33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

# From Laboratory to Clinic: the Development of Web-based Tools for the Estimation of Retinal Diagnostic Parameters

Alfredo Ruggeri, *Senior Member, IEEE,* Enea Poletti, Diego Fiorin, Lara Tramontan

*Abstract*—**Over the years, tools for the analysis of retinal images have been developed by several research groups but their usage has been mainly confined within the developing institutions. One possibility to foster their adoption is to develop them as web-based tools. We present here three such systems we recently developed. They are specifically focused on the estimation of retinal vascular parameters, such as arteriolar narrowing (AVR parameter), vessel tortuosity, and vessel caliber narrowing and tortuosity in retinopathy of prematurity (ROP) images. These systems have been successfully evaluated as regards their reliability and will soon be publicly available to interested health care providers.**

## I. Introduction

THE analysis of retinal images can provide important information for the diagnosis and clinical evaluation of retinopathy, which is one of the main complications of severe and widespread pathologies such as hypertension and diabetes. The retina represents indeed the best example of body window, through which it is possible to visually inspect, in a easy, fast, and non-invasive way, the inner region of the human body, and in particular the micro-circulation and its possible alterations.

The availability of specific algorithms for image analysis allows the quantitative and objective evaluation of the occurrence of signs of retinopathy, even when they are barely detectable. The diagnostic parameters extracted in an automatic, objective, and reproducible way allow screening and diagnostic and therapeutic evaluations with quality unattainable by conventional visual inspection.

Over the years, several research groups have proposed automatic or semi-automatic computerized systems for the analysis of retinal images. However, despite the encouraging results obtained, very often these systems are used only within the developing institutions. In our opinion, two requirements should be met in order to foster a wider adoption of such systems. The first one is the possibility to apply manual correction to any operation performed by the system, since to date no automated system proved able to provide by itself results accurate enough for clinical application. The other one is to develop the system as a web-based tool, which can be used simply with a web browser, such as IE, Firefox or Chrome, via an internet connection.

Just along these lines, we recently developed three computerized systems for the vascular analysis of retinal images, which are described in the following. They were all designed as client-server applications: a client program, running locally on the user's computer, interacts with a remote server application allowing to choose images, setup configuration parameters, perform vascular tracing, and compute clinical indexes. Additional advantages of such systems are the possibility of exploiting multiple processors for parallel operations at server site, their availability in any operating system, and the centralized software upgrade.

Manuscript received March 24, 2011.

All authors are with the Department of Information Engineering, University of Padua, Italy (corresponding author: Alfredo Ruggeri; phone: +39 049 827 7624; fax: +39 049 827 7699; e-mail: alfredo.ruggeri@ unipd.it).

## II. The AVRnet system

### A. Description

One of the first diagnostic signs to appear in retinopathy from hypertension and diabetes is the generalized arteriolar narrowing, expressed by the arteriolar-venular ratio (AVR). This measure allows the early diagnosis of the aforementioned diseases, as well as their grading and pharmacologic treatment follow-up. It is calculated as the ratio between the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) and estimates the (equivalent) caliber of arteries against the (equivalent) caliber of veins, this latter less subject to diameter changes [1]. The Knudtson formulas to calculate AVR consider vessels in a specific circular region, centered at the optic disc, and take into account only the six largest arteries and the six largest veins [2].

The AVR parameter is not widely adopted in a clinical context, and difficulties are present also in a research context, because of the lack of a fast, precise, and accurate tool for its measurement. IVAN is the most popular software used for this purpose [3], but the time for the analysis of a single image is about 20 min and not all the operations can be manually edited. In addition, this tool was not developed for a telemedicine context.

The system we developed, AVRnet, is composed of three modules: 1) an algorithm for the vascular tracking [4,5], which detects the structure of the vascular tree; 2) an interactive editing interface (**Fig. 1**), which allows the user to set the required parameters for analysis, highlights critical situations, and, when necessary, helps in the correction process; 3) the analysis algorithm [6], which takes into account the settings entered by the user and, according to the vascular tracking information, computes the clinical parameters.

