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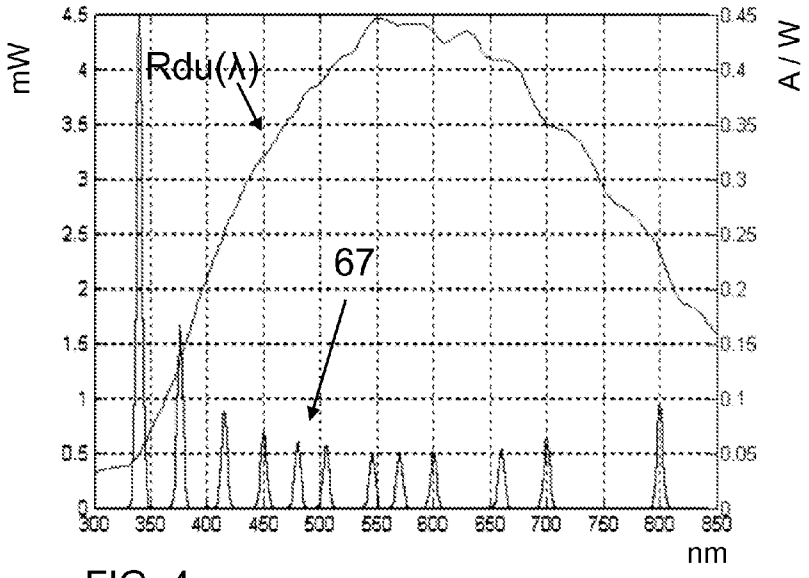

FIG. 4a

(57) Abstract: The present invention refers to an optical device (100) for determining the presence and/or concentration of analytes in a sample (10), the optical device comprising a detection unit (50) comprising optical path components and a detector (70), said detection unit (50) having wavelength-dependent responsivity, the optical device further comprising a light source (60) for emitting light of different respective usable wavelength ranges, wherein light from the light source is guided through the optical path (51) to the detector (70) to generate baseline signals and response signals relative to said baseline signal indicative of the presence and/or concentration of analytes in a sample (10) being located in the optical path, characterized in that the intensity of the light reaching the detector (70) is being adjusted in a manner reciprocal to the wavelength-dependent responsivity of the detection unit (50) with respect to at least two respective usable wavelength ranges so that a reduction of at least 50 % of the ratio between the maximum baseline signal at one of the selected usable wavelength ranges and the minimum baseline signal at another of the selected usable wavelength ranges is obtained.

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Increase of usable dynamic range in photometry

FIELD OF THE INVENTION

The present invention is in the field of optical devices for determining the presence and/or concentration of analytes in a sample, comprising a detection unit having a wavelength-dependent responsivity. The present invention refers in particular to optical devices and methods for compensating said wavelength-dependent responsivity of the detection unit.

BACKGROUND OF THE INVENTION

Several analyzers used in the analysis of samples, such as biological samples, comprise a light source to illuminate the sample and a photodetector to perform a photometric measurement. In clinical chemistry analyzers, for example, optical transmission through a cuvette containing a liquid sample is measured. The results are used to generate extinction data, which is the ratio between light intensity input and output through the sample. Optical extinction can be caused either by absorption or by scattering of the light in the sample. Both processes lead to a measurable extinction. In this way, the presence and/or concentration of analytes in a sample, which may be indicative of a diagnostic condition, can be determined by measuring response signals of the detector, typically at usable wavelengths. These are wavelengths at which the type of analytes being determined are typically absorbing or scattering light so that the smaller variations can be detected.

Typically, photodiodes are used as detectors due to their linearity of output current as a function of incident light, low noise, compact size and light weight, long lifetime, high quantum efficiency, and lower cost compared to photomultipliers. On the other side, the overall sensitivity of photodiodes compared to photomultipliers is lower, their area is small, there is no internal gain and the response time is usually slower. Thus, photodiode arrays are more typically used in order to allow higher speed parallel read out.

The material chosen to manufacture photodetectors operative in the visible wavelength range is normally silicon. Silicon is capable of generating significant photocurrent in a wavelength range comprised between about 190 and about 1100 nanometers, which is a usable range for the analysis of biological samples.

The response of a silicon-based photodetector versus wavelength of the incident light is however variable. In other words, the responsivity of said photodectors is wavelength dependent. This means that provided the same light power would be input into the photodetector for the whole wavelength range, the measured signal or baseline signal would vary over the wavelength range following a curve, which resembles the curve of the responsivity.

The responsivity is defined as the ratio of generated photocurrent (A) to incident light power (W), typically expressed in A/W (Ampere/Watt). The responsivity may also be expressed as quantum efficiency, or the ratio of the number of photogenerated carriers to incident photons.

A "baseline signal" is defined as the signal derived from the conversion of electro-magnetic energy guided from a light source to the detector through an optical path without passing through a sample or with a sample being replaced by a blank or reference solution. The baseline signal is therefore a function of the light source intensity and photodetector responsivity at different wavelengths. In other terms, the baseline signal at each selected usable wavelength range may be defined as a blank signal, any deviation from which is to be interpreted as an attenuation of signal caused by analytes present in the sample.

Moreover, it is not only the photodector, which has a wavelength-dependent responsivity. Most of the components, which may be part of an optical path, such as lenses and dispersion elements have different properties at different wavelengths, so that the overall baseline signal is a function of several components used in a detection unit.

The wavelength-dependent responsivity is an inherent property of a detection unit, that means of the detector and at least some of the components of the optical path, typically all components which have an effect on the way light is transmitted, reflected, diffracted, refracted, scattered, etc… which may vary according to the wavelength used.

With reference to the detector, "inherent property" refers to the material inherent property, e.g. to the silicon wavelength-dependent responsivity of silicon-based detectors, which generate variable photocurrent in the wavelength range typical of the silicon material, as it is well known.

With reference to optical path components, the wavelength-dependent responsivity may be due to both material and form or geometry of the components, e.g. material and geometry of a lens, material and space resolution of a grating, etc... which, at parity of light source intensity, may cause light of different wavelengths to reach the detector with different intensity. In extreme cases it may even block or deviate wavelengths out of a certain range in a manner that light of those wavelengths never reaches the detector.

Also a sample container itself being placed in the optical path may have a wavelength-dependent responsivity. For example if glass or plastic cuvettes are used, it is known that these will absorb part of the radiation, e.g. in the ultraviolet range.

Also, currently used light sources, such as halogen lamps, have a variable intensity spectrum, which is lower at certain wavelengths, typically sloping down towards the ultraviolet and/or the infrared at the range boundaries and have a peak in the central part of the wavelength range, which is at about 700 nanometers.

Typically, in proximity of the boundaries of the range, especially in the UV range, where the relative intensity of the light source is lower also the responsivity of the detector is lower, while where the relative intensity of the light source is higher also the responsivity of the detector is higher. As a consequence, at parity of concentration, the response signal of an analyte being detected at a wavelength in proximity of the boundaries of the range may be too weak while the response signal of another analyte being detected at a wavelength where both the intensity of the light source and the responsivity of the detector are high may lead to signal saturation. For this reason the dynamic range for the measurement is limited as the baseline signal is typically set according to the usable wavelength where the relative intensity of the light source and the responsivity of the detector are lowest. This is done so that small concentrations of an analytes can be measured.

This however means that a very broad dynamic range for the detector is needed while the usable dynamic range is small. This in some cases may result in the need to dilute a sample being analyzed and repeat the measurement if the measured extinction was too high.

Photodiode arrays with a preamplifier for each pixel are normally used to best deal with this problem, at the expense however of complexity and cost. An alternative way would be to vary the integration time at different wavelengths but this method is not suitable when fast measurements are needed.

An object of the present invention is to provide an optical device, which is simple and cost efficient and which is less dependent on the dynamic range of the detector.

