Automatic Optic Nerve Measurement: A New Tool to Standardize Optic Nerve Assessment in Ultrasound B-Mode Images

AUTomatic Optic Nerve MeAsurement (AUTONoMA): a new tool to standardize the optic nerve assessment in ultrasound B-mode images

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Abstract

Transorbital sonography provides reliable information about the estimation of intracranial pressure by measuring the optic nerve sheath diameter (ONSD), while the optic nerve (ON) diameter (OND) may reveal ON atrophy in multiple sclerosis patients. Here, an AUTomatic Optic Nerve MeAsurement (AUTONoMA**)** system for OND and ONSD assessment in ultrasound B-mode images based on deformable models is presented. The automated measurements were compared to manual ones obtained by two operators, with no significant differences. AUTONoMA correctly segmented the ON and its sheath in 71 out of 75 images. The mean error compared with the expert operator was 0.06 ± 0.52 mm and 0.06 ± 0.35 mm for the ONSD and OND respectively. The agreement between operators and AUTONoMA was good and a positive correlation between the readers and the algorithm with errors comparable with the inter-operator variability was found. The AUTONoMA system may allow a standardization of OND and ONSD measurements, reducing manual evaluation variability.

Keywords: Ultrasound, Optic nerve segmentation, Intracranial pressure, Optic nerve diameter, Optic nerve sheath diameter.

Introduction

Transorbital sonography (TOS) is a promising technique for the non-invasive evaluation of the optic nerve (ON) structures. This tool is particularly versatile and can be performed both in remote, prehospital setting and hospital context, either in invasive or non-invasive departments (Houzé-Cerfon et al. 2018; Lochner et al. 2015). The main use of TOS concerns the assessment of the optic nerve sheath diameter (ONSD) for the estimation and monitoring of increased intracranial pressure (ICP), particularly when the invasive referenced methods are contraindicated or unavailable (Goeres et al. 2016; Robba et al. 2015; Soliman et al. 2018). Moreover, TOS can be useful to detect ON atrophy in patients with multiple sclerosis (Carraro et al. 2014). In the past, transorbital sonography has been performed by using amplitude-mode (A) standardized ultrasonography, which provides simple displays plotted as a series of peaks whose height represents the depth of the echoing structure from the transducer (Ossoinig 1979; Schroeder 1976). Due to software improvement and the development of higher frequency probes, Brightness-mode (B) scan replaced the A-Mode sonography. The advantages of B-Mode sonography includes the generation of a two-dimensional image, allowing a better topography of the tissue with direct visualization of lesions. The current application fields of B-Mode TOS in the clinical practice have been recently described (Lochner et al. 2019).

A good intra and interobserver reproducibility using high-frequency (>7.5 MHz) linear probe, which allows a lateral spatial resolution <0.4 mm, can be obtained for the ultrasonographic assessment of optic nerve diameter (OND) and ONSD (Bäuerle et al. 2012; Lochner et al. 2014; Lochner et al. 2018a). Although this, the manual evaluation of

OND and ONSD can be affected by the operator's experience and artefactual images (Ballantyne et al. 2002; Copetti and Cattarossi 2009). In addition, different methods are currently described in literature for the ONSD evaluation, leading to possible misunderstanding in the results interpretation (Bloria et al. 2019).

Even if a greater experience or a continuous training have demonstrated to reduce operator variability, for a better use of the technique, a unique model of measurements and a standardization of the method are required (Zeiler et al. 2013; Zeiler et al. 2014). The development of computerized automated systems for the segmentation of structures in B-mode ultrasound images is an auspicious research field that may help reduce thereupon the operator-dependency, accelerate the acquisition time and mitigate the issue of inter-operator variability (Meiburger et al. 2018). In this context, Gerber et al. (Gerber et al. 2017) developed an algorithm to automatically estimate the ONSD from 23 ocular ultrasound images and on an eye phantom using 3D-printed optic nerves embedded under gelatin orbs, and Soroushmehr et al. (Soroushmehr et al. 2019) developed a method based on super-pixel analysis to measure the ONSD in 50 ultrasound images. However, to the best of our knowledge, except from these works which employed a smaller dataset of in-vivo images and estimated only the ONSD, there are no described methods focused on a completely automatic segmentation of the optic nerve and optic nerve sheath in ultrasound B-mode images in a series of patients affected by neurological diseases with increased ICP and healthy subjects.

