Liquid crystal foil for the detection of breast cancer

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1. ABSTRACT

Breast cancer is the most common malignant tumor in females around the world, representing 25.2% of all cancers in women. About 1.7 million women were diagnosed with breast cancer worldwide in 2012 with a death rate of about 522,000[1, 2]. The most frequently used methods in breast cancer screening are imaging methods, i.e. ultrasonography and mammography. A common feature of these methods is that they inherently involve the use of expensive and advanced equipment.

The development of advanced computer systems allowed for the continuation of research started already in the 1980s.[3] and the use of contact thermography in breast cancer screening. The physiological basis for the application of thermography in medical imaging diagnostics is the so-called dermothermal effect related to higher metabolism rate around focal neoplastic lesion. This phenomenon can occur on breast surface as localized temperature anomalies[4].

The device developed by Braster is composed of a detector that works on the basis of thermotropic liquid crystals, image acquisition device and a computer system for image data processing and analysis. Production of the liquid crystal detector was based on a proprietary CLCF technology (Continuous Liquid Crystal Film).

In 2014 Braster started feasibility study to prove that there is a potential for artificial intelligence in early breast cancer detection using Braster's proprietary technology. The aim of this study was to develop a computer system, using a client-server architecture, to an automatic interpretation of thermographic pictures created by the Braster devices.

Keywords: breast cancer detection, liquid crystal, contact thermography, Braster device, image analysis, computer vision

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2. INTRODUCTION

Cholesteric liquid crystals capable of selective reflection of the light in the function of the temperature have been known for many years[5-7]. They are applied for the imaging of thermal signatures of technical objects[8], thermal flows and loads[9], as well as in the medical diagnosis[10]. In medicine the research is focused on the possibilities of differentiating the detected thermal anomalies that are caused by pathophysiological processes. This is so as the proliferative pathologies (of neoplastic nature) are characterized by a significant majority of anabolic processes related to an intensive neoangiogenesis[11], what in turn is associated with the occurrence of hyperthermic changes in the thermogram.

The first attempts to apply the liquid-crystal technology for the detection of breast cancer were made already in the 70s of the 20th century. At the beginning, in order to obtain a colorful representation of thermal distribution, the breast surface was covered with a soot followed by a layer of properly prepared liquid-crystal mixture[12]. However, due to an oily nature of the liquid crystals and the necessity of using organic solvents to remove them from the breast surface after examination, this method was abandoned and the scientists began to search for a new, more flexible method that would be based on the dispersing of the liquid-crystal material in a film-forming material. In this way the first thermographic films were created which served as a detector of thermal changes on the body surface.

In the 80s. the first tests with the use of thermographic film were carried out[13-17]. Initially, in the breast screening the film was applied against the breast surface and an attempt was made to interpret the thermal image obtained during the examination. However, it quickly became clear that the quality of the thermograms obtained with the use of the film available at that time left a lot of room for improvement. Moreover, it was still not possible to analyze visually the thermographic images during the examination. The problem with the interpretation forced the use of techniques for thermographic image processing, which, at that time, were not yet available. The thermograms were photographed for archiving purposes. Unfortunately, the analysis of photographs also did not prove effective. Additionally, a parallel development of mammography and thermovision contributed to the fact, that the use of contact thermography with regard to medicine has been given up for 20 years.

Together with the contact thermography another method of thermal imaging has been developed – thermovision. Thermovision, unlike contact thermography that is based on conducting, consists in radiation heat transfer. The thermovision allowed for obtaining a more accurate representation of thermal distribution in the breasts, and following the digital revolution in the 90s., it also allowed for obtaining a digital image that was easy to process. Moreover, in the second half of the 90s. of the 20th century, a significant technological breakthrough was achieved, namely, relatively cheap matrices for uncooled thermal detectors were constructed what resulted in radical reduction in the price of thermovision camera. Thermovision became much more common and broadly used also in medicine, in particular in the breast cancer screening[18-23]. Despite the easier access, the unit price of a thermovision camera was still very high. Additionally, the unsolved problem of the analysis and processing of thermal images resulted in a very limited application of thermovision in breast cancer screening.

