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(54) Title: MICROELECTRONIC SENSOR DEVICE FOR DETECTING LABEL PARTICLES

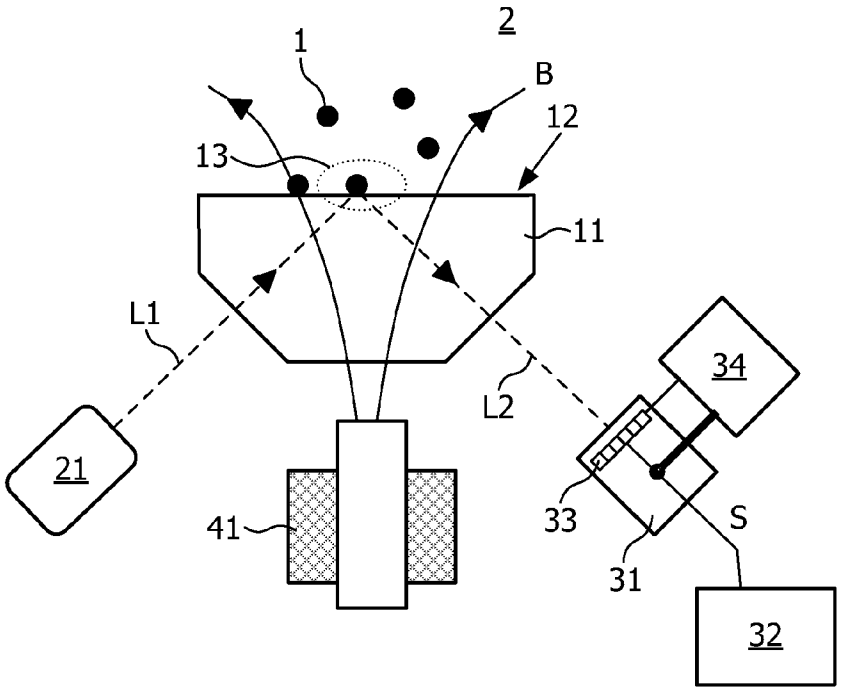


FIG. 1

(57) Abstract: The invention relates to a microelectronic sensor device for optical examinations like the detection of target components that comprise label particles, for example magnetic particles (1). An input light beam (Ll) is transmitted into a carrier (11) and e.g. totally internally reflected at a binding surface (12). The amount of light in a resulting output light beam (L2) is then detected by a light detector (31) that comprises an array (33) of pixels, wherein a pixel correction module (34) corrects the signals of the pixels with respect to their individual characteristics (e.g. dark- light-offset, linearity). These characteristics may optionally be determined under definite operating conditions before or during the use of the microelectronic sensor device.

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# MICROELECTRONIC SENSOR DEVICE FOR DETECTING LABEL PARTICLES

The invention relates to a microelectronic sensor device and a method for making optical examinations in an investigation region of a carrier, particularly for the detection of target components like biological molecules comprising label particles, with the help of a pixelated detector.

The US 2005/0048599 A1 discloses a method for the investigation of microorganisms that are tagged with particles such that a (e.g. magnetic) force can be exerted on them. In one embodiment of this method, a light beam is directed through a transparent material to a surface where it is totally internally reflected. Light of this beam that leaves the transparent material as an evanescent wave is scattered by microorganisms and/or other components at the surface and then detected with e.g. a CCD (Charge Coupled Device) chip. A problem of such setups which use pixelated detectors like a CCD is that the accuracy of measurements may be affected by random pixel-to-pixel variations.

Based on this situation it was an object of the present invention to provide means for improved optical examinations, e.g. a detection of target components comprising label particles, with the help of pixelated detectors. In particular, it is desired that the method is simple and that its sensitivity and/or accuracy is improved with respect to the state of the art.

This object is achieved by a microelectronic sensor device according to claim 1, and a method according to claim 6. Preferred embodiments are disclosed in the dependent claims.

The microelectronic sensor device according to the present invention serves for optical examinations in an investigation region of a carrier (wherein the

investigation region and the carrier do not necessarily belong to the device). In this context, the term "examination" is to be understood in a broad sense, comprising any kind of manipulation and/or interaction of light with some entity in the investigation region. The investigation region will typically be a small volume at a surface of the (preferably transparent) carrier in which material of a sample to be examined can be provided. The examinations may preferably comprise the qualitative or quantitative detection of target components comprising label particles, wherein the target components may for example be biological substances like biomolecules, complexes, cell fractions or cells. The term "label particle" shall denote a particle (atom, molecule, complex, nanoparticle, microparticle etc.) that has some property (e.g. optical density, magnetic susceptibility, electrical charge, fluorescence, radioactivity, etc.) which can be detected, thus indirectly revealing the presence of the associated target component. The "target component" and the "label particle" may optionally also be identical. The carrier usually comprises a binding surface at which target components can collect. The term "binding surface" is chosen primarily as a unique reference to a particular part of the surface of the carrier, and though the target components will in many applications actually bind to said surface, this does not necessarily need to be the case. All that is required is that the target components can reach the binding surface to collect there (typically in concentrations determined by parameters associated to the target components, to their interaction with the binding surface, to their mobility and the like).

