[19] Methods for digital analysis of human vascular system. Literature review

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Abstract

A review of key approaches to the digital analysis of the human vascular system images is given in the paper. We outline major stages of diagnostic image processing and analyze different approaches to the extraction and quantification of blood vessel morphological features.

Keywords: *human vascular system, image processing*

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Introduction

Computer-aided image analysis has become a main instrument for medical diagnostic systems that allow to significantly improve the diagnosis quality. Modern medicine is one of the most high-technology industries the most important task of which is to develop new and efficient methods for early diagnostics of various health problems. The last few decades have been characterized by a significant breakthrough in the field of technological infrastructure of medicine. For the time being almost all examination techniques in ophthalmology, cardiology, and other areas of medicine have been computerized.

As for ophthalmology, with the appearance of digital fundus cameras and then laser scanning ophthalmoscopes, the fundus imaging may be obtained and printed out within a few seconds. Retina digital photographs are widely used in large-scale studies to identify glaucoma, diabetic retinopathy, age-related macule degradation and cardiovascular diseases. The human fundus imaging system contains the information about vascular, ophthalmic and even systemic diseases such as diabetes, hypertonia and arteriosclerosis. Except for the usage in large monitoring programs, the digital image analysis of the human vascular system is capable to help in assessing the severity of diabetic retinopathy [1], age-related retinopathy [2], retinopathy of prematurity [3], as well as in finding a foveal avascular zone [4], narrowing of arterioles [5]; measuring a diameter within the framework of hypertonia diagnostics [6], to define relationships between vascular tortuosity and hypertensive retinopathy [7], in early detection of such diseases as degeneration of the optic nerve and the retinal separation. Analysis of changes of characteristics of blood vessels and various diseases contributes to early disease detection and treatment still in early stages. Computer-aided analysis is also used in computerized laser surgery and for biometric identification [8].

In addition to the development of biomedical computer technologies and analysis and image processing systems, the semi-automatic and later fully automated computerized systems of recognition and quantitative analysis of microvascular changes turned to appear.

Creating of digital analysis technique for the human vascular system (VS) is impossible without solving a number of issues, i.e. detection of blood vessels in digital images, selection of methodology for the blood vessel analysis and a computing model of a vascular bed for subsequent calculations, and determination of standard values for diagnostic parameters.

Detection of blood vessels and determination of their morphological features are the key stages of computerized methodologies of the diagnostic analysis of the human vascular system (VS), since the diagnostic results will be dependent on the accuracy of detection and measurement of its elements.

1. Review of digital analysis of the human vascular system (VS)

Detection of blood vessels and determination of their morphological features such as width, length, tortuosity, angles of bending vessels, etc., is now widely used for diagnostic purposes, monitoring, medical care and evaluation of various cardiovascular, ophthalmic and other diseases. Manual processing and analysis of diagnostic images (segmentation of blood vessels and measuring their width and tortuosity) is a long-term and fatigue issue which also requires special training and professional skills [9]. Specialists have to learn to distinguish damages in the human vascular system (VS) from its visual appearance without pathologies. Moreover, a human subjective factor has always occurred in such kind of analysis that often results to differences in diagnosis determined by physicians.

It is not surprise that with the growing number of human patients and the necessity of searching ways to improve monitoring quality of the human vascular system (VS), some significant efforts were made during the last 20 years to develop computer technologies capable to detect changes in the human vascular system. The medical community has agreed that automatic quantification of the human vascular system (VS) is the first step in the development of computerized diagnosis systems for human diseases [9]. Many algorithms and methods of numerical analysis of the human vascular system have been published.

In order to identify health problems the image analysis of human vascular systems is narrowed down to the image recognition. Detection of multiple patterns and their connection with images of blood vessels is associated with some operations or stages, the usage of low-quality image processing methods which allow to proceed to the more sophisticated analysis. Digital images of blood vessels shall be processed using algorithm sequencing that may consist of one or more stages of the pre-processing proceeding to the stages of image segmentation, assessment and classification. The pre-processing may be used to align the image brightness, non-uniformity correction, noise suppression or distortion elimination. Segmentation divides the image into fragments containing individual objects, for example, blood vessels, an optic nerve root or cancerous injuries. When evaluating features the numerical information about specific objects obtained by means of segmentation should be assessed. The evaluated features may be used to classify objects according to predetermined criteria such as size, structure or color.

In 2003 in the report on Health Technology Assessment made to the NHS (National Health System) Sharp published the review of Standard Operating Procedures for digital images in the field of diabetic retinopathy which had been completed in 1998. According to the authors, their original purpose was to conduct the numerical analysis of different technologies operating with digital diagnostic images. In paper [10] it is noted that they failed to do so, since digital technologies were only at early stages of their development in this field. The first reviews of algorithms for detection of blood vessel-like structures in medical images may be seen in papers [11,12]. For example, Kirbas and Quek [13] presented a comparative review of methods and algorithms for detection of blood vessels and oblong objects both in two-dimensional and three-dimensional medical images applied in different tasks. A summary review of algorithms of segmentation and retina registration was represented by Mabrouk et al. [14], who had limited the discussion by the tasks of detection of boundaries and central lines of blood vessels. Algorithms of automatic diagnostics of diabetic retinopathy in retinal images have been discussed in the latest discoveries. The review [10] is unique since it has presented the analysis and categorization of the literature related to digital image processing technologies in the field of the diabetic retinopathy (DR) published in the period from 1998 to 2008, and has focused on algorithms and methods of segmentation in retinal two-dimensional color images obtained with the help of fundus cameras. This review is still the best of all available ones used for diabetic retinopathy. The paper has emphasized only DR and includes the analysis of such characteristic of DR as microaneurysms, small petechial hemorrhages, blood stains, lipid exudates and gossypium-like patches which, as a matter of fact, are considered to be microinfarctions of nerve fibrils.

The paper [9] provides an overview of algorithms mainly focusing on selection of blood vessels on retinal two-dimensional color images obtained by means of fundus cameras or by Fluorescein angiography for the period from 1995 to 2010, and the emphasis is mode only on researches related to segmentation of retinal vessels.

The paper provides a classification of digital analysis milestones of the human vascular system in diagnostic tasks of vascular pathology, classification and review of methods and algorithms used by researchers to detect blood vessels and to evaluate their morphological features. The works included in the review were examined for the presence of new computer algorithms to detect symptoms of vascular pathologies. The bibliography of references was used as a secondary source in the statistical analysis. When analyzing the papers we have categorized them in accordance with their reference to various processing stages of diagnostic imaging of the human vascular system. Totally 216 papers have been examined in the review including 312 secondary sources [9,10]. The following seven milestones of the analysis of key features of blood vessels have been defined: evidence-based medicine (A), pre-processing (B); localization and segmentation of the optic nerve disk (C); vascular segmentation (D); vascular tracing (E), diameter evaluation (F), diagnostic characteristics evaluation (G). Fig. 1 shows a number of papers relating to each stage of the above sequence (A through G).

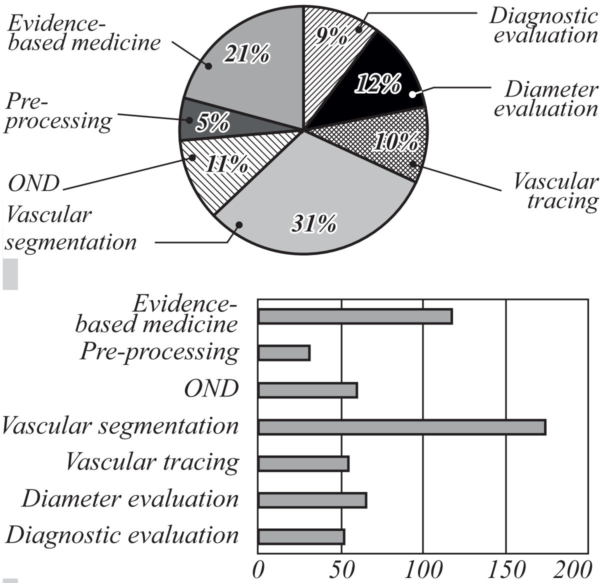

Fig 1. Distribution of papers in accordance with stages of vascular imaging: evidence-based medicine (Stage A), pre-processing (Stage B); processing of the optic nerve disk (OND) (Stage C); vascular segmentation (Stage D); vascular tracing (Stage E), diameter evaluation (Stage F), diagnostic characteristics evaluation (Stage G)

The largest number of publications (175 papers) is connected with segmentation of the human vascular system (VS). The smallest number of papers relates to diagnostic characteristics evaluation (Stage G). The problem of image pre-processing is discussed totally in 31 publications. Fig. 2 shows what number of papers relates to a particular method of pre-processing. Methods of color normalization have been discussed in 11 papers which amounts 35.5%. Totally 22.6% of the whole number of discovered publications has been devoted to the local contrast enhancement and 26% – to the illumination intensity justification.

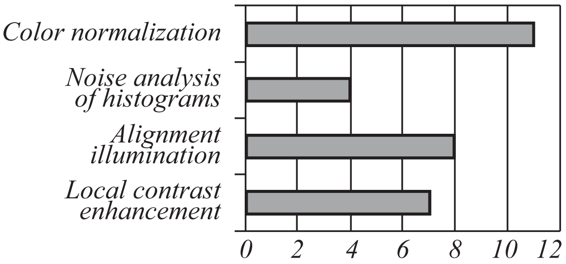

Fig. 2. Usage frequency for various pre-processing techniques

The problem of digital analysis of blood vessels of the optic nerve disk (OND) has been discussed in 60 publications. Fig. 3 shows that the largest number of papers has been devoted to the problem of localization of the optic nerve disk and much less to evaluation algorithms of features of the optic nerve disk to diagnose pathologies (they are only 12%).

2. Classification of vessel selection methods

Two basic approaches are used to select blood vessels, i.e. vascular segmentation that allows to identify the whole vessel tree during one single processing stage, and vascular tracing or step-by-step vascular tracking. Vascular segmentation is further divided into some subcategories.

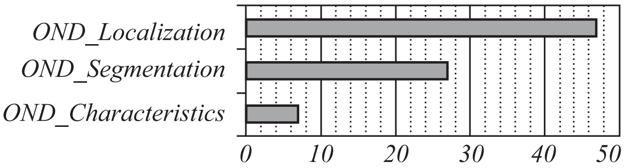

Fig. 3. Distribution of papers in accordance with stages of the optic nerve disk (OND) imaging: OND localization, OND vascular segmentation, OND diagnostic characteristics evaluation

In literature the algorithms of vessel-like objects detection in medical images are usually divided into the following classes: algorithms based on identification of object's boundaries; algorithms of areas' enlargement; pattern-matching techniques; model-based techniques; neural network-based techniques; algorithms based on objects tracking [9,10]. A set of vascular selection algorithms would be presented by the following six categories:

- classification of image readings (without learning, with learning);
- matched filtering;
- mathematical morphology;
- multiscale approaches;
- model-based approaches;
- vascular tracking and tracing.

Some of these categories have been further splitted into sub-categories.

A total of 218 papers among all being under consideration including segmentation and tracing approaches has been dedicated to the problems of vascular detection. Fig. 4 shows the usage frequency in papers related to each of the above approaches and a share of the total number of papers dedicated to vascular selection.

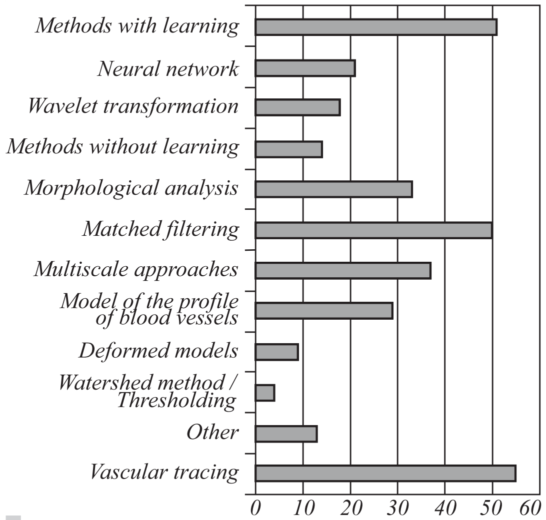

Fig. 4. Usage frequency in papers related to different methods of vascular selection

Fig. 4 shows that among the approaches relating to vascular selection the following three methods shall prevail: 25% of the analyzed articles have used vascular tracing techniques, whereas the other 22.9% and 23.4% have applied the approaches based on matched filtering and pixels-classification user participation approaches (with learning), whereof neural network-based techniques amounted to 32%. Approximately 17% of the papers used multiscale approaches, the morphological analysis (15%), model-based approaches (17%), and 6.4% used the automated recognition algorithms without learning.

The computerized image processing was first applied in 1982 [16], and the first article about vascular selection was published by Thackray et al. [17] in 1982. A total of 115 articles among 410 papers (without evidence-based medicine) was published in the period before 2000. Distribution of papers by years of their publication is given in Fig. 5. There were 18 publications in 2000, then 31 – in 2001, and 19 and 24 – in 2002 and 2003, respectively. The number of articles increased up to 27 in 2004, and significantly decreased to 17 in 2005, then to 19 in 2006 and to 14 in 2009, and then it increased up to 34 by October 2010, and there was a noticeable reduction up to 21 in 2011. A total of 26 publications were found during the period of 2012-mid 2013.

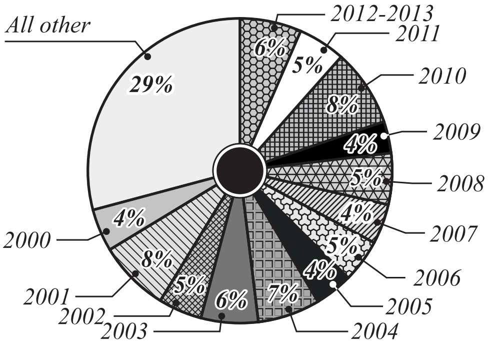

Fig. 5. Papers distribution by years

Fig. 6 provides also the papers distributed by years and stages of the vascular image analysis (stages A-G) that shows the contribution of year-to-year researches made into each stage of the vascular image processing.

