A Cloud-based Infrastructure for Interactive Analysis of RNFLT Data

Thomas Peschel[1,2], Mengyu Wang[1,4], Toralf Kirsten[1,2,3,5], Franziska G Rauscher[1,2,*] and Tobias Elze[1,4]

[1]Leipzig Research Centre for Civilization Diseases (LIFE), Leipzig University, Germany
[2]Institute for Medical Informatics, Statistics, and Epidemiology, Leipzig University, Germany
[3]Institute for Medical Data Science, Leipzig University Medical Center, Germany
[4]Schepens Eye Research Institute, Harvard Medical School, Boston, MA, USA
[5]Applied Computer Science and Biosciences, University of Applied Sciences Mittweida, Mittweida, Germany
[*]Corresponding author: Franziska G. Rauscher, franziska.rauscher@medizin.uni-leipzig.de

Good functional vision until old age benefits from early detection of eye diseases. Investigation of retinal structure enables monitoring of eye health. To detect early changes potentially leading to optic neuropathies, such as Glaucoma, retinal nerve fiber layer thickness (RNFLT) is measured with optical coherence tomography (OCT) as an early marker. Different manufacturers provide OCT devices, most implement a 'normative database' allowing to interpret RNFLT immediately after the measurement by the ophthalmologist.

However, vendor-specific normative data is often neither published nor publicly available. Moreover, most OCT devices provide vendor-specific software for measurement and basic analysis but do not allow to extend or exchange normative data. We address both aspects by a) reusing already created published normative data and b) by designing and providing the RNFLT(D)-Visualizer. The published normative data for RNFLT rely on investigations in a large population-based sample taken from the LIFE Adult study at the Leipzig Research Centre for Civilization Diseases. These normative data represent a reference population, with nearly balanced subsets along dimensions such as age, sex and ocular laterality, against which the RNFLT measurement is compared to detect retinal changes.

The RNFLT(D)-Visualizer is part of the Leipzig Health Atlas (LHA), a larger cloud-based infrastructure. The LHA is a platform providing publication data, novel phenotypes, algorithms, and - as in our case - applications for novel normative data. The RNFLT(D)-Visualizer aims to compare individual patient RNFLT data and their differences to our normative database. In this way, the RNFLT-(D)-Visualizer takes the OCT device read-out as input and visualizes the patient measurement regarding both the vendor-specific normative data and those that are already published by us. Most importantly, the comparison of individual measurements to our normative data allows evaluation with age and sex, as well as specific to eye laterality. Additionally, we en-

Publiziert in: Vincent Heuveline, Nina Bisheh (Hg.): E-Science-Tage 2021.
Share Your Research Data. Heidelberg: heiBOOKS, 2022.
DOI: https://doi.org/10.11588/heibooks.979.c13718

able longitudinal data visualization by taking reports from multiple measurements (at different time points) showing the ongoing retinal changes. Moreover, this application is designed to add new RNFLT normative data as they are published and made available in future. The RNFLT(D)-Visualizer is designed as R Shiny application. The application never saves any data that has been imported. Instead it visualizes and allows download of the plotted information. The RNFLT(D)-Visualizer is accessible via an internet browser with no access restriction. It is freely usable for research purposes but presently not yet approved for clinical applications.

1 Introduction

For many diseases of the eye, early diagnosis and accurate monitoring over time is essential to initiate or adjust treatment to prevent the onset or progression of vision loss. Optical coherence tomography (OCT) is a three-dimensional imaging technology frequently applied to visualize the retina for this purpose. Particularly for the diagnosis of optic neuropathies like glaucoma, one of the leading causes of blindness in the developed world, OCT is used to determine retinal nerve fiber layer thickness (RNFLT), as the thinning of the nerve fiber layer indicates disease onset or progression. To determine if RNFLT is abnormally thin, the normal range of RNFLT needs to be appropriately determined and available at the time of the clinical assessment of the eye. For this purpose, OCT manufacturers provide their machines with custom normative databases to highlight those retinal locations which present as abnormally thin during an ophthalmic measurement.

The manufacturer RNFLT databases, however, are typically based on only a few hundred healthy subjects over a large age range (usually between around 20 to 80 years) and only consider age as a normative parameter, which might be insufficient to represent the natural variation in healthy eyes, which may result in false positive or false negative abnormality marks. By analyzing large datasets of clinical OCT measurements, we could previously show, for example, that individual anatomical characteristics associated with myopia were associated with machine induced abnormality patterns related to overdiagnosis or missing of glaucoma [1, 2].

The availability of more personalized RNFLT norms would therefore improve the clinical diagnosis of eye diseases, which requires OCT measurements of larger populations of healthy individuals. The population-based Leipzig Research Centre for Civilization Diseases – LIFE Adult study [3] acquired retinal OCT scans of about 10,000 randomly chosen, age and sex stratified participants from the medium-sized city of Leipzig, Germany. We previously used this large dataset to investigate additional parameters to explain RNFLT variance and to generate novel norms based not only on age but also ocular magnification [4], sex [5], or ocular laterality [6].