Therefore, the aim of this work is to present and validate a completely automatic system for measuring the OND and ONSD, requiring no interaction with the user.

Materials and Methods

The measurement of the OND and ONSD with TOS is based on the difference in echogenicity and morphology of the different retro-orbital structures. The developed algorithm is based on the assumption that the ultrasound image presents hypoechoic structures like the vitreous, the inside of the optic nerve and the arachnoid, and hyperechoic structures like pia and dura mater and the surrounding adipose tissue. The anterior part of the optic nerve is depicted in an axial plane showing the papilla and the optic nerve in its longitudinal course. ONSD and OND are assessed 3 mm behind the papilla (Helmke and Hansen 1996) and should be calculated perpendicularly to the optic nerve centerline.

The OND is typically measured manually as the distance between the right profile of the optic nerve and the left one. To measure the ONSD, we quantified the distance between the external borders of the hyperechogenic area surrounding the optic nerve (Ertl et al. 2014), as shown in Fig. 1.

Image acquisition and database

A total of 75 images were included in this study: 30 images came from 15 patients who were diagnosed either with primary or secondary intracranial hypertension (IH) according to the current diagnostic criteria (Friedman et al. 2013) and 45 images from 23 healthy controls. The study was approved by the local ethical committee (Bolzano, 20/2014) and all participants provided written informed consent before being included. All images were acquired by an expert neurosonologist with more than 10 years of

experience in TOS using a Vivid 7 sonography system with a 7 to 11 MHz linear array probe with a central frequency of 10 MHz (GE Healthcare, Milwaukee, Wisconsin).

For image acquisition, a standard protocol was followed. Specifically, the patient was asked to lie in a supine position on a bed with the head reclined at a 20°-30° angle. With the patient's eyes closed, the linear array ultrasound probe was gently placed on the closed eyelids (never in direct contact with the cornea or sclera), and the image was acquired. All images were exported from the ultrasound device and transferred to a workstation for offline processing.

AUTONoMA architecture

An overview of our proposed AUTomatic Optic Nerve MeAsurement (AUTONoMA) system is presented in Fig. 2. It consists of a computer aided diagnosis (CAD) system that takes a B-mode image obtained from transorbital ultrasonography and gives forth an automated measurement of the optic nerve diameter and the optic nerve sheath diameter, without requiring any interaction from the user. The proposed system can be summarized in two main automatic steps:

1. Stage I: coarse localization of the region-of-interest through the automatic recognition of the ocular bulb profile and the optic nerve centerline tracing.
2. Stage II: fine segmentation of the optic nerve and the optic nerve sheath through dual snakes and automatic measurement of OND and ONSD.

Stage I: coarse localization of ocular bulb and optic nerve centerline

In order to accurately locate the ocular bulb within the ultrasound image frame, a preprocessing step is first necessary to isolate the ultrasound information from the entire image frame. To do so, an automatic image cropping step was developed, using morphological operations and gradients. Fig. 3a shows the original image and Fig. 3b shows the automatically cropped image.

The automatic recognition of the ocular bulb is then done on the cropped image. First of all, the image is sharpened by summing the original image with the image obtained with the First Order Absolute Moment (FOAM), an edge operator which has been applied previously in ultrasound images (Faita et al. 2006). Subsequently, a gaussian derivative filter (sigma = 7) was applied to the image (Fig. 3c). In the obtained image, the bottom border of the optical bulb is automatically located through a column-wise heuristic search. The beginning of the column-wise search region is found by locating the first pixel (starting from the top of the image) that is above a certain intensity and that presents a reasonably large hypoechogenic region above it (i.e., the bulb) (Fig. 3c). The point of the optical bulb boundary for the analyzed column is then automatically located by finding the first discontinuity from a hypoechoic zone to a hyperechoic zone on the B-mode cropped image. The profile obtained by analyzing each column, $AUTONoMA_{bulb}$, is then interpolated to give forth the final segmentation of the ocular bulb (Fig. 3d).

The identification of the bottom boundary of the ocular bulb makes the search for an estimation of the optic nerve centerline significantly easier by limiting the search of the optic nerve within a specific area of the image. Specifically, a gaussian derivative filter was again applied to the ultrasound image and the optic nerve centerline was located

thanks to a heuristic search below the found AUTONoMA$_{bulb}$ profile similar to the one previously described but considered row-wise. The obtained centerline, AUTONoMA$_{ONc,}$ is shown in Fig. 3e.

