this section, attention is focused only on the anterior segment of the human eye. The anterior segment of the eye is divided into two parts: 1) The region between the iris and the cornea, called the anterior chamber and 2) The region between the iris and the hyaloid, called the posterior chamber. The depth of the anterior chamber of the human eye is approximately 3 mm [54] and diameter in the plane of the iris root is 11-12 mm [54]. Therefore, the anterior chamber is modeled as part of a sphere of radius 7.2 mm [54] and the depth along the central axis is taken to be 3 mm. The anterior chamber is bounded by the inner surface of the cornea and by the inner surfaces of the trabecular meshwork. The cornea is modeled as rigid shell with thickness of 0.6 mm, Fig. 3-1(b). On the posterior side, the anterior surface of the iris and the pupillary portion of the anterior lens surface bound the anterior chamber. The iris, which is a front extension of the ciliary body, has a slightly elliptical shape with a vertical axis of 11-12 mm long. It is perforated by a pupil, which changes its diameter depending on the amount of the light.
falling on the eyeball. The iris is modeled here as a rigid elliptical disc of uniform thickness of 0.4 mm with a circular papillary hole of radius 2 mm [18] at the center, Fig. 3-1(b). The circular aperture at the center represents the pupil through which flow from the posterior chamber enters the anterior chamber. The anterior and posterior surfaces of the iris are modeled as part of spherical surfaces of radius 21.6 mm and 22.1 mm respectively.

The posterior chamber is bound posteriorly by the hyaloid membrane; anteromedially by the contact of the iris with the lens; anteriorly by the pigment epithelium of the posterior iris surface and anterolaterally by the junctional zone of the iris and ciliary body [54]. The hyaloid membrane is treated as a plane surface bounding the posterior chamber from the vitreous side. The lens is described as an ellipsoid of 4 mm diameter in the anterior-posterior axis and 9 mm diameter in the two other axes. Its center is located in such a way that the depth of the anterior chamber is 3 mm and only the anterior surface of the lens needs to be meshed. Under certain conditions, the lens is subjected to significant movement but in the present study it is assumed to remain stationary. The temperature of the lens is also assumed to be constant and equal to the body core temperature. The curved boundary surrounding the posterior chamber is treated as the ciliary body, which secretes the fluid at constant volume flow rate of 2.5 µL/min. The AH secreted in the posterior chamber, enters the anterior chamber through the small gap between the iris and the lens, is estimated to be few microns (10-25 ≈µm) wide [18]. In the present study, the gap between the iris and the lens surface is assumed to be 15 µm. AH exits the anterior chamber through a drainage system located at the angle formed where the iris and the cornea meet, where it passes through a sieve-like system of spongy
tissue called the trabecular meshwork and drains into a channel called Schlemm's canal. This channel connects to numerous small connector channels buried in the sclera and forming the intrascleral plexus. From this plexus the blood, containing the aqueous humour, passes into more superficial vessels; it finally leaves the eye in the anterior ciliary veins.

The TM is modeled as a porous annular ring located at the root of iris. The AH pass through the pores of the TM whose characteristics changes in the outflow direction. The structure of this region is similar to that of a well-designed filter, so a precise modeling of this region is very important. TM consists of three regions: 1) Uveoscleral meshwork (UM), positioned immediately next to the anterior chamber, 2) Corneoscleral meshwork (CM), located next to the uveal meshwork and 3) Juxtacanalicular Tissue
(JCT), which is widely believed to generate the bulk of aqueous humor outflow resistance [4]. In the present model, the TM is defined as a two-layered region. The pore size for the normal UM and CM is large (25-10 \( \mu m \)) and it is believed to offer little resistance. As this region does not act as the major site of resistance, they are modeled as a single region. This region is treated as a porous region at the entry of the annular porous zone with a resistance coefficient corresponding to 10 \( \mu m \) pore size [54]. The CM consists of 50 % collagen fibrils [17] which causes an increase in the resistance. The TM has a tapering cross-section and its height towards the anterior side (i.e., toward the anterior chamber) is 640 \( \mu m \) whereas the length is 160 \( \mu m \) [Fig 3-2(b)]. The length of this porous region over which the pressure changes is defined by a combination of Darcy's Law and an additional inertial loss term. The JCT is the outermost portion of the TM and the length of this tissue was found by Ethier et al. [6] to be in the range 8-16 \( \mu m \). In the present study, the length of this tissue is assumed to be 10 \( \mu m \).

In the human eye, the circumference of the SC is about 36mm [17]. The lumen of SC in human eye varies from 200-400 \( \mu m \) in meridional axis whereas 10-25 \( \mu m \) in opposite axis [5]. In the present study the dimensions of the SC is considered to be 300 \( \mu m \) in meridional axis and 10 \( \mu m \) in the opposite axis [Fig. 3-2(b)]. The SC is assumed to be in the form of a single circumferential gutter. AH is drained away from the SC through numerous collector channels (i.e., 25-35 in number) [17]. In the current study, it is assumed that there are 30 collector channels evenly spaced around the corneoscleral limbus, and therefore each collector channel is spaced out at a distance of 1.2 mm [5]. Collector channels are assumed to be of uniform diameter 30 \( \mu m \) [17]. The rate at which aqueous humor is produced from the ciliary body is 3 \( \mu l \) min\(^{-1} \) in a normal eye of which
20 % leaves through Uveoscleral outflow and therefore 2.4 µl min$^{-1}$ exits through the TM. This 2.4 µl min$^{-1}$ is drained by these 30-collector channels, each draining 0.08 µl min$^{-1}$. The aqueous humor is finally drained out into the aqueous veins, where the venous pressure is estimated to be close to 9 mm of Hg (1.2 KPa).

Intraocular pressure (IOP) is a measurement of the fluid pressure inside the anterior chamber of the eye. In the normal eye this pressure is around 2000 Pa whereas in the diseased condition i.e., glaucoma this pressure can increase up to 8000 Pa [47]. In the present study, both cases (1) Normal and (2) Glaucomatous Condition are considered. For the normal eye, different approaches are used to progressively improve and understand the resistance due to the TM and the IW of SC and finally obtain a 6 mm Hg (or 800 Pa) pressure drop between the outlet pressure of the venous system (9 mm Hg or 1.2kPa) and the anterior chamber (average IOP 15 mm Hg or 2000 Pa). Two different approaches are considered (1) JCT as the main source of resistance and (2) The IW of SC as the main source of resistance. The following different models are developed for the normal eye:

- **Case 1: JCT as the source of resistance (JCT-R case)**

  In the simplest case considered, the JCT and the IW of SC are considered to be coupled together. Using conventional transmission electron microscopy combined with Carmen-Kozey theory, Ethier et al. [4] found that the pore diameter in the JCT is in the range of 1-1.5 µm. In the current model, the pore diameter is assumed to be 1.5 µm and the void fraction in JCT is tailored to obtain the normal eye pressure i.e., 2000 Pa. The void fraction value is found to be 0.044. For this case, where the JCT is considered to generate the bulk of aqueous outflow resistance [66], the permeability value was calculated by Johnson et al. [66] to be in the range 3 e-18 – 6.5 e-17 m$^2$. The permeability
values obtained by the current model $K=2.743 \times 10^{-17}$ m$^2$, for the present case where JCT is the main site of resistance, lies in the range of permeability value obtained by Johnson et al. [66].

Table 3-1: Characteristics of TM for Normal condition

<table>
<thead>
<tr>
<th>Region</th>
<th>Pore Diameter “d” µm</th>
<th>Void fraction “ε”</th>
<th>Permeability K (m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM + CM</td>
<td>10</td>
<td>0.5</td>
<td>8.399e-13</td>
</tr>
<tr>
<td>JCT</td>
<td>1.5</td>
<td>0.044</td>
<td>2.743e-17</td>
</tr>
</tbody>
</table>

- **Case 2 A: IW of the SC as the source of resistance (IW-R case)**

The idealized model discussed above can be improved by separating the JCT and the IW of SC as two distinct regions. The IW of SC is modeled as a porous zone of 1 µm length. The characteristics of the JCT are obtained from the experimental results of Ethier et al. [3-4], where using Carmen-Kozeny theory combined with conventional transmission electron microscope, it was found that the porosity of JCT was approximately 15-25% and the diameter of the pore is approximately 1-1.5 µm and hence the permeability value was calculated to be in the range 2-10 e-11 cm$^2$. The diameter of pores in the IW is in the range 0.1-3 µm [30] and void fraction is in the range 0.0002-0.02. The values of “d” and “ε” calculated [Table 3-2], lie in the range provided by Johnson et al. [66].

Table 3-2: Characteristics of TM and IW for Normal condition

<table>
<thead>
<tr>
<th>Region</th>
<th>Pore Diameter “d” µm</th>
<th>Void fraction “ε”</th>
<th>Permeability K (m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM + CM</td>
<td>10</td>
<td>0.5</td>
<td>8.399e-13</td>
</tr>
<tr>
<td>JCT</td>
<td>1.5</td>
<td>0.25</td>
<td>2.1839e-15</td>
</tr>
<tr>
<td>IW of SC</td>
<td>1.5</td>
<td>0.015</td>
<td>2.14e-18</td>
</tr>
</tbody>
</table>

- **Case 2 B: IW with distributed pores as the sources of resistance (IWP-R case)**

A more accurate and detailed geometrical representation will be to represent the individual pores located along the IW of SC. Ethier et al. [30] showed that in normal eye
only 0.2 % area of the IW is open for the AH to drain into aqueous veins. Here in this case, the IW of SC is modeled as a wall and only 0.2 % of the total area is open. The characteristics of UM + CM and JCT in the TM are as described in Table 3-2.

Parc et al. [26] showed that the vacuoles are preferentially found near collector channels, indicating that the aqueous flow across the inner wall is sensitive to downstream pressure. They also showed that twice as many vacuoles were present in the region underlying the collector channel ostia as in the region between the channel ostia. Therefore, in the current model, the IW is divided into two regions. The region underlying the collector channel has twice the number of pores than the region away from the collector channel. Each pore is considered to be of square cross-section with the length of 3µm. As only 0.2 % of the IW area is open, the number of pores in the inner wall is calculated to be n=121 (approximately). The pores are distributed in such a way the region underlying the collector channel has n=81 pores and the region away from the collector channel has n=20 pores.

For Glaucomatous Condition, where the IOP=8000 Pa [47] two approaches were used to progressively improve and understand the resistance due to the trabecular meshwork and Inner Wall of Schlemm’s canal and finally get a 51 mm Hg (or 6800 Pa) pressure drop between the outlet pressure of the venous system (9 mm Hg or 1200 Pa)
and the anterior chamber (average IOP 60 mm Hg or 8000 Pa).