The microelectronic sensor device comprises the following components:

a) A light source for emitting a light beam, called "input light beam" in the following, towards the investigation region of the aforementioned carrier. The light source may for example be a laser or a light emitting diode (LED), optionally provided with some optics for shaping and directing the input light beam.

b) A light detector with an array of light sensitive elements, which are called "pixels" in the following, wherein the light detector provides an output signal that indicates the amount of light in an output light beam which comes from the investigation region. The output light beam usually comprises light that stems from an interaction of the input light beam with some entity in the investigation region, e.g. from a (frustrated) total internal reflection of the input

light beam, from a scattering, and/or from a stimulated fluorescence. The pixelated detector may for example be realized by a Charge Coupled Device (CCD) or a CMOS chip as it is well known from digital photography. This makes a spatially (and optionally also spectrally) resolved measurement of the output light beam possible as well as simultaneous measurements of several output light beams.

c) A "pixel correction module" for correcting the output signal of the light detector with respect to individual pixel characteristics. The pixel correction module may be realized by dedicated electronic hardware, digital data processing hardware with associated software, or a hybrid design with a mixture of both.

The described microelectronic sensor device takes into account that the typically several thousands of pixels in pixelated light detectors will usually have individually different characteristics. Moreover, they may comprise a (small) number of defective pixels, for example "dead pixels" that provide no signals or "hot pixels" that permanently provide maximal signals. The proposed pixel correction module helps to avoid a deterioration of the measurements of the light detector by such unavoidable variations and pixel defects.

The pixel correction module may comprise a memory for storing parameters of the individual pixel characteristics, e.g. an individual dark-exposure offset of each pixel. This allows a fast, real-time access to the parameters, and if desired an easy update of their values.

It was already mentioned that pixels may be completely malfunctioning, i.e. their output signal may have no significant or reproducible correlation to the impinging light. Particularly "hot pixels" that permanently yield maximal signals may be a problem for accurate measurements in a low-light environment in which small signals have to be detected. To deal with these issues, the pixel correction module may be adapted to exclude the signal of malfunctioning pixels completely from a further processing.

The microelectronic sensor device may further comprise a "pixel calibration module" for determining the individual pixel characteristics during measurements under definite operating conditions. Such measurements may for example

comprise the production of dark exposures (revealing "hot pixels"), of maximally illuminated exposures (revealing "dead pixels"), or of exposures at intermediate levels of illumination (revealing non-linear or otherwise ill-functioning pixels).

The described microelectronic sensor device can be applied in a variety of setups and apparatuses. In a particular example, the output light beam comprises light of the input light beam that was totally internally reflected in the investigation region. To this end, the investigation region must comprise an interface between two media, e.g. glass and water, at which total internal reflection (TIR) can take place if the incident light beam hits the interface at an appropriate angle (larger than the associated critical angle of TIR). Such a setup is often used to examine small volumes of a sample at the TIR-interface which are reached by exponentially decaying evanescent waves of the totally internally reflected beam. Target components – e.g. atoms, ions, (bio-)molecules, cells, viruses, or fractions of cells or viruses, tissue extract, etc. – that are present in the investigation region can then scatter the light of the evanescent waves which will accordingly miss in the reflected light beam. In this scenario of a "frustrated total internal reflection", the output light beam of the sensor device will comprise of the reflected light of the input light beam, wherein the small amount of light missing due to scattering of evanescent waves contains the desired information about the target components in the investigation region. Thus the signal one is interested in (missing light) is very small and prone to disturbances by pixel-to-pixel variations in the light detector. The proposed use of a pixel correction module helps in this situation to improve the accuracy of the measurements.

In a preferred embodiment of the invention, the microelectronic sensor device comprises a field generator for generating a magnetic and/or an electrical field that can affect the above mentioned label particles. The field generator may for example be realized by a permanent magnet, a wire, a pair of electrodes, or a coil. The generated field may affect the label particles for instance by inducing a magnetization or a polarization and/or by exerting forces on them. Such a microelectronic sensor device allows a versatile manipulation of target components via fields, which may for example be used to accelerate the collection of target components at the binding surface and/or to remove undesired (unbound or, in a stringency test, weakly bound) components from the binding surface.