According to one embodiment of the invention this is achieved by providing a light source comprising a plurality of light emitting elements for emitting light of different respective usable wavelength ranges, wherein the intensity of at least some of the light emitting elements is being adjusted to compensate at least in part for the wavelength-dependent responsivity of the detection unit at least with respect to selected usable wavelengths. According to another embodiment this is achieved by providing at least one light regulator in the optical path to compensate at least in part for the wavelength-dependent responsivity of the detection unit at least with respect to selected usable wavelengths. According to another embodiment this is achieved by sequentially adjusting the intensity of the light source to compensate at least in part for the wavelength-dependent responsivity of the detection unit at least with respect to selected usable wavelengths.

An advantage of the present invention is the possibility to make nearly full use of the available dynamic range of the detector for the measurement, i.e. for determining the presence and/or concentration of analytes in a sample. Another advantage of the present invention is the possibility to use cheaper detectors such as CCD or CMOS type detectors. Another advantage is that while the dynamic range of the detector may be small, the usable dynamic range for detection may be maximized to nearly cover the full available dynamic range of the detector. Another advantage is that the need to dilute the sample and repeat the analysis if the measured signal was too high can be prevented.

Another advantage of the present invention is that it enables to reduce stray light in the optical device.

DESCRIPTION OF THE INVENTION

The present invention refers to an optical device for determining the presence and/or concentration of analytes in a sample, the optical device comprising a detection unit comprising optical path components and a detector, said detection unit having a wavelength-dependent responsivity. The optical device further comprises a light source comprising at least two light emitting elements for emitting light of different respective usable wavelength ranges. The optical device is set up such that light from the light source is guidable through an optical path to the detector to generate baseline signals at said respective usable wavelength ranges and to generate response signals relative to said baseline signals when a sample is located in the optical path, said response signals being indicative of the presence and/or concentration of analytes in the sample. The optical device is set up such that the intensity of at least a first and a second light emitting elements is inverse to the wavelength-dependent responsivity of the detection unit with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first usable wavelength range than at said second usable wavelength range, so that the ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range, preferably 50% or less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range

According to another embodiment, the optical device comprises a detection unit comprising optical path components and a detector, said detection unit having a wavelength-dependent responsivity. The optical device further comprises at least one light source for emitting light in usable wavelength ranges. The optical device is set up such that light from the light source is guidable through an optical path to the detector to generate baseline signals in said usable wavelength range and response signals relative to said baseline signals when a sample is located in the optical path, said response signals being indicative of the presence and/or concentration of analytes in the sample. The optical device further comprises at least one light regulator located in the optical path to compensate the wavelength-dependent responsivity of the detection unit with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first wavelength range than at said second usable wavelength range, so that the ratio between the first baseline signal at the first usable wavelength

range and the baseline signal at the second usable wavelength range is is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range, preferably 50% or less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range.

According to the present invention an "optical device" is either a self-standing instrument or an integrated component within an analyzer or a module within an analytical system, suitable for the optical analysis of analytes present in a sample and particularly for measuring the optical transmission through a sample.

The optical device is particularly suitable for analyzing biological samples. Samples are preferably liquid solutions in which one or more analytes of interest can be potentially found, such as body fluids like blood, serum, plasma, urine, milk, saliva, cerebrospinal fluid, etc... Samples may be analyzed as such or after being diluted with another solution or after having being mixed with reagents e.g. to carry out one or more diagnostic assays like e.g. clinical chemistry assays and immunoassays. Thus the optical device may advantageously be used to detect the result of a chemical or biological reaction or to monitor the progress of a chemical or biological reaction, e.g. in a coagulation assay, agglutination assay, turbidimetric assay. Other diagnostic assays include for example the qualitative and/or quantitative analysis of analytes such as albumin, ALP, Alanine Aminotransferase, Ammonia, Amylase, Aspartat Aminotransferase, Bicarbonate, Bilirubin, Calcium, Cardiac Markers, Cholesterol, Creatinine Kinase, D-Dimer, Ethanol, g-Glutamyltransferase, Glucose, HBA1c, HDL-Cholesterol, Iron, Lactate, Lactate Dehydrogenase, LDL-Cholesterol, Lipase, Magnesium, Phosphorus inorganic, Potassium, Sodium, Total Protein, Triglycerides, UREA, Uric Acid. The list is of course not exhaustive.

The "detection unit" is hereby defined as a system within the optical device comprising optical path components and a detector, which make it possible to guide light through a sample in a controlled manner and to measure optical transmission, such as absorption and/or scattering or reflection. The detection unit may be however configured to carry out any other spectroscopic measurement. It may also entail temporally static measurements, time resolved measurements, or both.

The optical path may comprise components such as lenses, mirrors, apertures, filters, a shutter, a heat shield, fiber optics, a dispersion element, etc… A dispersion element may be a transmission or reflection diffraction grating, and may be a scanning monochromator or a polychromator, which is configured to receive transmitted light and disperse it into multiple spectral components. A dispersion element may be also a refractive element, such as a prism.

A "detector" according to the present invention is an optical detector or photodetector, which is a device that converts electro-magnetic energy into an electrical signal, including both single element and multi-element or array optical detectors. Thus an optical detector is a device capable of monitoring an optical electro-magnetic signal and providing an electrical output signal or response signal relative to a baseline signal indicative of the presence and/or concentration of an analyte in a sample being located in the optical path. Such devices include, for example, photodiodes, including avalanche photodiodes, phototransistors, photoconductive detectors, linear sensor arrays, CCD detectors, CMOS optical detectors, including CMOS array detectors, photomultipliers, and photomultiplier arrays. According to certain embodiments, an optical detector, such as a photodiode or photomultiplier, may contain additional signal conditioning or processing electronics. For example, an optical detector may include at least one pre-amplifier, electronic filter, or integrating circuit. Suitable pre-preamplifiers include integrating, transimpedance, and current gain (current mirror) pre-amplifiers. According to a preferred embodiment, the detector is of the CCD or CMOS type. According to another embodiment the detector is of the photodiode or PMT type.

A light source according to the invention is a unit within the optical device comprising at least one light emitting element capable of emitting usable light. The term "usable" refers to a selected wavelength or wavelengths or to a wavelength range or ranges within a broader wavelength range, at which wavelength(s), light guided through a sample can be used to measure with sufficient sensitivity small variations in analyte concentrations present in a sample and/or minimum concentrations relative to a baseline signal. Of course, the at least one light emitting element may emit light in a non-usable range as far as it emits light in at least one usable range. Also, the term usable has to be intended as a relative term, in the sense that a certain wavelength range may be usable to measure one or a group of analytes, while for other analytes it may be less usable, which means that it could still be used also for other analytes if a loss of sensitivity is

accepted. On the other hand if optimal measurement conditions are required a different usable wavelength range would need to be selected.

The term "wavelength range" has also to be interpreted in a broad manner including both narrow ranges, e.g. of a few nanometers, e.g. 2-20 nanometers, and broader ranges, e.g. of 20-100 nanometer or more. It is also to be understood that ranges may be at least in part overlapping.

A "light emitting element" is an electric powered radiation source such as an incandescent lamp, an electroluminescent lamp, a gas discharge lamp, a high-intensity discharge lamp, a laser.

According to one embodiment the at least one light emitting element is for example a halogen lamp, which like all incandescent light bulbs, produces a continuous broad spectrum of light, from near ultraviolet to deep into the infrared.

According to a preferred embodiment the at least one light emitting element is a light emitting diode. The term "light emitting diode" or "LED" is used herein to refer to conventional light-emitting diodes, i.e., inorganic semiconductor diodes that convert applied electrical energy to light. Such conventional LEDs include, for example, aluminum gallium arsenide (AlGaAs), which generally produce red and infrared light, gallium aluminum phosphide, which generally produce green light, gallium arsenide/phosphide (GaAsP), which generally produce red, orange-red, orange, and yellow light, gallium nitride, which generally produce green, pure green (or emerald green), and blue light, gallium phosphide (GaP), which generally produce red, yellow and green light, zinc selenide (ZnSe), which generally produce blue light, indium gallium nitride (InGaN), which generally produce bluish-green and blue light, indium gallium aluminum phosphide, which generally produce orange-red, orange, yellow, and green light, silicon carbide (SiC), which generally produce blue light, diamond, which generally produce ultraviolet light, and silicon (Si), which are under development. LEDs are not limited to narrowband or monochromatic light LEDs; LEDs may also include broad band, multiple band, and generally white light LEDs.

