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Original article

Mathematical modeling of aqueous humor flow and intraocular pressure under uncertainty: towards individualized glaucoma management

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Abstract

Purpose: The aim of the proposed analysis is to provide both a qualitative description and a quantitative assessment of how variations in aqueous humor (AH) flow parameters influence intraocular pressure (IOP) and the outcome of IOP-lowering medications.
Methods: We developed a mathematical model that describes the steady-state value of IOP as the result of the balance between AH production and drainage. We performed stochastic simulations to assess the influence of different factors on the IOP distribution in ocular normotensive and ocular hypertensive subjects and on the IOP reduction following medications.
Results: The distribution of the relative frequency of a given IOP value for ocular normotensive subjects fits a right-skewed Gaussian curve with a frequency peak of 25% at 15.13 mmHg and a skewness of 0.2, in very good agreement with the results from a population-based study on approximately 12,000 individuals. The model also shows that the outcomes of IOP-lowering treatments depend on the levels of

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pre-treatment IOP and blood pressure. The model predicts mean IOP reductions of 2.55 mmHg and 4.31 mmHg when the pre-treatment IOP mean values are 15.13 mmHg and 20.12 mmHg, respectively; these predictions are in qualitative and quantitative agreement with clinical findings.
Conclusion: These findings may help identify patient-specific factors that influence the efficacy of IOP-lowering medications and aid the development of novel, effective, and individualized therapeutic approaches to glaucoma management.

Key words: aqueous humor flow, glaucoma management, intraocular pressure, mathematical modeling, sensitivity analysis

1. Introduction

Aqueous humor (AH) flow plays an important role in determining the level of intraocular pressure (IOP).[1-3] AH production and drainage can be modulated via topical medications aimed at lowering IOP in glaucoma patients.[4] Although clinical and experimental studies have elucidated some of the mechanisms of action of many IOP-lowering agents, important questions concerning the significant variability of their efficacy observed among individuals still remain unanswered.[5-8] For example, latanoprost, a prostaglandin analog (PGA), seems to induce larger IOP reductions when pre-treatment IOP is higher[7,8] and when the glaucomatous damage is at its early stages.[7] Travoprost, another PGA, seems to be more effective in lowering IOP in African American patients when compared to non-African Americans.[9] Age, gender and eye color have also been suggested as potential factors influencing the IOP-lowering efficacy, but the results are not consistent among the different studies.[5,7,10,11] In addition, the circadian rhythm has been shown to alter the drug efficacy between day and night for some IOP-lowering agents but not for others.[6,12-15]

The observed differences in drug efficacy may be explained by other physiological factors. Blood pressure in the capillaries of the ciliary body (*cBP*), total inflow facility (*L*), blood/AH osmotic pressure difference ($\Delta\pi_s$), trabecular outflow facility (C_0), uveoscleral outflow facility (k_1) and episcleral venous pressure (*EVP*) are just some examples of the parameters that contribute to establishing the balance between AH production and drainage.[3] Consequently, they can potentially influence the IOP level and the IOP-lowering effects of the drugs. Interestingly, these factors have also been shown to vary with age, gender, ethnicity and health conditions.[16,17]

Since it is extremely difficult to identify and isolate variations in *cBP, L,* $\Delta\pi_s$, C_0, k_1 and *EVP* in clinical and experimental studies, we propose a complementary mathematical approach. Only a few modeling works have studied AH flow and its relation to IOP-lowering medications;[1-3,18-20] importantly, none of them explicitly accounted for uncertainties and variabilities in the model parameters. In this study, we compute IOP as the solution of a simplified mathematical model describing the

balance between AH production and drainage; we then perform a sensitivity analysis aimed at quantifying the influence of parameters' variations on the IOP distribution in various situations of clinical interest. Accounting for variability in a systematic manner can help identify some patient-specific factors that influence the efficacy of IOP-lowering medications and aid in the development of novel, effective, and individualized therapeutic approaches in glaucoma management.