### B. Evaluation

In order to assess the reproducibility of the measures provided by AVRnet, we had three graders use the system and independently grade the retinal images of the validation dataset. This dataset comprises 30 color fundus images acquired with a commercial fundus camera at King's College

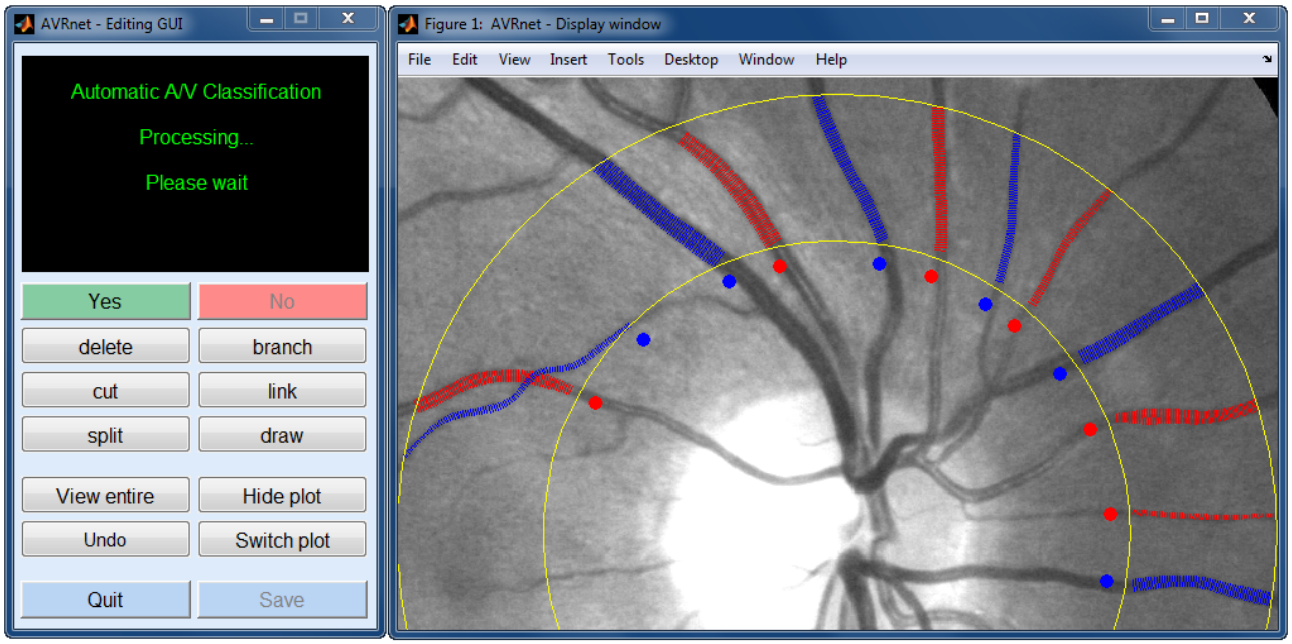


Fig. 1. AVRnet system GUI: command console (left) and intermediate results (right) with traced arteries (red) and veins (blue).

(London, UK) in normal healthy subjects, with a 50° field of view, focused centrally between the temporal margin of the optic disc and the the macula, and size 1664x1664 pixels.

The Pearson correlation coefficient was computed for each pair of graders, to provide a measure of the linear association between each grader (see Table I). All values are larger than 0.84, indicating that the three graders' assessments are coherently associated over the whole range of measured AVR values (0.49-0.91). The total time required to analyze one image was on average 3 min (range 1-5 min).

TABLE I
AVRNET EVALUATION RESULTS: PEARSON CORRELATION COEFFICIENT

| | Grader 1 | Grader 2 | Grader 3 |
|---|---|---|---|
| Grader 1 | - | 0.87 | 0.84 |
| Grader 2 | 0.87 | - | 0.86 |
| Grader 3 | 0.84 | 0.86 | - |

## III. THE TORTNET SYSTEM

### A. Description

An increase in retinal vessel tortuosity has been shown to be correlated with the severity of several diseases, such as retinopathy of prematurity [7] and hypertensive retinopathy [8]. However, no objective and quantitative grading has been adopted so far to assess vessel tortuosity in the clinical context. Even if a five level grading scale was proposed for the evaluation of tortuosity [8], grading was based only on a subjective and qualitative measure.