The term LED is also used herein to refer to Organic Light Emitting Diode (OLED), that can be polymer-based or small-molecule-based (organic or inorganic), edge emitting diodes (ELED),

Thin Film Electroluminescent Devices (TFELD), Quantum dot based inorganic "organic LEDs," and phosphorescent OLED (PHOLED).

Thus, according to certain embodiments, the LED can be a standard semiconductor device, an organic LED, or an inorganic LED. Examples of organic LEDs are QDOT-based LEDs and a nanotube-based LEDs. The LED can be a stack of LED's such as a stack of organic LEDs or a stack of organic LED layers.

According to a preferred embodiment, the light source comprises a plurality of light emitting elements with different respective usable wavelengths or wavelength ranges. For example, the light source comprises a combination of two, three, or more LEDs, such as, having a first usable relatively short wavelength spectrum (e.g., UV-blue) LED, a second usable "redder" or longer wavelength spectrum LED, a third usable even redder or longer wavelength spectrum LED and so on up to eventually the infrared wavelengths depending on the number and type of usable wavelengths needed.

Each LED may be configured to generate e.g. between about 500 μW and about 1 W of emission energy. Alternatively or in combination, some LEDs of the array may be configured to generate a low emission energy, some a medium emission energy, some a high emission energy.

The light source may comprise a cooling device such as a heat sink or fan to take away the heat generated by the light emitting element(s) and to prevent fluctuations of illumination and/or spectral shifts.

The light source and the optical path components are so configured that light from the light source is guided through an optical path to the detector to generate baseline signals at said respective usable wavelength ranges and to generate response signals relative to said baseline signals when a sample is located in the optical path, said response signals being indicative of the presence and/or concentration of analytes in the sample. The sample may be located e.g. in a cuvette, flow-through cell, or the like, being located in the optical path.

According to certain embodiments, the optical device comprises a light mixing element consisting of light shaping and homogenizing optics, such as for example a mixing rod, for

homogenizing the light emitted by the plurality of light emitting elements and improving illumination uniformity before illuminating a sample being located in the optical path.

The light mixing element may be a component of the optical path or of the light source.

According to one aspect of the invention the light source comprises a plurality of light emitting elements, e.g. at least two light emitting elements. In particular, the intensity of at least a first light emitting element and a second light emitting element is being adjusted in a manner inverse to the wavelength-dependent responsivity of the detection unit with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first usable wavelength range than at said second usable wavelength range. In this way, a ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is obtained, which is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range.

In mathematical terms the baseline signal $BL(\lambda)$ is the spectrum of the light source $S(\lambda)$ as a function of the wavelength λ, times the detector responsivity $Rd(\lambda)$, which is also a function of the wavelength λ, times the optical path responsivity $Rop(\lambda)$, which is also a function of the wavelength λ. The formula can thus be written as $BL(\lambda)= S(\lambda)x\ Rd(\lambda)x\ Rop(\lambda)$. This can be abbreviated by as $BL(\lambda)= S(\lambda)x\ Rdu(\lambda)$ wherein $Rdu(\lambda)$ is the responsivity of the detection unit, which corresponds to $Rd(\lambda)x\ Rop(\lambda)$. $S(\lambda)$ is expressed in Watt (W). $Rdu(\lambda)$ is expressed in Ampere/Watt (A/W). $BL(\lambda)$ is thus expressed in Ampere (A), which is the current measured by the detector and converted into a baseline signal.

The level of the baseline signal is variable in a wavelength-dependent manner according to the above formula. This means that, in a set of selected usable wavelength ranges, there will be a wavelength range at which the baseline has a maximum level and one at which it has a minimum level. It is therefore possible to normalize the baseline signals at all selected usable wavelengths by dividing for the maximum baseline signal. Thus, the maximum baseline line will be given a 100% value, while all other will be expressed as a fraction or per cent of the maximum baseline signal. The ratio between maximum and the minimum baseline signal among the selected wavelength ranges defines the dynamic range of the baseline signal. If the light source S was not a function of the wavelength λ, that is if the light source was constant at all wavelengths, e.g. 1

W, then the spectrum of the baseline signal would match the responsivity curve of the detection unit Rdu(λ).

Adjusting the intensity of light emitting elements to compensate for the wavelength-dependent responsivity of the detection unit, in a manner inverse to the wavelength-dependent responsivity of the detection unit, means that the light source is being configured such that individual light emitting elements emit light with an intensity, which is higher where the responsivity of the detection unit is lower and is lower where the responsivity of the detection unit is higher respectively, at least with respect to selected usable wavelengths. This means that by selecting e.g. a first and a second wavelength range, λ1 and λ2 respectively, the responsivity of the detection unit being higher at said first usable wavelength range than at said second usable wavelength range, i.e. Rdu(λ1) > Rdu(λ2), the intensity of a light source S(λ2), i.e. of a second light emitting element emitting light in that second wavelength range is being increased compared to the intensity of a first light source S(λ1), i.e. of a first light emitting element emitting light in said first wavelength range. In particular, the formula for λ1 is BL(λ1)= S(λ1)x Rdu(λ1). The formula for λ2 is BL(λ2)= S(λ2)x Rdu(λ2). The relation between λ1 and λ2 is given by the formula BL(λ1)/ BL(λ2)= S(λ1)/ S(λ2)x Rdu(λ1)/ Rdu(λ2). If S(λ1) was equal to S(λ2) then the ratio between BL(λ1) and BL(λ2) would be equal to the ratio between Rdu(λ1) and Rdu(λ2).

Obtaining a ratio between a first baseline signal at a first usable wavelength range and a baseline signal at a second usable wavelength range, which is e.g. 50% or less of the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range, means adjusting the intensity of a second light emitting element S(λ2) relative to that of a first light emitting element S(λ1) such that BL(λ1)/ BL(λ2) x Rdu(λ2)/Rdu(λ1) is 0.5 or less, preferably less than 0.1 or 10%. By adjusting S(λ1) and S(λ2) inversely proportional to Rdu(λ1) and Rdu(λ2) respectively, a baseline BL(λ1) is obtained for λ1, which is the same as the baseline BL(λ2) for λ2, i.e. BL(λ1)/ BL(λ2)= 1.

Preferably, S (λn) wherein λn stands for any selected wavelength range is adjusted so that the dynamic range of the baseline signal, which is the ratio between the maximum baseline signal BL(λmax) and the minimum baseline signal BL(λmin) among the selected wavelength ranges is reduced by at least 50%, preferably at least 90% up to 100% compared to a baseline generated by a light source, which is constant at all wavelength ranges. In other words BL(λmax)/ BL(λmin) x Rdu(λmin)/Rdu(λmax) is 0.5 or less, preferably less than 0.1. By adjusting S(λn)

inversely proportional to Rdu(λn), a baseline BL(λn) is obtained which is the same at any selected wavelength.

Adjusting the intensity of light emitting elements to compensate for the wavelength-dependent responsivity of the detection unit contributes also to minimize the often encountered and undesired problem of stray light. "Stray light" is defined as light in the optical device, particularly in the detection unit, which reaches the detector at wavelengths (λn) other than the one(s) intended. As a result, the base signal and/or the response signal generated by detector is not due only to light of wavelength λn as intended but also to light of wavelength other than λn, which is not intended, thus producing an error, i.e. a deviation from the correct signal, which biases the measurement. This error due to stray light is negligible as far as the signal due to the intended light is much larger than the signal due to stray light. However, where the responsivity of the detector is lower at an intended wavelength and higher at one or more wavelengths other that the intended wavelength, the error due to stray light may be significant. The effect of stray light may be even more severe when in addition to a lower responsivity at the intended wavelength compared to non-intended wavelengths, the intensity of the light of the intended wavelength is lower than that of light of non-intended wavelengths. Therefore compensating for the wavelength-dependent responsivity of the detection unit according to the invention reduces also possible errors due to stray light. According to one embodiment, at least for one or more wavelengths where the stray light problem is more significant, the intensity of the respective light emitting elements is further adjusted, i.e. further increased compared to the intensity of the other light emitting elements emitting light in other usable wavelength ranges and/or the intensity of the light emitting elements emitting light in the other usable wavelength ranges may be further decreased. This means that, by selecting e.g. a first and a second wavelength range, λ1 and λ2 respectively, the responsivity of the detection unit being higher at said first usable wavelength range than at said second usable wavelength range, i.e. $Rdu(\lambda 1) > Rdu(\lambda 2)$, the intensity of the second light emitting element S(λ2) may be increased compared to the intensity of the first light emitting element S(λ1) and/or the intensity of the first light emitting element S(λ1) may be decreased compared to that of the second light emitting element S(λ2) such that $BL(\lambda 1)/ BL(\lambda 2) < 1$.

