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A non-invasive expert system for diagnosis of intraocular tumours: the system concept

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Abstract

The aim of the project is to developand introduce to the market a new safe, non-invasive expert system for analysis and diagnosis of intraocular tumours. It will consist of a novel non-invasive ultrasonic tissue characterisation instrument - attachment to the conventional ultrasound diagnostic system for acquisition of ultrasound RF signals, sophisticated software for ultrasonic data analysis and the innovative digital ophthalmoscope for acquiring, processing and parameterisation of images of intraocular tumours.

Keywords: ultrasound, intraocular tumour, radio-frequency signal, non-invasive expert system, sophisticated software

1. Introduction

The clinical reasoning behind the project is that differential diagnosis of human eye tumours is one of the most important problems in ophthalmology in dealing with cancer prevention and diagnostics. Malignant eye tumours make 0.2 % of all malignant tumours diagnosed, but it is a direct reason of death for each third patient. In ophthalmological practice and treatment, intraocular tumour differentiation is one of determinant factors for management and outcomes of a disease. Recently, the main method for differentiation of intraocular tumours globally has been the use of invasive methods (e.g. fine needle biopsy) and like all invasive methods, it has had it's limitations. Therefore, offering an early non-invasive diagnosis and characterization of tumour's tissue is crucial for a proper treatment prognosis of the tumours and death prevention.

The overall aim of the project is to develop and introduce to the market a new expert system for analysis and diagnosis of intraocular tumours. It will consist of a new non-invasive ultrasonic tissue characterisation instrument (which will be developed and prototypes produced in the course of this project) to the conventional ultrasound diagnostic system for acquisition of ultrasonic RF signals, sophisticated software for ultrasonic data analysis, and the innovative digital ophthalmoscope for acquiring images of intraocular tumours. The ultrasonic tissue characterisation instrument – an option to the conventional ultrasonic diagnostic systems for advanced data acquisition, processing and analysis system with automatic decision feature (further referred to as "Device RF") will fulfil the market demand, because it will respond to the clinical needs for a reliable method of intraocular tumours diagnostics. It will be compatible with the majority of commercially available diagnostic systems and will fit the advanced requirements of the end-users at a competitive price.

The most common current method for the eye tumour diagnosis is ophthalmoscopy - optical subjective evaluation of the eye fundus. Ophthalmoscopy is an obligatory method in an ophthalmological examination. It is sufficient to diagnose an intraocular tumour but insufficient for differential diagnosis and evaluation of its structure.

Complex optical and ultrasound- based investigations are the leading non-invasive methods for the intraocular tumours diagnosis, differentiation, tumour geometrical and structural parameters evaluation. There are several indicators used for ultrasonic diagnosis of intraocular tumours in vivo: geometry, size, shape and structure are frequently used in a clinical practice. Non-invasiveness, high resolution and informative ness make the ultrasound investigation one of the most effective and efficient diagnostic methods in ophthalmology. A-scan (one-dimensional detected signal), B-scan (two-dimensional image), 3D and ultrasound biomicroscopy (UBM) technique are used for a tumour characterization. However, an ultrasound radiofrequency (RF) signal provides more information in comparison with the detected signal or images. Therefore, the reliable way to increase a resolution of commercially available ultrasound imaging systems and characterization of biological tissues is acquisition and processing of ultrasound RF signals. However, of acquisition RF signals is not available in the equipment currently available on the market worldwide. This makes a gap between the demand and availability and creates a market opportunity [1-8].

The ultrasonic diagnostic system that will be developed in the course of this project could be implemented into other clinical areas (such as oncology, dermatology). The developed product will be offered for end-users (doctors) and beneficiaries (patients/the society) and is going to be a high value-adding system enabling faster and better-informed diagnostic decisions of potentially terminal diseases at a reasonable cost. As the result, quality of a diagnostics and treatment will be improved essentially and the probability of the patient mortality related to malignant eye tumours will be reduced.