- **Case 3: JCT as the source of the resistance (JCT-R)**

  Ethier et al. [4] found that the pore diameter in JCT is in the range 1-1.5 µm. In the current model, the pore diameter is assumed to be 1.0 µm and the void fraction in JCT is tailored to obtain the eye pressure drop i.e., 6800 Pa.

  Table 3-3: Characteristics of TM for Glaucomatous Condition

<table>
<thead>
<tr>
<th>Region</th>
<th>Pore Diameter “d” µm</th>
<th>Void fraction “ε”</th>
<th>Permeability K (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM + CM</td>
<td>10</td>
<td>0.5</td>
<td>8.399e-13</td>
</tr>
<tr>
<td>JCT</td>
<td>1.5</td>
<td>0.018</td>
<td>3.2875e-18</td>
</tr>
</tbody>
</table>

- **Case 4: IW of the SC as the source of resistance (IW-R)**

  Here in this case, the IW of SC is modeled as a porous zone of 1 µm length. As described in IW-R case, the characteristics of JCT are obtained from the experimental results of Ethier et al. [4]. The diameter of pores in the IW is in the range 0.1-3 µm [26] and the void fraction is in the range 0.0002-0.02. The values of “d” and “ε” calculated [Table 3-4], lie in the range provided by Johnson et al. [66].

  Table 3-4: Characteristics of TM and IW for Glaucomatous Condition

<table>
<thead>
<tr>
<th>Region</th>
<th>Pore Diameter “d” µm</th>
<th>Void fraction “ε”</th>
<th>Permeability K (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM + CM</td>
<td>10</td>
<td>0.5</td>
<td>8.399e-13</td>
</tr>
<tr>
<td>JCT</td>
<td>1.5</td>
<td>0.25</td>
<td>2.1839e-15</td>
</tr>
<tr>
<td>IW of SC</td>
<td>1.0</td>
<td>0.007</td>
<td>1.589e-19</td>
</tr>
</tbody>
</table>

3.2 Numerical Details

3.2.1 Grid Generation

The three-dimensional geometry of the human eye is generated using the commercial software Grid-Pro. A structured multi-block mesh with 6,541,250 hexahedral cells of aspect ratio less than two are used in the computational domain. The entire geometry is divided into 3,922 blocks with 2,250 blocks representing the trabecular
meshwork and the Schlemm’s canal region. The UM-CM and JCT are modeled as two different layers with different specific hydraulic permeability. In order to account for the pores in the IW of SC, which are around 1-3 µm [30], only 12-degree section of the eye is taken into consideration for computation. In the porous medium region, i.e. the TM region, the pressure drop appears as a momentum source term, which yields a loss of diagonal dominance and poor convergence rates. To avoid exacerbating convergence issues, it is critical to have high quality orthogonal grids with moderate aspect ratios. Nested topology is used [Fig. 3-2(c)] to obtain large number of cells only in the JCT and the SC region in order to accommodate the pores of 3µm length in the IW of SC.

### 3.2.2 Boundary Conditions

![Boundary Conditions Diagram](image)

Figure 3-4: (a) Boundary condition applied to the computational domain and (b) zoomed view of the encircled region shown in Fig. 3-4(a)

The aqueous humor properties are very similar to those of water and are detailed in Table 3-5. As the computational domain is symmetrical and the problem of interest incorporates for the pores in the IW of SC which are around 1-3 µm in diameter,
therefore to accommodated such a small mesh size, the calculations are carried out for 12 degree section of the eye, [Fig. 3-4(a)]. As shown in Fig. 3-4, periodic boundary condition is applied to the section ends of the domain.

For the temperature, the iris and the incoming flow through the pupil are specified to be at the core body temperature (37°C). The temperature of the cornea is set at constant value of atmospheric temperature (35°C). The Boussinesq approximation is used to account for the buoyancy effects. This results in an extra term in the momentum equation, as we will see below. To satisfy the aqueous secretion rate of 2.5 µl/min, a mass flow inlet condition of 4.17e-8 kg/s is applied at the secretion surface of the ciliary body in the direction normal to the boundary [Fig. 3-4(a)].

A no slip condition is applied on the surfaces of the iris, lens, retina, cornea and non-secretive ciliary body surface. We should also recall that these parts remain stationary. Considering the fact that the aqueous outflow is drained radially through the trabecular meshwork to the collector channels, the no-slip condition is also applied to the anterior and posterior surfaces of the ring-like trabecular meshwork. As the collector channels lead the aqueous humor to the venous system, a pressure outlet boundary condition of 1200 Pa is applied at the outer part of the collector channel. The inclusion of the TM with its proper dimensions and characteristics in the present simulation, and the incorporation of a realistic pressure outlet boundary condition, is a distinct improvement over previously reported efforts [10, 18]. In this way, the model accounts for the normal venous pressure conditions. Recalling the TM, described by a porous zone, one of the objectives of the simulation is to determine the characteristics of this region under normal IOP i.e., 2000 Pa. Most of the diseases associated with the eye are consequence of
increase in IOP inside the anterior chamber. The elevated IOP is the main risk factor for glaucoma and this value goes to 8000 Pa in the diseased state [47]. Here the pore size and the void fraction in the JCT and IW region are tailored to get the required increase in IOP in the anterior chamber.

### 3.2.3 Material Properties

The cornea is a vascular and transparent tissue with thermal properties close to that of water. The AH is assumed to be linear viscous liquid with properties close to those of water. The properties used in the present simulations are listed in Table 3-5.

<table>
<thead>
<tr>
<th>Eye region</th>
<th>Thermal conductivity (W/m K)</th>
<th>Density (kg/m³)</th>
<th>Heat capacity (J/kg K)</th>
<th>Viscosity (kg/ m s)</th>
<th>Volume expansion coefficient (1/K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous Humor</td>
<td>0.58</td>
<td>1000</td>
<td>4200</td>
<td>0.001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cornea</td>
<td>0.58</td>
<td>1000</td>
<td>4200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lens</td>
<td>0.40</td>
<td>1000</td>
<td>4200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Iris</td>
<td>0.58</td>
<td>1000</td>
<td>4200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ciliary body</td>
<td>0.58</td>
<td>1000</td>
<td>4200</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### 3.2.4 Governing Equations

The complete three-dimensional incompressible Navier-Stokes equations are considered with the body force terms accounting for the buoyancy effects. The density appearing in the buoyancy term is assumed to satisfy the Bousinesq’s approximation. The pressure drop in the trabecular meshwork satisfies Darcy’s assumption. The resulting non-dimensional forms of the momentum and energy equations are

\[
\frac{\partial U_i}{\partial X_i} = \frac{1}{Re_D} \left( \frac{\partial^2 U_i}{\partial X_j \partial X_j} \right) + \delta_{im} \left( \frac{Gr_D}{Re_D^2} \right) \theta + \left( \delta_{im} - 1 \right) \frac{\partial P}{\partial X_i} - p_i
\]

where \( m \) represents the index of the co-ordinate direction in which gravity is acting,
where $P_i$ is the momentum sink term added in the momentum equation for porous zone.

The second term in right hand side of equation (1) (buoyancy term) is included in the momentum equation only for the co-ordinate direction in which body forces are acting (gravity forces). The gravity is applied assuming the horizontal upward facing position of the human eye, i.e. along the pupil axis perpendicular to the iris surface. For the other two co-ordinate directions this term is replaced by the term $\left(-\frac{\partial P}{\partial X_j}\right)$ as indicated by the equation (1).

Energy equation:

$$U_j \frac{\partial \theta}{\partial X_j} = \frac{1}{Pr_D \text{Re}_D} \left(\frac{\partial^2 \theta}{\partial X_j \partial X_j}\right)$$  \hspace{1cm} (2)

Continuity equation:

$$\frac{\partial U_j}{\partial X_j} = 0$$  \hspace{1cm} (3)

The following non-dimensional variables are used in Eqs. (1)-(3):

$$X = \frac{x}{D}, \quad Y = \frac{y}{D}, \quad Z = \frac{z}{D}; \quad U = \frac{u}{U_{in}}, \quad V = \frac{v}{U_{in}}, \quad W = \frac{w}{U_{in}}; \quad \theta = \frac{T - T_c}{T_{in} - T_c}$$

where $T_{in}$ is the temperature of aqueous humor at the inlet (37 °C) and $T_c$ is the corneal temperature (35 °C).

To model the porous regions representing the TM, the momentum sink term $\nabla P$ in the equation (1) is represented by the sum of a viscous loss term (the Darcy term) and an inertial loss term. Thus,

$$\nabla P = \frac{\mu}{\alpha} U_i + C_z \frac{\rho}{2} |U_i| U_i$$  \hspace{1cm} (4)
which is added in momentum equation in non-dimensional form as
\[ p_i = \frac{\text{Re}_p D^2 U_i}{\alpha} + \frac{C_2}{2} D U_i U_i. \]
This term is not included in the momentum equation for non-porous fluidic zone. The momentum sink contributes to the pressure gradient in the porous cell, creating a pressure drop that is proportional to the fluid velocity (or velocity squared) in the cell. The porous media model incorporates an empirically determined flow resistance in the porous region. Since the volume blockage that is present physically is not represented in the model, the velocity inside the porous medium is computed based on the volumetric flow rate, to ensure continuity of the velocity vectors across the porous medium interface. In laminar flows through porous media, the pressure drop is typically proportional to velocity. So, the viscous term (first term) in equation (4) is more important with respect to the inertial resistive term (second term). Here \( \alpha \) is the permeability and \( C_2 \) is the inertial resistance factor. To get appropriate values of the constants \( \alpha \) and \( C_2 \), a semi-empirical correlation, derived from the Ergun equation [53], is used. These correlations for the permeability and inertial resistance factor are applicable over a wide range of Reynolds number and for various packing levels, and are given as:
\[
\alpha = \frac{D_p^2 \varepsilon^3}{150(1-\varepsilon)^2}, \quad C_2 = \frac{3.5(1-\varepsilon)}{D_p^3 \varepsilon^3},
\]
where \( D_p \) is the mean particle diameter of the packed bed or pore size and \( \varepsilon \) is the void fraction. Void fraction is defined as the volume of voids divided by the volume of the packed bed region. Based on the data in [17] the void fraction of UM and CM was considered to be 0.5 and \( D_p = 15.87 \ \mu\text{m} \). These values of \( \varepsilon \) and \( D_p \) lead to a specific hydraulic permeability of \( 8.399 \times 10^{-13} \text{ m}^2 \) for UM and CM. In the current model for JCT,
the pore diameter is assumed to be 1.5 µm and the void fraction in JCT is tailored to obtain the normal eye pressure i.e., 2000 Pa. In JCT-R case for the normal eye, the values of $\varepsilon$ and $D_p$ are calculated to be 0.044 and 6.64 µm [Table 3-1] whereas for the IW-R case this value is calculated to be 0.25 and 3.43 µm [Table 3-2]. For JCT-R case for the glaucomatous eye, the values of $\varepsilon$ and $D_p$ are calculated to be 0.018 and 9.03 µm [Table 3-3] whereas for the IW-R case this value is calculated to be 0.25 and 3.43 µm [Table 3-4].