Stage II: fine segmentation of optic nerve and optic nerve sheath

The fine segmentation of the optic nerve and the optic nerve sheath is done by implementing a dual snake model, similar to the one presented by Molinari et al. (Molinari et al. 2012b; Molinari et al. 2012a). Since both the optic nerve diameter and the optic nerve sheath diameter are of clinical interest, two different dual snake models were developed: one for the calculation of the optic nerve diameter, and the other for the optic nerve sheath diameter.

As all active contour models, the dual snake algorithm requires a first initialization of the snakes, which then evolve in time and adapt to the optic nerve and sheath boundaries. The snakes initialization and evolution are described in the following paragraphs.

Snakes initialization

The snakes initialization can be summarized as follows: 1) starting from the located optic nerve centerline, the ON dual snake (ONDS) model was initialized by locating the rough nerve boundary; 2) similarly, the optic nerve sheath dual snake (ONSDS) model was initialized by locating the rough sheath boundary starting from the rough nerve boundary located in the previous step 1.

The rough boundaries of both the optic nerve and the optic nerve sheath, hence the snakes initialization, were located thanks to a row-wise heuristic search on the original image filtered with a gaussian derivative filter in two directions. Briefly, starting from the centerline/optic nerve boundary going outwards, the first pixel in the gaussian derivative filtered image that is higher than a specific threshold is taken as the candidate point for the optic nerve/optic nerve sheath. The snake initialization then is taken as joining together all candidate points.

Fig. 4a and 4b shows the snakes initialization for the ONDS and ONSDS, respectively.

Snakes evolution

Once the snakes are initialized, the dual snake models ($v(s)$) then evolve in time thanks to three energy models: the internal, external, and mutual interaction energies. The internal energy serves to constrain the shape of the contour and prevents the active contour from presenting an excessive curvature, which is especially necessary in this clinical application, in which the optic nerve and optic nerve sheath are represented by more or less straight lines. This energy is defined as:

$$E_{int}(v(s)) = \int_0^1 \alpha |v'(s)|\, ds \tag{1}$$

where *s* is the curvilinear coordinate on the image, $v'(s)$ is the first-order derivative of the snake curve $v(s)$ and α is a parameter used to give a specific weight to the internal energy, controlling the curvature of the snake.

The external energy is what attracts the snake model toward the image discontinuities. This energy is defined as:

$$E_{ext}(v(s)) = -\int_0^1 \beta e(v(s))\ ds \tag{2}$$

where β is a parameter used to give a specific weight to the external energy and the functional $e(x, y)$ is a first order gaussian derivative filter, an edge operator that has been used in numerous ultrasound clinical applications (Caresio et al. 2017).

The mutual interaction energy, which can be considered as a second term of external energy, is necessary to ensure that the two models of the dual snake do not either collapse on one another or converge. So, this energy is inversely proportional to the distance between the two curves (the left and right snake, $v_L(s)$ and $v_R(s)$, respectively) and is defined as:

$$E_{mut}(v(s)) = \int_0^1 \gamma \frac{1}{|v_R(s) - v_L(s)|} ds \tag{3}$$

where γ is a parameter used to give a specific weight to the mutual energy.

The values of the parameters used for each of the dual snake models are shown in Tab. 1. As can be seen, the external energy and mutual energy parameters are dependent on the conversion factor (CF), expressed in $mm/pixel$, in order to make the models independent of both zooming and of the ultrasound device used to acquire the images. The value of CF_{base} was equal to $0.116\ mm/pixel$.

The final segmentation of the optic nerve and the optic nerve sheath is shown in Fig. 4c and 4d, respectively.

Calculation of the OND and ONSD

Once the optic nerve and optic nerve sheath are correctly segmented, the diameters of the two structures (OND and ONSD) were automatically measured. This was done by using the optic nerve centerline that was found automatically and locating the point that is 3 mm behind the optic bulb. From here, the Centerline Distance (Saba et al. 2012) between the two final snake models was calculated to give forth the final OND and ONSD values (Fig. 4e). In order to reduce the variability of the final OND and ONSD measurements, the centerline distance was calculated right at 3 mm behind the optic bulb, slightly before 3 mm, and slightly after 3 mm, and the average distance was taken to be the final diameter measurement.

