Classifiers differences method for experimental modeling of intraocular pressure altitudes versus ultrasonic corneal thickness variables

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Abstract
The amplitude of intraocular pressure (IOP) variation was defined via experimental modeling, conditioned by age, sex, complementary diseases, pharmaceuticals, exposure to allergens, etc. The subject of our study was to provide additional numerical analysis for fixing the reliability of the measured IOP magnitudes with Goldmann applanation tonometer (GAT) and ultrasonically measured central cornea thickness (CCT), while employing the experimental data of created correlation matrix and artificial neural networks via classifiers differences method. The clinical experimental data were restricted by 99 eyes of 53 subjects (65 ocular hypertension cases and 34 somatically healthy eyes). Experimental data in terms of IOP, CCT, age matrix indicated that variation of ultrasonically measured central corneal thickness is a positively correlated source of variation in IOP measurements among ocular hypertension subjects (R=0.648, p=0.073). Optimizing the distribution among classes, i.e. dominance of IOP error and the absence of IOP error, the fitting of radial basis function (RBF) network and multilayer perceptron (MLP) was provided and minimal error of the networks was obtained.
Key words: Intraocular pressure (IOP), Goldmann applanation tonometer (GAT), ultrasonic measurement of central corneal thickness (CCT), artificial neural networks

Introduction

Intraocular pressure (IOP) is an important risk factor, significantly influencing the diagnosis, treatment options and forecasting prognosis of various forms of glaucoma. Manometry and tonometry are the standard IOP measurement techniques. Tonometric pressure readings are widely employed in clinical practice. Manometric estimation of IOP is the invasive one.

Goldmann applanation tonometry (GAT) almost half of the century was adopted to be the most valid and reliable indirect IOP measurement method and was named as "Gold standard", while the main is performance based on the Imbert-Fick law. Goldmann and Schmidt acknowledged, that the premises of their construction were based on apropos central corneal thickness (CCT) value. When employing the applanation tonometry, we assume that the cornea is of standard rigidity. But in fact, thicker corneas are more rigid for the frontal deformation, whereas the thinner corneas are more flexible – the measurable IOP values increase if a cornea is thick, meanwhile if the cornea is thin, underestimation of IOP is possible; as a consequence resistance versus corneal applanation is being recorded. The dependence of tonometry results in respect of corneal thickness (determined by ultrasonic echoscopy) was noticed by some investigators, though there are several sampling, experimental and analytical results [1-4]. Error sensitivity analysis of experimental data proved CCT to be confounding factor for GAT and additional analysis must be provided for measured IOP values, when fixing the reliability of the IOP magnitudes via GAT [5, 6].

Experimental modeling was used to define the amplitude of IOP variations, conditioned by the age, the sex, complementary diseases, pharmaceuticals, exposure to allergens, etc. CCT differences, observed among various racial and ethnic groups [7-10], day and season variability [7,11] and CCT influenced by chronic and acute diseases can determine incorrect classification of patients with normal tension glaucoma [12-15] and ocular hypertension [16-20]. Accordingly, the GAT error requires the creation of new IOP measurement devices, calibration methods and mathematical models. The goal of our study was to provide an additional numerical analysis for fixing the reliability of the measured IOP magnitudes with GAT and ultrasonically measured CCT, while employing the experimental data of the created correlation matrix and artificial neural networks via classifiers differences method.

Data acquisition methods

Fifty-three individuals (99 eyes) were recruited into prospective cohort – analytical correlation survey. 65 ocular hypertension eyes forming ocular hypertension group and the second one of 34 healthy control eyes with no observed eye and systemic pathology, i.e. healthy subject. The observations were provided fully with respect to each individual eye.

Subjects involved into the study had to satisfy the following inclusion criteria: 1) no diagnosed systemic diseases (diabetes mellitus, systemic hypertension, calogenosis, etc.); 2) no surgery, topical and systemic medications at least three months before starting the study; 3) no anamnesis of ocular trauma; 4) no myopia or

hypermetropia over 6D; 5) astigmatism not exceeding three diopters; 6) no contact lens holders; 7) open anterior chamber angle in gonioscopy; 8) no optic disc changes during eye fundus examination.

The following parameters were fixed up during the investigation: age of individual, gender, systemic diseases, topical and systemic medication applications, ocular diseases and trauma, visual acuity and correction, gonioscopic and eye fundus data, IOP, ultrasonic measurement of central corneal thickness. All measurements were provided amid 9 p.m. and 11 p.m., targeting to minimize the fluctuation of parameters.