2. Methods

To analyze AH flow, we utilized a mathematical model that describes the steady-state value of IOP as the result of the balance between AH production and drainage. Changes in ocular blood volume, mainly localized in the choroid, are conjectured to affect the time variations of IOP,[2] but they are not considered here.

AH is produced at the level of the ciliary body by a combination of a passive mechanism, the *ultrafiltration*, and an active mechanism, the *ionic secretion*, and is modulated by the total inflow facility (L).[1,3,19] Here the term facility indicates hydraulic conductance, namely a flow rate per units of pressure. The total flow $J_{in\square}$ of AH entering the eye is therefore given by

$$J_{in\square} = J_{uf} + J_{sec}, \tag{1}$$

where J_{uf} and J_{sec} are the flows due to ultrafiltration and active secretion, respectively. The ultrafiltration from the ciliary circulation consists of flow of transparent fluid across semipermeable membranes (including vascular walls, stroma and epithelial cells) and is driven by blood/AH differences in hydrostatic pressures ($cBP - IOP$) and oncotic pressures ($\Delta\pi_p$): the latter is modulated by a protein reflection coefficient (σ_p). We thus model J_{uf} as

$$J_{uf} = L[(cBP-IOP)-\sigma_p \Delta\pi_p]. \tag{2}$$

The inflow, as a result of the active ionic secretion, is proportional to the blood/AH osmotic pressure difference ($\Delta\pi_s$), via a reflection coefficient for low-molecular components (σ_s), and it is similarly modeled by

$$J_{sec} = L[-\sigma_s \Delta\pi_s]. \tag{3}$$

The drainage of AH from the eye is driven by passive mechanisms through two different pathways. The *trabecular pathway*, also known as conventional pathway, consists of AH flow through the trabecular meshwork, into the Schlemm's canal and the episcleral veins. The *uveoscleral pathway*, also known as the non-conventional pathway, consists of AH flow through the ciliary muscle and into the supraciliary

space. Thus, the total flow J_{out} of AH leaving the eye is given by

$$J_{out} = J_{tm} + J_{uv}, \tag{4}$$

where J_{tm} and J_{uv} are the flows via the trabecular and uveoscleral pathways, respectively. As proposed by Brubaker,[18] the trabecular pathway model consists of a flow through a nonlinear resistor positioned between the anterior chamber (where pressure is equal to *IOP*) and the episcleral veins (where pressure is equal to EVP), with outflow facility (C_{tm}) and is given by the following equation:

$$J_{tm} = C_{tm}\,(IOP - EVP), \text{ with } C_{TM} = \frac{1}{R_0[1 + Q\,(IOP - EVP)]} \tag{5}$$

where R_0 is the resistance when *IOP* equals *EVP*, and Q is the outflow obstruction coefficient. The contribution of the uveoscleral pathway is modeled as the flow through a non-linear resistor connected to the ground,[3] with outflow facility (C_{us}) depending non-linearly on the pressure through the Michaelis-Menten-type relation[21]:

$$J_{tm} = C_{tm}\,(IOP - 0), \text{ with } C_{uv} = \frac{k_1}{k_2 + IOP}, \tag{6}$$

where k_1 is the maximum value attainable by the uveoscleral flow rate. k_2 is the Michaelis constant for the uveoscleral flow rate, namely the pressure value for which the uveoscleral flow rate is half of k_1.

The steady state value of *IOP*, resulting from the balance between production and drainage of AH, namely $J_{in} = J_{out}$, can be written as:

$$J_{uf} + J_{secr} = J_{tm} + J_{uv}, \tag{7}$$

or, equivalently:

$$L[(cBP - IOP) - \sigma_p \Delta\pi_p - \sigma_s \Delta\pi_s] = \frac{1}{R_0[1 + Q(IOP - EVP)]}\,(IOP - EVP) + \frac{k_1}{k_2 + IOP} IOP. \tag{8}$$

This is a scalar third-order polynomial equation in the sole unknown *IOP* and can be explicitly computed from the previous formula. Control state values for the parameters, defined to represent typical conditions of a healthy eye, are indicated with an overline bar in Table 1.

