Segmental aqueous humour outflow and eye orientation have strong influence on ocular drug delivery

Chai Y Loke\textsuperscript{a}, Ean H Ooi\textsuperscript{a,b,*}, Mohmed S Salahudeen\textsuperscript{a}, Norlina Ramli\textsuperscript{c}, Amir Samsudin\textsuperscript{c}

\textsuperscript{a} School of Engineering, Monash University Malaysia, Bandar Sunway, Selangor 47500, Malaysia
\textsuperscript{b} Advanced Engineering Platform, Monash University Malaysia, Bandar Sunway, Selangor 47500, Malaysia
\textsuperscript{c} Department of Ophthalmology, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia

\begin{abstract}
The present study is motivated by the recent concerns raised over the existence of segmental outflow and its implications on ocular drug delivery. A 3D model of the human eye is developed, where hydrodynamic and mass transport analyses after eye drop instillation, are carried out. To model segmental outflow, the permeability of the trabecular meshwork (TM) is assumed to vary spatially following a rectangular function. The choice of the rectangular function is based on the results from the tracer distribution study of Chang et al., 2014. Results from the numerical simulations show that segmental outflow causes the majority of the available drugs to egress through the active region, while non-active region experiences very minimal drug exposure. This supports the experimental findings of Chang et al. Additionally, it was found that eye orientation can affect the delivery of ophthalmic drugs by influencing the aqueous humour hydrodynamics. The results obtained here suggest that there may be a need to re-evaluate the design of ocular drug delivery system by taking into consideration the effects of segmental outflow and eye orientation.

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\end{abstract}

1. Introduction

Aqueous humour (AH) is a watery substance that resides in the anterior and posterior chambers of the eye. Its motion is driven primarily by thermally-induced buoyancy forces and to a lesser extent, by its production and drainage, with the velocity due to thermally driven flow being two orders of magnitude larger than that of production and drainage \cite{1}. Aqueous humour exits the anterior chamber via the conventional and unconventional outflow pathways. The latter accounts for approximately 10% of the total outflow and its hydraulic contribution is often neglected in the hydrodynamics study of AH. The conventional outflow pathway comprises three major components, namely the trabecular meshwork (TM), the Schlemm’s canal (SC) and the collector channels (CC). Glaucoma is an ocular disease that is commonly associated with an increase in the intraocular pressure (IOP). The elevation in IOP has been attributed to the rise in the hydraulic resistance inside the conventional outflow pathway, which reduces the outflow of AH and subsequently elevates the IOP. The excessive stress exerted onto the optic nerve head (ONH) by the elevated IOP can cause irreparable mechanical damage that can lead to blindness. As such, the majority of the anti-glaucoma drugs are designed to lower the IOP in order to alleviate the stress.
on the ONH. These drugs are typically administered via eye drops, whereby the drugs diffuse from the corneal surface into the cornea and subsequently into the anterior chamber. Therefore, the flow of AH forms a major route for the delivery of anti-glaucoma drugs.

The sensitivity of the human eye to physical contact has led to the majority of the studies on AH hydrodynamics to be carried out in *silico*. To the authors’ knowledge, all the existing computational models reported in the literature have assumed the flow of AH through the conventional outflow pathway to be uniform and homogeneous [1–5]. Nevertheless, several recent studies have found this not to be the case. Experimental studies carried out on human and bovine eyes *ex vivo* have demonstrated that the outflow of AH is segmental and heterogeneous, i.e. some parts of the conventional outflow pathway are active, while others are not [6–9]. This phenomenon has been attributed to the irregular distribution of CC across the conventional outflow pathway [6–8], while non-uniform distribution of pores across the inner wall endothelium of the SC has also been suggested as another cause for the observed segmental outflow [9].

The discovery of segmental outflow has raised some concerns on whether the non-uniform AH outflow through the TM can affect the delivery of anti-glaucoma drugs. In the presence of segmental outflow, drugs that enter the anterior chamber have a tendency to flow through the active regions, while flow through the non-active regions is limited by the slower and less effective diffusion process [8]. For anti-glaucoma drugs that specifically target the conventional outflow pathway, the heterogeneous drug deposition across the TM can create conditions of potentially ‘over-treating’ and ‘under-treating’ the disease, thereby affecting the efficacy of the drugs. In spite of this, there have been no reported studies on the effects of segmental outflow on the drug distribution across the anterior and posterior chambers. The majority of the computational studies carried out on ocular drug delivery have focused on the understanding of the mechanisms by which drugs transport from the corneal surface into the anterior chamber [10], the comparison between different modes of drug delivery [2,11,12], drug delivery to the posterior of the eye [13] and the development of pharmacokinetic-based models [14]. Consequently, there is a lack of understanding on how segmental outflow influences drug delivery into the ocular system.

Motivated by this, the present study seeks to investigate through a computational fluid dynamics study, the effects of segmental outflow on the hydrodynamics of AH inside the human eye and their implications on ocular drug delivery. Additionally, the effects of different eye orientation are examined to contrast the significance between segmental outflow and buoyancy-induced AH flow on the delivery of ophthalmic drugs. A three-dimensional model of the human eye is developed and simulations are carried out using the commercial finite element software COMSOL Multiphysics 5.3 ®. Flow of AH inside the anterior and posterior chambers is governed by the Navier–Stokes equations. The conventional outflow pathway is modeled as a porous medium, where the flow is described using the Stokes–Brinkman equation. Segmental outflow is modeled by assuming the permeability of the TM to be heterogeneous. A baseline permeability value is prescribed across the active regions to mimic high outflow facility, while non-active regions are assigned near zero permeability to retard outflow. To model ocular drug delivery, the most common method for delivering anti-glaucoma drugs, i.e. via topical eye drops, is considered. The present study considers only the transport of drugs within the anterior-posterior chambers and the TM, while transport into the gel-like substance of the vitreous is ignored.