The IOP measurements of all subjects involved into the study were provided employing the Goldman applanation tonometry (Model AT 900 C/M). The IOP was analyzed separately for left and right eye having measured those in a corneal center. The IOP was identified with ±0.5mmHg GAT systematic error. An average magnitude with respect to three tonometry readings (in mmHg) per eye was employed for a subsequent analysis.

The central corneal thickness measurements were performed via ultrasonic pachymeter (Quantel medical BVI France, model pocket, type BF, class II). The central corneal thickness was registered in the screen of the pachymeter light diodes with ±5 μm device systematic error. In order to reduce uncertainty of the ultrasonic measurement the average magnitude of three central corneal thickness measurements (in μm) per eye was employed for a further analysis.

The data were processed applying the "SPSS for windows Version 12.0" software package assigned for data systems analysis by employing the following mathematical statistical models: *t*-test for independent and dependent samples; Pearson correlation coefficient; λ^2 test; multiple regression analysis method. The confidence level of investigation (P) was adopted to be 95%; a significance level (p) of 0.05 was interpreted as statistically reliable one. Classification is a very important aspect in decision-making, the possibilities of the optimal decision applied for series biomedical data were experimentally provided in the previous papers by authors [6, 21]. To assess the relative risk for IOP error estimation artificial neural networks were applied; i.e. for classification purpose to identify the IOP error via GAT for a particular subject.

Experimental approximation IOP versus ultrasonically measured CCT

The sample of 65 ocular hypertension eyes consisted of 23 women (23 right and 18 left eyes) and 13 men (13 right and 11 left eyes). The 34 healthy eyes sample consisted of 11 women (11 right and 11 left eyes) and 6 men (6 right and 6 left eyes respectively). An identified ratio of ocular hypertension eyes versus healthy eyes was of proportional distribution with respect both to quantity and gender determinant. The age dispersion of the investigated subjects covered the bounds of a maximal risk i.e. age minimum was 51 years that of maximum – 79 years. While sampling of considered groups with respect to age is reasonable one.

The scattering parameters of IOP dependence on ultrasonically measured CCT corresponding to hypertension eyes group versus that of the healthy eyes group were analyzed. The scatter plot of the measured IOP values dependences on CCT is presented in Fig.1.

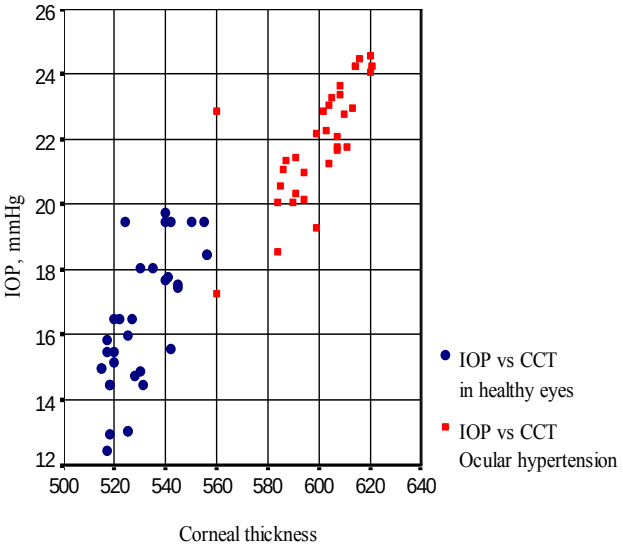

Fig.1. **Scatter plot of the measured IOP values amid ocular hypertension and healthy eyes**

The mean of IOP magnitude and standard deviation was 21.69 ± 0.164 mmHg among ocular hypertension subjects (21.59 ± 0.124 mmHg for men, 21.74 ± 0.185 mmHg for women), meantime that of the healthy group was 16.44 ± 2.15 mmHg (15.65 ± 0.120 mmHg for men, 16.88 ± 0.244 mmHg for women). The difference between groups was statistically significant ($p<0.01$); while the gender indicator per se does not influence in a statistically reliable way to variation of IOP magnitudes.

