CCD-or CMOS-lab-on-a-chip based on discrete converters of different physical and chemical parameters of samples into the optical signals with positional sensitivity for morphometry of non-optical patterns

A novel ultra-compact analytical system for simultaneous analysis of a variety of physical and chemical parameters of different biological samples (medical or veterinary analytes, food, soil microbiota, hydrobiological water probes etc.) both in the field and laboratory conditions has been developed on the basis of a single multiparametric microchip with a set of replaceable cartridges / converters, which allows to perform a complex diagnostic procedure of the analyte. The prototypes of automatic microfluidic devices for multiparametric mapping of biochemical and synthetic analytes using planar converters-visualizers have been designed. We propose to use a lab-on-a-chip with a number of replaceable cartridges-converters of various physical parameters / variables to optical signals, which can be detected using CMOS or CCD, as a single analytic and microelectronic platform for mapping and visualization of different physical and chemical parameters. The above system allows to perform a simultaneous mapping, detection and visualization of a number of the sample characteristics, such as: magnetic field (using magnetic film indicators and flux-detectors); electrochemical parameters (potentiometric indicators); laser beam transmission outside the visible spectral range (using the doped solid matrices); distribution of the emitting regions in autoradiography (using the scintillation detectors with different quenching factors or "position-sensitive spinthariscopes"); polarization characteristics and the angular fluorescence polarization (using polaroid films with the rotation angles changed by the stepper motors); the local biothermogenesis temperature of the sample at different points on a chip (according to the NIR-HDRI thermography principles), etc.

Difficulté **Très difficile** | Durée **1 mois**

Catégories **Électronique, Alimentation & Agriculture, Science & Biologie** | Coût **100 EUR (€)**

Sommaire

Introduction

The literature analysis suggestes that a complex characterization of physiological activity of a living organism requires dozens or hundreds of chips depending on the task. For example, there are both active and passive chips used in biophysical, molecular metabolomic and genomic studies in fundamental and applied molecular medicine:

a. allergology (Taira, 2009; Lupinek, 2014; Seyfarth, 2014; Zienkiewicz, 2014; Williams, 2016);

b. haematology and transfusiology (Hassan, 2015; Nguyen, 2015; Chen, 2015; Kuan, 2015; Rafeie, 2016; Mielczarek, 2016), including blood-brain barrier research / modeling (Shao, 2016; Bonakdar, 2016; Brown, 2015; Deosarkar, 2015);

c. lymphology (Hanna, 2003; Shimizu, 2007; Moura, 2016) and phlebology (Franco, 2012; Brivo, 2012; Zhou, 2012; Ryu, 2015);

d. cardiology (Tanaka, 2007; Chean, 2010; Grosberg, 2011; Agarwal, 203; Wang, 2014; Rismani, 2015; Jastrzebska, 2016; Marsano, 2016; Zhang, 2016);

e. gastroenterology-on-a-chip (Yang, 2009; Esh, 2012, 2014), including gut-on-a-chip techniques (Bjerketorp, 2008; Kim, 2008, 2016; Tottey, 2013; Lee, 2016);

f. cellular neurophysiology-on-a-chip and neuromorphogenesis-on-a-chip (Millet, 2010; Ling, 2010; Kim, 2014; Huang, 2014; Wei, 2014; Kunze, 2015; Yamada, 2016);

g. endocrinology (Marchesini, 2007; Bovet, 2007; Srivastava, 2014);

h. immunology (Yakovleva, 2002; Yang, 2005; Corgier, 2007; Liu, 2011; Zhang, 2011; Kayo, 2013; Wang, 2015; Ali, 2016);
i. general "splanchnology-on-a-chip" based on N principally equivalent approaches: "organ-on-a-chip" (Wikswo, 2013; Ahmad, 2014; van der Helm, 2016; Mousavi, 2016) / "organ-on-a-chip" (Lee, 2013; Bhise, 2014; Odjik, 2015; Kim, 2015; Caplin, 2015; Sticker, 2015; An, 2015; Zheng, 2016; Cho, 2016), "organoid-on-a-chip" (Skardal, 2016) and "physiome-on-a-chip" (Stokes, 2015), which can be integrated in the frame of concept "body-on-a-chip" (Esh, 2011, 2016; Williamson, 2013; Reif, 2014; Sung, 2014; Kelm, 2014; Ryu, 2015; Perestrelo, 2015); {etc.}

The above problem made the study so complicated, that it became quite unfeasible, since the "multi-chip" analysis (see Terminological remark No. 1) turned to be very expensive and the large sample volume required for such a complex analysis could not satisfy the principles of non-destructive diagnostics on a chip (for example, see (Takahashi, 2004; Feng, 2015)) due to many biomaterial sampling points (for example, see (Ando, 1987; Nikolaidis, 2012)) standardized in the protocols for biomedical and veterinary diagnostics.

