

Computer Aided Diagnosis of Atopic Dermatitis

Joanna Czajkowska^{a,*}, Szymon Korzekwa^b, Ewa Pietka^a

^a Faculty of Biomedical Engineering, Silesian University of Technology

^b Department of Temporomandibular Disorders, Division of Prosthodontics, Poznan University of Medical Sciences

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ABSTRACT

Skin diseases with an allergic background such as atopic dermatitis are commonly noticed in children. This requires an urgent need to develop an objective and non-invasive method to examine the skin condition before and during the therapy. The newest clinical research mention the benefit of using high frequency ultrasound to image inflammation of the skin. A characteristic feature of inflammatory dermatoses is the presence of a superficial hypoechoic band below the echo entry in high frequency ultrasound images. Its measurement can be useful in the assessment of atopic dermatitis. To meet this need, this paper presents a novel fully automatic method for the characteristic hypoechoic band segmentation. A three step methodology includes epidermis echo entry layer detection and segmentation and on this basis the segmentation of the sought skin abnormality. The algorithm is dedicated to 75MHz US probe, which enables visualisation of a skin area of a 12mm length and 4mm depth. The accuracy of the proposed framework was verified on 45 clinical images annotated by two independent experts. The obtained results prove the benefits of using the ultrasound-based skin disease assessment framework.

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1. Introduction

Atopic dermatitis (AD) is a chronic, pruritic, recurrent, inflammatory cutaneous disease, mainly occurring in children (60% of all cases begin in the first year of life, and 90% - before age of 5), with a susceptibility to regress during childhood (60 – 90% up to 15th year of life) [Spergel \(2010\)](#). However, it may persist in a chronic, recurrent course until adulthood being resistant to any treatment strategy [Napolitano et al. \(2016\)](#) and coexist with other atopic diseases dependent on IgE: bronchial asthma, allergic rhinitis and food allergy. AD is the result of complex genetic, epigenetic, environmental and immunological interactions with the overlapping defect of the epidermal barrier [Schlapbach and Simon \(2014\)](#), [Garmhausen et al. \(2013\)](#). The incidence of AD increases worldwide with no standardization of diagnostic criteria using high-resolution non-invasive methods and an urgent need for accurate assessment and monitoring of treatment results [Napolitano et al. \(2016\)](#), [Silvestre Salvador et al. \(2017\)](#). There is no laboratory test to determine the severity of the disease. An invasive skin biopsy also does not show any specific histological characteristics [Tong and Mihm \(2017\)](#). The scoring indicators require subjective judgment and have poor reproducibility [Charman et al. \(1999\)](#).

High frequency ultrasound (HFUS) is one of the non-invasive methods of imaging skin inflammation. A characteristic ultrasound feature of inflammatory dermatoses is the presence of a superficial hypoechoic band below the echo entry, which may represent an acute inflammatory process with edema or infiltration in the upper dermis [Borut et al. \(2000\)](#), [Danczak-Pazdrowska et al. \(2012\)](#). It has been shown that there is a strong correlation between HFUS and histological features in the assessment of AD [Polanska et al. \(2013\)](#). Ultrasound refers to mechanical density waves with a frequency above 20 kHz.

Improvement of inflammatory skin condition may be visualized as a decrease of the thickness of superficial hypoechoic band (SLEB) and increase in the intensity of the dermis image [Polańska et al. \(2017\)](#).

The depth of the skin penetration (4 – 6mm of the 75MHz probe) is sufficient to image the epidermis, dermis, subcutaneous tissue and subcutaneous fat [Schmid et al. \(2005\)](#). The reflection of ultrasound waves from the border between tissues with different acoustic density is the basis for ultrasound skin imaging. This principle allows for the differentiation of tissues with only 0.1% difference in density [Bezugly \(2015\)](#).

As the HFUS becomes more and more popular in dermatological diagnosis [Polanska et al. \(2013\)](#), [Danczak-Pazdrowska et al. \(2012\)](#), [Polańska et al. \(2017\)](#), the HFUS image processing methods are developed [Gao et al. \(2013\)](#), [Sciolla et al. \(2015, 2018\)](#). However, since the US imaging is still not a standard procedure in derma-

* Corresponding author.

E-mail address: joanna.czajkowska@polsl.pl (J. Czajkowska).

tology, the described methods apply to various US frequencies (10MHz Gao et al. (2013) - 50MHz Sciolla et al. (2018)). As reported in Polańska et al. (2017), although 20MHz is well-established for scanning the whole skin, higher resolutions allow for a much more detailed imaging of the epidermis and the upper dermis layers. To meet this need, this developed methodology is addressed to 75MHz US image analysis. This allows the measure of SLEB thickness to be more accurate and robust. As reported above Gao et al. (2013), Sciolla et al. (2015, 2018), the different skin layer segmentation techniques have already been developed. Starting from the oldest, Gao et al. (2013) present an Automatic Skin Segmentation Tool (ASST) to evaluate the skin toxicity in breast cancer radiotherapy. The developed algorithm was based on a geometric framework and as the author reported, it outperforms the parametric approach. The overall goal of this work was the skin thickness measurement and the obtained values were compared with the expert annotations, resulting in 95% accuracy. The analysed database consists of 730 images acquired by a 10MHz frequency ultrasound. The frequency was lower than the frequencies typically used in dermatology (> 20MHz) yet it was imposed by the other measurements performed during the examinations.