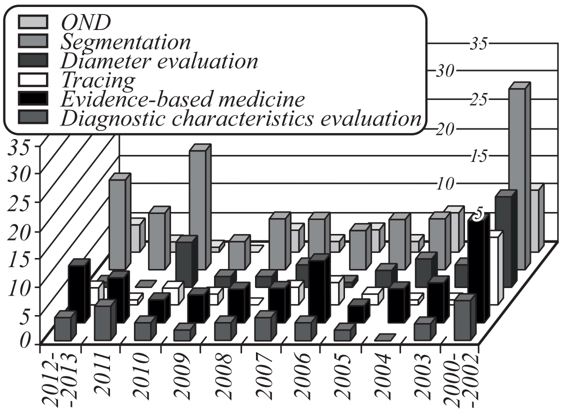

Fig. 6. Papers distribution by years and stages of the vascular image analysis

Thus, the techniques described in the papers have been categorized in accordance with their belonging to one of the stages of the image analysis:

A. Evidence-based medicine.
B. Pre-processing.
(1) Elimination of illumination unevenness .
(2) Color matching.
(3) Contrast enhancement.
C. Processing of optic nerve disk (OND) images.
(1) Optic disk localization.
(2) Optic disk segmentation .
(3) Optic disk parameters evaluation.
D. Segmentation of the vascular system.
(1) Classification of image readings (without learning, with learning)
(2) Matched filtering.
(3) Mathematical morphology.
(4) Multiscale approaches.
(5) Model-based approaches.

E. Vascular tracking and tracing.
F. Diameter evaluation.
G. Diagnostic characteristics evaluation.

3. Evidence-based medicine (A)

A total of 118 papers devoted to the evidence-based medicine has been reviewed that amounts 21% of the total number of papers dedicated to the analysis of vascular system images, and it has shown the great interest of physicians to this research area. These papers proved that the detection of blood vessels and estimation of their morphological features, such as length, width, tortuosity, angles of bending vessels, etc., can be used for diagnosis, monitoring, treatment, and evaluation of various cardio-vascular, ophthalmic diseases such as diabetes, hypertension, arteriosclerosis and neovascularity of the vascular membrane, etc. [18]. A wide range of various researches has been also demonstrated in this field. The authors have widely used numerical measurements of the vascular system (VS) as auxiliary tools to study the relationship between structural changes of blood vessels and different diseases.

It is shown in papers that the automated detection and the digital analysis of the human vascular system can help to implement monitoring systems in diabetic retinopathy [1,19,20] and senile retinopathy [1,21]. Injuries occur in case of hypertension of the elderly, as well as in humans with a low birth weight. According to studies [22,23] both of these factors are associated with frequent morbidity and even with the mortality from the cardiovascular diseases. In papers [24,25] the link between changes in the vascular system and cardiovascular diseases is shown.

The first project on the diagnostic automation of retinal images entitled STARE (Structured Analysis of the Retina) was launched in 1975 in the US by Dr. Michael Goldbaum and his research team [26]. They created a database of medical images called STARE and did a lot of important things in the field of diagnostic automation. In 1989 they designed a matched filter, also known as the North filter, for the segmentation of vessels [26], and as of today it still remains the most reliable vascular detector. In 1996 they published a review [27] which collected the majority of studies existed at that time in the field of diagnosing. They presented the following algorithms of diagnosing [28]:

- Localization of the most important areas such as blood vessels and the optical disk using segmentation methods.
- Search for pathologies characteristics such as venous expansion, excessive bending of vessels, etc., using the classification approach.
- Establishing diagnosis based on identified pathology characteristics.

They have also published their researches in the field of medicine [29] which served as a theoretical basis for the automated diagnostics. They noted that the eye retina would tell about the hundreds of diseases, and their system could make at least 13 different diagnostics on the basis of at least 39 characteristics of vascular changes. Despite of the fact that this system was considerably inferior to an physician experienced in diagnostics issues it demonstrated fairly good results at that time [28].

A project on creation of the EyeCheck diagnostic system was also launched in Europe wherefore Dr. Michael Abramov and his team had been working [30]. They created the DRIVE image database and performed a great job in the field of vascular segmentation [19,31]. Numerous studies in the diagnosis of vascular pathologies have focused on the recognition of the retinal image [1,19,21,26,32] as the first step in building automated systems for the vascular diagnostics [28]. The most significant retina areas are as follows: the optical disc, the fovea and the retina vascular system. The identification of these areas would help professionals to detect diseases which affect these areas in the first place [28]. It is glaucoma which causes expansion of the optic nerve, hypertension which makes blood vessels more tortuous, diabetic retinopathy that would cause the growth of new blood vessels which have a specific curving form, etc. [33-36]. The optical disk can also serve as a reference or a starting point for the algorithms of the vascular selection. The authors of [28] also noted that notwithstanding the existence of many diseases which could cause retinopathy, the majority of researchers have focused on diabetic retinopathy for the following reasons: 1) diabetic retinopathy (DR) is a serious disease that causes blindness; it can even cause the death; 2) this disease affects a large number of people and there is the possibility of its early detection and successful treatment [33-36]; 3) to detect diabetic retinopathy the localization of the optic nerve disk and the vascular detection should be required, and considerable experiences have been already accumulated in this field.

In paper [37] physicians studied the correlation between an increasing diameter, elongation or distortion of coronary arteries and the age of patients with myocardial infarction. Physicians have shown the increase in diameter and tortuosity within a long period of time after myocardial infarction. In paper [38] we investigated the link between the diameter of blood vessels and the incidence of coronary artery disease (CAD) in type 1 diabetes (PD1) using the data received from the Epidemiology of Diabetes

Complications (EDC) from Pittsburgh. The authors confirm that a smaller caliber of arterioles may indicate an increased risk of coronary artery disease (CAD) for women with type 1 diabetes (PD1), and additional researches shall be required to further investigate the role of microvascular diseases in the pathogenesis of coronary artery disease (CAD) for women type 1 diabetes (PD1).

Many papers is devoted to the study of retinopathy of prematurity (ROP) [3, 39-43]. Retinopathy of prematurity is a disease that is reflected in eyes of many prematurely born infants. If retinopathy is not found within the first few days after the birth, blindness may occur. Researches have shown [44] that the analysis of vascular changes may help to identify a disease at an early stage and its timely treatment can save a baby's eye. The authors have developed a new tool to evaluate retinopathy of prematurity based on quantitative estimation of tortuosity and expansion of blood vessels. The authors of paper [40] have shown that tortuosity happened to be a more reliable and promising parameter than the vessel width to detect ROP. In paper [45] the physicians studied the connection between the diameter change rate of retina vessels and a high risk of severe retinopathy of prematurity (ROP). In paper [46,47] the authors have presented new methods for tracking and estimating tortuosity of vessels to analyze the progress and the severity of ROP and have studied the correlation of the severity of ROP with the width of vessels and their tortuosity.

In paper [20] the authors have set a goal to evaluate relations between retinal vascular calibers associated with AIDS and death factors. They have shown that there are changes in retinal vascular calibers associated with HIV-specific factors. These changes are considered to be as markers of increased risk of mortality. Relations between calibers are consistent with a theory that vascular changes are associated with the known atherogenic effects of highly active anti-retroviral therapy (HAART) or with longstanding chronic phlogotic health conditions associated with AIDS [20].

4. Pre-processing of digital vascular images (B)

An important feature of the vascular image is its quality that is affected by such factors as opacity, defocusing, the presence of a noise component or uneven illumination, and the main purpose of pre-processing methods is to increase the quality of the diagnostic image for its subsequent analysis. Distortions appear in single images due to the difference in light scattering in different parts of the object being photographed, as well as due to changing of its thickness [10]. Differences between the images of the same object appear because of different cameras, the difference in lighting, shooting angles and different pigmentation. Pre-processing of both gray halftone and color images of blood vessels can be splitted into the elimination of illumination unevenness, contrast enhancement and color alignment. Issues of this processing of the human vascular system (VS) have been discussed more detailed in paper [10].

5. Segmentation methods (D)

The selection and quantification of blood vessels are of primary interest in diagnostics tasks and treatment of some diseases. As mentioned above, the precise detection of the human vascular system (VS) is considered to be frequently an important step in localization issues for various anatomical parts of the body, as well as in localization of pathology characteristics. Difficulties in precise detection of blood vessels are connected with the following facts: 1) the width of blood vessels may vary within wide limits; the retina vascular system is a tree-like structure where the closer the vessels are located to a tree bottom, the thicker they are; the thickness may vary from 1 to 20 pixels depending on the location of the blood vessel and the image resolution, 2) the intensity of the blood vessel may be slightly distinguished from the background intensity, and 3) various retinal damages can cause a false operation of segmentation algorithms.

There are two basic approaches to select blood vessels, i.e. vascular segmentation that allows to detect the whole vessel tree as one iteration, and vascular tracking (tracing). The following approaches would be identified with regard to the development of vascular segmentation algorithms according to the references [9,10]:

- classification of image readings (without learning, with learning);
- matched filtering;
- mathematical morphology;
- multiscale approaches;
- model-based approaches.

Classification algorithms of diagnostic images. Pattern recognition algorithms are based on the detection of anatomical parts of the organ being investigated or on the classification of blood vessels and other objects including the background. They are divided into the following two categories: user participation methods which use the information previously indicated to decide whether a pixel belong to the vessel, and completely independent methods which carry out the segmentation without user involvement.

Methods with learning. These methods apply the rules developed by the algorithm based on a learning sample of the images marked by an ophthalmologist manually with a sufficiently high accuracy [9,48]. A set of such images is usually called the gold standard. However, as it was noted in [49], there are significant differences in marking even among professionals. Issues of this approach to vascular system segmentation shall be discussed in more details in paper [10]. Since such methods are based on the images already classified, their efficiency is usually higher if compared with any other methods.

Methods without learning. Approaches based on the pixel classification without learning samples shall carry out search patterns that are typical for blood vessels in retinal images. Direct use of the learning sample is not required in these algorithms [51-60].

Matched filtering. Matched filtering allows to define vessels by means of the image convolution with a two-dimensional filter core [9,10]. The core shall be designed so as to fit the model of an object in the absence of information about its location and space orientation, and the matched filter response (MFR) shall indicate the presence of the object in the image. When designing the filter the following aprior information about blood vessels is usually used: the vessel bending is limited, the vessel itself can be approximated by means of the piecewise linear function; the vessel diameter decreases with increasing a distance from the center of the optic nerve disk (OND); a cross-section of the vessel can be approximated by means of the Gaussian curve. In paper [9] it was emphasized that the filter core should be fairly large, and the filter itself must be applied in several ways that should lead to a significant increase in computational complexity. The filter core should also comply with the blood vessel scale to be identified. As a result, the filter will not give a clear response to the blood vessel which has a profile with an excellent scale. Changing of the image background and the presence of various pathological artifacts shall also increase the rate of filter false responses, since pathologies may have the parameters which are similar to the parameters of blood vessels. The usage of matched filtering shall be justified in combination with other methods of the image processing [49,61-65].

In paper [26,66] the authors have proposed to use a two-dimensional filter core for vascular segmentation on the basis of the Gaussian function or its derivative coefficient. The filter's profile shall be designed thus to match the blood vessel profile in the best way which usually has the shape of the Gaussian function or its derivative. In [26] the filter core is rotated in increments of 15 ° to better match the vessels with different space orientation. In order to obtain binary images of blood vessels, the best filter response should be identified for each pixel that will be further subjected to thresholding. Some other image processing methods are to be further applied to obtain the segments containing blood vessels.

Morphological processing. Mathematical morphology is used as a tool to extract parts of the image which are useful to describe different forms such as boundaries and a vessel's skeleton. Mathematical morphology provides a powerful tool to solve many problems of image processing. Morphological operators have been used for localization of microaneurysms and also for vascular segmentation [68-74].

Morphological processing is a set of approaches for the digital image processing based on the mathematical morphology. Morphological operators apply structural elements (SE) to the image and usually operate with binary images, though the area of application may be extended to gray halftone images. Two basic morphological operators shall be used: erosion and dilation. Dilation expands the object by means of the structural element (SE) thus to fill holes and to connect separated areas. Erosion compresses the object by means of SE. There are two other operations: morphological closing (first the dilation operation and then the erosion operation are applied to the object) and opening (dilation follows the erosion). The following two similar operations are applied in the segmentation of medical images: the TopHat transformation [69,75] and the watershed method [76]. Blood vessels should be underlined by means of the TopHat transformation (its effect is associated with the morphological opening) which evaluates a local background, and then subtracts it from the original image, thus highlighting blood vessels. It is priori known that the basic structure of the human vascular system can be represented by means of interconnected line segments. Morphological processing for identification of certain forms has the advantage of high operational speed and noise resistance. The main disadvantage of using only morphological methods is that they do not use the information about the shape of the vessel profile. In addition, when searching for only oblong structures we may neglect highly-tortuous blood vessels.

The combination of morphological filters and the vessel profile evaluation for segmentation of vessel-like structures has been proposed in [68,69]. In order to underline blood vessels in monochromatic retinal images the mathematical morphology uses the fact that blood vessels have a strait shape in the local scale, they are interconnected and their curvature can vary only within certain limits. The profile evaluation is used to filter objects which are not the blood vessels.

In [1] the DoOG-based algorithm (Difference of Offset Gaussian) of the filter and multiscale morphological reconstruction was used for segmentation of blood vessels. Central lines of blood vessels were selected be using the DoOG filter and the vessels themselves were underlined by means of the modified TopHat transformation based on structural elements with different sizes to select blood vessels of various widths. The binary image of blood vessels was obtained for 4 different scales by using the morphological reconstruction combined with the thresholding approach. The final image containing segmented blood vessels was obtained by means of the iterative algorithm of outgrowing areas.

The automatic hybrid algorithm which consists of a combination of mathematical morphology and the fuzzy clustering was presented in paper [75]. Selection of blood vessels and removal of the background was carried out using the morphological TopHat operation, and then the vessels were extracted on the basis of the fuzzy clustering. Sun et al. [76] has used the morphological multiscale processing in combination with the fuzzy filtering and the watershed method to extract the vascular system on angiographic images. The background was estimated by means of the nonlinear multiscale operation of morphological opening on the basis of structural elements with different sizes, and then was subtracted from the image thus to align its contrast. Normalized angiograms were processed by means of the fuzzy morphological operation on the basis of 12 structural elements, each 9 pixels in size, rotated at an angle from 0 to 180 degrees in increments of 15 degrees. The central line of the vessel was derived by means of the thinning operation which followed the threshold filtration. In conclusion, the boundaries of the blood vessel were determined by the watershed method. The algorithm was tested in angiographic images of the retina of 7 patients and showed the resistance to Gaussian noise that overlaid on images.

Multistructural mathematical morphology [71] together with FDCT transformation (Fast Discrete Curvelet Transform) was used for the detection of blood vessels. FDCT transformation was used to improve the contrast, and the boundaries of vessels were detected using the morphological multistructural conversion. Falsely determined boundaries were removed by the morphological opening option. The adaptive analysis of interconnected components was used for the whole vascular system tree. The algorithm of the vascular selection based on the method of morphological amoebas has been considered in paper [77]. There was reviewed the usage of algorithms in the task of vessel extension from a set of points being certainly considered to be vascular points. The best accuracy of vascular selection was shown in the method proposed by Mendoca and Campilho [78].

