Dynamic Optical Imaging

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The main direction in modern imaging is increasing the spatial resolution and selectivity for pathology pattern recognition at the microscale. Dynamic optical imaging (DOI) has enormous potential in the selectivity of description of living tissue state at cellular and subcellular levels. However, multiple light scattering creates considerable difficulties in revealing the tissue microstructure in its depth. On the other hand, along with changes in the microstructure, pathology should also manifest itself in the integral macroscopic pattern of the tissue. Actually, living tissue, as a distributed active media with well-developed reception and self-regulation, is characterized by a high spatial synergy. In such a media, even morphologically small pathology could disturb tissue functioning in a rather extended area. As a result, after some definite time, a diffuse "field" of the pathological phenomena appears even in the morphological image. Since optical contrast is determined by tissue components (such as blood), which actively participate in physiological functioning, the distributed functional pattern of the tissue is reflected in optical images in the form of spatio-temporal modulation of the optical density. This observation opens up the possibility of investigating the diffuse pattern of the pathology at the functional stage of its development, even before the actual appearance of noticeable morphological changes.

FUNCTIONAL IMAGING APPROACH

The functional pattern of living tissue, which is controlled by various mechanisms of physiological regulation (neural, humoral, etc.) with a wide range of time constants, includes a hierarchy of spatio-temporal scales. The spatial scale is dependent on the temporal one: as a rule, it increases together with the time constant. On the basis of a priori available information, we estimated the spatio-temporal scale of the integral tissue variability which is optimal from two points of view: on one side, the scale should be sufficiently

informative for revealing pathology; on another side, the scale should be within the capabilities of conventional optical technology. The scale we chose is described by the characteristic length equal to a centimeter, and by the characteristic time constant of about 1 minute. In order to reflect this scale, it was sufficient to use conventional optical imaging, including transillumination, in a dynamic mode.

However, considerable increase in the accuracy of the optical density measurements was necessary to achieve, since the amplitude of the physiological modulation of the optical image was small (relative change in brightness was less than 10^{-2} for a 10-second temporal scale and a spatial scale of about 1 cm).

Based on our experience in revealing low amplitude spatially distributed dynamic patterns of living tissue by means of infrared and microwave dynamic imaging,[1] we developed an approach to the early functional diagnostics of pathologies using investigation of the above-described modulation of optical images.

To recognize the pathology based on the integral functional pattern of the tissue, it is necessary to reflect the main details of this pattern: the spatial functional units of the pattern and the distinctive features in the temporal dynamics. For this purpose some criteria of spatial and temporal continuity in the dynamic imaging should be fulfilled. Continuity in time means that a sufficient number of frames should be recorded between sequential external points in the tissue physiological dynamics. The time scale of seconds is sufficient to reflect blood microcirculation dynamics as the main physiological process modulating optical images.

The image segments characterized by a highly correlated dynamics within them were determined as functional units of the integral pattern. As a result, spatial resolution was given by the cross-correlation length of the physiological dynamics, which is incomparably larger than the morphological structure.

Investigation of the tissue physiological reactions on various tests was the most effective method of revealing the spatio-temporal organization of the tissue functional reactivity. Functional segmentation was used to separate optical image on the spatial segments differing by the parameters of the transient processes. Various approaches such as cluster analysis, factor analysis, and dynamic segmentation method[4] were used for this purpose.

The simplest type of functional segmentation can be obtained by selecting some appropriate parameter of temporal dynamics (amplitude, velocity, time constant of temporal changes) at each spatial location of an image and by plotting the spatial distribution of these selected parameters. In a more general case, the temporal dynamics cannot be adequately described by a small number of parameters, and spatial structure of the tissues should be determined as spatial regions of correlated dynamics.

The described procedures give the possibility of reconstructing the functional organization of the tissue and presenting the result in the form of a functional map.

At the initial stage of our investigations, the main attention was devoted to elaboration of the methodology of the optical functional imaging described above. The framework of this methodology is given below in more detail and accompanied by several examples of its clinical application in mammoscopy.