2. Materials and methods

2.1. Model geometry

The three-dimensional model of the human eye developed in the present study consists of the cornea, anterior and posterior chambers, lens, vitreous, iris and sclera. The layers of the retina, choroid and sclera are modeled as a single homogeneous domain due to the relatively thin structures of the retina and the choroid [15]. The dimensions of the eye model follow closely those reported by Ooi and Ng [4]. An additional ring-like domain, 497 μm in length and 174 μm in height, is added to the outer circumference of the anterior chamber to represent the conventional outflow pathway. Since the length in the flow-wise direction of the SC and the CC are approximately two orders of magnitude smaller than the TM, the conventional outflow pathway is modeled as a homogeneous domain, which hereafter, is simply referred to as the TM. A gap of 25 μm is created between the tip of the iris and the lens to allow AH to flow from the posterior chamber into the anterior chamber. As such, the anterior and posterior chambers belong to the same piecewise-homogeneous domain. Fig. 1a shows the model of the human eye developed, where only one-half of the model is shown to illustrate the internal structures of the eye. A sagittal plane view is depicted in Fig. 1b.

2.2. The flow model

The flow model is prescribed only in the TM and the anterior and posterior chambers, as shown in Fig. 1c. Flow of AH inside the anterior and posterior chambers is assumed to be laminar and incompressible, such that the flow may be described using the Navier–Stokes equations:

\[
\rho (\mathbf{u} \cdot \nabla \mathbf{u}) = -\nabla p + \mu \nabla^2 \mathbf{u} + \rho \mathbf{g},
\]

(1)

\[
\rho \nabla \cdot \mathbf{u} = 0,
\]

(2)

where \(\mathbf{u} = (u, v, w)\) is the velocity vector, \(p\) is pressure, \(\rho\) and \(\mu\) are the density and dynamic viscosity of AH, respectively and \(\mathbf{g}\) is the vector representing gravitational acceleration. For the model developed here, which represents an individual in

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the standing position, \( \mathbf{g} \) is pointed in the \( -y \) direction, as shown in Fig. 1a. Flow of AH is driven primarily by the thermally-induced buoyancy forces [1]. This can be described using the Boussinesq approximation:

\[
\rho(T) = \rho_{\text{ref}} \left[ 1 - \beta (T - T_{\text{ref}}) \right],
\]

where \( T \) is temperature, \( \beta \) is the thermal expansion coefficient of AH and the subscript \( \text{ref} \) refers to the parameter evaluated at a reference value. Eq. (3) is substituted into the third term on the right hand side of Eq. (1).

The TM is modeled as a porous medium such that flow through this domain can be described using the Stokes–Brinkman equation [1]:

\[
\nabla p = -\frac{\mu}{\kappa} \mathbf{u} + \frac{\mu}{\epsilon} \nabla^2 \mathbf{u},
\]

where \( \kappa \) and \( \epsilon \) are the permeability and the porosity of the TM, respectively. Buoyancy is not considered inside the TM due to its relatively small scale structure.

2.3. The thermal model

The thermal model is applied across all the domains of the human eye model. In the absence of external heat sources and negligible viscous dissipation effects, the equation governing the temperature distribution inside the anterior and posterior chambers is given by:

\[
\rho C_p (\mathbf{u} \cdot \nabla T) = k \nabla^2 T,
\]

where \( k \) and \( C_p \) are the thermal conductivity and specific heat of AH, respectively, and \( \mathbf{u} \) is the velocity of AH, which is obtained by solving Eqs. (1)–(4) subject to the prescribed boundary conditions. For the other ocular components, such as
the cornea, the lens, the iris, the vitreous and the sclera, heat transfer here is solely due to conduction:

\[ k\nabla^2 T = 0. \]  \hspace{1cm} (6)

It is noteworthy that the thermal effects due to blood perfusion and metabolic heat generation, which are commonly associated with biological tissues, are omitted from Eq. (6) due to the majority of the ocular components being avascular. Although the iris is vascularized, blood perfusion rate and metabolic heat generation here are assumed to be negligible due to its relatively small volume compared to the whole eye [15]. On the other hand, the thermal effects of blood flow inside the retina and choroid are modeled as part of the applied boundary conditions (see Section 3.1), as described by Lagendijk [16].

2.4. The transport model

When an eye drop is administered, it mixes immediately with the tear film that is on the corneal surface. The majority of the drugs is drained via the tear drainage system, leaving only a small portion that permeates into the multi-layered cornea. Within the cornea, metabolic activity consumes some of the drugs, while the rest enters into the anterior chamber and into the AH circulation. Inside the anterior chamber, some of the drugs are cleared via the penetration into the systemic circulation across the blood-aqueous barrier [17]. The remaining drugs exit the anterior chamber through the active region of the TM. These drug delivery phenomena are included into the present model and are applied only to the cornea, the TM and the anterior and posterior chambers of the eye, as depicted in pink in Fig. 1b. The mathematical equations describing the evolution of the eye drop concentration are adapted from the work of Zhang et al. [10].

