Prediction of the axial lens position after cataract surgery using deep learning algorithms and multilinear regression

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ABSTRACT.

Background: The prediction of anatomical axial intraocular lens position (ALP) is one of the major challenges in cataract surgery. The purpose of this study was to develop and test prediction algorithms for ALP based on deep learning strategies.

Methods: We evaluated a large data set of 1345 biometric measurements from the IOLMaster 700 before and after cataract surgery. The target parameter was the intraocular lens (IOL) equator plane at half the distance between anterior and posterior apex. The relevant input parameters from preoperative biometry were extracted using a principal component analysis. A selection of neural network algorithms was tested using a 5-fold cross-validation procedure to avoid overfitting. The results were then compared with a traditional multilinear regression model in terms of root mean squared prediction error (RMSE).

Results: Corneal radius of curvature, axial length, anterior chamber depth, corneal thickness, lens thickness and patient age were identified as effective predictive parameters, whereas pupil size, horizontal corneal diameter and Chang–Waring chord did not enhance the model. From the tested algorithms, the Gaussian prediction regression and the Support Vector Machine algorithms performed best (RMSE = 0.2805 and 0.2731 mm), outperforming the multilinear prediction model (0.3379 mm). The mean absolute prediction error yielded 0.1998, 0.1948 and 0.2415 mm for the respective models.

Conclusion: Modern prediction techniques may have the potential to outperform traditional multilinear regression techniques as they can deal easily with nonlinearities between input and output parameters. However, in all cases a cross-validation is mandatory to avoid overfitting and misinterpretation of the results.

Key words: anatomical lens position – axial IOL position – deep learning – optical biometry – prediction model – regression model

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catact surgery, the power of the implanted IOL, and the achieved refraction after cataract surgery. This back-tracing of the ELP (Melles et al. 2019; Savini et al. 2020) is routinely performed using a formula constant optimisation strategy, in which the biometric data, the power of the implanted lens and the refractive outcome of a sufficient number of clinical cases are used to determine post hoc the appropriate ELP and formula constant.

The purpose of this paper is to derive biometric measures of the eye prior to cataract surgery, using a large data set containing data from cataract surgeries from 1 clinical centre. The data recorded include corneal radius of curvature, axial length, central corneal thickness, anterior chamber depth, crystalline lens thickness, horizontal corneal diameter, Chang–Waring chord (as the difference between the coaxial light reflex and the pupil centre) in horizontal and vertical direction, and the patient’s age and sex. These were developed to both a classical regression-based prediction model and a neural network-based algorithm for predicting the axial position of the lens equator plane after cataract surgery.

Methods

Data set for the prediction model

A data set of 2231 measurements of a cataractous population before (at the timepoint of biometry for IOL power calculation) and 6 weeks to 3 months after cataract surgery with the biometer (IOLMaster 700, Carl-Zeiss Meditec, Jena, Germany) was evaluated in this study. Three hydrophobic monofocal aspherical lenses were considered: Clareon, Alcon, Fort Worth, USA; Vivinex, Hoya Surgical, Tokyo, Japan; and ZCB00, Johnson & Johnson, New Brunswick, USA. These 3 lenses do not differ significantly in the general optical design or in the optimized formula constants (Clareon119.1; ZCB00: 119.4; Vivinex: 119.2, data derived from https://IOLCon.org at 12th October 2021).

