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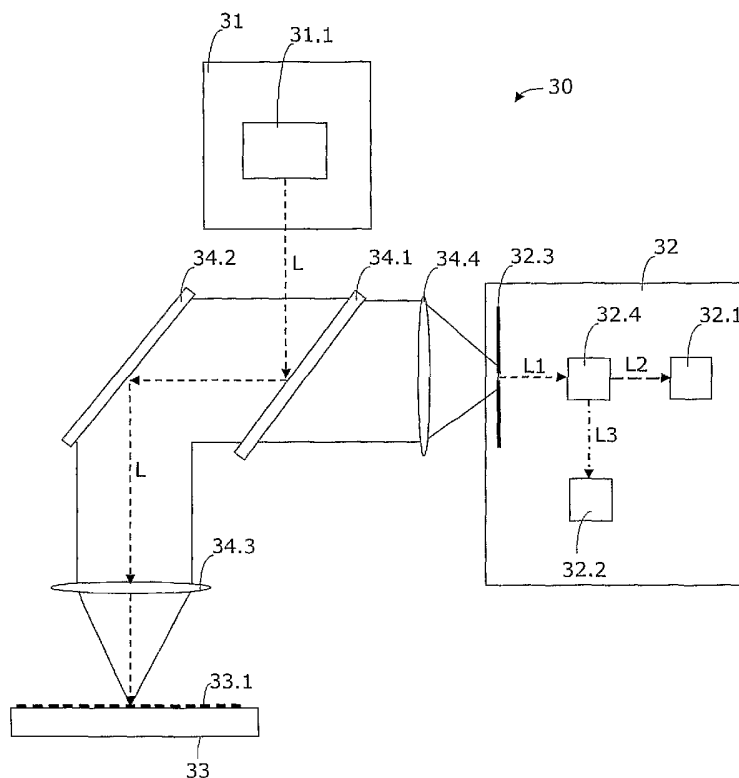
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(54) Title: COMBINING PHOTON COUNTING AND ANALOG DETECTION



(57) Abstract: The invention relates to systems (10; 20; 30) with an emitter (11; 21; 31) for at least partial optical scanning of samples (P, 33.1) and with a receiver (12; 22; 32; 42) for receiving optical signals sent or excited by the emitter (11; 21; 31) and/or a sample (P, 33.1), whereby the receiver (12; 22; 32; 42) operates in a photon counting mode and in an analogue detection mode, the systems (10; 20; 30) comprising a switching means (15; 25; 42.1, 42.5) for automatically switching from one mode to the other. An alternative system according to the invention comprises a similar emitter (31) and receiver (32; 42), whereby the receiver (32; 42) comprises a photon counting sensor (32.1; 42.1, 42.2) that operates in a photon counting mode. This alternative system is characterized in that the receiver (32; 42) comprises at least two avalanche diodes that are simultaneously operated, wherein each one of the avalanche diodes is individually protected from overexposure by an electronics circuit and/or a software algorithm; a beam splitting element (32.4), which un-symmetrically splits a light beam (L1) that arrives from a sample (P, 33.1) into at least two light beams (L2, L3, etc.), which individually are directed to one of the

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COMBINING PHOTON COUNTING AND ANALOG DETECTION

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The present invention relates, according to the preamble of independent claims 1 and 2, to a system with an emitter for at least partial optical scanning of samples and with a receiver for receiving optical signals sent or excited by the emitter and/or a sample, whereby the receiver operates in a photon counting mode and in an analogue detection mode, the system comprising a switching means for automatically switching from one mode to the other. The present invention also relates to corresponding methods, according to the preamble of claims 15 and 16. The present invention further relates, according to the preamble of the independent claims 22 and 25, to an alternative system and a corresponding method.

20 The alternative system comprises an emitter for at least partial optical scanning of samples and with a receiver for receiving optical signals sent or excited by the emitter and/or a sample, whereby the receiver comprises a photon counting sensor that operates in a photon counting mode.

25 Numerous applications are based on acquiring an amount of light. By doing this, very often photo multiplier tubes are used to amplify a light signal prior to supplying it to analysis. Photo multiplier tubes of this type are deemed to be more or less suited for application, depending from the application area and the wavelengths of the light to be analyzed. Especially in the red range of the light spectrum, photo multiplier tubes exhibit relatively low quantum efficiency. This often results in "wasting" up to 99 % of the light intensity or amount of light, in that 30 this portion of light is not acquired. Furthermore, photo multiplier tubes are relatively expensive to purchase and extremely delicate in use.

Frequently, classical photon counting is applied for acquiring an amount of light. However, particularly when time-critical applications are targeted, a trade-off between the dynamic measurement range on the one hand and the measuring speed on the other hand has to be carried out. Especially with automated optical systems that e.g., optically scan micro-arrays, scan rates have to be applied, which require a relatively high measuring speed.

When applying photon-counting techniques, a dynamic range of less than 100 results from typical scan rates of several hundred kilohertz (kHz) and maximum counting rates of about 10 megahertz (MHz). Thus, scanners usually are operated in an analogue mode. Utilizing this analogue mode, photo detectors are used that deliver an output signal, which is proportional to the optical input signal. In particular for the interpretation of high-density micro-arrays, there exists a need to enhance the sensitivity on the one hand and to increase the processing speed (the throughput of samples) on the other hand.

From US 2003/0076924 A1, a tomographic scanning X-ray inspection system using transmitted and Compton scattered radiation is known. This screening system for airport luggage or the like is used for the detection of weapons, narcotics, explosives or other contraband. Utilization of photon counting and photon integration modes is reported to reduce noise and to significantly increase overall image quality.

Considering the prior art and drawbacks already described, the present invention has the object to provide for an alternative system or a method, which possesses or enables measurements with enhanced sensitivity while a higher or at least similar processing speed is applied, and which works without loss of dynamics if compared with recent systems.

This object is achieved according to a first aspect, in that a system is proposed according to the independent claim 1. This system comprises an emitter for at least partial optical scanning of samples and a receiver for receiving optical signals sent or excited by the emitter and/or a sample, whereby the receiver oper-

ates in a photon counting mode and in an analogue detection mode. The system further comprises a switching means for automatically switching from one mode to the other. The system according to a first embodiment is characterized in that the receiver comprises a photon counting sensor with at least one avalanche diode.

This object is achieved according to a second aspect, in that an alternative system is proposed according to the independent claim 2. This system also comprises an emitter for at least partial optical scanning of samples and a receiver for receiving optical signals sent or excited by the emitter and/or a sample, whereby the receiver operates in a photon counting mode and in an analogue detection mode. The system further comprises a switching means for automatically switching from one mode to the other. The system according to the alternative embodiment is characterized in that it comprises a fluorescence detection device and imaging means for providing an image from signals that have been acquired in the photon counting mode and/or in the analogue detection mode.

This object is achieved according to a third aspect, in that a method is proposed according to the independent claim 15. This method to operate a system, in particular according to claim 1, comprises the step of operating an emitter for at least partial optical scanning of samples and a receiver for receiving optical signals sent or excited by the emitter and/or a sample, wherein the receiver is operated in a photon counting mode and in an analogue detection mode. The method further comprises automatically switching from one mode to the other with a switching means. The method is characterized in that the receiver comprises a photon counting sensor with at least one avalanche diode, which receiver is switched from one mode to the other as soon as a specified threshold value of the measured light intensity is reached.