The AUTONoMA system was developed in Matlab and showed an average computational time of 2 seconds for processing a single image, providing an almost real-time analysis.

Performance evaluation

In order to validate the results of the developed AUTONoMA algorithm, different performance evaluation metrics were used.

First of all, the OND and ONSD measurements that were obtained automatically were compared with the manual measures of an expert with more than 10 years of experience in transorbital ultrasonography and a non-expert operator (referenced as Op1 and Op2 from here on out, respectively), considered as ground truth. To do the manual measurement, an in-house program in Matlab was developed to allow adequate zooming

of the image, and the subsequent manual tracing of the optic nerve centerline. Using the calibration factor, the perpendicular line at 3mm was drawn and the operator was asked to use the mouse to measure the OND and ONSD at the correct depth. So, for each image, the error between the automatic computer-based measure and the ground truth measure was calculated. Three types of error were used to describe the overall system performance: the mean error (defined as the mean difference between the manual measure and the automatic one), the mean absolute error (MAE) and the mean squared error (MSE), along with the respective standard deviations. Another parameter, the Figure of Merit (FoM), which characterizes the overall performances of the algorithm, was calculated. This parameter is defined as:

$$FoM_{OND} = 100 - \left|\frac{mean(OND_{auto}) - mean(OND_{man})}{mean(OND_{man})}\right| \cdot 100 \quad (4)$$

$$FoM_{ONSD} = 100 - \left|\frac{mean(ONSD_{auto}) - mean(ONSD_{man})}{mean(ONSD_{man})}\right| \cdot 100 \quad (5)$$

where $mean(OND_{auto})$ and $mean(ONSD_{auto})$ are respectively the average OND and ONSD values found automatically, and $mean(OND_{man})$ and $mean(ONSD_{man})$ are the average OND and ONSD values measured manually, respectively.

Morover, we calculated the correlation coefficient and the 95% confidence interval between the ground truth diameter values and the automated diameter values. Finally, to determine if the automatic and manual measurements present a statistically significant difference between the measurements or not, the Wilcoxon signed rank test was used.

In order to assess inter-operator variability in OND and ONSD measurements, the correlation between the manual measurements was also calculated. For each image, the manual measurements were obtained offline and independently by the two operators involved (both blinded with regard to AUTONoMA performance). The developed AUTONoMA system is completely automated and independent from the user; therefore the system does not present any measurement variability.

Results

The proposed AUTONoMA system was able to process 71 out of 75 images, presenting a 95% success rate. Fig. 5 shows some example segmentation results obtained with the AUTONoMA system, whereas Fig. 6 shows two examples of images that were not able to be processed automatically.

The performance values for the optic nerve and the optic nerve sheath diameter are reported in Tab. 2 and Tab. 3, respectively. No statistically significant differences were observed between AUTONoMA and the operators for the OND values ($p > 0.05$), whereas a statistically significant difference was found for the ONSD values between only AUTONoMA and the inexpert operator ($p < 0.05$). Considering the OND measurements, the automatic algorithm gave forth mean errors equal to $0.06 \pm 0.35\ mm$ and $0.05 \pm 0.38\ mm$ when compared with Op1 and Op2, respectively. In both cases the algorithm underestimated the measure. The FoM was equal to 98.2% when comparing results with Op1 and equal to 98.3% when considering Op2. When considering the ONSD, on the

other hand, the mean error compared to Op1 and Op2 was found to be equal to $0.06 \pm 0.52\ mm$ and -$0.37 \pm 0.55\ mm$, and the FoM was 99.0% and 93.5%, respectively.

The Pearson correlation coefficient, the 95% confidence interval and the p-value between the automatic measure, both for the OND and the ONSD, and the manual one performed by Op1 and Op2 are reported in Tab. 4. A statistically significant correlation between our developed AUTONoMA algorithm and the manual operators was found, showing p-values ≤ 0.05 in all cases, considering both the OND and the ONSD. The inter-operator variability also showed a statistically significant correlation (p-value ≤ 0.05, considering both OND and ONSD).

The Bland-Altman plots of the AUTONoMA optic nerve diameter and optic nerve sheath diameter compared to Op1 and Op2 are shown in Fig. 7a. The Bland-Altman plots related to the inter-operator analysis for the OND and ONSD are reported in Fig. 7b. It can be appreciated that there is an absence of any visible bias and the automated measurements were all close to the manually measured values.