3.2.5 Computer Code

The commercial package FLUENT [56], is used to solve the flow and energy equations associated to this model. This code is based on a control volume approach where the computational domain is divided into a number of cells, and the governing equations are discretized into algebraic equations in each cell. The control-volume approach leads to a discretized set of equations which satisfies the integral conservation of the mass and the momentum over each control volume. For solving the system of algebraic equations a Gauss-Siedel scheme is used. Although the Gauss-Siedel scheme rapidly removes the high frequency errors in the solution, low frequency errors are reduced at a rate inversely related to the grid size. A W-cycle multi-grid scheme is used to accelerate the convergence rate by applying corrections to coarser grid levels. The coupling between velocity and pressure is handled using the SIMPLEC-algorithm [57], which uses the conservation of mass equation to derive a pressure corrector equation, and uses a pressure and velocity correction step to yield continuity satisfying velocity fields at each iteration. The pressure and velocities are then corrected so as to satisfy the continuity constraint. The discrete values of the variables are stored at the cell-centers,
but the convection terms in the discretized equation must be interpolated at the cell faces from the cell-center values. A second order upwind scheme is used for deriving the face values of different variables in the momentum equation. For the pressure Poisson equation, a second order accurate discretization scheme is used. As the number of hexahedral cells is high, it is difficult to solve on a single processor. The entire computational domain is solved on a parallel platform with 4 processors.

3.3 Results and Discussion

3.3.1 Grid Independence Study

![Figure 3-5: Velocity magnitude along the central axis of the anterior chamber for 1,250,000 and 6,541,250 hexahedral cells.](image)

To demonstrate grid independence, simulations are run with 1,250,000 and 6,541,250 hexahedral cells for the case where JCT is considered to be the main source of resistance (JCT-R case). Figure 3-5 shows the plot of the velocity magnitude along the central axis of the anterior chamber. Less than 2\% variation in the magnitude of the maximum velocity is observed between the 1,250,000 and the 6,541,250 cell calculation. In order to accommodate the pores of the IW of SC, large number of grid points i.e. 6,541,250 cells were considered for the calculations.
3.3.2 Pressure, Velocity, Temperature and Shear Stress Contours (Normal Eye)

Figure 3-6: Distribution in the anterior segment of human eye (a) Streamlines mapped on contours of velocity magnitude, (b) Temperature distribution and (c) Contour of static pressure

Kumar et al. [10] showed that the gravity plays a major role in determining the flow pattern of AH inside the anterior chamber. In this study, we have assumed the horizontal upward-facing position of the human eye where the gravity direction is perpendicular to the iris surface, and the flow field is axi-symmetric. Figure 3-6(a) shows the streamlines mapped on the contours of velocity distribution in the anterior segment of the human eye. As seen in the Fig. 3-6(a), the AH is first secreted by the ciliary body. AH then flows through the posterior chamber slowly converging towards the pupil at a
velocity of around 1E-3 mm/s. When approaching the small iris-lens gap, velocity increases up to 0.119 mm/s at the pupil margin. Entering the anterior chamber through the pupil, the warm AH first rises upwards to the cooler cornea and then the flow descends along the corneal surface towards the TM due to the effects of gravity. When reaching the iris root, the aqueous humor either enters the TM or goes along the iris surface to finally join the fluid entering the chamber. So a re-circulation zone is created [Fig. 3-6 (a)]. In the anterior chamber, the highest velocity occurs midway along the pupil axis (70E-3 mm/s). As seen, a small portion of the re-circulating fluid exits through the TM. The velocity magnitude at the TM entry is approximately 2 E-3 mm/s, which also corresponds to the velocity of the fluid turning back along the iris surface. It was observed that flow profile is almost independent of pore size in the TM, but the IOP of the anterior chamber increases with decreasing the pore size.

Figure 3-6 (b) shows the temperature distribution in the anterior segment of the human eye. Within the anterior chamber, the temperature contour shows a thermal plume from a cool temperature (35°C) on the corneal surface to the core body temperature (37°C) characterizing the iris surface and the lens. This temperature difference is the main source to drive the AH within the anterior chamber. Temperature gradient seems uniform throughout the posterior chamber but is higher in the anterior chamber i.e., in the region between the cornea and the lens surface.

The pressure variations in the anterior and posterior chamber region are considerably smaller than the pressure drop across the porous TM. The variation in the pressure of the anterior chamber is less than 0.01 Pa (Fig. 3-6(c)), which indicates that the anterior chamber pressure is nearly constant. Heys et al. [18] also reported that the
pressure is essentially uniform inside the anterior chamber; the present model supports this observation. Along the TM, i.e., from the anterior chamber to the aqueous veins, the pressure decreases from the normal IOP of 15 mm of Hg (~2 Kpa) to 9 mm of Hg (~1.2 Kpa) corresponding to the pressure in the aqueous veins. The quantities like pressure, velocity and temperature in the anterior chamber do not change with the different modeling representations of the TM (i.e., JCT-R, IW-R and IWP-R case), and so the rest of the chapter is mainly concentrated on the distribution of these quantities in TM region.

The velocity of the aqueous humor decreases when it enters the JCT, where the pore size is low. In order to achieve a better understanding of the outflow of the AH from the TM to collector channels, the results are plotted in the vicinity of the pores. Fig. 3-7 shows the streamlines mapped on the contours of velocity distribution in the vicinity of JCT and SC. In the idealized case where JCT is modeled as a main source of resistance (i.e., JCT-R case), the IW effects are neglected [i.e., effects of IW pores are not considered]. In this case, as the pore size in JCT is small (d=1.5 µm and ε=0.044), the
AH velocity decreases to 2.8 E-3 mm/s while passing through JCT. It is seen that the velocity decreases as the AH passes through the porous medium but it gains the velocity when it reaches the non-porous region [i.e., SC] and then exits out through the collector channel. It is seen that in Fig. 3-7(a), the aqueous velocity increases to a maximum value of 0.216 mm/s near the collector channel. Figure 3-7(b) shows the velocity distribution for the case where IW is modeled as a porous medium (i.e., IW-R case). The velocity distribution pattern is comparable to the case where JCT is modeled as a porous medium. In the case where 0.2% of area of IW is open (i.e., IWP-R case), flow through the JCT is confined to the region near the IW pores, forcing a funneling pattern of aqueous streamlines, as illustrated in Fig. 3-7(c). To enter the SC, AH must converge to pass through discrete openings along the IW of SC, which decreases the available area for flow and increases the outflow resistance. Darryl et al. [16] showed that the separation of the IW of SC from the JCT eliminates the funneling pattern. This is because of the increases in the available area for flow and the subsequent increase in the outflow facility during washout [Fig. 3-7(a)], where the effects of IW are neglected. The maximum velocity in the eye is found in the vicinity of these pores. It is seen that due to the effects of funneling of the AH, the velocity increases to a maximum value of 0.42 mm/s in the vicinity of pores.

Figure 3-8 shows that velocity distribution along the axial length of the TM and SC passing through the IW pore and the center of the collector channel. Here Y* is defined as the Y-distance/total length of TM and SC [i.e., distance between points A and B in Fig. 3-8(b)]. It is seen that in Fig. 3-8(a), that the AH velocity is constant as it passes through the JCT. In the JCT-R case, the AH velocity increases by 25.3 % as it approaches
Figure 3-8: (a) Line plot of velocity magnitude in axial direction passing through the collector channel and (b) diagrammatic representation of total length of TM and SC the collector channel. In the IWP-R case, the velocity of aqueous increases as it passes through the pores and reaches to a maximum value of 0.42 mm/s. The velocity around the pore increases by an order of $10^2$ compared to the aqueous velocity in the JCT. It is seen that the AH exits with a very high velocity through the IW pores and enters the SC. Hence the velocity of AH is very high in the vicinity of the IW pores while throughout the remainder of the JCT, the fluid velocities are small.

Figure 3-9 shows the velocity distribution around the pores located in the IW of SC, which are near and away from the collector channel. It is seen that the aqueous velocity is high only in the vicinity of IW pores. It is also seen that the velocity of AH is higher in the SC region near the collector channel compared to the region away from the collector channel. Figure 3-9 shows the line plot of the velocity in the vicinity of the IW pores in the axial direction. Here X axis is non-dimensionalized with respect to the distance between two pores [Fig. 3-9(d)]. It is seen that the AH velocity funneling out of the IW pores is higher (i.e., approx. 40%) in the region underlying the collector channel than in the region away from it.
Figure 3-9: Velocity contour in the vicinity of pore (a) Near collector channel, (b) Away from collector channel, (c) Line plot for the velocity magnitude near and away from collector channel (i.e., between point A and B) and (d) diagrammatic representation of distance between two pores

Figure 3-10: Contour of static Pressure in the TM region
The variation in the pressure of the TM is shown in the Fig. 3-10. As seen, the major pressure drop is located in the TM, hence in order to keep figures as clear as possible, pressure contours are plotted separately for the TM from the rest of the eye [Fig. 3-10]. It is seen that the pressure of the AH decreases when it enters the porous JCT, i.e., where the pore size is low. In order to achieve a better understanding of the pressure distribution from JCT to collector channel, the results are plotted along the line passing through the pore and center of the collector channel [Fig 3.8(b)].

Figure 3-11 shows the pressure distribution in JCT and SC region passing through the pore and center of the collector channel. Here, \( Y^* \) is defined as the y-distance/total distance of JCT and SC [Fig. 3-11(b)]. It is seen that the entire pressure drop occurs in the JCT and the IW region. The comparison of the pressure drop can be readily analyzed by overlapping the pressure drop for all the three cases. It is seen that the pressure variation occurs only in the JCT region whereas the SC is at the venous pressure (i.e., at normal IOP). In the JCT-R case, where JCT is modeled as a porous medium, pressure
decreases linearly (approximately) from normal IOP to venous pressure. In the IW-R case where IW of SC is modeled as a porous medium, as the pore size in the IW is small ($d=1.5$ µm and $\varepsilon=0.015$), the entire pressure drop occurs in the IW of SC region. In the IWP-R case where pores of IW of SC act as a main source of resistance, it is seen that the entire pressure drop (i.e., the 800 Pa pressure drop) occur in the vicinity of the IW pores.