Central corneal thickness measured by the ultrasonic echoscopy for the ocular hypertension group was 594.65 ± 16.91 μm (586.25 ±16.39 μm for men, 599.56 ± 15.37μm for women); in the healthy eyes group was as following 530.85 ± 12.80 μm (527.42 ± 9.75μm for men, 532.73 ± 14.05 μm for women). The histogram curve of eye hypertension and the overlapping interval of healthy eyes histogram data do not exceed the 0.05 magnitude of the significance level, thus the difference between IOP magnitudes under distribution of the investigated populations assumed as the statically reliable one. Analyzing the influence of a gender determinant on numerical CCT parameters, one can state that the gender is a clinically negligible factor, thus the more detailed analysis with respect to gender factor is unreasonable.

Subsequently the hypothesis, stating that the central corneal thickness of eyes under ocular hypertension diagnosis is 10% thicker to compare with healthy eyes, was raised. This hypothesis was verified via the *t*-test, employed for independent samples. The test numerical magnitudes agreed with the study data ($p<0,01$). Mathematical association of ocular hypertension, pachymetry (ultrasonic measurement of CCT), tonometry and age parameters was created applying the Pearson correlation coefficient. The analysis have pointed a high positive correlation between the IOP measured via the Goldmann applanation tonometry and that of the ultrasonic

pachymetry data (r=0,648; p<0,001) amidst ocular hypertension subjects. A matrix of ocular hypertension, pachymetry, tonometry and age data is presented in Table 1.

Table 1. **The correlation matrix of pachymetry, tonometry, age variables**

Variables		IOP	CCT	AGE
Pearson Correlation	IOP	1,000	0,648	-0,224
	CCT	0,648	1,000	-0,172
	AGE	-0,224	-0,172	1,000
Sig. (2-tailed)	IOP	0,000	0,000	0,073
	CCT	0,000	0,000	0,172
	AGE	0,073	0,172	0,000
Number	IOP	65	65	65
	CCT	65	65	65
	AGE	65	65	65

The linear regression analysis was performed for CCT (determined by the ultrasonic echoscopy) and tonometry variables. The observed IOP magnitudes distribution area versus a central corneal thickness, created via the linear regression analysis method is presented in Fig. 2.

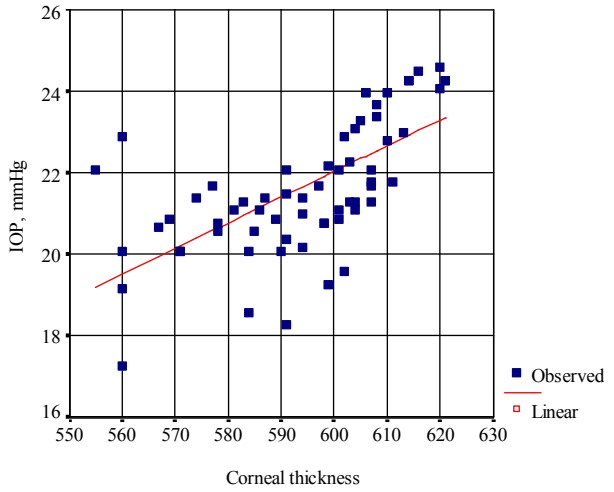

Fig 2. **Observed IOP magnitudes distribution area versus CCT**

When applying the mathematical model for the equation, obtained via the regressive analysis method, it was obtained that the 10 μm increment of central corneal thickness results the 0,63 mmHg rise of the measured IOP.

Classification of IOP error performance

Tonometric error detection is an important issue since the exact value of IOP unambiguously defines and modulates the treatment course. Knowledge of the true IOP value allows escaping of invasive procedures, treatment based on side effects and incurable disease stigma, which in some cases is only the result of the device reading error. The discrete model while applying the artificial neural network and the fitting to the real bio - object was developed with the purpose to classify the frequency of diagnostic mistakes in a daily clinical practice. The error of IOP obtained in GAT measurement was minimized by the classical error elimination procedure:

$$p(h) = p'(h) - \varepsilon(h); \qquad (1)$$

where $\varepsilon(h)$ - experimental pressure error, mmHg; $p'(h)$ - experimental pressure data, mmHg; $p(h)$ - real pressure data, mmHg, h - CCT, μm. The function $\varepsilon(h)$ apriori is undetermined, as the result of the uncontrollable CCT versus IOP relation which is unavailable even in the invasive estimation.