All data were obtained from one clinical centre (2 experienced surgeons, Augen- und Laserklinik, Castrop-Rauxel, Germany). This study was registered at the local Ethics Committee (Ethikkommission der Ärztekammer des Saarlandes with the registration number 157/21). The data were anonymised by the source and transferred to a .csv data table using the software module for batch data export. The data tables were reduced to the relevant parameters required for our data analysis, consisting of the following measurements extracted from the preoperative measurement: the patient’s age (Age) in years as the time interval from date of birth to the preoperative measurement, the laterality (left or right eye), sex (female or male), flat (R1) and steep (R2) corneal radius of curvature both in mm, axial length (AL) in mm, anterior chamber depth (ACD) in mm (measured from corneal epithelium to lens), central thickness of the crystalline lens (LT) in mm, pupil diameter (PD), horizontal corneal diameter (CD) in mm, plus the Chang–Waring chord as the distance between the light reflex originating from a coaxial light source (Purkinje reflex P I) and the pupil centre (Chang & Waring GO 4th 2014, distance CWchord in mm and axis CWchordA in °). From the postoperative measurement, we extracted the pseudophakic anterior chamber depth (ACDpo) in mm and the central IOL thickness (LTpo) in mm. Only one eye from each subject was included in this study. Where measurements of both eyes were available, one eye was randomly selected. Subjects with missing data or data with a ‘Failed’ or ‘Warning’ in the internal quality check of the IOLMaster 700 for R1, R2, AL, CCT, ACD, LT, PD, CD, CWchord, CWchordA, ACDpo or LTpo were excluded. After checking for ‘Successful’ measurement for corneal front and back surface curvature data, a data set of N = 1345 measurements was used for training, validation and test of our prediction algorithm. The data were transferred to Matlab (Matlab Version 2019b, MathWorks, Natick, USA) for further processing.

Data preprocessing in Matlab

From the corneal curvature in the flat and steep meridian, we derived the mean corneal curvature R in mm as R = 0.5(R1 + R2). The Chang–Waring chord as given by the IOLMaster 700 in distance and direction was converted to vector components in the horizontal (CWX = CWchord-cos(CWchordA)) and vertical (CWX =
CWchord-sin(CWchordA)) axes, both in mm. In addition, to consider the laterality, the horizontal component of CWX was flipped in sign for left eyes (CWXcor) to get negative values for a temporal shift and positive values for a nasal shift. The equator plane of the IOL (LEQ) in mm as target parameter was considered as the prediction error (LEQ – LEQpred).

**Modelling in Matlab**

In a first step, a feature selection in terms of a principal component analysis (PCA) was used to identify the relevant input parameters for our prediction models (Herrmann 1997). PCA is a commonly used strategy to decompose the parameters in the parameter space into an orthonormal basis in order to extract the most relevant input parameters for dimensionality reduction in explorative data analysis and prediction models (Kleesiek et al. 2020). The order of principal components within the parameter space is chosen to maximize the variance of the data set. In our setup, we defined a benchmark of 99% of the variance of the data set to be preserved with the PCA and dimensionality reduction.

In a second (qualification) step, a selection of classical neural network types (Bechtel 2008; Welsch et al. 2018; Sramka et al. 2019; Carmona González & Palomino Bautista 2021; Langenbucher et al. 2020) was tested on the data set to determine the performance in terms of predicting the LEQ from the relevant input parameters identified by the PCA. The following neural network algorithms were tested:

- **Regression models**: 4 different options were implemented with simple multilinear regression, multilinear regression with interactions between input parameters, a robust setup with individual weighting of the data points and a stepwise linear fitting by including and excluding components.
- **Regression trees**: 3 different options were implemented. A tree with a high resolution (fine tree) and plenty of leaves with a minimum leaf size of 4, a tree with a normal resolution (normal tree) and an average leaf size of at least 12, and a tree with a coarse resolution (coarse tree) with a restriction to some large leaves with a minimum leaf size of 36.
- **Support vector machines (SVM)**: 4 different options were implemented. SVM were considered with a linear kernel, with a quadratic kernel, a cubic kernel and a Gaussian kernel. The preset kernel size was selected as ¼ of the square root of the number of effective predictive parameters.
- **Gaussian process regression (GPR)**: 3 different options were tested in our setup: with a GPR with a squared exponential function for the kernel, with an exponential function for the kernel, and a GPR with a rational quadratic kernel, which allows a flexible model fit with variation to different scales. To evaluate the performance of each algorithm under test, we extracted the root mean squared prediction error (Welsch et al. 2018).

To avoid overfitting of the models, the entire data set of \( N = 1345 \) measurements was split randomly into 5 equally sized clusters (\( N = 269 \) each), and with a 5-fold cross-validation strategy, the neural network algorithms were trained with the training set (\( N = 1076 \), excluding the test set) and validated with the test set (\( N = 269 \), with permutations until each cluster was excluded once (Bechtel 2008).