The two newest approaches Sciolla et al. (2015, 2018) address the problem of high frequency (> 20MHz) US image segmentation. The first work Sciolla et al. (2015), being rather preliminary study targets in skin layers as well as tumour segmentation and introduces a generic Level Set (LS) segmentation algorithm based on the statistics of the envelope signal. The methodology was tested on simulated and medical images, yet the obtained segmentation results were not compared with expert delineations. The extension of the developed technique reported in Sciolla et al. (2018) presents a novel joint segmentation and characterization algorithm for the assessment of skin aging using 50MHz frequency US images. Authors proposed a segmentation method which allows a fine determination of the envelope signal statistics in the dermis as a function of depth. The accuracy of the automatic segmentation was validated using 20 annotated HFUS images. The SLEB area was also indicated by the algorithm, but the segmentation results in this case were not validated. Moreover, the analysed database did not contain the inflammatory cutaneous disease cases.

In this study a fully automated atopic dermatitis assessment framework targets in the segmentation and measurement of superficial hypoechoic band (SLEB) below the echo entry. The method enables the analysis of the inflammatory skin condition in patients with AD while monitoring the therapy results. The processing steps yield also the epidermis layer detection and segmentation for further numerical analysis. To the best of our knowledge, the SLEB segmentation methods for AD is not addressed in the literature. The methodology is dedicated to 75MHz US images, which is sufficient to visualize all the interesting skin layers. It consists of an automated entry echo layer detection followed by the LS method for epidermis segmentation. The main part providing the SLEB thickness is based on Weighted Fuzzy C-Means Clustering and active contour technique. The obtained segmentation results are compared with the expert delineations and the skin US image segmentation methods described in literature.

The paper is organized as follows. Section 2 presents the methods of the skin layer segmentation and skin abnormality analysis. The evaluation of the overall system is shown in Section 3 followed by Discussion (Section 4) and Conclusion (Section 5).

2. Methods

The algorithm of hypoechoic band segmentation contains three parts (Fig. 1). The first one automatically detects an Entry Echo Area. Then, the epidermis layer - highly echogenic band of entrance echo

is segmented. Finally, the last part focuses on the segmentation of the hypoechoic band between previously segmented epidermis part and the dermis area. The last area (hypoechoic band) will be interchangeably called SLEB and abnormality. The input images are acquired in the RGB colour space (see Figure 2). In various processing steps either separate channels or their combination are being subjected to analysis.

2.1. Entry Echo Area Detection

The detection algorithm is based on image I of a size of $N \times M$ pixels, being a linear combination of R and B channels, i.e. $I = R + B$. Let a matrix I_m be a rolling average of input image I calculated as

$$I_m[i, d] = \sum_{j=1+a(d-1)}^{a+a(d-1)} \frac{I[i, j]}{a}, \quad (1)$$

where a is a predefined window size.

The detection result is a vector $\mathbf{x}$ containing the row numbers, estimated for each column d of I_m , referring to j -th $j = (1 + a(d - 1), a + a(d - 1))$ column of analysed image I :

$$\mathbf{x}[j] = \max_i I_m[i, d] \quad i = 1, \dots, N. \quad (2)$$

The resulting vector $\mathbf{x}$ is then subjected to a median filtering procedure which is repeated iteratively and in each iteration the outlier most influencing the final result is removed from the analysis. This yields an $\mathbf{x}'$ vector. The obtained vector elements, filtration results and its visualisation in image I space are shown in Figure 3.

2.2. Entry Echo Layer Segmentation

The two step segmentation algorithm applies two different approaches, to Upper and Lower Edge, respectively (Fig. 1). Both introduce the Level Set (LS) segmentation Sethian (2000), Li et al. (2010) technique, with different starting contour selection and input image definition. Due to their flexibility to adapt to different problems the level set methods found a lot of applications in image segmentation Li et al. (2010, 2011), Göçeri et al. (2014), Göçeri (2016). This method makes it easy to follow shapes that change topology by breaking or merging during the evolution. Its main advantage is that one can perform numerical computations involving curves and surfaces on a fixed Cartesian grid without having to parameterize these objects Vineetha (2013).

As the starting contour for the Upper Edge segmentation, the area above a linear approximation $\mathbf{l}$ of the vector $\mathbf{x}'$ is taken (see Figure 1). The input image I_i further processed by the LS algorithm is obtained in following steps:

- 1 The image $I = R + B$ is subjected to the thresholding procedure, resulting in the binary mask $I_t = R_t + B_t$, where R_t and B_t are referred to R and B channels, respectively.
- 2 The regions indicated by the vector $\mathbf{x}'$ create the input image I_i for the LS approach.

According to the LS algorithm, the sought contour is a surface intersecting some plane, updated by forces derived from the image. The surface is represented as a zero level set ($\phi(i, j, t) = 0$) and can be divided into an internal and external region of the contour. Let be a time depended signed distance function defined on the surface:

$$\phi(i, j, t = 0) = \rho, \quad (3)$$

with the value ρ corresponding the shortest distance between the point on the surface and the contour. The function ϕ takes negative values inside the zero level contour, and positive outside. On the basis of this assumption Li et al. (2010, 2011):