Multiscale analysis. Cross-section of a vessel can be approximated by the Gaussian function; it is a straightway object by its local scale with a smoothly decreasing diameter. The idea of using the space-and-scale analysis to extract blood vessels means to identify the scale-independent information about blood vessels [79-82]. In [83] a method to extract the center line of the vessel has been presented which found a lowest-cost way using the vector multiscale representation of the image. First, the image of a blood vessel segment at different scales was constructed using the eigendecomposition of the Hessian matrix, and then a 3D-matrix of cost was formed on its basis to search for the minimum-cost ways for the wave propagation between two or more points defined by the user, allowing to extract the central line of the vessel. The technique was tested on testing and actual angiographic images and showed the opportunities for the correct processing of advanced stenosis and image artifacts.

The likelihood ratio technique [84] was used for extracting cenral lines of the blood vessel combined with the matched filtering and the evaluation of vessel boundaries. A multiscale matched filter required for the extracting of blood vessels has been developed in order to separate blood vessels with different diameters. The filter's response was supplemented by the likelihood ratio which was defined as a vector projection formed from normalized values of surrounding pixels to a normalized profile of an ideal vessel. Evaluation of boundaries of the blood vessel and the associated likelihood ratio were calculated at the points of a supposed boundary. The evaluation vector consisting of 6 values was calculated by means of combining filter's responses. The likelihood ratio of the vessel was used for vascular tracing to select the central lines of the whole vascular tree.

In paper [85] a modular-based learning algorithm was proposed for vascular segmentation in retinal images without a red component. The background image was aligned and then blood vessels were underlined based on the space-and-scale approach. The optimization procedure was used to determine the best scale factor and the thresholding of the segmented image.

In paper [9] the authors have shown that the approaches [51,52] should demonstrate the best accuracy in images from STARE and DRIVE databases.

Model-based approaches. These approaches use direct models of blood vessels to extract the vascular system (VS) [86]. In paper [9] the authors have divided these approaches into 2 categories: (1) the vessel profile models ; (2) the deformed models.

In the first approach (*vessel profile models*) the cross-section of blood vessels is approximated by means of the Gaussian curve or by a combination of curves in case of the presence of the central reflex. The second differential coefficient of the Gaussian function, cubic splines or Hermite polynomials may also be used. More sophisticated models sould include bright or dark retinal damages and background characteristics in order to improve the segmentation accuracy in sophisticated images. Some models also took into consideration the uniform background. Accounting of vascular branchings and crossings would cause the further sophistication of the model. In [87] the blood vessel profile was modeled by means of the Laplace's function thus to take into account the effect of a central reflex of the blood vessel. For this purpose the image convolution with a two-dimensional core of the Laplace's operator was carried out. In order to eliminate voids in the vessel's image the morphological closing option was used. The algorithm's accuracy depended on the settings to be used with different sets of images.

Mahadevan et al. [88] has introduced a series of algorithms to create a reliable modular tool for the detection of blood vessels in noisy images. The authors have presented a method of probability estimates of the parameters of blood vessels using various models of the vessel's profile such as a model based on the Gaussian function, Gaussian differential coefficients and various noise models such as Gaussian noise and Poisson noise. The device was tested both by simulated data and in clinical images. The technique was compared with the matched filtering method [26] and tracing search algorithms [89], and the significant increase of the segmentation efficiency was demonstrated. Other authors have proposed different modifications of this device [90] based on a double Gaussian model to improve the vascular segmentation containing the central reflex.

The multiscale Hermite model applied for the vascular segmentation which was proposed by Li et al. [91] used a two-dimensional model of the vessel's profile based on the Hermite function. Vessel modeling and evaluation techniques based on Hermite polynomials and combinations of functions [92,93] are used to account for the effect of the central reflex. The vessel's segmentation occurs together with the evaluation of local areas, the width and angles of branching vessels taking into consideration the slow background changes. Zhu [94] has proposed a universal representation of the crossing profile of blood vessels in the Fourier-area by means of the phases conformity. The incoming image has been transformed by a set of 24 Gabor filters covering at least 6 spatial directions and having 4 scales in each of them.

In the second approach (*deformed models*) the authors of paper [9] have split vessel segmentation techniques based on deformed models into 2 categories: (a) parametric models; (b) the geometric deformed models.

a) Parametric models. The method of active contours also known as a 'snake' approach [95-97] is based on changing the contour's shape around the object influenced by internal and external forces. External and internal forces are arranged in such a way that, being affected by them, the contour line will be compressed up to the object's boundaries. The internal forces enhance the contour's stiffness thus limiting its behavior and shape. The advantages of this technique compared to other approaches include the ability to adapt to objects of different shapes and to find the minimum-energy state in which internal and external forces will be well balanced. The method of active contours can be used to track objects both in space and in time. The main limit of the method is to use the information only about the object's boundaries with no regard to other image parameters. In order to provide correct operation, it is necessary to define an original position of the contour's line as being close enough to the object, otherwise the contour line would not be able to converge the boundaries having caught on a small local object. The method accuracy is adjusted by means of setting the convergence parameter. The greater accuracy will require to increase the computation time. The 'snake' approach is often used in such areas as tracing, recognition of the object's shape, segmentation and identification of object's boundaries. Many authors have been engaged in researches of how to use active contour models in vascular segmentation.

In paper [98] the authors have used the classical 'snake' approach combined with topological properties of blood vessels to provide their segmentation in retinal images. Setting of the original position and the deformation of the snake was carried out in accordance with the energy determined by the bending of the blood vessel. The gravity forces generated by the blood vessel make the snake to flow along its boundary. The internal forces enhancing the snake's stiffness do not let it to leak through small gaps in the body of the blood vessel. In paper [99] the authors have proposed a number of refinements of this approach including morphological operations to evaluate the bending of the blood vessel and the exact setting of snake parameters to minimize the initial energy.

b) Geometric models. The geometric model of active contours is based on the theory of evolution of geometric forms. These models are usually implemented by using numerical algorithms [9]. One of the implementations of such models, i.e. the level set method (LSM), is a numerical algorithm to trace certain surfaces and forms [102]. The advantage of LSM is that the numerical processing of various curves and surfaces can be carried out without mentioning the parameters of these objects. The technology based on nonlinear projections has been proposed in paper [103]. Non-linear projections can be used to capture textural image patterns. The image (a green channel) is projected onto a closed dome-shaped area consisting of oscillating functions with a zero average number. A segmented vessel tree is obtained by applying the method of adaptive segmentation based on the variable algorithm of the binary images [104]. The morphological post-processing was applied to the binary images obtained. The authors of [9] noted that among algorithms of the model-based approach the algorithm developed by Lam [105] and based on the divergence of vector fields has the best accuracy .

6. Vascular tracing (E)

Tracing algorithms define the blood vessel between its two points using the local information, and they operate at the level of one blood vessel, not the entire vascular system. When tracing, the algorithm moves step-by-step along the way of the blood vessel. The central point of the blood vessel profile is determined by using various properties of the blood vessel including its average diameter and tortuosity measured during the tracing. The tracing allows to monitor the central line of the blood vessel using the local information usually aimed at identification of the point where the intensity distribution corresponds to the blood vessel profile in the best way. The main advantage of tracing methods is the high accuracy in measurement of the blood vessel diameter and information retrieval about each blood vessel that is inaccessible when using any other technique. One more advantage is that the tracing algorithms shall require less number of calculations. Given that all the vessels are linked to each other in the overall vascular system, the tracing algorithm can define the entire tree without time loosing to process those parts of the image which do not contain blood vessels. Thus, unlike other approaches, the tracing can provide information about the structure of the vascular tree, i.e. about bifurcations and connections of individual branches [109].

Tracing algorithms are different and they use a variety of different approaches [53,110-121]. What connects the techniques is the stage of iteration: the next point of the blood vessel is located using the information about the current point (position and direction of a tangent line to the blood vessel coming from the center). The difference between algorithms lies in the way of blood vessel processing at sites of their intersections and branching, as well as in the form of a sliding window. In [110] we have presented the tracing technique for blood vessels by means of a round scanning frame characterized by simple implementation, high speed and accurate evaluation of local characteristics of the blood vessel.

There are many problems associated with this image processing technique including inability to track and to detect blood vessels or their segments for which no starting points have been identified or incorrect detection of a specific branch because of missing a bifurcation point. Thus, some part of the vascular tree is being lost. Some improvements and modifications proposed in the references shall solve these problems. For example, for the correct vascular tracing with the central reflex [92] it is proposed to approximate the blood vessel profile by means of a model based on two Gaussian functions. The tracing algorithms are often used in combination with the matched filtering or morphological operators.

The fuzzy clustering method is another approach to the problem of the vessel detecting. This tracing technique is applied to every probable site after the image segmentation [111]. Tolias and Panas [53] solve the problem with the blood vessel tracing by means of fuzzy logic criteria. The tracing process is based on the fuzzy clustering of pixels which might belong to the blood vessel. Two classes are under consideration, i.e. a ''vessel'' and "not a vessel." The criterion of pixel involvement into one or another group is changeable; this is because of statistics taken from the cross section of the blood vessel (straight or perpendicular to the tracing direction) at each iteration. Analyzing these sections the algorithm detects T-shaped intersections of blood vessels and their branchings. The process ends in case of low contrast or when more than two groups of pixels per one iteration belong to the "vessel" class. Alyward [112] uses a simple approach of the upsurge-of-intensity analysis to approximately detect the central lines of tubular-shaped objects such as blood vessels. A more sophisticated approach is used when the blood vessel is presented as a graph. In this case the process of segmentation comes down to identifying an optimal path in the graph representation of the image. Lecournu in paper [113] has identified blood vessels on angiography by means of simultaneous tracing of both two edges using the theory of graphs. A complete model is built which identifies some properties of the blood vessel such as location, size and curveness of the given segment. The heuristic method is used in which the best edge is searched in the image which is defined as the optimal path on the graph representation of branches. The algorithm has been improved by using a new node concept at which both opposite brink edges act as a vessel segment.

Hart and Holly [114] have developed the automated method of coronary artery tracing which collects information from several sites of the image to provide a more stable tracing effect. Using the first-order forecasting scheme the system iteratively manupulates with parts of the image. Such data as the blood vessel width and its direction collected at the stage of a n-number are used as initial information at the next stage. Then the system selects a window size that is optimal for a given width of the blood vessel and its direction for the next stage. The width and direction of the blood vessel at the first stage is to be defined by the user. This algorithm is relatively slow and works poorly in blood vessel branching and in case of quick changes of its width.

In paper [115] the tracing algorithm has been used together with a filter based on the Gaussian function and the Kalman filter. The intensity distribution along the line which is perpendicular to the previous direction of the blood vessel is rolled with the core of the matched filter based on the second differential coefficient of the Gaussian function, and the position of the next point of the central line of the blood vessel is evaluated by the best response. The matched filtering allows to ignore small branches of the blood vessel without using any additional operations allowing the algorithm to follow along one large blood vessel. The Kalman filter was used to determine the next trace point based not only on the local information, but also on the information obtained during the whole tracing process, just the same as it is done when tracking the flying objects. The appropriate technology was used to account branching points of blood vessels.

Introduced in paper [116] the semi-automatic method of tracing of blood vessels in the retina images involves the usage of multiscale filters designed to select blood vessels by means of the Livewire software [117]. Some rare starting points are determined along the boundary of the vessel, then the optimal contours are to be found which connect these points with the Dijkstra's algorithm. The method showed 77.2% accuracy. In paper [119] the multiscale tracing algorithm has been proposed. After adjusting of illumination and contrast the starting points of the algorithm were chosen using an appropriate rule. The tracing algorithm was used on several scales to take into consideration blood vessels of various widths. After vascular tracing the vessel-likelihood matrix was calculated. Median filtering was used after the restoration of broken blood vessels. At the final stage the post-processing eliminated the mistakenly defined blood vessels by analyzing the direction of blood vessels and the morphological reconstruction. The algorithm has shown a high sensitivity to the choice of starting points for tracing.

Marc Lalondet et al. [120] has performed the tracing of edges of the blood vessel individually (thus the second boundary is herewith fixed) until either the line is completed or the bifurcation does not occur. As a result, each vessel is twice analyzed. Moreover, the results of both passes have to be agreed. This approach ensures the correct recognition of differences and intersections of blood vessels and improves the quality of recognition. This method uses a mechanism for creating new starting points when dealing with breaks and bifurcations that enables to completely process all the vessels. After the tracing process is finished, there occurs a comparison of boundaries one after another, and the middle line of the respective blood vessel and its diameter are to be defined along the whole path.

In paper [121] the probability tracing method was used for detecting blood vessels in the retinal images. The window size is dynamic and it is chosen at each stage depending on the width of the blood vessel (1.5 – 2 times more). Thus the following three possible configurations of blood vessels shall be considered: 1) one blood vessel is located in the window (2 edge points), 2) one vessel is divided into two (three edge points), 3) the intersection of two bloods vessels (4 boundary points). Further, the probability approach is used in each iteration to determine one of three possible configurations. The article does not consider the case of blood vessels passing very close to each other.

The most frequently encountered problem for algorithms, if not taking into account their effectiveness, relates to the recognition of bifurcations. Lecornu (1994) considered the tracing as an optimization problem where two best paths were chosen between two edge points of the blood vessel (these paths should obviously coincide with the boundaries of the blood vessel). The contrast at the edges of the object and its parallelism are considered as parameters of the minimizing function, however there isn't any parameter which would enable to correctly find and process bifurcations. Other tracing algorithms (including Zhou, 1994) are based on the usage of the filter which is considered to be a one-dimensional Gaussian function of the intensity distribution. In this case the algorithm may ignore or even stop any branchings when encountering them. However, there are some exceptions, i.e. Liu and Sun (1993), though they used similar filters, have provided the algorithm with an opportunity to manage with branching and crossing of blood vessels. All stages of the detection technology and the tracing algorithm itself have been also discussed in more details in papers [118,122].

If we consider all vascular selection algorithms then, according to [9,10], the efficiency of algorithms based on the preliminary learning classification is generally better than that of their analogues. The best efficiency was provided by the algorithm proposed in [32]. However, these methods do not work well with images with uneven illumination, because it provides false responses at the edges of the optical disk, in hemorrhages and other pathologies which have a strong contrast. The matched filtering was widely used for automatic segmentation of blood vessels. The matched filtering was firstly used on the basis of the Gaussian function in [26] and since then many modifications and improvements of this approach have been proposed. For the parametric optimization of the matched filter the specialized searching algorithms [67] and the formic optimization [64] have been used that considerably increased the accuracy of the algorithm of the vascular selection. The usage of the concept of controlled filters [61] would enable to reduce the image processing time. The matched filtering alone can not correctly perform the vascular segmentation, therefore, it is often used in combination with other image processing techniques [64,84]. The problem of having the central reflex is solved by means of the blood vessel profile model based on the combination of Gaussian functions [92,90] and the usage of a tape consisting of two pairs of active contours [100]. Gabor wavelets are very useful in the image analysis of vascular systems. In addition to the vascular segmentation [32,50,107] and the detection of the optical disk [108] the transformation based on Gabor wavelets are used for reliable fractal analysis of the vascular system (VS) [109].