Discussion

Apart from a recent pilot study presented by Gerber et al. (Gerber et al. 2017), this is the first work that proposes an automatic optic nerve system to calculate both the OND and the ONSD. We used a three times larger dataset of ocular ultrasound images, comparing the automated measurements with those of two investigators with different expertise who independently examined both parameters.

The main findings of our work are as follows:

Firstly, the developed AUTONoMA algorithm is fully automated and was able to process 95% of the images present in the dataset. On further analysis, it was found that the automatic algorithm provided a segmentation that the manual expert deemed as acceptable in all cases except for 5 images (7%), where the AUTONoMA segmentations diverged from the actual ON and ONS borders.

Secondly, the mean value of ONSD obtained from AUTONoMA, $6.2 \pm 0.6\, mm$, is very similar to the ONSD value achieved by the expert operator, $6.2 \pm 0.6\, mm$ $(p = 0.28)$, and significantly different from the inexpert operator, 5.8 ± 0.6 mm $(\mathrm{p} < 0.05)$. Moreover, the mean absolute and mean squared errors exclude a systematic error from AUTONoMA. Similarly, the OND measurements obtained from AUTONoMA were not significantly different from those achieved by both the operators (p = 0.08 and p = 0.21, respectively). Thirdly, regarding the inter-observer reliability according to the Bland-Altman analysis, we found a good agreement between the operators. Moreover, the difference of measurements of ONSD is inferior to the intrinsic error of the machine (Ballantyne et al. 2002) and comparable with the inter-operator reproducibility reported in prior studies (Bäuerle et al. 2012; Lochner et al. 2014).

Finally, AUTONoMA calculates the OND/ONSD value simultaneously and in a very short time, approximately two seconds per image. Manual measurements take about 30 seconds for each image, hence the automatic algorithm provides a result fifteen times faster than an expert operator. Moreover, since the developed system is completely automatic and independent from the user, there is no OND/ONSD measurement variability.

Translating into clinical practice, the AUTONoMA system may represent the first step to reduce the wide variability of ONSD and OND measurements currently described in literature. These differences reflect the operator's experience, the use of different ultrasonographic machines, and a non-homogeneous and standardized method for image acquisition and measurements (Bloria et al. 2019). The presence and use of an automated system such as AUTONoMA could – at least in part – mitigate and minimize these differences, promoting a more comparable interpretation of results among studies.

To date, both OND and ONSD are used to study neurological conditions that imply variations in their value. Meanwhile, the spectrum of applications for TOS in the context of neurological diseases has progressively extended (Lochner et al. 2019). This is due to the versatility of the ultrasonographic evaluation because of its availability, inexpensiveness, repeatability and bedside use. For these reasons, the sonographic assessment of the ONSD is considered an alternative to the invasive evaluation for the estimation of increased ICP, especially in pre-hospital settings or when radiological or neurosurgical care are not available or contraindicated (Robba et al. 2018). However, a clear cut-off value to identify intracranial hypertension is not available, probably due to differences in sex, ethnicity, age, body mass index and technical limitations cited above; also anatomical factors or previous ocular or cerebral pathologies may be implied in generating a variability of optic nerve structures (Bäuerle et al. 2016; Naldi et al. 2019; Wang et al. 2016). Thus, the emergent concept of monitoring ONSD values from a basal level is taking place: if a growing trend is observed, it may guide the decision-making (Thotakura et al. 2017). Similar considerations may be done in case of a progressive reduction of ONSD when suspecting intracranial hypotension syndrome (Fichtner et al.

2016). In these contexts, it seems unlikely that a series of ONSD examinations to monitor ICP could be performed by the same operator; in addition, the inter/intra –observer variability is higher between expert and inexpert sonologists (Zeiler et al. 2013; Zeiler et al. 2014). Indeed, an automated system could be extremely useful for a standardization of measurements.