By ignoring the losses of drugs through the palpebral and bulbar conjunctiva [2], the rate of change of the eye drop concentration is given by:

\[ \frac{d\chi}{dt} = -\frac{S}{V_L + V_I \exp(-k_d t)} \chi. \]  \hspace{1cm} (7)

where \( \chi \) represents the drug concentration that has been normalized against its initial value, \( t \) is time, \( S \) is the lacrimal secretion rate, \( k_d \) is the tear drainage constant, \( V_L \) is the normal lacrimal volume and \( V_I \) is the initial tear volume after eye drop instillation. Eq. (7) assumes that the distribution of drug across the corneal surface is homogeneous. For more details on how Eq. (7) is derived, one may refer to the work of Zhang et al. [10].

The diffusion of drugs inside the cornea may be described using [10]:

\[ \frac{\partial \chi_{\text{cornea}}}{\partial t} = D_{\text{cornea}} \nabla^2 \chi_{\text{cornea}} - K_c \chi_{\text{cornea}}, \]  \hspace{1cm} (8)

where \( \chi_{\text{cornea}} \) is the normalized drug concentration inside the cornea, \( D_{\text{cornea}} \) is the mean corneal drug diffusion coefficient and \( K_c \) is the mean rate of metabolic consumption of drugs inside the cornea. The mean values are chosen to represent these parameters since the existence of sublayers within the cornea has not been considered.

Inside the anterior and posterior chambers, the transport of drugs may be described using [10]:

\[ \frac{\partial \chi_{\text{ap}}}{\partial t} + \mathbf{u} \cdot \nabla \chi_{\text{ap}} = D_{\text{ap}} \nabla^2 \chi_{\text{ap}} - \frac{C_i}{V_a} \chi_{\text{ap}}, \]  \hspace{1cm} (9)

where \( \chi_{\text{ap}} \) is the normalized drug concentration inside the anterior and posterior chambers, \( D_{\text{ap}} \) is the overall drug diffusion coefficient inside the anterior and posterior chambers, \( V_a \) is the distribution volume of solute inside the anterior chamber and \( C_i \) represents the drug clearance rate by the anterior chamber, which accounts for the losses of drugs due to metabolism and systemic uptake by the nearby vascular tissues, such as the anterior uvea and iris. Finally, the transport of drugs inside the TM may be written as:

\[ \frac{\partial \chi_{\text{tm}}}{\partial t} + \mathbf{u} \cdot \nabla \chi_{\text{tm}} = D_{\text{tm}} \nabla^2 \chi_{\text{tm}}, \]  \hspace{1cm} (10)

where \( \chi_{\text{tm}} \) and \( D_{\text{tm}} \) are the normalized drug concentration and the drug diffusion coefficient inside the TM, respectively.

3. Model implementation

3.1. Initial-boundary conditions

3.1.1. The flow field

An inlet velocity is prescribed across the surface representing the posterior chamber-ciliary body interface (see Fig. 1c) to model the secretion of AH into the posterior chamber:

\[ \mathbf{u} \cdot \mathbf{n} = -\frac{Q_{\text{in}}}{A_{\text{in}}}, \]  \hspace{1cm} (11)

where \( Q_{\text{in}} \) is the production rate of AH inside the ciliary body, \( A_{\text{in}} \) is the area of the posterior chamber-ciliary body interface and \( \mathbf{n} \) is the outward unit normal vector. The inlet velocity is assumed to be laminar and fully-developed and the magnitude
is estimated from the production rate of $Q_{in} = 2.4 \, \mu l/min$ [18] and the TM surface area of $A_{in} = 0.21 \, cm^2$. Across the outer surface of the TM, the Dirichlet condition:

$$p = p_{vein},$$

(12)
is prescribed, where $p_{vein} = 9 \, mmHg$ is the episcleral vein pressure [19]. The remaining surfaces of the anterior and posterior chambers are assumed to be solid, where the no slip wall condition $u = 0$ is applied.

At the interface between the anterior chamber and the TM, matching and continuity conditions are prescribed. Here, the pressure across the interface is continuous, while the velocity exiting the anterior chamber through the interface is taken to be the same as the velocity entering the TM:

$$p_{ac} = p_{tm},$$

(13)$$u_{ac} \cdot n = u_{tm} \cdot n,$$

(14)

where the subscripts ‘ac’ and ‘tm’ correspond to the anterior chamber and the TM, respectively. Note that the normal vector $n$ across the anterior chamber-TM interface is taken to point outwards from the anterior chamber and inwards into the TM. This is unlike the normal vectors across the boundaries of the anterior and posterior chambers, which are taken to be pointing in the outward direction.

3.1.2. The thermal field

The boundary conditions describing ocular heat transfer are similar to those reported by Ng and Ooi [15]. Across the corneal surface, heat transfer to the surrounding takes place via convection, radiation and tears evaporation:

$$-k_{cornea} \frac{\partial T}{\partial n} = h_{amb}(T - T_{amb}) + \varepsilon \sigma (T^4 - T_{amb}^4) + E_{eap},$$

(15)

where $\partial T/\partial n$ is the rate of change of temperature in the outward normal direction, $h_{amb}$ is the ambient convection coefficient, $T_{amb}$ is the ambient temperature, $\varepsilon$ is the emissivity on the corneal surface, $\sigma$ is the Stefan–Boltzmann constant and $E_{eap}$ is the heat loss due to tears evaporation. Across the scleroid surface, the flow of heat from the surrounding blood vessels into the eye can be described using [16]:

$$-k_{sclera} \frac{\partial T}{\partial n} = h_{bl}(T - T_{bl}),$$

(16)

where $h_{bl}$ is the blood convection coefficient and $T_{bl}$ is the blood temperature.