While our novel normative data are publicly available and accessible to researchers, practicing clinicians might be challenged by the effort to work with raw data from repositories and would typically still rely on machine generated printouts based on the insufficient device manufacturer norms. The usability of our new norms would be strongly facilitated by an interface that accepts existing machine printouts as an input and generates a graphical representation very similar to the original printout but replaces the machine norms with our new normative data.

Here, we provide such an application as part of a larger cloud-based infrastructure, the so-called Leipzig Health Atlas (LHA), `https://www.health-atlas.de`. The LHA is a platform that provides the publication and visualization of raw data, novel phenotypes, algorithms, or - as in our case - novel normative data to provide more personalized abnormality marks for clinical retinal OCT scans.

The LHA provides an environment for our app, termed RNFLT(D)-Visualizer, that makes the aformentioned normative data accessible to clinicians and scientists. The application is specifically aimed at making the new norms available for individual comparison of measurement data. In the following, we describe the input data that clinicians can incorporate into the RNFLT(D)-Visualizer. Furthermore, we detail the cloud environment for running this application.

2 Materials and methods

Investigation of retinal structure enables monitoring of eye health. To detect early changes potentially leading to optic neuropathies, such as Glaucoma, retinal nerve fibre layer thickness is measured with optical coherence tomography (OCT) as an early marker. Different manufacturers provide OCT devices, these implement a normative database allowing to interpret RNFLT immediately after the measurement by the ophthalmologist. The delivered normative data should rely on a large cohort, ideally a population-based sample. Therefore, we have created new normative data for RNFLT based on investigations in the large population-based Leipzig Research Centre for Civilization Diseases - LIFE Adult study [4], [5], [6]. Our normative data establishes a reference population, with nearly balanced subsets along dimensions such as age, sex and ocular laterality, against which the RNFLT measurement is compared to detect retinal changes.

2.1 Input data

Acquired raw data is typically measured for 768 equally distant points arranged in a circle around the optic nerve head. OCT devices provide a read-out of such data in a proprietary report customized for each patient that can be exported into a PDF file. The benefit of the app is the provision and further processing of measurements of retinal nerve fiber layer thickness routinely determined with an OCT device and available in digital form as a PDF document. The patient data prepared in such documents enable the eye specialist to identify early signs of disease via the graphic presentations, which are provided in front of a background of manufacturer-specific normative data.

Further processing of such patient data, such as comparison with other normative reference values, is thus not possible. This problem is solved by the RNFLT(D)-Visualizer.

The RNFLT(D)-Visualizer can directly import such PDF files of a specific patient, extract the measured data from diagrams included in the PDF file and visualizes measurements in comparison to normative data.

There are different sources for normative data. First, OCT device manufacturers typically provide such data with the read-out PDF file. Our application extracts this kind of information for visualizations. Secondly, we employ normative data that has been created based on the large population-based LIFE Adult study. For the RNFLT(D)-Visualizer, we refer to the Wang and Elze et al. normative data [4] and their inter-ocular differences [6], sex-specific differences can also be accounted for, this will be implemented into the app in due course [5]. Therefore, the RNFLT(D)-Visualizer can provide individual comparison to different normative data, taking into account refractive error (i.e. measurement diameter) and allowing evaluation with age and sex, specific for eye laterality.

2.2 Leipzig Health Atlas

The RNFLT(D)-Visualizer is part of the Leipzig Health Atlas which provides publications, corresponding data, (e.g. supplements), and methods. Such entities can be uploaded by registered scientists. The LHA structure contains projects, where publications and applications and their meta-data are linked to each other. Apps such as the RNFLT(D)-Visualizer are accessed via an URL that is managed and provided by the LHA. These apps, as well as associated data and documents, can also be found through a search on the LHA website `https://www.health-atlas.de` if the user only has topic keywords. The RNFLT(D)-Visualizer can be accessed via `https://apps.health-atlas.de/rnflt-visualizer`. Typically, applications are free to use, only a few are restricted to a prespecified user group. Due to medical device regulations applications are aimed for research purposes. For clinical settings we provide a disclaimer at the moment.

The LHA environment with all linked applications is managed by a cloud-based Kubernetes infrastructure which is physically hosted by Leipzig University computing centre. This infrastructure requires to package each new application using up-to-date containerization technology, such as Docker. We use the University GitLab system to manage the application source code from which a Docker image is automatically created and shipped to the Kubernetes infrastructure (continuous deployment) whenever changes to the source code arrive. This speeds up the process bringing the latest development to the public. Moreover, the app is provided by a R Shiny server that allows to scale up / down when new requirements, e.g., a higher number of concurrent users, arise.Additionally, the app's environment in the Docker container can be customized to meet other requirements such as the R version or package dependencies.

2.3 RNFLT(D)-Visualizer application

The RNFLT(D)-Visualizer is developed as a R Shiny app. Shiny `https://shiny.rstudio.com` is a R package enabling quick and easy web application development in R for visualizing statistical data.

A R Shiny web application is made available via a Shiny server and, thus, allows multiple clients to use the app in parallel. A modern responsive design was realized by the package bs4Dash [7] through its bootstrap functionality. Moreover, the R packages ShinyWidgets [8] and ShinyJS [9] are used to improve the visual impact. All plots are made with the Plotly-Package [10]. The R-package used for statistical computations is GAMLSS [11]

The RNFLT(D)-Visualizer is structured in sections e.g. 'Import Data' section or 'Analysis' section, accessible on the left panel, see Figure 1.