Adjusting the intensity of light emitting elements is achieved for example by varying the electrical power input for individual light emitting elements, e.g. by providing more electrical power input to the light emitting elements which emit light of usable wavelengths or wavelength ranges at which the responsivity of the detection unit is lower and optionally by providing less

electrical power input to the light emitting elements which emit light of usable wavelengths or wavelength ranges at which the responsivity of the detection unit is higher. It may be sufficient to adjust the intensity of only one light emitting element for a selected usable wavelength range, e.g. where the responsivity of the detection unit is lower. Typically, the closer the selected usable wavelength ranges are, the smaller is the difference in the value or level of the respective baseline signals, which means that it is less important to compensate for this difference. Thus adjusting the intensity of at least two light emitting elements has to be interpreted in a relative manner, which includes setting or fixing the intensity of a first light emitting element and adjusting the intensity of a second light-emitting element relative to the intensity of the first light emitting element, irrespective of whether the first light emitting element is used for that particular analysis. Alternatively, since the wavelength-dependent responsivity is an inherent property of the detection unit, different light emitting elements of respectively different energy power according to the emission wavelength can be used.

Depending on the nature of the light emitting elements, the number of the light emitting elements and the emission wavelengths, either a continuous broadband emission spectrum comprising usable wavelengths or discrete narrow emission spectra comprising selected usable wavelengths can be generated. Consequently also the baseline signal may be either continuous or discontinuous with signal zones for each of the selected usable wavelengths and gaps in between. The light source can be also configured such that only selected light emitting elements, e.g. those emitting light usable to detect selected analytes are turned on or used while the others may remain off.

Ideally, a baseline signal for each of said selected usable wavelengths is obtained, which is nearly flat and/or nearly at the same level, wherein the dynamic range would be 1. In practice, however, any reduction in the baseline signal variation brings considerable advantages, since this increases of an equal amount the available dynamic range for the measurement.

The dynamic range of an analyte is defined as the range of concentrations, which are typical for that analyte in a sample. The dynamic range of the detector is defined as the ratio between the maximum detectable light at or near saturation and the lowest detectable light, which is typically limited by the noise level. The dynamic range of the baseline signal is defined as the ratio between the maximum baseline signal $BL(\lambda max)$ and the minimum baseline signal $BL(\lambda min)$ for a set of selected usable wavelength ranges. The available dynamic range for the measurement is the dynamic range which can be effectively used for detection, in other words the usable dynamic range. This is defined as the ratio between the maximum detectable change in

concentration of analyte and the minimum detectable change in concentration of analyte, which is limited by BL(λmin). The usable dynamic range is thus the dynamic range of the detector minus the dynamic range of the baseline signal. It is thus smaller than the dynamic range of the detector. The dynamic range of the analyte may thus exceed the available dynamic range for the measurement, meaning that the highest concentrations of analyte may not be measurable. That's why it is important to reduce the dynamic range of the baseline signal.

In order to get closer to the ideal status, electronic compensation on the detector side, e.g. by means of pre-amplifiers or electronic filters, can also be combined with the compensation of light intensities.

According to another embodiment, in order to compensate the wavelength-dependent responsivity of the detection unit at least with respect to selected usable wavelengths such that a ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is obtained, which is less than, preferably 50% or less of, the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range, at least one light regulator is being located in the optical path.

A light regulator is an optical element which enables to reduce the amount of light reaching the detector at least with respect to selected wavelengths. A light regulator may be for example a light filter or an obscuring object such as a slit or diaphragm.

The light filter may be a patterned filter, e.g. a hybrid filter comprising a multi-band filter over a patterned filter layer, or may comprise multiple filters, e.g. an array or stack of filters, for different wavelengths to compensate the wavelength-dependent responsivity of the detection unit at least with respect to selected usable wavelengths. This means that light is dimmed at those wavelengths where the responsivity of the detection unit is higher, that is in a manner inverse to the responsivity of the detection unit at least with respect to selected usable wavelengths.

The at least one light regulator may be mounted over the detector, e.g. covering at least in part the detector sensor surface. Alternatively the light regulator may be coupled to the light source to cover at least in part the at least one light emitting element, or be a component of the optical path.

The at least one light source may be a broadband light source, e.g. comprise one broadband light emitting element. The light source may however comprise a plurality of light emitting elements with narrow- or broad-band emissions.

The light regulator compensation may be combined with compensation of light intensities and/or with electronic compensation so that a baseline signal for each of said selected usable wavelengths is obtained with even less variation.

The present invention also refers to an analyzer for determining the presence and/or concentration of analytes in samples, the analyzer comprising said optical device. An analyzer according to the present invention is an apparatus assisting users with the detection, e.g. qualitative and/or quantitative optical evaluation of samples for diagnostic purpose. Examples of such an analyzer are: a clinical chemistry analyzer, a coagulation chemistry analyzer, an immunochemistry analyzer, a urine analyzer, either as self-standing instruments or modules within a system comprising a plurality of said modules, used to detect the result of chemical or biological reactions or to monitor the progress of chemical or biological reactions.

In particular, the analyzer may comprise units assisting with the pipetting, dosing, mixing of samples and/or reagents, units for loading and/or unloading and/or transporting and/or storing sample tubes or racks comprising sample tubes, units for loading and/or unloading and/or transporting and/or storing reagent containers or cassettes. The analyzer may also comprise identification units comprising sensors, e.g. barcode readers. Alternative technologies such as RFID may also be used for identification.

The pipetting unit may comprise a reusable washable needle, e.g. a steel needle, or disposable pipette tips. Typically, the pipetting unit is operatively coupled to an automated positioning device for moving the pipette tip or needle with respect to the analytical device and, e.g., may be mounted to a transfer head that can be moved in two directions of travel in a plane, e.g., by means of guiding rails and a third direction of travel orthogonal to the plane, e.g., by means of a spindle drive.

The analyzer may also comprise a cuvette handling unit for transporting cuvettes comprising samples, including reaction mixtures, to be analyzed into a detection position being located in the optical path of the detection unit. The cuvette handling unit may be embodied as a conveyor,

e.g. a linear or rotor like conveyor, moving in at least one direction or as a robotic arm capable of performing translation movements along one or more of possible orthogonal axis, driven by one or more electrical motors. According to one embodiment the cuvette handling unit comprises several cuvette sections for receiving and transporting at least one cuvette at a time into at least one detection position.

According to one embodiment, the optical path may comprise a plurality of detection positions to receive a plurality of cuvettes, for analyzing a plurality of samples in parallel.

According to one embodiment the analyzer comprises a plurality of optical devices.

The analyzer may further comprise incubation units for maintaining sample/reagent mixtures at a certain temperature during reaction, wash stations for washing pipette tips or needles, mixing paddles, etc…

The analyzer preferably comprises a controller for controlling the automated analysis of samples according to a predetermined process operation plan which, e.g., may be embodied as programmable logic controller running a computer-readable program provided with instructions to perform operations in accordance with the process operation plan.