3.1.3. The concentration field

Upon instillation, the eye drop mixes with the layer of tear film across the corneal surface. In this study, the tear film has been excluded from the eye model due to its very thin structure compared to the rest of the eye. Therefore, to model the evolution of drug concentration across the corneal surface, a time-dependent concentration, which is obtained by solving Eq. (7) subject to an initial normalized drug concentration of $\chi = 1$. is prescribed across the corneal surface:

$$\chi(t) = \left( \frac{V_i \exp(k_{t, t}) + V_j}{V_i + V_j} \right) - \frac{s \chi_{0}^{2}}{\phi_{\chi}}$$

(17)

where the description of each parameter is similar to those listed in Eq. (7). The profile of Eq. (17) is plotted in Fig. 2a, which shows a drop in the drug concentration across the corneal surface due to the losses into the lacrimal system, as mentioned in Section 2.4. Eq. (17) assumes that the drug concentration across the tear film is homogeneous and that the tissue-to-water distribution coefficient has a value of one [2]. An outflow condition given by:

$$-D \frac{\partial c}{\partial n} = 0,$$

(18)
is prescribed across the outer surface of the TM to allow the drug to exit the TM by fluid motion, where $\partial c/\partial n$ is the rate of change of concentration in the outward normal direction. Across the remaining surfaces, the zero flux condition:

$$-D \frac{\partial c}{\partial n} + \mathbf{u} \cdot \mathbf{n} c = 0,$$

(19)
is prescribed, which indicates that no drugs are transported across these surfaces.

3.2. Segmental outflow

One of the unique features of segmental outflow is that the flow of AH through the TM is non-uniform, with patches of near zero flow observed across certain quadrants of the TM [8]. To capture this behavior, it is proposed here that the permeability of the TM, which governs the outflow facility, is assumed to be a function that varies spatially along the circumferential direction of the TM. However, the choice of which function to use is an open question. In the present study,
3.3. Material properties

The values of the material properties used in this study are obtained from the literature and they are tabulated in Table 1. The majority of the thermal and hydraulic properties used are similar to those employed by Ooi and Ng [4], while the transport properties are obtained from the work of Ferreira et al. [2] and Zhang et al. [10]. The porosity of the TM is chosen as 0.15, based on the estimations of Ethier et al. [20] and Murphy et al. [21]. Estimations based on photomicrographs of normal eyes put the TM permeability in the range of $2 \times 10^{-15}$ to $10 \times 10^{-15}$ m² [20–22]. However, it has been suggested that this range may overestimate the actual TM permeability [22]. In view of the lack of information available, the value of $2 \times 10^{-15}$ m² is selected to represent the baseline TM permeability.
Values of material properties used in the present study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
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</thead>
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<td>Cornea</td>
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<td>[4]</td>
</tr>
<tr>
<td>Anterior &amp; posterior chambers</td>
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<td>[35]</td>
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<td>Iris and sclera</td>
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<td>[36]</td>
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<td>Lens</td>
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<td>Vitreous</td>
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<tr>
<td>Anterior &amp; posterior chambers</td>
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<td>[2]</td>
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<tr>
<td>Trabecular meshwork*</td>
<td>$1.62 \times 10^{-11}$</td>
<td>[2]</td>
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<tr>
<td>Aqueous humour</td>
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<td>Thermal expansion coefficient, $\beta$ (K$^{-1}$)</td>
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<td>Dynamic viscosity, $\mu$ (Pa s)</td>
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<tr>
<td>Porosity of TM, $\epsilon$</td>
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<td>[20,21]</td>
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* Estimated using the Stokes–Einstein equation for 20 nm particle radius

Values of different model parameters used in the present study.

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<td>Ambient temperature, $T_{\text{amb}}$ (K)</td>
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<td>Blood convection coefficient, $h_{\text{Bu}}$ (W/(m$^2$ K))</td>
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<td>Corneal surface emissivity, $\epsilon$</td>
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<td>Drug clearance rate from AC, $C_{\text{ic}}$ ($\mu$l/min)</td>
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3.4. Mesh convergence study

Prior to the simulation study, a mesh convergence test is carried out to determine the minimum number of elements required to obtain numerical solutions that are independent of the mesh size. Since the primary activity occurs inside the anterior chamber, mesh convergence is examined at nine sampling points across the anterior chamber for all the dependent variables, i.e. the velocity magnitude, temperature and drug concentration. The eye model is discretized into tetrahedral elements. The velocity and pressure variables across each element are approximated using first order Lagrange polynomials, while second order Lagrange polynomials are used for temperature and concentration. Convergence is acquired by systematically decreasing the maximum element size across the anterior chamber from 0.5 to 0.2 mm. Mesh convergence is assumed to be reached when the average percentage difference of the velocity magnitude across the sampling points is smaller than 5%. For the coupled nonlinear problem solved here, this threshold is deemed to be sufficient to obtain mesh-independent solutions.

The results showed that a maximum element size of 0.225 mm prescribed across the anterior chamber is sufficient to achieve mesh convergence. When carrying out discretization of the entire eye model, domains that are slender, such as the TM and the area around the gap between the iris and the lens, are meshed with maximum element size that is smaller than 0.225 mm; ensuring that variations in the physical parameters are captured accurately. Additionally, domains that have very small thickness such as the cornea and the iris are given higher concentration of elements. This results in a model with approximately 2.89 million elements. The model first solves in steady state, the velocity distribution inside the TM and the anterior and posterior chambers under the influence of thermally-induced buoyant forces (Eqs. (1)–(6)). The velocity distribution is then used as inputs to solve for the transient distribution of drugs inside the anterior and posterior...
chambers, and the TM. It is assumed here that the drugs within the AH circulation have no effect on the hydrodynamics of AH flow.