3 Results

In the following, we describe and discuss different steps along the analysis workflow of a typical usage of the RNFLT(D)-Visualizer.

3.1 User specific data import

A document is uploaded by the user and stored only for the period of the session. For demonstration purposes, we also provide some sample files which can be directly used to feed the application. After uploading a PDF file, the RNFLT(D)-Visualizer provides an overview in tabular form, see Figure 1. This table provides information of the measurement data, the patient's age, the eye side, and the available norms the data can be analyzed with. Moreover, some analyses require further data, for instance, the diameter of the RNFLT measurement ring and Bruch's Membrane Opening (bmo). The user can add and modify this data directly in this table. The position of graphics in the PDF file is arbitrary. This is caused by the OCT device software, since there are a number of different document types depending on the measurement and the type of generated print-out. In a first step, the app extracts meta-data about the examination, (red framed box in Figure 1), such as specified patient birth date, date of measurement, eye side, and sex. This information extraction is realized by the help of the R package 'pdftools' [12]. It extracts the complete text of the PDF document and provides it as a single string. Finding and extracting relevant data is easily implemented by using regular expressions.

After uploading patient data into the application in the Import Data Section, the user can edit missing meta data, as illustrated in Figure 1. These meta data are measurement diameter, specific eye (ocular laterality), sex, age, and the Bruch's Membrane Opening (for further invesigations). After checking that all necessary data were correctly uploaded or entered, the user stores the PDF with its (amended) meta data in the Data Store

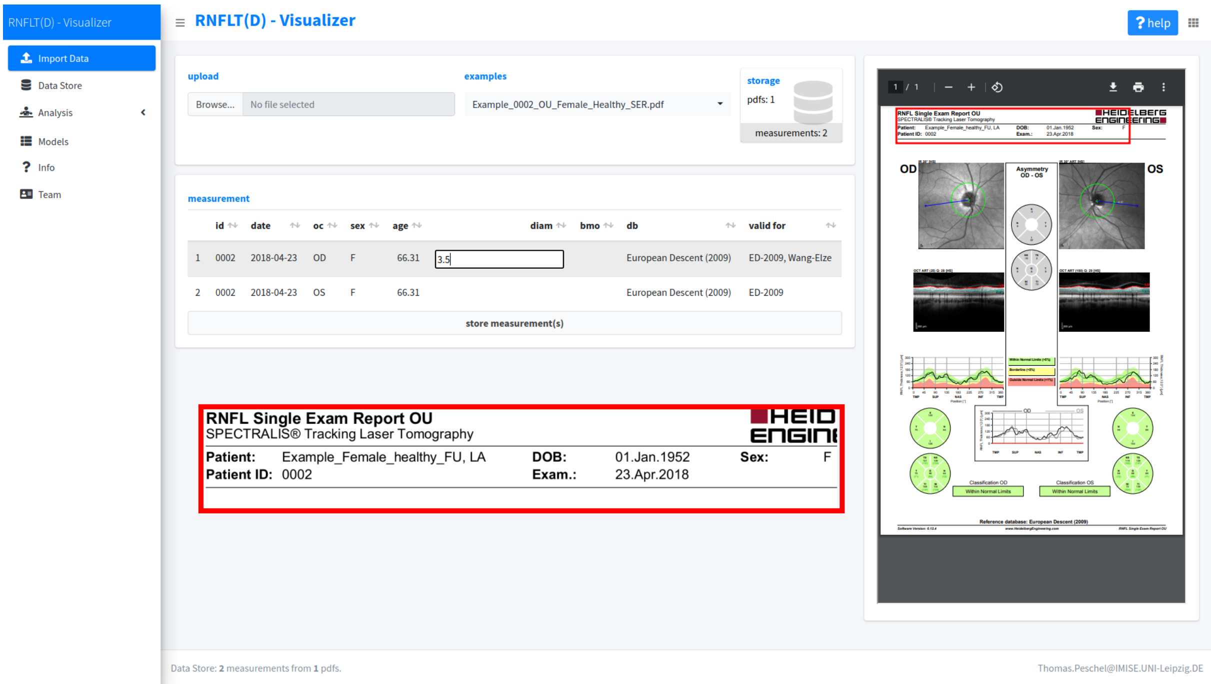


Figure 1: RNFLT(D)-Visualizer during data import. This scene shows the app directly after an upload of an OCT PDF. As shown, the user here adds the measurement diameter value in the presented table. After a click on the button 'store measurement(s)', the data will be scanned and stored with the meta data. The red frame in the middle is only used to highlight this zoom of the PDF's header to show how meta data are extracted from the document's header and copied to the table.

Section by pressing the button 'store measurement(s)'. Now the application extracts the measurement data by searching and scanning the graphs inside the document. That is why it also works for unusual formats, e.g. PDF with notes footer.

Next, measurements are extracted. Both, the patient-specific measurements and the related normative data, are include graphically in the PDF file in plots. And also some meta-data are placed in the header and additionally in the footer sometimes. Therefore and depending on the document type, the positions of graphics need to be determined in a second step before data values can be read out. In order to detect the graphics' positions, the PDF file is rendered at a low resolution of 72 DPI. This allows a approximate detection of position of the plots.