On the other hand, the difference and variety of the sampling and the sample preparation techniques for different microchips and standard diagnostic methods made the problem of analyzing the complex biochemical physiological state of the organism unimplementable and poorly informative. It is quite obvious that for the purpose of compatibility and comparability of the measurement using different analytical devices (see Terminological note No. 2) it is necessary to provide the compatibility and comparability of the sampling and the sample preparation methods. In the ideal case, all the analytical procedures should be performed with a single uniformly calibrated device using the same sample for all the tests without moving the sample from one device to another. To date there are independent calibration methods for chips (Gillot, 2007; Binder, 2008; Karsunke, 2009; Nakamoto, 2010; März, 2010; Song, 2012; Buchegger, 2014), as well as the calibration protocols for other analytical methods (including the imaging ones) using chips (Su, 2016; Garnica-Garza, 2009). Hence, we need an equivalent of cross-calibration in the interpretation close to that given by NIST for cytometry (Hoffman, 2012), although the term was used much earlier in radiology (including tomography) and nuclear medicine (Paans, 1989; Genant, 1994; Tothil, 1995; Grampp, 2000; Geworski, 2002; Hetland, 2009; Garnica-Garza, 2009), as well as in the number of spectroscopic methods applied for the biomaterial analysis (Kwiatkowska, 2008; Wang, 2012; Poto, 2015; Liu, 2016).

In addition, when we deal with the structured samples such as biological tissues, it is also important to obtain information on the spatial distribution of the substance or property analyzed in the image form, for example:

- magnetic field imaging;
- electrochemical parameters and field gradient;
- laser beam transmission outside the visible spectral range;
- distribution of the emitting regions in autoradiography;
- polarization characteristics and the angular fluorescence polarization;
- the local temperature of the sample at different points on a chip{etc.}

Moving the sample from one microscope to another makes it difficult to establish the correspondence (colocalization) between the regions of interest (ROI) for different wavelength ranges (or different physical characteristics) allowing to perform the mapping and identification of the components under investigation due to the difference of visualization in different spectral ranges (or different physical "descriptors"). This prevents one from combination of the signal distribution maps from different spectral regions, and hence, makes it impossible to establish the correlations between the presence and distribution of the certain components or physical and chemical properties in the sample / tissue.

Since different components of the analyte possess a number of colocalized characteristics in different spectral ranges (Zimmermann, 2005; Gavrilovic, 2009), it is possible to perform either a simultaneous or a sequential mapping and identification of several tissue components based on the physically different properties. For example, some target components can be visualized using non-spectral properties, such as magnetic fields (Gruschke, 2012; Kim, 2015; Hejazian, 2015), labeled atom diffusion (for example, see: Parker, 1981; Galbraith, 1981; Blakely 1986; Hein, 1986; Nemecz, 1988; Pouteau, 2003), temperature maps (Choudhury, 2012; Rosenthal, 2014; Karadimitriou, 2014; Meng, 2015 Lo, 2016) or redox maps (including ratiometric those (Herman, 2005; Hilderbrand, 2008; Zhang, 2015; Chen, 2015; Pan, 2016)) on a chip (Jezierski, 2013; Gashti, 2016). We propose to implement a full range of methods for mapping the biological tissue parameters with or without specific labels using planar transducers / converters of the non-optical signal to the optical one, as will be described below.