The project “A Non-Invasive Expert System for Diagnosis of Intraocular Tumours” will be implemented by a consortium that will include clinical, technological and market expertise and will consist of Stratelus, a telemedicine development and services company, Optomed OY (Finland), Biomedical Engineering Institute of the Kaunas University of Technology, Ultrasound Institute of the Kaunas University of Technology and Department of Electrical and Information Technology of Lund University (Sweden).

The scope of the project is to create a qualitative new, safe, non-invasive system, consisting of a specialized technical equipment - the Device RF – the option to a conventional ultrasound scanner for acquisition and collection of RF signals from intraocular tumours and a sophisticated software for data processing and parameterization. The created product will be compatible with most ultrasonic diagnostic equipment (scanners) on the market and will give a new information about tumour tissue parameters and will satisfy the specific clinical/technological demands of end users.

The fact that an ultrasound RF signal carries more information for the clinical decision making, for intraocular tumours in particular, is not a new knowledge and technologies for processing the ultrasound RF signal have existed, but this technology hasn't been developed to the hi-end level and applied in a commercially available medical equipment offered to end-users.

2. The role of ultrasound in ophthalmology

Ophthalmological non-invasive devices (ultrasound scanners) are the most effective part of the ophthalmological diagnostic equipment which is gradually improved and have been applied in the world already for 30-40 years and about 30 years in Lithuania. However contemporary and technological achievements exceed the possibilities of an ophthalmological diagnostic equipment offered in the market. As a result, the ophthalmological diagnostic equipment recently proposed in the market uses conventional methods, like detected imaging of the A-scan echographic signal (biometry), B-scan, 3D scan, UBM. Such imaging does not give possibility for user to apply more sophisticated data processing (time-frequency filtering, application of the modern model-based processing algorithms and etc.) Hence, innovations in this area are implemented with notably delays. This makes a gap in the market and provides possibility to create an innovative ultrasound system for original collection of ultrasound RF signals, processing and differentiation of intraocular tumours [1-8].

The main alternative to the developments envisaged in the project is to analyse the conventional B-scan images using special image processing methods and algorithms including texture analysis, calculation statistical and morphological parameters of the image regions under interest.

However in order to get as much as possible valuable information about eye tumours and their structure there is needed to create methods and tools for extraction of a qualitative new and valuable information from ultrasound radiofrequency signals (RF). The RF ultrasound signal is a non-detected A-scan signal, which provides a much more information about a tissue structure than conventional images, like a detected A-scan signal or B-scan image. The extraction and processing of RF signals in the time and the frequency domains is a possibility to improve the accuracy of medical imaging systems present in the market for diagnosis and characterization of eye tumours. This also gives possibility for automatic classification of tumours. Tools and complementary informative methods of signal acquiring and processing for evaluation of valuable quantitative parameters must be created for getting a valuable information about the eye tumours. A rapid progress in the area of digital signal acquiring and processing enables to solve this technological task. Hereby there comes a possibility to improve the ophthalmological ultrasound non-invasive equipment and by integration with the optical imaging to increase reliability of differential diagnostics [1-8].

The product to be developed will have to meet the technical and clinical requirements set for it which will be based on what is needed for a clinical evaluation and decision making. The overall challenge is delivering a product that would be technologically advanced but easy to operate by medical/clinical people and able to withstand intensive usage at large hospitals with large numbers of patients.

The main problem and demand arises from the fact that available devices don’t ensure sufficient resolution of tissue characterisation. CT, MRI, conventional ultrasonic scanners, optical devices are not able to classify tumour tissues by the fine internal microstructure.

The technological challenge of this project is moving from conventional A/B-scan images to the raw RF ultrasound signal processing and allowing acquisition and processing of a RF signal at a significantly higher resolution (approximately more than 60 %) level. Such resolution will be achieved under the complex analysis in the time and the frequency domains.

The quality of images used for the intraocular tumours diagnostics can be characterised by the following parameters: A-scan signal can provide up to 20 % clinical information, B-scan image can provide up to 40% clinical information, RF signals could provide with a maximum of 100 % clinical information. For a clinical use in the intraocular tumours diagnostics, the RF signal should provide with at least 60 % more clinical information (suitable to evaluate/perform a priori diagnosis) as compared with ordinary A or B scans to be perceived as a more advanced solution by medical/clinical people [1-8].