In step three, the imported PDF document is then rendered at a resolution of 312 DPI and the measurement data and background percentile data are scanned and internally managed in a tabular form (R data type Data Frame). In case the user missed to properly edit meta data, further information can be added in the Data Store Section. So it is possible to upload data in an unusual format. For example, a PDF with missing header can be analyzed. Additional information with relevance to norms, e.g. age and sex, can be manually entered into the application table of meta data.

Having tabular measurement data available, it can either be downloaded for the user's own investigations or subsequently analyzed with this app, in particular, the RNFLT-related analyses and inter-ocular RNFLT differences. The app allows to upload multiple PDF files for the same or different patients. All data is managed within the app but only saved temporarily while the session runs. The user can select the data set in the 'Analysis' section by selecting the file name and the meta-data of the specific measurement.

The imported data sets can be analyzed in two different ways, the retinal nerve fiber layer thickness and inter-ocular retinal nerve fiber layer thickness differences. We describe both in the next two subsections.

3.2 Retinal nerve fiber layer thickness analysis

The retinal nerve fiber layer thickness analysis is comparable to that already available on the OCT device but the app supplies improved analysis methods. In particular, the app provides multiple normative reference values (e.g. Wang and Elze et al. norm) allowing to compare patient measurements with OCT device built-in normative data (e.g. 'European-Descent-2009'). The app is constructed to enable implementation of future normative data if and when they become available to extend the opportunities of analysis.

For all visualizations, the user can select the normative data-set for analysis. Values of European-Descent-2009 norm do not factor in age, sex and measurement diameter. In contrast, the normative data by Wang and Elze et al. specifically take these two variables into account. As an extension, sex will be included as a further factor.

Based on imported patient measurements, the app provides different visualizations, each of them is available by tabs on the top. Figure 2 shows four different visualizations as a montage. The top two graphs represent visualizations of the sector analysis and the lower two graphs represent the continuous analysis (768 individual equally distributed measuring points of the 360° ring scan). Both use normative reference values, selectable by radio buttons in the menu seen on the top of the montage, as comparative data. Second and fourth graph are the z-standardized representation of first and third graph. Each visualization consists of two parts, a polar plot on the left and a colored line chart on the right, representing the same data.

The polar plot shows data taken from 768 measuring points on a circle around the optic nerve head of the human eye together with the selected normative data. In the sector analyses, the 360° ring scans are divided into sectors of either 45° or 90° as common for such RNFLT data analysis in Ophthalmology. Parameters are averaged in each sector. Such sectors are employed to analyse directions of retinal nerve fiber layer entering the optic nerve of the human eye.

In the RNFLT analysis, the measurement is seen against a percentile background corresponding to the selected reference standard data (European-Descent-2009 or Elze-Wang). In the z-space analysis, the measurement is shown as a standard deviation score or z-score against a z-space background. Unlike the percentile plot, which is essentially the same as the plot from the PDF document, the z-score plot provides easier access to what is happening. The polar plots are generally more intuitive. To account for eye side, direction of the plots can be selected by the check boxes 'direction'.

The black line in all plots represents the patient measurement whereas the dark green line depicts the 50% percentile, and the green (yellow, red) colored area symbolizes the 95% (5%, 1%) percentiles as taken from normative data. Since the normative data by Wang and Elze et al. account for confounding variables described above, the diameter and the age must be given at import time. In general, age is implicitly given as part of the uploaded PDF document by dates of birth and measurement or can be added afterwards.

3.3 Inter-ocular retinal nerve fiber layer thickness differences

Similar to the RNFLT analysis, for the inter-ocular retinal nerve fiber layer thickness difference analysis we provide four visualizations combining sector and continuous analyses with normative percentiles and z-scores. The sector analysis utilizes a parameter-free Box-Cox-T model over age and the measurement diameter for the absolute magnitude of the nerve fiber layer thickness differences. The Box-Cox-T model models the first four moments (i.e., mean μ, standard deviation σ, skewness ν, and kurtosis τ) of the distribution of absolute thickness values. Conversely, continuous analysis assumes a normal distribution of thickness differences.

3.4 Patient-specific analysis result

Besides the shown visual representation, the RNFLT(D)- Visualizer provides all data in tabular format (see Fig 4) for all analyses. The user can freely access this data and download it in different formats, e.g. xslx, csv, tsv and RData format. All plots can be downloaded in png-format via press on the camera icon inside the plot as seen in the lower graph in Figure 2.

3.5 Patient-specific normative data

Additional to the visual representation described in the last two sub-sections, the RNFLT(D)-Visualizer provides Elze-Wang normative data for both, RNFL thickness and inter-ocular RNFLT differences. The normative data for RNFLT are represented by the parameters μ, standard deviation σ of a normal distribution in the sectors and as well as in the continuum analysis. The sectors of the RNFLTD analysis are described with the Box-Cox-T model with the parameters mean μ, standard deviation σ, skewness ν, and kurtosis τ, and the continuum analysis of RNFLTD is also modelled by a normal distribution.