EXPERIMENT

The experimental setup for dynamic optical mammoscopy was based on the conventional transillumination optical scheme. The recording systems contained a CCD-camera with digital interface board for frame-by-frame accumulation and processing data in a personal computer. To provide the necessary high accuracy of up to 10-4, the CCD-camera should work in the photon shot noise limitation mode. The shot noise level for such accuracy exceeds the room-temperature dark current noise; therefore an uncooled CCD-camera can be used. The interface board with not less than 12-bit resolution is needed for this purpose. The frame size 128 x 128 (and even 64 x 64) is sufficient for reflecting the functional structure of the dynamic images. Usually up to 100 sequential frames with 1-second time interval were recorded in one test. In the three-dimensional space (two spatial and one temporal

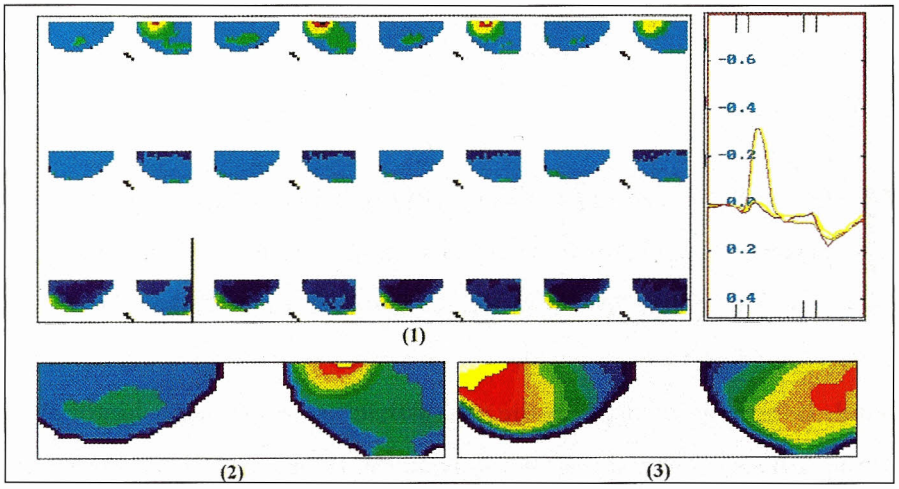

Figure 1. Dynamic optical images (DOI) of breast tissue recorded by an 8-bit system. Patient with cyst at the left mammary gland. (1) Sequence of optical frames reflecting transient reaction (hereafter referred to as transient image) of the breast tissue on two tests: holding of breath and hyperventilation. Diagrams at the right part of the figure represent temporal behavior of the pixels marked by corresponding numbers, time in seconds is plotted on the x-axis, and relative changes in brightness, dI/I, on the y-axis. Interframe intervals, 3 seconds. (2) The frame recorded at the peak of the reaction on the holding of breath test. (3) The frame recorded using conventional transillumination mode.

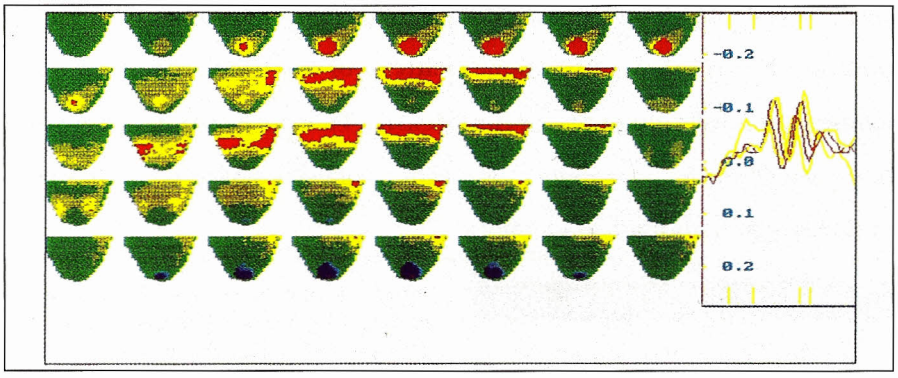

Figure 2. Transient image of the breast tissue reaction on the holding of breath test for a patient with breast cancer. Designations and recording parameters as in Figure 1.

dimensions), image size is 128 x 128 x 100 of 12-bit pixels or approximately 25 Mbyte. A computer with adequate memory should be used for this purpose.