This object is achieved according to a fourth aspect, in that a method is proposed according to the independent claim 16. This method to operate a system, in particular according to claim 2, comprises the step of operating an emitter for at least partial optical scanning of samples and a receiver for receiving optical sig-

nals sent or excited by the emitter and/or a sample, wherein the receiver is operated in a photon counting mode and in an analogue detection mode. The method further comprises automatically switching from one mode to the other with a switching means. The method is characterized in that the system comprises a fluorescence detection device and imaging means, wherein images are provided from signals that have been acquired in the photon counting mode and/or in the analogue detection mode.

This object is achieved according to a fifth aspect, in that an alternative system is proposed according to the independent claim 22. This system also comprises an emitter for at least partial optical scanning of samples and a receiver for receiving optical signals sent or excited by the emitter and/or a sample, whereby the receiver comprises a photon counting sensor that operates in a photon counting mode. This alternative system is characterized in that the receiver comprises:

- (a) at least two avalanche diodes that are simultaneously operated, wherein each one of the avalanche diodes is individually protected from overexposure by an electronics circuit and/or a software algorithm;
- (b) a beam splitting element, which un-symmetrically splits a light beam L1 that arrives from a sample into at least two light beams L2, L3, etc., which individually are directed to one of the parallel sensing avalanche diodes; and
- (c) a processing system (25) for the production of information from signals that arrive from the at least two avalanche diodes.

This object is achieved according to a sixth aspect, in that a method is proposed according to the independent claim 25. This method to operate the alternative system that is equipped with an emitter for at least partial optical scanning of samples and with a receiver for receiving optical signals sent or excited by the emitter and/or a sample, wherein the receiver is operated in a photon counting mode, in particular according to claim 22, is characterized in that it comprises the steps of:

- (a) simultaneously operating at least two avalanche diodes of the receiver, while individually protecting each one of the avalanche diodes from overexposure by an electronics circuit and/or a software algorithm;

- (b) splitting a light beam that arrives from a sample into at least two light beams with a beam splitting element, which splitting is preformed unsymmetrically;
- (c) individually directing the at least two light beams to one of the parallel sensing avalanche diodes,
- (d) processing of signals that arrive from the at least two avalanche diodes in a processing system; and
- (e) producing information from these signals.

10 Additional preferred embodiments and inventive features derive from the dependent claims.

An important feature of the present invention is the protection of the at least one avalanche diode utilized in the system. Of particular advantage is the application of the present invention in a micro-array scanner (biochip scanner), in a cell imager, or in fluorescence scanning microscopy. The system according to the invention therefore may comprise a device for the detection of fluorescence signals that are emitted by a sample and for providing an image according to these fluorescence signals; such a device may be a fluorescence scanning device or a fluorescence microscope. The invention is also applicable in an apparatus that works with light scattering (Rayleigh Scattering or Raman Scattering) or in a fluorescence and/or luminescence reader.

The systems according to the present invention are also characterized in that they possess a sensitivity, which lies close to the statistic physical limit. In addition, these systems according to the invention exhibit an enlarged dynamic range, depending on the particular implementation. Especially through its implementation of combined photon counting and analogue detection modes, the system provides images with a dynamic range that is at least an order of magnitude higher than an image achieved with a system that only works in the photon counting mode. Quantum efficiency is enhanced by the special utilization of avalanche diodes according to the invention, without however destroying the extremely sensitive avalanche diodes.

The system and the method according to the present invention is now discussed in detail with the help of schematic drawings that are not intended to limit the scope of the invention and that are showing exemplary embodiments. It is shown in:

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Fig. 1 a schematic block diagram of a first embodiment of the invention;

Fig. 2 a schematic block diagram of a second embodiment of the invention;

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Fig. 3 a schematic block diagram of a third embodiment of the invention;

Fig. 4 a schematic block diagram of a fourth embodiment of the invention;

Fig. 5 a schematic block diagram of a receiver according to the invention.

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In the following, preferred and exemplary embodiments of the invention are described. These embodiments comprise different variants of the entire invention as well as components and individual parts of the invention. In general, the components and individual parts of the different embodiments described can be
20 combined with each other or the components and individual parts of particular embodiments described can be replaced by the components and individual parts of other embodiments. The combinations achieved herewith may require smaller adaptation or adjustment familiar to a skilled person and are not described or discussed in more detail. Such adaptation or adjustment may be necessary to
25 enable interaction or engagement of the components and individual parts with each other.

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In the context of the present invention, often samples are mentioned. The term "sample" should not be interpreted as narrowing the scope of the present invention, which can be utilized to optically investigate samples from different sources. Samples can be single samples or multitudes of samples prepared on a platform. Suitable as a platform for a sample or samples are glass plates (e.g., in the form of microscope slides), micro plates or MICROTITRE™ plates (Trade Mark of Beck-

man Coulter, Inc., Fullerton, CA 92834, USA), micro arrays on micro plates, carriers, discs, chips or similar. According to the platform utilized, the sample can be present as e.g., body fluids, microorganisms, food and preparations thereof; cells or tissue parts suspended in a buffer solution and kept within the wells of a micro plate. The samples can also be present as cell smears, grown up cell layers or in the form of tissue sections or gel preparations that are immobilized on the surface of a microscope slide or supported by a glass plate. The samples typically are labeled with fluorescent markers; however, the invention is not limited to the utilization of fluorescent markers or fluorescence microscopes. The present invention can also be applied in a light scattering apparatus, such as Rayleigh Scattering or Raman Scattering devices or variants therefrom (e.g., SERS = Surface Enhanced Raman Scattering or Spectroscopy).

Figure 1 shows a first system 10 according to the invention. The system 10 shown comprises an emitter 11 for optical scanning of a sample to be investigated. The sample preferably is situated in the region of a focusing plane and is depicted in Figure 1 as P. A light source 11.1, e.g., a laser is a part of the emitter 11. The light source 11.1 emits a light beam L, which is symbolized in Figure 1 by a dashed arrow. Typically, such an emitter 11 comprises additional elements that are not shown in Figure 1 for simplicity reasons. Examples for additional elements of the emitter 11 are a scan unit for deflecting the light beam as well as several optical lenses and/or filters. A focusing system that may be operated automatically or interactively can also be envisaged.

The system 10 further comprises a receiver 12 for receiving optical signals (called a light beam or a light cone) sent or excited by the emitter 11. Such a light beam is reflected, scattered or emitted by the sample P. According to the invention, the receiver 12 operates in two modes. Fully automatic switching from one mode to the other is possible. The first mode is a photon counting mode and the second mode is an analogue detection mode. As can be seen from schematic Figure 1, the receiver of this example comprises two detectors 12.1 and 12.2.

The first detector 12.1 is active in the first, photon counting mode and provides a digital output signal, which is transferred via a line 12.3 to counting electronics 13. In this case, the digital output signal represents photon counting pulses. The second detector 12.2 is active in the second, analogue detection mode and provides an analogue output signal, which is transferred via a line 12.4 to converter 14, i.e., an analog digital converter.

The counter 13 and the converter 14 provide a processing system 15 with the respective signals. This processing system 15 preferably is a calculator or computer, into which an appropriate software is introduced or loaded. The software loaded and activated in the processing system 15 provides information on the basis of the signals received from the counter 13 and the converter 14. This information is presented to the user on a screen or by another means for presenting information, such as a printer or plotter.

Another embodiment of the invention is presented in Figure 2. The elements of the embodiment that are essentially identical with the elements depicted in Figure 1, or that at least are constructed similarly, are provided with the same reference numbers. Figure 2 shows an interface 16, which is situated between the receiver 12 and the processing system 15. This interface 16 receives a signal from the receiver 12 from that it is recognizable, whether the receiver 12 is presently operating in the first, photon counting mode or in the second, analogue detection mode. Interface 16 prepares this signal and provides the processing system 15 with the respective information. This enables the processing system 15 to appropriately process the information received from the counter 13 and from the converter 14.

