Multispectral lens-less microscopes and optofluidic chip readers with discrete convertors of chemical and non-optical physical signals into spectrozonal optical ones as novel instruments for medical ecology, biodiagnostics and material quality control

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ABSTRACT

A concept of the new type of biological morphometry for the cellular and tissue levels of organization has been developed, which makes it possible to morphometrize not an optically detectable form (morphology, habitus) or other related tissue parameters, but the patterns of its response to the external stimuli / field recorded by a chip on a CMOS/CCD array, or the patterns of its own non-optical characteristics (for example, the distribution of magnetic properties and isotopy in radioautography on a chip, or a radioisotope label), forming a compartment or compartmentalized (in vesicular or liposomal compartments) pool of a substance/label, characterized by a physical property—a descriptor, the contours of which are morphometrized by the chip due to the multilevel signal conversion technique. Using multilevel signal conversion techniques in sandwich chips with multiple converters, one can achieve not only mapping of the individual characteristics, the sample descriptors, but also establish colocalization of these descriptors/characteristics over the sample area or in the microfluidic channels, that is, to obtain a correlation map of the sample properties on a chip. Using the film converters of various physical signals and sample properties into an optical signal/response in different spectral ranges on the chips with three spectrozonal channels (either with Bayer mosaic filters or their analogs with other spectrocolorimetric characteristics, or with the unified pixels capable of capturing information from all the three channels in the case of APC-S sensors, or with multilayer implementation of the spectrozonal color separation into the additive channels as in the FOVEON X3 arrays), it is possible to colocalize at least three sample parameters on a chip if each of these parameters is converted into an optical signal that strictly corresponds to the parameters of the chromatic coordinates of a particular filter (or a photodiode layer of different depths in the case of X3). In the latter case, one-to-one colocalization/mapping can be established, in which all the parameters are fixed at each point, and pixels or “sensels” of different descriptors are superimposed, which is unattainable in the case of Bayer mosaic filters and their analogues. Being not just an image, but a resolved distribution map of the certain sample properties converted into an optical signal, the sample registration file itself (a bitmap without a discrete cosine transform) is simultaneously a file containing information about the descriptors characterizing the sample with position sensitivity. For each pixel of the image, a descriptor can be determined from the codes (image parameters) for a given conversion of a non-optical signal into an optical one, characterizing a compartmentalized sample.

Keywords: multispectral lens-less microscopy, environmental optofluidcs, lab-on-a-chip; biochips, chemical ecology, chemical sensors, chemical pixels, biomedical ecology, pollution control, bioindication, biodiagnostics, biomass quality control, green building materials, material quality assurance in green building

1. INTRODUCTION

To date, medical ecology, food quality analysis, and cytological and histological biodiagnostics require a technique for objective recognition, multiparametric morphophysiological control and automatic classification of the living cell and tissue states *in vivo* or *in situ*, especially in real time in the course of the surgical/miraculous manipulations, experimental photo- and radiobiological effect studies, as well as during the chronic experiment[1-6]. A unified solution of such a technical problem for various biological objects will eliminate many ambiguities in the raw data interpretation and artifacts of a subjective operator-mediated diagnostics leading to the non-optimal treatment procedures.

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A serious difficulty of complex analysis of any biological sample or living organism results from the multiparametric nature of its states and, consequently, the objective diagnostic criteria, particularly in the case of position-sensitive diagnostics aimed to establish correspondence between the specific variants of the diagnosed states and pathologies (the so-called diagnostic predictors) with the corresponding sample areas with the known morphological and physical properties (the so-called diagnostic descriptors) in the whole sample / organism and in real time[7-9]. The solution of such a problem in the ideal case includes the development of a special technique able to perform the measurements and mapping, as well as to establish one-to-one correspondence between the spatial localization points and the values of many physical variables, i.e. the descriptor values forming predictors of multiparametric diagnostics.

From the standpoint of functional relationship analysis, the output information (diagnosis) of such a system in terms of informatics should be data sets and diagrams of the functional relationships based on using "non-surrogate" keys with their functions performed by the descriptors as the initial data for an artificial neural network which produces diagnostic predictors.

Manual processing of multiparametric data sets is either impossible due to the known big data problem[10,11] or does not posses sufficient heuristic value for diagnostics without extraction and deep data analysis (a so-called medical data mining[12-15]). Thus, the diagnostic problem in this case is also a problem of systems biology with SBGN (Systems Biology Graphical Notation) visualization, including the interaction diagrams, the process diagrams and their activity flow diagrams. From the other hand, since the problem of the descriptor and predictor mapping towards the real objects (descriptor colocalization) is not a conventional problem of the surface shape reconstruction optimization (rendering), a complex of problems of analytical/quantitative "morphomics" emerges, defined as the systems biology in three-dimensional space[16,17], as well as the diagnostic and identification tool for pathophysiological risks[18], i.e. the predictor formation based on the morphologically-associated descriptors.