While the identification of certain features of the image is considered to be an important objective in the design of automated diagnostic systems, no less important task is the calculation of the objective characteristics of the human vascular system (VS). In articles assembled to category A it was proved that many diseases had caused changes in the geometry of the retina vascular system, as well as the formation of new blood vessels which had a peculiar wavy shape [18]. Still the early changes of the human vascular system caused by DR allow to detect the disease and to predict its consequences. These diseases can be examined and diagnosed by measuring the geometric parameters of blood vessels such as diameter, angles of bending vessels, length of vessel branches, vascular tortuosity, a ratio of diameters of blood vessels, their curvature, etc. [124,22].

7. Vessel diameter evaluation (F)

The diameter of arterioles is associated with ethnicity, gender, age, blood pressure, smoking and obesity factors [125,126]. The caliber of venols is associated with age, blood pressure, blood sugar level, smoking, obesity and phlogotic processes [127]. According to [127] the diameter of retinal arteriolars are within the range of 50-200 microns. Narrowing of arterioles is an early symptom of DR, whereas narrowing of main arteries causes hypertension, diabetes and many autoimmune diseases [129]. The length-to-diameter ratio of the blood vessel is much greater for hypertensive patients compared to healthy people [130]. In paper [20] the authors have evaluated the ratios of retinal vascular calibers associated with AIDS and death factors.

First attempts to measure a width of blood vessels were undertaken in 1947 by Wagener. The digital image analysis appeared in the mid-1980s allowed to make more objective measurements [128,130-132]. Since then many different approaches have been developed to estimate the diameter of blood vessels, and moreover, all of them are based on the idea of measuring the diameter along the line that is perpendicular to the local direction of the blood vessel. A common method of estimating the width of the blood vessel is to measure a distance between the intensity halftime value (the point where intensity is an average value between the maximum and the minimum intensity) of the profile cross-section of the blood vessel [127,131,133]. Such approach minimizes a defocusing effect of imaging [131]. Poor quality images may be improved by means of various transformations (linear contrast enhancement, histogram equalization, etc.) to enhance the contrast between the background and blood vessels. Another difficulty of measuring the diameter of blood vessels is associated with heartbeating that causes vasomotor phenomena [134]. Small cross-sectional dimensions of blood vessels force out to use higher resolution images for more accurate measurements of the size of blood vessels that can be as low as 15 – 20 pixels in diameter. In paper [128] Richard and Newsom have used diameter measurements on a small section of the blood vessel to increase the measurement accuracy, and they have calculated an average value of three measurements, whereas the diameter has been estimated by the intensity halftime value.

In paper [135] a more dynamic method of diameter measurements has been proposed together with the tracing procedure taking into account statistical characteristics of the image. In paper [136] the local diameter of the blood vessel has been estimated in images with a selected green channel. The image contrast enhancement was used as the primary processing based on the area growth technique and the wavelet transformation used to select blood vessels. The image binarization was carried out at the final stage by using the threshold processing and evaluation of the local diameter of the blood vessel. The algorithm has shown a good accuracy within the range of 92% to 95% in images from the DRIVE open ophthalmic database.

Other approaches of diameter measurements are based on the approximation of the brightness profile of the blood vessel. Such approaches contains the "kick-point" method [137], matched filtering techniques mentioned above in paper [66] and SLRF (sliding linear regression filters) [23,66]. The disadvantage of such techniques, in spite of the high accuracy measurement of the diameter of the blood vessel, is the high labor intensity and the error probability when measuring near the boundary of the blood vessel or on local vasoconstriction or bending points.

Usually, the brightness profile of the blood vessel contains the Gaussian profile, therefore in order to estimate the diameter of the blood vessel the approximation of its cross section is often used by means of the Gaussian curve [124,132]. However, injured blood vessels tend to have the strongly marked boundaries, therefore their profile reminds a combination of two Gaussian distributions that might creates some problems in the measurement of the their diameter by means of the automated systems, as well as the false detection of one blood vessel as the two ones. Therefore, on high-resolution images, when the blood vessel shows the central line effect (the center of the blood vessel has a lower brightness than its edges), a combination of two Gaussian curves or parabolic curves is used to approximate the profile of the blood vessel [93]. In paper [138] the intensity profile is approximated to estimate the diameter by means of a model consisting of the Gaussian curve and a constant that allowed to take into account a background component. In segmentation algorithms they also used a parametric model of the profile of blood vessels [119], the Baysian probability model [59] and the multiscale profile [120] in order to determine the points at which the intensity distribution would comply with the model in the best way.

In paper [23] the comparative analysis has been made to determine the accuracy of the following approaches to the blood vessel diameter measurement: manual evaluation by experts; approximation of the blood vessel profile using a combination of two Gaussian functions; the standard algorithm of selecting the object's boundaries by means of the Sobel filter, as well as by using the sliding linear regression filter (SLRF). The SLRF method has shown the best coincidence with the expert evaluation and has demonstrated the best result repeatability. The Gaussian-based approach has shown the poor result reproducibility. The Sobel filter has showed bad results for the blood vessels with the central line effect. According to the authors, the SLRF method is the best among all of the above mentioned, however this method would become unreliable when the blood vessel diameter is less than 10 pixels. The usage of different profile models have been described in detail in one of the categories of segmentation methods dedicated to the model-based approaches.

While the measurement of the width of one blood vessel can provide some important information, the analysis of articles from the evidence-based medicine category has shown that the quantitative assessment of morphological changes of the human vascular system is the more useful for diagnostics.

8. Vascular characteristics evaluation (G)

Blood vessels gather around and penetrate with all organs of a human body. Almost every disease, from cancer to a cold, affects characteristics of blood vessels (e.g. number of blood vessels, caliber changes in blood vessels, radius of distortion, frequency of branching and tortuosity). Cancer, for example, would stimulate the growth of pathological assemblies of abnormally tortuous vessels (Folkman, 2000; Baish and Jain, 2000), and the successful treatment would normalize a form of blood vessels (Jain, 2001). Hypertension, diabetes and many autoimmune diseases can cause the narrowing of large arteries and increasing the vascular tortuosity (Hiroki et al., 2002; Spangler et al., 1994). Chronic inflammations can cause the angiogenesis (McDonald, 2001). Even a common cold would affect the morphology of blood vessels causing their expansion (Ferguson and Eccles, 1997). The automated quantitative measurement of two– and three-dimensional parameters of blood vessels can hereby provide a new method of disease diagnostics and diagnosing.

The arteriovenous ratio (AVR) has been widely used in recent times as a quantitative characteristic of vascular changes in medical practice [20,22,125,139-148].

Arteriovenous ratio. The arteriovenous ratio (AVR) was first proposed by Stokoe and Turner in 1966 as a parameter for the study of morphological changes of the eye's vascular system. The parameter was proposed as a basic ratio set between the average diameter of arteries and veins. It consisted of two components, i.e. the central arterial equivalent (CRAE) proposed by Parr and Spears in 1974, and the central venous equivalent (CRVE). CRAE was calculated by the following rule: since the vascular system had a tree-type structure they started to evaluate the diameter from the blood vessels with no branches. The blood vessels were further grouped according to their pertaining opportunities to a particular parent blood vessel. Based on the estimates of their diameters they calculated diameters of respective parent blood vessels which in its turn were also grouped properly. This process continued iteratively until a root blood vessel was reached, i.e. the calculation of CRAE has been completed [147]. The Parr's approach to calculate the arterial equivalent was too time-consuming. In 1992 Hubbard invented a similar equivalent to calculate the central venous equivalent. Hubbard's further studies [148] were focused on opportunities to group blood vessels in accordance with a certain rule where the biggest blood vessel was combined with the smallest one, and the second largest blood vessel was partnered with the second smallest blood vessel, and so on. Things proceeded in this train until all blood vessels had been partnered. If the number of vessels turned out to be odd, the other blood vessel was to be transferred to the next iteration. This approach was much less time-consuming; moreover, it has demonstrated a good correlation with the equivalent calculated by the Parr's method. The arteriovenous ratio (AVR) was calculated based on the caliber of all veins and arteries which lay in a concentric zone of the optic nerve disk (OND) at a distance of between 0.5 and 1 radius of the optic disk.

The limitation of the Parr-Hubbard formula is the fact that the number of blood vessels involved in the calculation of the equivalent has a large impact on its value [143]. Knudtson has developed a new AVR-equivalent based on the measurement of 6 largest arteries and veins which are, as before, in the concentric zone at a distance of between 0.5 and 1 radius of the optic disk from its center. This updated formula was heavily dependent on the previous one but it did not depend on the number of blood vessels. All measurements were chosen randomly to measure six largest arterioles and venols and a "branching factor" was calculated based on the width of a root blood vessel and two associated vessels [147]. Based on the retina images sample of 44 healthy young adults the branching ratios have been calculated, ant it turned out that in 95% of cases it was 1.28 for arterioles and in 95% of cases it was 1.11 for venols (Sherman, 1981). Using the same iterative procedure and comparing the largest and the smallest vessels pairs, the CRAE and CRVE equivalents, as well as their quotient ration — AVR, have been calculated. Since only six venols and arterioles were used, only five iterations were required to calculate the arterio-venous ratio (AVR). As of today, exactly this updated formula has being used in all studies of cardio-vascular diseases aimed at calculating the arterio-venous ratio (AVR), because it is much easier in computation being highly competitive in its accuracy with the old formula (Ikram, 2004; Wong, 2004).

The automatic method for calculation of the arterio-venous ratio (AVR) was proposed by Tramontan et al. [144]. It contained a stage of the vascular selection by tracing and localization of the optic nerve disk, and AVR was calculated based on the analysis of blood vessels with the diameter over 45 microns. The arterio-venous ratio (AVR) measuring method proposed by Nam et al. [145] is based on the measurement of the diameter of blood vessels based on a semi-circular profile, whereas the blood vessels larger that 7 pixels were used to calculate the arterio-venous ratio. Niemeijer et al. [146] has proposed a completely automated method for calculation of the arterio-venous ratio (AVR). In this paper the blood vessels have been reduced in thickness by means of morphological thinning. The TopHat transformation and the double-ring filtering (DRF) applied to the green image channel were used for segmentation, since in this case the blood vessels have the best contrast. In order to detect the optical disk the method of active contours was applied which had been described in [149]. A discriminant linear classifier was used to separate vessels on arteoriols and venols [142].

The limitation to use the arterio-venous ratio (AVR) is the fact that venols and arterioles may vary differently depending on the presence of various diseases. Thus, venols may reduce their thickness in phlogotic processes whereas in contrast the form of arterioles may change because of hypertension. Thus, the independent usage of CRAE and CRVE may give information about changes of blood vessels in various pathologies which can not be seen when using AVR [147]. Mosher [141] compared the central arterial equivalent (CRAE) and central venous equivalent (CRVE) measured in images with a resolution of 6.3 megapixels and obtained with the help of a digital camera and a digital video camera. Some distortions such as glares from a nerve filament are more well expressed in high-resolution images that might reduce the accuracy of algorithms.

The classification of blood vessels on arterioles and venols is a key objective in evaluation of diameters of blood vessels and in calculation of such global parameters of the human vascular system as CRAE / CRVE / AVR. Therefore it is necessary to create vast databases of medical images containing markings made by experts, including the detection of blood vessels and other anatomical parts of the retina, as well as the classification of blood vessels on venols and arterioles. Apart from such well-known databases as DRIVE and STARE, there are also the following databases: REVIEW [101] – to measure the diameter of blood vessels, MESSIDOR [150], ImageRet [151], ARIA Online [152] – to use in diagnostics of diabetic retinopathy and VICAVR [153] – to calculate the arterio venous ratio (AVR).

Branching ratio. In order to describe the relationship between the parent and associated blood vessels, a "branching ratio" which appears in the equation connecting diameters of blood vessels has been entered in paper [147]. The branching ratio can be used to calculate the AVR coefficient when the associated vessels have the same diameter (Knudtson et al., 2003). In case when the diameter of an associated blood vessel is greater than the diameter of a parent vessel it is impossible to calculate the branching ratio. To avoid this problem Chapman et al. [154] has introduced an analog to the branching ratio, i.e. an optimality parameter that is used to characterize the branching of blood vessels. This parameter is less sensitive to computation errors. When calculating this parameter, Chapman has discovered a significant difference in its meaning for healthy and sick people.

Vascular tortuosity. One of the symptoms of many vascular diseases is the change of vascular tortuosity. The automated evaluation of vascular tortuosity is a powerful tool for early diagnosticating of vascular diseases [155,156]. In papers written by Hiroki et al. [129] and Spangler et al. [157] it is considered that such diseases as hypertension, diabetes and many autoimmune diseases may cause the increase in vascular tortuosity. The tortuosity can be increased at an elongation of the blood vessel, as in the case of age-dependent retinopathy (Hart et al. [158], Capowski [159]), hypertension and ageing (Spangler et al. [157], King [129]), as well as at other changes caused by any diseases. The blood vessel may often crankle with a small oscillation amplitude that related to the growth of new blood vessels affected by malignant tumors (Baish and Jain, 2000).

To evaluate clinical consequences of tortuosity changes or to compare different degrees of retinopathy it is extremely important to develop tortuosity estimation methods. First, it is necessary to identify critical factors affecting the classification of blood vessels in accordance with their tortuosity rate. This is especially important for the analysis of retina images which have not only straight blood vessels but also the long round-shaped vessels which are not considered by ophthalmologists as crankled. The necessity to develop the above factor-related features follows from observations that previously proposed estimation methods are not always capable to distinguish between structures whose tortuosity seems to be visually diverse [158]. Tortuosity estimation methods have no precise medical formulation, however experience has proven that the tortuosity estimation may be conducted based on other easily measured parameters [161]. In order to obtain a clinically meaningful way of estimation of the vascular tortuosity, i.e. a measure function that will coincide with ophthalmologists' opinion, it is necessary to explicitly define these parameters. Its value can be calculated then by using a suitable mathematical tortuosity model.

The first numerical estimate of vascular tortuosity was described in 1979 by Lotmar, Freiburghaus and Bracher [162] and was updated by Bracher [163]. With the advent of digital photography in medicine there emerged an opportunity of computer-aided evaluation of vascular parameters. Many different approaches were proposed to measure tortuosity, i.e. by measuring the length of blood vessels [159,164,165]; by the integral curvature of blood vessels [158,159,168,169]; based on a number of inflection points [166], on the change of blood vessel angles [164,167]; by the standard deviation of vessel co-ordinates along its midline from the straight line connecting starting and end points of the blood vessel [170].