The present invention also refers to a method for determining the presence and/or concentration of analytes in a sample, the method comprising the steps of

- guiding light from a light source comprising at least two light emitting elements for emitting light of different respective usable wavelength ranges to a detection unit comprising an optical path and a detector, said detection unit having a wavelength-dependent responsivity, such as to generate baseline signals at said respective usable wavelength ranges,

- adjusting the intensity of at least a first and a second light emitting elements in a manner inverse to the wavelength-dependent responsivity of the detection unit with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first wavelength range than at said second usable wavelength range, so that a ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is obtained, which is less than, preferably 50% or less of,

the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range,

- generating response signals relative to said baseline signals when a sample is located in the optical path and associating said response signals to the presence and/or concentration of analytes in the sample.

The term "relative to a baseline signal" is herein used to mean any deviations from the baseline signal due to the sample being analyzed, which can be either above or below the baseline signal, typically below as transmission values are recorded as extinction.

According to a preferred embodiment, adjusting the intensity of light emitting elements comprises the step of adjusting the level of the baseline signal so that the dynamic range of the detector comprises the dynamic range of the analyte concentrations being determined, at least with respect to selected usable wavelengths. This means that at least with respect to selected usable wavelengths, the light intensity of the light emitting elements emitting light at those wavelengths can be adjusted so that the baseline signal is near the saturation limit of the detector. In this way, the full dynamic range of the detector until the limit of detection of the detector can be used to determine the concentration of analytes without the need to eventually dilute the sample if the concentration of the analyte was too high. For example if a detector, e.g. a detector of the CCD or CMOS type is used, the dynamic range of this detector type is typically about 1000:1. If the intensity of the light emitting elements was not adjusted such as to compensate the wavelength-dependent responsivity of the detection unit, the available dynamic range for determining analyte concentrations throughout the usable wavelength range would be reduced below 4:1, since a considerable portion of this dynamic range is used up by the baseline, thus making this type of detectors not suitable for detecting changes in analyte concentrations which may be in the order of 1000:1. Thus, by compensating the wavelength-dependent responsivity of the detection unit, the usable dynamic range for measurement can be maximized by nearly covering the dynamic range of the detector, thus enabling the use of detectors with smaller dynamic range, which means the use of cheaper detectors. Of course detectors such as photodiode arrays and photomultiplier tubes may still be used, wherein the available dynamic range for the measurement would be even greater, thus enabling detection of analytes in a broader concentration range, without the need e.g. to dilute the sample for highly concentrated samples.

According to one embodiment, adjusting the level of the baseline signal is carried out in function of the type of sample or of type of analytes being determined, meaning that the baseline signal may be adjusted for individual usable wavelengths or ranges according to the analytes being detected and/or according to the expected dynamic range typical of samples and/or analytes present in the samples. It may be for example also possible to shift the baseline signal towards the central part of the detector dynamic range to be sufficiently far from the saturation limit and from the limit of detection of the detector in case low analyte concentrations or small concentration changes are expected. In other words it is possible not only to adjust the level of the baseline signal so that the dynamic range of the detector comprises the dynamic range of the analyte concentrations being determined, but also to place the baseline signal at an optimum level within this range, e.g. by centering the dynamic range of the analyte concentrations with respect to the center of the dynamic range of the detector, at least with respect to selected usable wavelengths.

The present invention also refers to a method for determining the presence and/or concentration of analytes in a sample, the method comprising the steps of

- guiding light from one light source for emitting light in usable wavelength ranges to a detection comprising an optical path and a detector, said detection unit having a wavelength-dependent responsivity, such as to generate baseline signals at said respective usable wavelength ranges,

- compensating the wavelength-dependent responsivity of the detection unit with respect to at least a first and a second usable wavelength ranges respectively by sequentially adjusting the intensity of the light source, so that a ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is obtained, which is less than, preferably 50% or less, of the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range,

- sequentially generating response signals relative to said baseline signals when a sample is located in the optical path and associating said response signals to the presence and/or concentration of analytes in the sample.

According to some embodiments the method comprises the step of compensating at least in part the wavelength-dependent responsivity of the detection unit at least with respect to selected

usable wavelengths by means of at least one light regulator being located in the optical path, that is by combining the compensation achieved by adjusting the intensity of the light source with the compensation achieved by a light regulator.

The present invention also refers to a method for determining the presence and/or concentration of analytes in a sample, the method comprising the steps of

- guiding light from at least one light source for emitting light in usable wavelength ranges to a detection unit comprising an optical path and a detector, said detection unit having a wavelength-dependent responsivity, such as to generate baseline signals at said respective usable wavelength ranges,

- compensating the wavelength-dependent responsivity of the detection unit with respect to at least a first and a second usable wavelength ranges respectively, by means of at least one light regulator being located in the optical path, the responsivity of the detection unit being higher at said first wavelength range than at said second usable wavelength range, so that a ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is obtained, which is less than, preferably 50% or less, of the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range,

- generating response signals relative to said baseline signals when a sample is located in the optical path and associating said response signals to the presence and/or concentration of analytes in the sample.

This means that compensation achieved by adjusting the intensity of the light source and/or with the compensation achieved by a light regulator can be still further combined with electronic compensation in order to achieve even lower variations of the baseline signal.

According to a preferred embodiment a ratio between the first baseline signal at the first usable wavelength range and the baseline signal at the second usable wavelength range is obtained, which is less than 10% of the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range.

Other and further objects, features and advantages of the invention will appear from the following description and accompanying drawings, which illustrate preferred embodiments and serve to explain the principles of the invention more in detail.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts schematically an optical device for determining the presence and/or concentration of analytes in a sample being located in the optical path according to certain embodiments of the invention.

FIG. 2 depicts schematically an optical device for determining the presence and/or concentration of analytes in a sample being located in the optical path according to other embodiments of the invention.

FIG. 3a depicts on the same graph the wavelength dependent responsivity typical of state of the art detection units as well as the wavelength dependent intensity typical of state of the art broad spectrum light sources, mimicked with a plurality of light emitting elements each emitting light in a usable wavelength range.

FIG. 3b depicts the state of the art baseline signal at each of the usable wavelength ranges of FIG. 3a as a function of the wavelength dependent responsivity of the detection unit and the intensity of the light source at that respective wavelength.

FIG. 4a depicts on the same graph the wavelength dependent responsivity of the detection unit as well as the intensity of light for each of a plurality of light emitting elements emitting light in respective usable wavelength ranges, wherein the intensity is being adjusted in a manner reciprocal to the wavelength-dependent responsivity of the detection unit.

FIG. 4b depicts the baseline signal at each of the usable wavelength ranges of FIG. 4a.

FIG. 4c shows in comparison to FIG. 4a one example of how the light intensity for each of the plurality of light emitting elements is adjusted in order to further reduce stray light effects at one usable wavelength range.

FIG. 4d shows how the baseline signals obtained according to the light intensities of FIG. 4c change when compared to those of FIG. 4b. FIG. 5 shows how a ratio between the first baseline

signal at a first usable wavelength range and the baseline signal at a second usable wavelength range, which is 50% of the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range is calculated.

FIG. 6a depicts schematically the typical state of the art relationship between the dynamic range of the detector, the dynamic range of the baseline and the dynamic range of the analyte concentrations.

FIG. 6b depicts schematically the relationship between the dynamic range of the detector, the dynamic range of the baseline and the dynamic range of the analyte concentrations after reducing the dynamic range of the baseline.

FIG. 1 depicts schematically an optical device 100 for determining the presence and/or concentration of analytes in a sample 10 comprised in an optical cuvette 20 being located in the optical path 51 of a detection unit 50. The detection unit 50 comprises optical path components such as lenses 52, apertures 53, mirrors 54, a shutter 55, and a diffraction grating 56, which is configured to receive light 67 transmitted through the sample 10 and disperse it into multiple spectral components 68. The detection unit 50 further comprises an optical detector 70, comprising an array optical sensor 71 such as CCD sensor, which converts electro-magnetic energy from light 68 into an electrical signal. The sensor 71 is divided in sectors, each of which dedicated to a usable wavelength range. The optical device 100 further comprises a light source 60 comprising an array of light emitting elements, in this case LEDs 61, for emitting light of different respective usable wavelength ranges, wherein light from the LEDs is mixed by a mixing rod 62 and guided through the optical path 51 to the detector 70 to generate a response signal relative to a baseline signal indicative of the presence and/or concentration of analytes in the sample 10. The light source further comprises a heat shield 63 to shield the heat from entering the detection unit 50, and a heat sink 64 heat sink to take away the heat generated by the LEDs 61. The direction of the light is indicated by arrows along the optical path 51.