In the general case, the space next to the carrier at the side of the binding surface may be arbitrarily designed. It is for example possible that this space is exterior to the microelectronic sensor device and that target components are applied to the binding surface by spraying or painting; the space may also be open to the surroundings for detecting target components in e.g. the ambient atmosphere. Moreover, it is possible that the target components reach the binding surface through the carrier, e.g. by diffusion. In preferred embodiments of the invention, the microelectronic sensor device comprises however a sample chamber which is located adjacent to the binding surface and in which a sample with target components can be provided. The sample chamber is typically an empty cavity or a cavity filled with some substance like a gel that may absorb a sample substance; it may be an open cavity, a closed cavity, or a cavity connected to other cavities by fluid connection channels.

As was already mentioned, the microelectronic sensor device may be used for a qualitative detection of target components, yielding for example a simple binary response with respect to a particular target molecule ("present" or "not-present"). Preferably the sensor device comprises however an evaluation module for quantitatively determining the amount of target components in the investigation region from the detected output light beam. This can for example be based on the fact that the amount of light in an evanescent light wave, that is absorbed or scattered by target components, is proportional to the concentration of these target components in the investigation region. The amount of target components in the investigation region may in turn be indicative of the concentration of these components in an adjacent sample fluid according to the kinetics of the related binding processes.

In a further development of the aforementioned embodiment, the microelectronic sensor device comprises a recording module for monitoring the determined amount of light in the output light beam over an observation period. Thus it will be possible to monitor the kinetics with which target components collect at or depart from the binding surface. This may reveal valuable information about the target components and/or the prevailing ambient conditions. The evaluation module and/or the recording module are typically coupled to the light detector and may be realized by some data processing hardware, e.g. a microcomputer, together with associated software.

Up to now the description of the microelectronic sensor device included

the case that only a single investigation region is present on the carrier. In the following, several embodiments of the microelectronic sensor device will be considered in which the carrier comprises a plurality of investigation regions at which different input light beams can be totally internally reflected. One carrier then allows the processing of several investigation regions and thus for example the search for different target components, the observation of the same target components under different conditions and/or the sampling of several measurements for statistical purposes. The "different input light beams" may optionally be components of one broad light beam that is homogeneously generated by the light source.

The different input light beams that are used in the aforementioned embodiment may be different with respect to time. This is for example the case if the microelectronic sensor device comprises a scanning module for sequentially coupling the light source to different investigation regions. Alternatively or additionally, it may comprise a scanning module for optically coupling the light detector to different investigation regions on the binding surface. The scanning modules may for example comprise optical components like lenses or mirrors for directing the input or the output light beam in a suitable way. The scanning modules may also comprise means for moving the carrier with respect to the light source and/or light detector.

In another embodiment of the microelectronic sensor device with a plurality of investigation regions, a plurality of light sources and/or a plurality of light detectors is present that are directed to different investigation regions at the binding surface. In this case it is possible to process a plurality of investigation regions simultaneously, thus speeding-up the associated measurement process accordingly. This embodiment can of course be combined with the previous one, i.e. there may for example be a scanning module for scanning the input light beams of a plurality of light sources over different arrays of investigation regions and/or a scanning module for directing the output light beams from different arrays of investigation regions to a plurality of light detectors. By using scanning modules, the number of light sources/detectors can be kept smaller than the number of investigation regions.

In another embodiment with a plurality of investigation regions, the microelectronic sensor device comprises a plurality of individually controllable (magnetic or electrical) field generators that are associated to different investigation regions. In this

case it is possible to manipulate the label particles in each investigation region individually according to the requirements of the particular tests that shall be performed there.

The microelectronic sensor device may in principle be used with any kind of label particles. It is however preferably provided with label particles that specifically fit to the other components of the device. The sensor device may especially comprise label particles with a mantle of a transparent material, wherein this mantle typically covers (completely or partially) one or more kernels of another material, e.g. iron-oxide grains. In this case light of an evanescent light wave at the binding surface can readily enter the label particles where it is absorbed and/or scattered and thus lost for the output light beam. The transparent material of the mantle may particularly be a material with a similar refractive index as the material of the carrier, because this optimizes the transition of light from the carrier to the label particles. The mantle may for example consist of the same material as the carrier.

The microelectronic sensor device may optionally comprise a "second light detector" for determining (qualitatively or quantitatively) fluorescence light emitted by target components at the binding surface. The fluorescence can be stimulated by the evanescent wave of the input light beam in a small volume adjacent to the binding surface and then be detected, thus indicating the presence (and amount) of fluorescent target components.