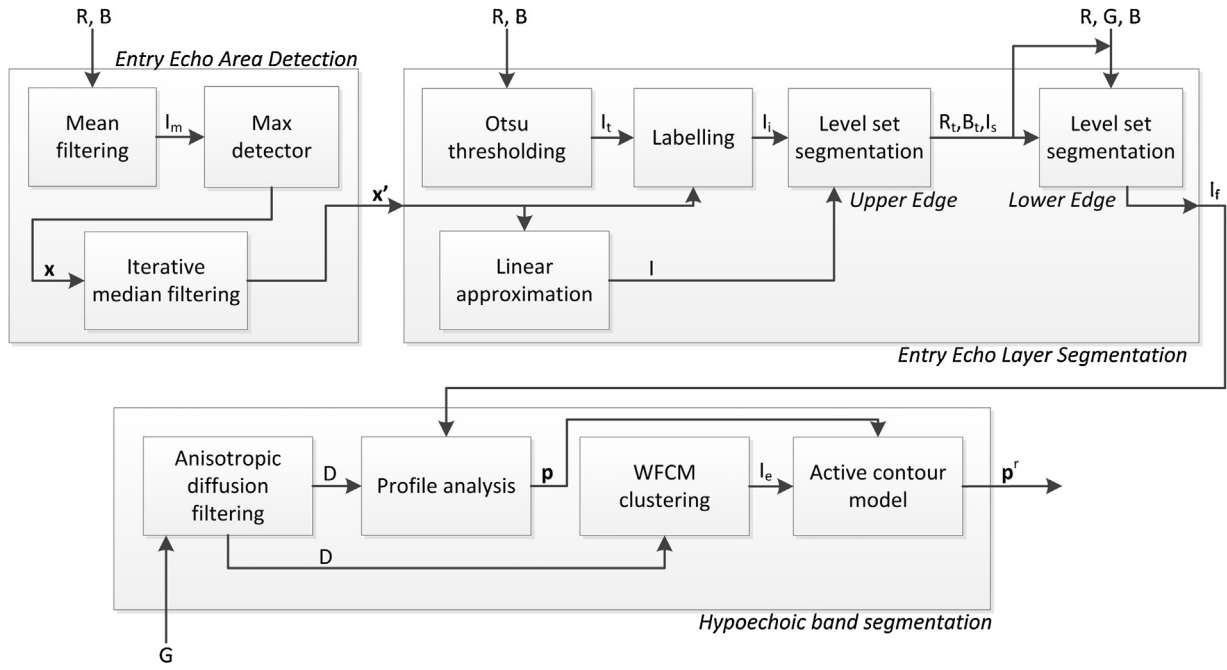


Fig. 1. Block diagram of hypoechoic band segmentation algorithm.

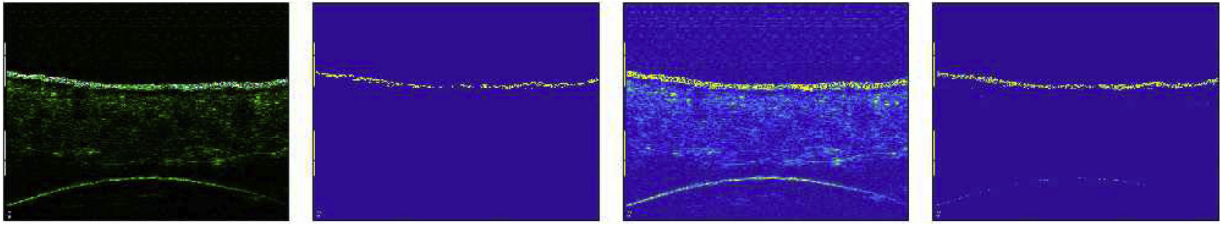


Fig. 2. Input US image in different channels: from the left - original image, R, G, B channel.

1 The curve evolution can be defined as

$$\frac{\partial \phi}{\partial t} = F|\nabla \phi|, \quad (4)$$

where ∇ is a gradient operator (L^2), and speed function F controls the contour motion.

2 The energy functional $\epsilon(\phi)$ is defined as

$$\epsilon(\phi) = \mu R_p(\phi) + \epsilon_{ext}(\phi), \quad (5)$$

where R_p is the level set regularization term, μ is a constant, and $\epsilon_{ext}(\phi)$ is the external energy depending on the image context.

3 The energy functional ϵ is then approximated by

$$\epsilon_\epsilon(\phi) = \mu \int_{\Omega} p(|\nabla \phi|) dx + \lambda \int_{\Omega} g \delta_\epsilon(\phi) |\nabla \phi| dx + \alpha \int_{\Omega} g H_\epsilon(-\phi) dx, \quad (6)$$

and can be minimized by solving the gradient flow equation defined as

$$\frac{\partial \phi}{\partial t} = \mu \operatorname{div}(d_p(|\nabla \phi|) \nabla \phi) + \lambda \delta_\epsilon(\phi) \operatorname{div} \left(g \frac{\nabla}{|\nabla \phi|} \right) + \alpha g \delta_\epsilon(\phi), \quad (7)$$

where $\mu > 0$, $\lambda > 0$ and $\alpha \in \mathbb{R}$ are the coefficients of the energy functionals associated with three energy terms: distance regularization term, weighted length term and weighted area term, respectively. The three values were chosen experimentally as: $\mu = 0.02$, $\lambda = 5$, $\alpha = 1.5$ based on 138 HFUS images of skin,

including the 45 of AD. δ_ϵ is the Dirac delta function, div is a divergence operator, d_p is defined as $d_p = \frac{\Delta p(s)}{s}$ with $p(s)$ being a parametrized potential function, with respect to s .

4 A speed function g is represented by

$$g = \frac{1}{1 + |\nabla(G_\sigma * I_i)|^2}, \quad (8)$$

where G_σ refers to a Gaussian Filter and I_i is the input image.

The obtained Upper Edge segmentation results are shown in Figure 4 as the green line. The already created contour is shifted down by 1 mm (the shift is twice as thick as the epidermis in human) creating the starting contour ϕ_s for the Lower Edge segmentation step. The input image I_s for the LS algorithm is defined as $I_s = a I_g + \max(I_g) * (b I_R + c I_B)$, where I_g is the analysed HFUS image converted to the grey scale and the values a , b , c are constants. They are selected in such a way, that the detected Echo Entry Area influences the final segmentation result the most, but the original image impact makes it possible to take care of epidermis details¹. The exemplary final level set contour I_f is shown in Figure 4 in red.

2.3. Skin Abnormalities Analysis

The skin abnormality is the superficial hypoechoic band below the echo entry. The entire analysis is performed on the previ-

¹ They are exponentially selected as: $a = 0.08$, $b = 10$, $c = 5$.