The light source 60 is being configured such that the intensity of the light emitted by the individual LEDs 61 is being adjusted in a manner reciprocal to the wavelength-dependent responsivity of the detection unit 50 at those respective wavelengths, the wavelength-dependent responsivity depending both on the optical components and the detector sensor 71. By this compensation, a reduction of the ratio between the maximum baseline signal at one of the

selected usable wavelength ranges and the minimum baseline signal at another of the selected usable wavelength ranges is obtained. In other words a reduction of the baseline dynamic range is obtained.

FIG. 2 depicts schematically another optical device 200 for determining the presence and/or concentration of analytes in a sample 10 comprised in an optical cuvette 20 being located in the optical path 51 of the detection unit 50. Since most of the features of this embodiment are in common with that of FIG. 1, only the differences will be explained. In particular, the light source 60 comprises one light emitting element, in this example a halogen lamp, which emits light in a broad usable wavelength range. The optical device 200 also comprises a light regulator 72 being located in the optical path to compensate for the wavelength-dependent responsivity of the detection unit at least with respect to selected usable wavelength ranges. In this example, the light regulator 72 is a patterned obscuring filter extending over the surface of the detector sensor 71. The light regulator 72 dims the light reaching the sensor 71 at those wavelengths where the responsivity of the detection unit 50 is higher and with a degree inversely proportional to the responsivity of the detection unit 50 at least with respect to selected usable wavelengths.

The effect of compensating for the wavelength-dependent responsivity of the detection unit 50 is best understood by comparing FIG. 3a with FIG. 4a and FIG. 3b with FIG. 4b respectively.

The graph of FIG. 3a indicates on the left ordinate axis the intensity values of the light source in milliwatt (mW) at different wavelengths, and in particular at selected usable wavelength ranges (on the abscissa). Discrete light emissions 67 are obtained with a set of LEDs, each emitting light in a respective usable wavelength range, the resulting intensity spectrum being roughly equivalent to that emitted by a typical halogen broad spectrum lamp used in similar applications. The wavelength-dependent responsivity Rdu(λ) of a typical state of the art detection unit is indicated by curve Rdu(λ) with reference to the ordinate axis on the right, wherein the unit is Ampere per Watt (A/W).

FIG. 3b depicts the normalized baseline signals 90, indicated in percent (%), obtained at each of the usable wavelength ranges of FIG. 3a according to the formula $BL(\lambda) = S(\lambda) \times Rdu(\lambda)$. The term normalized here means that the maximum baseline signal is given a relative value of 100% and all other baseline signals are expressed as a fraction or % of this relative value. It can be seen that the baseline signal 92 at 340 nm is only 0.3% of the baseline signal 91 at 660 nm (100 %)

representing the minimum and maximum baseline signal respectively in this range of selected usable wavelengths. The dynamic range of the baseline is in this case 330:1.

When comparing FIG. 4a with FIG. 3a the difference is that the intensity of the light emissions 67 of the individual LEDs 61 is being adjusted in a manner reciprocal to the wavelength-dependent responsivity Rdu(λ) of the detection unit 50.

FIG. 4b depicts the normalized baseline signals 90, indicated in percent (%), obtained at each of the usable wavelength ranges of FIG. 4a according to the formula BL(λ)= S(λ)x Rdu(λ). In comparison with FIG. 3b, it can be seen that a baseline signal 90 is obtained, which is the same at each of said selected usable wavelengths. The dynamic range of the baseline has now been reduced to 1:1.

FIG. 4c shows for comparison the same wavelength dependent responsivity of the detection unit Rdu(λ) as well as the same intensity of light emissions 67 (dashed lines) for each of a plurality of light emitting elements emitting light in respective usable wavelength ranges as shown in FIG. 4a. In addition, on the same graph, FIG. 4c shows with continuous lines one example of how the intensity of the light emissions 67 for each of the plurality of the light emitting elements is adjusted in order to further reduce stray light effects at one usable wavelength range, in this case at 340 nm. In particular, it can be noted that the intensity of the light emitting element at 340 nm is higher than as in FIG. 4a, while all others are proportionally lower than as in FIG. 4a.

This difference in light intensity causes a difference in the baseline signals 90 as shown in FIG. 4d when compared to FIG. 4b. The dynamic range of the baseline is in this case still 1:1 if the first wavelength range at 340 nm is not taken into account. It is slightly larger if also the first wavelength range is taken into account, but nevertheless smaller if compared to that of FIG. 3b. This minor increase of dynamic range for one or more usable wavelength ranges may be acceptable when the advantage of reduced stray light is considered.

FIG. 5 depicts the normalized baseline signals 90, indicated in percent (%), obtained at each of the usable wavelength ranges as in FIG. 3a and 4a according to the formula BL(λ)= S(λ)x Rdu(λ) and assuming that the intensity of the light source was constant at all wavelenghts. The baseline signals thus fit with the responsivity curve of the detection unit Rdu(λ). It can be seen that the baseline signal 92 at 340 nm is only 11% of the baseline signal 91 at 550 nm (100 %) representing the minimum and maximum baseline signal respectively in this range of selected

usable wavelengths. In this case 11% is also the ratio between Rdu at 550 nm and Rdu at 340 nm. By increasing the intensity of the light emitting element in the range of 340 nm so that the minimum baseline signal 92 becomes 22% of the maximum baseline signal at 550 nm, the ratio between the maximum baseline signal and the minimum baseline signal is 50% of the ratio between the responsivity of the detection unit at 550 nm and the responsivity of the detection unit at 340 nm.

FIG. 6a depicts schematically the typical state of the art relationship between the dynamic range AC of the detector (between lines A and C), the dynamic range AB of the baseline (between lines A and B), and the dynamic range BD of the analyte concentrations (between lines B and D). It can be seen that a considerable part of the dynamic range AC of the detector is used up by the baseline, thus reducing the dynamic range of the detector from AC to BC (between lines B and C). BC can be also defined as the usable dynamic range, or the dynamic range, which is really available for the measurement of analyte concentrations. If the dynamic range BD of the analyte concentrations exceeds the usable dynamic range BC of the detector, signal saturation may occur and the measurement needs to be repeated after diluting the sample. In alternative more complex and expensive detectors with a broader dynamic range may be used.

FIG. 6b depicts schematically the effect of reducing the dynamic range AB' of the baseline signal (between lines A and B') according to any of the embodiments of the invention. In particular, it can be seen that the usable dynamic range B'C of the detector (between lines B' and C) is accordingly increased. The dynamic range B'D' of the analyte concentrations (between lines B' and D') remains the same as BD in FIG. 6a but the lines have shifted to be comprised within the dynamic range AC of the detector, which may also remain constant.

Obviously many modifications and variations of the present invention are possible in light of the above description. It is therefore to be understood, that within the scope of the appended claims, the invention may be practiced otherwise than as specifically devised.

Claims

1. Optical device (100) for determining the presence and/or concentration of analytes in a sample (10), the optical device (100) comprising

   - a detection unit (50) comprising optical path components and a detector (70), said detection unit (50) having a wavelength-dependent responsivity (Rdu(λ)),

   - a light source (60) comprising at least two light emitting elements (61) for emitting light (67) of different respective usable wavelength ranges, light from the light source (60) is guidable through an optical path (51) to the detector (70) to generate baseline signals (90, 91, 92) at said respective usable wavelength ranges and to generate response signals relative to said baseline signals (90, 91, 92) when a sample (10) is located in the optical path (51), said response signals being indicative of the presence and/or concentration of analytes in the sample (10),

   characterized in that the intensity (67) of at least a first and a second light emitting elements (61) is inverse to the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first usable wavelength range than at said second usable wavelength range, so that the ratio between the first baseline signal (91) at the first usable wavelength range and the baseline signal (92) at the second usable wavelength range is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range.