3. The hardware concept

Requirements for the methodology for acquisition, processing and storing of A/B-scan images and RF signals/images are coming from recent 10 years study of clinical practise and demands, it gives motivation to develop such device [1-14].

As the system created is going to be used primarily by medical/clinical people, the technical support and maintenance required should be minimal - therefore, the system (hardware and software) must be designed the way it would be simple to operate (user-friendly), require a minimum maintenance and technical qualification of operators, and have a low error probability in classification of eye tumours.

According to the technical requirements (Table 1) of the main ultrasonic systems which are used in ophthalmology [11-14], the block diagram of the system/attachment which is necessary to be developed was proposed by us.

The block diagram of the advanced system which is being developed is presented in Fig.1.

Table 1. **Specification overview of B-scan diagnostic systems.**

Manu-factures	Accutome, Inc.	Alcon Labora-tories	OTI Corp.	Tomey Corp.
Model	Advent AB	Alcon® Ultra-Scan®	OTI-Scan 2000	UD-1000
Frequency	7.5 MHz, 12.5 MHz, 15.0 MHz for B-scan. (11MHz broadband	10 MHz and 20 MHz	10 MHz supplied (optional 20 MHz)	10 MHz & 20 MHz
Gain range	50-90 dB	40 to 80 dB	30-114 dB	1-60 dB
Depth range	20/35/50/70 mm	2,3,4, 5,6 cm	43 or 50 mm	34.5 or 46 mm
Resolution	n.s.	0.1 ± 0.05 mm axial 0.4 ± 0.10 mm lateral, at 20MHz	Axial direction 0.15 mm, Lateral direction max. 0.2 mm	lateral 0,4mm axial 0,3mm,; distance in curacy 0,5mm