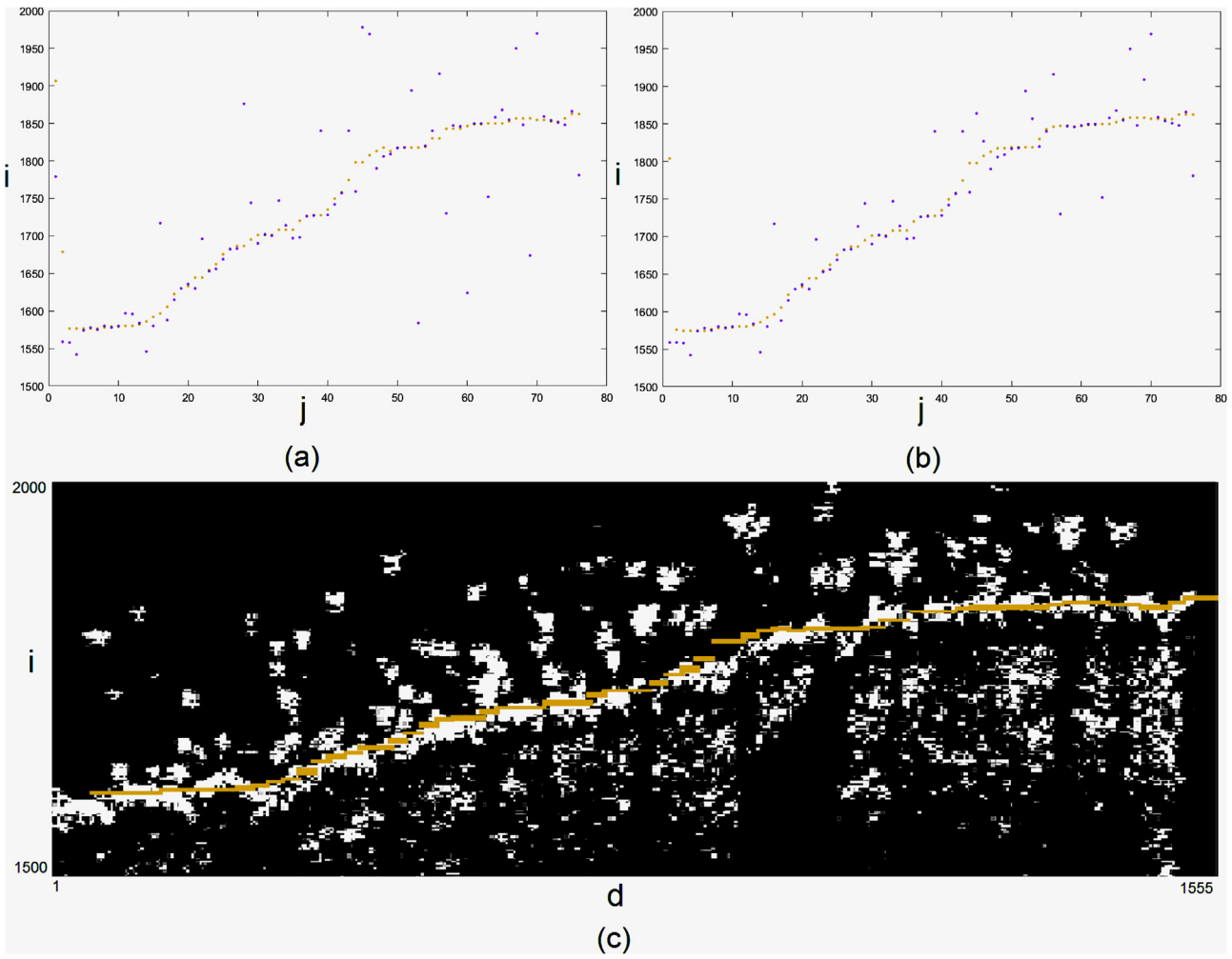


Fig. 3. Echo entry layer detection results: (a) – detected entry layer points (according to eq. (1) and (2)) – blue, median filtering results – yellow, (b) – outlier removal – 10th iteration, (c) detection results (yellow) in input image I .

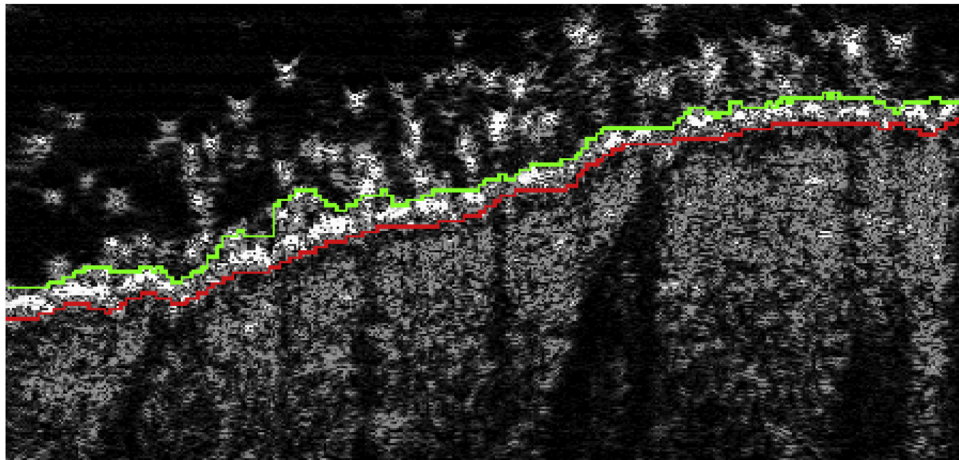


Fig. 4. The obtained Entry Echo Layer results, green – upper, red – lower edge, respectively.

ously filtered G channel, $I = G$. The filtering procedure incorporates anisotropic diffusion filter [Romeny \(1994\)](#), which removes artefacts and noise preventing the edges. The resulting image, in the block diagram (Figure 1), is denoted as D . The SLEB is segmented using Weighted Fuzzy C-Means Clustering (WFCM) [Szwarc et al. \(2015\)](#)

technique followed by a developed active contour algorithm. The WFCM clustering results shown in Figure 5 are treated as the internal force field I_e for the active contour model. On the other hand, the external force imposes the contour movement in the i -th coordinate direction.