2. Optical device (100) according to claim 1 wherein the light source (60) comprises a plurality of light emitting diodes (61).

3. Optical device (200) for determining the presence and/or concentration of analytes in a sample (10), the optical device (200) comprising

   - a detection unit (50) comprising optical path components and a detector (70), said detection unit having a wavelength-dependent responsivity (Rdu(λ)),

   - at least one light source (60) for emitting light in usable wavelength ranges, wherein light (67) from the light source is guidable through an optical path (51) to

the detector (70) to generate baseline signals (90, 91, 92) in said usable wavelength range and response signals relative to said baseline signals (90, 91, 92) when a sample (10) is located in the optical path (51), said response signals being indicative of the presence and/or concentration of analytes in the sample (10),

at least one light regulator (72) being located in the optical path to compensate the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first wavelength range than at said second usable wavelength range, so that the ratio between the first baseline signal (91) at the first usable wavelength range and the baseline signal (92) at the second usable wavelength range is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range.

4. Optical device (200) according to claim 3 wherein the at least one light regulator (72) is a light filter or obscuring object.

5. Optical device (200) according to claim 3 or 4 wherein the light filter (72) is a patterned filter or comprises multiple filters for different wavelengths to compensate the wavelength-dependent responsivity (Rdu(λ)) of the detection unit at least with respect to selected usable wavelengths.

6. Optical device (100, 200) according to any of the preceding claims wherein the detector (70) is of the CCD or CMOS type.

7. Analyzer for determining the presence and/or concentration of analytes in a sample (10), the analyzer comprising an optical device (100, 200) according to any of the claims 1 to 6.

8. Method for determining the presence and/or concentration of analytes in a sample (10), the method comprising the steps of

- guiding light from a light source (60) comprising at least two light emitting elements (61) for emitting light (67) of different respective usable wavelength ranges to a detection unit (50) comprising an optical path (51) and a detector (70), said detection unit (50) having a wavelength-dependent responsivity (Rdu(λ)),

such as to generate baseline signals (90, 91, 92) at said respective usable wavelength ranges,

- adjusting the intensity (67) of at least a first and a second light emitting elements (61) in a manner reciprocal to the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) with respect to at least a first and a second usable wavelength ranges respectively, the responsivity of the detection unit being higher at said first wavelength range than at said second usable wavelength range, so that a ratio between the first baseline signal (91) at the first usable wavelength range and the baseline signal (92) at the second usable wavelength range is obtained, which is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range,

- generating response signals relative to said baseline signals (90, 91, 92) when a sample (10) is located in the optical path (51) and associating said response signals to the presence and/or concentration of analytes in the sample (10).

9. Method according to claim 8 wherein adjusting the intensity (67) of the light emitting elements comprises the step of adjusting the level of the baseline signal (90) at selected usable wavelength ranges so that the dynamic range (AC) of the detector comprises the dynamic range (B'D') of the analyte concentrations being determined.

10. Method according to claim 9 wherein adjusting the level of the baseline signal is carried out in function of the type of sample (10) or of type of analytes being determined.

11. Method for determining the presence and/or concentration of analytes in a sample (10), the method comprising the steps of

- guiding light from one light source (60) for emitting light in usable wavelength ranges to a detection unit (50) comprising an optical path (51) and a detector (70), said detection unit (50) having a wavelength-dependent responsivity (Rdu(λ)), such as to generate baseline signals (90, 91, 92) at said respective usable wavelength ranges,

- compensating the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) with respect to at least a first and a second usable wavelength ranges respectively by sequentially adjusting the intensity of the light source (60), so that a ratio between the first baseline signal (91) at the first usable wavelength range and the baseline signal (92) at the second usable wavelength range is obtained, which is less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range,

- sequentially generating response signals relative to said baseline signals (90, 91, 92) when a sample (10) is located in the optical path (51) and associating said response signals to the presence and/or concentration of analytes in the sample (10).

12. Method according to any of the claims 8 to 11 comprising the step of compensating at least in part the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) at least with respect to selected usable wavelengths by means of at least one light regulator (72) being located in the optical path (51).

13. Method for determining the presence and/or concentration of analytes in a sample (10), the method comprising the steps of

- guiding light from at least one light source (60) for emitting light (67) in usable wavelength ranges to a detection unit (50) comprising an optical path (51) and a detector (70), said detection unit (50) having a wavelength-dependent responsivity (Rdu(λ)), such as to generate baseline signals (90, 91, 92) at said respective usable wavelength ranges,

- compensating the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) with respect to at least a first and a second usable wavelength ranges respectively, by means of at least one light regulator (72) being located in the optical path (51), the responsivity of the detection unit being higher at said first wavelength range than at said second usable wavelength range, so that a ratio between the first baseline signal (91) at the first usable wavelength range and the baseline signal (92) at the second usable wavelength range is obtained, which is

less than the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range,

- generating response signals relative to said baseline signals (90, 91, 92) when a sample (10) is located in the optical path (51) and associating said response signals to the presence and/or concentration of analytes in the sample (10).

14. Method according to any of the claims 8 to 13 comprising the step of compensating at least in part the wavelength-dependent responsivity (Rdu(λ)) of the detection unit (50) at least with respect to selected usable wavelengths by means of preamplifiers or electronic filters.

15. Method according to any of the claims 8 to 14 wherein a ratio between the first baseline signal (91) at the first usable wavelength range and the baseline signal (92) at the second usable wavelength range is obtained, which is 50% or less of the ratio between the responsivity of the detection unit at the first usable wavelength range and the responsivity of the detection unit at the second usable wavelength range.