To include potential sources of uncertainties as well as to identify and rank parameters having the most important influence on *IOP*, we applied a global stochastic sensitivity analysis to the model described above. We considered stochastic variations in *cBP* following a normal distribution, and in L, $\Delta\pi_s$, $C_0 = 1/R_0$ (trabecular outflow facility), k_1 and *EVP* following a uniform distribution, both within physiological ranges. By using the probability distribution of *IOP*, we computed vari-

Table 1. Control state values for the parameters in the model for AH flow (8).

Parameter		Value	Unit	Source
Total inflow facility	$\underline{L}$	0.3	µl/min/ mmHg	Lyubimov *et al.*[19]
Blood pressure in the capillaries of the ciliary body	$\underline{cBP}$	27.5	mmHg	Kiel[2], Kiel *et al.*[3], Lyubimov et al.[19]
Blood/AH oncotic pressure difference	$\underline{\Delta\pi_p}$	25	mmHg	Lyubimov *et al.*[19]
Reflection coefficient for proteins	$\underline{\sigma_p}$	1	[-]	Lyubimov *et al.*[19]
Blood/AH osmotic pressure difference	$\underline{\Delta\pi_s}$	-450	mmHg	Lyubimov *et al.*[19]
Reflection coefficient for low-molecular components	$\underline{\sigma_s}$	0.0515	[-]	Lyubimov *et al.*[19]
Episcleral venous pressure	$\underline{EVP}$	8	mmHg	Kiel *et al.*[3]
Trabecular outflow resistance (when pressure gradient equals 0)	R_0	2.2	mmHg min/ µl	Brubaker[18]
Trabecular outflow obstruction coefficient	$\underline{Q}$	0.012	$mmHg^{-1}$	Brubaker[18]
Maximum uveoscleral flow rate	$\underline{k_1}$	0.4	µl/min	Kiel *et al.*[3]
Pressure at which uveoscleral flow rate is at half maximum	$\underline{k_2}$	5	mmHg	Kiel *et al.*[3]

ance-based sensitivity indices, also known as Sobol indices[22] and the probability density function,[23] which describes the relative frequency of a given *IOP* value. For each parameter, its direct influence on *IOP* is quantified in terms of *first-order Sobol indices,* and the influence through interactions with other parameters is identified by means of the *total Sobol indices*. The values of first-order and total indices can be estimated via Monte Carlo simulations,[22] or via reduced order models using polynomial chaos expansion.[24] The former method is very costly from the computational viewpoint as it requires many evaluations to ensure convergence, whereas the latter requires considerably less evaluations. Both methods have been compared and provide similar results. We report in the sequel the results obtained using the polynomial chaos reduced model.

3. Results

This model is used to compute the *IOP* distribution in four different cases of clinical interest: (i) ocular normotensive healthy subjects (ONT); (ii) ocular hypertensive subjects (OHT); (iii) ONT subjects treated with IOP-lowering medications (ONTm); and (iv) OHT subjects treated with IOP-lowering medications (OHTm). The IOP probability density function and first and total Sobol indices are reported in Fig. 1 for the four cases. Mean values, standard deviations, and skewness of the IOP distribution in the four cases are reported in Table 2. Model simulations and results are described below.

3.1. ONT subjects

The mean values of *cBP*, *L*, $\Delta\pi_s$, C_0, k_1 and *EVP* are set equal to their control state values and are summarized in Table 1. Variations in *cBP* are deduced from variations in mean arterial pressure (*MAP*). Specifically, we write $cBP = \alpha\, MAP$, where $\alpha = 0.296$ is chosen as to obtain $cBP = 27.5$ mmHg when $MAP = 93$ mmHg; we assumed a normal distribution for *MAP* of 93 ± 7.6 mmHg.[25] Variations in *L*, $\Delta\pi_s$, C_0, k_1 and *EVP* are assumed to follow a uniform distribution with a variation of ± 15%.