Nowadays, the ultrasonography and mammography are used together with histopathological confirmation as a gold standard for breast cancer diagnosis. There are, however, several disadvantages of the above-mentioned modalities what makes it reasonable to continue research and development in the area of alternative methods for diagnosing and screening breast cancers. Since the liquid-crystal matrix technology enables programming a temperature range of detection with a thermal resolution that corresponds to the difference in physiological temperature between the developing cancerous tumor and surrounding healthy mammary gland, the contact thermography introduces significant potential in breast cancer screening as a complementary and adjunctive modality to the current clinical gold standard.

3. LIQUID CRYSTAL MATRICES

The liquid-crystal thermographic films, also referred to as the thermochromic liquid-crystal matrices (TLC), are composite layered materials containing thermo-optic liquid-crystal layer in their structure (fig.1). In physics, the thermo-optic layer is a suspension of dispersed spheres of 2–10 μm that contain liquid crystals inside.

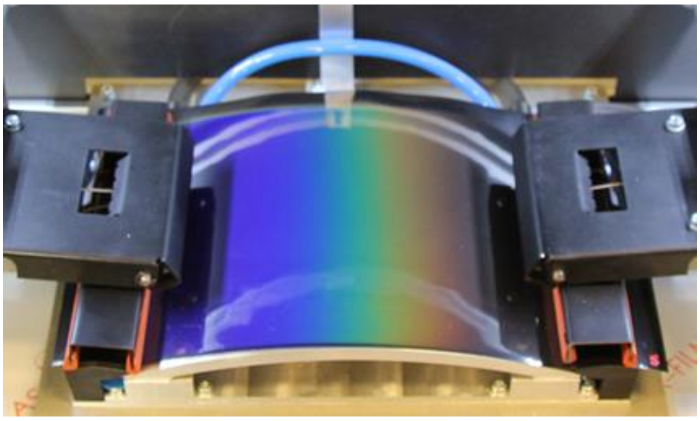

Fig.1 Thermographic film placed on a heating table

The thermo-optic liquid-crystal layers are formed in a process of micro-encapsulation or emulsyfication[24], in which a properly prepared mixture of liquid crystals[25] is sealed through the dispersion in a film-forming material, and in this form the is applied on the base material.

Depending on the designation and the planned scope of the thermal detection of the TLC matrices an appropriate composition of liquid crystals, e.g. chiral nematics, is chosen. For instance, in order to obtain a color response in the temperature range of 31–36°C, the mixtures of cholesteryl nonanoate and cholesteryl oleylcarbonate are used. By modifying the composition of the liquid-crystal mixtures it is possible to adjust the scope and the resolution of the temperature–color dependency.

The production of liquid-crystal matrices (TCL) consists in an application of a properly prepared thermo-optic layer on the base material (support). Among many methods of matrix production, a particular attention should be driven to the one developed by the Braster company – the so called CLCF method, which is a modified version of the Knife Coating method. In the CLCF technology (Continuous Liquid Crystals Film) two micro-layers are simultaneously applied on the base polyester film and subsequently are dried under the conditions of a quasi-laminar air flow. When the drying process is over, the last layer – i.e. the absorption layer – is applied, which ensures contrast for the radiation selectively reflected in the thermo-optic layer.

The liquid-crystal matrices produced with the use of this method consist of several layers. The most important of them are: the polyester base layer, the thermo-optic liquid-crystal layer, the protective layer and the absorption layer, as illustrated in fig. 2.