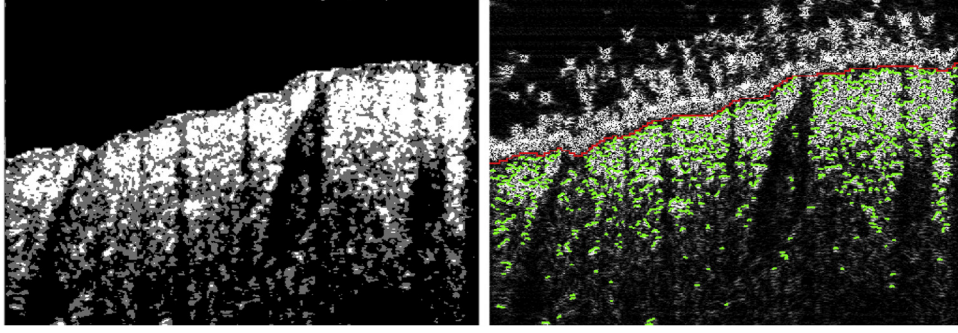


Fig. 5. Hypoechoic band segmentation step: Left - skin area WFCM clustering results, right - gradient field (green), starting contour (red).

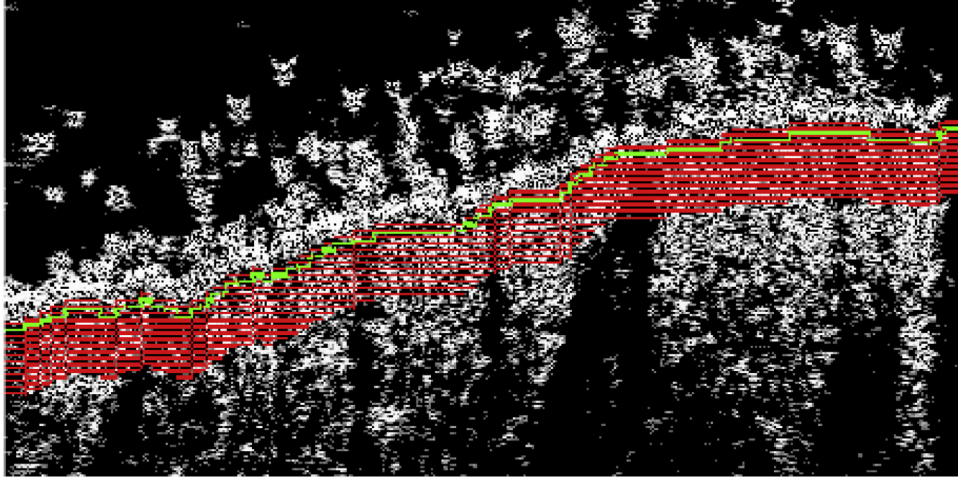


Fig. 6. Hypoechoic band segmentation step. Starting contour selection. Analysed lines - red, the line selected as starting contour - green.

- 1 Let the starting contour $\mathbf{p}$ be a line of the shape corresponding to the already obtained lower entry echo edge, placed below it - $\mathbf{x}_k$ (in the area of suspected hypoechoic band $k = 2, 4, \dots, K$), where $I_f(\mathbf{x}_0) = 1$, with the minimal mean intensity value h calculated (see Figure 5 left and Figure 6) as

$$h = \min_k \left(\frac{\sum_{n=1}^N \mathbf{x}_k(n)}{N}, k = 2, 4, \dots, K \right), \quad (9)$$

where K limits the searched area.

- 2 From this, the starting contour $\mathbf{p}$ is defined as

$$\mathbf{p} = \{(i^k, j^k); i^k = i + k, j^k = j\}, \quad (10)$$

where i and j are the coordinates of the lower echo entry edge so that

$$\forall_{(i,j)} I_f[i, j] = 1. \quad (11)$$

All the analysed lines and the chosen one are shown in Figure 6

Next, the contour $\mathbf{p}$ is moved in the i -coordinate direction. The resulting contour $\mathbf{p}^r = \{i^k + h_j, j^k\}$ and $h_j = \min(i_j^g - i_j^k)$, where i_j^k is the j -th coordinate i of contour $\mathbf{p}$ and i_j^g is a j -th coordinate estimated on the basis of an energy E :

$$E(i, j) = \begin{cases} 1 & \text{if } G_y(I_e) > 0 \\ 0 & \text{else,} \end{cases} \quad (12)$$

where G_y stands for the gradient in i -th coordinate.

The exemplary gradient field is shown in Figure 5, right. To avoid the influence of hair follicle appearing as vertical hypoechoic bands

the obtained contour $\mathbf{p}^r$ is subjected to median filtering, yielding the final segmentation results shown in Figure 7.