Figure 3-12 shows the contours of the pressure distribution along the circumferential length of the TM and the SC for all the three cases (at $Z=0.0371$). As the pressure plots are symmetrical, Fig. 3-12(a-c) are plotted only for the half section i.e., between $X=-0.00063$ and $X=0$. It is seen that the TM is at a higher pressure compared to the SC. It is seen that the highest pressure in the canal is at the midpoint between the two collector channels i.e., in the region away from the collector channel. The pressure falls near the collector channel which implies that the IW of SC will experience more pressure difference towards the collectors and the canal should show a greater tendency to collapse near and at the collector channel exits. Figure 3-12(d) shows the pressure drop in the vicinity of IW pores. Figure 3-12(e) shows the line-plot of the pressure distribution along the circumferential length of SC for all the three cases. In the JCT-R and IW-R case, it is seen that there is around 0.066% increase in pressure in the region away from the collector channel compared to the venous pressure. In the IWP-R case, where only 0.2% of IW is open, the pressure increase is only 0.043%.

Figure 3-13(a) shows the pressure distribution in the IW of SC for the IWP-R case. It is seen that the entire pressure drop occurs in the IW of SC pores. The pressure on the IW region away from the pore is very high and is approximately equal to the IOP [Fig. 3-13(a)]. In order to accomplish a better understanding of the pressure in the
Figure 3-12: Pressure contour along the horizontal cross-section of the TM and SC (a) JCT-R case, (b) IW-R case, (c) IWP-R case, (d) zoomed view of the encircled region around the pore shown in Fig. 3-12(c) and (e) Pressure line-plot along the center-line of the circumferential length of SC.
Figure 3-13: Pressure distribution on the Inner wall of SC in the vicinity of pores and (a) Contour plot towards the JCT, (b) Contour plot towards the SC side, (c) Line plot in the axial direction and (d) zoomed view of the encircled region shown in Fig. 3-13(c) vicinity of pores, the results are plotted along the line passing through the pore. Figure 3-13(c) shows the pressure line plot in the vicinity of pores in the axial direction. Here X axis is non-dimensionalized with respect to the distance between two pores [Fig. 3-9(d)]. For the idealized case, where JCT is modeled as a porous medium i.e., JCT-R case, the IW is at a constant pressure $P=1256$ Pa i.e., approximately venous pressure. In the IWP-R case, it is seen that the pressure decreases from IOP to a value of $P=1423$ Pa in the IW pores i.e., the entire pressure drop occurs in the 3µm pore region.

Figure 3-14 shows the contours of the pressure distribution along the circumferential length of the outer wall of SC. It is seen that the pressure is lower in the
Figure 3-14: Pressure contour on the outer wall of Schlemm’s canal (a) JCT-R case, (b) IW-R case, (c) IWP-R case and (d) Pressure line-plot along the center-line of the circumferential length of SC (e) diagrammatic representation of outer wall of SC along which Fig. 3-14(d) is drawn.

region near the collector channel and it increases gradually away from the collector channel. The maximum pressure on the outer wall is in the region between the two collector channels. This decrease in pressure near the collector channel is due to the increase in the velocity of the AH flowing into the collector channel. Figure 3-14(d) shows the line-plot of the pressure distribution along the circumferential length of outer wall of SC for all the three cases [Fig. 3-14(e)]. In the JCT-R and the IW-R case, it is seen that there is approximately 0.066% increase in pressure in the region away from the collector channel.
collector channel compared to the venous pressure whereas in the IWP-R case, the pressure increase is only 0.043%.

Figure 3-15: Wall shear stress contour on the surface of the lens and on the anterior surface of iris

Figure 3-15 shows the shear stress distribution on the anterior surface of the iris and on the surface of lens. Significant shear stresses are located in very specific areas of anterior chamber: 1) At the pupil margin on both the lens and iris surfaces and 2) On the iris surface at the trabecular meshwork entrance. However, the order of magnitude of the shear stress is different depending on the location. The shear stress reaches to a maximum value of 1.38 E-2 Pa at the pupil margin on the lens surface, where the AH enters the anterior chamber through a very shallow gap lens-iris [i.e., high velocity magnitude region Fig. 3-6(a)]. The shear stress of the order of 3.49 E-3 Pa is found near the trabecular meshwork entrance or iris root [Fig. 3-15]. This increase in shear stress at the iris root may be a factor explaining the liberation of pigments or depletion of proteins from this surface of iris. These particles could then further obstruct the trabecular meshwork [9].
Figure 3-16: Shear Stress on the Inner wall of Schlemm’s canal (a) JCT-R case (b) IW-R case, (c) IWP-R case and (d) Line plot of shear stress

Figure 3-16 shows the shear stress distribution on the IW of SC. It is seen that the region underlying the collector channel ostia has higher shear stress compared to the region away from the collector channel. This implies that the inner wall will experience more shear stress near the collector channel and that the canal should show a greater tendency to collapse near the collector channel. For the JCT-R case, the shear stress reaches to a maximum value of 0.0037 Pa near the collector channel. This increase in shear stress value in the collector channel ostia may be a factor explaining the higher number of pores in this region. Parc et al. [26] showed that the region underlying the collector channel has double the number of pores in the inner wall; the present model supports this observation. Figure 3-16(b) shows the shear stress distribution for the IW-R case where IW is modeled as a porous medium. The stress distribution trend in this case is comparable to the case where JCT is modeled as a porous medium. Figure 3-16(c)
shows the contour of shear stress distribution for the IWP-R case on the IW of SC. It is seen that the shear stress is high only in the vicinity of the IW pores whereas the shear stress is uniformly low in the region away from the pores. Figure 3-16(d) shows the shear stress line plot on the IW of SC in the axial direction (i.e., \(X = 0.000482\) to 0.00065). Here X axis is non-dimensionalized with respect to the distance between four pores. In the JCT-R and IW-R case, the shear stress increases to a value of 0.023 Pa whereas in the IWP-R case, it is seen that the shear stress reaches to a maximum value of 0.49 Pa in the vicinity of the IW pores. While comparing the results of JCT-R and IWP-R case, the value of maximum shear stress increases by 20 times in the later case. When compared to the shear stress value at the iris-lens gap, the shear stress value in the vicinity of pore increases by 96%.

Figure 3-17: Shear stress contour on the outer wall of Schlemm’s canal (a) JCT-R case, (b) IW-R case, (c) IWP-R case and (d) Shear stress line-plot along the center-line of the circumferential length of SC.
Figure 3-17 shows the shear stress distribution on the surface of outer wall of Schlemm’s canal. It is seen that the shear stress is higher in the region near the collector channel and decreases gradually away from the collector channel. This increase in shear stress is due to increase in the velocity of the AH gushing into the collector channel, as shear stress is directly proportional to velocity gradient. Figure 3-17(d) shows the line plot of shear stress distribution along the mid-plane [Fig. 3-14 (e)]. In JCT-R case, the shear stress value reaches to a maximum value of 0.067 Pa in the vicinity of collector channel. In the IWP-R case (i.e., for the case where 0.2% of IW of SC is open), 13 % higher shear stress is observed compared to the other two cases. The increase in the shear stress is due to the high velocity of AH gushing out of the pores of the IW.

3.3.3 Pressure, Velocity and Shear Stress (Glaucomatous Eye)

Most of the diseases associated with the eye are consequence of increase in IOP inside the anterior chamber. The blockage of the eye-drainage system raises the IOP to abnormal values, which leads to glaucoma. For Glaucomatous condition, where the IOP=8000 Pa [47] two approaches were used to progressively improve and understand the resistance due to the trabecular meshwork and IW of SC and finally obtain a 51 mm Hg (or 6800 Pa) pressure drop between the outlet pressure of the venous system (9 mm Hg or 1200 Pa) and the anterior chamber (average IOP 60 mm Hg or 8000 Pa).

Figure 3-18 shows that velocity distribution along the length of the TM and SC passing through the IW pore and the center of the collector channel. Here Y* is defined as the Y-distance/total length of TM and SC [i.e., distance between points A and B in Fig. 3-8(b)]. It is seen in Fig. 3-18(b) that the velocity of AH increases in the TM for the glaucomatous eye compared to the normal eye condition.
Figure 3-18: (a) Line plot of velocity magnitude in axial direction passing through the collector channel and (b) zoomed view of the encircled region shown in Fig. 3-18(a).

Figure 3-19: (a) Contour of static pressure (a) Anterior chamber, (b) zoomed view of the encircled region shown in Fig. 3-19(a) and (c) Line plot of the pressure drop in the JCT and SC.
The variation in the pressure for the glaucomatous eyes is shown in the Fig. 3-19(a-b). The pressure variations in the anterior and posterior chamber region are considerably smaller than the pressure drop across the porous TM. The pressure is essentially uniform inside the anterior chamber. Along the TM, from the anterior chamber to the aqueous veins, the pressure decreases from the normal IOP of 60mm of Hg (~8 Kpa) inside the anterior chamber to 9 mm of Hg (~1.2 Kpa) corresponding to the pressure in the aqueous veins. Figure 3-19(c) shows the line-plot of the pressure distribution in JCT and SC region passing through the pore and center of the collector channel. Here, Y* is defined as the y-distance/total distance of JCT and SC center [Fig. 3-11(b)]. It is seen that the entire pressure drop occurs in the JCT and IW region. The comparison of the pressure drop can be readily analyzed by overlapping the pressure drop for the two cases along with the normal IOP case. It is seen that the pressure variation occurs only in the JCT region whereas the SC is at the venous pressure. For the case, where JCT is modeled as a porous medium, pressure decreases linearly (approximately) from high IOP (i.e., 8000 Pa) to venous pressure. In the IW-R case, where IW of SC is modeled as a porous medium, as the pore size in the IW is small (d=1.0 µm and ε=0.007), the entire pressure drop occurs in the IW of SC region.

![Figure 3-20: Shear Stress on the Inner wall of Schlemm’s canal (a) JCT-R case (b) IW-R case](image)
Figure 3-20 shows the shear stress distribution on the surface of IW of SC for both the cases. The shear stress trend for glaucomatous condition is comparable to the normal eye. It is seen that the region underlying the collector channel ostia has higher shear stress compared to the region away from the collector channel. The shear stress value is smallest between the two collector channels. In the glaucomatous condition the shear stress reaches to a maximum value of 0.0052 Pa near the collector channel and this increase in the shear stress value near the collector channel ostia may be a factor explaining the higher number of pores in this region. As seen in this case, for glaucomatous condition there is 40% increase in the maximum value of the shear stress compared to normal eye condition.

Figure 3-21: Shear stress contour on the outer wall of Schlemm’s canal (a) JCT-R case, (b) IW-R case and (c) Shear stress line-plot along the center-line of the circumferential length of SC
Figure 3-21 shows the shear stress distribution on the surface of outer wall of SC. It is seen that the shear stress is higher in the region near the collector channel and decreases gradually away from the collector channel. The shear stress value is smallest between the two collector channels. Here in this case the shear stress reaches to a maximum value of 0.105 Pa near the collector channel. This increase in shear stress is due to the increase in the velocity of the aqueous humor flowing into the collector channel. There is approximately 97% of increase in shear stress magnitude near the collector channel than in the region away from the collector channel.