The manometrical and tonometrical association was accepted of the linear dependence character defined by Cohan et al. [22] and the experimental IOP is assessed concerning the present equation:

$$p(h) = 40(p'(h) + 5)/55 - \varepsilon_d(h). \qquad (2)$$

where $p'(h)$ – experimental pressure, mmHg; ε_d – persistent ultrasonic CCT error. As the threshold factors are known apriori from a statistical approximation IOP versus CCT. We define the discriminative function for separation the two classes, represent the dominance of the measured IOP error (via GAT) and the absence of it for a particular subject:

$$y = \begin{cases} 0, p(h) < p_T \wedge h < h_T \\ 1, p(h) \geq p_T \wedge h \geq h_T \end{cases}, \qquad (3)$$

where p_T - manometrical pressure threshold, h_T - CCT threshold.

The persistent ultrasonic CCT error (ε_d) is identified from the edge conditions of the statistically approximated data set. Particular cases are selected, i.e. subjects with an increased ultrasonic CCT value in association with ocular hypertension erroneous diagnosis (hyper-diagnostic condition), vice versa reduced ultrasonic CCT value while ocular hypertension is not diagnosed while it is persist (hypo-diagnostic condition). The real error function is identified when the number of edge condition subjects (ECS) is approaching the infinity:

$$\varepsilon_d(h) = \eta(h) \cdot \lim_{N \to \infty} f_D(h), \qquad (4)$$

where $\eta(h)$ - function fitting the dimension for $\varepsilon_d(h) \equiv f_D(h)$; N - ECS number; $f_D(h)$ - ECS appearance frequency. When CCT values are discrete ones, ECS frequency is defined as follows:

$$f_D(h) = \frac{N(h)}{M}, \qquad (5)$$

while $N(h)$ - ECS number for corresponding h; M - total subjects number. $N(h)$ is calculated applying the created error detection system.

IOP error analysis applying RBF and MLP

The applied IOP error detection algorithm numerically models target relations: the IOP error (via GAT) versus ultrasonic CCT variance, while applying the method of difference between the threshold classifier and the radial basis function RBF network versus MLP. The threshold classifier is not learnable; contrarily, the classifier based upon artificial neural network (ANN) is trained before simulating with test patterns. The ANN training matrix is

constructed of averaged vectors (p,h) for which p is equal. The ANN test matrix is derived from the vectors (p,h) for which p is identical.

The designed error detector identifies difference between classification results: erroneous are vectors (p,h) for which $y_1(i) \neq y_2(i)$, when i is the number of the test matrix. $N(h)$ is found when the vectors with the same h are counted to appropriate bins.

Optimizing the discern among classes, the fitting of the RBF network was provided, which adapts its weights optimally (in reference of the interpolation theory) according to the distribution function hidden in the training set. Fig.3 presents the RBF classificatory model: the blank curve presents the average association between IOP and ultrasonic CCT after ten approximation cycles; the lined curve derived via equation (2) regarding the experimental IOP measurements. The created RBF model consists of the first layer's weights (the exponential function parameters) identified by optimization methods from training vectors, while the second layer's weights are evaluated as the linear equation's assertion. The optimal designed radial-basis function width is 20 and maximal count of neurons – 20, when obtaining a minimal error of the network.

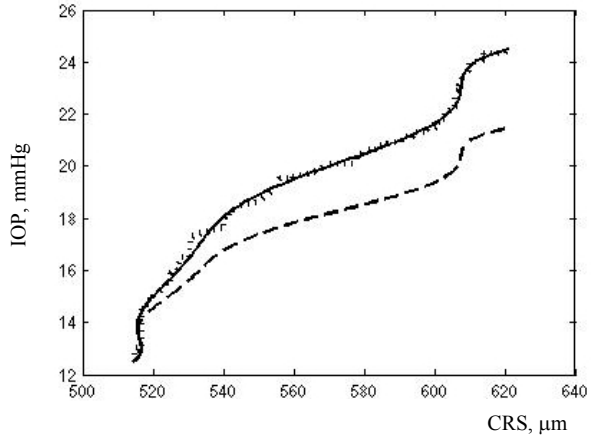

Fig. 3. **IOP versus CCT variance applying RBF network**

For numerical modeling of the IOP error (via GAT) detection via MLP, two-layers perceptron was introduced. The quantitative characteristics of analyzed objects were evaluated through MLP, while construction of a non-linear discriminative function was applied of following assertion:

$$z(\vec{x},\vec{w}) = \sum_{i=1}^{N} w_i \varphi_i(\vec{x}). \qquad (6)$$

The set of ANN inner parameters $\vec{w}$ were modified when difference between systems' output values $y'(\vec{w},\vec{x})$ and target values was minimal one. The IOP versus CCT variance applying MLP is presented in Fig.4: the blank curve presents the average association between IOP and ultrasonic CCT; the dashed curve derived via Eq. 2 regarding the experimental IOP measurements. Employing network training, the backpropagation algorithm was applied with the experimentally rated training parameters: maximum epochs – 2000, error limit – 0.017, hidden layer neurons number – 20.