4. Results

4.1. Effects of segmental outflow on AH hydrodynamics

For brevity, the results obtained on the effects of segmental outflow on AH hydrodynamics are presented in the Supplementary Material.

4.2. Effects of segmental outflow on ocular drug delivery (eye in the standing position)

The effects of segmental outflow on the delivery of ophthalmic drugs are investigated for five outflow locations defined by the range \( \theta \in [30^\circ, 150^\circ], [-15^\circ, 105^\circ], [-60^\circ, 60^\circ], [-105^\circ, 15^\circ] \) and \([-150^\circ, -30^\circ]\). These are shown in Fig. 2c. For simplicity, these outflow locations are hereafter denoted by north (N), north-east (NE), east (E), south-east (SE) and south (S), respectively. Fig. 3 shows the drug concentration distribution across the \( x = 3.75 \text{ mm} \) plane (see Fig. 1b) 10 and 20 min after instillation of eye drops. The white ring indicated by the red arrow represents the interface between the anterior chamber and the TM. The regions shaded in grey represent the active regions of the TM. Significant drug activity, indicated by the large concentration, can be found across the active regions 10 min after instillation of eye drops, while the concentration across the non-active regions remains low. The non-active regions show higher concentration than the active regions 20 min after eye drop instillation. The contrast in the results at 10 and 20 min may be explained by the different mechanisms driving drug transport across the active and non-active regions. The high outflow facility across the active regions suggests that drug activity here is driven primarily by convection. This process has a shorter timescale; hence, significant drug activity can be observed in the active regions during the first 10 min. Conversely, drug transport across the non-active regions is dominated by the slower diffusion process. As such, drugs tend to accumulate around the TM-anterior chamber interface during the first 10 min (see black arrows in Fig. 3). Over time, the concentration build-up becomes sufficiently large to drive diffusion across the non-active region of the TM. In the active regions, the concentration decreases as the majority of the drugs have egressed from the TM during the first 20 min.

Fig. 4 shows the plots of the dimensionless drug concentration against time at seven points distributed across the centreline of the TM. The seven points are defined by the angular coordinates of \( \theta = -90^\circ \) : 30° : 90° and they are represented by the red points in Fig. 2b. The concentration at the centre of the anterior chamber is also plotted for comparison. Except for the point \( \theta = 90^\circ \), the points that are within the active regions show a rapid increase in concentration during the first 5–7 min after eye drop instillation. This is followed by a rapid decrease until approximately the 40 min mark, where a gradual decrease towards zero concentration is observed. This coincided with the time when all the drugs from the corneal surface have either leaked into the lacrimal system or diffused into the cornea (see Fig. 2a). Therefore, the drugs that flow through the TM after 40 min are those that remain in circulation inside the anterior chamber. The point \( \theta = 90^\circ \) has the lowest drug concentration regardless of the location of active outflow. This is also depicted by the contours in Fig. 3. This may be explained by the velocity profile of AH inside the anterior chamber. In the standing position, the action of gravity in the downwards direction meant that the flow of AH changes direction around the point \( \theta = 90^\circ \). As a result, most of the drugs would be directed downwards leaving only a very small amount to egress through the TM. This is illustrated in Fig. 5. The remaining points that are not within the active regions show a delay from the time of eye drop instillation to the time when the concentration starts to increase. This delay indicates the time needed for the diffusion process to start taking effect across these points. The curves representing the point at the centre of the anterior chamber appear to be identical regardless of the location of the active regions. This suggests that segmental outflow has very little influence over the drug concentration distribution inside the anterior chamber.

To better understand the effects of segmental outflow on the delivery of ophthalmic drugs, the total amount of drugs that egress through the TM is calculated by evaluating the spatial and temporal integral given by:

\[
M_{\text{conv}} = \int_0^{t_a} \int_{\Gamma} u \chi dS d\tau, \quad (21)
\]

for convective transport and:

\[
M_{\text{diff}} = \int_0^{t_a} \int_{\Gamma} -D \frac{\partial \chi}{\partial n} dS d\tau, \quad (22)
\]

for diffusive transport, where \( M_{\text{conv}} \) and \( M_{\text{diff}} \) are the total amount drugs (in dimensionless units) transported via convection and diffusion, respectively. \( \Gamma \) represents either the active or non-active interface between the anterior chamber and the TM and \( t_a \) is the duration of drug exposure, taken at 5, 10 and 15 min. The spatial integral was evaluated using a 4th order quadrature method, while the temporal integral was evaluated using the Simpson’s 1/3 rule. The results are illustrated in Fig. 6a, where the data in groups 1 and 3 represent the values of \( M_{\text{conv}} \) across the active and non-active regions, respectively, while the data in groups 2 and 4 represent the values of \( M_{\text{diff}} \) across the active and non-active regions, respectively.
Fig. 3. Normalized drug concentration distribution across the $x = 3.75$ mm plane a) 10 and b) 20 min after eye drop instillation for the eye in the standing position.

Fig. 6a, it is apparent that the drug transport through the active region is dominated by convection, while across the non-active region, diffusion is more effective, albeit at a lesser significance. Fig. 6a also suggests that the location of filtration-active region has an influence over the behavior of drug transport through the TM. When the filtration-active region is located towards the bottom half of the eye, larger amount of drugs egress through the TM via convection. Conversely, when the filtration-active region is located towards the top half of the eye, drugs transported via diffusion becomes larger across parts of the TM that are non-active.