3.4 Concluding Remarks

A complete three-dimensional model is developed and a model of the complex TM is proposed. The TM is represented as a multi-layered porous zone of specified pore sizes and void fraction for the UM, the CM and the JCT layer. In this study, the following cases are presented: (1) JCT as the source of resistance (JCT-R), (2) IW as the source of resistance (IW-R) and (3) IW with distributed pores as the source of resistance (IWP-R). The IOP predicted inside the anterior chamber and the pressure drop across the TM (corresponding to real pore size of the JCT) are found to be close to experimental observations for a normal eye. The following major observations are made from the computed results.

(1) The hydraulic permeability of porous structures, i.e., TM and IW is calculated and is reported in Table 3-1 to 3-4.

(2) Predictions verify the dominance of the buoyancy as the driving mechanism for the AH flow. The temperature difference between cornea and core body temperature is the main source to drive the AH within the anterior chamber.
(3) The pressure drop mostly occurs across the JCT and IW of SC. Within the anterior chamber, the variations in pressure are relatively small.

(4) It was observed that flow profile is almost independent of pore size in the TM, but the IOP of the anterior chamber increases with decreasing the pore size.

(5) The highest pressure in the canal is at the midpoint between the two collector channels and the pressure falls near the collector channel. This implies that the IW will experience more pressure difference towards the collectors, and that the canal should show a greater tendency to collapse near and at the collector channel exits.

(6) The pores of the inner wall are found to cause a “funneling effect” in which the AH flows preferentially through those regions of the JCT nearest the inner wall pores.

(7) It is seen that the velocity of AH is higher in the SC near the collector channel than in the region away from the collector channel. It is seen that there is approximately 40% increase in velocity of AH near the collector channel.

(8) It is seen that the region underlying the collector channel ostia has higher shear stress compared to the region away from the collector channel. The shear stress value is smallest between the two collector channels. There is approximately 97% of increase in shear stress near the collector channel than in the region away from the collector channel.

(9) While comparing the results of the IWR-P (i.e., where 0.2% area of IW is open), with the JCT-R case, the value of maximum shear stress increases by 20 times.

(10) For the glaucomatous eye, there is 40% increase in the maximum value of the shear stress on the IW of SC compared to normal eye.

In future, the model will be extended to account the elasticity of the IW of SC, to demonstrate the collapse of this canal in the case of high pressure condition. Further the
model can be developed to study the interactions of ocular particles trapped in the TM and formations of some structures associated with specific eye disease. These issues have been ignored in the present study.
CHAPTER 4. DRUG DELIVERY IN VITREOUS SUBSTITUTES

4.1 Mathematical Model

4.1.1 Geometrical Model of Posterior Segment of Human Eye

![Diagram of the human eye with labels](image)

The geometrical model adopted in the present study, shown in Fig. 4-1 (b), is based on the physiological dimensions of a human eye provided by L’Huillier et al. [19]. The vitreous chamber is mainly composed of vitreous humor and comprises about two-thirds of the eye with a volume of approximately 4 mL [47]. The viscous properties of the
vitreous humor allow the eye to return to its normal shape if compressed. The crystalline lens is located just behind the iris and is modeled here as a stationary ellipsoid of 4 mm diameter along the anterior-posterior axis and 9 mm diameter along the two other axes. The hyaloid membrane is composed of loosely packed collagen fibers and hyaluronic acid, and spans the gap between the lens and the ciliary body. Although the hyaloid membrane forms a boundary between the nearly stagnant vitreous and the flowing aqueous humor, it does not form a limiting boundary to the transport of small molecules such as fluorescein. The retina is a light-sensitive layer at the back of the eye that covers about 65 percent of its interior surface and is immediately adjacent to the vitreous. The retina is a remarkably fragile tissue, having a thickness of 250 µm [48] and is modeled here as a sphere with a radius of 9.1 mm. The distance between the lens and retina centre is 5 mm. The choroid lies between the retina and the sclera. It is composed of layers of blood vessels that nourish the back of the eye. The sclera is commonly known as "the white of the eye." It is the tough, opaque tissue that serves as the eye's protective outer coat. The average thickness of sclera is assumed to be 0.065 cm [47].

4.1.2 Drug Delivery Model

The traditional approach of drug delivery is the direct injection of the drug in a solution form. More recently, micro-spheres of biodegradable polymer such as poly (lactic acid) have been used as drug carriers. The micro-spheres of poly (lactic acid) are resolved into monomers of lactic acid by hydrolytic deesterification before they finally disappear. In this study, we have explored both these approaches of drug delivery, i.e., (i) direct injection where the injected drug is instantaneously released from a specified volume and (ii) Time-released drug injection where the drug is released as a function of
time. There are many parameters that potentially control how the drug is initially distributed in the vitreous chamber which include: needle gauge, needle length, penetration angle of the needle, speed of the injection, rheology of the injected solution, and rheology of the vitreous. Numerical analysis carried out by Friedrich et al. [36-37] showed that the results obtained by modeling the initial drug injection site as a cylinder or a sphere were identical. Therefore, in the present study we have assumed that the drug is released at the center of the vitreous chamber and that the injected drug initially has a homogenous distribution within a cylindrical region after injection. The initial size of the cylindrical region was assumed to be 0.075 cm in diameter and 0.15 cm in height [38]. The density of the drug is assumed to be same as that of water i.e., 1000 Kg/m$^3$. The initial normalized mass fraction of the drug is assumed to be 1 (normalized with respect to the concentration of the drug in the water base) within the domain of the drug injection site while it is 0 in rest of the vitreous.

The diffusivity of small molecules, such as gentamicin, fluorescein and fluorescein glucuronide in the vitreous humor was found experimentally by Araie et al. [34] and Kaiser et al. [64] to be 6 E-10 m$^2$/s, whereas for larger molecule drugs, FITC Dextran, the diffusivity is found to be 3.9 E-11m$^2$/s [77] and moreover for very large molecules e.g., an antibody, the diffusivity is lower and is of the order of 1 E-11 m$^2$/s [33]. Therefore, for the current study we have considered three possible diffusion coefficients for the drugs, i.e., 6 E-10 m$^2$/s, 3.9 E-11 m$^2$/s and 1 E-11 m$^2$/s are considered. There is no published data that provides the diffusion coefficient of drug in vitreous substitutes. Rashidnia et al. [50] using interferometric measurements and the Wiener model calculated the diffusion coefficient of silicone oil with different kinematic
viscosities. They found out that the diffusion coefficient of 1 cSt oil (viscosity comparable to water) in 1000 cSt Silicone oil to be 2.48 E-10 m²/s. In the absence of quantitative information about the diffusion coefficient of drug with silicone oil, a range of values are chosen, we have considered five possible diffusion coefficients for the drugs (i.e., 6 E-10 m²/s, 3.9 E-11 m²/s and 1 E-11 m²/s, 6 E-12 m²/s and 1 E-12 m²/s), so that the results can be used to evaluate the role of the diffusion coefficients within an order of magnitude variation (from E-10 to E-12).

For Time-released injection, since we are interested in controlling the drug delivery release rate, we have modeled the source term in the scalar concentration with the following volumetric release rate of the drug,

$$q = \frac{M \times k}{V \times \sqrt{t}}$$  \hspace{1cm} (1)

where M is the initial loading of the drug (Kg), k is the rate constant of the release (s⁻¹) and V is the volume of the drug injection (m³). The source term above is defined only at the injection site and is zero for all other positions within the vitreous. In earlier studies by Falk et al. [51], who studied the release of gentamicin from poly-(L-lactic) microspheres in cadaveric bovine vitreous, the value of k was taken to be 0.057 day¹/² and the initial mass of the drug M was assumed to be 795 µg.

4.2 Numerical Details

4.2.1 Grid Generation

The three-dimensional geometry of the human eye is generated using the commercial software Grid-Pro. A structured multi-block mesh with 541,250 hexahedral cells of aspect ratio less than three are used in the computational domain. The entire
geometry is divided into 922 blocks with 5 blocks representing the drug injection position. The retina and the choroid-sclera are modeled as two different layers with different hydraulic conductivity. As described earlier, the drug is released at the center of the vitreous chamber and is assumed be cylindrical in shape at t=0. The drug injection position is shown encircled in Fig. 4-1(b). As the drug injection site is very small the grid is refined in the drug injection region.

4.2.2 Boundary Conditions

The hyaloid membrane separates the vitreous humor from the aqueous humor and the anterior segment of the eye. Therefore, we have considered pressure at the hyaloid membrane to be same as that of aqueous humor, which is close to the intraocular pressure of the eye. Normal IOP ranges between 15-20 mmHg (~2000-2666 Pa) but can be nearly double this value when malignant glaucoma occurs. In the present study, we have assumed the pressure at the hyaloid membrane to be 2000 Pa. As in Refs. [33, 38], the concentration is set to zero i.e., C=0 at the hyaloid membrane. This boundary condition is based on the assumption that the aqueous flow rate is high relative to the release of the drug. The lens is assumed to be impermeable to both flow and the drug concentration. Therefore, at the surface of the lens a no-flux boundary condition is applied. The retina and the sclera are treated as two different layers and each layer is treated as a porous zone with their respective permeability. In the present work, permeability values from the literature are used for the retina and the sclera. Drugs with small molecule have higher retinal permeability, whereas the drugs with large molecules have lower retinal permeability. It is shown by Friedrich et al. [36] that retinal permeability plays a very important role in drug distribution. For retina, i.e., for small molecule drugs where D=6
E-10 m^2/s the retinal permeability values reported by Arai [34] 2.33 E-5 cm/s is used and moreover for large molecule drugs where D=3.9 E-11 m^2/s the retinal permeability value reported by Pitkänen [77] 1 E-8 cm/s is used. For the sclera, which is a dense connective tissue, Ethier et al. [47] reported a permeability value of 1.96 E-9 cm/s and the pressure along this surface is assumed to be the normal venous pressure i.e. 1200 Pa. The choroid layer, which is situated outside the retina, is highly vascularized; therefore, a reasonable assumption is that choroid will act as a perfect sink for drug transport across the retina. Therefore, at the outer surface of the retina the drug concentration is set to zero i.e., C=0 [36, 37].

### 4.2.3 Material Properties

The most widely used vitreous substitutes is silicone oil [61]. Silicone oil has low density compared to water, which causes it to float upon the residual fluid and thus helps in retinal tamponade in the case of superior breaks. Table 4-1 shows the material properties of silicone oil and water. As seen in Table 4-1, silicone oil has higher viscosity compared to water (approx. 3 orders higher in magnitude).

<table>
<thead>
<tr>
<th>Vitreous Substitute</th>
<th>Density (Kg/m^3)</th>
<th>Viscosity (Kg/ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1000</td>
<td>0.001</td>
</tr>
<tr>
<td>Silicone Oil</td>
<td>970</td>
<td>1.067</td>
</tr>
</tbody>
</table>

### 4.2.4 Governing Equations

The complete three-dimensional incompressible Navier-Stokes equations along with species transport equation are solved to obtain the velocity, pressure and concentration fields.