In contrast to the second embodiment just described, the embodiment according to Figure 1 is only capable to detect, in which mode the receiver 12 momentarily is working, if the signals received from the counter 13 and the converter 14 are processed in the processing system 15.

Another embodiment of the invention is shown in Figure 3. The system 20 as shown here comprises an emitter 21 for optical scanning of a sample to be investigated. The sample preferably is situated in the region of a focusing plane and is depicted in Figure 3 as P. A light source 21.1, e.g., a laser is a part of the emitter 21. The light source 21.1 emits a light beam L, which is symbolized in Figure 3 by a dashed arrow. In addition, the system 20 comprises a receiver 22 for receiving optical signals (called a light beam or a light cone) sent or excited by the emitter 21. Such a light beam is reflected, scattered or emitted by the sample P, preferably situated in the region of a focusing plane. Light beams L1, L2 emitted by the sample may also be produced by photoluminescence, chemoluminescence or other effects (e.g., light scattering). According to the invention, the receiver 22 operates in two modes. A part L1 of the light beam for this reason is guided to a first detector 22.1 and another part L2 of the light beam arrives at a second detector 22.2. The first detector 22.1 detects the impinging light beam L1 in a first photon counting mode and the second detector 22.2 detects the impinging light beam L2 in a second, analogue detection mode. These modes preferably are utilized alternating; i.e., only one of the detectors – either the first or the second – is operating at the same time. Fully automatic switching from one mode to the other is possible. Switching may be performed by an electronical or software switch. The first mode is a photon counting mode and the second mode is an analogue detection mode: As can be seen from schematic Figure 1, the receiver of this example comprises two detectors 12.1 and 12.2.

The first detector 22.1 is active in the first, photon counting mode and provides counting electronics 23 with a digital output signal via a line 22.3. In this case, the digital output signal represents photon counting pulses. The second detector 22.2 is active in the second, analogue detection mode and provides an analogue output signal, which is transferred via a line 22.4 to converter 24, i.e., an analog digital converter.

The counter 23 and the converter 24 provide a processing system 25 with the respective signals. This processing system 25 preferably is a calculator or computer, into which an appropriate software is introduced or loaded. The software

loaded and activated in the processing system 25 provides information on the basis of the signals received from the counter 23 and the converter 24. This information is presented to the user, e.g., as an image, as a curve, as a set of values, or as a single value, displayed on a screen or by another means for presenting information, such as a printer or plotter. This information may also be provided to a data processing system for storage and/or further processing, such as comparison with similar information contained in a database.

So far, keeping one or another detector in operation and switching between these detectors according to a actual light intensity that is detected by these detectors has been described. In an other preferred embodiment of the invention, a system (not shown) is provided that comprises a photon counting sensor and an analogue detection sensor that both are operated simultaneously. When operating this system, photon counting data and analogue detection data continuously are created and outputted by the two sensors. The processing system, enabled appropriately by a loaded and an activated adequate software, sorts out and calculates these data according to a specified schedule. This schedule specifies a first and second threshold value of light intensity detected by the sensors. If the detected light intensity actually is below this specified first threshold, only the photon counting signal is selected. If the detected light intensity actually is above this specified second threshold, only the analogue detection signal is selected. If however, the detected light intensity actually is between these two thresholds, a combination of these signals is selected. If appropriate, the two thresholds can be merged into one single specified threshold. It is expressly noted here, that in this combination of the signals, the percentage of the signals arriving in the processing system may be varied such that they can be selected from a predefined ratio, e.g., 10/90, 20/80, 30/70, 40/60 or 50/50.

In the third embodiment according to Figure 3, the processing system 25 is implemented such that it is capable to detect by software processing of the signals received from the counter 23 and from the converter 24, in which mode the receiver 22 momentarily is working. This third embodiment may be varied in that the receiver 22 sends a mode signal to the processing system 25 via a separate

line (not shown in Fig. 3). Receiving this mode signal from the receiver 22, the processing system always is aware, which one of the detectors 22.1 or 22.2 is actually in duty; thus, the processing system 25 can take this into consideration during processing the signals received from the counter 23 and from the converter 24.

Laser diodes, solid-state lasers and gas lasers are particularly well suited as light sources of the system according to the invention. The invention can be used or implemented in confocal as well as in non-confocal working systems. Contrary to non-confocal imaging, the light of a point in the intermediate image plane is guided through a very small aperture during confocal imaging. This results in that only light originating from the focusing plane can reach the receiver with the detectors. Light originating from all other planes that are not in focus is faded out.

A fourth embodiment of the invention is shown in figure 4. The system 30 as shown here is a confocal system with an emitter 31 for optical scanning of samples 33.1. The samples are located on a plate 33 (e.g., microscope slide or microplate) and are placed in the area of a focusing plane defined by a focusing lens 34.3. A light source 33.1, e.g., a laser is a part of the emitter 31. Light source 33.1 emits a light beam L, which is represented in Figure 4 by a dashed arrow. The system 30 comprises several optical elements, the function of which is explained in the following. After that the light beam L exits the emitter 31, it impinges on a mirror element 34.1 and it is focused via an other mirror element 34.2 and the lens 34.3 already addressed, on the sample 33.1. Depending on the application, the samples may be e.g., labeled with a fluorescence marker, which is excited at the wavelength of the light L. The fluorescent marker of the sample then emits light of a second wavelength. This light is displayed in Figure 4 in grey color as a spread light beam. The emitted light of the second wavelength is collimated by the lens 34.3 and it is then reflected by the mirror element 34.2. The mirror element 34.1 is coated such, or it is of such a composition, that the laser light L (of the first wave length) is reflected, that however the emitted light of the second wavelength penetrates this mirror. Thus, the mirror

element 34.1 separates the light beam L (known as excitation light for fluorescence measurements of microscopy) and the emitted light beam (shown in grey color). The mirror element 34.1 preferably is a dichroic mirror. Behind the mirror element 34.1, is arranged another lens 34.4 in order to focus the light of the
5 second wavelength in direction of an aperture 32.3.

The system 30 comprises a receiver 32 that may comprise several elements. In Figure 4, only the elements that are essential to understand the present invention are shown. The light of a point of the sample 33.1 is guided in an intermediate image plane through an aperture 32.3 with a very small hole in order to only
10 allow light beam L originating from the focusing plane to arrive at the detectors 32.1 and 32.2. All planes that are not in focus are faded out. Fully automatic switching from one detector 32.1 to the other 32.2 is carried out according to the invention. Switching here is performed by an optical element 32.4. Depending
15 on the actual situation or position of this element 32.4, light L2 of a first intensity is directed to detector 32.1 and light of a second intensity is directed to detector 32.2.

In an exemplary embodiment, element 32.4 is a passive beam splitter, preferably
20 implemented so that more than 50 % of the impinging light intensity of light beam L1 is directed to the first detector 32.1. It is preferred that the beam splitter directs more than 80 % of the impinging light intensity of light beam L1 to the first detector 32.1. The remaining light portion L3 is directed to the second detector 32.2. Particularly with this embodiment, but also in applications with other
25 embodiments, an avalanche diode situated in one or both detectors 32.1, 32.2 may be irradiated with a too high light intensity. In order to avoid destruction of the one or more avalanche diodes, at least one of these diodes is wired such that it can only be operated in the photon counting mode (Geiger Mode), if the light intensity is below a threshold value.

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In another embodiment, element 32.4 may be an active element, such as for example a mirror system, a prism or another element to influence the light beam (e.g., a switchable LCD screen, which transmits or reflects a light beam), which is

capable to switch very quickly. In realizing such a system, it is to be taken into consideration that the light L2 is directed to the detector 32.1 with low intensity. As soon as the intensity of light beam L1 reaches a threshold value, the light beam L1 is deflected and a light beam L3 reaches the detector 32.2. If switching
5 is carried out quickly enough, the avalanche diode of detector 32.1 can be protected from too high irradiation.