In a third step, the 2 most promising neural network approaches from the tested neural network types in terms of smallest root mean squared prediction error were analysed more in detail. For reference, we defined a classical multilinear regression model having the same input parameters, predicting LEQ as the output parameter. To ensure a fair comparison, we implemented a cross-validation strategy for the multilinear regression model using the data partitions defined for the neural network approaches.

**Statistics**

The input parameters and the target parameter are shown in Table 1 with mean, standard deviation, median and 90% confidence interval (5% and 95% quantile). For the 3 prediction models (the 2 neural network approaches with the least root mean squared prediction error and the classical multilinear regression model), we provide the mean prediction error (ME) with standard deviation (SD), the mean absolute prediction error (MAE), the 95% quantile (CL90) of the absolute prediction error (as the absolute prediction error shows in general a one-sided distribution) and the root mean squared prediction error (RMSE). For the multivariate linear prediction model, we used maximum likelihood estimation with iterative ECM algorithm (Meng et al. 1993; Sexton & Swensen 2000), and the respective results are described with the coefficient of determination (r²), Sigma and LogL as the value of the log likelihood objective function after the final iteration.

**Results**

We included \( N = 1345 \) measurements from 669 left eyes in this study (787 eyes from female patients). Table 1 shows a listing of the mean value, standard deviation, median, minimum and maximum, as well as the 90% confidence intervals of biometrical input and target parameters used for our modelling. The CW chord shows a trend towards the inferior direction and a horizontal shift in the temporal direction (which can be seen from the data of CWXcor, but not from CWX).

In a first step, the feature selection in terms of a PCA was applied to identify the most relevant input parameters: age, R, AL, CCT, ACD and LT were included in the prediction models as input parameters (or effective predictive parameters), whereas the sex, PD, CD, CWX and CWY were identified as parameters, which did not significantly improve the model performance.

In the second step of testing, the performance of prediction models using a selection of neural network strategies we determined that the family of regression networks yielded a RMSE in a range between 0.32123 mm (linear regression with interactions between parameters) and 0.32801 mm (robust linear regression). With the family of regression trees, the RMSE ranged between 0.33442 mm (coarse tree) and 0.34588 mm (fine tree). With the family of support vector machines, we obtained a RMSE in the range of 0.28052 mm(SVM with a quadratic
Table 1. Explorative data of the input parameters and the target parameter for our prediction model in terms of mean value, standard deviation, median and 90% confidence interval.

| N = 1345 | Age in years | R in mm | ACD in mm | LT in mm | CCT in mm | CD in mm | PD in mm | CWX in mm | CWXcor in mm | CWY in mm | LEQ in mm |
|----------|--------------|---------|-----------|----------|-----------|---------|---------|-----------|-------------|-----------|-----------|
| Mean     | 70.63        | 7.73    | 3.13      | 4.63     | 0.56      | 12.00   | 4.15    | −0.03     | −0.26       | −0.11     | 5.14      |
| Standard deviation | 9.72        | 0.28    | 0.42      | 0.46     | 0.04      | 0.42    | 1.23    | 0.34       | 0.22        | 0.20      | 0.43      |
| Median   | 72.22        | 7.71    | 3.17      | 4.61     | 0.56      | 11.99   | 3.90    | −0.03     | −0.26       | −0.11     | 5.12      |
| 5% quantile | 52.57        | 7.30    | 2.42      | 3.88     | 0.50      | 11.36   | 2.54    | −0.55     | −0.60       | −0.39     | 4.46      |
| 95% quantile | 83.85        | 8.23    | 3.77      | 5.41     | 0.62      | 12.68   | 6.81    | 0.50       | 0.04        | 0.16      | 5.86      |

Age refers to the patient age at the timepoint of the biometric measurement before cataract surgery, R to the average corneal curvature (mean value of left eyes, and LEQ to the axial position of the equator plane of the intraocular lens considered as half the distance between the anterior and posterior apex of the intraocular lens.