In order to quantitatively assess the clinical significance of tortuosity, we proposed a tortuosity measure for a single vessel, which proved to match quite well with the clinical perception of ophthalmologists [9]. We describe here the TorTnet system, that builds upon that measure, but, combining its values from all the vessels in the image, is capable to provide a tortuosity assessment for the whole image/patient. The web-system TorTnet shares many aspects with AVRnet, e.g., the automatic vessel tracking module. The interactive editing interface (**Fig. 2**), however, is designed to better assist the user in the analysis of vessels over the whole image, at variance with the AVR analysis, which is confined to an area near the optic disc. At the end of the editing step, the system provides to the user three results: 1) every single vessel is labelled with its value of tortuosity and displayed in a green-to-red color scale; 2) three charts describe tortuosity *vs.* calibers, *vs.* length, and *vs.* optic disc distance, for a better understanding of the feature distribution over the image; 3) the global tortuosity measure is reported. The latter is computed by means of a custom weight-average procedure, where the contribution of every vessel is expressed by the product of its normalized tortuosity by its caliber. An histogram analysis is then performed on these addends, to fine-tune the final measure.

### B. Evaluation

Accuracy of the complete system was assessed on two datasets: DS1 is composed of 26 images, manually classified over a range of 5 classes by retina experts from the Moorfields Eye Hospital (London, UK); DS2 is composed of 48 images, manually ordered by the same experts by increasing vessel tortuosity. The images were all acquired at Moorfields with a Topcon Retinal Camera TRC-50IX and their size is 3008*x*2000 and 1654*x*1100 pixels for DS1 and DS2, respectively.

As shown in Table II, the association between the manual and automated classification was assessed in DS1 by the Pearson correlation coefficient, while the Spearman rank