According to the present invention, also receiver 32 works in two modes. In order to achieve this, a part L2 of the light beam L1 is directed to the first detector
10 32.1 and another part L3 of the light beam L1 is directed to the second detector 32.2. The first detector 32.1 is working in a first, photon counting mode and detects the impinging light beam L2. The second detector 32.2 is working in a second, analogue detection mode and detects the impinging light beam L3. These modes preferably are utilized alternating, i.e., only one of the detectors – either
15 the first or the second – is operating at the same time and provides signals that can be processed. In an alternative embodiment discussed already, photon counting data and analogue detection data may be continuously created and outputted by the two simultaneously operated sensors. The processing system then selects the photon counting signal, or the analogue detection signal, or a combination of these signals provided by two simultaneously operated sensors, according
20 to the actual light intensity in the receiver.

Fully automatic switching from one mode to the other is carried out by element 32.4. If no element 32.4 is present, electronical switching may be performed as
25 explained earlier. Preferably, the at least one avalanche diode is protected from overexposure by automatically switching from one sensor to the other or by automatically selecting one mode or the other. Alternatively, the switching means is part of a driver for the at least one avalanche diode that is incorporated into the receiver. This alternative switching means in the avalanche diode driver
30 can be utilized when alternating the operation of the sensors between the photon counting and analogue detection mode or when simultaneously operating both sensors at the same time.

As already explained in connection with the Figures 1 to 3, the detectors may be connected to a processing system that analyzes the signals, which are provided by the detectors 12.1, 22.1; 12.2, 22.2. It is preferred that also in the embodiment according to Figure 4, wiring or circuits are utilized, which convert and process signals that are provided by the detectors 32.1, 32.2.

In an embodiment of the invention that is particularly preferred, the first detector comprises at least one avalanche diode. Avalanche diodes are also known as (APD) avalanche photo-diodes. Especially preferred is the utilization of a so-called "single photon avalanche diode". A detector with an avalanche diode is implemented such that it can be operated in the photon counting mode. In order to achieve this, the impinging light is focused (preferably with lenses) onto the active region of the avalanche diode. It is preferred that the detector is wired such that it provides digital pulses as output signal.

In the detectors according to the invention, preferably photo multiplier tubes or (PIN-) diodes are also utilized. Diodes normally guide the electric current only in one direction. If one applies to a diode a voltage in blocking polarity, only a minimal blocking current flows. If however, a certain voltage (the breakdown voltage of UBR) is exceeded, the electric current suddenly and strongly increases. In simple terms: the electrical field within the diode is so powerful now that the few free electrons present are accelerated such that they free additional electrons when impinging on the crystal lattice. A multitude of these events releases an avalanche of electrons. Using a detector with such an avalanche diode, this avalanche effect is even supported by a particular construction. In order to achieve this, the avalanche diode is operated in the so-called "Geiger Mode" in that the avalanche diode is wired in series with a resistance R1 having a large value in the order of 100 or more kOhm. Resistance R1 is chosen such that the current is limited to small values below 50 μ A. This ensures that, after initiating an electron avalanche, no more electrons are present in the multiplication region and that the current is stopped again.

When operating a system according to the invention, a voltage U close to and above U_{BR} is then applied to the avalanche diode. In doing this, even when U_{BR} is slightly exceeded, a current just can be avoided, because there are no free electrons present in the multiplication region of the avalanche diode. The avalanche diode is very sensitive in this situation. If only one electron is freed by the absorption of a photon, this electron is accelerated within the avalanche diode because of the very powerful electric field present and this electron then releases an avalanche of electrons as described already. The result is a current pulse or avalanche pulse that can be processed by the sensitive counting electronics 13 or 23, respectively. Crucial for the photon counting is however, that such an avalanche pulse immediately stops as soon as no additional electrons are freed by impinging photons. This is the most important difference between the avalanche diode and a conventional photo diode.

The avalanche pulses all are of essentially the same amplitude and length and can therefore be counted, processed, and converted into digital pulses in the sensitive circuit of the counting electronics 13 or 23.

Preferably, the avalanche diode is cooled thermoelectrically, e.g., with a Peltier element in order to reduce so-called "dark counts", which result from thermal excitation of electrons. Particularly preferred are avalanche diodes from silicon (Si), germanium (Ge), or an indium/gallium/arsenic compound (InGaAs). Si avalanche diodes are well suited for wavelengths between 300 nm and 1100 nm. Ge avalanche diodes are well suited for wavelengths between 800 nm and 1600 nm. Whereas InGaAs is well suited for wavelengths between 900 nm and 1700 nm. According to the present invention, a detector with a standard photo diode or with a photomultiplier is wired such that the detector is producing a continuous analogue voltage, which enables the evaluation of the intensity of the light beam L1. Preferably, a photomultiplier or an avalanche diode in the analogue mode is utilized.

According to an especially preferred circuit however, the one and only avalanche diode is utilized in the photon counting mode (Geiger Mode) and, if the light in-

tensity exceeds a certain value, in the analogue detection mode. Appropriate wiring enables fast switching from the first, photon-counting mode to the second, analogue detection mode.

- 5 An embodiment that refers to this is shown in Figure 5. Here, a receiver 42 is shown. The light beam L1 impinges on a detector 42.4, which comprises a diode as schematically shown in Figure 5. This diode is an avalanche diode that is operated in the photon counting mode as well as in the analogue detection mode. The diode provides an output signal to a circuit 42.1 via a connection 42.2. This
- 10 circuit 42.1 processes the output signal in order to be able to provide for a quick evaluation of the intensity of the light beam L1. As soon as the light intensity reaches a threshold value, the circuit 42.1 provides another circuit 42.5 with a signal. This circuit 42.5 can be any voltage source that can be regulated. If the light intensity is above the threshold value, the circuit 42.5 provides a voltage
- 15 that lies below the breakdown voltage UBR. With this voltage, the diode of the circuit 42.2 is operated. Working in this mode, the diode provides circuit 44 with an analogue output signal that is guided by the circuit 42.1 via a connection 41.2. This circuit 44 preferably is an analog digital converter.
- 20 At an intensity that lies below the threshold value, the diode of the circuit 42.4 is operated in the photon counting mode. For this purpose, the circuit 42.5 provides a voltage that lies above the breakdown voltage UBR. Working in this mode, the diode behaves as an avalanche diode and each single photon releases an avalanche pulse to the output 42.2. These pulses are directed via the circuit
- 25 42.1 and the connection 41.1 to the circuit 43. The circuit 43 may comprise counting electronics 13 that count the single photons by counting the avalanche pulses. The circuits 43 and 44 preferably are connected to a calculator or computer as described in connection with the other Figures.
- 30 It is noted that in connection with the present invention, several times a first and a second detector is mentioned. These two detectors not necessarily are two distinct different detectors however; a single avalanche diode may be incorpo-

rated in an appropriate circuit (see e.g., Fig. 5) as a detector that can be operated in the two modes.

The digital signal that is provided by the first detector or the first mode respectively preferably is sequentially stored and then processed. The digital signal then relates to the number of the received photons and can be assigned to respective image pixels or points. The processing system may provide an output in form of an image, in which all photons detected for an individual sample are displayed in a two-dimensional picture. To this image, information that is provided by the second detector may be added by super positioning, the second detector operating in the second, analogue detection mode. However, a different display arrangement may be chosen in that two different sets of information, achieved by photon counting on the one hand and by analogue detection on the other hand, are presented separately for each one of the investigated samples.