While it is in principle possible that the carrier has some dedicated structure with multiple components of different materials, it is preferred that the carrier is homogenously fabricated from a transparent material, for example a transparent plastic. The carrier can thus readily be produced for example by injection moulding.

The investigation region of the carrier has preferably a high smoothness in order to minimize unwanted influences on the (frustrated) total internal reflection. With $\lambda$ being a characteristic (e.g. peak or average) wavelength of the light constituting the input light beam, the smoothness of the investigation region is preferably better than 0.5 $\lambda$, most preferably better than 0.1 $\lambda$ (which means that the height difference between microscopic "valleys" and "tips" of the carrier surface in the investigation region is smaller than these values).

The investigation region of the carrier may optionally be covered with at

least one type of capture element that can bind one or more target components. A typical example of such a capture element is an antibody to which corresponding antigens can specifically bind. By providing the investigation region with capture elements that are specific to certain target components, it is possible to selectively enrich these target components in the investigation region. Moreover, undesired target components can be removed from the binding surface by suitable (e.g. magnetic) repelling forces (that do not break the bindings between desired target components and capture elements). The binding surface may preferably be provided with several types of capture elements that are specific for different target components. In a microelectronic sensor device with a plurality of investigation regions, there are preferably at least two investigation regions having different capture elements such that these regions are specific for different target components.

According to another embodiment of the invention, the surface of the carrier is substantially perpendicular to the input light beam and/or to the output light beam in the region where this beam enters or leaves the carrier, i.e. the angle of incidence lies in a range of about ±5° around 90°. In this case the direction of the input light beam and/or the output light beam will not or only minimally change during the transition from a surrounding medium into the carrier or vice versa. Moreover, reflection will be minimized. Additionally or alternatively, the corresponding regions may also have an anti-reflection coating. To prevent feedback into the light source (e.g. a laser), it may be preferable to have the input beam (at most) a few degrees off-perpendicular.

The carrier may particularly comprise at least one surface with a form similar or identical to a hemisphere or a truncated pyramid. These forms function like lenses and/or prisms and thus provide a favorable guidance of the incident and the output light beam.

The carrier may further optionally comprise a cavity in which a (magnetic or electrical) field generator can at least partially be disposed. The source of the field can thus be positioned as close as possible to the binding surface, allowing to generate high field strengths in the investigation region with minimal effort (e.g. electrical currents) and with minimal disturbances for other regions (e.g. neighboring investigation regions). Moreover, such a cavity can be used to center the carrier with respect to the field generator, the light source and the light detector.

While the microelectronic sensor device may in principle be constructed as a "one-piece" unit of solidly mounted components, it is preferred that the carrier is designed as an exchangeable component of the device, for example a well-plate. Thus it may be used as a low-cost disposable part, which is particularly useful if it comes into contact with biological samples and/or if its coating (e.g. with antibodies) is used up during one measurement process.

The invention further relates to a method for making optical examinations in an investigation region of a carrier, particularly for the detection of target components comprising label particles, wherein said method comprises the following steps:

a) Directing an input light beam towards the investigation region.

b) Providing an output signal, which indicates the amount of light in an output light beam coming from the investigation region, with the help of a light detector with an array of light sensitive "pixels".

c) Correcting the output signal of the light detector with respect to individual pixel characteristics.

The method comprises in general form the steps that can be executed with a microelectronic sensor device of the kind described above. Therefore, reference is made to the preceding description for more information on the details, advantages and improvements of that method.

The individual pixel characteristics that are corrected by the method and in the previously described microelectronic sensor device may especially comprise the dark-light offset of the pixel (i.e. the basic signal if no illumination falls on the pixel), the gain of the pixel (i.e. the relation between illumination input and output signal of the pixel), and/or a malfunction-indicator of the pixel (i.e. a flag or other value that indicates a malfunction of the pixel).

If a malfunctioning pixel is detected, it may optionally be excluded from a further processing to avoid negative effects on the measurement results.

The individual pixel characteristics may preferably be determined during measurements under definite operating conditions. Thus a permanent update of the correction parameters is possible, guaranteeing a maximum of accuracy. The "definite operating conditions" may in this context for example comprise an exposure of the pixels to a known illumination, particularly a dark "illumination" (i.e. a shielding from any light input).

In a preferred embodiment of the method, the label particles are manipulated by a magnetic and/or an electrical field, wherein this manipulation may particularly comprise the attraction of the particles to or their repulsion from the investigation region.