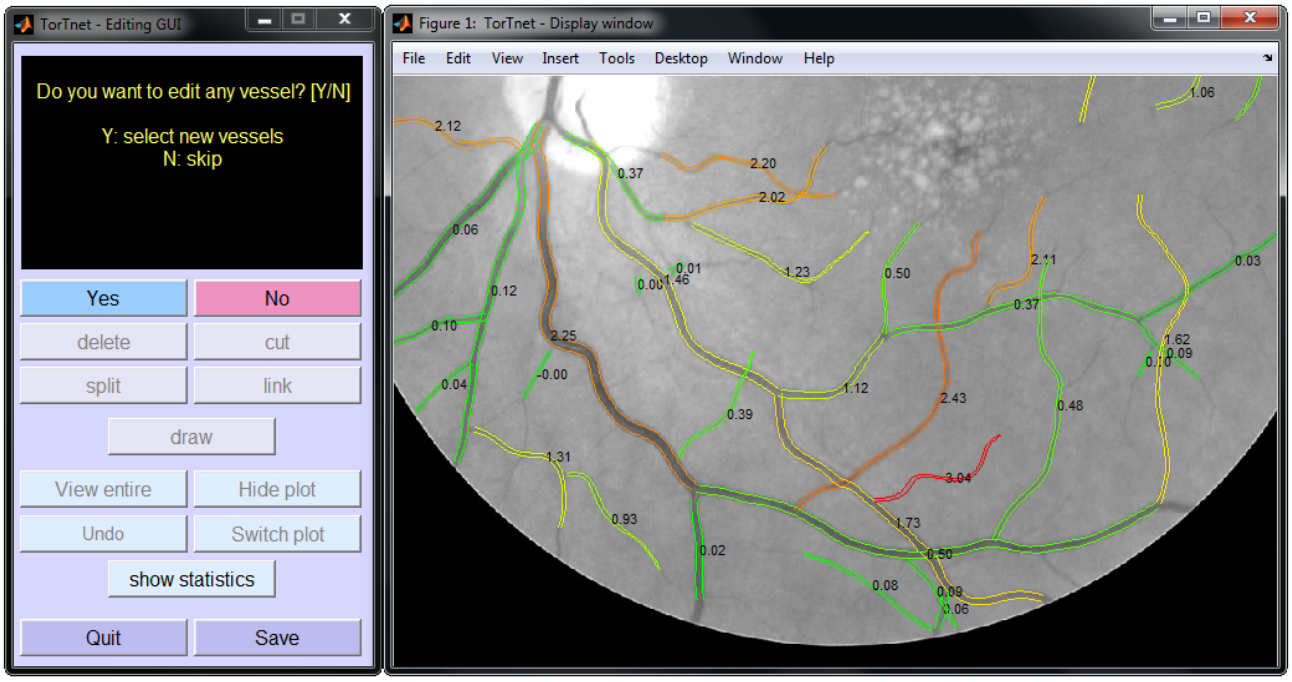


Fig. 2. TorTnet system GUI: command console (left) and intermediate results with traced vessels and their tortuosity estimates (value and color, see text).

correlation was employed in DS2. The total time required to analyze one image was on average 5 min (range 1-12 min).

TABLE II
TORTNET EVALUATION RESULTS

| | DS1 | DS2 |
|---|---|---|
| **Nr. of images** | 26 | 48 |
| **Correlation coefficient** | 0.92 (Pearson) | 0.81 (Spearman) |

## IV. THE ROPNET SYSTEM

### A. Description

Retinopathy of prematurity (ROP) results from abnormal development of retinal vasculature in premature infants, which can lead to retinal detachment and visual loss. Retinal venous dilatation and arteriolar tortuosity have been identified as indicators of ROP [10] and the regular monitoring of these parameters in the first months after birth is of paramount importance to reduce the risk in premature infants.

Several systems for computer aided diagnosis have been recently developed to measure retinal vascular geometrical and morphological properties in ROP images, such as CAIAR [11] and ROPtool [12]. Despite their potentially interesting results, all of these programs have some drawback or limitation and none is accessible through the web nor is widely used outside the developing institutions.

ROPnet, the web-based, client-server system we developed, is capable to perform vessel tracing and provide a quantitative assessment of vascular width and tortuosity in ROP images (**Fig. 3**). At the beginning of the procedure, the user can choose from the local folders an image, which is sent to the server, and temporarily stored until the analysis is finished. A GUI is automatically loaded client-side, to allow the user's manual input of necessary information.

The optic disc can be manually drawn by clicking on its center and then dragging and the user can select the vessel to be analyzed simply by clicking on its end-points. A number of additional intermediate points can then be manually inserted, to more precisely outline the vessel centerline and guide the subsequent automatic vessel tracking. An interpolating spline, connecting the inserted points, is drawn and displayed over the vessel and updated every time a point is manually added or moved.

Once the user is through with these steps, the client sends the entered information to the server, where vessel tracking is performed using a custom procedure based on Canny edge detector. When the analysis is finished, the server displays the results on a web page: the tracking results (vessel centerline and diameters) are drawn on top of the original image, together with vessel diameter values. The returned clinical parameters for the analyzed vessel are the average width and the tortuosity index.

### B. Evaluation

To test the accuracy of estimated parameters, 15 retinal images were acquired in the neonatal intensive care units at the Scheie Eye Institute and The Children's Hospital of Philadelphia (both in Philadelphia, PA, USA). Images were acquired with the noncontact Nidek NM200D camera (Nidek Co, Gamagori, Japan) with a 30° field of view and saved in digital format as 1280x960 pixels JPEG compressed images. Twelve vessels were used for width evaluation and twelve for tortuosity assessment.


Fig. 3. ROPnet system GUI: manual insertion of image analysis information (left) and final results (right).

Ground-truth reference was obtained with a manual analysis of the vessel segments. Using a public-domain image manipulation program (GIMP v. 2.6.6), a retina imaging expert identified on screen-displayed enlarged versions of the images all the pixels belonging to vessels. The same algorithm used in ROPnet was then used to estimate the width of these manually segmented vessels. For tortuosity, ground-truth reference consisted in a manual ranking of the vessels, provided by an expert ophthalmologist who ordered them by increasing perceived tortuosity.