According to the invention, the second detector operates in the so-called analogue detection mode. Typically, the detector is equipped with at least a photo detector, e.g., with a PIN photo diode or with a photo multiplier for this purpose. As mentioned already, a single avalanche diode may be operated in the photon counting mode as well as in the analogue detection mode.

Important is however, that all different embodiments guarantee that the first photon counting mode is only applied for optical signals with an intensity that is below a specified threshold value. When an avalanche diode (utilized as a photon counting sensor) simultaneously is operated with an analogue detection sensor, this specified threshold is equal to the specified second threshold mentioned earlier. In particular for the application of an avalanche diode, timely switching to the other operation mode is required, because a light intensity that too far exceeds the threshold value may destroy the avalanche diode operated in the Geiger Mode. In order to allow automatic switching or to automatically release a different safety mechanism that protects the avalanche diode, an assertion is required, which describes the momentary intensity of the light beam that arrives at the receiver. If a system shall be simultaneously operated with two different

wavelengths, a second optical channel may be built up in the optical path by incorporating the required optical elements.

In another variant of the inventive system, the light beam is only partially scanning a sample. The sample is situated on a movable platform, which may be moved in a way that the individual points of a sample array can be positioned in the impinging light beam. Especially preferred is a combined variant, wherein a sample array mechanically is moved into the correct position e.g., step by step, and wherein a scanner deflects the light beam slightly in order to scan all samples on the array that can readily be reached. After completion of this partial scanning, the sample array is moved into the following position, where optical scanning again is performed.

Systems according to the present invention easily can be realized to comprise an enlarged dynamic range. Such systems can provide signals with a bit format (i.e., with a resolution) of 16 bit and more. The invention may be implemented in a variety of optical systems. The present invention is especially suited for implementation into optical scanners, which need to possess a high scan rate, a high sensitivity, and a large dynamic range. The sensitivity and the resolution are of particular importance for micro array scanners. By implementation of the present invention, micro array scanners may be realized, which present a scan rate, sensitivity, and a dynamic range that lies beyond the performance of all systems existing so far.

A further alternative embodiment of the present invention comprises a system with an emitter 31 for at least partial optical scanning of samples P, 33.1 and with a receiver 32; 42 for receiving optical signals sent or excited by the emitter 31 and/or a sample P, 33.1. The receiver 32; 42 comprises a photon counting sensor 32.1; 42.1, 42.2 that operates in a photon counting mode. According to the invention, the receiver 32; 42 comprises at least two avalanche diodes that all are simultaneously operated. As these avalanche diodes are extremely sensitive against too high light intensity, they are constantly and individually protected from such overexposure by an electronics circuit and/or a software algorithm.

This protecting means preferably is implemented as an electronics circuit in one or more drivers for the avalanche diodes. (see also earlier explanation).

The system also comprises a beam splitting element 32.4, which un-symmet-
5 trically splits a light beam L1 that arrives from a sample P, 33.1 into at least two
light beams L2, L3, etc., which individually are directed to one of the parallel
sensing avalanche diodes. In a processing system 25 that also forms a part of
the inventive system 30, information is produced from the signals that arrive
10 from the at least two avalanche diodes. This information may be presented to
the user, e.g., as an image, as a curve, as a set of values, or as a single value,
displayed on a screen or by another means for presenting information, such as a
printer or plotter. This information may also be provided to a data processing
system for storage and/or further processing, such as comparison with similar in-
formation contained in a database.

15 The aim of this system is to simultaneously expose a number of photon counting
sensors, i.e., avalanche diodes with different intensities of the same signal. Such
a signal may be sent or excited by the emitter 31 of the system and/or may be
emitted by a sample P, 33.1 that is examined with the system in order to pro-
20 duce relevant information with respect to this sample. A software loaded into
and activated in a data processing system, i.e., in a computer or in a printed cir-
cuit, directs the data processing system to select the sensor signal of one of the
avalanche diodes, which is most appropriate for processing and information pro-
duction. In this processing system, an image is reconstructed from the signal ar-
25 riving from the different avalanche diodes according to preset criteria. These cri-
teria define different sub-ranges of the full dynamic range of an image, and they
further define, which one of the signals shall be taken from these sub-ranges for
image reconstruction.

30 In order to enable the system to perform so, the beam splitting element 32.4
e.g., is implemented as a cascade mirror that defines the transmission/reflection
ratio of the light beams L1, L2, L3, etc. This cascade mirror preferably is defining
a static cascade, e.g., a 1/10 or 10/1 ratio, such that from L1 (100%) there are

formed three light beams L1 with 90%, L2 with 9%, and L3 with 0.9% intensity for example. Other examples comprise different ratios and a different number of diodes. The dynamic range of an individual avalanche diode is very limited for imaging applications because of the extremely short measurement time per pixel (typically a few microseconds). Because the maximum counting rate of known photon counting systems does not exceed 10^7 counts/sec; this limitation of the dynamic range results in about 10-100 counts/pixel. This very limited range can be extended by a factor of 100 according to the above mentioned example, when applying an intensity cascade to a number of avalanche diodes.

It remains to be defined by a skilled person, whether the software selects the appropriate avalanche diode on the base of the incoming signals or on the base of status signals individually established for each one of the avalanche diodes and sent to the processing system 25 by the diode itself or by one or more drivers dedicated to the diodes.

The present invention also comprises a corresponding method to operate a system 30 that is equipped with an emitter 11; 21; 31 for at least partial optical scanning of samples P, 33.1 and with a receiver 12; 22; 32; 42 for receiving optical signals sent or excited by the emitter 11; 21; 31 and/or a sample P, 33.1. as already pointed out, the receiver 12; 22; 32; 42 is operated in a photon counting mode in a method that comprises the following steps:

- (a) simultaneously operating at least two avalanche diodes of the receiver 32; 42, while individually protecting each one of the avalanche diodes from overexposure by a by an electronics circuit and/or a software algorithm;
- (b) splitting a light beam L1 that arrives from a sample P, 33.1 into at least two light beams L2, L3, etc. with a beam splitting element 32.4, which splitting is preformed un-symmetrically;
- (c) individually directing the at least two light beams L2, L3, etc. to one of the parallel sensing avalanche diodes;
- (d) processing of signals that arrive from the at least two avalanche diodes in a processing system 25; and
- (e) producing information from these signals.

Preferably, the beam splitting element 32.4 defines a static cascade, which is splitting the light beams L1, L2, L3, etc., and this cascade preferably is carried out with a constant ratio of transmission/reflection. In a preferred embodiment, a software selects the appropriate avalanche diode on the base of the incoming
5 signals or on the base of status signals individually established for each one of the avalanche diodes and sent to the processing system 25 by each diode itself or by one or more drivers dedicated to the diodes. If e.g., the incoming signal is 100% of the capacity of a particular avalanche diode, the software may decide that this avalanche diode overruns and thus, to take the signal of another diode.

10

Similar to the other embodiments of this invention, the information produced by the processing system 25 is presented to the user or is provided to a data processing system.