These and other aspects of the invention will be apparent from and elucidated with reference to the embodiment(s) described hereinafter. These embodiments will be described by way of example with the help of the accompanying drawings in which:

| | |
|---|---|
| Figure 1 | schematically shows the general setup of a microelectronic sensor device according to the present invention; |
| Figure 2 | shows a section of a pixel array of the microelectronic sensor device of Figure 1; |
| Figure 3 | shows schematically various characteristics of pixels of the array of Figure 2. |

Like reference numbers in the Figures refer to identical or similar components.

Figure 1 shows a general setup with a microelectronic sensor device according to the present invention. A central component of this setup is the carrier 11 that may for example be made from glass or transparent plastic like poly-styrene. The carrier 11 is located next to a sample chamber 2 in which a sample fluid with target components to be detected (e.g. drugs, antibodies, DNA, etc.) can be provided. The sample further comprises magnetic particles 1, for example superparamagnetic beads, wherein these particles 1 are usually bound as labels to the aforementioned target components (for simplicity only the magnetic particles 1 are shown in the Figure). It should be noted that instead of magnetic particles other label particles, for example electrically charged or fluorescent particles, could be used as well.

The interface between the carrier 11 and the sample chamber 2 is formed by a surface called "binding surface" 12. This binding surface 12 may optionally be coated with capture elements, e.g. antibodies, which can specifically bind the target components.

The sensor device comprises a magnetic field generator 41, for example an electromagnet with a coil and a core, for controllably generating a magnetic field B at the binding surface 12 and in the adjacent space of the sample chamber 2. With the help of this magnetic field B, the magnetic particles 1 can be manipulated, i.e. be magnetized and particularly be moved (if magnetic fields with gradients are used). Thus it is for example possible to attract magnetic particles 1 to the binding surface 12 in order to accelerate the binding of the associated target component to said surface.

The sensor device further comprises a light source 21, for example a laser or an LED, that generates an input light beam L1 which is transmitted into the carrier 11 through an "entrance window". The input light beam L1 arrives at the binding surface 12 at an angle larger than the critical angle $\theta_c$ of total internal reflection (TIR) and is therefore totally internally reflected in an "output light beam" L2. This output light beam L2 will typically comprise additional light components leaving the carrier, e.g. light of the input light beam that was scattered inside the carrier. The output light beam L2 leaves the carrier 11 through another surface ("exit window") and is detected by a light detector 31. The light detector 31 determines the amount of light of the output light beam L2 (e.g. expressed by the light intensity of this light beam in the whole spectrum or a certain part of the spectrum). The measurement results are evaluated and optionally monitored over an observation period by an evaluation and recording module 32 that is coupled to the detector 31.

As light source 21, a commercial DVD ( = 658 nm) laser-diode can be used. A collimator lens may be used to make the input light beam L1 parallel, and a pinhole of e.g. 0.5 mm may be used to reduce the beam diameter.

Figure 2 shows schematically that the light detector 31 comprises an array 33 of several (thousands of) light sensitive elements 33.1, 33.2, 33.3, 33.4. As usual, these elements will be called "pixels" in the following. The array 33 may be realized by a CCD or CMOS imaging chip, which allows for spatially resolved, multiplexed measurements of several output light beams.

However, CCD and CMOS detector chips, such as also used in digital photography, are known to exhibit some pixel-to-pixel variation in their response. This is (exaggeratedly) illustrated in Figure 3 which shows exemplary characteristic curves C representing the output signal s (e.g. a voltage) of four individual pixels 33.1 to 33.4 in

dependence on their illumination I. The extreme case is marked by "dead pixels" 33.3 and "hot pixels" 33.4 which give no or a large output value s, respectively, independent of the illumination I. This effect can lead to systematic, but a priori unknown offsets in the total output signal S of the light detector 31, affecting the accuracy of the measurements.

To solve this problem, it is proposed to use a "pixel correction and calibration module" 34 that determines and stores the detector response prior to a measurement, for example the "dark exposure" response when the light source 21 is switched off. This stored response can then be used to correct the measurement signal from the detector 31 on a pixel-by-pixel basis.

The aforementioned "dark" or offline response of the pixelated detector 31 can be determined during manufacturing and permanently stored in the device for on-the-fly correction. Alternatively, it can be acquired by the pixel correction and calibration module 34 directly prior to each measurement, or it can even be updated during the measurement (e.g. by modulating source light on/off during measurement and updating during "off" and measuring/correcting during "on" states).