These parameters are dependent on age, measuring diameter, and measuring diameter differences respectively, which one can choose in the menu of the 'Models' section. All

Figure 2: Montage of the 4 provided RNFLT-Visualization. All pictures show the patient's data against percentiles background (1%, 5% and 95%) related to the selected normative data. The sector analyses use norms averaged on the sectors. The continuum analyses use normative data for each of the 768 measure points. The graphs in the pictures 1 and 3 are plotted in real space where the graphs 2 and 4 are plotted in z-space. In the left column we have polar plots and in the right one filled line charts. The visualizations can be selected by tabs on the top. RNFLT is evaluated in six sectors (T: temporal, TS: temporal-superior, TI: temporal-inferior, N: nasal, NS: nasal-superior, NI: nasal-inferior) and overall average (G; used in table only).

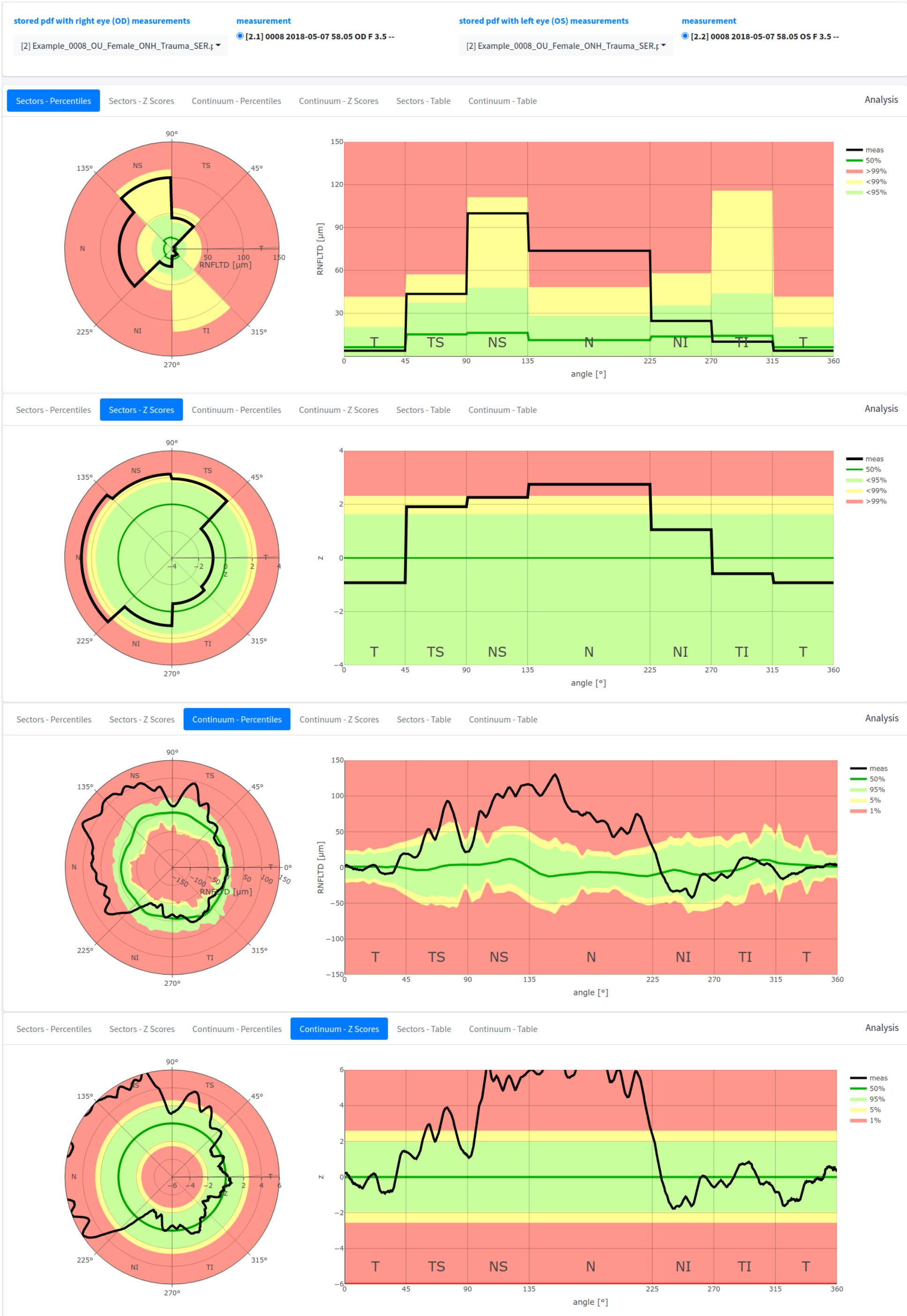
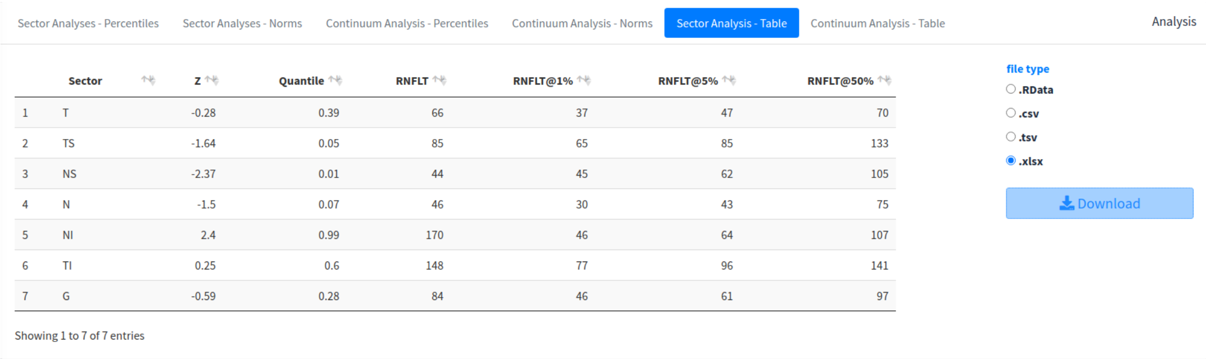