Patent Claims

- 5 1. System (10; 20; 30) with an emitter (11; 21; 31) for at least partial optical scanning of samples (P, 33.1) and with a receiver (12; 22; 32; 42) for receiving optical signals sent or excited by the emitter (11; 21; 31) and/or a sample (P, 33.1), whereby the receiver (12; 22; 32; 42) operates in a photon counting mode and in an analogue detection mode, the system (10; 20; 10 30) comprising a switching means (42.1, 42.5) for automatically switching from one mode to the other, **characterized in that** the receiver (12; 22; 32; 42) comprises a photon counting sensor (12.1; 22.1; 32.1; 42.1, 42.2) with at least one avalanche diode.
- 15 2. System (10; 20; 30) with an emitter (11; 21; 31) for at least partial optical scanning of samples (P, 33.1) and with a receiver (12; 22; 32; 42) for receiving optical signals sent or excited by the emitter (11; 21; 31) and/or a sample (P, 33.1), whereby the receiver (12; 22; 32; 42) operates in a photon counting mode and in an analogue detection mode, the system (10; 20; 20 30) comprising a switching means (42.1, 42.5) for automatically switching from one mode to the other, **characterized in that** the system (10; 20; 30) comprises a fluorescence detection device and imaging means (15; 25) for providing an image from signals that have been acquired in the photon counting mode and/or in the analogue detection mode.
- 25 3. The system (10; 20; 30) of claim 1 or 2, **characterized in that** the switching means (42.1, 42.5) is accomplished to activate switching from a photon counting sensor to an analogue detection sensor, as soon as a specified light intensity in the receiver is reached.
- 30 4. The system (10; 20; 30) of claim 1 or 2, **characterized in that** the switching means (42.1, 42.5) is accomplished to select the photon counting signal, or the analogue detection signal, or a combination of these signals provided

by two simultaneously operated sensors, as soon as a specified light intensity in the receiver is reached.

- 5 5. The system (10; 20; 30) of claim 3 or 4, **characterized in that** the switching means is realized as software that is loaded into and activated in a calculator or computer for monitoring the system or that is implemented as an electronics circuit in a calculator, computer, or in a driver for at least one avalanche diode that is incorporated into the receiver (12; 22; 32; 42).
- 10 6. The system (10; 20; 30) according to any one of the preceding claims, **characterized in that** the receiver (12; 22; 32; 42) comprises an avalanche diode and a photomultiplier.
- 15 7. The system (10; 20; 30) according to any one of claims 1 to 5, **characterized in that** the receiver (12; 22; 32; 42) comprises two avalanche diodes, one of which is operated in the photon counting mode, and one of which is operated in the analogue detection mode.
- 20 8. The system (10; 20; 30) according to any one of claims 1 to 5, **characterized in that** the receiver (12; 22; 32; 42) comprises a single avalanche diode that is operable in the photon counting mode as well as in the analogue detection mode.
- 25 9. The system (10; 20; 30) according to any one of the preceding claims, **characterized in that** the system through its implementation of combined photon counting and analogue detection modes provides images with a dynamic range that is at least an order of magnitude higher than an image achieved with a system that only works in the photon counting mode.
- 30 10. The system (10; 20; 30) according to one of the claims 1 or 5 to 9, **characterized in that** the at least one avalanche diode is protected from overexposure by automatically switching from one sensor to the other or for automatically selecting one mode or the other.

11. The system (10; 20; 30) according to any one of the preceding claims,
characterized in that the system comprises a micro array scanner.
12. The system (10; 20; 30) according to any one of the preceding claims,
5 **characterized in that** the system comprises a cell imager.
13. The system (10; 20; 30) according to any one of the preceding claims,
characterized in that the system comprises a fluorescence microscope or
an apparatus that works with Rayleigh scattering or Raman scattering.
- 10 14. The system (10; 20; 30) according to any one of the preceding claims,
characterized in that the system comprises a fluorescence and/or lumi-
nescence reader.
- 15 15. Method to operate a system (10; 20; 30) that is equipped with an emitter
(11; 21; 31) for at least partial optical scanning of samples (P, 33.1) and
with a receiver (12; 22; 32; 42) for receiving optical signals sent or excited
by the emitter (11; 21; 31) and/or a sample (P, 33.1), wherein the receiver
(12; 22; 32; 42) is operated in a photon counting mode and in an analogue
20 detection mode, the system (10; 20; 30) comprising a switching means
(42.1, 42.5) for automatically switching from one mode to the other, **char-
acterized in that** the receiver (12; 22; 32; 42) comprises a photon count-
ing sensor (12.1; 22.1; 32.1; 42.1, 42.2) with at least one avalanche diode,
which receiver (12; 22; 32; 42) is switched from the photon counting sen-
25 sor to an analogue detection sensor as soon as a specified threshold level of
the measured light intensity is reached.
16. Method to operate in a system (10; 20; 30) that is equipped with an emitter
(11; 21; 31) for at least partial optical scanning of samples (P, 33.1) and
30 with a receiver (12; 22; 32; 42) for receiving optical signals sent or excited
by the emitter (11; 21; 31) and/or a sample (P, 33.1), wherein the receiver
(12; 22; 32; 42) is operated in a photon counting mode and in an analogue
detection mode, the system (10; 20; 30) comprising a switching means

(42.1, 42.5) for automatically switching from one mode to the other, **characterized in that** the system (10; 20; 30) comprises a fluorescence detection device and imaging means (15; 25), wherein images are provided from signals that have been acquired in the photon counting mode and/or in the analogue detection mode.

17. The method of claim 15 or 16, **characterized in that** the photon counting mode is only applied to optical signals with an intensity that is below the specified threshold level, in order to protect from overexposure at least one avalanche diode that is incorporated into the receiver (12; 22; 32; 42).

18. The method of one of claims 15 to 17, **characterized in that** the switching means (42.1, 42.5) selects the photon counting signal, or the analogue detection signal, or a combination of these signals provided by two simultaneously operated sensors, according to the actual light intensity in the receiver.

19. The method of claim 18, **characterized in that** only the photon counting signal is selected below a first specified threshold; only the analogue detection signal is selected above a second specified threshold; and a combination of these signals is selected between the two thresholds.

20. The method of claims 15 to 19, **characterized in that** the photon counting mode is applied to optical signals that are in the red and/or near infrared wavelength range.

21. The method according to any one of claims 15 to 19, **characterized in that** the analogue detection mode is applied to optical signals with an intensity that is above the threshold value.

22. System (30) with an emitter (31) for at least partial optical scanning of samples (P, 33.1) and with a receiver (32; 42) for receiving optical signals sent or excited by the emitter (31) and/or a sample (P, 33.1), whereby the

receiver (32; 42) comprises a photon counting sensor (32.1; 42.1, 42.2) that operates in a photon counting mode, **characterized in that** the receiver (32; 42) comprises:

- (a) at least two avalanche diodes that are simultaneously operated,
5 wherein each one of the avalanche diodes is individually protected from overexposure by an electronics circuit and/or a software algorithm;
- (b) a beam splitting element (32.4), which un-symmetrically splits a light beam (L1) that arrives from a sample (P, 33.1) into at least two light beams (L2, L3, etc.), which individually are directed to one of the parallel sensing avalanche diodes; and
10
- (c) a processing system (25) for the production of information from signals that arrive from the at least two avalanche diodes.