The correction of original measurements can involve a direct (pixel-by-pixel) subtraction of the offline response from the original measured pixel signals. Better results may be achieved by eliminating dead or hot pixels 33.3, 33.4 from the measurement and subtraction for the remaining pixels. Dead or hot pixels can give very large values, which may vary by a fair amount, especially compared to the relatively small values of the surrounding pixels (i.e. the real signal). In such cases, a direct subtraction may only give a sub-optimal improvement. When the number E of eliminated pixels in the detection area is significant, it is worthwhile to correct the total (integrated) signal S (minus eliminated pixels) by multiplication with a factor equal to the total number A of pixels in this area divided by the same number of pixels minus the number of eliminated pixels in this area, i.e. by A/(A-E).

For determining which pixels are hot or dead, a pre-defined threshold value can be used. Any pixels with a negative value or a value larger than this threshold value should be excluded from the measurement. A more advanced method could not only check the "dark" offset for each pixel, but also its functionality and linearity: increasing the source light intensity should yield a corresponding increase in output

value s (cf. Figure 3). If not, the pixel is dead, and should also be excluded from the measurement. For this method, the source light needs to be on during (part of) the offline measurement. This is no problem when performed prior to starting the biomedical measurement. When this method is used during the biomedical measurement in a source modulation scheme such as mentioned above, the modulation scheme needs to be adapted from a simple off/on: part I of the scheme (offline measurement) subsequently switches (or leaves) the source in the off-state, then to a first level, if desired then to a second level and possibly additional levels. In part II of the scheme, the source is switched to the predetermined measurement level after which data acquisition is started. The acquired data is then corrected using the offline information obtained during part I (possibly in combination with previous versions of this information e.g. for some time-averaging stability improvement). It should be noted that part I and part II do not need to be equally long in time. This can be advantageous to combine a fast update of the sensor response with a high and almost continuous sampling rate of the measurement (i.e. if part I is much smaller than part II).

It is possible to use the detector 31 also for the sampling of fluorescence light emitted by fluorescent particles 1 which were stimulated by the evanescent wave of the input light beam L1, wherein this fluorescence may for example spectrally be discriminated from reflected light L2. Though the following description concentrates on the measurement of reflected light, the principles discussed here can mutatis mutandis be applied to the detection of fluorescence, too.

The described microelectronic sensor device applies optical means for the detection of magnetic particles 1 and the target components one is actually interested in. For eliminating or at least minimizing the influence of background (e.g. of the sample fluid, such as saliva, blood, etc.), the detection technique should be surface-specific. As indicated above, this is achieved by using the principle of frustrated total internal reflection. This principle is based on the fact that an evanescent wave propagates (exponentially dropping) into the sample 2 when the incident light beam L1 is totally internally reflected. If this evanescent wave then interacts with another medium like the magnetic particles 1, part of the input light will be coupled into the sample fluid (this is called "frustrated total internal reflection"), and the reflected intensity will be reduced (while the reflected intensity will be 100% for a clean interface and no interaction).

Depending on the amount of disturbance, i.e. the amount of magnetic beads on or very near (within about 200 nm) to the TIR surface (not in the rest of the sample chamber 2), the reflected intensity will drop accordingly. This intensity drop is a direct measure for the amount of bonded magnetic beads 1, and therefore for the concentration of target molecules. When the mentioned interaction distance of the evanescent wave of about 200 nm is compared with the typical dimensions of anti-bodies, target molecules and magnetic beads, it is clear that the influence of the background will be minimal. Larger wavelengths $\lambda$ will increase the interaction distance, but the influence of the background liquid will still be very small.

The described procedure is independent of applied magnetic fields. This allows real-time optical monitoring of preparation, measurement and washing steps. The monitored signals can also be used to control the measurement or the individual process steps.

For the materials of a typical application, medium A of the carrier 11 can be glass and/or some transparent plastic with a typical refractive index of 1.52. Medium B in the sample chamber 2 will be water-based and have a refractive index close to 1.3. This corresponds to a critical angle $\theta_c$ of 60°. An angle of incidence of 70° is therefore a practical choice to allow fluid media with a somewhat larger refractive index (assuming $n_A = 1.52$, $n_B$ is allowed up to a maximum of 1.43). Higher values of $n_B$ would require a larger $n_A$ and/or larger angles of incidence.

Advantages of the described optical read-out combined with magnetic labels for actuation are the following:

- Cheap cartridge: The carrier 11 can consist of a relatively simple, injection-molded piece of polymer material.
- Large multiplexing possibilities for multi-analyte testing: The binding surface 12 in a disposable cartridge can be optically scanned over a large area. Alternatively, large-area imaging is possible allowing a large detection array. Such an array (located on an optical transparent surface) can be made by e.g. ink-jet printing of different binding molecules on the optical surface.

The method also enables high-throughput testing in well-plates by using multiple beams and multiple detectors and multiple actuation magnets (either mechanically moved or electro-magnetically actuated).