To get higher accuracy in the brightness measurements, it is necessary to trade off between spatial and temporal resolutions. The best trade off could be ideally obtained by an adaptive procedure, adjusted during image recording in accordance with current values of spatial and temporal derivatives.

The measurements were performed using conventional NIR spectral range (wavelengths $\lambda > 0.63$ μm). Red filter was placed before the CCD-camera to give the possibility of measurements in room illuminated by blue or green light. The latter is important for clinical investigations.

To separate redistribution of oxy- and desoxy- hemoglobin in the integral dynamic pattern, optical filters ($\lambda < 0.85$ μm and $\lambda > 0.7$ μm) were used.

In the reflective optical mode, which we term "dynamic colorvision," a shorter wavelength range was used—blue light was the most sensitive to the microcirculation dynamics of the skin. The dynamic colorvision reflecting blood volume dynamics in skin is supplemental to dynamic infrared thermovision,[5] the latter representing blood flow dynamics in skin.

To achieve sufficient contrast of the temporal variation of optical images, the stationary high level brightness distribution should be suppressed and small temporal variations of the image should be enhanced. To achieve this goal, the following interframe operations were applied: subtraction of the reference frame (i.e., the frame just before the test), dividing of the subtracted frames by the reference one, logarithmic derivative, etc.

Tissue layers at different depths have different contributions to the distribution of the image brightness: deep tissues result in relatively large scale (low spatial frequency) structures, while upper tissue layers contribute mainly to the smaller scale (higher spatial frequency) structures. Fourier spatial filtration was applied for separation of the contributions from the tissue layers of different depth.

By means of the above-described functional segmentation, only the predefined types of tissue temporal behavior (transient processes)—normal or pathological—can be extracted from experimental data containing image noise and artifacts (mechanical movements, for example).

In the beginning, the simplest and most natural tests were applied to initiate the tissue reactions during measurements. Among them were variations in the external breathing parameters: bold breathing (to initiate hipoxia), intensive breathing (hyperventilation), breathing air enriched with oxygen, etc. The application of a blood pressure cuff on the arm was also used to initiate blood redistribution at the mammary gland. The investigations of the breast tissue during and after breast compression and decompression were also effective, as separate tests. In this latter case, we observed both non-inertial reactions, due to changes in the light scattering during the tissue deformation, and delayed reactions, reflecting redistribution of the blood content. Various combinations of the above-mentioned tests were applied to increase the potential for functional pathology pattern recognition.

Two examples illuminating the possibilities of the methodology are shown in Figures 1 and 2. These data were obtained by means of our previous 8-bit recording system.

Figure 1 shows the data for a patient with a cyst in the left mammary gland.