The results above may be explained by the hydrodynamics of AH for the eye in the standing position. In this orientation, gravity acts in the negative y-direction, as depicted in Fig. 1a. This produces a flow profile (see Supplementary Material),

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The plots in Fig. 4 show the normalized drug concentration against time at seven points across the centreline of the TM defined the angular coordinates $\theta = -90^\circ$ : $30^\circ$ : $90^\circ$ and at the centre of the anterior chamber (AC centre) for active regions defined by (a) N, (b) NE, (c) E, (d) SE, (e) S and (f) the uniform outflow case, for the eye in the standing position.

where the downwards velocity is greater than the velocity going upwards. Consequently, when the filtration-active region is located at the bottom half, the majority of the drugs are directed downwards towards the egress site; leaving only very small amounts to egress through the non-filtration-active regions at the top. When filtration-active region is at the top, the restricted outflow at the bottom limits the egress of drugs via convection. Some of the drugs accumulate near to the interface between the anterior chamber and the TM, while the rest are directed upwards by the flow of AH. However, because of the slower upwards velocity and owing to the AH flow profile, the delivery of the drugs to the active region at the top becomes less effective. As a result, more of the drugs are retained inside the anterior chamber for diffusion through the non-active regions at the lower half of the eye.

To understand the bioavailability of the drugs to the TM, a mass balance assessment of the drugs entering and leaving the anterior-posterior chambers is carried out. When drugs enter the anterior chamber from the cornea, some of them egress
through the TM, while the others are either cleared by the metabolic activity and systemic uptake of the nearby vascular tissues, $M_{cl}$ (see last term on the right hand side of Eq. (9)) or remain in circulation inside the anterior chamber, $M_{rem}$. The latter two are computed from:

$$M_{cl} = \int_{t_0}^{t_f} \int_{V} C_{ap} \frac{dV}{a} dV dt,$$

and

$$M_{rem} = \int_{V} \chi_{ap}(t_0) dV,$$

where $V$ is the domain representing the anterior and posterior chambers. Results from the mass balance assessment of the anterior-posterior chambers are summarized in Table 3. Overall, drug transport through the active region is at least one order of magnitude greater than those through the non-active region. Moreover, the difference between the active and non-active region becomes larger as time progresses. It is noteworthy that the majority of drugs remain inside the anterior chamber up to the 20th minute. This is followed by the drugs that have been cleared by the vascular tissues, transport through the active region of the TM and finally transport through the non-active region. The results showing the smaller amount of drugs being transported through the TM suggests that the bioavailability of the drugs to the TM is very poor.

### 4.3. Effects of segmental outflow on ocular drug deliver (supine position)

It is possible to deduce from the results presented in Section 4.2 that the orientation of the eye, coupled with segmental AH outflow, has an influence on the delivery route of ophthalmic drugs through the TM. To further investigate this, all simulations are repeated with gravity acting in the $x-$direction. This represents an individual in the supine position. For brevity, results from the hydrodynamic analysis for the eye in the supine position are presented in the Supplementary Material.

Fig. 7 illustrates the contours of the drug concentration distribution across the $x = 3.75$ mm plane for the models in the supine position 10 and 20 min after eye drop instillation. There is a clear difference in the contours between the eye in the supine position and those in the standing position. Generally, the point $\theta = 90^\circ$, which has the lowest concentration when the eye is in the standing position, is no longer found when the eye in the supine position. In the model with uniform outflow, the concentration across the TM is now homogeneous. These observations support the argument presented in Section 4.2, where eye orientation and gravity can also influence the delivery of ophthalmic drugs. With the effects of gravity nullified in the supine position, the sole contribution of segmental outflow on the drug distribution can be observed and investigated. At 10 min, the dominant convection process led to high concentrations across the active regions of the TM. Across the non-active regions, the concentration levels are negligible due to the slower diffusion process still not in effect. Two spots of peak drug concentration are found at the ends of the active regions of the TM owing to the high velocity of AH here (see Supplementary Material). Unlike the model in the standing position, the accumulation of drugs around the non-active regions occurs at a slight distance away from the TM-anterior chamber interface. This may be explained by the recirculation of AH that occurs in the vicinity of the anterior chamber-TM interface. This results in the drugs being
Fig. 6. Values of $M_{\text{conv}}$ and $M_{\text{diff}}$ across the active and non-active region of the TM for the eye in the (a) standing and (b) supine position. Data in groups 1 and 3 represent values of $M_{\text{conv}}$ in the active and non-active region respectively. Data in groups 2 and 4 represent values of $M_{\text{diff}}$ in the active and non-active region respectively.

directed away from the TM-anterior chamber interface, as shown in Fig. 8. The concentration across the non-active regions increases 20 min after eye drop instillation. However, the concentration is lower, unlike the case when the eye is in the standing position. This may be explained by the lower concentration of accumulated drugs around the TM-anterior chamber interface, which restricts the diffusion process through the TM.

Fig. 9 plots the transient concentration distribution across the seven points of the TM defined by the angular coordinates $\theta = -90^\circ : 30^\circ : 90^\circ$. Unlike the eye in the standing position, the majority of the curves tend to overlap. The reason that the points $\theta = -60^\circ$ and $-30^\circ$ for outflow at N and E, and the points $\theta = 30^\circ$ and $60^\circ$ for outflow at S, have drug concentration that peaked higher than the other points is due to these points being located at the edges of the active regions, where the large outflow velocity here enhances the convection process (see Supplementary Material). Apart from these points, two sets of curves can be distinguished. The first set, which corresponds to points that fall within the active regions, have higher concentration during the first 20 min than the second set, which represent the points across the non-active regions.