The results of measurement of vascular tortuosity based on the Fourier analysis have been published in papers [171]. The paper [159] has presented an approach to the tortuosity evaluation based on the frequency analysis. Smedby et al. [166] has described a number of approaches to measuring tortuosity which is used to determine curvature in the femoral artery. It included measurement of the integral curvature along the blood vessels, the number of points of inflection of the blood vessel and a part of the blood vessel which has the greatest curvature.

In paper [172] the authors have proposed to distinguish the following three types of tortuosity:

The blood vessel is elongated and becomes wavy as in the case of age retinopathy [158], hypertension, ageing (Spangler et al., 1994) and other changes caused by diseases.

The blood vessel often changes its direction and becomes like a bag of worms in the area of arterio-venous malformation (Burger et al., 1991) and in a softer hypervascular tumor.

Type 3 is characterized by the high frequency, a low oscillation amplitude or twisting and it relates to the growth of new blood vessels and the occurrence of malignant tumors (Baish and Jain, 2000).

The authors have also presented the following two metrics of tortuosity to detect pathological tortuosity:

a) The number of vessel curvatures plus 1. It well suits to evaluate tortuosity type 1 and 2 but not 3. The method can detect the pathological tortuosity in the intracranial vascular system (Bullitt et al., 2003a).

b) The sum of curvature angles. Angles of blood vessel curvatures are summarized followed by normalization of its length. This parameter well describes tortuosity type 3 and is sensitive to uncertainty of angles measurement.

The average radius of vessel bending and the branching frequency have also been calculated for each blood vessel [172] (ratio of total number of vessel branches to the length of the blood vessel). The same characteristics have been calculated for groups of blood vessels by means of characteristics averaging with regard to weighting factors of each blood vessel. The less the weighting factor was considered the more the order of the blood vessel was, if counted from the root of the optic nerve.

Thus, among all tortuosity evaluation methods discussed in the paper, the following three critical approaches would be identified:

Tortuosity evaluation by vessel length measured. It is constructed as a ratio of the vessel length to the shortest distance between its extreme points [1,47,158]. Brey et al. (2002) have expanded this metric on 3D-structures to analyze blood vessels in histological section. This is the simplest and the most commonly used approach for measuring tortuosity (Smedby et al., 1993; Bracher, 1982; Zhou et al., 1994; Gol'dbaum et al., 1994; Hart et al., 1999). The idea is that the larger the ratio is the more the vessel remotes from the straightline, i.e. the more tortuous it is. The disadvantage of this approach is that if we have a shorter pathological blood vessel with a twisted shape or high-frequency vibrations, then the measured tortuosity will be less than it will be for completely straight (non-oscillating) long blood vessel but of a ''S'' or ''U'' shape. In fact, the blood vessel with constant or small curvature and without regard to the amplitude of its describing arc (as for the basic retina blood vessels) will be considered by a physician as a slight curvature. Baish and Jain (2000) and Sabo et al. (2001) attempted to solve a problem of tortuosity evaluation by means of recursive measurements of microvessels on histological sections to determine the malignancy based on fractal dimensionality. Swanson et al. have used the first approach in paper [160] in which he described a semi-automatic system for the estimation of diameter and tortuosity of blood vessels in preterm infants.

Tortuosity evaluation by vessel curvature measured. Hart [158] has introduced a number of approaches to define tortuosity by using the integral from the absolute curvature or squared curvature. The idea is that the tortuosity should reflect the variability of curvature of the blood vessel at each point of its space. The advantage of this approach is the accounting of parameters of the blood vessel at each point of its space that allows to receive a more objective evaluation [173]. This approach is sensitive to the accuracy of curvature measuring. In order to reduce the sensitivity of the approach the vessel shape should be approximated using a model based on which the curvature is calculated [173]. Similarly to this, in paper [169] the tortuosity is described as the change of vessel curvature. The fast Fourier transformation (FFT) of vessel curvature is used as a measure of tortuosity. This paper presents the spectral analysis of a set of simulated blood vessels (phantom) and full-scale clinical data. The spectrum analysis allowed to identify curvature local changes. The curvature spectral analysis has provided a compact and graphic presentation of tortuosity.

Tortuosity as a degree of variation of the vessel direction. This approach to tortuousity evaluation is based on the assessment of the rate of change of the local direction of the blood vessel and was proposed in [174]. The angle which changes the vessel direction at every point is to be calculated for evaluation. The approach is highly sensitive to the accuracy of estimation of the vessel detection on the image and of evaluation of its direction. The sensitivity of the method can be reduced if the shape of the *blood vessel* is approximated by means of a particular model. The line passing through the center of theb lood vessel may be approximated by polynomials, splines, etc. [173]. Approximation of the form of vessels is often carried out by means of a sinusoidal model [175]. While estimating waviliness ophthalmologists combine the information about how much time the blood vessel twists (changes in convexity or curvature sign) and how big is the amplitude of each vortex. Therefore, in [173] there proposed an upgrade of this approach by means of introducing a threshold on vessels curvature.

In paper [154] an algorithm for semi-automatic measurement and evaluation of geometric and topological properties of a retinal vascular tree is considered based on multiscale segmentation algorithm [51]. The algorithm consists of semi-automatic marking of a skeleton-typed vessel tree followed by the automatic measurement of length, area, diameter and angle of branching blood vessels. This information is generated in the form of tables and is used for clinical analysis. Also some geometric and topological factors were rated. The results of the method were compared with manual measurement and the method was used to test the study of 10 normal and 10 abnormal images of the retina of patients with hypertension by searching differences in morphological characteristics between the two groups. The numerical measurement of vascular tortuosity and a vessel curvature trajectory was performed on retinal digital images centered on the optical disk by using a computer aided program SIVA (Singapore I Vessel Assessment, Department of Computer Science, National University of Singapore, Singapore). The procedure has been previously published [176]. On the first stage the program determined the optical disk and divided it into three concentric zones (A, B, and C) located between the 0.5, 1.0 and 2.0 diameters of the optic disk. The program then sequentially selected blood vessels within each of the three zones. The accuracy of selection was about 70% and 80%. Then based on the six largest venols and arterioles the vessel tortuosity index was rated [158]. The index was calculated as an integral of squared local curvature of the blood vessel divided by its length. Measuring of curvature has provided good results: the accuracy of 80% for the quadratic tortuosity index and 90% for the simple tortuosity index [176]. In this paper such parameters of the human vascular system (VS) as the average diameter, the volume of blood vessels, nodes branching density per unit volume and the length of blood vessels were measured [177].

The ratio of length of the blood vessel to its diameter has also been used to assess the vessel. King et al. [129] has developed this parameter to evaluate the *degree of thinning* of the vessel. He noted in his work that the parameter value increases in hypertension.

Venous image intelligibility and neovasculization are the key indicators of preproliferant and proliferant retinopathy [178].

In [179] the authors have presented the estimation algorithm of venous image intelligibility. In progressive diabetic retinopathy at a dangerous “preproliferant” stage its numerous indicators shall appear, i.e. swollen disk, swollen gossypium, increased venous image intelligibility. Venous image intelligibility has been described as “the most powerful indicator” of transition to proliferant retinopathy [178]. In order to detect venous image intelligibility and neovasculization many authors have proposed the methods based on the difference in diameter of the vessel and its tortuosity, respectively [158,159,162]. Though these methods of measurement have shown good results, its disadvantage is that the authors have not fully automated the process of allocation of analyzed areas and that it is necessary to select starting and end points on blood vessels. It is clear that the computerized detection of vascular anomalies is the most useful point of this issue than the segmentation process. Nevertheless, this stage shall advance significant demands to the segmentation process since abnormal vessels are generally more difficult processed than healthy vessels, because some significant distracters including large hemorrhages and exudates can appear in images at the preproliferant stage. This would lead to multiple changes in the diameter and angle measurements, thus jeopardizing opportunities to detect image intelligibility and neovascularization.

Development of research applications which include various auxiliary algorithms to analyze images of heart and retinal vascular systems such as extraction of blood vessels and identification of basic image elements, including the optical disk, measurements of diameter, angles of branching vessels and other diagnostic features of the vascular system, is a promising line for research . All these types of applications can accelerate the rate of studying the links between changes in the anatomy of vascular systems and different diseases.

Summary

A review of key approaches to the digital analysis of the human vascular system images is given in the paper. We outline major stages of diagnostic image processing and analyze different approaches to the extraction and quantification of blood vessel morphological features.

The statistics collected allows you to show which of the approaches was used the most frequently within the framework of each of the stages. Despite the fact that the usage frequency is not necessarily associated with the best efficiency it shows which method was tested the most thoroughly. The analysis allowed to group the articles according to the methods used in each stage and to identify existing trends and problems in the field of digital processing of blood vessels and future directions. It was found that in most cases the existing methods had some disadvantages, and many of the articles were aimed at the development of improved approach based on the already existing one. It is rather difficult for researchers to determine an optimal algorithm for every stage to ensure the most efficient image processing of blood vessels. This idea is confirmed by Abramoff et al. in his article [180] saying that “at the present time the usage of the automated system to detect DR (diabetic retinopathy) based on the existing algorithms is not recommended for clinical usage.”

Thus, despite the fact that many problems of operation with imaging vascular systems have been solved, the issue to determine an optimal set of algorithms to create the automated system for monitoring and diagnosis of vascular pathologies still continues to be relevant.

The diagram in Fig. 1 shows that a fairly large number of articles has been devoted to evidence-based medicine (21%), the question of medical formulation of the problem has been well worked up, the necessary requirements of physicians to the problems of digital analysis of blood vessels have been identified, and multiple researches in this area to link changes in the morphology of vessels with major diseases have been conducted. The diagram also shows that basically all minds of researchers have been put to solving the problems of detection of vascular systems (31% – in segmentation, 10% – in tracing). Though the result of evidence-based medicine was the need for quantitative analysis of the human vascular system (VS) for disease diagnostics, namely, improving the accuracy of diameter estimation of blood vessels and the evaluation of vascular morphological characteristics, it is shown on the charts that the smallest number of articles has been devoted to this concept (only 10%) that indicates that this issue was still unexplored in this area. Therefore, issues of the development of new and efficient diagnostics morphological characteristics and methods of their valuation, as well as creation on their basis of the automated system of digital analysis of human vascular systems are still pending. The automated analysis of quantitative indicators will enable to standardize the diagnosing process and to significantly reduce the time and cost of checkups [181].

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References

1. Teng, T. Progress towards automated diabetic ocular screening: a review of image analysis and intelligent systems for diabetic retinopathy / T. Teng, D. Claremont, M. Lefley // Med. Biol. Eng. Comput. – 2002. – Vol. 40(1). – P. 2-13.

2. Heneghan, C. Characterization of changes in blood vessel width and tortuosity in retinopathy of prematurity using image analysis / C. Heneghan, J. Flynn, M. O'Keefe, M. Cahill // Med. Image. Anal. – 2002. – Vol. 6(4). – P. 407-29.

3. Cheung, C.S. Computer-assisted image analysis of temporal retinal vessel width and tortuosity in retinopathy of prematurity for the assessment of disease severity and treatment outcome / C.S. Cheung, Z. Butty, N.N. Tehrani, W.C. Lam // J AAPOS. – 2011. – Vol. 15(4). – P. 374-380.

4. Haddouche, A. Detection of the foveal avascular zone on retinal angiograms using Markov random fields / A. Haddouche, M. Adel, M. Rasigni, J. Conrath, S. Bourennane // Digital Signal Processing. – 2010. – Vol. 20(1). – P. 149-154.

5. Grisan, E. A divide et impera strategy for automatic classification of retinal vessels into arteries and veins / E. Grisan, A. Ruggeri // Engineering in Medicine and Biology Society 2003 / Proceedings of the 25th Annual International Conference of the IEEE. – 2003. – Vol. 891. – P. 890-893.

6. Lowell, J. Measurement of retinal vessel widths from fundus images based on 2-D Modeling / J. Lowell, A. Hunter, D. Steel, A. Basu, R. Ryder, R.L. Kennedy // IEEE Trans Med Imaging. – 2004. – Vol 3(10). – P. 1196-1204.

7. Foracchia, M. Extraction and quantitative description of vessel features in hypertensive retinopathy fundus images / M. Foracchia // Book Abstracts / 2nd International Workshop on Computer Assisted Fundus Image Analysis. – 2001. – P. 6.

8. Kose, C. A personal identification system using retinal vasculature in retinal fundus images / C. Kose, C. Ikibas // Expert Systems with Applications. – 2011. – Vol. 38(11). – P. 13670-13681.

9. Fraz, M.M. Blood vessel segmentation methodologies in retinal images / M.M. Fraz, P. Remagnino, A. Hoppe, B. Uyyanonvara, A.R. Rudnicka, C.G. Owen, S.A. Barman // Comput Methods Programs Biomed. – 2012. – Vol. 108(1). – P. 407-433.

10. Winder, R.J. Algorithms for digital image processing in diabetic retinopathy / R.J. Winder, P.J. Morrow, I.N. McRitchie, J.R. Bailie, P.M. Hart // Computerized Medical Imaging and Graphics. – 2009. – Vol. 33(8). – P. 608-622.

11. Felkel, P. Vessel tracking in peripheral CTA datasets – an overview / P. Felkel, R. Wegenkittl, A. Kanitsar. – Computer Graphics (Spring Conference on), 2001. – P. 232-239.

12. Buhler, K. Geometric methods for vessel visualization and quantification – a Survay / K. Buhler, P. Felkel, A.L. Cruz // Geometric Modelling for Scientific Visualization. – 2003. – P. 399-421.

13. Kirbas, C. A review of vessel extraction techniques and algorithms / C. Kirbas, F. Quek // ACM Computing. – 2004. – Vol. 36(2). – P. 81-121.

14. Mabrouk, M.S. Survey of retinal image segmentation and registration / M.S. Mabrouk, N.H. Solouma, Y.M. Kadah // GVIP Journal. – 2006. – Vol. 6(2). – P. 1-11.

15. Faust, O.R.A.U. Algorithms for the automated detection of diabetic retinopathy using digital fundus images: a review / O.R.A.U. Faust, E.Y.K. Ng, K.-H. Ng, J.S. Suri // Journal of Medical Systems. – 2012. – Vol. 36(1). – P. 145-57.

16. Akita, K. A computer method of understanding ocular fundus images / K. Akita, H. Kuga // Pattern Recognition. – 1982. – Vol. 15. – P. 431-443.

17. Thackray, B.D. Semi-automatic segmentation of vascular network images using a rotating structuring element (rose) with mathematical morphology and dual feature thresholding / B.D. Thackray, A.C. Nelson // IEEE Trans. Med. Imaging. – 1993. – Vol. 12(3). – P. 385-392.

18. American Academy of Ophthalmology, Ophthalmic Pathology // in Basic and Clinical Science Courses. – section 11, 179,1991.