Simulation outcomes: The *IOP* probability density function for ONT subjects (Fig. 1a) fits a right-skewed Gaussian curve with a frequency peak of % at mmHg and a skewness of *0.2*, which is in a very good agreement with the results from a population-based study on approximately subjects[26] (green curve in Fig. 1a). The results for the Sobol indices (Fig. 1b) suggest that *IOP* is strongly influenced by *cBP* and $\Delta\pi_s$ and mildly influenced by the levels of *L*, C_0 and *EVP*. The influence of k_1 on *IOP* appears to be minimal.

Table 2. Mean values, standard deviations and skewness of the distribution of intraocular pressure (IOP) resulting from the sensitivity analysis of the mathematical model in equation (8) for four cases of clinical interest.

	IOP [mmHg] (mean ± standard deviation)	**Skewness of IOP distribution**
Ocular normotensive (ONT)	15.13 ± 1.58	0.2
Ocular hypertensive (OHT)	20.12 ± 2.35	0.09
Ocular normotensive treated with IOP-lowering medications (ONTm)	12.58 ± 1.32	0.17
Ocular hypertensive treated with IOP-lowering medications (OHTm)	15.81 ± 2.03	0.08

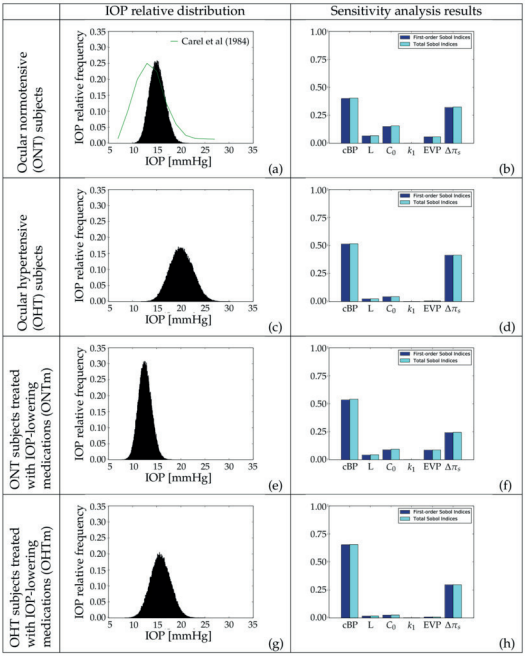

Fig. 1. Probability density function of intraocular pressure (IOP) and Sobol indices resulting from the sensitivity analysis performed on the mathematical model of equation (8) when variations in ciliary capillary blood pressure (*cBP*), total inflow facility (*L*), blood/AH osmotic pressure difference ($\Delta\pi_s$), trabecular outflow facility (C_0), uveoscleral outflow facility (k_1) and episcleral venous pressure (*EVP*)are considered.

3.2. OHT subjects

OHT condition is simulated by decreasing the mean value of the trabecular meshwork outflow facility as suggested by several clinical observations.[27,28] Thus, here we set $C_0 = 0.3\ \underline{C_0}$, leaving the mean values of the other parameters at control state values.

Simulation outcomes: probability density function in the OHT case (Fig. 1c) fits a Gaussian curve, but with a frequency peak of *15*% at *20.12* mmHg and with a more symmetric profile than ONT Gaussian curve (skewness = 0.09). The Sobol indices values for OHT subjects (Fig. 1d) show a stronger dependence of *IOP* on *cBP* and $\Delta\pi_s$ and a weaker dependence of *IOP* on *L*, C_0 and *EVP* than for ONT subjects. The influence of k_1 on *IOP* remains minimal.

3.3. ONT subjects treated with IOP-lowering medications (*ONTm*)

We model the effect of IOP-lowering medications by reducing the active ionic secretion by *25*%, which sets the mean value of the blood/AH osmotic pressure difference to $\Delta\pi_s = 0.75\ \underline{\Delta\pi_s}$; the mean values of the other parameters remained at control state. This modeling choice is justified by the fact that the sensitivity analyses in both the ONT and OHT cases have identified $\Delta\pi_s$ as an important determinant of *IOP* levels; in addition, clinical evidence and studies also support this notion.[1-3]

Simulation outcomes: The *IOP* probability density function in the ONTm case (Fig. 1e) fits a right-skewed Gaussian curve with a frequency peak of *30*% at *2.55* mmHg and a skewness of *0.08*. Thus, our simulations predict a reduction of *2.55* mmHg in the mean value of *IOP* when IOP-lowering medications are administered to ONT subjects. The results of Sobol indices (Fig. 1f) suggest that *IOP* is strongly influenced by *cBP* and $\Delta\pi_s$ and mildly influenced by the levels of *L*, C_0 and *EVP*. The influence of k_1 on *IOP* is again minimal.