However, to date there are no proven medical and physiological principles allowing to introduce morphomics into the mainstream of multiparametric data set analysis, projected to the morphology of either a living or a prepared object/sample, as well as there is no dynamic or comparative time-lapse analytical morphomics. This, from the one hand, suggests that this area is not yet ready for practical implementation into clinical and laboratory diagnostics, but, on the other hand, indicates the significant fundamental research prospects in the development of multiparametric diagnostics within the morphomics direction with the full and objective risk diagnostics due to the objectivity and plurality of the descriptors used which correspond to the measurable physical properties, such as the spectrum at the point of analysis.

Nowadays the problem of multiparametric (i.e. multidescriptor) analysis determining colocalization of the descriptor and predictor maps is either not put at the level required for diagnostics, or can not be solved using modern technologies which produce raw data sets instead of a complex analytical signal. This statement can be proved by a number of examples. Colocalization analysis in most techniques for microscopic diagnostics includes morphometry, correlation and statistical processing of graphical files of the optical microscopy data[19], and fluorescent microscopy[20] (including quantitative one using Pearson correlation coefficient and Manders' overlap coefficient in data processing[21] at the best case). In confocal laser scanning microscopy which allows to perform 3D-reconstruction (layer rendering) establishing colocalization within many channels[22] with the latter being either colorimetric or pseudospectral optical (immunofluorescent) measurements[23], rather than the objective spectra as the data in a full wavelength range—a set of multiple descriptors. In most cases multiparametric analysis involves multiparametric data processing by a single method or within a single technological unit, and less often—several combined units not statistically or methodologically coupled in the single experimental scheme (such an approach is sometimes defined as simultaneous). For example, a widespread diagnostic approach includes "multivariative analysis" of near-IR and Raman spectroscopic data[24-27], while cluster analysis and identification according to the data from either a single method or two methods which produce results from the same data array (spectral range) can not be sufficient for correct diagnostics. In IR spectral analysis (as well as in mass spectrometry) spectra of different substances (especially within homological series) often overlap, requiring verification by an independent method for spectral data validation[28] (it is often called spectral diagnostic data qualimetry[5,6]). This problem becomes even more complicated in position-sensitive tissue analysis.

Therefore, it is necessary to find, test and apply a number of methods and procedures (and hence, descriptors and variables) providing type I and type II error resistance during one-sided diagnostics achieved by cross-validation of diagnostic data sets from different methods with different data sources. In this case data unification by the reference model is very important, since even similar equipment from different distributors usually has different characteristics and calibration requirements[29].

An alternative to this diversity and uncertainty is the development of multiparametric analytical techniques combining a complex of sufficient complementary position-sensitive procedures of descriptor acquisition with the diagnostic predictor formation based on at least two descriptors. Finally, a criterion of chemometric (in our case—biometric) position-sensitive diagnostic analysis should be a hyperspectral study at the cellular discretization level[30]. Considering extended biomarker screening[31] as multiparametric analysis, the above system, being a compact laboratory for a set of different measurements at a single platform, should perform screening and validation with each marker, fluorescent agent/probe or any other selective chemical or physical label being either a positive (presence) or a negative (absence) indicator of a certain visualized process or diagnostic agent using any suitable detection method implemented on this platform (or two complementary methods differing in the source of the analytical signal or detection principle).

In the ideal case, for *in vitro* tissue diagnostics this system should be a kind of a compact lab-on-a-chip[32]. However, most of the microfluidic and microanalytical devices capable of parallel or simultaneous analysis lack position sensitivity and general calibration methods of the chip for subsequent layering or comparative analysis of the data obtained from different measuring methods as the set of points for clustering. At the same time, it is possible to perform multiparametric analysis of the cellular effects, such as MTT test for cytotoxicity[33], using imaging and mapping on microfluidic devices, particularly, microfluidic chips. However, this requires a novel step of development of such devices, providing mapping of a number of qualitatively different descriptors on a single chip-imager, i.e. a sensitive element, as well as precise positioning of the chip relative to the external sources and complementary detectors which perform registration and mapping of spatial distribution of the analytical signal.