This will also result in the substitution of a number of independent expensive diagnostic devices with a simple unified complex diagnostic and analytical device. The operator of such a complex lab-on-a-chip will predominantly perform data analysis and processing (a so-called data mining, which is now mainly used not in the active mapping or imaging chips, but in the passive chips for genomic and peptidomic investigations (Lee, 2001; Smith, 2005; Abascal, 2008; Ghanekar, 2008; Usui, 2009; Nussbeck, 2013)) rather than routine analytical procedures (such as sampling and dropping (Fang, 2002; Du, 2005; Cellar, 2005; Huynh, 2006; Zhang, 2007; Do, 2008; Jang, 2009; Kertesz, 2010; Sun, 2010; Coskun, 2010; Wu, 2012)) due to an automatic machinery. This is in consistence with the modern trends in the development of the information society and the extension of the applicability of the chemoinformatic ("chemobioinformatic" (Basak, 2012)) software for biomedical and pharmaceutical (Weinstein, 2001; Shedden, 2003; Shedden, 2004; Parker, 2004; Ghose, 2006; Kong, 2008; Speck-Planche, 2014; Capasso, 2015; Gromova, 2016), agrobiological and biotechnological problems (Speck-Planche, 2012; Grädow, 2014). In this regard, the design of the above proposed complex devices for multi-parametric analysis and mapping of the samples is of great importance for analytical practice both for improving the quality and information content of the analysis and for the rational use of the working time of the analyst. The possibility of connecting such devices to the PC and mobile network resources (Lillehoi, 2013; Wu, 2014; Pan, 2014; Koydemir, 2015; Bhavnani, 2016) allows to improve the quality of telemedicine (Fleck, 1999; Bishara, 2011; Balsam, 2015), GIS – coupled analysis / sample analysis in the field conditions with the geodetic reference (Senbanjo, 2012 Gerald, 2014; Ferguson, 2016), quality control on a chip (Shearstone, 2002; Hartman, 2005; Zhang, 2005; Stokes, 2007; Pierzchalski, 2012) in chemical and biotechnological industry using SCADA and similar systems (Gieling, 1996; Ozdemir, 2006; Smith, 2006; Moya, 2009).

The implementation of the technology proposed will increase the labor productivity of the analysts and researchers, since the performance of N analyses with a single device equals to the N-times reduction of the amount of the auxiliary routine work compared to the performance of each analysis with an independent device requiring different sampling procedures and sample treatment protocols. Since the first labs-on-

a-chip were developed by the author for his own research problems and were tested in the routine research practice, he could easily appreciate the ergonomics and usability of such devices with the maintenance of the quality and increase in the rapidity of the analysis.

Novel approach

The contemporary analysis of the literary and the preliminary calculations, suggested using an optical channel for analytical data acquisition with the CMOS and CCD detectors. However, the serial CMOS and CCD allow detection only the optical parameters providing the analyte concentration measurements by absorbance or transmittance or fluorescence of a selectively bound dye. Modern CMOS- and CCD-based labs-on-a-chip fail to perform visualization of a number of characteristic descriptors for many biological and medical samples, such as magnetic fields, temperature profiles, localization of radioisotope sources and selective emission from cells and tissues in autoradiography, etc. Meanwhile, nothing prevents us from using the primary signal converters of the required parameters / variables into the optical signal. There are known:

· magnetooptical converters and indicator films (Anderson, 1968; Harms, 1980; Aulich, 1980; Papp, 1980; Arkhangel'skii , 1986, 1989; Challener, 1987; Mao, 1989; Challener, 1990; Krafft, 2004; Fratello, 2004);

· radiation-optical (spectro-)colorimetric converters (Apanasenko, 1981; Kulagin, 1983, 1984, 1985, 1987; Bazylev, 1992; Mikhailov, 1996; Kulagin, 2003, 2006; Kulagin, 2007; Sadulenko, 2009) and thin film scintillators (Albul, 1968; Avdeyev, 2001; Garcia-Murillo, 2003; Berdnikov, 2013; Tolstikhin et, 2014; Inami, 2015; Rincón-López, 2016; Park, 2016);

· thermo-optical effect transducers-converters (Malashko, 1974; Dolgov, 1979; Pálfalvi, 2004; Liberts, 2005; Gunyakov, 2006; Nedosekin, 2007; Loiko, 2012), including thermochromic ones (Soloway, 1955; Chivian, 1972; Yang, 1979; Mazumder, 1995; Qazi, 2003; Siegel, 2009; Sia, 2009; Shelton, 2010; Qian, 2012; Heo, 2012; Zhou, 2013; Funasako, 2013; Li, 2013; Bond, 2013; Seeboth, 2014; Kim, 2014; Wan, 2015; Liu, 2016; Zhang, 2016), including infrared-sensitive metamaterials;

· chemo-optical active interfaces (van Gent, 1990; Wroblewski, 1997), colorimetric or flouorimetric indicator films (Chen, 1997; Nakamura, 2003; Kowada, 2004; Lü, 2006; Thomas, 2009; Gao, 2011; Kassal, 2014; Mills, 2016; Choi, 2017) and papers (Yeoh, 1996; Ostrovsakaya, 2004; Gaiduk, 2009; Ganesh, 2014);