3. Measurements and Results

The images employed in this study were acquired with a digital ultrasonic DUB Skinscanner (tpm GmbH, Germany) with a 75MHz linear mechanical probe and scanning depth set to 4mm. The image resolution was equal to 2067×1555 pixels. In total, 45 HFUS images were acquired and delineated by two independent experts. The obtained final segmentation results of the hypoechoic band below the echo entry are compared with the expert delineations in 4 independent tests, referring to 4 aspects of the analysis: (1) - The measured thickness of the segmented band is compared with the measurements resulting from two expert delineations; (2) - The spatial overlap of two segmented regions (the abnormality area resulting from the expert delineation and developed algorithm application) is assessed using the Dice index:

$$DI = \frac{2 \cdot TP}{2 \cdot TP + FN + FP}, \quad (13)$$

where TP , FN , FP denote the number of true positive, false negative, and false positive pixels, respectively; (3) - The upper edge of the segmented band is compared with the expert delineations; (4) - The lower edge of the segmented band is compared with the expert delineation. For the last two measurements (3,4) the directed distance dD is defined as:

$$dD(A, E) = \text{mean}_{a_i \in A, e_j \in E} \min \|a_i - e_j\|, \quad (14)$$

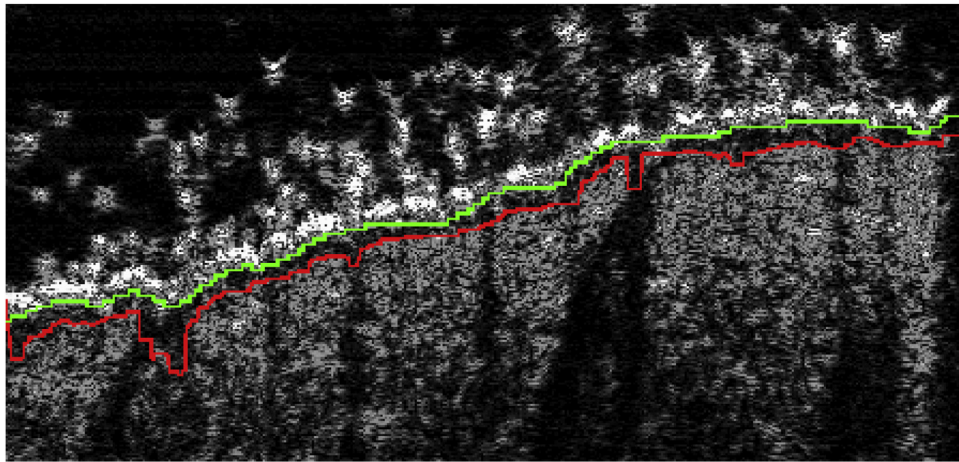
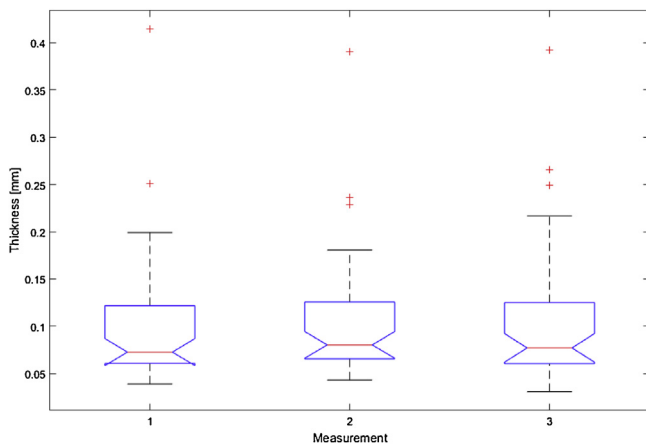


Fig. 7. Final segmentation results. Green (upper) - epidermis layer, red (lower) - abnormality area.



pK = 0.9369	(1) DM	(2) Exp 1	(3) Exp 2
Median	0.0728	0.0804	0.0772
Mean	0.1009	0.1019	0.1048
Std	0.0684	0.0641	0.0723

Fig. 8. The measured thickness in [mm] of the segmented band compared with the measurements resulting from two expert delineations. From the left: Developed Algorithm, Expert 1, Expert 2.

where $A = \{a_1, \dots, a_n\}$ and $E = \{e_1, \dots, e_n\}$ are two finite data sets representing algorithm and expert delineation, respectively. The results obtained (the mean values) and assessing boxplots are shown in Figures 8–10. In each step 3 test-dependent measurements are considered. For test 1 the hypoechoic band thickness is measured based on the developed algorithm (DM), and two expert delineations. Test 2 employs the Dice index and tests 3 and 4 – the distance measures for the inter-expert and computerized vs experts delineation discrepancy.

For statistical evaluation of the hypotheses, that the obtained results are comparable to those provided by the experts, the statistical analysis of multiple groups is introduced. First, the Shapiro-Wilk test ($\alpha = 0.05$) is applied to verify the null hypothesis that the 3 measurements came from normally distributed populations. On the basis of the test results the null hypothesis is rejected. Then, the Kruskal-Wallis H test has been used to verify the null hypothesis that the medians of all groups are equal. On the basis of the obtained p-Values (see pK in Figures 8–10) there is no reason

Table 1

The results of all the considered algorithms

Authors	no of cases	acq. freq [MHz]	dD [μm]	diff [%]
Czajkowska	45	75	8.5	4
Sciolla	20	50	62	-
Chan-Vese	20	50	160	-
Gao	20	50/10	99	5

to reject the null hypothesis. In the analysis of the lower edge of the segmented band (Figure 11), the inter-expert delineations differ significantly from the distance measures between the algorithm (DM), and each expert ($pK \approx 0$).

The results obtained have been compared with the latest skin layer segmentation techniques described in literature. Since, the problem of the SLEB segmentation is not yet addressed in 75MHz US, it was only possible to roughly compare the dD values estimated for the upper edge of the segmented band and the obtained skin layer thickness measurements. The results of all the considered algorithms are collected in Table 1. As reported in Sciolla et al. (2018), the mean dD was equal to $62\mu\text{m}$, that outperformed the other segmentation algorithms by Chan-Vese (2001) or Gao (2013). The mean dD for the developed technique is equal to $8.5\mu\text{m}$, that outperforms all the mentioned techniques. The percentage difference of skin thickness between ASST and two experts obtained in the experiments reported in Gao et al. (2013) were less than 5%, whereas in our approach the obtained SLEB thickness differs in less than 4% in comparison with both experts. However, it is important to mention, that the databases analysed in the experiments differ in analysed cases, their amount (in our work it is 45 and in Sciolla et al. (2018) it is 20) and acquisition technique (50MHz and 75MHz HFUS). Different applied acquisition techniques impose different image resolution, that influence the direct comparison of the obtained results.