The trainscg function was applied for optimizing the weights of each neuron according to particular training error function.

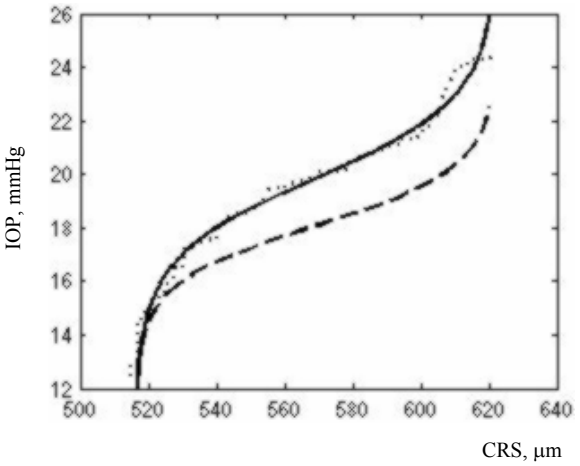

Fig. 4**. IOP versus CCT variance using MLP classifier**

The $\varepsilon(h)$ interval obtained via RBF network is narrower than that obtained through MLP: the RBF determines identical results for all experimental cycles and the stable error function had been observed; while adapting MLP for targeting expression, the detection is not concluded for more than 50% of experimental loops for the reason, that the MLP redesigns the training data in each experimental cycle, as a result the increasing non-linear function is observed for those loops where the error has been detected.

Conclusions

1. Ultrasonic measurement of CCT is important for IOP (via GAT) error correction. The ultrasonic CCT average was determined to be 595 μm in the ocular hypertension eyes group, and the average of ultrasonic CCT was determined to be 531 μm in the healthy eyes group. Non-linear dependences of IOP versus the ultrasonic CCT for IOP value correction were derived.
2. For classification purposes the artificial neural networks classifier difference method was applied. Comparison of RBF and MLP usage have shown that an accuracy of a true value of IOP have risen by 80 to 95 percent adopting the proposed methodology while the left percent depends on subjects individualities.
3. In prospect determination of the factors, conditioning the individual true and the measured IOP magnitudes variations with respect to quantity and quality aspects is required, and subsequently adopting diagnostic–expert programs for realizing GAT systemic error elimination is evident.

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Klasifikatorių skirtuminio metodo taikymas eksperimentiniam matuojamojo akispūdžio ir ultragarsinių ragenos įverčių modeliavimui

Reziumė

Eksperimentiniškai modeliuojant matuojamojo akispūdžio įverčius, nustatyta, jog amžius, gretutinės ligos, lytis, medikamentai, alergenų ekspozicija etc. veikia matuojamo akispūdžio svyravimų amplitudę. Mūsų tyrimo tikslas - atlikti papildomą skaitinę Goldmano aplanaciniu tonometru (GAT) matuojamojo akispūdžio tikslumo analizę, naudojant eksperimentinės aibės koreliacinės matricos korekcijos faktorių ir adaptuojant dirbtinius neuronų tinklus (klasifikatorių skirtuminis metodas). Klinikiniai tyrimai apėmė penkiasdešimt trijų subjektų 99 akis (65 akies hipertenzijos ir 34 somatiškai sveikų akių atvejus). Sudarius matuojamojo akispūdžio, centrinės ragenos storio (ultragarsinis matmuo) ir amžiaus eksperimentinių duomenų koreliacinę matricą, nustatytas teigiamas ryšys tarp matuojamojo akispūdžio ir centrinės ragenos storio (ultragarsinis matmuo) akies hipertenzijos subjektų grupėje (R=0,648, p=0,073). Panaudojant radialinių bazinių funkcijų bei daugiasluoksnio perceptrono neuronų tinklus, tyrimų rezultatai suklasifikuoti į dvi klases – tyrimus, kuriuose dominuoja akispūdžio matavimo paklaida ir tyrimus, kuriuose ji nedominuoja. Pateiktos rekomendacijos kaip koreguoti išmatuotas akispūdžio reikšmes priklausomai nuo ultragarsiniu metodu išmatuoto ragenos storio.

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