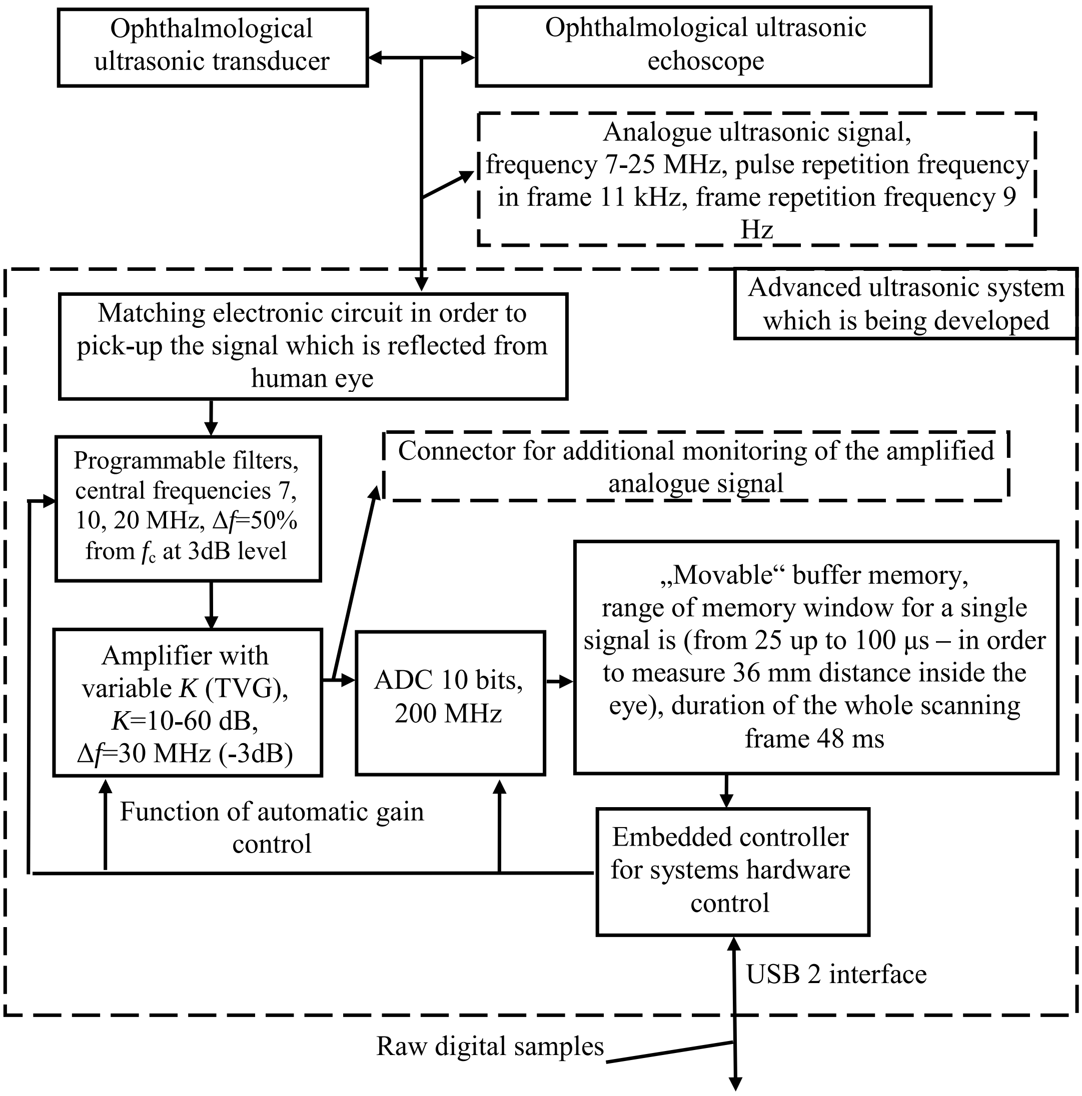

Fig.1. **Block diagram of the advanced ultrasonic signal capturing system concept: TVG – time varying gain; ADC – analog/digital converter**

4. Review of cancer tissue characterization methods

Intraocular images, shapes and geometrical parameters obtained from conventional systems are valuable in diagnostics and treatment monitoring. In cases of complicated cancer diseases, planning and monitoring brachytherapy, eye physicians are facing with lake of differential diagnostics parameters and methodologies implemented in clinical practice. During review of ultrasound diagnostics research in intraocular cancer characterization methods we found many approaches.

Many international research papers [8,15-20] show the attempts and possibilities of tumour tissues characterization using radio-frequency signal processing.

We can list few specific examples of tumour tissue characterisation in eye. Primary malignant melanoma of the choroid and ciliary body has been investigated by [21]. They assumed that histological composition of tumour is to be detected with ultrasound backscatter analysis. Digital ultrasound data were processed to generate parameter images representing the size and concentration of ultrasound scatterer, and authors conclude that radio-frequency signal can be used non-invasively to classify tumours into high-risk and low-risk groups. Studies of [22] demonstrated a correlation between acoustic backscatter parameters and survival in ocular melanoma. Authors conclude that smaller scatterer size, lower acoustic concentration and greater spatial variability were found to correlate with high-risk microvascular patterns. In the research paper [23] was presented objective to standardize the tissue characterization. Measurements of frequency dependence of backscatter are more consistent (inter-laboratory results) than measurements of absolute magnitude. Researchers [24] examined two mouse models of mammary cancer (a carcinoma and sarcoma) using quantitative ultrasound (QUS). Scatterer property estimates, i.e., the average scatterer diameter (ASD) and average acoustic concentration (AAC), were estimated from regions-of-interest (ROIs) inside the tumours. Authors [24] concluded the statistically significant differences observing for both the ASD and AAC estimates when using the new analysis bandwidth. The [25] report describes research results for spectral comparisons of four classes of human intraocular tumours and four classes of implanted tumours in the mouse. Three parameters of the power spectrum [25] have found to be collectively more significant for tumour characterization; specifically, these parameters are spectral slope (dB/MHz), intercept (dB), and statistical standard error. These parameters found significantly different among human spindle cell malignant melanomas, mixed/epithelioid malignant melanomas, metastatic carcinomas, and hemangiomas.

Also Lithuanian researchers [5,26-30] have been investigating problem of intraocular tumours.