Thus, realization of a fundamental idea which will not soon be able to provide significant progress in diagnostics requires a solution of many problems at a high technical level in the areas of microfluidics, mechatronics, automatic classification of heterogeneous data sets, microminiaturization of the data acquisition systems, the problems of control and transmission of information, etc. For this reason there are no complex works in this area according to our bibliographic data. However, an evident usefulness and a significant scientific interest of colocalizational diagnostics beyond the optical spectral range and beyond the principles of optical micrographic registration lead to its inevitable emergence and development in the nearest future. The possibility of pseudo-3D representation of the surface structure from the chip, as well as of the descriptor set projection onto it (and later – of the predictors calculated from them) is a novel approach in microtomography and confocal microscopy if they can be applied for the diagnostic biopsy on a chip, test cell cultures in the cultural microreactor, etc. with the preservation of the main chip functions.

2. MATERIALS AND METHODS

For the purpose of morphometric visualization CCD or CMOS active pixel sensors[34-43] can be proposed as the basic sensor elements for multiparametric labs-on-a-chip: lensless microscopes with Bayer filters or other filter arrays, where the image is captured in three or more spectrozonal channels, but in each channel there is a possibility of precision colorimetry of the separated colors or spectral bands using a light source with a narrow (or limitedly tunable) spectral band to obtain complex multichannel identification patterns of the certain structures or states of the structures in the samples. This approach can be especially effective when a specific set of the identification wavelengths is known, for example, when introducing special dyes, labels or indicators into the sample, that change their color during a specific reaction. It is possible to achieve a sufficiently high resolution in histological analysis carried out using spectrozonal lensless microscopes operating in the modes with different detection ranges.

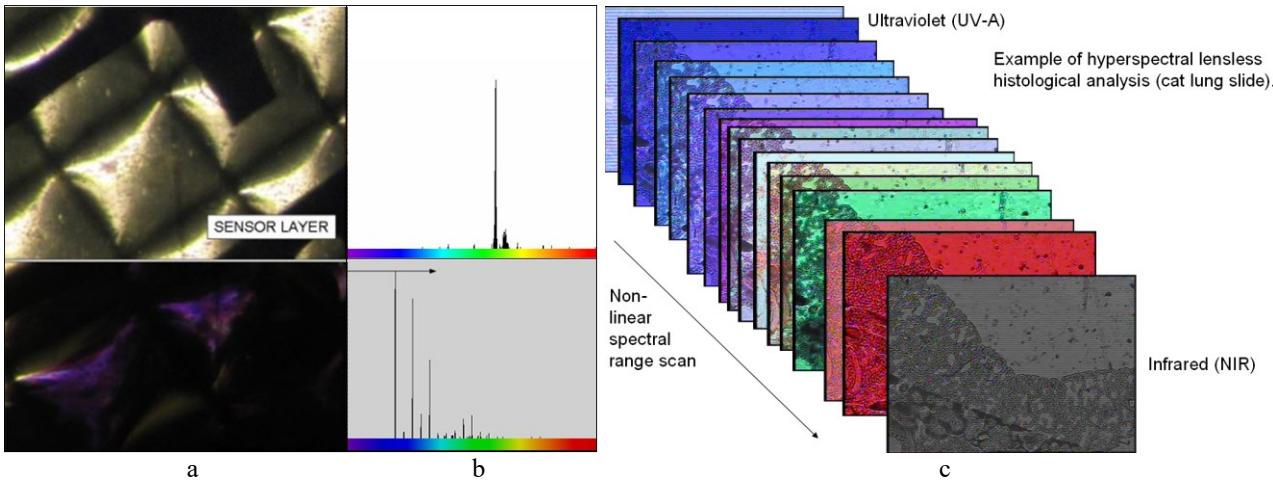
A special version of lens-less registration is presented by lensless RGB microscopes with a full colocalization of the spectrozonal channels, for example, based on the sensor arrays “Foveon X3”, which also capture NIR spectral range. Such systems without Bayer filters allow registering all the spectrozonal channels at a single measurement point with full pixel-to-pixel colocalization of the measurement data. A lensless device for the chip reading during the measurements of medical and food samples is shown in Figures 1a and 1b, and an example of a colorimetric analysis palette changing after the sample labeling is shown in Figures 2a and 2b.

a b

Figure 1. A lens-less 3D chip reader for registration of colorimetric reactions in a positional sensitive mode with discrete “reticular” transducers with sensor layers of different composition (Figures 2a and 2b). (a): The first version with an autonomous keyboard. (b): The second version with an imbedded keyboard. A trackball is used for searching and/or positioning on the discrete “chemical pixels” or “biopixels” (in general: “sensels” - “sensitive elements”).