- Actuation and sensing are orthogonal: Magnetic actuation of the magnetic particles (by large magnetic fields and magnetic field gradients) does not influence the sensing process. The optical method therefore allows a continuous monitoring of the signal during actuation. This provides a lot of insights into the assay process and it allows easy kinetic detection methods based on signal slopes.

- The system is really surface sensitive due to the exponentially decreasing evanescent field.

- Easy interface: No electrical interconnect between cartridge and reader is necessary. An optical window is the only requirement to probe the cartridge. A contact-less read-out can therefore be performed.

- Low-noise read-out is possible.

While the invention was described above with reference to particular embodiments, various modifications and extensions are possible, for example:

- In addition to molecular assays, also larger moieties can be detected with sensor devices according to the invention, e.g. cells, viruses, or fractions of cells or viruses, tissue extract, etc.

- The detection can occur with or without scanning of the sensor element with respect to the sensor surface.

- Measurement data can be derived as an end-point measurement, as well as by recording signals kinetically or intermittently.

- The particles serving as labels can be detected directly by the sensing method. As well, the particles can be further processed prior to detection. An example of further processing is that materials are added or that the (bio)chemical or physical properties of the label are modified to facilitate detection.

- The device and method can be used with several biochemical assay types, e.g. binding/unbinding assay, sandwich assay, competition assay, displacement assay, enzymatic assay, etc. It is especially suitable for DNA detection because large scale multiplexing is easily possible and different oligos can be spotted via ink-jet printing on the optical substrate.

- The device and method are suited for sensor multiplexing (i.e. the

parallel use of different sensors and sensor surfaces), label multiplexing (i.e. the parallel use of different types of labels) and chamber multiplexing (i.e. the parallel use of different reaction chambers).

- The device and method can be used as rapid, robust, and easy to use point-of-care biosensors for small sample volumes. The reaction chamber can be a disposable item to be used with a compact reader, containing the one or more field generating means and one or more detection means. Also, the device, methods and systems of the present invention can be used in automated high-throughput testing. In this case, the reaction chamber is e.g. a well-plate or cuvette, fitting into an automated instrument.

Finally it is pointed out that in the present application the term "comprising" does not exclude other elements or steps, that "a" or "an" does not exclude a plurality, and that a single processor or other unit may fulfill the functions of several means. The invention resides in each and every novel characteristic feature and each and every combination of characteristic features. Moreover, reference signs in the claims shall not be construed as limiting their scope.

CLAIMS:

1. A microelectronic sensor device for optical examinations in an investigation region (13) of a carrier (11), particularly for the detection of target components comprising label-particles (1), comprising

a) a light source (21) for emitting an input light beam (L1) towards the investigation region;

b) a light detector (31) with an array (33) of light sensitive "pixels" (33.1-33.4), wherein the light detector provides an output signal (S) that indicates the amount of light in an output light beam (L2) coming from the investigation region;

c) a "pixel correction module" (34) for correcting the output signal (S) of the light detector with respect to individual pixel characteristics.

2. The microelectronic sensor device according to claim 1, characterized in that the pixel correction module (34) comprises a memory for storing parameters of the individual pixel characteristics.

3. The microelectronic sensor device according to claim 1, characterized in that the pixel correction module (34) is adapted to exclude the signal of malfunctioning pixels (33.3, 33.4) from a further processing.

4. The microelectronic sensor device according to claim 1, characterized in that it comprises a "pixel calibration module" (34) for determining the individual pixel characteristics during measurements under definite operating conditions.

5. The microelectronic sensor device according to claim 1, characterized in that the output light beam (L2) comprises light of the input light beam (L1) that was totally internally reflected in the investigation region (13).

6. A method for making optical examinations in an investigation region (13) of a carrier (11), particularly for the detection of target components comprising label particles (1), comprising

a) directing an input light beam (L1) towards the investigation region (13);

b) providing an output signal (S), which indicates the amount of light in an output light beam (L2) coming from the investigation region, with the help of a light detector (31) with an array (33) of light sensitive "pixels" (33.1-33.4);

c) correcting the output signal of the light detector with respect to individual pixel characteristics.

7. The microelectronic sensor device according to claim 1 or the method of claim 6, characterized in that the individual pixel characteristics comprise the offset, the gain, and/or a malfunction-indicator of the pixel (33.1-33.4).

8. The method according to claim 6, characterized in that the signal of malfunctioning pixels (33.3, 33.4) is excluded from a further processing.

9. The method according to claim 6, characterized in that the individual pixel characteristics are determined during measurements under definite operating conditions.

10. The method according to claim 9, characterized in that the definite operating conditions comprise an exposure of the pixels (33.1-33.4) to a known illumination, particularly a dark illumination.