3.4. OHT subjects treated with IOP-lowering medications (OHTm)

We simultaneously account for OHT conditions and IOP-lowering treatment by setting the mean values of C_0 and $\Delta\pi_s$ to $C_0 = 0.3\ \underline{C_0}$ and $\Delta\pi_s = 0.75\ \underline{\Delta\pi_s}$, leaving the mean values of the other parameters at control state values.

Simulation outcomes: IOP probability density function in the OHTm case (Fig. 1g) fits a Gaussian curve with a frequency peak of *20 %* at *15.81* mmHg and has a more symmetric profile than the curve in the ONTm case (skewness = *0.08*). Thus, our simulations predict a reduction of *4.31* mmHg in the mean value of *IOP* when IOP-lowering medications are administered to OHT subjects. The results on Sobol indices (Fig. 1h) are similar to those obtained in the ONTm case, but with a weaker contribution from *L*, C_0 and *EVP*.

Our results demonstrate that first-order and total Sobol indices do not present noticeable differences in any of the four simulated scenarios, suggesting that higher order interactions among the selected factors are minimal.

4. Discussion and conclusions

The model reproduced conditions of normal ocular tension, with blood pressure and *IOP* values within physiological ranges, and was subsequently used to simulate the effect of IOP-lowering medications in different conditions of clinical interest. The proposed model suggests that the outcomes of IOP-lowering treatments depend on the initial *IOP* level of the patient and on its individual clinical condition. Specifically, the model predicts mean *IOP* reductions of *2.55* mmHg and *4.31* mmHg when the pre-treatment *IOP* mean values are *15.13* mmHg and *18.4* mmHg, respectively. These predictions are in good agreement with Rulo *et al*.[8] who reported mean *IOP* reductions of *15.3* mmHg and *18.4* mmHg for pre-treatment mean values of mmHg

and mmHg, respectively. However, it is important to remark that the study by Rulo *et al*. utilized Latanoprost, a prostaglandin analog that increases AH drainage, whereas we modeled IOP-lowering medications by decreasing AH production. Other studies reported *IOP* reductions ranging from *3* mmHg to *4.4* mmHg in response to brinzolamide,[20] from *4.5* mmHg to *6.1* mmHg in response to dorzolamide,[30] and from *2.4* mmHg to *4.5* mmHg in response to Latanoprost.[7] The mean IOP reductions reported in these studies[31] are close or slightly higher than those predicted by our model; this might be due to the fact that these studies started from higher pre-treatment IOP levels (ranging from *23.8* mmHg to *28.9* mmHg) than those considered in our simulations.

Our analysis also suggests that IOP-lowering effects are more pronounced when AH production is affected rather than AH drainage. The effects of lowering IOP are also more apparent when trabecular outflow is increased instead of the uveoscleral outflow. Another interesting finding of our analysis is that a patient's blood pressure strongly influences the outcomes of IOP-lowering treatments, which may explain why the effect of some drugs differ between day-time and night-time and/or amongst individuals.[5-8] A further investigation that incorporates a theoretical model coupling AH production and drainage with ocular blood flow may lead to a better understanding of this delicate, yet important, relationship.[3,32,33]

In conclusion, this study suggests that the inclusion of uncertainty in the AH flow parameters of our model is a promising approach that can aid patient-specific assessment of glaucoma management. Future developments of the model will include the coupling between AH flow and blood flow,[3,33] the simulation of IOP time-fluctuations[2,3] and the influence of specific biomechanical factors, such as axial length, scleral thickness and rigidity on these fluctuations.[34]

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