Continuity Equations: \[
\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0
\] (2)
Momentum Equations:
\[
\frac{\partial \vec{v}}{\partial t} + (\vec{v} \cdot \nabla) \vec{v} = -\frac{1}{\rho} \nabla P + \frac{\mu}{\rho} \nabla^2 \vec{v} + \vec{g}
\]  
(3)

Species Transport Equation:
\[
\frac{\partial c}{\partial t} + \vec{v} \cdot \nabla c - D \nabla^2 c - q = 0
\]  
(4)

where \( P \) is the pressure, \( c \) is the concentration of the drug, \( D \) is the diffusion coefficient and \( q \) is the release rate as a function of position and time. The source term \( q \) is modeled using equation (1).

Porous media is modeled by the addition of a momentum source term to the standard fluid flow equations. The source term is composed of two parts: a viscous loss term and an inertial loss term. To model the porous region of the retina and the sclera, the \( VP \) term in the momentum equation (2) is represented by the following equation

\[
\nabla P = \frac{\mu}{\alpha} V_i + C_2 \frac{\rho}{2} |V_i| V_i
\]  
(5)

where \( \alpha \) is the permeability and \( C_2 \) is the inertial resistance factor. To get appropriate values of constant \( \alpha \) and \( C_2 \), a semi-empirical correlation, derived from the Ergun equation [53], is used. These correlations for the permeability \( \alpha \) and inertial resistance factor \( C_2 \) are applicable over a wide range of Reynolds number and for various packing levels, and are given as:

\[
\alpha = \frac{D_p^2 \varepsilon^3}{150(1-\varepsilon)^2} \quad C_2 = \frac{3.5(1-\varepsilon)}{D_p \varepsilon^3}
\]  
(6)

where \( D_p \) is the mean particle diameter of the packed bed and \( \varepsilon \) is the void fraction.

Void fraction is defined as the volume of voids divided by the volume of the packed bed region. The sclera consists of 89.7% of water and 7.75% of collagen and glycosaminoglycans (GAG’s) [49], which causes an increase in the resistance. Based on
the data in [58] the void fraction for sclera was considered to be 0.91 and $D_p=1.35$ nm. These values of $\varepsilon$ and $D_p$ lead to specific hydraulic permeability of $2 \times 10^{-18}$ m$^2$ for sclera which is consistent with those reported by Ethier et al. [47] for the sclera. For the retina, i.e., for small molecule drugs where $D=6 \times 10^{-10}$ m$^2$/s the retinal hydraulic conductivity is $2.6 \times 10^{-5}$ cm/s [34] and for large molecule drugs where $D=3.9 \times 10^{-11}$ m$^2$/s the retinal hydraulic conductivity is $1 \times 10^{-8}$ cm/s [77] is used. The void fraction of retina is taken to be $\varepsilon=0.6$ as provided in [54]. Using Equation (6), for small molecule drugs, $D_p$ is calculated to be $1.71 \times 10^{-6}$ m and for large molecule drugs $D_p$ is calculated to be $3.36 \times 10^{-8}$ m. These values lead to a specific hydraulic permeability value of $2.65 \times 10^{-14}$ m$^2$ and $1.019 \times 10^{-17}$ m$^2$ respectively.

4.2.5 Computer Code

The commercial code FLUENT [56] is used in this study. This code is based on a control volume approach where the computational domain is divided into a number of cells, and the governing equations are discretized into algebraic equations in each cell. The control-volume approach leads to a discretized set of equations which satisfies the integral conservation of the mass and the momentum over each control volume. For solving the system of algebraic equations a Gauss-Siedel scheme is used. Although the Gauss-Siedel scheme rapidly removes the high frequency errors in the solution, low frequency errors are reduced at a rate inversely related to the grid size. A W-cycle multi-grid scheme is used to accelerate the convergence rate by applying corrections to coarser grid levels. The coupling between velocity and pressure is handled using the SIMPLEC-algorithm [57], which uses the conservation of mass equation to derive a pressure corrector equation, and uses a pressure and velocity correction step to yield continuity.
satisfying velocity fields at each iteration. The pressure and velocities are then corrected so as to satisfy the continuity constraint. The discrete values of the variables are stored at the cell-centers, but the convection terms in the discretized equation must be interpolated at the cell faces from the cell-center values. A second order upwind scheme is used for deriving the face values of different variables in the momentum equation. For the pressure Poisson equation, a second order accurate discretization scheme is used.

4.3 Results and Discussion

4.3.1 Grid Independence Study and Validation

Figure 4-2: Velocity magnitude along the center of vitreous chamber for 541,250 and 1,121,000 hexahedral cells

To demonstrate grid independence, simulations are run with 541,250 cells and 1,121,000 cells. Figure 4-2 shows the velocity plot along the centerline of the anterior chamber for 541,250 cells and 1,121,000 cells. As seen in Fig. 4-2, less than 1% variation in the magnitude of the maximum velocity is observed between the 541,250 cell calculation and the 1121,000 cell calculation. This good agreement between the solutions from the two grid levels justifies the use of 541,250 cells for the simulation.
As a further validation of the numerical model, the results are compared with the predictions of Friedrich et al. [65] who carried out a finite element analysis to predict the concentration of injected at different locations in vitreous chamber for phakic and aphakic eyes. In the study carried out by Friedrich et al. [65], vitreous was assumed to be stagnant, i.e., effects of convection were neglected. The permeability of retinal surface is considered to be $1 \times 10^{-7}$ cm/s and the drug injection volume is considered to be 15 µL. For the present validation, the central injection case was considered and the diffusion coefficient of drug was considered to be $5.6 \times 10^{-10}$ m²/s [65]. Figure 4-3(a) shows the concentration contours for the half section of the vitreous chamber for the current model. As seen in Fig. 4-3(b), the current prediction of the concentration along the center of vitreous chamber agrees well with the results obtained by Friedrich et al. [65].

### 4.3.2 Steady Flow Results

The first step in the simulation process was the determination of the pressure and the velocity profiles within the vitreous at steady state. The liquid vitreous case was compared with the predictions in which vitreous was modeled as a porous medium as in Xu [38]. In the case of vitrectomy, as mentioned above, the vitreous is removed...
completely along with the collagen fibers and is replaced with different vitreous substitutes. Therefore, for these cases the vitreous cannot be modeled as a porous medium and has to be treated as a liquid.

4.3.2.1 Pressure Contour

Figure 4-4: Pressure contour (a) Vitreous modeled as porous medium (b) Vitreous modeled as liquid (water), (c) Pressure plot along the center of the vitreous chamber and (d) Pressure plot along the circumference of the retinal surface

Figure 4-4(a) shows the pressure distribution for the cases where the vitreous is modeled as a porous medium and Fig. 4-4(b) shows the corresponding pressure distribution with the vitreous modeled as a fluid (water). The higher pressure specified at the hyaloid membrane drives the aqueous from the hyaloid to the sclera, which is maintained at a venous pressure of 1200 Pa. When the vitreous is considered as a porous medium, there is a pressure drop of about 180 Pa across the vitreous humor [Fig. 4-4(c-
These results are consistent with the earlier results obtained by Xu [38]. In the case of a liquid vitreous, as seen in the Fig. 4-4(b), the vitreous humor is at a uniform pressure of 2000 Pa and the pressure drop essentially occurs across the retinal and the scleral tissues. This implies that the entire retina and the lens are at higher pressure relative to the porous media case. These higher pressures on the lens surface may be responsible for the reported cataract complications occurring after vitrectomy [54, 61].

4.3.2.2 Velocity Contour

Figure 4-5 shows the predicted velocity profile within the vitreous chamber for water and silicone oil as vitreous substitutes. Velocity magnitudes in the posterior segment are very low and are smaller than 0.009 μm/s. However, as shown later, for low
diffusivity drugs, convective effects can be important. Therefore, it is important to study the behavior of the flow distribution within the vitreous chamber.

Figures 4-5(a) and 4-5(b) shows the path-lines superimposed on the velocity magnitude contour for the porous-media vitreous and the liquid vitreous respectively. The path-lines for both the cases are nearly identical with the flow directed from the hyaloid membrane to the retinal surface. The velocity magnitudes are lower for the porous medium due to higher flow resistance and appear to have a flatter distribution in the x-direction. Figs. 4-5(c) and 4-5(d) show the velocity magnitude along the centerline of the vitreous chamber for different vitreous substitutes. The peak velocity location in the case of porous medium is shifted upwards towards the lens compared to the cases with vitreous fluids since the porous medium acts as a momentum sink and rapidly decelerates the flow. When compared to the case of water as vitreous substitute, it is seen that there is a 25% decrease in the peak velocity with the porous medium. Silicone oil has higher dynamic viscosity compared to water (approx. order of $10^3$ higher), as a result of which, silicone oil has considerably lower velocity (approx. order of $10^3$ lower) compared to the other two cases. As seen later, this huge variation in velocity plays a major role in the drug distribution within the vitreous chamber.

4.3.3 Concentration Contours

4.3.3.1 Direct Injection

Results will be first presented for direct injection technique of drug injected into water and silicone oil. With direct injection technique, the drug is released instantaneously from a pre-defined volume as shown in Fig 4-1(b). Retinal hydraulic conductivity for small molecule drugs e.g., gentamicin, fluorescein, etc., has been
reported to be 2.6e-5 cm/s [34]. To analyze the effects of low diffusion co-efficient, two
different drugs are studied (1) FITC-Dextran with D=3.9 E-11 m²/s and (2) Antibody
with D=1 E-11 m²/s. To show the effects of diffusion co-efficient, for low diffusion co-
efficient drugs the retinal permeability is fixed and the drug diffusion co-efficient is
varied. Retinal hydraulic conductivity for large molecule drugs e.g., FITC-Dextran has
been reported to be 1e-8 cm/s [77].

Figure 4-6 shows the contour plots for the concentration of the drug on the central
plane of the vitreous chamber at time t=100 hrs after the drug is released. At this time
instance, the drug has reached the retinal surface, and a fraction of the drug has crossed
the retinal interface entering the aqueous veins. Qualitatively, the numerical results
obtained by current model are comparable to the experimental results obtained by Araie
[34] for rabbit eye. The results cannot be exactly comparable because the volume of
rabbit vitreous is 1.46 mL whereas for human eye is 4mL. For high diffusion co-efficient
drugs [Fig. 4-6(a-b)], the concentration contour lines are parallel to the retina, which
implies that the flux of fluorescein across the retinal surface was the main route of drug
elimination. For highly viscous vitreous substitutes like silicone oil, where velocities are
lower, the drug is transported across the retinal layer more slowly compared to water.
Thus, as seen in Fig. 4-6(b), at t=100 hrs, a higher amount of drug is still present for the
case of silicone oil compared to water where, due to the higher transport rates, a
significant fraction of the drug has already crossed the retinal boundaries. Figure 4-6(c-d)
shows the concentration contours of the drugs with low diffusion coefficient, D=3.9 E-11
m²/s (e.g., FITC-Dextran) at time t=100 hrs after injection. In this case, as the diffusion
coefficient of the drug is lower, the diffusive transport of the drug is reduced in the
Figure 4-6: Concentration contours at time $t=100$ hrs: (a) Water for $D=6e-10 m^2/s$, (b) Silicone oil for $D=6e-10 m^2/s$, (c) Water for $D=3.9e-11 m^2/s$, (d) Silicone oil for $D=3.9e-11 m^2/s$, (e) Water for $D=1e-11 m^2/s$ and (f) Silicone oil for $D=1e-11 m^2/s$.