Figure 3: Montage of the four provided RNFLTD presentations. All graphs show the patient's data against percentiles background (1%, 5% and 95%) related to the selected normative data. The sector analyses use Elze-Wang Box-Cox-T normative data computed for each sector. The continuum analysis employs normative data for the difference of each of the 768 measuring points of both eyes. The first and third graphs are plotted in real space whereas the second and fourth graphs are plotted in z-space. Similar to the RNFLT plots, the left column depicts polar plots and the right column depicts filled line charts.



	Sector	z	Quantile	RNFLT	RNFLT@1%	RNFLT@5%	RNFLT@50%
1	T	-0.28	0.39	66	37	47	70
2	TS	-1.64	0.05	85	65	85	133
3	NS	-2.37	0.01	44	45	62	105
4	N	-1.5	0.07	46	30	43	75
5	NI	2.4	0.99	170	46	64	107
6	TI	0.25	0.6	148	77	96	141
7	G	-0.59	0.28	84	46	61	97

Figure 4: Table of data for a RNFLTD sector analysis ready for download. The columns are sector id, z-score and quantile of the patient's measurement followed by the thickness difference values related to Elze-Wang normative data that includes 1%, 5% and 50% of measurements assuming a Box-Cox-T-Distribution.

plots and their related tables are therefore interactive. For the thickness we also provide a plot that shows the differences between the models of Elze-Wang and the European-Descent-2009. This can be found in the section 'Models', see Figure 5.

The parameters of normative data are visualized either as bar charts for sectors or in a line chart for continuum analysis. All graphics and tabular data can be downloaded (see Fig. 5) by the user for own examinations and further analysis purposes.

3.6 Help

We include a context specific help button for every section of the app. This is a specific help window as seen in Figure 6. It can be accessed by pressing the help button in the top right corner of the app as seen in Figure 6.

4 Conclusions

Our app employs the latest technique using R Shiny app and Docker/Kubernetes with continuous integration via Gitlab. This set of software offer a solution for fast and easy web application development and role out. This has lead to a very user friendly graphical user interface with direct access to new reference values for eye specialists. The RN-FLT(D)-Visualizer app offers the latest normative data, which is not accessible directly otherwise.

For the first time the app offers new opportunities for retinal nerve fiber layer analysis. Furthermore, the eye specialist or scientist can directly and easily apply the new normative data to analyse own patient measurements on the basis of the latest normative reference values.