· electroluminescent (Vlasenko, 1966; Shaposhnikov, 1970; Ramazonov, 1972; Samokhvalov, 1993; Brigadnov, 1993; Gurin, 1997; Savikhib, 1997; Zabudskii, 2000; Maltsev, 2011; Rodionov, 2013; Meshkov, 2014; Evsevichev, 2016) and cathode-luminescent indicators / phosphors (Tebrock, 1968; De Mets, 1971; Suzuki, 2009; Obraztsov, 2013; Kaz, 2013; Shi, 2014; Li, 2016)

and other position-sensitive target signal converters into the optical signal[1], which allow a direct realization of the "two-level conversion" including a first conversion of the analytical signal into the optical one by the planar converter located above the photosensitive CMOS / CCD detector with the subsequent conversion of the optical signal into the electrical one by the optoelectronic converter (CMOS or CCD). The above converters being placed into the cartridge or cassette system, or the rotating disc (this is a reversible idea from lab-on-a-disc design (Park, 2012; Glass, 2012; Hwang, 2013; Bosco, 2013; Delgado, 2016)) can be replaced by one another in real time allowing to vary the measuring parameters, and hence, providing the sequential mapping and measuring of the above parameters.

At the first step the single devices (chips and the corresponding readers) have been developed for the single parameter registration (e.g. a special compact device for magnetic field visualization has been designed using the magnetic film converter (flux detector) and a similar radiographic visualizer has been developed based on the scintillation plates). Later these devices were combined into a single hybrid device with the incomplete set of the primary converters for the purposes of the complex analysis (see Figures 1-3). At the final step we are going to overcome those limitations and to develop a hybrid multi-functional lab-on-a-chip allowing to perform in a single run of the cassette with the cartridges-converters the full position-sensitive mapping of the spatial distribution of the following parameters:

I. spectral / colorimetric, densitometric and fluorescent parameters of the analyte for histochemistry and immunofluorescent analysis;

II. luminosity distribution beyond the optical spectral range for laser diagnostics or the on-chip LDV, LDA, LDF, laser-accisted PIV;

III. magnetic field for selective staining of biological tissues with the magnetic nanoparticles or for the on-chip testing of the pharmaceuticals' targeting in the external field;

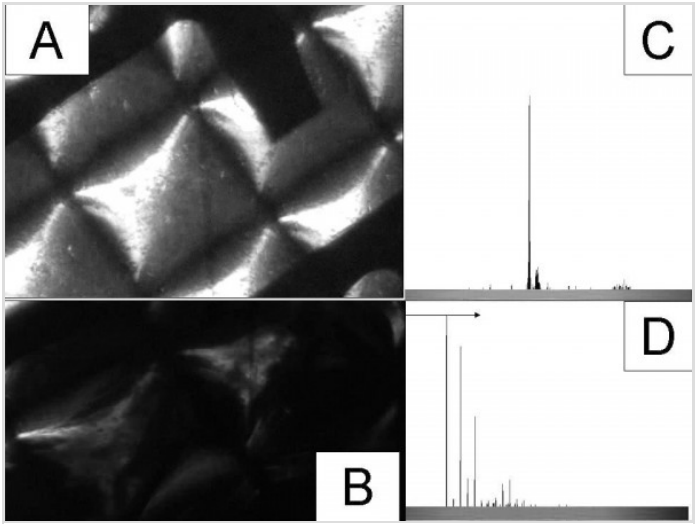
IV. distribution of the emitting regions in autoradiography and for the sample analysis with the radioactive contamination;

V. polarization parameters and the fluorescence polarization for those cases when the rotation of the polarization plane is a diagnostic criterion, from simple saccharimetry to the chirality-based analytical methods introduced from molecular biology;

VI. the slide temperature (for the living slices and tissue cultures) for determination of the biothermogenesis intensity or the redox transformation intensity, which is one of the most important diagnostic criteria of the neoplastic processes in biopsy;

VII. pH, Eh, pX, etc. using discrete indicator films by the colorimetric, spectrocolorimetric or fluorescence response signal (see Figure 4).

The cartridges-converters can be either built into the chip reader (the most suitable configuration for the ultracompact disposable chips without the recording and processing units) or implemented directly into the autonomic chips in the case of the autonomous reusable devices. In the early prototypes developed by the author the chip was combined with the reader forming a so-called self-reading chip capable of the telemetric data translation through a radiofrequency channel (Notchenko, 2012, 2013).



Matériaux

Redox-signal conversion into the optical signal using colorimetric / spectrocolorimetric “chemical pixels” (“chemical resells” / “sensels”): A,C – baseline (reactive film without detective dye response); B,D – indicator signal. Equivalent mosaic sensor-converter elements may be assembled using different converters and indicators (not only “pH-pixels” / “pX-pixels”, but also “electric luminescence pixels”, “magnetic field pixels”, “radiation pixels”).

Outils

Étape 1 -

Notes et références

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