Vitreous chamber. For low diffusion co-efficient drugs, the concentration contour lines are perpendicular to both retina and lens boundaries along their entire length, indicating that the flux across these surfaces was negligible whereas the concentration contour lines were almost parallel to the hyaloid membrane, indicating that the diffusional flux was normal to this tissue. This is in contrast to the higher diffusivity drug case in Fig. 4-6(a-b) where the concentration lines are parallel to the retinal surface. For the drugs with $D=1e$-
11 m²/s [Fig. 4-6(e-f)], the retinal permeability is kept constant K=1e-8 cm/s. As seen, with the decrease in diffusion co-efficient by 4 times the drug distribution becomes more localized. At this time it is seen that for water [Fig. 4-6(e)], most of the drug concentration has reached the lower retinal surface and the concentration levels have diminished or disappeared in the upper half of the vitreous chamber. This, in turn, implies that nearly all the drug is transported through the lower portion of the retinal surface. In Fig. 4-6(f), it is seen that for silicone oil, the peak concentration of drug is still at the drug injection site (due to the low transport rates), and that the iso-concentration lines are circular (indicative of the dominance of diffusion).

Figure 4-7: Concentration plot at the center of the retinal surface (a) D=6e-10 m²/s and (b) D=3.9e-11 m²/s and D=1e-11 m²/s

Figure 4-7 shows the concentration plot of the drug at the center of retinal surface with respect to time for water and silicone oil as vitreous fluids. It is seen that, the concentration of the drug reaching the center of retina increases quickly after the injection and then decays as the drug is transported across the surface of the retina. For high diffusion co-efficient drugs [Fig. 4-7(a)], the drug reaches the maximum concentration at time t=4.6 hrs which is in agreement with the numerical analysis carried
out by Friedrich et al. [37]. For highly viscous vitreous substitutes like silicone oil, where velocities are lower, the drug is transported across the retinal layer more slowly compared to water. It is seen that [Fig. 4-7(b)] decreasing the drug diffusivity through the vitreous increases the time required for the drug molecules to travel from the drug injection site to an elimination boundary. The concentration of the drug reaching the center of retinal surface increases quickly for drugs with \( D=3.9 \text{ e-11 m}^2/\text{s} \) after the injection compared to drugs with lower diffusion coefficient \( D=1\text{e-11 m}^2/\text{s} \) and then decays as the drug is transported across the lower surface of the retina. For drugs with \( D=3.9 \text{ e-11 m}^2/\text{s} \) for the case of water, the concentration reaches the highest value of 0.5373 Kg/m\(^3\) at about \( t=56 \) hrs whereas for lower diffusion co-efficient drugs \( D=1\text{e-11 m}^2/\text{s} \) the drug reaches the maximum concentration of 0.979 Kg/m\(^3\) at time \( t=166 \) hrs. Here it is seen that with decrease in diffusion co-efficient by approximately 4 times the time required to reach the maximum concentration increases by 66% while the concentration increases by 45%. Similarly, for silicone oil with \( D=3.9 \text{ e-11 m}^2/\text{s} \), the concentration of the drug reaches the highest value of 0.4012 Kg/m\(^3\) at time \( t=64 \) hrs whereas for lower diffusion co-efficient drug i.e., \( D=1\text{e-11 m}^2/\text{s} \) the drug reaches the maximum concentration of 0.4024 Kg/m\(^3\) at time \( t=256 \) hrs. For the case of silicone oil it is seen that there is hardly any increase in the peak concentration but the time required for the drug to reach the maximum concentration increases by 75%.

The higher decay rates for water reflect the greater role of convection in this case. In contrast, the time required to reach the peak retinal concentrations for silicone oil is increased by a factor of approx. 1.5. Therefore, drug-retention in the vitreous chamber is significantly enhanced with silicone vitreous substitutes. These significantly different
drug distributions in space and time for different vitreous fluids underscore the relative importance of understanding drug-vitreous fluid interactions before making decisions on appropriate therapy.

Figure 4-8: Concentration line plot along the center of the vitreous chamber at t=100 hrs

Figure 4-8 shows the concentration plot along the centerline of the vitreous chamber at t=100 hrs. The peak concentration of the drug, for drugs with $D=3.9\times10^{-11} \text{ m}^2/\text{s}$, is shifted towards the retinal surface ($y/D=1$) whereas for drugs with $D=1\times10^{-11} \text{ m}^2/\text{s}$ the peak concentration of the drug has still not reached the retinal surface. For drugs with $D=1\times10^{-11} \text{ m}^2/\text{s}$, for water as the vitreous substitute the peak concentration is slightly shifted towards the retinal surface. This observation can be analyzed using the Péclet number defined as $Pe = \frac{v}{D/d}$ where $v$ is the average velocity along the centre of vitreous chamber, $d$ is the characteristic length and $D$ is the diffusivity of the drug in the vitreous. Péclet number greater than 1 indicates that transport by pressure-induced convective flow is important. For water with $D=1\times10^{-11} \text{ m}^2/\text{s}$, Péclet number is 12.54, indicating that convection is the primary mode of drug delivery. For silicone oil with
D=1e-11 m²/s, Pécel number is 0.01216 which indicates that diffusion is the primary mode of drug delivery.

Figure 4-9: (a) Concentration line plot along the circumference of retinal surface at time \( t=10 \text{ hrs} \) and (b) zoomed view of the encircled region in Fig. 4-9(a)

Figure 4-9 shows the concentration of the drug along the circumferential surface of the retinal surface at \( t=10 \text{ hrs} \). As the problem is symmetrical, the results are plotted only for the one half section of the retinal surface. For water and silicone oil, with drug diffusion co-efficient \( D=3.9 \times 10^{-11} \text{ m}^2/\text{s} \), drug quickly reaches the maximum concentration compared to drug with lower diffusion coefficient. As seen, concentrations are highest at the center of the retinal surface, but approximately 6% of the peak concentration of the drug reaches the anterior portion of retinal surface i.e., at \( S=0 \). At this time, there is
approximately 6 orders of decrease in magnitude of drug reaching the retinal surface for the case of \( D = 1 \times 10^{-11} \text{ m}^2/\text{s} \) compared to drug with \( D = 3.9 \times 10^{-11} \text{ m}^2/\text{s} \).

![Figure 4-10: Concentration line plot along the circumference of retinal surface at time \( t = 100 \text{ hrs} \)](image)

Figure 4-10 shows the concentration of the drug along the circumferential surface of the retinal surface at \( t = 100 \text{ hrs} \). In the case of water with \( D = 3.9 \times 10^{-11} \text{ m}^2/\text{s} \), the drug reaches the maximum concentration of 4.61E-01 Kg/m\(^3\) whereas for silicone oil as vitreous substitute the drug reaches the maximum concentration of 3.77E-01 Kg/m\(^3\). Due to increased effects of convection in the case of water approximately 18% increased amount of drug reaches the retinal surface. For silicone oil, due to the dominance of diffusion, it is seen that approximately 68% more amount of drug reaches the anterior surface of retina when compared to water as vitreous substitute. Moreover at this time, it is seen that for water with \( D = 1 \times 10^{-11} \text{ m}^2/\text{s} \), the drug reaches the maximum concentration of 7.09E-01 Kg/m\(^3\), whereas for the drugs with same diffusion co-efficient maximum concentration of 2.01E-01 Kg/m\(^3\) is attained with silicone oil as vitreous substitute. Because of the higher effects of convection for water as vitreous substitute, it is seen that there is approximately 71% increase in the amount of drug reaching the retinal surface. When compared to the drugs with \( D = 3.9 \times 10^{-11} \text{ m}^2/\text{s} \), it is seen that there is approximately
54 % increase in the amount of drug reaching the retinal surface. Moreover, when comparing the amount of drug reaching the anterior surface of the retina, the concentration is approximately zero for drugs with $D=1 \ E^{-11} \ m^2/s$. This implies that higher diffusion co-efficient drugs are more suitable if therapy is needed in the anterior portion of the retinal surface.

To show the effects of different diffusion coefficient, the peak concentration reaching the retinal surface and the time are tabulated in the Table 4-2.

Table 4-2: Maximum concentration and the corresponding residence time (Water)

($D=\text{Diffusion coefficient of the drug, } C=\text{Maximum concentration reaching the centre of the retina and } t=\text{Time required to reach the maximum concentration}$)

<table>
<thead>
<tr>
<th>D (m$^2$/s)</th>
<th>C (Kg/m$^3$)</th>
<th>t (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 E-10</td>
<td>0.41122</td>
<td>4.6</td>
</tr>
<tr>
<td>3.9 E-11</td>
<td>0.5373</td>
<td>56</td>
</tr>
<tr>
<td>1 E-11</td>
<td>0.979</td>
<td>166</td>
</tr>
</tbody>
</table>

Table 4-2 shows the concentration of the drug at the center of retinal surface with respect to time for water with drugs with different diffusion co-efficient. As seen the decrease in the drug diffusion co-efficient increases the effects of convection and moreover there is an increase in amount of drug reaching the retinal surface. For low diffusion coefficient drugs, it is seen that there is approx. 45 % increase in the peak concentration reaching the retinal surface.

Table 4-3: Maximum concentration and the corresponding residence time (Silicone Oil)

($D=\text{Diffusion coefficient of the drug, } C=\text{Maximum concentration reaching the centre of the retina and } t=\text{Time required to reach the maximum concentration}$)

<table>
<thead>
<tr>
<th>D (m$^2$/s)</th>
<th>C (Kg/m$^3$)</th>
<th>t (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 E-10</td>
<td>0.3985</td>
<td>4.5</td>
</tr>
<tr>
<td>3.9 E-11</td>
<td>0.4012</td>
<td>64</td>
</tr>
<tr>
<td>1 E-11</td>
<td>0.4024</td>
<td>256</td>
</tr>
<tr>
<td>6 E-12</td>
<td>0.4029</td>
<td>436</td>
</tr>
<tr>
<td>1 E-12</td>
<td>0.405</td>
<td>2410</td>
</tr>
</tbody>
</table>
Table 4-3 shows the concentration of the drug at the center of retinal surface with respect to time for silicone oil with drugs with different diffusion co-efficient. As the diffusion co-efficient of drug in silicone oil is unavailable, simulations for range of values of diffusion co-efficient are carried out (i.e., from 6 E-12 m²/s to 1 E-12 m²/s). For silicone oil as Pé number is less than 1, diffusion is the dominant mode of drug distribution. It is seen in Table 4-3 that the peak concentration reaching the retinal surface is approximately constant.