4. Discussion

The main problem addressed in our study is the accurate SLEB segmentation and its thickness measurement. The solution was possible by the development of a three stages algorithm, which besides of SLEB segmentation, automatically detects and segments the epidermis layer. On the basis of the numerical data presented in Figures 8–10 one can conclude, that the obtained segmentation results are comparable with those generated by the experts. The estimated hypoechoic band thickness – the sought diagnostic parameter is similar to the values obtained by the experts. For

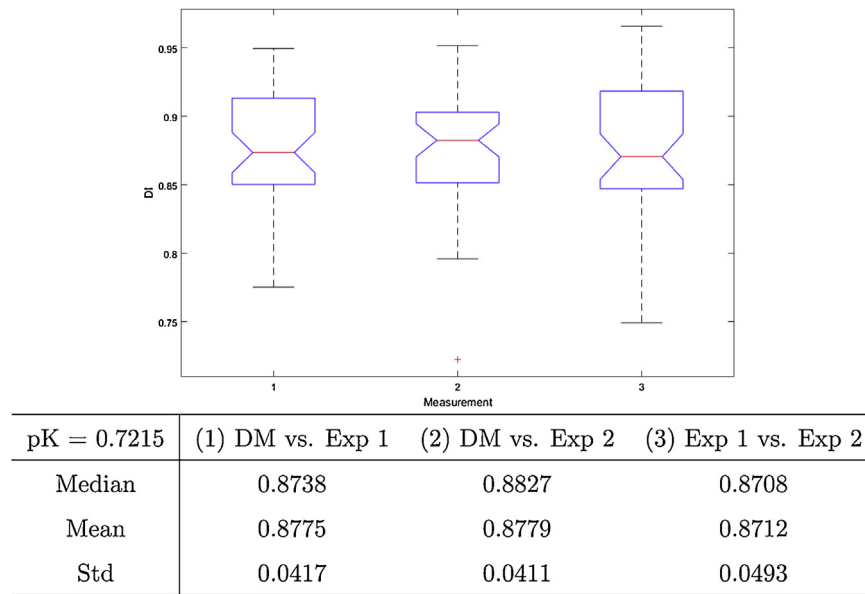


Fig. 9. The spatial overlap of two segmented regions - Dice index. From the left: Developed Algorithm vs. Expert 1, Developed Algorithm vs. Expert 2, Expert 1 vs. Expert 2.

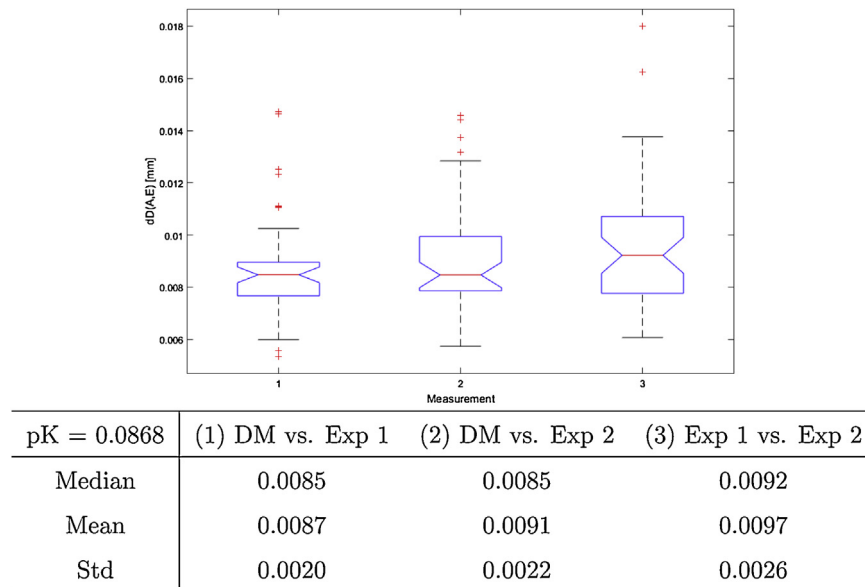


Fig. 10. The upper edge of the segmented band compared with the expert delineations - directed distance [mm]. From the left: Developed Algorithm vs. Expert 1, Developed Algorithm vs. Expert 2, Expert 1 vs. Expert 2.

the Dice index, the spacial overlap of the obtained results and two expert delineations, in each case are higher than the overlap between experts. In the analysis of the lower edge of the segmented band (Figure 11), the inter-expert delineations differ significantly from the distance measures between the algorithm (DM), and each expert. However, on the basis of the empirical comparison, we conclude that the discrepancies result from a more detailed DM segmentation. The expert delineation is more general and yields smoother edges. This is noticeable in HFUS examination of high epidermis inequalities. After excluding this part of data from the statistical analysis the obtained results are comparable to the expert delineations (see Figure 12). Moreover, the difference in some pixel segmentation results does not affect the final hypoechoic band thickness and all the obtained results are annotated by the experts as acceptable/good.