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After that, the concentration of the points in the second set becomes larger than the first set, as diffusion begins to take effect. The overlapping curves obtained for the supine model with uniform outflow further demonstrates the influence of eye orientation and direction of gravity on the distribution of drugs.

Fig. 6b plots the values of $M_{\text{conv}}$ and $M_{\text{diff}}$, 5, 10 and 15 min after eye drop instillation for the eye in the supine position. As in the case of the standing position, the amount of drugs that egress through the active region is greater than the non-active region. However, the different outflow locations do not appear to have any influence on the egression of drugs through the TM. This is depicted in Fig. 6b by the lack of variation among the data set in each group. This may be explained by the absence of preferential flow induced by the actions of gravity, which for the eye in the supine position, has been nullified.

Table 4 summarizes the results obtained following a mass balance assessment of drugs across the anterior chamber for the eye in the supine position. Except for the lack of variation in the data for different outflow locations, the trend of the data shown in Table 4 is similar to those in Table 3, where the same explanation presented in Section 4.2 applies. Interestingly, the total amount of drugs that flows through the TM when the eye is in the supine position is greater than the case when the eye is in the standing position. The implication of this observation will be further discussed in Section 5.

### 5. Discussion

One of the concerns raised following the discovery of segmental outflow is their potential influence on the delivery of anti-glaucoma drugs [8]. Motivated by this, a 3D model of the human eye was developed to investigate the effects of segmental outflow on the hydrodynamics of AH and the distribution of drugs inside the anterior and posterior chambers following instillation of eye drops. The present study departs from existing studies in the literature due to the inclusion of segmental outflow. To model segmental outflow, the permeability of the TM is assumed to be a function of space such that regions that are filtration-active have permeability at baseline value to allow flow, while regions that are non-filtration-active have near-zero permeability value in order to restrict outflow. The rectangular function was chosen to describe the TM permeability based on the results from a tracer distribution study carried out by Chang et al. [8]. Zones of high velocities matched well with the zones of high tracer concentration, suggesting that the use of the rectangular function to describe heterogeneous TM permeability is capable of modeling segmental outflow.

From a hydrodynamic standpoint, the existence of segmental outflow affected only the flow profile across the TM. There is negligible difference in the AH flow profile inside the anterior and posterior chambers between the models with uniform and segmental outflows. Likewise, the different locations of the active regions have negligible impact on the overall AH flow profile inside the anterior and posterior chambers. These results suggest that if one is interested in investigating only the AH flow inside the anterior and posterior chambers, then the existence of segmental outflow can be omitted from the model without significantly affecting the accuracy of the predictions.

From a drug delivery standpoint, the findings from the present study concur with the hypothesis of Chang et al. [8], where the presence of segmental outflow causes irregular distribution of ophthalmic drugs into the TM. As it stands, the large outflow facility of the active region promotes greater flow of drugs via the convection-dominated transport, while significantly smaller amount of drugs exit through the diffusion-restricted non-active regions. Such preferential flow of drugs through the TM can impact negatively the treatment of glaucoma, where the primary target site of the drugs is the non-active region. With the majority of the drugs flowing through the non-targeted site of the active region, there is a high
Fig. 7. Normalized drug concentration distribution across the $x = 3.75$ mm plane a) 10 and b) 20 min after eye drop instillation for the eye in the supine position.

risk for the non-active region becoming ‘under-treated’, which undermines the efficacy of the drugs in treating the disease. Although increasing the drug dosage and frequency of eye drop administration could potentially overcome this problem, at the same time, these steps may cause the active region to be ‘over-treated’, which may lead to some unknown adverse effects to the physiology of the eye.

It is important to point out that there are discrepancies between the amount of drugs entering the anterior chamber and those that exit and remain when carrying out the mass balance assessment. These differences may be due to errors introduced when computing the flux and when evaluating Eqs. (21)–(24) numerically. At 5 min, the mass balance assessment indicated an average percentage difference between incoming and outgoing drugs of 1.45% and 7.16% for the eyes in the standing and supine positions, respectively. As time progresses to 10 and 20 min, these values increase to 8.05% and 9.44%, and 21.11% and 11.88%, respectively for the standing and supine cases. The increase in the percentage difference may be explained by the accumulation of error in the numerical computation of the integrals over longer periods. Such errors may
be reduced by decreasing the time step and by increasing the number of elements; however, these were not attempted in the present study due to limitations in the computational resources available to the authors.

The numerical results obtained in the present study suggest that eye orientation can also affect ocular drug delivery through the actions of buoyancy, which alters the hydrodynamics behavior of AH. For the eye in the standing position, the flow profile of AH promotes greater delivery of drugs towards the bottom half of the eye. Depending on the location of active outflow, this phenomenon could potentially affect the efficacy of the drugs. To illustrate this, consider the hypothetical case where the top half of the TM is the primary target site of the drugs, i.e., the active region is located at the bottom half of the eye. The tendency for the drugs to egress through the bottom half of the TM indicates insufficient drug delivery to the target site, which is at the top. This can severely affect the efficacy of the treatment due to the low drug exposure of the diseased regions. The preferential flow induced by gravity can be nullified if the eye is in the supine position. As stated in Section 4.3, it is interesting to note that the total mass of drugs egressing through the TM for the eye in the supine position is greater than those in the standing position. This raises the possibility of increasing glaucoma treatment efficacy, since the non-active regions in the supine position would have higher drug exposure than in the standing position, albeit still lower than in the active regions. If the observation based on the present numerical model is indeed true in the actual eye, then there may be a need to re-evaluate the design of ocular drug delivery protocols that takes into consideration the potential of instilling eye drops when the patient is in the supine position.

