



## Ophthalmology and mathematics: crossroad or scientific interface?

The progress of science is discontinuous. However, accepting the dynamic nature of science, most of us have experienced the point of research crossroads when it was hard to choose the correct path. In 1962, Thomas Samuel Kuhn published his controversial book *The Structure of Scientific Revolutions* introducing the term 'paradigm shift' raising the idea that progress is not a continuous accumulation, but rather a revolutionary process where brand new ideas are adopted and old ideas are abandoned.<sup>1</sup>

Without trying to accept or argue philosophical aspects, today we experience a rapidly-growing amount of research in ophthalmology. The goal of the current evidence-based approach in medicine is to optimize everyday clinical practice based on comprehensive research. However, results coming from the basic sciences sometimes may not be directly applicable to an individual patient. The latest developments, scientific achievements and research in ophthalmology steer to the exciting new perspective based on a multidisciplinary approach. Bringing together scientists whose expertise encompasses ophthalmology, physiology, mathematics, physics and engineering and who explore different aspects of the same problems empowering to make scientific progress.

Can ophthalmologists think mathematically? Is it possible to provide a quantitative representation of the biophysical processes in the eye? Application of objective scientific methods and subjective perspectives can open up a wide range of educational and professional opportunities leading to a better understanding of the pathogenesis and the natural course of the disease, progression and new ways of treatment.

Introducing the second issue of Journal for Modeling in Ophthalmology, we hope the reader will enjoy both clinical and theoretical insights on glaucoma in short papers that followed the International Congress on Advanced Technologies and Treatments for Glaucoma (ICATTG15) held in Milan (Italy), October 29-31, 2015 (<http://www.icatto.com/archive/icattg2015/>).

Normal-tension glaucoma is a particularly difficult type of glaucoma both in terms of diagnosis and treatment. Lester points out that different types of glaucoma exist and are probably based on the presence of different risk factors. The cut-off value of 21 mmHg is not used anymore to differentiate healthy subjects from glaucoma patients. The paper by Quaranta *et al.* analyses the rationale for IOP measurements throughout the 24-hour cycle. IOP is not a static number; rather, it exhibits time-de-

pendent variations that can reach up to 6 mmHg over a 24-hour period in healthy eyes, and even more in eyes with glaucoma.<sup>2-5</sup> Regarding 24-hour IOP characteristics, only IOP peak was correlated to visual field progression, while 24-hour IOP fluctuation was not an independent risk factor.<sup>6</sup> Indeed, 24-hour mean, peak and fluctuation were all associated and a strong correlation was found between mean and peak IOP, and between fluctuation and peak IOP. Mean IOP is a strong predictor of glaucomatous damage. A desired therapeutic target is therefore a uniform reduction of IOP throughout the 24 hours. A reliable method of continuous IOP measurement would be desirable, making 24-hour IOP phasing easier and opening new pathways for research.

Interestingly, the papers by Szopos *et al.* and Mauri *et al.* lead to new perspectives of mathematical modeling of aqueous humor flow and intraocular pressure towards individualized glaucoma management. Szopos *et al.* aim to provide both a qualitative description and a quantitative assessment of how variations in aqueous humor flow parameters influence IOP and the outcome of IOP lowering medications. They developed a mathematical model that describes the steady state value of IOP as the result of the balance between aqueous humor production and drainage and performing stochastic simulations to assess the influence of different factors on the IOP distribution in ocular normotensive and ocular hypertensive subjects and also on the IOP reduction following medications. This model 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.

Mauri *et al.* theoretically analyzed new aspects of electro-fluid dynamics of aqueous humor production. The connection between  $\text{HCO}_3^-$ ,  $\text{Na}^+$  and topical medications in the regulation of aqueous humor production is still controversial and difficult to study experimentally by trying to isolate the role of a single electrolyte in regulating aqueous humor production. The use of a mathematical model appeared to be a promising approach to help unravel such a connection through simulation and comparison of different predicted scenarios.