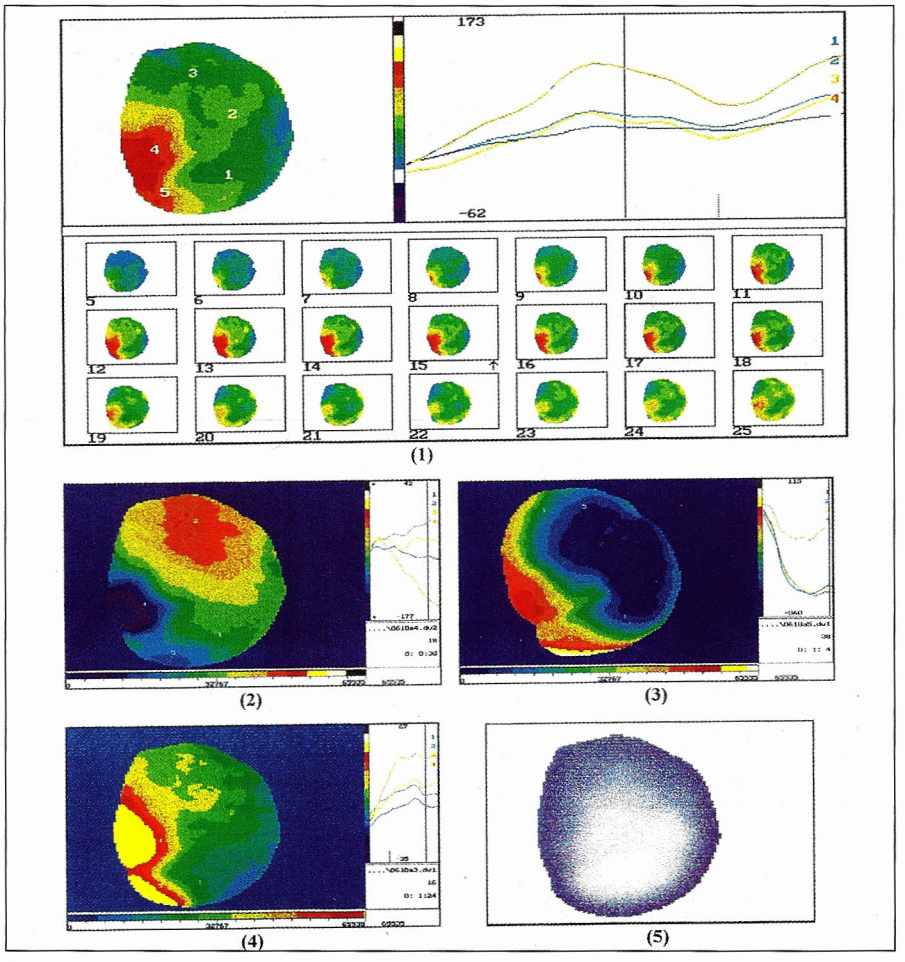

Figure 3. Dynamic optical images obtained by 12-bit recording system. Patient with dense masses at 12 o'clock and 9 o'clock positions located in the left mammary gland. (1) The transient image of the reaction on the application of cuff on the left arm. (2) Frame recorded near the peak of the breast tissue reaction on the hyperventilation test. (3) The same as in (2) except that decompression test was applied. (4) The same as in (2) except that holding of breath test was used. (5) The frame recorded by means of conventional transillumination mode.

Two sequential tests were applied: holding breath and hyperventilation. In this particular case, local functional contrast—high reactivity—was observed at the area of 1.5 to 2.0 cm^2 of the cyst's projection to the skin. Contrasted pathological spot existed for only a limited time during and just after the test. This is a principal difference between the proposed approach and morphological imaging. It follows that dynamic optical imaging opens up the possibility of revealing even temporarily appearing pathological phenomena.

Figure 2 presents the results of DOI application for a patient with breast cancer. In this case a spatio-temporal phenomenon of propagating waves was observed. Similar phenomenon was earlier observed by dynamic infrared thermovision during investigation of spreading depression in rat brain cortex.[6]

The results of the higher accuracy (12-bit) recording system for breast pathology diagnostics are shown in Figures 3, 4, and 5. For these images, the chest wall is at left