19. Staal, J.J. Ridge based vessel segmentation in color images of the retina / J.J. Staal, M.D. Abramoff, M. Niemeijer, M.A. Viergever, and B. van Ginneken // IEEE Transactions on Medical Imaging. – 2004. – Vol. 23(4). – P. 501-509.

20. Gangaputra, S. Retinal vessel caliber among people with acquired immunodeficiency syndrome: relationships with disease-associated factors and mortality / P.S. Kalyani, A.A. Fawzi, M.L. Van Natta, L.D. Hubbard, R.P. Danis, J.E. Thorne, G.N. Holland // Am. J. Ophthalmol. – 2012. – Vol. 153(3). – P. 434-444.

21. Gelman, R. Diagnosis of Plus Disease in Retinopathy of Prematurity Using Retinal Image multiScale Analysis / R. Gelman, M.E. Martinez-Perez, D.K. Vanderveen, A. Moskowitz, A.B. Fulton // Investigative Ophthalmology and Visual Science. – 2005. – Vol. 46(12). – P. 4734-4738.

22. Stanton, A. Vascular network changes in the retina with age and hypertension / A.V. Stanton, B. Wasan, A. Cerutti, S. Ford, R. Marsh, P.P. Sever, S.A. Thom, A.D. Hughes // J. Hypertens. – 1995. – Vol. 13(12). – P. 1724-1728.

23. Chapman, N. Computer algorithms for the automated measurement of retinal arteriolar diameters / N. Witt, X. Gao, A.A. Bharath, A.V. Stanton, S.A. Thom, A.D. Hughes // Br. J. Ophthalmol. – 2001. – Vol. 85(1). – P. 74-79.

24. Wong, T.Y. Retinal microvascular abnormalities and incident stroke: the atherosclerosis risk in communities study / T.Y. Wong, R. Klein, D.J. Couper, L.S. Cooper, E. Shahar, L.D. Hubbard, M.R. Wofford, A.R. Sharrett // Lancet. – 2001. – Vol. 358(9288). – P. 1134-1140.

25. McClintic, B.R. The relationship between retinal microvascular abnormalities and coronary heart disease: a review / B.R. McClintic, J.I. McClintic, J.D. Bisognano, R.C. Block // Am. J. Med. – 2010. – Vol. 123(4). – P. 374.e1-374.e7.

26. Chaudhuri, S. Detection of Blood Vessels in Retinal Images Using Two-Dimensional Matched Filters / S. Chaudhuri, S. Chatterjee, N. Katz, M. Nelson, M. Goldbaum // IEEE Transactions on Medical Imaging. – 1989. – Vol. 8(3). – P. 263-269.

27. Goldbaum, M. Automated diagnosis and image understanding with object extraction, object classification, and inferencing in retinal images / M. Goldbaum, S. Moezzi, A. Taylor, S. Chatterjee, J. Boyd, E. Hunter, R. Jain // IEEE conference on ICIP. – 1996. – Vol. 3. – P. 695-698.

28. Li, Q. Colour Retinal Image Segmentation For Computer-aided Fundus Diagnosis Department of Computing / Qin Li. – The Hong Kong Polytechnic University, 2010. – 126 p.

29. 29. **Pai, R.** Automated Diagnosis of Retinal Images Using Evidential Reasoning / R. Pai, A. Hoover, M. Goldbaum. – International Conference on SENG, 2002.

30. Abramoff, M. Web-based screening for diabetic retinopathy in a primary care population: The eye check project / M. Abramoff, M. Suttorp // Telemedicine and e-Health. – 2005. – Vol. 11(6). – P. 668-674.

31. Niemeijer, M. Automatic detection of red lesions in digital color fundus photographs / M. Niemeijer, B. van Ginneken, J. Staal, M.S.A.S. Schulten, M.D. Abramoff // IEEE Transactions on Medical Imaging. – 2005.– Vol. 24(5). – P. 584-592.

32. Soares, J. Retinal vessel segmentation using the 2-d gabor wavelet and supervised classification / J. Soares, J. Leandro, R. Cesar, H. Jelinek, M. Cree // IEEE Transactions of Medical Imaging. – 2006. – Vol. 25(9). – P. 1214-1222.

33. Sussman, E.J. Diagnosis of diabetic eye disease / E.J. Sussman, W.G. Tsiaras, K.A. Soper // J. Am. Med. Assoc. – 1982.– Vol. 247. – P. 3231-3234.

34. 34. **Klonoff, D.** An economic analysis of interventions for diabetes / D. Klonoff, D. Schwartz // Diabetes Care. – 2000. – Vol. 23(3). – P. 390-404.

35. Bresnick, G. A screening approach to the surveillance of patients with diabetes for the presence of vision-threatening retinopathy / G. Bresnick, D. Mukamel, J. Dickinson, D. Cole // Opthalmology. – 2000. – Vol. 107(1). – P. 19-24.

36. Wilkinson, C.P. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales / C.P. Wilkinson, F.L. Ferris, R.E. Klein, P.P. Lee, C.D. Agardh, M. Davis, D. Dills, R. Pararajasegaram, A. Kampik, J.T. Verdaguer // Ophthalmology. – 2003. – Vol. 110(9). – P. 1677-1682.

37. Hutchins, G.M. Tortuosity as an index of the age and diameter increase of coronary collateral vessels in patients after acute myocardial infarction / G.M. Hutchins, M.M. Miner, B.H. Bulkley // Am. J. Cardiol. – 1978. – Vol. 41(2). – P. 210-215.

38. Miller, R.G. Retinal vessel diameter and the incidence of coronary artery disease in type 1 diabetes / R.G. Miller, C.T. Prince, R. Klein, T.J. Orchard // Am. J. Ophthalmol. – 2009. – Vol. 147(4). – P. 653-660.

39. Ugurbas, S.C. Comparison of UK and US screening criteria for detection of retinopathy of prematurity in a developing nation / S.C. Ugurbas, H. Gulcan, H. Canan, H. Ankarali, B. Torer, Y.A. Akova // J. AAPOS. – 2010. – Vol. 14(6). – P. 506-520.

40. Wilson, C.M. Digital image analysis in retinopathy of prematurity: A comparison of vessel selection methods / C.M. Wilson, K. Wong, N. Jeffery, K.D. Cocker, A. Ells, A.R. Fielder // J. AAPOS. – 2012. – Vol. 16 – P. 223-228.

41. Ghodasra, D.H. The rate of change in retinal vessel width and tortuosity in eyes at risk for retinopathy of prematurity / D.H. Ghodasra, A. Thuangtong, K.A. Karp, G.S. Ying, M.D. Mills, C.A. Wilson, A.R. Fielder, G.E. Quinn // J. AAPOS. – 2012. – Vol. 16(5). – P. 431-446.

42. Tereshchenko, A.V. Digital technology for diagnostics of retinopathy of prematurity / A.V. Tereshchenko, M.S. Tereshchenkova, Y.A. White, I.G. Trifanenkova, Y.A. Yudina // Kuban science medical Herald. – 2011. – № 1. – C. 79-82.

43. Mintz-Hittner, H.A. Treatment of retinopathy of prematurity with vascular endothelial growth factor inhibitors / H.A. Mintz-Hittner // Early Human Development. – 2012. – Vol. 88(12). – P. 937-1041.

44. Jomier, J. Aylward, quantification of retinopathy of prematurity via vessel segmentation / J. Jomier, K.D. Wallace, R. Stephen // In: MICCAI 2013 proceedings. – 2003. – Vol. 62879, LNCS 2879. – P. 620-626.

45. Grunwald, L. The rate of retinal vessel dilation in severe retinopathy of prematurity requiring treatment / L. Grunwald, D.M. Mills, S. Keegan, K.A. Karp, G.E. Quinn, Y. Gui-Shuang, J.E. Grunwald // Am. J. Ophthalmol. – 2009. – Vol. 147 (6). – P. 1086-1091.

46. Shah, D.N. Semiautomated digital image analysis of posterior pole vessels in retinopathy of prematurity / D.N. Shah, C.M. Wilson, G.S. Ying, K.A. Karp, A.R. Fielder, J. Ng, M.D. Mills, G.E. Quinn // J. AAPOS. – 2009. – Vol. 13(5). – P. 504-516.

47. Wallace, D.K. Computer-automated quantification of plus disease in retinopathy of prematurity / D.K. Wallace, J. Jomier, S.R. Aylward, M.B. Landers // J. AAPOS. – 2003. – Vol. 7(2). – P. 126-130.

48. Adjeroh, D.A. Texton-based segmentation of retinal vessels/ D.A. Adjeroh, A. Kandaswamy, J.V. Odom // J. Opt. Soc. Am. A: Opt. Image Sci. Vis. (OSA-A). – 2007. – Vol. 24(5). – P. 1384-1393.

49. Hoover, A. Locating blood vessels in retinal images by piecewise threshold probing of amatchedfilter response / A. Hoover, V. Kouznetsova, M. Goldbaum // IEEE Trans Med Imaging. – 2000. – Vol. 19(3). – P. 203-210.

50. Osareh, A. Automatic blood vessel segmentation in color images of retina / A. Osareh, B. Shadgar // Iranian Journal Of Science And Technology Transaction. – 2009. – Vol. 23(B2). – P. 191-206.

51. Martinez-Perez, M.E. Retinal blood vessel segmentation by means of scale-space analysis and region growing / M.E. Martinez-Perez, A.D. Hughes, A.V. Stanton, S.A. Thom, A.A. Bharath, K.H. Parker. – Proc. 2nd MICCAI, 1999. – Vol. 1679. – P. 90-97.

52. Martinez-Perez, M.E. Segmentation of blood vessels from red-free and fluorescein retinal images / M.E. Martinez-Perez, A.D. Hughes, S.A. Thom, A.A. Bharath, K.H. Parker // Medical Image Analysis. – 2007. – Vol. 11(1). – P. 47-61.

53. Tolias, Y.A. A fuzzy vessel tracking algorithm for retinal images based on fuzzy clustering / Y.A. Tolias, S.M. Panas // IEEE Transactions on Medical Imaging. – 1998. – Vol. 17(2). – P. 263-273.

54. Salem, S.A. Segmentation of retinal blood vessels using a novel clustering algorithm (RACAL) with a partial supervision strategy / S.A. Salem, N.A. Salem, A.K. Nandi // Medical and Biological Engineering and Computing. – 2007. – Vol. 45(3). – P. 261-273.

55. Kande, G.B. Unsupervised fuzzy based vessel segmentation in pathological digital fundus images / G.B. Kande, P.V. Subbaiah, T.S. Savithri // Journal of Medical Systems. – 2010. – Vol. 34(5). – P. 849-858.

56. Villalobos-Castaldi, F. A fast, efficient and automated method to extract vessels from fundus images / F. Villalobos-Castaldi, E. Felipe-Riveryn, L. S nchez-Fern ndez // Journal of Visualization. – 2010. – Vol. 13(3). – P. 263-270.

57. Ng, J. Maximum likelihood estimation of vessel parameters from scale space analysis / J. Ng, S.T. Clay, S.A. Barman, A.R. Fielder, M.J. Moseley, K.H. Parker, C. Paterson // Image and Vision Computing. – 2010. – Vol. 28(1). – P. 55-63.

58. Condurache, A. P. Segmentation of retinal vessels with a hysteresis binary-classification paradigm / A.P. Condurache, A. Mertins // Computerized Medical Imaging and Graphics. – 2012. – Vol. 36(4). – P. 325-335.

59. Adel, M. Statistical-based tracking technique for linear structures detection: Application to vessel segmentation in medical images / M. Adel, A. Moussaoui, M. Rasigni, S. Bourennane, L. Hamami // IEEE Signal Process. – 2010. – Vol. 17(6). – P. 555-558.

60. Xinge, Y. Segmentation of retinal blood vessels using the radial projection and semi-supervised approach / Y. Xinge, Q. Peng, Y. Yuan, Y. Cheung, J. Lei // Pattern Recognition. – 2011. – Vol. 44(10-11). – P. 2314-2324.

61. Kochner, B. Course tracking and contour extraction of retinal vessels from color fundus photographs: Most efficient use of steerable filters from model based image analysis / B. Kochner, D. Schuhmann, M. Michaelis, G. Mann, K.H. Englmeier // Proc. SPIE Medical Imaging. – 1998. – Vol. 3338. – P. 755-761.

62. Sukkaew, L. Automatic extraction of the structure of the retinal blood vessel network of premature infants / L.B. Uyyanonvara, S.A. Barman, A. Fielder, K. Cocker // Journal of the Medical Association of Thailand. – 2007. – Vol. 90(9). – P. 1780-1792.

63. Yao, C. Automated retinal blood vessels segmentation based on simplified PCNN and fast 2D-Otsu algorithm / C. Yao, H.-j. Chen // Journal of Central South University of Technology. – 2009. – Vol. 16. – P. 640-646.

64. Cinsdikici, M.G. Detection of blood vessels in ophthalmoscope images using MF/ant (matched filter/ant colony) algorithm / M.G. Cinsdikici, D. Aydin // Computer Methods and Programs in Biomedicine. – 2009. – Vol. 96(2). – P. 85-95.

65. Bankhead, P. Fast retinal vessel detection and measurement using wavelets and edge location refinement / P. Bankhead, C.N. Scholfield, J.G. McGeown, T.M. Curties // PLoS ONE. – 2012. – Vol. 7(3). – P. 1-12.

66. Gang, L. Detection and Measurement of Retinal Vessels in Fundus Images Using Amplitude Modified Second-Order Gaussian Filter / L. Gang, O. Chutatape, S.M. Krishnan // IEEE Tran. Biomedical Engineering. – 2002. – Vol. 49(2). – P. 168-172.

67. Al-Rawi, M. An improved matched filter for blood vessel detection of digital retinal images / M. Al-Rawi, M. Qutaishat, M. Arrar // Computers in Biology and Medicine. – 2007. – Vol. 37(2). – P. 262-267.

68. Zana, F. Registration Algorithm of Eye Fundus Images Using Vessels Detection and Hough Transform / F. Zana, J.C. Klein // IEEE Transactions on Medical Imaging. – 1999. – Vol. 18(5). – P. 419-428.

69. Zana, F. Segmentation of vessel-like patterns using mathematical morphology and curvature evaluation / F. Zana, J.C. Klein // IEEE Trans Image Processing. – 2002. – Vol. 10(7). – P. 1010-1019.

70. Ayala, G. Different averages of a fuzzy set with an application to vessel segmentation / G. Ayala, T. Leon, V. Zapater // IEEE Transactions on Fuzzy Systems. – 2005. – Vol. 13(3). – P. 384-393.

71. Miri, M.S. Retinal image analysis using curvelet transform and multistructure elements morphology by reconstruction / M.S.

Miri, A. Mahloojifar // IEEE Transactions on Biomedical Engineering. – 2011. – Vol. 58(5). – P. 1183-1192.

