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

*Original*

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(Article begins on next page)

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

3

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23

24

25 **Abstract**

26 Transorbital sonography provides reliable information about the estimation of intracranial  
27 pressure by measuring the optic nerve sheath diameter (ONSD), while the optic nerve  
28 (ON) diameter (OND) may reveal ON atrophy in multiple sclerosis patients. Here, an  
29 AUTomatic Optic Nerve MeAsurement (AUTONoMA) system for OND and ONSD  
30 assessment in ultrasound B-mode images based on deformable models is presented.  
31 The automated measurements were compared to manual ones obtained by two  
32 operators, with no significant differences. AUTONoMA correctly segmented the ON and  
33 its sheath in 71 out of 75 images. The mean error compared with the expert operator was  
34  $0.06 \pm 0.52$  mm and  $0.06 \pm 0.35$  mm for the ONSD and OND respectively. The agreement  
35 between operators and AUTONoMA was good and a positive correlation between the  
36 readers and the algorithm with errors comparable with the inter-operator variability was  
37 found. The AUTONoMA system may allow a standardization of OND and ONSD  
38 measurements, reducing manual evaluation variability.

39

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

42

43

## 44 Introduction

45 Transorbital sonography (TOS) is a promising technique for the non-invasive  
46 evaluation of the optic nerve (ON) structures. This tool is particularly versatile and can be  
47 performed both in remote, prehospital setting and hospital context, either in invasive or  
48 non-invasive departments (Houzé-Cerfon et al. 2018; Lochner et al. 2015). The main use  
49 of TOS concerns the assessment of the optic nerve sheath diameter (ONSD) for the  
50 estimation and monitoring of increased intracranial pressure (ICP), particularly when the  
51 invasive referenced methods are contraindicated or unavailable (Goeres et al. 2016;  
52 Robba et al. 2015; Soliman et al. 2018). Moreover, TOS can be useful to detect ON  
53 atrophy in patients with multiple sclerosis (Carraro et al. 2014). **In the past, transorbital**  
54 **sonography has been performed by using amplitude-mode (A) standardized**  
55 **ultrasonography, which provides simple displays plotted as a series of peaks whose**  
56 **height represents the depth of the echoing structure from the transducer (Ossoinig 1979;**  
57 **Schroeder 1976). Due to software improvement and the development of higher frequency**  
58 **probes, Brightness-mode (B) scan replaced the A-Mode sonography. The advantages of**  
59 **B-Mode sonography includes the generation of a two-dimensional image, allowing a**  
60 **better topography of the tissue with direct visualization of lesions.** The current application  
61 fields of **B-Mode** TOS in the clinical practice have been recently described (Lochner et al.  
62 2019).

63 A good intra and interobserver reproducibility using high-frequency (>7.5 MHz) linear  
64 probe, which allows a lateral spatial resolution <0.4 mm, can be obtained for the  
65 ultrasonographic assessment of optic nerve diameter (OND) and ONSD (Bäuerle et al.  
66 2012; Lochner et al. 2014; Lochner et al. 2018a). Although this, the manual evaluation of

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

71 Even if a greater experience or a continuous training have demonstrated to reduce  
72 operator variability, for a better use of the technique, a unique model of measurements  
73 and a standardization of the method are required (Zeiler et al. 2013; Zeiler et al. 2014).

74 The development of computerized automated systems for the segmentation of structures  
75 in B-mode ultrasound images is an auspicious research field that may help reduce  
76 thereupon the operator-dependency, accelerate the acquisition time and mitigate the  
77 issue of inter-operator variability (Meiburger et al. 2018). In this context, Gerber et al.  
78 (Gerber et al. 2017) developed an algorithm to automatically estimate the ONSD from 23  
79 ocular ultrasound images and on an eye phantom using 3D-printed optic nerves  
80 embedded under gelatin orbs, and Soroushmehr et al. (Soroushmehr et al. 2019)  
81 developed a method based on super-pixel analysis to measure the ONSD in 50  
82 ultrasound images. However, to the best of our knowledge, except from these works  
83 which employed a smaller dataset of in-vivo images and estimated only the ONSD, there  
84 are no described methods focused on a completely automatic segmentation of the optic  
85 nerve and optic nerve sheath in ultrasound B-mode images in a series of patients affected  
86 by neurological diseases with increased ICP and healthy subjects.

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

89

## 90 **Materials and Methods**

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

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

104

### 105 ***Image acquisition and database***

106           A total of 75 images were included in this study: 30 images came from 15 patients  
107 who were diagnosed either with primary or secondary intracranial hypertension (IH)  
108 according to the current diagnostic criteria (Friedman et al. 2013) and 45 images from 23  
109 healthy controls. The study was approved by the local ethical committee (Bolzano,  
110 20/2014) and all participants provided written informed consent before being included. All  
111 images were acquired by an expert neurosonologist with more than 10 years of

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

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

120

121

## 122 ***AUTONoMA architecture***

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

129

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

134

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

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

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

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



158 thanks to a heuristic search below the found AUTONoMA<sub>bulb</sub> profile similar to the one  
159 previously described but considered row-wise. The obtained centerline, AUTONoMA<sub>ONc</sub>,  
160 is shown in Fig. 3e.

161

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

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

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

173

#### 174 *Snakes initialization*

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

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

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

189

#### 190 *Snakes evolution*

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

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

197

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

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

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

203  
204 where  $\beta$  is a parameter used to give a specific weight to the external energy and the  
205 functional  $e(x, y)$  is a first order gaussian derivative filter, an edge operator that has been  
206 used in numerous ultrasound clinical applications (Caresio et al. 2017).

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

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

212  
213 where  $\gamma$  is a parameter used to give a specific weight to the mutual energy.