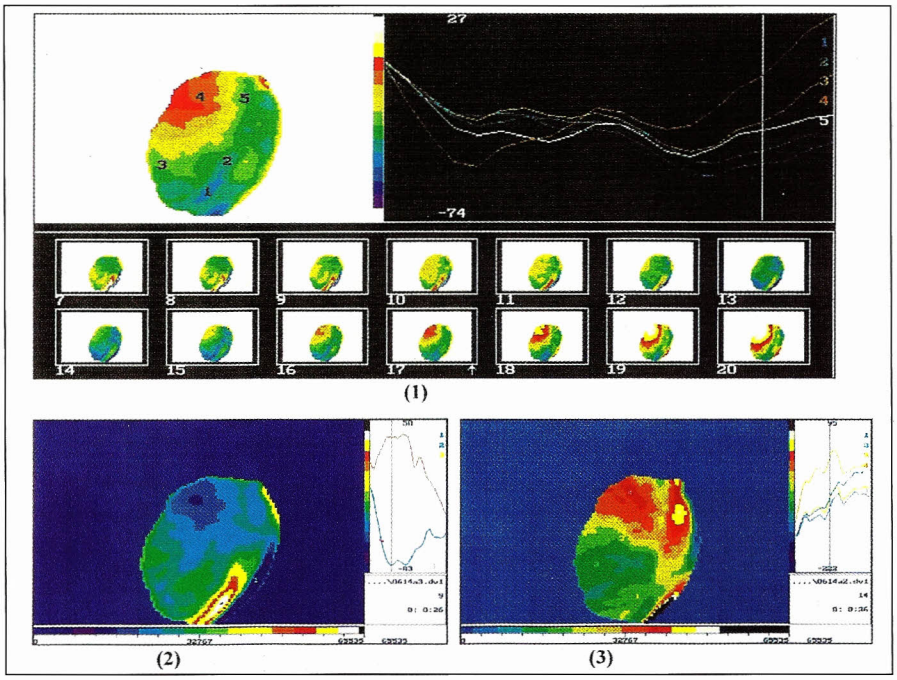

Figure 4. Dynamic optical image of dense breast with lump located at the right gland near 12 o'clock position. 12-bit recording system. All designations and experimental parameters are the same as in Figure 3. (1) The transient image of the reaction on holding of breath test. (2) The frame showing the pattern characteristic of the mechanical shift of the breast borders during the reaction in (1). The spot contrasted in this frame on the area of pathology projection reflects the tissue reaction for the first 20 seconds of the test. (3) The frame recorded near the peak reaction on the application of cuff on the right arm.

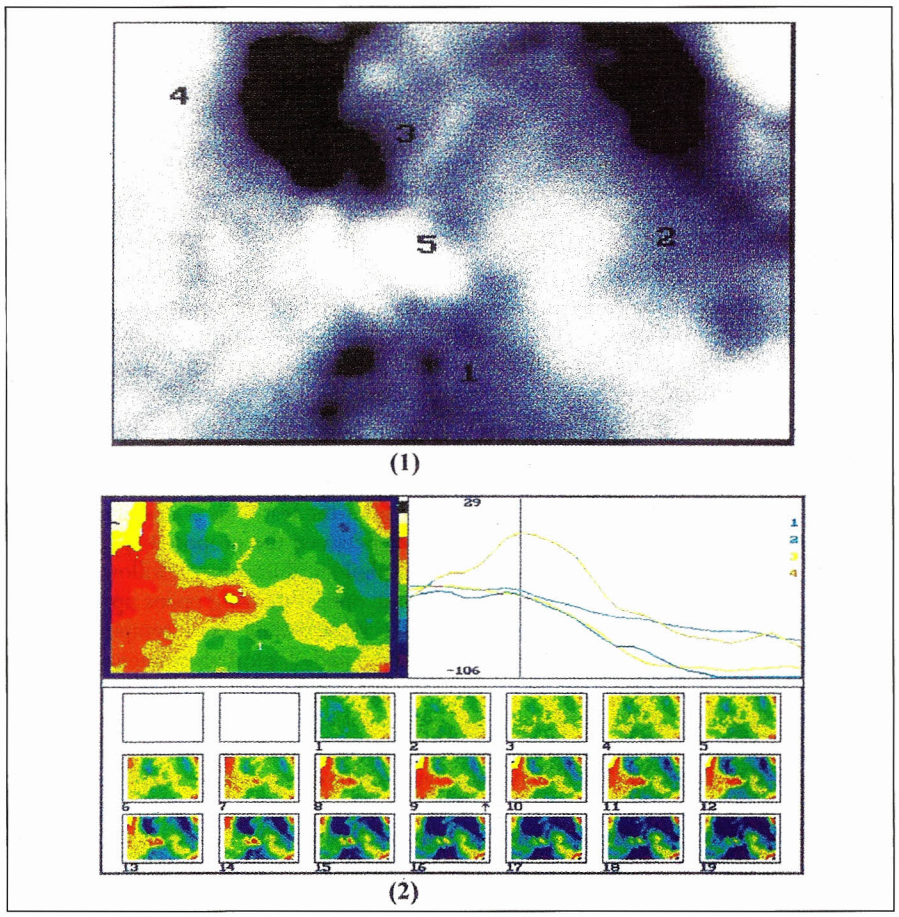

Figure 5. A zoomed part of the dynamic optical image of the breast with a cyst. (1) Frame recorded at the peak of the breast tissue reaction on the holding of breath test. (2) The transient image of the reaction on the same test as in (1). Designations and experimental parameters are the same as in Figures 3 and 4.

and the nipple at right.