In addition to providing an in-depth understanding on the effects of segmental outflow and eye orientation on ocular drug delivery, the results obtained from the present study may be used to further improve the delivery of ophthalmic drugs. If the location of the active outflow region of glaucoma patients are known, then knowledge of the transient concentration of drugs, such as those presented in Figs. 4 and 9, may be used as guidelines for designing customized treatment protocols that ensure proper amount of drugs are delivered to the targeted area; either through alterations of the eye drop dosage or the frequency of eye drop administration. Furthermore, the model may be used to evaluate the delivery of drugs for different orientations of the eye in order to determine the best orientation that could maximize the delivery of drugs to the non-active region.

It is necessary to point out that not all anti-glaucoma drugs are affected by segmental outflow or eye orientation for that matter. Anti-glaucoma drugs such as β-blockers, α-agonists and carbonic anhydrase inhibitors are designed to target the ciliary body to reduce the production of AH [23–25], while others, such as prostaglandin analogues target the unconventional outflow pathway to increase the overall AH outflow facility [26,27]. As the TM is not the target site, the efficacy of these drugs are not expected to be significantly influenced by segmental outflow. Recently, rho-kinase (ROCK) inhibitors [28,29] and nitric oxide donors [30] have been introduced as potentially new treatments for glaucoma. Unlike the anti-glaucoma drugs that are currently in use, ROCK inhibitors and nitric oxide donors specifically target the TM in order to relax the contractile cells and to reduce the fusion/thickening of their lamellae. This helps to improve the outflow facility, thus relieving the eye from the elevated IOP. With the TM as the specific target site of these newer drugs, the heterogeneous drug distribution across the TM caused by segmental outflow and gravity-induced AH flow can potentially disrupt the delivery of these drugs; hence, the capacity for them to treat glaucoma.
Fig. 9. Plots of the normalized drug concentration against time at seven points across the centreline for the TM defined the angular coordinates $\theta = -90^\circ : 30^\circ : 90^\circ$ and at the centre of the anterior chamber (AC centre) for active regions defined by (a) N, (b) NE, (c) E, (d) SE, (e) S and (f) the uniform outflow case, for the eye in the supine position.

There are some limitations to the model developed in this study that can be further improved in future investigations. Primarily, the results obtained from the numerical simulations have not been quantitatively validated against experimental results. To increase the confidence in the results obtained, qualitative comparisons with existing CFD models in the literature were carried out from a hydrodynamics point of view and they generally show good agreement. In trying to understand the effects of segmental outflow, five different active regions have been examined. This is because the precise location of the active region remains an active area of investigation. Furthermore, it is still undetermined if the active region exhibits individual variation, with some researchers suggesting that in vivo, the segmental outflow pattern is dynamic; indicating that the active region changes with time [31]. For the model and the results from the present study to be meaningful, these gaps in knowledge must be bridged through either in vivo or ex vivo experimental investigations.

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Some of the assumptions made in the present study need to be further investigated in order to ascertain their validity. For instance, the use of the rectangular function assumes that the active region correlates with the fluorescent tracer distribution study reported by Chang et al. [8]. The present model also assumes that the active region is continuous across the outflow width. This represents a simplistic view of segmental outflow, as the active regions need not be continuous and may be formed as patches across the entire TM [7,8]. The existence of segmental outflow may be caused by the irregular distribution of CC across the TM [6–8] and the heterogeneous distribution of pores across the inner wall endothelium of the SC [9]. These factors have been excluded from the present model due to their relatively small structures. Their inclusions, either through a multiscale modeling approach or by incorporating them into the model geometry, may further improve the accuracy of the model presented in this paper.

The present study has also ignored the effects saccade eye movement might have on the ocular drug delivery. Studies have shown that saccade eye movement is one of the main mechanisms that contribute to the motion and mixing of AH inside the anterior chamber [32,33]. Given that it is unlikely for the eye to remain stationary for 2 h after the administration of eye drops, as assumed in the present study, it is very likely that the movement of the eye could induce some form of mixing inside the anterior chamber. Furthermore, the present study did not account for drug transport to the vitreous. While this assumption is valid for an eye with gel-like vitreous, some individuals may have partially liquefied vitreous that can result in drug transport into the vitreous [34]. These aspects should be given extra attention in future studies.

6. Conclusions

The present study was set out to investigate the effects of segmental outflow and its implication on ocular drug delivery via topical eye drops. The results support the hypothesis of Chang et al. [8], which states that segmental outflow can lead to irregular drug distribution across the TM. Furthermore, the present study emphasizes the concern that segmental outflow can lead to non-active regions to become severely ‘under-treated’ in the case of glaucoma treatment. It was also found that the orientation of the eye, through the actions of gravity that alter the AH flow profile, can exert some influence on the delivery of ophthalmic drugs. Nevertheless, this gravitational effect can be nullified if the patient is in the supine position. The numerical results in this study call for the effects of segmental outflow and eye orientation to be given additional consideration in the future protocol planning of topical eye drop administration, particularly in the treatment of glaucoma.

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Supplementary material

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