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

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

221

## 222 *Calculation of the OND and ONSD*

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

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

235

## 236 ***Performance evaluation***

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

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

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

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

254

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

255

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

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

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

269

## 270 **Results**

271

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

276 The performance values for the optic nerve and the optic nerve sheath diameter  
277 are reported in Tab. 2 and Tab. 3, respectively. No **statistically** significant differences were  
278 observed between AUTONoMA and the operators for the OND values ( $p > 0.05$ ), whereas  
279 a **statistically** significant difference was found for the ONSD values between only  
280 AUTONoMA and the inexperienced operator ( $p < 0.05$ ). Considering the OND measurements,  
281 the automatic algorithm gave forth mean errors equal to  $0.06 \pm 0.35 \text{ mm}$  and  $0.05 \pm$   
282  $0.38 \text{ mm}$  when compared with Op1 and Op2, respectively. In both cases the algorithm  
283 underestimated the measure. The FoM was equal to 98.2% when comparing results with  
284 Op1 and equal to 98.3% when considering Op2. When considering the ONSD, on the

285 other hand, the mean error compared to Op1 and Op2 was found to be equal to  $0.06 \pm$   
286  $0.52 \text{ mm}$  and  $-0.37 \pm 0.55 \text{ mm}$ , and the FoM was 99.0% and 93.5%, respectively.

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

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

299

300

## 301 **Discussion**

302

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

308 The main findings of our work are as follows:

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

314 Secondly, the mean value of ONSD obtained from AUTONoMA,  $6.2 \pm 0.6 \text{ mm}$ , is very  
315 similar to the ONSD value achieved by the expert operator,  $6.2 \pm 0.6 \text{ mm}$  ( $p = 0.28$ ), and  
316 significantly different from the inexperienced operator,  $5.8 \pm 0.6 \text{ mm}$  ( $p < 0.05$ ). Moreover, the  
317 mean absolute and mean squared errors exclude a systematic error from AUTONoMA.  
318 Similarly, the OND measurements obtained from AUTONoMA were not significantly  
319 different from those achieved by both the operators ( $p = 0.08$  and  $p = 0.21$ , respectively).  
320 Thirdly, regarding the inter-observer reliability according to the Bland-Altman analysis, we  
321 found a good agreement between the operators. Moreover, the difference of  
322 measurements of ONSD is inferior to the intrinsic error of the machine (Ballantyne et al.  
323 2002) and comparable with the inter-operator reproducibility reported in prior studies  
324 (Bäuerle et al. 2012; Lochner et al. 2014).

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



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

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

354 2016). In these contexts, it seems unlikely that a series of ONSD examinations to monitor  
355 ICP could be performed by the same operator; in addition, the inter/intra –observer  
356 variability is higher between expert and inexpert sonologists (Zeiler et al. 2013; Zeiler et  
357 al. 2014). Indeed, an automated system could be extremely useful for a standardization  
358 of measurements.

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

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

377 An increasing number of studies examined the role of TOS for neurological  
378 disorders that may affect the OND. Candelieri Merlicco et al. (Candelieri Merlicco et al.  
379 2018) found that patients affected by multiple sclerosis present an atrophy of ON  
380 compared to healthy subjects, and that OND values are correlated with the Kurtzke  
381 Expanded Disability Status Scale (EDSS) as well as with the duration of the disease.  
382 Some authors also suggested that the ultrasonographic assessment of the OND could be  
383 potentially used as a biomarker for the detection of early disability in relapsing-remitting  
384 multiple sclerosis (Koraysha et al. 2019). Because AUTONoMA was able to correctly  
385 detect also the OND, analogue considerations of the potential role of an automated  
386 measurements system can be extended for this parameter.

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

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

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

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

410

## 411 **Conclusion**

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

423

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426

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561

562

563 **Figures Captions List**

564

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

567

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

575

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

581

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

585 segmentations (AUTONoMA<sub>ONSL</sub> and AUTONoMA<sub>ONSR</sub>). E) Final calculation of the  
586 automatic OND and ONSD measurements (AUTONoMA<sub>OND</sub> and AUTONoMA<sub>ONSD</sub>).

587

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

590

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

595

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

600

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

605

606

607

608 **Tables**

609

610 Table 1

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

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

613

614 Table 2

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

OND	AUTONoMA	Operator 1	Operator 2
Mean value [mm]	$3.1 \pm 0.3$	$3.1 \pm 0.4$	$3.0 \pm 0.4$
Mean error [mm]		$0.06 \pm 0.35$	$-0.05 \pm 0.38$
Mean absolute error [mm]		$0.28 \pm 0.22$	$0.30 \pm 0.24$
Mean squared error [mm <sup>2</sup> ]		$0.12 \pm 0.17$	$0.15 \pm 0.25$
FoM		98.2%	98.3%

617

618 Table 3

619 Performance evaluation results of the AUTONoMA system compared to manual  
620 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 <sup>2</sup> ]		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

621

622

623

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.

Analysis	Measure	Correlation coefficient	Confidence interval		p-value
			Lower limit	Upper limit	
AUTONoM	OND	0.47	0.27	0.63	3.590 · 10 <sup>-5</sup>
A vs Op1	ONSD	0.64	0.48	0.76	1.541 · 10 <sup>-9</sup>
AUTONoM	OND	0.35	0.12	0.54	0.0031
A vs Op2	ONSD	0.61	0.44	0.74	1.375 · 10 <sup>-8</sup>
Op1 vs	OND	0.69	0.55	0.80	2.543 · 10 <sup>-11</sup>
Op2	ONSD	0.65	0.49	0.77	7.222 · 10 <sup>-10</sup>

627