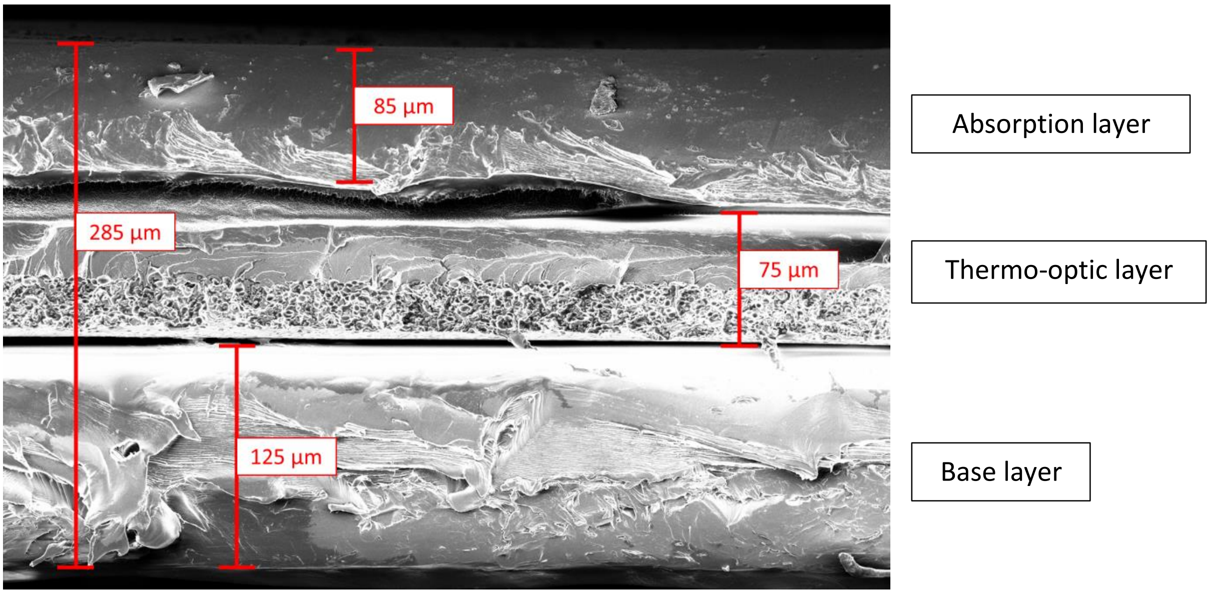

Fig. 2 Sectional view of the TLC matrix obtained with the electron microscope.

By applying the TLC matrix to a surface under examination with a temperature corresponding to the scope of responsiveness of the thermal matrix, a color image of thermal signature occurs already after a few seconds. This phenomenon results from the optical rotation, i.e. a selective reflection of light in the liquid crystals. The thermochromic phases of the liquid crystals have created layered structures, in which the molecules contained in a single layer take the same direction vector (along director). For each layer this vector changes the direction by the same value, depending on the temperature. Therefore, as the temperature rises, the pitch of the helix is changed, what determines the capability of selective light reflection. When the TLC matrix is illuminated with the polychromatic light (white), a certain length of wave is selectively reflected, and the remaining part is absorbed by the absorption layer. In this way, as the temperature on the matrix rises, there appear consecutively the red color, the green one and, in the end, the blue one. Figure 3 presents the dependency between the color, represented in the HSV or RGB space, and the temperature[26].

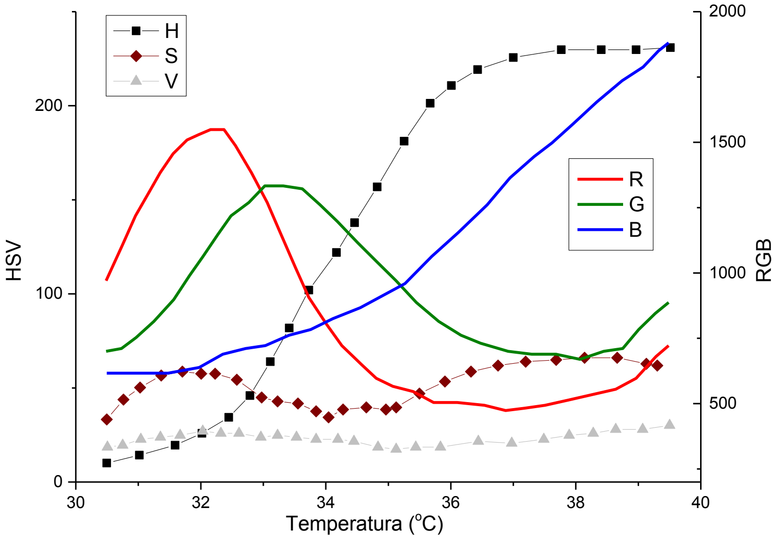

Fig. 3 Dependency between the color, represented in the HSV and RGB space and the temperature in TLC matrix, a) RGB space, b) HSV space