In addition, because of the variability of measurements, most ultrasonographic studies use the averaging of at least two values (frequently three) to obtain the reference of the ONSD, thus extending the execution time. Instead, due to the absence of measurement variability when using AUTONoMA, we speculate that a single (well-acquired) image could be sufficient for the ONSD measurement by using the automated system, with a reduction of calculation time in comparison with the manual evaluation (approximately 3-5 minutes). We specify that the automated system was able to correctly segment images that presented a certain amount of variability in appearance and direction of the optic nerve. In 4 images, the automated algorithm was unable to correctly segment the ON and ONS due to the fact that the structures were not sufficiently hypoechoic or hyperechoic (Fig. 6). Since the algorithm must make certain assumptions on how specific structures are represented in the ultrasound B-mode image, if the actual representation is excessively different from a typical transorbital ultrasonography image, the algorithm does not properly process the image.

From a clinical perspective, most studies documented a 1 mm difference between ONSD of healthy and pathological conditions (Lochner et al. 2017; Lochner et al. 2018b; Moretti et al. 2009). Since the measured error is inferior, it is likely that the AUTONoMA algorithm could distinguish between most pathological and healthy conditions.

An increasing number of studies examined the role of TOS for neurological disorders that may affect the OND. Candeliere Merlicco et al. (Candeliere Merlicco et al. 2018) found that patients affected by multiple sclerosis present an atrophy of ON compared to healthy subjects, and that OND values are correlated with the Kurtzke Expanded Disability Status Scale (EDSS) as well as with the duration of the disease. Some authors also suggested that the ultrasonographic assessment of the OND could be potentially used as a biomarker for the detection of early disability in relapsing-remitting multiple sclerosis (Koraysha et al. 2019). Because AUTONoMA was able to correctly detect also the OND, analogue considerations of the potential role of an automated measurements system can be extended for this parameter.

This study presents some limitations. An analysis on a larger number of images is mandatory to further validate the method. To correctly process the image, AUTONoMA required a substantial difference between hyperechoic and hypoechoic structures: in case of insufficient quality, the automated system is not able to recognize the optic nerve. Further efforts are needed to improve this algorithm in order to recognize the boundary between the hypoechogenic and hyperechogenic structure of the nerve. However, it is important to point out that images with a very low quality should also be excluded from a manual evaluation.

Then, AUTONoMA was tested on images obtained from a single ultrasound machine and we have no data from different ultrasound machines. Finally, a sub-analysis of our data showed that AUTONoMA tended to underestimate the OND measurements compared to both operators, while no conclusive information can be deducted for the ONSD. We suggest that further observations are warranted in order to clarify this issue.

Despite these limits, our preliminary data are encouraging and can justify the use of AUTONoMA as a non-invasive tool for the assessment of ONSD and OND. It is important to also point out that, in the present study, the true ONSD and OND values are not known and are estimated by manual measurements, which are considered as ground truth. A phantom study with known OND and ONSD values would help confirm the algorithm accuracy and results even further; however, this is outside the scope of the present study, which aims to present a tool that can automatically measure the OND and ONSD as would be done by a manual expert on a B-Mode ultrasound image.

In order to improve the AUTONoMA system, further investigations will be object of our future studies.

Conclusion

A novel CAD system to automatically measure the OND and ONSD in ultrasound images is presented. The algorithm is based on initially locating the optic bulb and optic nerve centerline and then two dual snake models are implemented for the final nerve and sheath segmentation. The technique was validated on a database of 71 images by comparing the results with two manual operators (an expert and a non-expert operator). We obtained a low mean measurement error and showed automatic results that can be considered within the range of inter-operator variability. The developed system can help clinicians evaluate pathologies related to the variations of the optic nerve morphology in a short time and mitigate the issue of inter-operator variability. In the future, we plan on testing the presented technique on a larger database to further validate the developed AUTONoMA system.

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Figures Captions List

Figure 1. Example of manual optic nerve diameter (OND) and optic nerve sheath diameter (ONSD) calculation.

Figure 2. Overview of steps for the developed AUTONoMA system. The image is first acquired, and then automatically cropped. Stage I consists in the automatic recognition of the bulb and optic nerve centerline. Stage II then consists in the initialization of the two dual snake models by a rough segmentation of the optic nerve and optic nerve sheath. The dual snake models then evolve in time until they reach the borders of the actual optic nerve and optic nerve sheath. Then the final value of the OND and ONSD is automatically measured from the final dual snake boundaries.

Figure 3. Overview of the AUTONoMA Stage I architecture. A) Original image. B) Automatically cropped image. C) First order gaussian derivative of (b), showing the initialization of the search region for the bulb profile tracing. D) AUTONoMA bulb ($AUTONoMA_{bulb}$)profile segmentation results. E) AUTONoMA optic nerve centerline ($AUTONoMA_{Onc}$) tracing.