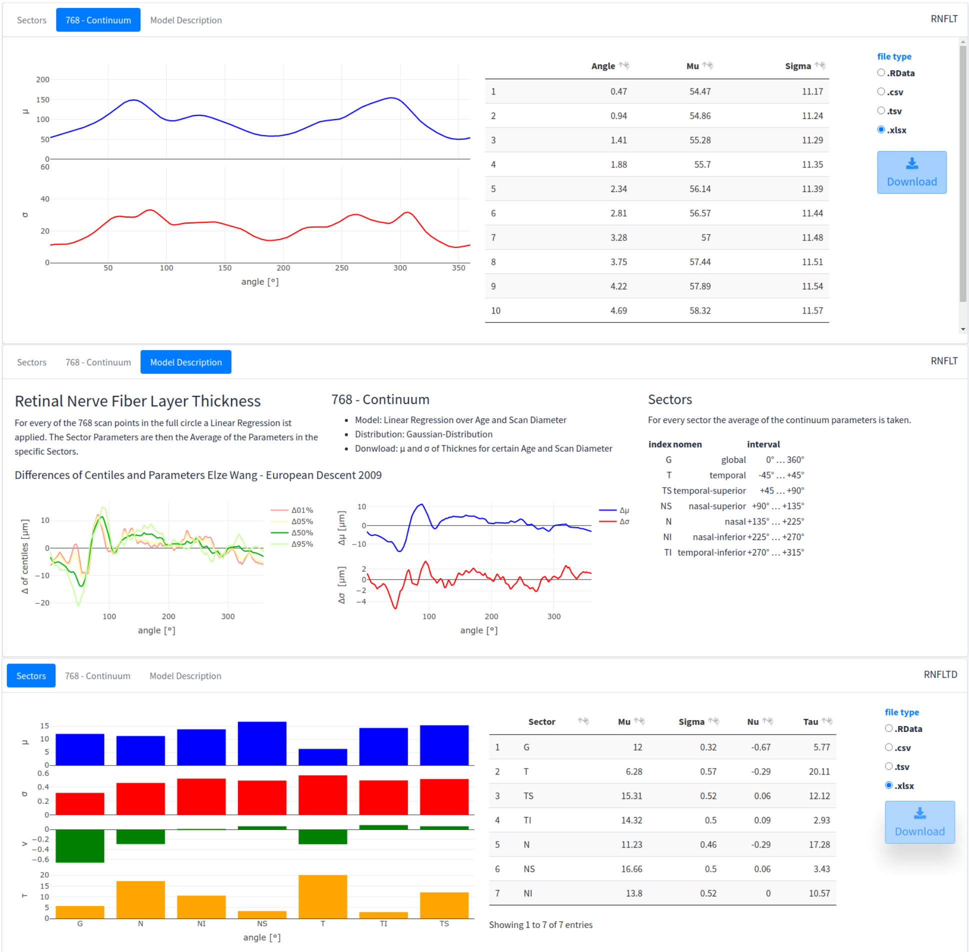


Figure 5: Montage of screenshots of the 'Models' section. The two upper graphs show the RNFLT model and the lower graph presents the Box-Cox-T model for the magnitude of thickness differences in the specific sectors.

This enables new ways of detection of early changes of the retinal nerve fiber layer thickness and thickness differences.

5 Outlook

In future, the app will implement our current work on sex [5] and ocular laterality [6], taking into account these influencing factors to enable finer differentiation of early signs of disease. Furthermore, reports will be offered for download in PDF and HTML format. Additionally, we will enable longitudinal data visualization by taking reports from multiple measurements (at different time points) showing the ongoing retinal changes.

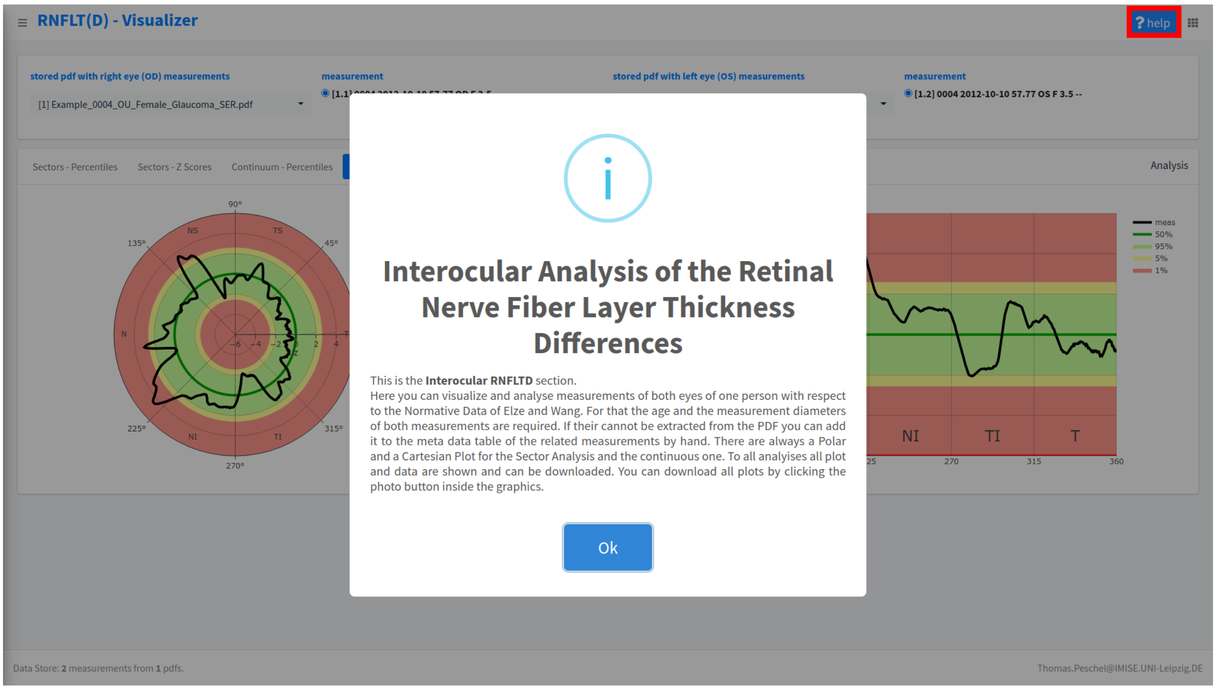


Figure 6: Example of help window for 'inter-ocular RNFLTD' section. In this context the help button highlights the necessary steps for the user.

Acknowledgements

The authors wish to thank the LIFE Adult study participants for their time and furthermore we gratefully acknowledge the LIFE Adult study team for their commitment to the eye investigation and corresponding exams to make this analysis possible.

Funding

This research was supported by LIFE Leipzig Research Center for Civilization Diseases, Leipzig University (LIFE is funded by the EU, the European Social Fund, the European Regional Development Fund, and Free State Saxony's excellence initiative; project numbers: 713-241202, 14505/2470, 14575/2470); Lions Foundation; Grimshaw-Gudewicz Foundation; Research to Prevent Blindness; BrightFocus Foundation; Alice Adler Fellowship; NIH K99EY028631 to MW; NEI Core Grant P30EYE003790; NIH R21 EY030142; R21EY030631; R01EY030575; German Federal Ministry of Education and Research i:DSem - Integrative data semantics in systems medicine (031L0026).