Table 2. Descriptive performance data of the 2 neural network approaches with the least root mean squared prediction error out of the selection of algorithms under test. All data were derived with a 5-fold cross-validation strategy to avoid overfitting.

| N = 1345 | GPR with exponential kernel | SVM with quadratic kernel | Multilinear regression model |
|----------|----------------------------|--------------------------|----------------------------|
| Mean prediction error ME in mm | 0.0072 | −0.0260 | −0.0001 |
| SD of prediction error in mm | 0.2732 | 0.2794 | 0.3380 |
| Median prediction error in mm | 0.0228 | −0.0101 | −0.0358 |
| Mean absolute prediction error MAE in mm | 0.1948 | 0.1998 | 0.2415 |
| Root mean squared prediction error RMSE in mm | 0.2731 | 0.2805 | 0.3379 |
| 95% quantile of absolute prediction error in mm | 0.5390 | 0.5698 | 0.6900 |
| 99.5% quantile of absolute prediction error in mm | 0.9675 | 0.9524 | 1.1496 |

GPR = Gaussian process regression neural network; SD = standard deviation; SVM = support vector machine.

For the multilinear regression model, we used a robust ECM algorithm.

Discussion

The prediction of the axial IOL position with preoperative biometric data is one of the largest challenges in intraocular lens power calculation (Norrby & Koranyi 1997; Melles et al. 2019). Many competing concepts for estimating the lens position have been proposed. The simplest versions are based on K readings derived from corneal front surface curvature and axial length, or on several other parameters such as phakic anterior chamber depth, lens thickness, horizontal corneal diameter or patient age. However, we also have to take into consideration that most of the lens power calculation concepts involve estimation of an ELP, which does not match the anatomical position of the IOL in the
eye (Olsen & Hoffmann 2014; Scholtz et al. 2021). The ELP is back-calculated from the preoperative biometric data, the power of the inserted lens and the postoperative refraction, and typically covers all systematic errors of biometry, lens power-labelling errors or errors in refractometry (e.g. offset errors due to the measurement lane distance). Some modern formulae such as the Olsen (Olsen 2007) or the Castrop formula (Langenbucher et al. 2021) made a paradigm change in considering the ‘true’ axial lens position, either as the front apex plane or the equator plane of the lens, instead of the ELP. However, even with this ‘anatomical lens position’ (ALP), we cannot solve all problems in IOL power calculation as, while according to ISO 11979 standards, the equivalent power is labelled on the lens, the respective image-sided principal plane is still unknown because the shape of the lens is not provided by the IOL manufacturer. However, using a reliable concept for ALP (Norrby 2004) prediction, valid for all lens types and considering the lens optics and haptics characteristics such as the refractive index, the haptics shape and angulation, (and the shape factor step vault of the lens design) with a constant or individual offset to the ALP, might be a significant step towards better prediction of the refractive outcome.

Fig. 1. Performance plot of the 2 neural network approaches with the lowest root mean squared prediction error on our data set (Gaussian prediction regression (GPR) with an exponential kernel, upper graph; Support Vector Machine (SVM) algorithm with a quadratic kernel, middle graph) and the respective performance plot for the multilinear regression model (lower graph, also with 5-fold cross-validation) together with the red diagonal line indicating data where the predicted LEQ matches the LEQ derived from measured ACD and LT after surgery. Both neural network approaches show a trend, which is slightly flatter compared with the red line. This implies that large LEQ values are slightly underestimated and small LEQ values are slightly overestimated. In contrast, the multilinear regression shows a significantly flatter trend with a underestimation/overestimation of large/small LEQ values and a larger scatter compared with the neural network approaches.
(Olsen 2006; Xin et al. 2020). As the design data of IOLs on the market are currently unavailable, we decided to use a simple estimate for the IOL equator plane, defining this as half the distance between the lens front and back apex. This definition might be refined if data on the lens shape become available in the future.

The simplest way of predicting the ALP is based on a multilinear modelling, provided a data set with preoperative biometric data and the postoperative measurement of the axial lens position is available. In this case, the ALP is derived from a sum of intercept and weighted input parameters. Modern optical biometers are capable of measuring all the distances in the eye, not only for the phakic eye prior to cataract surgery, but also in the pseudophakic eye after cataract surgery (Cheng et al. 2020). If we have derived the IOL position—either the IOL front apex or an estimate for the lens equator as in this study—the relevant predictive parameters to keep the model simple and to avoid overfitting must be identified (Bechtel 2008; Welsch et al. 2018). In the present study, the predictive parameters were analysed using a feature selection strategy based on a principal component analysis. Alternatively, a stepwise iterative fit strategy was used, initialized as a constant model adding and subsequently removing potential parameters in a stepwise fashion to refine the model while explaining as much variance in the data set as possible. Subsequently, a multilinear model is set up with the relevant predictive parameters, either in a simple version by minimizing the root mean squared prediction error or in a more sophisticated version with some robustness constraints as was performed here with the ECM algorithm (Meng et al. 1993; Sexton & Swensen 2000).