We then compared the results obtained by using ROPnet on these vessels with the corresponding values from manual ground-truth reference and we obtained a correlation coefficient of 0.96 for width and 0.90 for tortuosity.

## ACKNOWLEDGMENT

We wish to thank the following institutions: Twin Research and Genetic Epidemiology, King's College London Division of Genetics and Molecular Medicine, St. Thomas' Hospital, London, UK; Department of Research and Development, Moorfields Eye Hospital, London, UK; Scheie Eye Institute, University of Pennsylvania, Philadelphia (PA), USA; Division of Ophthalmology, The Children's Hospital of Philadelphia, Philadelphia (PA), USA, for having kindly provided the images and the expert assistance for the projects described here.

## REFERENCES

[1] T. Wong, R. Klein, B. Klein, J. Tielsch, L. Hubbard, and F. Nieto, "Retinal microvascular abnormalities, and their relation to hypertension, cardiovascular diseases and mortality," *Survey Ophthalmol*., vol. 46, no. 1, pp. 59–80, Jul./Aug. 2001.

[2] M. Knudtson, K. Lee, L. Hubbard, T. Wong, R. Klein, and B. Klein, "Revised formulas for summarizing retinal vessel diameters," *Curr. Eye Res*., vol. 27, no. 3, pp. 143–149, Jul./Aug. 2003.

[3] L. D. Hubbard, R. J. Brothers, W. N. King, L. X. Clegg, R. Klein, et al., "Methods for evaluation of retinal microvascular abnormalities associated with hypertension/ sclerosis in the atherosclerosis risk in communities study„" *Ophthalmology*, vol. 106, no. 12, pp. 2269–2280, 1999.

[4] E. Poletti, D. Fiorin, E. Grisan, and A. Ruggeri, "Retinal vessel axis estimation through a multi-directional graph search approach," in Proc. *World Congress Med. Phys. Biomed. Eng*., vol. 25/11, Berlin/Heidelberg, Germany, Springer-Verlag, 2009, pp. 137–140.

[5] D. Fiorin, E. Poletti, E. Grisan, and A. Ruggeri, "Fast adaptive axis based segmentation of retinal vessels through matched filters," in Proc. *World Congress Med. Phys. Biomed. Eng*., vol. 25/11, Berlin/Heidelberg, Germany: Springer, 2009, pp. 145–148.

[6] L. Tramontan, E. Poletti, D. Fiorin, A. Ruggeri, "A Web-Based System for the Quantitative and Reproducible Assessment of Clinical Indexes From the Retinal Vasculature," IEEE *Trans Biomed Eng*, vol.58, no.3, pp.818-821, March 2011.

[7] J. S. Wolffsohn, G. A. Napper, S. Ho, A. Jaworski, and T. L. Pollard, "Improving the description of the retinal vasculature and patient history taking for monitoring systemic hypertension," *Ophthalmic Physiol. Opt*., vol. 21, no. 6, pp. 441–449, Nov. 2001.

[8] E. Grisan, M. Foracchia, A. Ruggeri. "A novel method for the automatic grading of retinal vessel tortuosity". *IEEE Trans. Med. Imag.* 27(3):310-9, Mar 2008.

[9] W. C. Owens, E. U. Owens, "Retrolental fibroplasia in premature infants", *Am J Ophthalmol*, vol. 32,pp. 1–18, 1949.

[10] S. F. Freedman, J. A. Klystra, M. S. Capowski, T. D. Realini, C. Rich, et al., "Observer sensitivity to retinal vessel diameter and tortuosity in retinopathy of prematurity: a model system", *J Pediatr Ophthalmol Strabismus*, vol. 33,pp.248–54, 1996.

[11] C. M. Wilson, K. D. Cocker, M. J. Moseley, C. Paterson, S. T. Clay, et al., "Computerized analysis of retinal vessel width and tortuosity in premature infants", *Invest Ophthalmol Vis Sci*, vol. 49(8),pp. 3577-85, 2008.

[12] D. K. Wallace, "Computer-Assisted Quantification of Vascular Tortuosity in Retinopathy of Prematurity", *Trans Am Ophthalmol Soc*, vol. 105,pp. 594-615, 2007.