The sponsor or funding organization had no role in the design or conduct of this research.

Bibliography

[1] Tobias Elze, Neda Baniasadi, Qingying Jin, Hui Wang, and Mengyu Wang. Ametropia, retinal anatomy, and OCT abnormality patterns in glaucoma. 1. impacts of refractive error and interartery angle. *Journal of Biomedical Optics*, 22(12):121713, 2017.

[2] Neda Baniasadi, Mengyu Wang, Hui Wang, Qingying Jin, and Tobias Elze. Ametropia, retinal anatomy, and OCT abnormality patterns in glaucoma. 2. impacts of optic nerve head parameters. *Journal of Biomedical Optics*, 22(12):121714, 2017.

[3] Markus Loeffler, Christoph Engel, Peter Ahnert, Dorothee Alfermann, Katrin Arelin, Ronny Baber, Frank Beutner, Hans Binder, Elmar Braehler, Ralph Burkhardt, Uta Ceglarek, Cornelia Enzenbach, Michael Fuchs, Heide Glaesmer, Friederike Girlich, Andreas Hagendorff, Madlen Haentzsch, Ulrich Hegerl, Sylvia Henger, Tilman Hensch, Andreas Hinz, Volker Holzendorf, Daniela Husser, Anette Kersting, Alexander Kiel, Toralf Kirsten, Juergen Kratzsch, Knut Krohn, Tobias Luck, Susanne Melzer, Jeffrey Netto, Matthias Nuechter, Matthias Raschpichler, Franziska G. Rauscher, Steffi G. Riedel-heller, Christian Sander, Markus Scholz, Peter Schoenknecht, Matthias L. Schroeter, Jan-Christoph Simon, Ronald Speer, Julia Staeker, Robert Stein, Yve Stoebel-richter, Michael Stumvoll, Attila Tarnok, Andrej Teren, Daniel Teupser, Francisca S. Then, Anke Toenjes, Regina Treudler, Arno Villringer, Alexander Weissgerber, Peter Wiedemann, Silke Zachariae, Kerstin Wirkner, and Joachim Thiery. The LIFE-adult-study: Objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in germany. *BMC Public Health*, 15:691, 2015.

[4] Mengyu Wang, Tobias Elze, Dian Li, Neda Baniasadi, Kerstin Wirkner, Toralf Kirsten, Joachim Thiery, Markus Loeffler, Christoph Engel, and Franziska G. Rauscher. Age, ocular magnification, and circumpapillary retinal nerve fiber layer thickness. *Journal of Biomedical Optics*, 22(12):121718, 2017.

[5] Dian Li, Franziska G. Rauscher, Eun Young Choi, Mengyu Wang, Neda Baniasadi, Kerstin Wirkner, Toralf Kirsten, Joachim Thiery, Christoph Engel, Markus Loeffler, and Tobias Elze. Sex-specific differences in circumpapillary retinal nerve fiber layer thickness. *Ophthalmology*, 127(3):357–368, 2020. `doi:https://doi.org/10.1016/j.ophtha.2019.09.019`.

[6] Neda Baniasadi, Franziska G. Rauscher, Dian Li, Mengyu Wang, Eun Young Choi, Hui Wang, Thomas Peschel, Kerstin Wirkner, Toralf Kirsten, Joachim Thiery, Christoph Engel, Markus Loeffler, and Tobias Elze. Norms of interocular circumpapillary retinal nerve fiber layer thickness differences at 768 retinal locations. *Translational Vision Science & Technology*, 9(9):23, 2020. `doi:https://doi.org/10.1167/tvst.9.9.23`.

[7] David Granjon, RinteRface, Almasaeed Studio (AdminLTE3 theme for Bootstrap 4), Winston Chang (Utils functions from shinydashboard), and Thomas Park (Bootswatch Sketchy theme CSS). *bs4Dash: A 'Bootstrap 4' Version of 'shinydashboard'*, 2019. R package version 0.5.0.

[8] Victor Perrier, Fanny Meyer, David Granjon, Ian Fellows, Wil Davis, and Spencer Matthews. *shinyWidgets: Custom Inputs Widgets for Shiny*, 2021. R package version 0.6.0.

[9] Dean Attali. *shinyjs: Easily Improve the User Experience of Your Shiny Apps in Seconds*, 2020. R package version 2.0.0.

[10] Carson Sievert, Chris Parmer, Toby Hocking, Scott Chamberlain, Karthik Ram, Marianne Corvellec, Pedro Despouy, and Salim Brüggemann. *plotly: Create Interactive Web Graphics via 'plotly.js'*, 2021. R package version 4.9.4.1.

[11] Mikis Stasinopoulos and Bob Rigby. *gamlss: Generalised Additive Models for Location Scale and Shape*, 2021. R package version 5.3-4.

[12] Jeroen Ooms. *pdftools: Text Extraction, Rendering and Converting of PDF Documents*, 2021. R package version 3.0.1.