4. DIAGNOSTIC THERMOGRAPHIC IMAGES - THERMOGRAMS

A result of a single application of the liquid crystal matrix to a breast surface is a colorful map in RGB scale which represents a thermal distribution of contact area, which is called a thermogram. Since the matrix is totally passive detector of the temperature changes, an image acquisition system is needed for registering and storing the thermograms. As soon as the matrix is applied to a breast surface, so-called heating process starts. A process of liquid crystal film heating from "0" status, through the stabilization stage of the colour map, until the moment of gaining a stabilized image is about ca.15 seconds. Return to the initial state, when there is no colour answer on the matrix, takes ca.10 seconds (Figure 4).

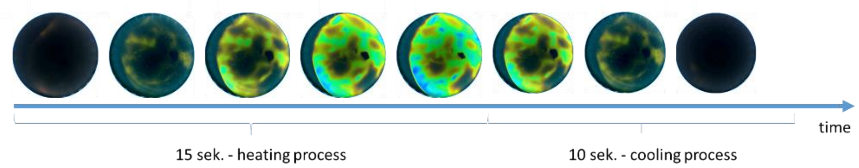

Figure 4. The process of heating after application and cooling down after putting away of the liquid crystal foil

To make the thermographic examination complete, it is necessary to perform the sequence of 6 or 10 applications (depending on breast size) to a breast in a specific order. For small breast it is suggested to perform 3 applications for left and right breast – summary 6 applications and for bigger breast 5 applications for left and right breast – summary 10 applications. It is crucial to cover whole surface of breast skin with matrix application in purpose of acquire complete thermographic map of breast.

Each thermogram consist of several contours depended of local temperature distribution, especially a difference between hotter and colder areas. Basing of these contours and other characteristic features of overall examination, the medical interpretation can be performed.

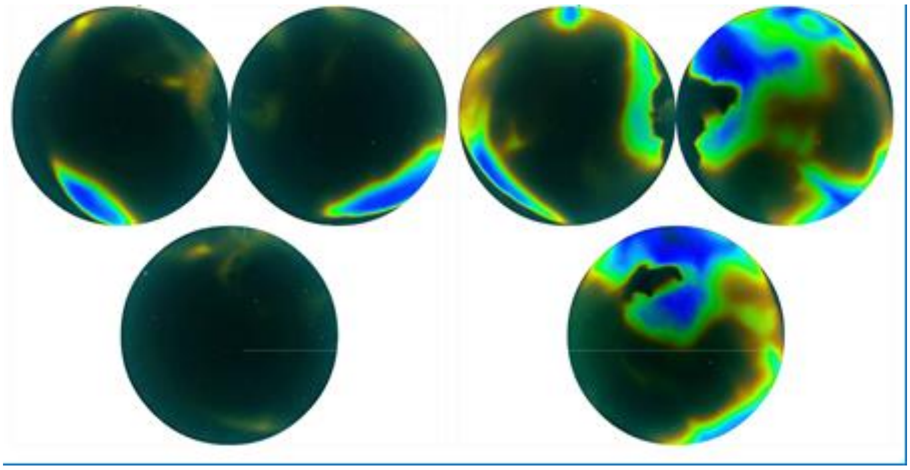

Figure 5. Full thermographic examination of a medium size breast consisted of 6 thermograms

During a medical examination, some additional information is collected by means of survey or questionnaire in which such data as age, breast size and structure, potential BRCA1/BRCA2 mutation, hormonal treatment are included. The set of thermograms together with the collected information can be analyzed and interpreted by thermographic expert or advanced image processing and classification system.

5. DIAGNOSTIC INTERPRETATION OF THERMOGRAMS

There are two major kind of approach to interpretation of the thermograms. First one is called a manual interpretation and is performed by experienced specialists – contact thermography experts, who use a manual interpretation algorithm. The manual interpretation algorithm is a kind of guidance which includes basic rules of interpretation, characteristic features definitions and features-based check-list equipped with graphic examples and exclusions definitions. The expert performs the interpretation by following the algorithm step by step, answering questions, analyzing the images and looking for characteristic features of the thermograms. During the manual interpretation process, several aspects are assessed:

- Is the examination informative? Was the examination performed according to procedure properly?
- Are there any undesired contours which can come from a belly or armpit?