72. Calvo, D. Automatic detection and characterisation of retinal vessel tree bifurcations and crossovers in eye fundus images / M. Ortega, M.G. Penedo, J. Rouco // Computer Methods and Programs in Biomedicine. – 2011. – Vol. 103(1). – P. 28-38.

73. Fraz, M.M. An approach to localize the retinal blood vessels using bit planes and centerline detection / M.M. Fraz, S.A. Barman, P. Remagnino, A. Hoppe, A. Basit, B. Uyyanonvara, A.R. Rudnicka, C.G. Owen // Comput Methods Programs Biomed. – 2012. – Vol. 108(2). – P. 600-616.

74. Bouraoui, B. 3D segmentation of coronary arteries based on advanced mathematical morphology techniques / B. Bouraoui, C. Ronse, J. Baruthio, N. Passat, P. Germain // Computerized Medical Imaging and Graphics. – 2010. – Vol. 34(5). – P. 377-387.

75. Yang, Y. An automatic hybrid method for retinal blood vessel extraction / Y. Yang, S. Huang, N. Rao // International Journal of Applied Mathematics and Computer Science. – 2008. – Vol. 18(3). – P. 399-407.

76. Sun, K. Morphological multiscale enhancement, fuzzy filter and watershed for vascular tree extraction in angiogram / K. Sun, Z. Chen, S. Jiang, Y. Wang // Journal of Medical Systems. – 2011. – Vol. 35(5). – P. 811-824.

77. Nasonov, A.V. Application of the method of morphological amoebas to blood vessels in the eye detection fundus images / A. Nasonov, A.A. Chernomorets, A.S. Krylov, A.S. Rodin // DSPA'2011. – 2011. – Vol. 2. – P. 158-161.

78. Mendonca, A.M. Segmentation of retinal blood vessels by combining the detection of centerlines and morphological reconstruction / A.M. Mendonca, A. Campilho // IEEE Transactions on Medical Imaging. – 2006. – Vol. 25(9). – P. 1200-1213.

79. Li, Q. Vessel segmentation and width estimation in retinal images using multiscale production of matched filter responses / Q. Li, Y. Jane, D. Zhang / Expert Systems with Applications. – 2012. – Vol. 39(9). – P. 7600-7610.

80. Nguyen, U.T.V. An effective retinal blood vessel segmentation method using multi-scale line detection / U.T.V. Nguyen, A. Bhuiyan, L.A.F. Park, K. Ramamohanarao // Pattern Recognition. – 2013. – Vol. 46(3). – P. 703-715.

81. Moghimirad, E. Retinal vessel segmentation using a multiscale medialness function / E. Moghimirad, S.H. Rezatofighi, H. Soltanian-Zadeh // Computers in Biology and Medicine. – 2012. – Vol. 42(1). – P. 50-60.

82. Lathen, **G.** Blood vessel segmentation using multi-scale quadrature filtering / G. Lathen, J. Jonasson, M. Borga // Pattern Recognition Letters. – 2010. – Vol. 31(8). – P. 762-767.

83. Frangi, A.F. Multiscale vessel enhancement filtering, in: Medical Image Computing and Computer-Assisted Interventation / A.F. Frangi, W.J. Niessen, K.L. Vincken, M.A. Viergever. – MICCAI'98, 1998. – Vol. 1496. – P. 130-137.

84. Sofka, M. Retinal vessel centerline extraction using multiscale matched filters, confidence and edge measures / M. Sofka, C.V. Stewart // IEEE Transactions on Medical Imaging. – 2006. – Vol. 25(12). – P. 1531-1546.

85. Anzalone, A. A modular supervised algorithm for vessel segmentation in red-free retinal images / A. Anzalone, F. Bizzarri, M. Parodi, M. Storace // Computers in Biology and Medicine. – 2008. – Vol. 38(8). – P. 913-922.

86. Biesdorf, A. Segmentation and quantification of the aortic arch using joint 3D model-based segmentation and elastic image registration / A. Biesdorf, K. Rohr, D. Feng, H. von Tengg-Kobligk, F. Rengier, D. Bockler, H.U. Kauczor, S. Worz // Medical Image Analysis. – 2012. – Vol. 16(6). – P. 1187-1201.

87. Vermeer, K.A. A model based method for retinal blood vessel detection / K.A. Vermeer, F.M. Vos, H.G. Lemij, A.M. Vossepoel // Comput Biol Med. – 2004. – Vol. 34(3). – P. 209-219.

88. Mahadevan, V. Robust model-based vasculature detection in noisy biomedical images / V. Mahadevan, H. Narasimha-Iyer, B. Roysam, H.L. Tanenbaum // IEEE Transactions on Information Technology in Biomedicine. – 2004. – Vol. 8(3). – P. 360-376.

89. Can, A. Rapid automated tracing and feature extraction from retinal fundus images using direct exploratory algorithms / A. Can, J.N. Turner, H.L. Tanenbaum, B. Roysam // IEEE Transactions on Information Technology in Biomedicine. – 1999. – Vol. 3(2). – P. 125-138.

90. Narasimha-Iyer, **H.** Improved detection of the central reflex in retinal vessels using a generalized dual-gaussian model and robust hypothesis testing / H. Narasimha-Iyer, V. Mahadevan, J.M. Beach, B. Roysam // IEEE Transactions on Information Technology in Biomedicine. – 2008. – Vol. 12(3). – P. 406-410.

91. Wang, L. Analysis of retinal vasculature using a multiresolution Hermite model / L. Wang, A. Bhalerao, R. Wilson // IEEE Transactions on Medical Imaging. – 2007. – Vol. 26(2). – P. 137-152.

92. Narasimha-Iyer, H. Automatic identification of retinal arteries and veins from dual-wavelength images using structural and functional features / H. Narasimha-Iyer, J.M. Beach, B. Khoobehi, B. Roysam // IEEE Transactions on Biomedical Engineering. – 2007. – Vol. 54. – P. 1427-1435.

93. Xiaohong, G. A method of vessel tracking for vessel diameter measurement on retinal images / G. Xiaohong, A. Bharath, A. Stanton, A. Hughes, N. Chapman, S. Thom // International Conference on Image Processing. – 2001. – Vol. 2. – P. 881-884.

94. Zhu, T. Fourier cross-sectional profile for vessel detection on retinal images / V. Mahadevan, H. Narasimha-Iyer, B. Roysam // Computerized Medical Imaging and Graphics. – 2010. – Vol. 34(3). – P. 203-212.

95. Osareh, A. Color morphology and snakes for optic disc localization / A. Osareh, M. Mirmehdi, B. Thomas, R. Markham // Pattern Recognition. – 2002. – Vol. 1. – P. 743-746.

96. Xu, J. Optic disk feature extraction via modified deformable model technique for glaucoma analysis / J. Xu, O. Chutatape, E. Sung, C. Zheng, Paul Chew Tec Kuan // Pattern Recognition. – 2007. – Vol. 40(7). – P. 2063-2076.

97. Hsiao, H.K. novel optic disc detection scheme on retinal images / H.K. Hsiao, C.C. Liu, C.Y. Yu, S.W. Kuo, S.S. Yu // Expert Systems with Applications. – 2012. – Vol. 39(12). – P. 10600-10606.

98. Espona, L. A snake for retinal vessel segmentation / L. Espona, M.J. Carreira, M. Ortega, M.G. Penedo // Proceedings of the 3rd Iberian conference on Pattern Recognition and Image Analysis / International Conference on Pattern Recognition, 2007. – Vol. 4478. – P. 178-185.

99. Espona, L. Retinal vessel tree segmentation using a deformable contour model / L. Espona, M.J. Carreira, M.G. Penedo, M. Ortega. – ICPR International Conference on Pattern Recognition, 2008. – Vol. 5197 – P. 683-690.

100. Al-Diri, B. An active contour model for segmenting and measuring retinal vessels / B. Al-Diri, A. Hunter, D. Steel // IEEE Transactions on Medical Imaging. – 2009. – Vol. 28(9).– P. 1488-1497.

101. Al-Diri, B. REVIEW – a reference data set for retinal vessel profiles, in: Engineering in Medicine and Biology Society / B. Al-Diri, A. Hunter, D. Steel, M. Habib, T. Hudaib, S. Berry. – EMBS Annual International Conference of the IEEE, 2008. – Vol. 2008. – P. 2262-2265.

102. Jiang, X. Structural performance evaluation of curvilinear structure detection algorithms with application to retinal vessel segmentation / M. Lambers, H. Bunke // Pattern Recognition Letters. – 2012. – Vol. 33(15). – P. 2048-2056.

103. Zhang, Y. Detection of retinal blood vessels based on nonlinear projections / Y. Zhang, W. Hsu, M. Lee // Journal of Signal Processing Systems. – 2009. – Vol. 55(1-3). – P. 103-112.

104. Tong, C.S. Variational image binarization and its multiscale realizations / C.S. Tong, Y. Zhang, N. Zheng // Journal of Mathematical Imaging and Vision. – 2005. – Vol. 23(2). – P. 185-198.

105. Lam, B.Y. A novel vessel segmentation algorithm for pathological retina images based on the divergence of vector fields / B.Y. Lam, Y. Hong // IEEE Transactions on Medical Imaging. – 2008. – Vol. 27(2). – P. 237-246.

106. Ramlugun, G.S. Small retinal vessels extraction towards proliferative diabetic retinopathy screening / G.S. Ramlugun, V.K. Nagarajan, C. Chakraborty // Expert Systems with Applications. – 2012. – Vol. 39(1). – P. 1141-1146.

107. Rapantzikos, K. Detection and segmentation of drusen deposits on human retina: potential in the diagnosis of age-related macular degeneration / K. Rapantzikos, M. Zervakis, K. Balas // Med Imaging Anal. – 2003. – Vol. 7(1). – P. 95-108.

108. Azemin, M.Z. Robust methodology for fractal analysis of the retinal vasculature / M.Z. Azemin, D.K. Kumar, T.Y. Wong, R. Kawasaki, P. Mitchell, J.J. Wang // IEEE Transactions on Medical Imaging. – 2011. – Vol. 30(2). – P. 243-250.

109. Patasius, M. Recursive Algorithm for Blood Vessel Detection in Eye Fundus Images / M. Patasius, V. Marozas, D. Jegelevieius, A. Lukosevieius // IFMBEProceedings – 2009. – Vol. 25(11). – P. 212-215.

110. Ilyasova, N.Yu. Information technologies of image analysis in medical diagnostics / N.Yu. Ilyasova, A.V. Kupriyanov, A.G. Khramov. – Moscow: “Radio i svyaz” Publisher, 2012. – 424 p.

111. Korepanov, A.O. A method of allocating the Central lines of blood vessels of the diagnostic images / A.O. Korepanov, N.Yu. Ilyasova, M. Chikulaev // Computer Optics. – 2006. – Vol. 29. – P. 146-151.

112. Aylward, S.R. Intensity ridge and widths for tabular object segmentation and registration / S.R. Aylward, S. Pizer, E. Bullitt and D. Eberl // Wksp on Math Image Analysis. – 1996. – Vol. 7. – P. 131-138.

113. Lecornu, L. Extraction of vessel contours in angiograms by simultaneous tracking of the two edges / L. Lecornu, C. Roux, J.J. Jacq // Engineering in Medicine and Biology Society. – 1994. – Vol. 1. – P. 678-679.

114. Hart, M. A method of automated coronary artey tracking in unsubtracted angiograms / M. Hart, L. Holley // IEEE Computers in Cardiology. – 1993. – P. 93-96.

115. Chutatape, O. Retinal blood vessel detection and tracking by matched Gaussian and Kalman filters / O. Chutatape, L. Zheng, S.M. Krishman // Proceedings of IEEE EMBS. – 1998. – Vol. 6. – P. 3144-3149.

116. Poon, K. Live-vessel: extending livewire for simultaneous extraction of optimal medial and boundary paths in vascular images / K.Poon, G.Hamarneh, R.Abugharbieh // Medical Image Computing and Computer-Assisted Intervention MICCAI-2007, 2007. – Vol. 4792 – P. 444-451.

117. Barrett, W.A. Interactive live-wire boundary extraction / W.A. Barrett, E.N. Mortensen // Medical Image Analysis. – 1997. – Vol. 1(4) – P. 331-341.

118. Delibasis, K.K. Automatic model-based tracing algorithm for vessel segmentation and diameter estimation / K.K. Delibasis, A.I. Kechriniotis, C. Tsonos, N. Assimakis // Comput. Methods Programs Biomed. – 2010. – Vol. 100(2). – P. 108-122.

119. Vlachos, M. Multi-scale retinal vessel segmentation using line tracking / M. Vlashos, E. Dermatas // Computerized Medical Imaging and Graphics. – 2010. – Vol. 34(3). – P. 213-227.

120. Lalonde, T. Non-recursive paired tracking for vessel extraction from retinal images / M. Lalonde, L. Gagnon, M.C. Bouchert. – Montreal: Proceedings of the Conference Vision Interface 2000, 2000. – P. 61-68.

121. Yin, Y. Retinal vessel segmentation using a probabilistic tracking method / Y. Yin, M. Adel, S. Bourennane // Pattern Recognition. – 2012. – Vol. 45(4). – P. 1235-1244.

122. Huang, Y. An automated computational framework for retinal vascular network labeling and branching order analysis / Y. Huang, J. Zhang, Y. Huang // Microvascular Research. – 2012. – Vol. 84(2). – P. 169-177.

123. Gao, X. Measurement of vessel diameters on retinal images for cardiovascular studies / X. Gao, A. Bharath, A. Stanton, A. Hughes, N. Chapman, S. Thom. – On-line Conference Proceedings: Medical Image Understanding and Analysis, 2001.

124. Liu, Y.P. Retinal arterio lar and venular phenoty pes in a Flemish populati on: Repro ducibility and correlates / Y.P. Liu, T. Richart, Y. Jin, H.A. Struijker-Boundierc, J.A. Staessen // Artery Research. – 2011. – Vol. 5(2). – P. 72-79.

125. Wong, T.Y. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis

(MESA) / T.Y. Wong, F.M. Islam, R. Klein, B.E. Klein, M.F. Cotch, C. Castro, A.R. Sharrett, E. Shahar // Invest. Ophthalmol. Vis. Sci. – 2006. – Vol. 47(6). – P. 2341-2350.

126. Ikram, M.K. Retinal vessel diameters and risk of impaired fasting glucose or diabetes / M.K. Ikram, J.A. Janssen, A.M. Roos, I. Rietveld, J.C. Witteman, M.M. Breteler, A. Hofman, C.M. van Duijn, P.T. de Jong // Diabetes. – 2006. – Vol. 55(2). – P. 506-510.

127. Newsom, R.S. Retinal vessel measurement: comparison between observer and computer driven methods / R.S. Newsom, P.M. Sullivan, S.M. Rassam, R. Jagoe, E.M. Kohner // Graefes Arch. Clin. Exp. Ophthalmol. – 1992. – Vol. 230(3). – P. 221-225.