It is worth mentioning, that the developed methodology is insensitive to hyperechoic hair appearance, what is problematic in the other segmentation techniques described in literature [Chan and Vese \(2001\)](#), [Gao et al. \(2013\)](#). An exemplary segmentation result in the HFUS image with visible hair echo is shown in Figure 7. The obtained segmentation and measurement results were verified by two independent experts and the statistical evaluation has proven their efficiency. The worst segmentation results in comparison with the expert delineations were observed in case of strong skin damage. In such cases the algorithm performed an accurate segmentation of the hypoechoic band, whereas the experts try to smooth the resulting inequalities. However, the visual verification of the segmentation results favored the developed method. The developed software can be used in the AD and other inflammatory cutaneous disease treatment monitoring, drug selection and skin condition evaluation. The benefit of using it is the accurate,

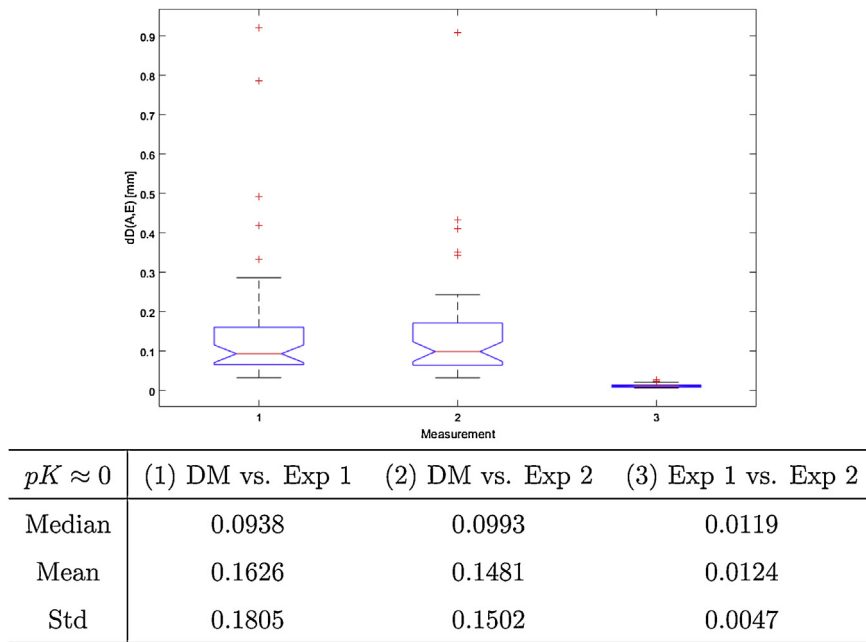


Fig. 11. The lower edge of the segmented band compared with the expert delineation - directed distance [mm]. From the left: Developed Algorithm vs. Expert 1, Developed Algorithm vs. Expert 2, Expert 1 vs. Expert 2.

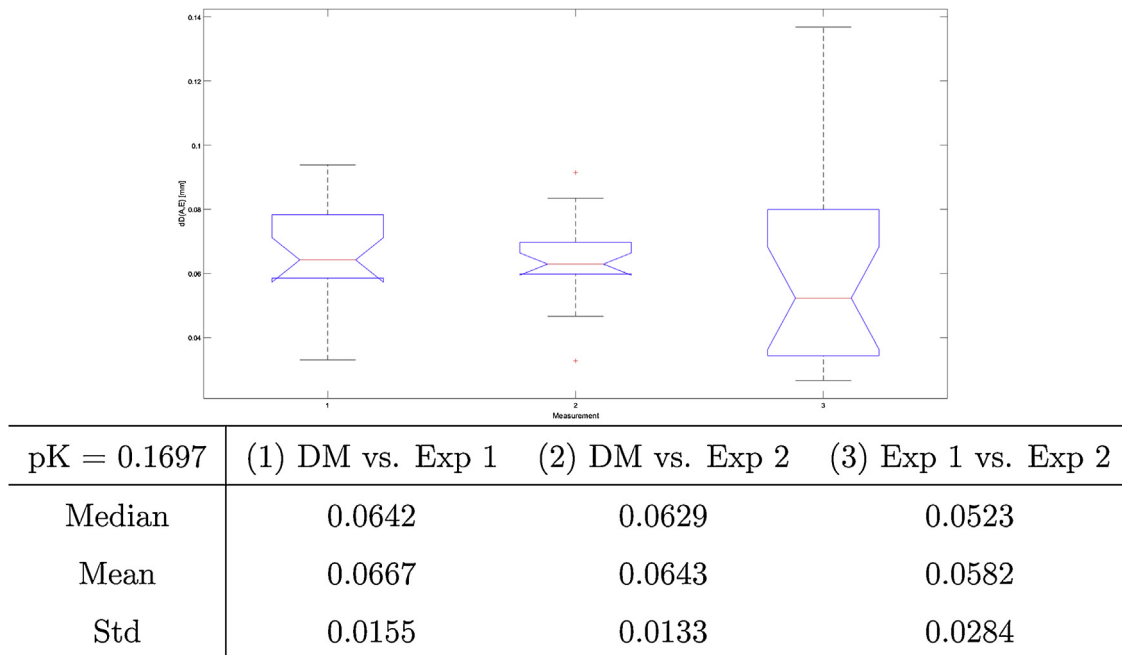


Fig. 12. The lower edge of the segmented band is compared with the expert delineation (23 images) - directed distance [mm]. From the left: Developed Algorithm vs. Expert 1, Developed Algorithm vs. Expert 2, Expert 1 vs. Expert 2.

repeatable and less time consuming (comparing with the manual delineation) measurement assessing the skin condition.

5. Conclusion

The paper presents the robust and efficient technique for the SLEB segmentation and therefore its measurement. Our work addresses the SLEB segmentation problem in 75MHz US images. The developed methodology can be used to monitor the skin condition during the AD therapy. The methodology contains three parts resulting in: epidermis layer detection, epidermis layer segmen-

tation and SLEB area delineation. The relevance of the algorithm is demonstrated on 45 clinical patients. The obtained SLEB segmentation and measurement results are compared with the expert annotations and is ready for clinical evaluation. Moreover, the obtained SLEB delineation is more accurate than the expert annotation in the cases, where the processed layer is not smooth any more - the experts agreed that mostly they simplify their delineations. The obtained results of skin measurements were, in the widest possible range, compared with the other skin segmentation approaches described in literature outperforming them in the skin layer thickness measurements.

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