In Figure 3, the patient had masses of approximately 1 cm size at 12 o'clock and 9 o'clock at the left mammary gland. All the tests applied reveal functional contrast at the area of the pathology's projection to the skin. There was no morphological contrast at the location of the pathology when the investigation was performed by conventional transillumination mode (Fig. 3[5]).

Figure 4(1,2) shows the data for a patient with a 12 o'clock lump in dense breast, absolutely opaque for X-ray mammography. Two components—fast and slow—could describe any pixel in the temporal behavior of the optical images. The fast component, appearing to be vasomotor oscillations with period of 20 to 40 seconds, was rather homogeneously distributed over the image. The slow component represents tissue reaction on the test applied with the time constant of about 1 min. Three main functional segments could be revealed in the recorded images (Fig. 4[1]). The first one, located inside the area of the pathology projection to the skin, was distinguished by a high amplitude of the slow component reaction. Surrounding normal tissue was presented as a second segment where the slow and fast components of the temporal dynamics were of comparable amplitudes. The third segment, near the gland border region, was specified by the oppositely directed variations in brightness of the nearby image stripes during the reaction (Fig. 4 [2]). This is typical of a mechanical shift that could be caused by the gland volume changes resulting from variation in the integral blood content during the reaction. The frame shown in Figure 4(3) demonstrates functional contrast revealed at the same pathological projection area as compared with the surrounding tissue after another test: cuff application to the arm.

Figures 5(1) and 5(2) represent the data of investigation of a breast with cyst. A zoomed part of the breast image is shown in Figure 5(1), demonstrating that the dynamically contrasted area is incomparably larger than the morphological structure details. The morphological structure is revealed in this image only in dynamic mode. Therefore, this is an additional modality ("morphological dynamics") which could be useful for pathology recognition. Figures 5(1) and 5(2) illustrate the difference between presentation of medical images by conventional gray scale, revealing morphological structure, and the color pallet capable of illuminating

even very small amplitude but more extended dynamic contrast.

It should be stressed that by identifying pathologies via their dynamic functional pattern, DOI opens up the possibility of overcoming the main disadvantage of conventional optical transilluminatlon: the high level of false positive diagnosis in dense breasts.[7]

DEVELOPMENT

DOI's methodology is undergoing further development now. Among the main problems under review are the following: development of a model of breast functional dynamics, the solution of dynamic direct and inverse problems, pathology functional pattern recognition, three-dimensional (two spatial and one temporal) representation and archiving, management of adequate databases, etc. The fundamental problem is the quantification of the integral functional patterns for earlier revealing and identification of pathologies. In order to reflect manifold functional patterns of pathology, a multi-parameter description of spatially distributed transient processes is necessary to be included in the quantification procedure. Qualitative models, including physiological information on the breast tissue, are needed for this purpose. Applied logic methods[8,9] are adequate for the development of such models.

Up to now we have mainly discussed the physics and engineering aspects of DOI methodology. However, our approach to optical imaging comprises a simple and natural imaging framework for accumulating and including in a database the clinical experience with the functional diagnostics of pathology at the early stage of its development. The development of clinical technology on the basis of this framework should include selection of the main physiological features to be reflected in the breast models as well as adjustment of appropriate tests for initiating the most antagonistic (and, thereby, most illuminating) tissue reactions, both pathological and normal. Specific tests are necessary to separate the functional patterns for different tissue layers: those of the skin, mammary gland, etc.

It seems promising for earlier breast diagnostics to combine dynamic optical mammoscopy with immune-endocrine parametric data. For this purpose, adequate intellectual assistance systems are under development with the use of the methods described elsewhere.[9,10]

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