128. Hiroki, M. Tortuosity of the white matter medullary arterioles is related to the severity of hypertension / M. Hiroki, K. Miyashita, M. Oda // Cerebrovasc Dis. – 2002. – Vol. 13(4). – P. 242-250.

129. King, L.A. Arteriolar length-diameter (L:D) ratio: a geometric parameter of the retinal vasculature diagnostic of hypertension / L.A. King, A.V. Stanton, P.S. Sever, S.A. Thom, A.D. Hughes // J. Hum. Hypertens. – 1996. – Vol. 10(6). – P. 417-418.

130. Rassam, S.M. Accurate vessel width measurement from fundus photographs: a new concept / S.M. Rassam, V. Patel, O. Brinchmann-Hansen, O. Engvold, E.M. Kohner // British Journal of Ophthalmology. – 1994. – Vol. 78(1). – P. 24-29.

131. Brinchmann-Hansen, O. Microphotometry of the blood column and light streak on retinal vessels in fundus photographs / O. Brinchmann-Hansen, O. Engvold // Acta Ophthalmologica. – 1986. – Vol. 64(S179). – P. 9-19.

132. Gao, X.W. Quantification characterisation of arteries in retinalimages / X.W. Gao, A. Bharath, A. Stanton, A. Hughes, N. Chapman, S. Thom // Computer Methods and Programs in Biomedicine. – 2000. – Vol. 63(2). – P. 133-146.

133. Pedersen, L. Quantitative measurement of changes in retinal vessel diameter in ocular fundus images / L. Pedersen, M. Grunkin, B. Ersboll, K. Madsen, M. Larsen, N. Christoffersen, U. Skands // Pattern Recognition Letters. – 2000. – Vol. 21(13-14). – P. 1215-1223.

134. Wong, T.Y. A prospective cohort study of retinal arteriolar narrowing and mortality / T.Y. Wong, M.D. Knudtson, R. Klein [et al.] // Am. J. Epidemiol. – 2004. – Vol. 159(9). – P. 819-825.

135. Yiming, W. A fast method for automated detection of blood vessels in retinal images / W. Yiming, Y. Wang, C. Lee // Signals, Systems & Computers. – 1997. – Vol. 2. – P. 1700-1704.

136. Fathi, A. Automatic wavelet-based retinal blood vessels segmentation and vessel diameter estimation / A. Fathi, A.R. Naghsh-Nilchi // Biomedical Signal Processing and Control. – 2013. – Vol. 8(1). – P. 71-80.

137. Vilser, W. Automated measurement of retinal vascular diameter / W. Vilser, S. Klein, P. Wulff, G. Fuchs // Fortschr. Ophthalmol. – 1991. – Vol. 88(5). – P. 482-486.

138. Tyrrell, J.A. 2-D/3-D model-based method to quantify the complexity of microvasculature imaged by in vivo multiphoton microscopy / V. Mahadeva, T. Tong, E.B. Brown, R.K. Jain, B. Roysam // Microvascular Research. – 2005. – Vol. 70(3) – P. 165-178.

139. Hanssen, H. Retinal vessel diameter, obesity and metabolic risk factors in school children (JuvenTUM 3) / H. Hanssen, M. Siegrist, M. Neidig, A. Renner, P. Birzele, A. Siclovan, K. Blume, C. Lammel, B. Haller, A. Schmidt-Trucksass, M. Halle // Atherosclerosis. – 2012. – Vol. 221(1). – P. 242-248.

140. Saez, M. Development of an automated system to classify retinal vessels into arteries and veins / M. Saez, S. Gonzalez-Vazquez, M. Gonzalez-Penedo, M.A. Barcelo, M. Pena-Seijo, G. Coll de Tuero, A. Pose-Reino // Comput. Methods Programs Biomed. – 2012. – Vol. 108(1). – P. 367-376.

141. Mosher, A. Comparison of Retinal Vessel Measurements in Digital vs Film Imags / A. Mosher, E.K. Klein, R. Klein, M.D. Knudtson, N.J. Ferrier // Am. J. Ophthalmol. – 2006. – Vol. 142(5). – P. 875-878.

142. Muramatsu, C. Automated selection of major arteries and veins for measurement of arteriolar-to-venular diameter ratio on retinal fundus images / C. Muramatsu, Y. Hatanaka, T. Iwase, T. Hara, H. Fujita // Computerized Medical Imaging an Graphics. – 2011. – Vol. 35(6). – P. 472 – 480.

143. Knudtson, M.D. Revised formulas for summarizing retinal vessel diameters / M.D. Knudtson, K.E. Lee, L.D. Hubbard, T.Y. Wong, R. Klein, B.E. Klein // Curr. Eye. Res. – 2003. – Vol. 27(3) – P. 143-149.

144. Tramontan, L. Computer estimation of the AVR parameter in diabetic retinopathy / L. Tramontan, A. Ruggeri // IFMBE Proc. – 2009. – Vol. 25(11) – P. 141-154.

145. Nam, H.S. Automated measurement of retinal vessel diameters on digital fundus photographs / H.S. Nam, J.M. Hwang, H. Chung, J.M. Seo // IFMBE Proc. – 2009. – Vol. 25(11) – P. 277-280.

146. Niemeijer, M. Automatic determination of the artery–vein ratio in retinal fundus images / M. Niemeijer, B. van Ginneken, M.D. Abramoff // Proc SPIE. – 2010. – Vol. 7624

147. Niall, P. Retinal image analysis: Concepts, applications and potential / P. Niall, M.A. Tariq, M. Thomas, J.D. Ian, D. Baljean, I.E. Robert, Y. Kanagasingam, J.C. Ian // Progress in Retinal and Eye Research. – 2006. – Vol. 25(1). – P. 99-127.

148. Sharrett, L.D. Retinal arteriolar diameters and elevated blood pressure: the atherosclerosis risk in communities study / L.D. Hubbard, L.S. Cooper, P.D. Sorlie, R.J. Brothers, F.J. Nieto, J.L. Pinsky, R. Klein // American Journal Epidemiology. – 1999. – Vol. 150(3) – P. 263-270.

149. Muramatsu, C. Automated segmentation of optic disc region on retinal fundus photographs: comparison of contour modeling and pixel classification methods / C. Muramatsu, T. Nakagawa, A. Sawada, Y. Hatanaka, T. Hara, T.Yamamoto // Comput Methods Programs Biomed. – 2011. – Vol. 101(1). – P. 23-32.

150. MESSIDOR: Methods for Evaluating Segmentation and Indexing techniques Dedicated to Retinal Ophthalmology, 2004. – URL: http://messidor.crihan.fr/index-en.php.

151. Kauppi, V. DIARETDB1 diabetic retinopathy database and evaluation protocol / T. Kauppi, V. Kalesnykiene, J.K. Kamarainen, L. Lensu, I. Sorri, A. Raninen, R. Voutilainen, J. Pietil, H. Klvilinen, H. Uusitalo. – Medical Image Understanding and Aberystwyth (MIUA2007), 2007. – Vol. 41 – P. 61-65.

152. ARIA Online, Retinal Image Archive. URL: http://www.eyecharity.com/aria online/. – 2006.

153. The VICAVR database. URL: http://www.varpa.es/vicavr.html. – 2010.

154. Chapman, N. Retinal vascular tree morphology: a semi-automatic quantification / N. Chapman, M.E. Martinez-Perez, A.D. Highes, A.V. Stanton, S.A. Thorn, A.A. Bharath, K.H. Parker // IEEE Trans. Biomedical Engineering. – 2002. – Vol. 49(8). – P. 912-917.

155. Dougherty, G. A quantitative index for the measurement of the tortuosity of blood vessels / G. Dougherty, J. Varro // Medical Engineering & Physics. – 2000. – Vol. 22(8). – P. 567-574.

156. Johnson, M.J. Robust measures of three-dimensional vascular tortuosity based on the minimum curvature of approximating polynomial spline fits to the vessel mid-line / M.J. Johnson , G. Dougherty // Med. Eng. Phys. – 2007. – Vol. 29(6). – P. 677-690.

157. Spangler, K.M. Arteriolar tortuosity of the white matter in aging and hypertension / V.R. Challa, D.M. Moody, M.A. Bell // A microradiographic study. J. Neuropathol. Exp. Neurol. – 1994. – Vol. 53(1). – P. 22-26.

158. Hart, W.E. Measurement and classification of retinal vascular tortuosity / W.E. Hart, M. Goldbaum, B. Cote, P. Kube, M.R. Nelson // International Journal of Medical Informatics. – 1999. – Vol. 53(2-3). – P. 239-252.

159. Capowski, J.J. A numeric index based on spatial frequency for the tortuosity of retinal vessels and its application to plus disease in retinopathy of prematurity / J.J. Capowski, J.A. Kylstra, S.F. Freedman // Retina. – 1995. – Vol. 15(6) – P. 490-500.

160. Swanson, C. Semiautomated computer analysis of vessel growth in preterm infants without and with ROP / C. Swanson, K.D. Cocker, K.H. Parker, M.J. Moseley, A.R. Fielder // Br. J. Ophthalmol. – 2003. – Vol. 87(12). – P. 1474-1477.

161. Ilyasova, N.Yu. Biomechanical characteristics of blood vessels for digital image analysis fundus / N.Yu. Ilyasova, A.V. Kupriyanov, N.A. Gavrilova, G.A. Shilkin, N.I. Lanevskaya // Biomehanika glaza. – 2002. – P. 18-30.

162. Lotmar, W. Measurement of vessel tortuosity on fundus photographs / W. Lotmar, A. Freiburghaus, D. Bracher // Graefe's Arch. Clin. Exp. Ophthalmol. – 1979. – Vol. 221(1). – P. 49-57.

163. Bracher, D. Changes in peripapillary tortuosity of the central retinal arteries in newborns / D. Bracher // Graefe's Arch. Clin. Exp. Ophthalmol. – 1982. – Vol. 218(4). – P. 211-217.

164. Brinkman, A.M. Variability of human coronary artery geometry: an angiographic study of the left anterior descending arteries of 30 autopsy hearts / A.M. Brinkman, P.B. Baker, W.P. Newman, R. Vigorito, M.H. Friedman // Ann Biomed Eng. – 1994. – Vol. 22(1). – P. 34-44.

165. Smedby, O. Tortuosity and atherosclerosis in the femoral artery: what is cause and what is effect / O. Smedby, L. Bergstrand // Ann. Biomed. Eng. – 1996. – Vol. 24(4). – P. 474-480.

166. Smedby, O. Two-dimensional tortuosity of the superficial femoral artery in early atherosclerosis / O. Smedby, N. Hogman, S. Nilsson, U. Erikson, A.G. Olsson, G. Walldius // J. Vasc. Res. – 1993. – Vol. 30(4). – P. 181-191.

167. Kimball, B. Angiographic features associated with acute coronary artery occlusion during elective angioplasty / B. Kimball, , S. Bui, N. Dafopoulos. J. Can // Cardiol. – 1990. – Vol. 6(8) – P. 327-332.

168. Cheung, C.Y. Retinal Vascular Tortuosity, Blood Pressure, and Cardiovascular Risk / C.Y. Cheung, Y. Zheng, W. Hsu, M.L. Lee, Q.P. Lau, P. Mitchell, J.J. Wang, R. Klein, T.Y. Wong // Ophthalmology. – 2011. – Vol. 118(5). – P. 812-818.

169. Martin Rodriguez, Z. Improved characterisation of aortic tortuosity / Z. Martin Rodriguez, P. Kenny, L. Gaynor // Med. Eng. Phys. – 2011. – Vol. 33(6). – P. 712-719.

170. Wenn, C.M. Arterial tortuosity / C.M. Wenn, D.L Newman // Phys. Eng. Sci. Med. – 1990. – Vol. 13(2) – P. 67-70.

171. Kaupp, A. Automatic evaluation of retinal vessel width and tortuosity in digital fluorescein angiograms, Invest / A. Kaupp, H. Toonen, S. Wolf, K. Schulte, R. Effert, D. Meyer-Ebrecht, M. Reim // Ophthalmol. – 1991. – Vol. 84. – P. 952-987.

172. Bullitt, E. Analyzing attributes of vessel populations / E. Bullitt, K.E. Muller, I. Jung, W. Lin, S. Aylward // Med. Image Anal. – 2005. – Vol. 9(1). – P. 39-49.

173. Grisan, E A novel method for the automatic evaluation of retinal vessel tortuosity / E. Grisan, M. Foracchia, A. Ruggeri // IEEE Trans. Med. Imaging Proc. – 2008. – P. 310-319.

174. Chandrinos, K.V. Image processing techniques for the quantification of atherosclerotic changes / K.V. Chandrinos, R.B. Fisher, P.E. Trahanias // Proc. MEDICO98 / Cyprus: Limassol, 1998.

175. Kylstra, J.A. The relationship between retinal vessel tortuosity, diameter and transmural pressure / T. Wierzbicki, M.L. Wolbarsht, M.B. Landers III, E. Stefansson // Clin. Exp. Ophthalmol. – 1986. – Vol. 224(5). – P. 477-480.

176. Sasongko, M.B. Alterations in retinal microvascular geometry in young type 1 diabetes / J.J. Wang, K.C. Donaghue, N. Cheung, A.J. Jenkins, P. Benitez-Aguirre, J.J. Wang // Diabetes Care. – 2010. – Vol. 33(6). – P. 1331-1336.

177. Leung, H. Does hormone replacement therapy influence retinal microvascular caliber? / H. Leung, J.J. Wang, E. Rochtchina, T.Y. Wong, R. Klein, P. Mitchell // Microvascular Research. – 2004. – Vol. 67(1). – P. 48-54.

178. Gregson, P.H. Automated grading of venous beading / Z. Shen, R.C. Scott, V. Kozousek // Computers And Biomedical. – 1995. – Vol. 28(4). – P. 291-304.

179. Hunter, A. Non-linear Filtering for vascular segmentation and detection of venous beading / A. Hunter, J. Lowell, D. Steel, A. Basu and R. Ryder // Tech. report, University of Durham. – 2003. – P.100-104.

180. Abramoff, M.D. Evaluation of a system for automatic detection of diabetic retinopathy from color fundus photographs in a large population of patients with diabetes / M.D. Abramoff, M. Niemeijer, M.S. Suttorp-Schulten, M.A. Viergever, S.R. Russell, B. van Ginneken // Diabetes Care. – 2008. – Vol. 31(2). – P. 193-198.

181. Ilyasova, N.Yu. Formation of features for improving the quality of medical diagnosis based on discriminant analysis methods / N.Yu. Ilyasova, A.V. Kupriyanov, R.A. Paringer // Computer Optics. – 2014. – Vol. 38(4). – P. 851-856.