![Schmidt Number VS time (Silicone Oil)](image)

Figure 4-11 shows the variation of Schmidt number with the time required to reach the peak concentration at the center of retinal surface. Schmidt number is proportional to (kinetic viscosity) / (molecular diffusivity) i.e., $Sc = \frac{\mu}{\rho D}$. It is seen that Schmidt number varies linearly with time, i.e., Decrease in the diffusion co-efficient of the drug increases the time required to reach the peak concentration on the retinal surface.

4.3.3.2 Time-Released Drug Injection

Attention is turned next to the case where the drug is released as a function of time from a pre-defined volume, as shown in the Fig. 4-1(b). The goal with time-released
injection is to achieve non-toxic drug concentration levels on the retinal surface relatively quickly, so that therapy is initiated shortly after drug injection, and to sustain suitable levels of retinal concentrations over reasonable time duration to maximize the benefit of the initial injection. In evaluating the time-released injection technique, we will make comparisons with the direct injection technique discussed in the previous section. In both cases, the same volume of drug was injected to enable this comparison.

Figure 4-12: Concentration contours at time t=300 hrs (a) Water for D=6e-10 m²/s, (b) Silicone oil for D=6e-10 m²/s, (c) Water for D=3.9e-11 m²/s, (d) Silicone oil for D=3.9e-11 m²/s, (e) Water for D=1e-11 m²/s and (f) Silicone oil for D=1e-11 m²/s.
Figure 4-12 shows the concentration contours of the drugs with the higher diffusion coefficient, $D=6 \times 10^{-10}$ m$^2$/s, when injected into water and silicone oil. In this case, transport rates are lower because of the lower diffusion coefficients, and therefore compared to Fig. 4-6, the concentration distributions are more localized. Compared to direct injection [Fig. 4-6], the peak concentrations are located further away from the retinal surface since the drug is released at a slower rate. Due to lower retinal permeability for large molecule drugs, as seen in Fig. 4-12(c-f), the concentration contour lines are perpendicular to both retina and lens boundaries along their entire length, indicating that the flux across these surfaces was negligible whereas the concentration contour lines were almost parallel to the hyaloid membrane, indicating that the diffusional flux was normal to this tissue which is in contrast to the higher diffusivity drug case in Fig. 4-12(a-b) where the concentration lines are parallel to the retinal surface. At $t=300$ hrs, Fig. 4-12(c,e) shows that for water, most of the drug concentration has reached the lower retinal surface and the concentration levels have diminished or disappeared in the upper half of the vitreous chamber. This, in turn, implies that nearly all the drug is transported through the lower portion of the retinal surface. In Fig. 4-12(d,f), it is seen that for silicone oil, the peak concentration of drug is still at the drug injection site (due to the low transport rates), and that the iso-concentration lines are circular (indicative of the dominance of diffusion).

Figure 4-13(a) shows the plot for the concentration of the high diffusion coefficient drug at the center of the retinal surface with respect to time for water and silicone oil. These results are consistent with those shown in Fig. 4-7 for direct injection, except that the time taken to reach the peak is longer and is nearly 2.8 days (67 hrs).
instead of the 4.6 hrs for direct injection. Further, the decay rate of the retinal drug concentration is reduced considerably with the time-released option. Thus, the residence time of the drug is longer (factor of 14.8) with time-released drugs compared to the case of direct injection. When compared to direct injection, it is seen that in the case of time-released drug injection with water as vitreous substitute only 0.15% of peak concentration drug reaches center of the retinal surface. Thus, when controlled quantity of the drug is required on the retinal surface over an extended period of time the Time-released drug delivery is the desired option. Because of slower transport rates in the case of silicone oil it is seen in Fig. 4-13(a) that peak concentrations of the drug are higher (by 4%), and decay rates are lower when compared to the case of water. For low diffusion co-efficient drugs, it can be seen that for water with D=3.9 E-11 m²/s [Fig. 4-13(b)], the drug reaches the peak concentration of 0.00224 Kg/m³ at t=216 hrs whereas for D=1 E-11 m²/s, the peak concentration attained is 0.005456 Kg/m³ at t=316 hrs. Compared to direct injection for D=3.9 E-11 m²/s, residence times with time-released injection is about 3.8 times longer with water as the vitreous fluid whereas for the drugs with D=1 E-11 m²/s the residence time is 1.9 times longer. In contrast, as noted earlier,
for the higher diffusion drug, residence times were nearly 14.8 times longer with time-
released injection. Therefore, the long residence time benefits of time-released injection
decrease for lower diffusion coefficient drugs.

Figure 4-14: Concentration line plot along the center of the vitreous chamber at t=400 hrs

Figure 4-14 shows the drug concentration along the center of the vitreous chamber at t=400 hrs. The peak concentration has still not reached the retinal surface since the drug is released slowly. The high concentration region in the center (in contrast to Fig. 4-8 with direct injection) is a reflection of the time-released injection process. At this time, a portion of the drug is still at the injection site or has been just released. As seen in Fig. 4-14, for drugs with D=1 E-11 m²/s for water less amount of drug is available at the drug injection position compared to silicone oil, as more amount of drug is swept away from the retinal surface due to increased effects of convection.

Figure 4-15: Concentration line plot along the circumference of retinal surface at time t=100 hrs
Figure 4-15 shows the drug concentration along the retinal surface at t=100 hrs. It is seen from the plot that the peak concentration for drugs with D=3.9 E-11 m²/s with water as vitreous substitute is maximum followed by the drugs with D=1 E-11 m²/s. Moreover, it is seen that for drugs with lower diffusion co-efficient i.e., D=1 E-11 m²/s, the amount of drug reaching the anterior portion of retina is approximately zero.

Figure 4-16 shows the drug concentration along the retinal surface at t=400 hrs.

As seen, for drugs with D=1 E-11 m²/s for water as vitreous substitutes there is 41% increase in the amount of the drug reaching the retinal surface compared to silicone oil. For drugs with D=1 E-11 m²/s, due to higher effects of convection only 0.004% of drug reaches the anterior portion of retina. This implies that lower diffusion co-efficient drugs are more suitable if therapy is needed in the posterior portion of the retinal surface. Moreover, for silicone oil with D=1 E-11 m²/s, due to higher effects of diffusion 9% of the drug reaches the anterior portion of retina and for drugs with D=3.9 E-11 m²/s, 17% of the drug reaches the anterior portion of retina. This implies that higher diffusion co-efficient drugs are more suitable if therapy is needed in the anterior portion of the retinal surface.
The results of the simulations carried out are summarized in Table 4-4. It is seen that in time-released drug injection, where the drug is released as a function of time, drug concentration levels are several orders of magnitudes lower than those of direct injection, and dangers of retinal toxicity are avoided. Further, drug residence times are considerably longer with time-released injection, being nearly 10-12 times greater for the higher diffusion coefficient drug. In the case of direct injection of drugs with low diffusion coefficient, the peak concentration levels of 0.979 Kg/m$^3$ for water with D=1 E-11 m$^2$/s is quite high, and potentially can lead to retinal toxicity.

Table 4-4: Maximum concentration and the corresponding residence time

(D=Diffusion coefficient of the drug, C=Maximum concentration reaching the centre of the retina and t=Time required to reach the maximum concentration)

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Injection Type</th>
<th>D (m$^2$/s)</th>
<th>C (Kg/m$^3$)</th>
<th>t (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Direct</td>
<td>6 E-10</td>
<td>0.41122</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9 E-11</td>
<td>0.5373</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 E-11</td>
<td>0.979</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>Time-released</td>
<td>6 E-10</td>
<td>6.69E-4</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9 E-11</td>
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4.4 Concluding Remarks

A three-dimensional computational strategy was developed to investigate drug delivery in eyes after undergoing vitrectomy. The geometrical model adopted uses a realistic representation of the retina and the sclera (modeled as porous layers with specific hydraulic permeability), and predictions are obtained for both the flow-field and the drug concentrations by solving the conservation equations for mass, momentum and
drug concentrations. Results are presented for water and silicone oil as the vitreous fluid. Two drug delivery techniques are considered: (a) direct injection, where the injected drug is released instantaneously into the vitreous and (b) time-released injection of a drug, where the drug is released in a specified time-dependent manner. (1) The results show that the concentration distribution depends on the vitreous fluids, permeability of retina and the diffusion co-efficient of the drug. (2) Water as vitreous fluids exhibit higher drug transport rates than silicone oil. This observation was related to convection effects which play a more important role in the case of water. For silicone oil, convection effects are small, and diffusion is dominant. (3) In the case of direct injection, for water as vitreous fluid, the retinal drug concentration levels reach high values, even for low diffusivity drugs, and such situations can lead to retinal toxicity. (4) For drugs with high diffusion co-efficient uniform distribution of the drug is obtained along the surface of the retina whereas for the low diffusion co-efficient drugs the concentration of drug is localized along the posterior surface of the retina. (5) Time-released injection is shown to provide considerably lower levels of drug concentration along the retinal surface for sustained periods of time. This is likely to reduce the local toxicity arising from high drug concentrations, and to provide sustained therapy over a longer period of time compared to direct injection. (6) For low diffusion coefficient drugs, due to higher effects of convection, the amount of drug reaching the anterior portion of retina is approximately zero. This implies that higher diffusion co-efficient drugs are more suitable if therapy is needed in the anterior portion of the retinal surface.
In future, the model will be extended to account for the choroid layer and the drug adsorption in the choroid, and to include issues pertaining to drug metabolism, variation in drug diffusion coefficient and retinal/choroid/sclera permeability, and the injection location. These issues have been ignored in the present study.
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VITA

Jyoti Kathawate was born in Bangalore; well known as the silicon valley of India. She is the daughter of Mrs. Alaknanda Kathawate and Mr. Gururaj Kathawate. She got her primary and secondary education from Gujarat. She received her Bachelor of Engineering in Mechanical Engineering from M S Ramaiah Institute of Technology, Bangalore, in 2002. She then joined the graduate program at Louisiana State University, Baton Rouge (LSU) in Spring, 2003. She worked on computational fluid dynamics during this graduate program specializing in modeling of ocular fluids. She is a candidate for the degree of Master of Science in Mechanical Engineering to be awarded at the commencement of Fall 2006. After completing her master’s degree she would be joining the Flowserve Corporation.