Groups of authors from Indianapolis and Milan universities contributed to glaucoma progression analysis. The paper by Hutchins *et al.* on clinical evaluation of baseline characteristics predictive of structural and functional progression in open-angle glaucoma patients with different demographic characteristics aims to examine ocular blood flow parameters that may predict structural and functional disease progression in open angle glaucoma patients of different diabetic status, gender, ethnicity, and body mass index. Messenio *et al.* evaluated the variations of IOP, morphometric papillary characteristics, perimetric indices and electrophysiological parameters before and after topical IOP lowering therapy in patients with

suspect normal tension glaucoma. They showed that electrophysiological tests could provide a more sensitive measure of retinal ganglion cell integrity and help distinguish between suspect normal-pressure glaucoma patients before perimetric alterations are evident and normal subjects with apparent larger disc cupping.

Over the past decades, color Doppler imaging (CDI) has gained popularity as a reliable tool to measure blood flow in a variety of vascular beds throughout the body. The use of CDI to measure blood flow parameters in retrobulbar vessels has become very common. Carichino et al. introduce a computer-aided identification of novel ophthalmic artery waveform parameters. The computed-aided analyses of ophthalmic artery velocity waveforms obtained via CDI were able to distinguish arterial waveform parameters values between healthy subjects and glaucoma patients, as well as between gender. Authors foresee further studies investigating the potential to predict severity and progression of glaucoma.

An interesting contribution by Cassani *et al.* on theoretical predictions of metabolic flow regulation in the retina aims to better understand the regulating mechanisms in health and disease. This study uses a theoretical model to investigate the response of retinal blood flow to changes in tissue oxygen demand. The increase in blood flow predicted by the model due to an increase in oxygen demand was not in the same proportion as the change in blood flow observed with the same decrease in oxygen demand, suggesting that vascular regulatory mechanisms may respond differently to different levels of oxygen demand.

Several studies have suggested an association between vascular factors and glaucoma.<sup>7-11</sup> Several epidemiological studies demonstrated the influence of ocular perfusion pressure on the prevalence, incidence and progression of glaucoma.<sup>12</sup> Ocular perfusion pressure refers to the pressure available to drive blood through the intraocular vasculature, with the degree of perfusion being influenced by the resistance to flow, which is a function of the vessel caliber or the vessel tone.<sup>13</sup> While it seems a very complex parameter, Guglielmi et al. utilized statistical techniques and analysis to show that it is the joint effect of IOP, ocular perfusion pressure and blood pressure, or, more precisely, of all the covariates in the selected logistic model, that determines the probability of disease, rather than the value of an individual covariate. Importantly, the main statistical interest should be the prediction of disease probabilities for new patients entering the study, presenting specific values of the covariates included in the model, rather than the estimated individual effect of a single predictor.

It has been shown that glaucoma, proliferative vitreoretinopathy, posterior capsule opacification, diabetic retinopathy, age-related macular degeneration, pterygium and keratoconus have been associated with modulation of Transforming Growth Factor beta (TGF- $\beta$ ) protein expression.<sup>14-20</sup> Therapeutic intervention targeting TGF- $\beta$ 2 protein expression may have multifold effects on relevant intraocular

tissues such as trabecular meshwork (cell invasion/migration), retina (scarring and wound-healing processes) and/or optic nerve head (neuroprotection), and warrant further evaluation in patients suffering advanced glaucoma and undergoing trabeculectomy. Hasenbach et al. used a murine model of glaucoma filtration surgery to evaluate the effect of intraocular ISTH0036 administration. They showed that treatment with ISTH0036 resulted in prolonged bleb survival and decreased scarring (downregulation of collagen-1 and -3 fibers) in a murine glaucoma filtration surgery model. Initial results rose a strong rationale that patients with glaucoma or other ocular diseases may benefit from treatment with TGF- $\beta$ 2 antisense oligonucleotides.

Paulaviciute-Baikstiene et al. performed a prospective 12-month study aiming to find the correlation between anterior segment OCT and functional outcomes of trabeculectomy by describing morphological features of successful and limited success filtering blebs. The detection of early postoperative scarring and the continuing development of surgical measures to reduce this risk represent a major challenge of filtering surgery. Authors suggest that larger internal fluid filled cavity, total bleb height, bigger bleb wall thickness and multiform bleb wall reflectivity are good indicators of successful bleb function.

The second Issue of the Journal for Modeling in Ophthalmology uniquely combines and balances clinical and mathematical aspects in the study of glaucoma and we believe that both ophthalmologists and modeling experts will find in it interesting aspects and new information on glaucoma and its risk factors. Enjoy your reading!

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## References

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