Summarising reviewed literature we found that tissue and tumour characterisation obtained from spectral features of ultrasound radiofrequency signal is perspective research direction. It is recommended to process signals in time-frequency domain, estimate central instantaneous frequency, instantaneous bandwidth, backscattering spectra, it is assumed that these parameters have physical origin in microstructure of tissues. The assumed frequency (scalar) and spectra (function) parameters relation to histological changes tissues microstructure (dimensions of tens of micrometers) are undetectable with conventional (frequency of tens of megahertz) ultrasound B-scan diagnostic systems. But ultrasound waves of that frequency can penetrate whole eye tissue until orbit where tumours should be detected. Therefore analysis of ultrasound signals of 10-20MHz frequency could enable estimation of pathological changes of intraocular tissues.

5. Algorithm structure for processing of primary signal

In this section we attempt to present concept of radio-frequency signal processing and user interface software. The overview of signal processing algorithm we presented in the Fig.2.

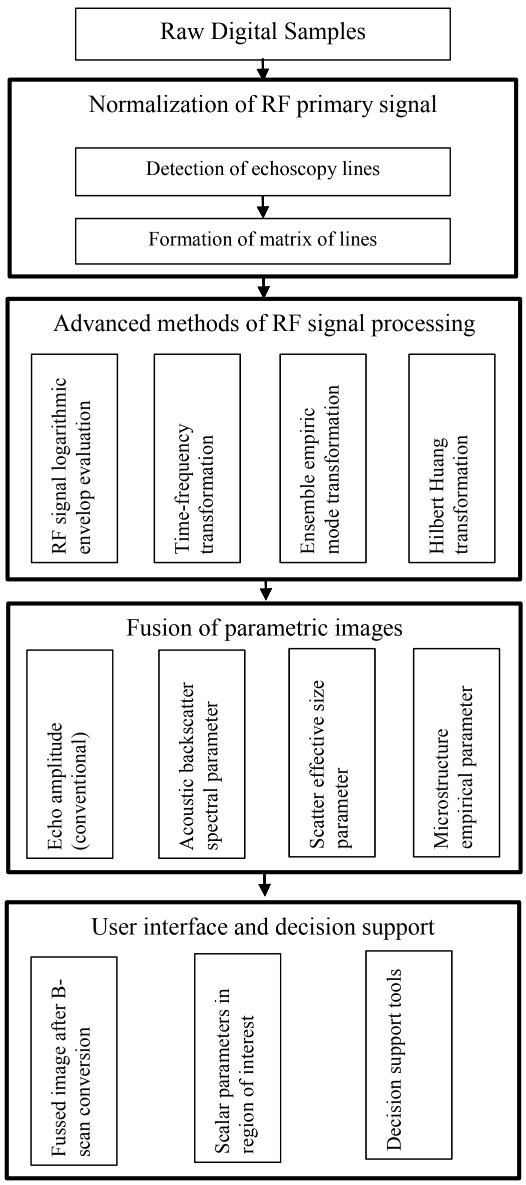

Fig. 2 **Block diagram of the primary radio-frequency signal processing concept.**

The captured raw samples of a primary (radio frequency) signal have to be analyzed first to determine instances of the start of the echoscopy line or instants of the ultrasound pulse excitation. The formed matrix of echographic signals then could be processed at a single line or between lines as well. This matrix of echographic radio-frequency data could be analysed using advanced methods which are described in the next section. After analysis the obtained parameters could be used to form parametric images fusing and supplementing a conventional B-scan image available from the diagnostic system. The user will manipulate the fused parametric images and will be able to select the region of interest and obtain scalar parameters for a decision support.