23. The system of claim 22, **characterized in that** the protecting means is implemented as an electronics circuit in one or more drivers for the avalanche diodes.
15

24. The system of claim 22 or 23, **characterized in that** the beam splitting element (32.4) is implemented as a cascade mirror that defines the transmission/reflection ratio of the light beams (L1, L2, L3, etc.).
20

25. Method to operate a system (30) that is equipped with an emitter (11; 21; 31) for at least partial optical scanning of samples (P, 33.1) and with a receiver (12; 22; 32; 42) for receiving optical signals sent or excited by the emitter (11; 21; 31) and/or a sample (P, 33.1), wherein the receiver (12; 22; 32; 42) is operated in a photon counting mode, **characterized in that** the method comprises:
25

- (a) simultaneously operating at least two avalanche diodes of the receiver (32; 42), while individually protecting each one of the avalanche diodes from overexposure by an electronics circuit and/or a software algorithm;
30

- (b) splitting a light beam (L1) that arrives from a sample (P, 33.1) into at least two light beams (L2, L3, etc.) with a beam splitting element (32.4), which splitting is preformed un-symmetrically;
 - (c) individually directing the at least two light beams (L2, L3, etc.) to one of the parallel sensing avalanche diodes;
 - (d) processing of signals that arrive from the at least two avalanche diodes in a processing system (25); and
 - (e) producing information from these signals.
- 10 26. The method of claim 25, **characterized in that** the beam splitting element (32.4) defines a static cascade, which is splitting the light beams (L1, L2, L3, etc.).
- 15 27. The method of claim 25 or 26, **characterized in that** a software selects the appropriate avalanche diode on the base of the incoming signals or on the base of status signals individually established for each one of the avalanche diodes and sent to the processing system (25) by each diode itself or by one or more drivers dedicated to the diodes.
- 20 28. The method of one of claims 25 to 27, **characterized in that** the information produced by the processing system (25) is provided to a data processing system.

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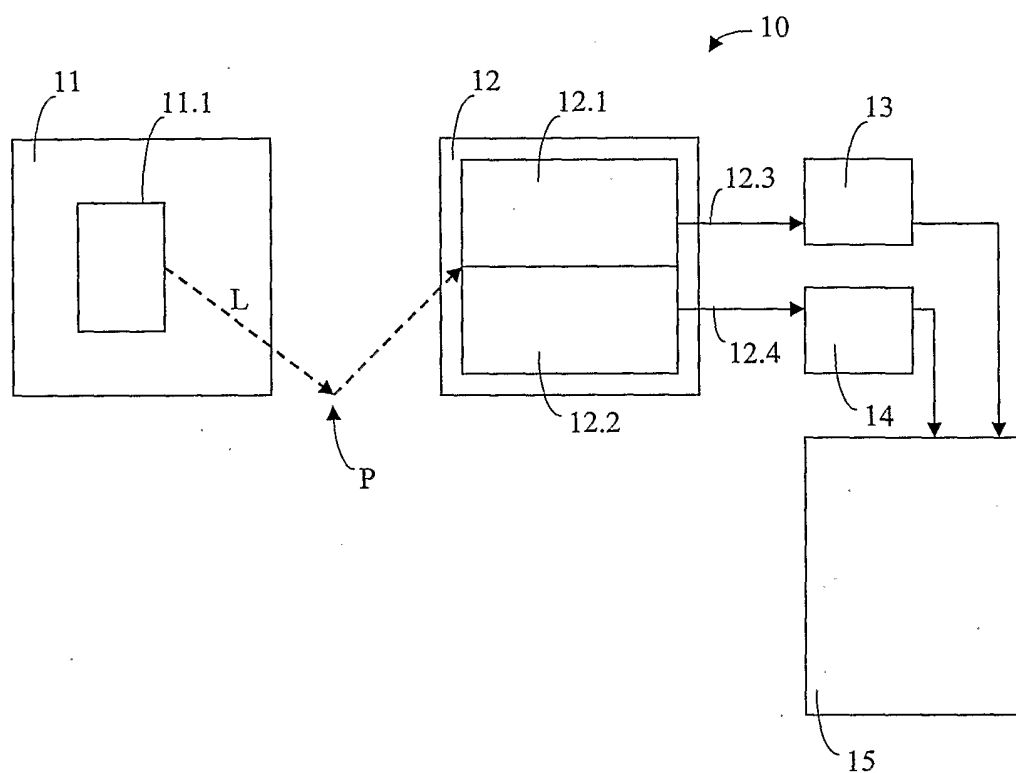


FIG. 1

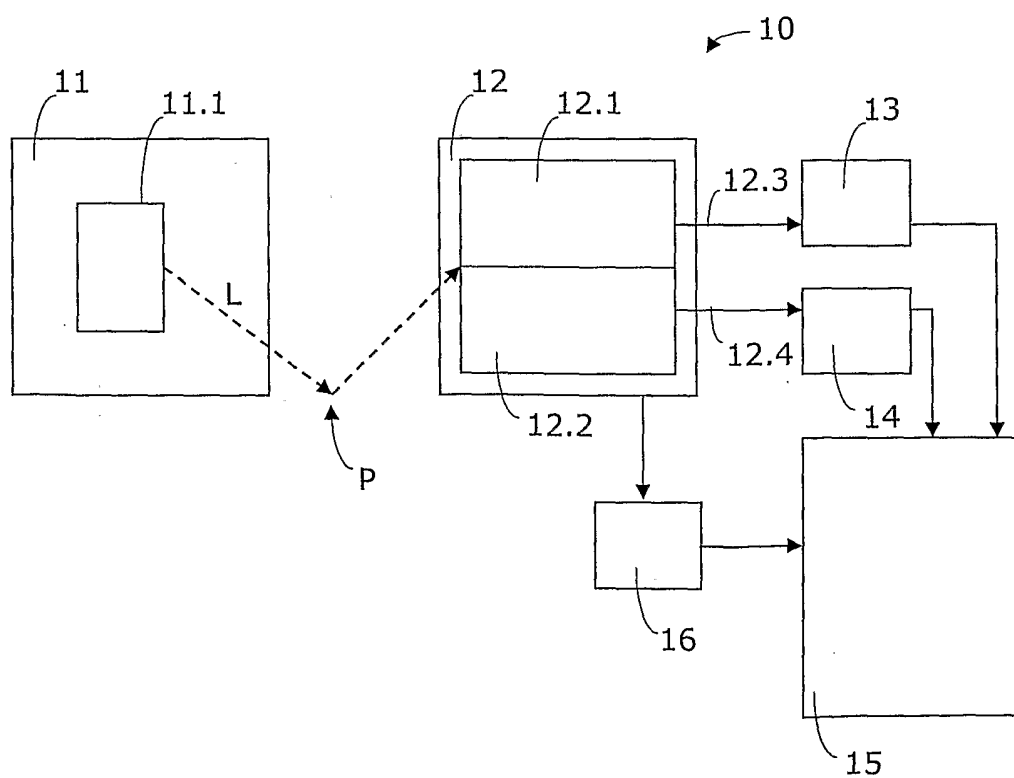


FIG. 2

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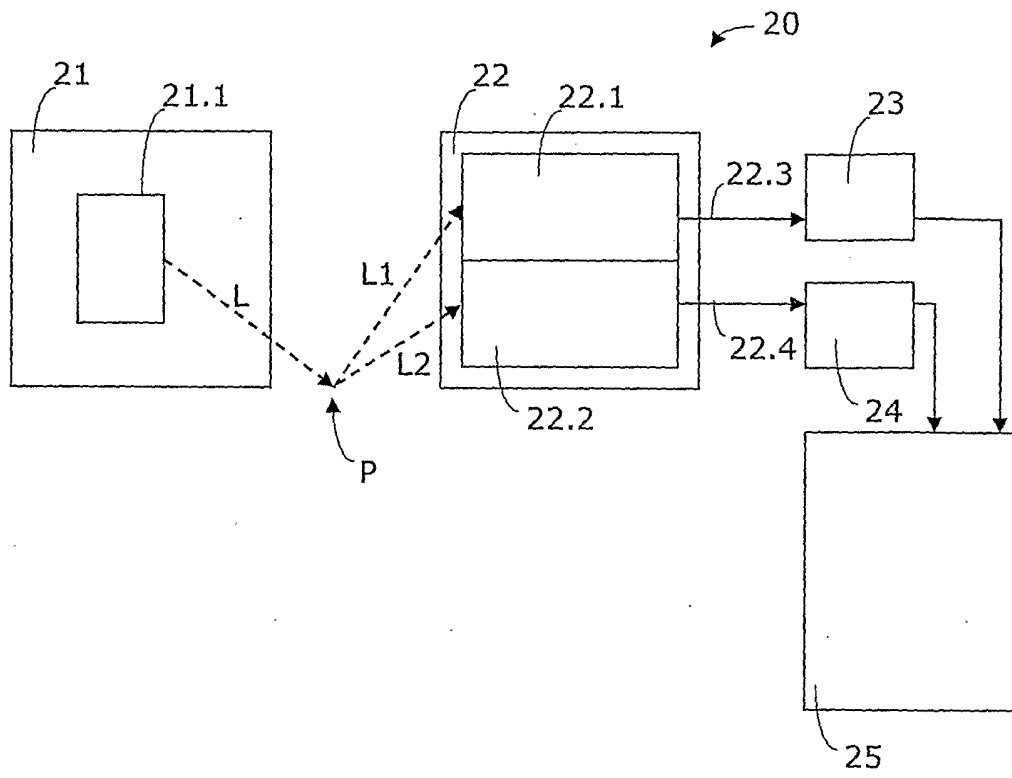