Figure 4. Overview of the AUTONoMA Stage II architecture. A) Optic nerve (ON) dual snake initialization. B) Optic nerve sheath (ONS) dual snake initializaion. C) Final ON dual snake segmentations ($AUTONoMA_{ONL}$ and $AUTONoMA_{ONR}$). D) Final ONS dual snake

segmentations ($AUTONoMA_{ONSL}$ and $AUTONoMA_{ONSR}$). E) Final calculation of the automatic OND and ONSD measurements ($AUTONoMA_{OND}$ and $AUTONoMA_{ONSD}$).

Figure 5. Segmentation and OND and ONSD measurement results of the developed AUTONoMA system.

Figure 6. Example error cases for the AUTONoMA system. A) Example where there is not a sufficient intensity difference between the hypoechogenicity of the optic nerve and the surrounding arachnoid space. B) Example of an image where the surrounding arachnoid space is excessively hyperechoic.

Figure 7a. Bland-Altman analysis comparing the optic nerve diameter (OND – first row) and the optic nerve sheath diameter (ONSD – second row) with Operator 1 (first column) and Operator 2 (second column). Continuous line depicts the mean of differences; dashed lines denote limits of agreement.

Figure 7b. Bland-Altman inter-operator analysis comparing the optic nerve diameter (OND – first column) and the optic nerve sheath diameter (ONSD – second column) with Operator 1 vs Operator 2. Continuous line depicts the mean of differences; dashed lines denote limits of agreement.

Tables

Table 1

Parameter values for Dual Snake models. ONDS: Optic Nerve Dual Snake; ONSDS: Optic Nerve Sheath Dual Snake

Dual Snake model	α (internal energy)	β (external energy)	γ (mutual energy)
ONDS	0.7	$\frac{0.3 \cdot CF_{base}}{CF}$	$\frac{9 \cdot CF_{base}}{CF}$
ONSDS	0.3	$\frac{0.1 \cdot CF_{base}}{CF}$	$\frac{6 \cdot CF_{base}}{CF}$

Table 2

Performance evaluation results of the AUTONoMA system compared to manual measurements for the calculation of the optic nerve diameter (OND).

OND	AUTONoMA	Operator 1	Operator 2
Mean value [mm]	3.1 ± 0.3	3.1 ± 0.4	3.0 ± 0.4
Mean error [mm]		0.06 ± 0.35	-0.05 ± 0.38
Mean absolute error [mm]		0.28 ± 0.22	0.30 ± 0.24
Mean squared error [mm^2]		0.12 ± 0.17	0.15 ± 0.25
FoM		98.2%	98.3%

Table 3

Performance evaluation results of the AUTONoMA system compared to manual measurements for the calculation of the optic nerve sheath diameter (ONSD).

ONSD	AUTONoMA	Operator 1	Operator 2
Mean value [mm]	6.2 ± 0.6	6.2 ± 0.6	5.8 ± 0.6*
Mean error [mm]		0.06 ± 0.52	-0.37 ± 0.55
Mean absolute error [mm]		0.41 ± 0.32	0.49 ± 0.45
Mean squared error [mm^2]		0.27 ± 0.37	0.44 ± 0.66
FoM		99.0%	93.5%

*statistically significant difference ($p<0.05$) between Operator and AUTONoMA using the Wilcoxon signed rank test

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624 Table 4

625 Correlation performance results between the AUTONoMA system and the manual
626 operators (Op1 and Op2) and the inter-operator variability performance analysis.

			Confidence interval		
Analysis	Measure	Correlation coefficient	Lower limit	Upper limit	p-value
AUTONoMA vs Op1	OND	0.47	0.27	0.63	$3.590 \cdot 10^{-5}$
	ONSD	0.64	0.48	0.76	$1.541 \cdot 10^{-9}$
AUTONoMA vs Op2	OND	0.35	0.12	0.54	0.0031
	ONSD	0.61	0.44	0.74	$1.375 \cdot 10^{-8}$
Op1 vs Op2	OND	0.69	0.55	0.80	$2.543 \cdot 10^{-11}$
	ONSD	0.65	0.49	0.77	$7.222 \cdot 10^{-10}$

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