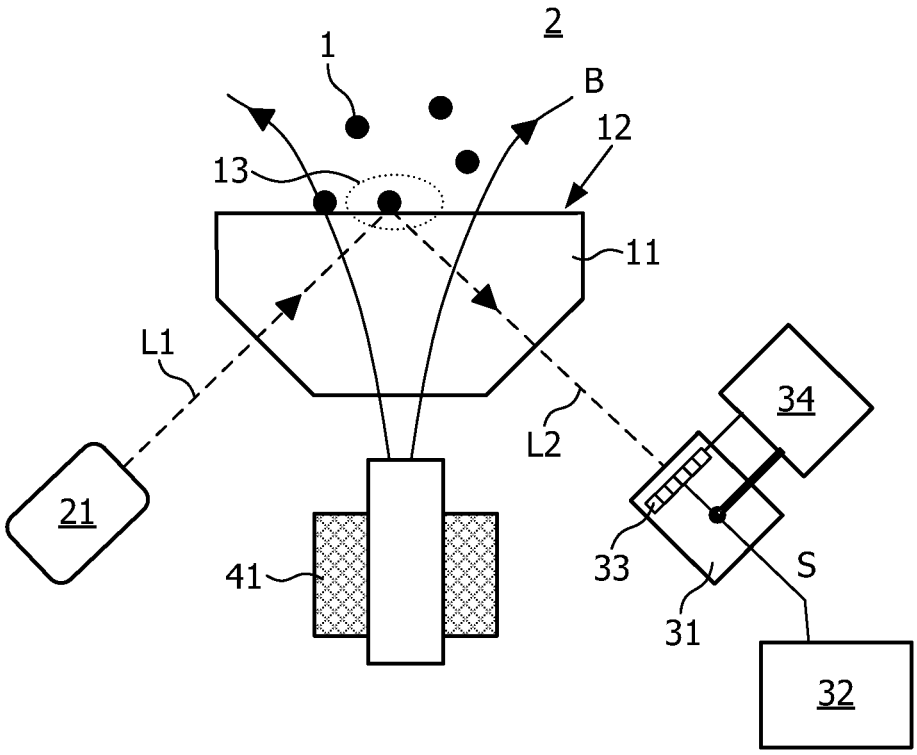


FIG. 1

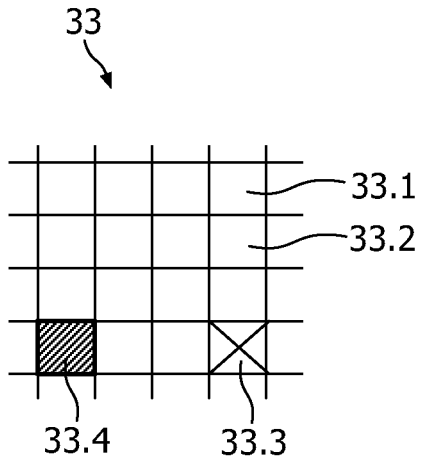


FIG. 2

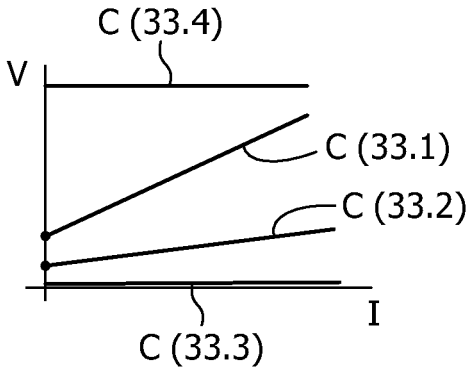


FIG. 3

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/052468

A. CLASSIFICATION OF SUBJECT MATTER
INV. H04N5/217 G01N21/64 G01N21/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
H04N G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2006/028563 A1 (TOMANEY AUSTIN B [US] ET AL) 9 February 2006 (2006-02-09)<br>paragraph [0005]<br>paragraphs [0032], [0035]<br>paragraph [0049] - paragraph [0051]<br>paragraph [0085] - paragraph [0099]<br>paragraph [0101] - paragraph [0104]<br>paragraph [0107]<br>figure 1b<br>figures 11a,b,c-13a,b,c | 1-10 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 6 November 2008 | 18/11/2008 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040,<br>Fax: (+31–70) 340–3016 | Verdoodt, Erik |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/052468

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2006028563 A1 | 09-02-2006 | EP 1779091 A2 | 02-05-2007 |
| | | JP 2008509399 T | 27-03-2008 |
| | | US 2007222983 A1 | 27-09-2007 |
| | | WO 2006017810 A2 | 16-02-2006 |