6. Advanced methods of RF signal processing

At the development stage RF signals are planned to be analyzed using original programs implemented in the Matlab software. Signal analysis is planned to be implemented in three domains: the time, the frequency and the joint time-frequency domain. The most perspective methods will be determined during modelling and evaluation stages. Based on literature review [31-36] and experience when analyzing other types of biomedical signals [37,38] the following methods were chosen for the further evaluation: ensemble empirical mode decomposition and discrete wavelet transform for the time domain analysis; the Fourier power spectrum and marginal Hilbert spectrum for the frequency domain analysis; the continuous wavelet transform (scalogram), short time Fourier transform (spectrogram) and the Hilbert – Huang transform (Hilbert nominal spectrum) for the joint time-frequency analysis. The ensemble empirical mode decomposition and the Hilbert – Huang transform methods were chosen since these are newest and are very well estimated by researches in methods [32, 33, 36, 37] for high resolution signal analysis. Such methods are completely adaptive to the analyzed signal and provide the more detailed frequency and time resolution than traditional time–frequency representations with fewer artefacts. The Fourier methods (Fourier power spectrum and a short time Fourier) were chosen because these methods are traditional in clinical applications and very widely used in a commercial medical equipment. These methods also could be a good reference for the new developments. The Wavelet analysis based methods (the discrete wavelet transform and the continuous wavelet transform) were chosen because these methods have a good mathematical background, propose a good balance between the time and the frequency resolution, provides an opportunity to control features wanted to be extracted by choosing the mother wavelet and scales of interest. Another argument to use wavelet based methods is a big number of successful biomedical signal applications, that already exists and which is difficult to say about empirical mode decomposition and the Hilbert – Huang transform methods since they are very new and still are in a development stage, e.g. Hilbert – Huang transform was introduced in year 1998, the ensemble empirical mode decomposition first time was announced in year 2005.

It is assumed that contents of backscattered RF signals should reflect a tissue microstructure and signal processing analysis should reveal differences in the RF signals between healthy tissue and tumour or differences between different types of tumours. In order to achieve this a fine structure of the high resolution signal should be analyzed. It is planned to use the time domain methods for a signal segmentation and determination of regions of interest, while after the frequency and the time-frequency domain analysis these regions of interest should provide data reflecting the analyzed tissue properties. These data are necessary for characteristic parameters calculation for a decision support stage. Characteristic parameters should be selected from a large number of various quantitative parameters and characteristics as obtained from modelled and clinical signals by applying on them the above mentioned signal processing methods. The final set of parameters and characteristics and their presentation form should be chosen during a clinical trialing and testing after which a stand alone signal analysis software should be developed.

Conclusions

As a result of this project, a scientific knowledge and competency of every partner will be elevated, the knowledge exchange process will be developed and possibilities for a new market development will appear.

The developed innovative hardware system combined with a sophisticated software using appropriate information and communication technologies will provide more convenient intercommunication among physicians by performing consultations, information and knowledge exchange for a fast differentiation of diagnosed tumour. Hereby the time between the right diagnosis of eye tumour and effective treatment will be minimized and the probability of patient’s death decreased.

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Neinvazinė ultragarsinė sistema automatinei akies vidaus auglių diagnozei: sistemos koncepcija

Reziumė

Projekto tikslas yra sukurti kokybišką, naują, saugią, neinvazinę sistemą, susidedančią iš specializuotos techninės įrangos – radijo dažnių (RD) įrenginio, skirto RD gauti ir surinkti iš akies vidinių auglių, ir modernios programinės įrangos duomenims apdoroti ir parametrizuoti. Oftalmologijoje populiariausias akies auglio diagnozės metodas yra subjektyvus optinis akies dugno įvertinimas. Kompleksiniai optiniai ir ultragarsiniai tyrimai yra labiausiai paplitę neinvaziniai metodai akies vidaus auglių diagnostikoje, taip pat atliekant diferencijavimą, auglio geometrinių ir struktūrinių parametrų įvertinimą.

Radijo dažnio (RD) (angl. RF) ultragarsinis signalas yra nedetektuotas A vaizdo signalas, kuris duoda kur kas daugiau informacijos apie audinių struktūrą nei standartiniai vaizdai, tokie kaip detektuotas A vaizdo signalas arba B vaizdas. Nagrinėjamas projekto technologinis sprendimas – RD signalo paėmimas iš standartinių A ir B vaizdų, leidžiantis RD signalą apdoroti daug geresne skiriamąja geba (daugiau nei 60 %), kas ypač svarbu diferencijuojant auglius mikrostruktūriniame lygyje.

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