In the last decade, traditional techniques such as (multi-)linear models have increasingly competed with modern machine learning strategies, as they can easily adapt to nonlinear behaviour of the target parameter with respect to the input parameters, whereas linear regression models mostly fail (Clarke & Burmeister 1997; Sramka et al. 2019; Carmona González & Palomino Bautista 2021; Langenbacher et al. 2020; Xia et al. 2020). The most complex aspect of implementing such deep learning techniques is in identifying the most reliable prediction algorithm from a large number of available algorithms. It is also necessary to avoid overfitting, which may result either from considering too many input parameters or from evaluating the performance of the algorithm using the same data set, which was used for training. In the present study, to avoid overfitting, we performed our PCA to extract the relevant input parameters and then implemented a cross-validation procedure involving a strict separation of training and test data during the validation process. To make cross-validation efficient, a 5-fold cross-validation was used. In this strategy, the data set is split into 5 partitions, and one partition excluded during training, to be used for testing later on. This procedure is repeated until all partitions have been used for validation. Where very large data sets are available, simpler strategies such as holdout or random subsampling could be applied as an alternative to cross-validation. The effect of ignoring cross-validation is shown for the multilinear prediction model on the performance plot in Fig. 2.

In generating this plot, we used the same multilinear fit algorithm with iterative ECM as was used to generate the lowest graph in Fig. 1, but without splitting the data into partitions for training and validation. The respective prediction errors if all \( N = 1345 \) measurements are used for training and validation yields: mean prediction error \( 0.0000 \) mm, standard deviation \( 0.3158 \) mm, median prediction error \( −0.0355 \) mm, mean absolute prediction error \( 0.2258 \) mm, root mean squared prediction error of \( 0.3157 \) and the upper limits of the 90% and 99% confidence intervals of the absolute prediction error \( 0.6437 \) and \( 1.0824 \) mm.

In the present study, we evaluated several versions of regression networks,

![Fig. 2. Performance plot of the multilinear regression model without cross-validation. The entire data set of \( N = 1345 \) measurements was used both for training and validation. The performance of the model is significantly better compared to the respective performance with 5-fold cross-validation (compare Fig. 1 lowest graph) indicated by a lower scatter of the data. The red line indicates data where the predicted LEQ matches the LEQ derived from measured ACD and LT after surgery.](image)
regression trees, Support Vector Machines and Gaussian process regression networks, as they are very popular (Welsch et al. 2018). The root mean squared prediction error was used as a target criterion for evaluating the performance of the algorithm and for ranking. Ultimately, we identified the Gaussian process regression network with an exponential kernel and the Support Vector Machine network with a quadratic kernel as the algorithms with the best performance. However, such a selection cannot be generalized to other applications as it mostly depends on the data set and on the performance criterion. The GPR algorithm outperformed the multilinear regression by around 19% (MAE) to 20% (RMSE). This does not, however, mean that the prediction error of lens power calculation could be reduced by the same amount, as the estimation of the axial IOL position is only one (albeit very important) determinant for predicting the refractive outcome after cataract surgery (Olsen 2006). Nevertheless, we feel that for IOL power calculation strategies, which use ALP instead of ELP, this might be a step towards better predictability of the refractive outcome. However, the advantages of such deep learning strategies for prediction of ALP have to be carefully validated with clinical studies.

In conclusion, in the present paper, we have attempted to develop and implement a strategy for predicting the position of the lens equator plane after cataract surgery derived from postoperative biometric measurements from biometric measurements before cataract surgery, which is routinely performed for lens power calculation. Modern techniques of machine learning algorithms were compared with the respective results of a traditional multilinear regression, and it seems that lens position prediction could significantly benefit from these deep learning strategies in the future.

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