- Is there any asymmetry in temperature distribution between left and right breast? If yes, is the asymmetry significant?
- What kind of contours can be recognized on the thermogram: hot spots, linear shapes, uniform areas?
- What are characteristic features of contours in terms of shape, localization, color gradient, sharpness of edges?

Second one is called an automatic interpretation as is performed by advanced computer system based on artificial intelligence algorithms and advanced image processing, which provides a result of interpretation without involvement of human. This system processes the thermal images of breasts to produce information for end user whether more detailed examinations (like mammography) are required. The image processing and machine learning algorithms are used. The system includes modules to remove noise from images, to find contours, to calculate features of contours [28,29] and to find asymmetry of corresponding images[27]. There are modules to classify contours [30] and finally classify examinations [31, 32]. The isolated incidents, examinations potentially hard to classify, are detected [33].

6. CLINICAL STUDIES

Braster has conducted 3 official observational studies under the supervision of the Ethic Committee and professional CRO, covering approx. 1350 women, which included almost 500 cancerous cases (table 1)

Observational study	**Population (cancers)**	**Dates**
ThermaCRAC	736 (72)	06.2013 – 03.2014
TharmaRAK	318 (318)	10.2014 – 05.2015
ThermaALG	278 (87)	04.2015 – 05.2016

Table 1. BRASTER clinical trials details

The observational studies were conducted in women with symptoms of breast anomalies, referred for enhanced diagnostics in specialist diagnostic units. The primary study objective was to determine the efficacy of the Braster device versus standard diagnostic procedures and therefore its clinical utility for breast cancer detection in women.

On the basis of the most important results obtained during the ThermaCRAC study, the study parameters for the Braster device were as follows: sensitivity and specificity of the thermographic examination versus standard diagnostic procedures was respectively 72% and 58% for the whole population. However, if we take into account the lack of experience with this method at that time, which was a pioneer attempt at establishing manual interpretation path for thermographic images and the resulting limited experience of the team of investigators and interpreters, the above results should be seen as a feasibility study. Recommendation formed on the basis of the ThermaCRAC study was to collect data of thermographic breast images and to improve manual interpretation algorithms. which were done after next observational study – ThermaRAK.

In April 2015 Braster has conducted an observational study – ThermaALG, which like ThermaCRAC had one primary objective: to determine the efficacy of new, improved manual interpretation algorithms. Sensitivity and specificity of the thermographic examination versus standard diagnostic procedures were improved, and amounted to approximately 80% and 70% for the whole population. Additionally, thermographic images were evaluated by a system of intelligent analysis and classification, which makes parametric evaluation through the use of artificial intelligence algorithms, including neural networks, support vector machines and regression analysis. Validation of the system of automatic interpretation in the range of sensitivity and specificity was respectively 71.8% and 75.2%.

7. CONCLUSIONS

Based on abovementioned description and considerations, a following conclusion can be drawn:

1. Contact thermography based on liquid crystal matrices is an innovative diagnostic modality used for early breast cancer detection as a method complementary to ultrasonography and mammography. The goal for contact thermography is not to be a competitive modality to gold standard in breast cancer diagnosis (ultrasonography, mammography) but to be adjunctive one, which gives to a user an early warning regarding her breast health and give opportunity to undergo a proper diagnosis process.
2. The interpretation of thermograms performed by experts is based on characteristic features of contours and quadrants asymmetry. During thermograms assessment, the expert follows a special guidance called the manual interpretation algorithm which includes basic rules of interpretation, characteristic features definitions and features-based check-list.
3. The thermograms can be processed using an algorithm of advanced image processing in order to enhance the human perception as well as define attributes.
4. There is a significant potential for machine learning and artificial intelligence in area of automatic recognition and classification of thermographic images.
5. Combining expert's experience with automatic recognition and classification may result in remarkable efficiency with early breast cancer detection.

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