FIG. 3

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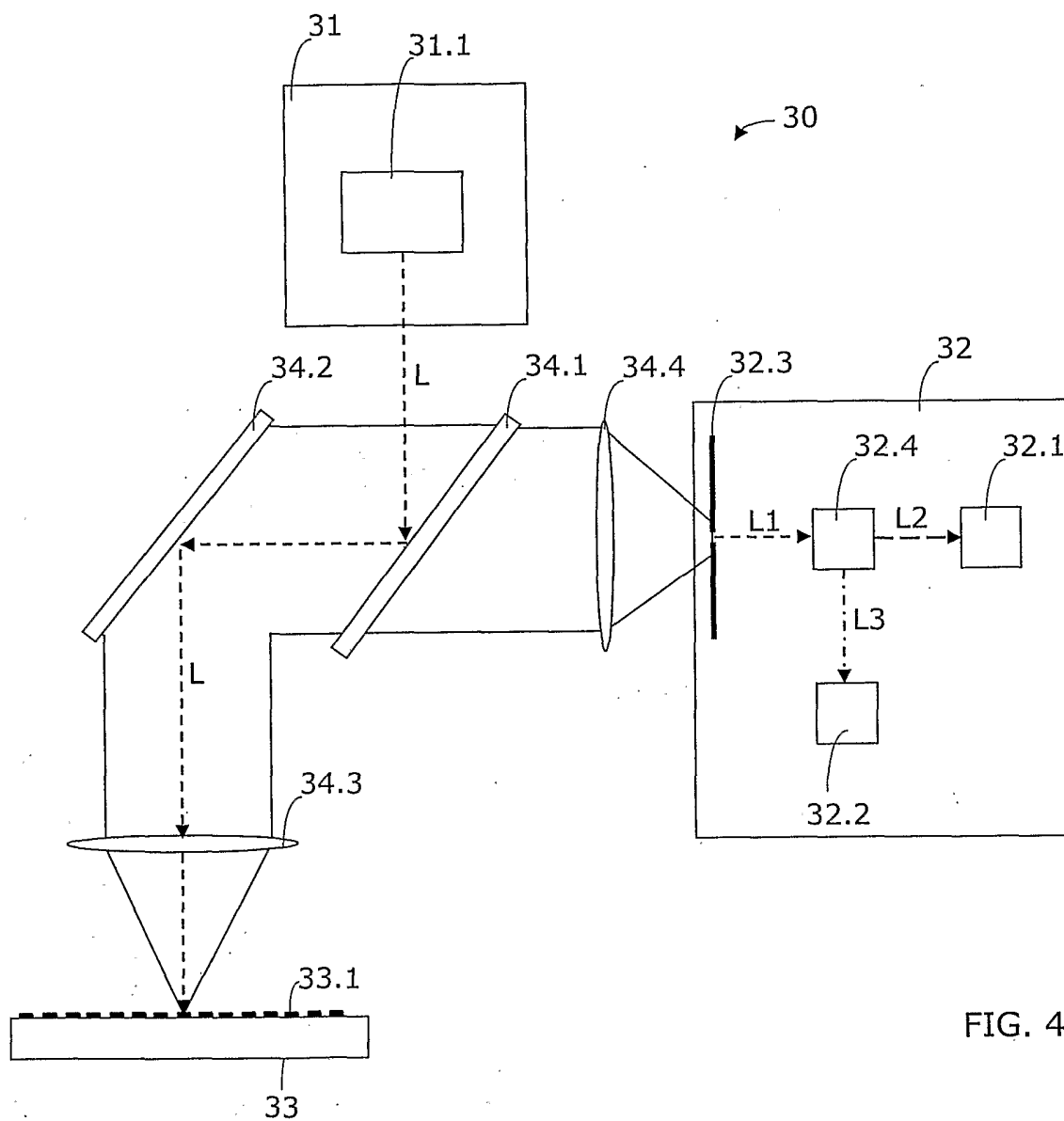


FIG. 4

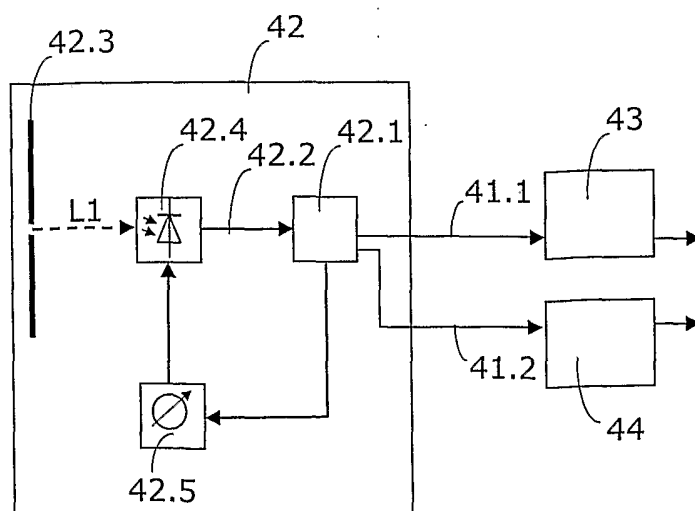


FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH2005/000571

A. CLASSIFICATION OF SUBJECT MATTER

G01J1/42

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)
G01J 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, PAJ, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/42817 A (LJL BIOSYSTEMS, INC; MODLIN, DOUGLAS, N; STUMBO, DAVID, P; STELLMACHER) 26 August 1999 (1999-08-26) page 8, line 18 - page 15, line 26 page 19, line 18 - page 22, line 12 page 27, line 18 - page 29, line 4 figure 9	1-21
X	GB 2 390 900 A (* AGILENT TECHNOLOGIES INC) 21 January 2004 (2004-01-21) the whole document	22-28
A	US 6 188 473 B1 (LEISTNER HERMANN ET AL) 13 February 2001 (2001-02-13) column 1, line 55 - column 2, line 20 column 3, lines 25-37 column 6, line 24 - line 36	1-21
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

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

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- *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.
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Date of the actual completion of the international search

15 December 2005

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28/12/2005

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH2005/000571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/076924 A1 (MARIO ARTHUR W ET AL) 24 April 2003 (2003-04-24) paragraphs '0025! - '0036! -----	1-28
A	US 5 136 373 A (KAMIYA ET AL) 4 August 1992 (1992-08-04) the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH2005/000571

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US 2003076924	A1	24-04-2003	US	2005089140 A1	28-04-2005
US 5136373	A	04-08-1992	NONE		