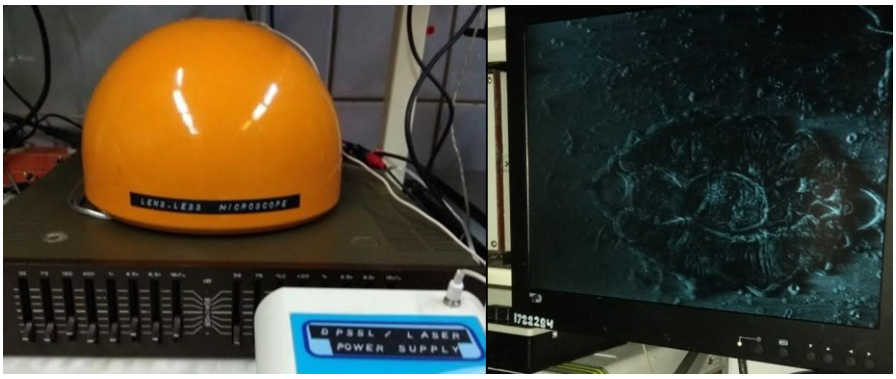
3. RESULTS

The reading process of the sensor layer with “chemical pixels” is shown in Figure 2a and its measurement result in the form of a colorimetric palette diagram (a discrete pseudospectrum) is shown in Figure 2b (an example of the colorimetric analysis palette changing after the sample labeling). Multispectral block / hyperspectral cube can also be obtained. In the previous works we preferred to implement most of the lens-less methods without using time-consuming digital processing in the analog mode using a CCD array as a detector and different LED combinations as the light sources. An example of the resulting analog image rendering obtained using a nonlinear spectral scan trajectory is shown in Figure 2c. An example of the resulting analog 3D image rendering for multispectral holographic lens-less microscope (Figure 3a) is shown in Figure 3b.



a b c

Figure 2. Examples of operation of the multispectral / hyperspectral lens-less imaging systems. The reading process of the sensor layer with chemical pixels is shown in Figure 2a and its result in the form of a colorimetric palette diagram (as a discrete pseudo-spectrum) is shown in Figure 2b. Multispectral block / hyperspectral cube with multi-wavelength visualizations of a histological sample (cat lung slide) in different spectrozonal channels (from UV-A to NIR spectral ranges) is shown in Figure 2c.



a b

Figure 3. Multispectral holographic lens-less microscope (a) and an example of the resulting analog volume image rendering (3D) of a biosample / histological section for multispectral holographic lens-less microscope with a frequency equalizer (b).

4. CONCLUSION

The list of research areas and technical solutions which can be further developed based on the above proposed principles includes:

(1) Development of a series of multispectral lensless microscopes for biomedical, ecological and food / industrial applications. Compactization due to the use of LED systems and a simplified photometric model for diffuse illumination.

(2) Introduction of machine learning methods into identification and qalimetry of the products and raw materials, biomedical diagnostic and ecological samples using the series of images from multispectral and hyperspectral lensless microscopes.

(3) Design of the systems with discrete “chemical pixels”, converting the signals from chemically heterogeneous structures into an optically detectable gradient distribution of ions, molecules or other specific analytes.

(4) Design of the systems with discrete “physical pixels”, converting physical non-optical signals/fields from heterogeneous structures into optically detectable ones. Design of portable and pocket lensless defectoscopes based on such physical principles (lensless visualization of magnetic fields for the powder method, microwave and acoustic fields, local heat sources, electroluminescent analysis of the leaks and cracks in fractography, etc.)

(5) Development of a series of industrially produced lensless devices for different branches of science and practice, for which industrial scalable production and technical implementation for the technological process operators and laboratory assistants of any qualification becomes possible. Such compact intellectual devices may include, in particular: lensless nanoliter osmometers/cryoscopes and recrystallometers; lensless evaporographs (analyzers of the liquid microdroplet evaporation rate); lensless water hardness analyzers; lensless pinning effect analyzers, tensiometers, and contact angle meters; lensless swellographs; lensless systems for rapid point-of-care/*in situ*/operando-biotesting; lensless flow granulometers; lensless diffusiometers; lensless sedimentographs; lensless FRAP and FLIP analyzers; lensless multispectral immunochromatographic test strip readers; lensless structural color analyzers based on ASP sensors; lensless “spinthariscopes” (detectors of ionizing radiation) and more than 30 other possible compact specified lensless device modifications (more than 20 of which were implemented or adapted by the author in 2009-2019).

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