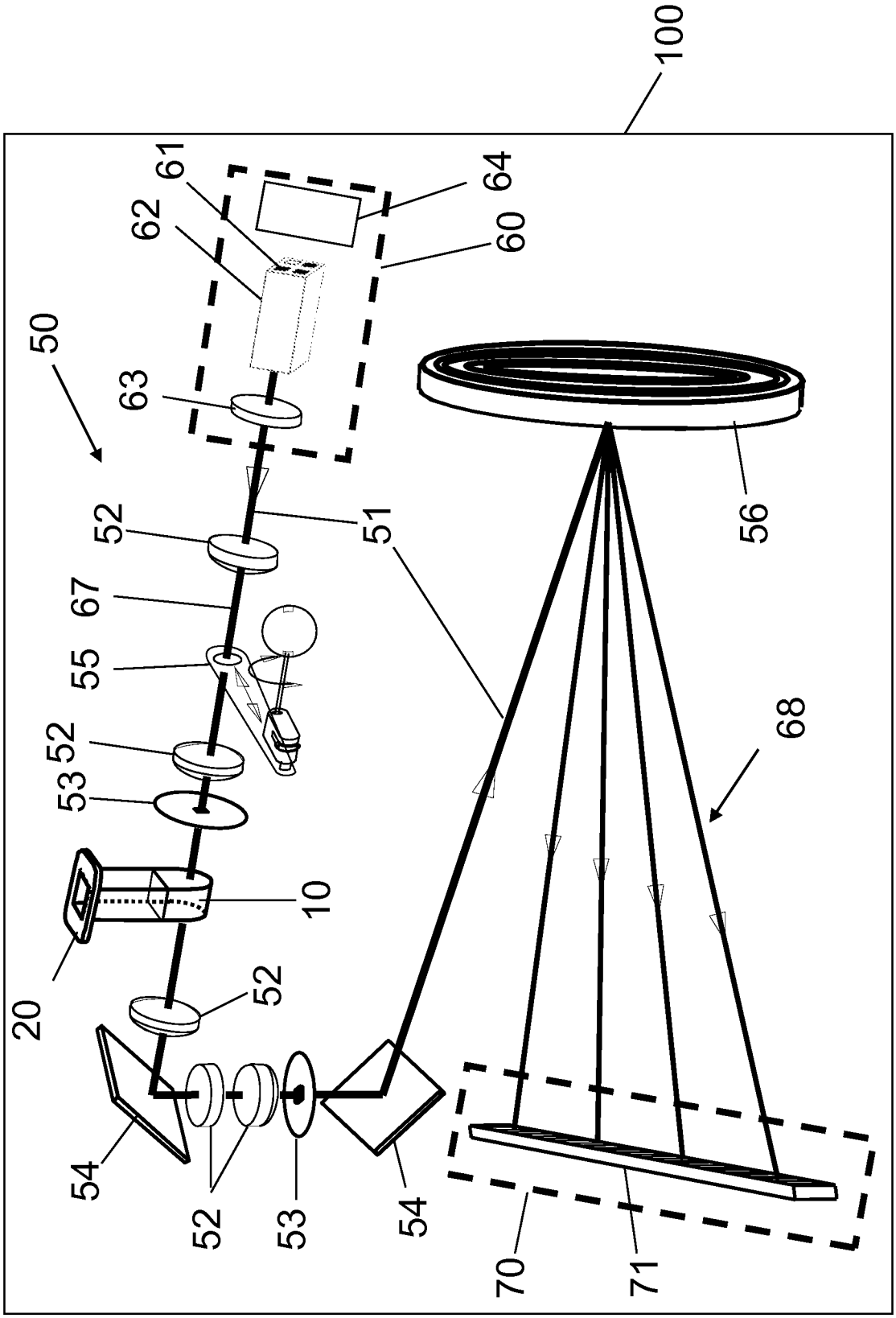
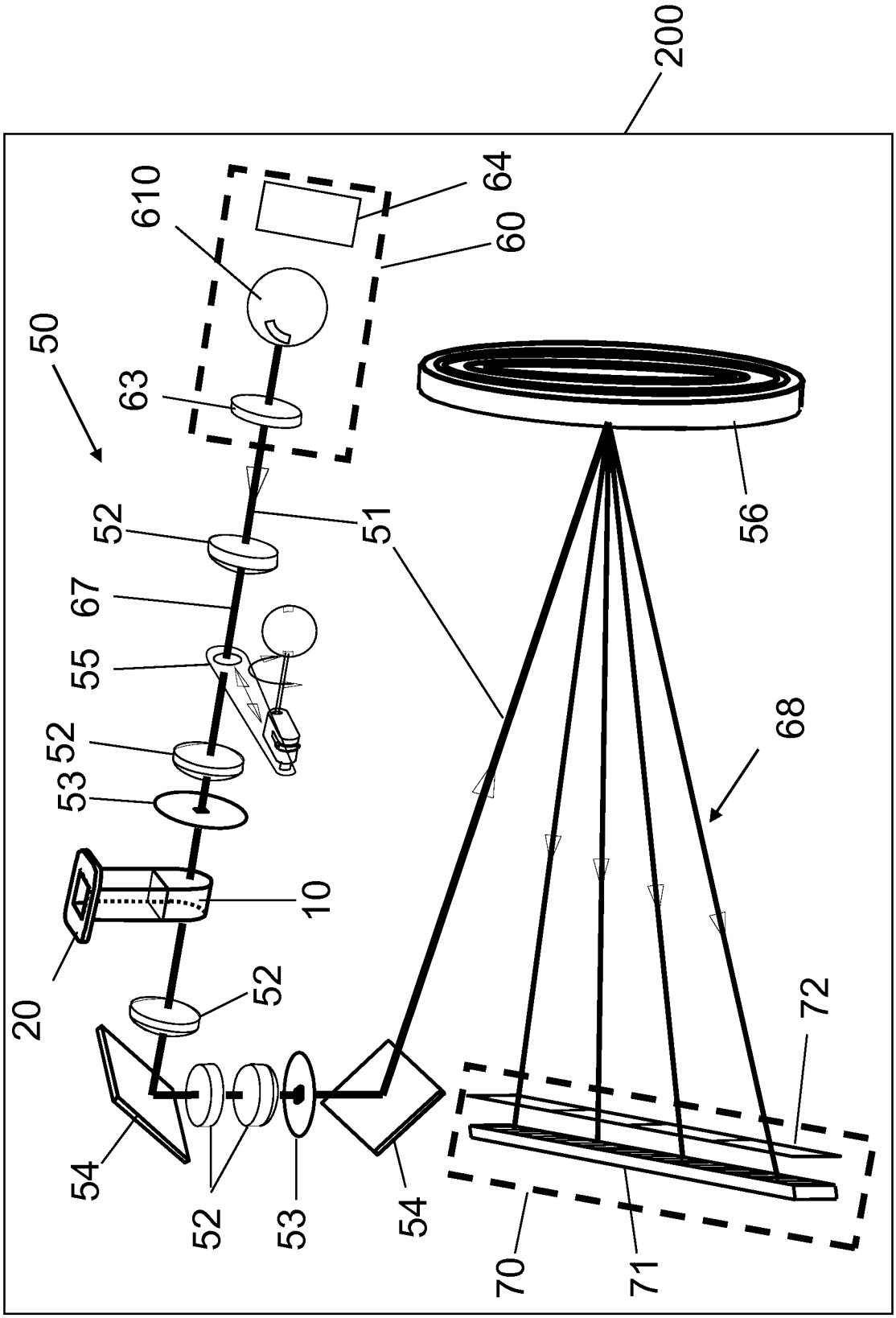


FIG. 1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71

FIG. 2

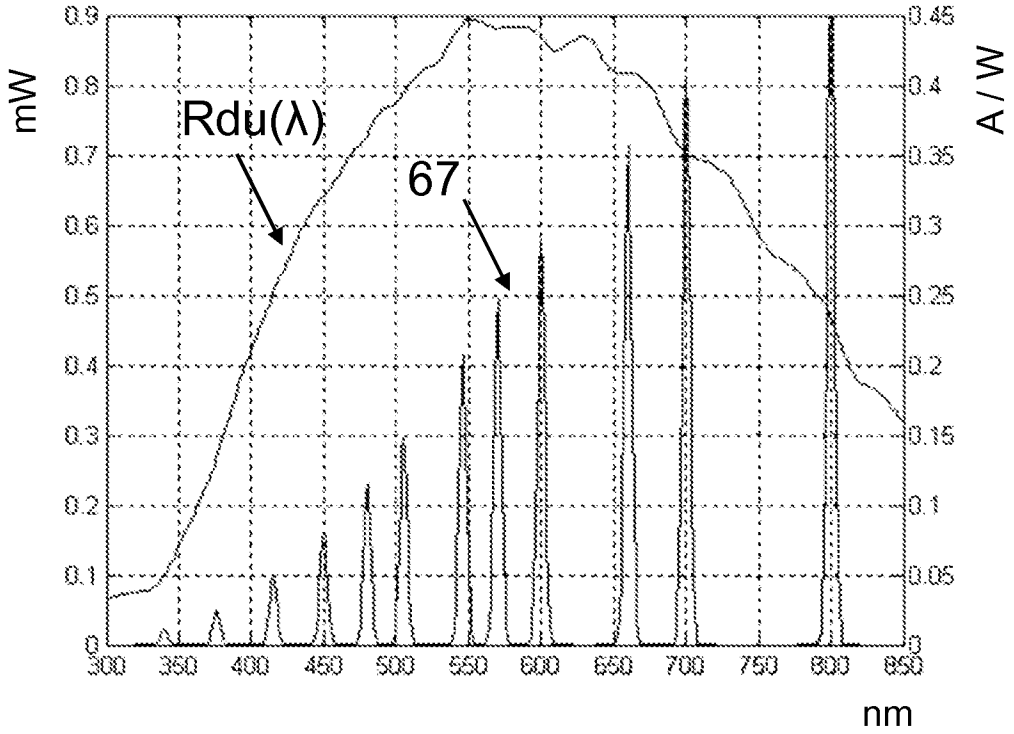
mW
A / W
Rdu(λ)
67
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
300 350 400 450 500 550 600 650 700 750 800 850
nm

FIG. 3a

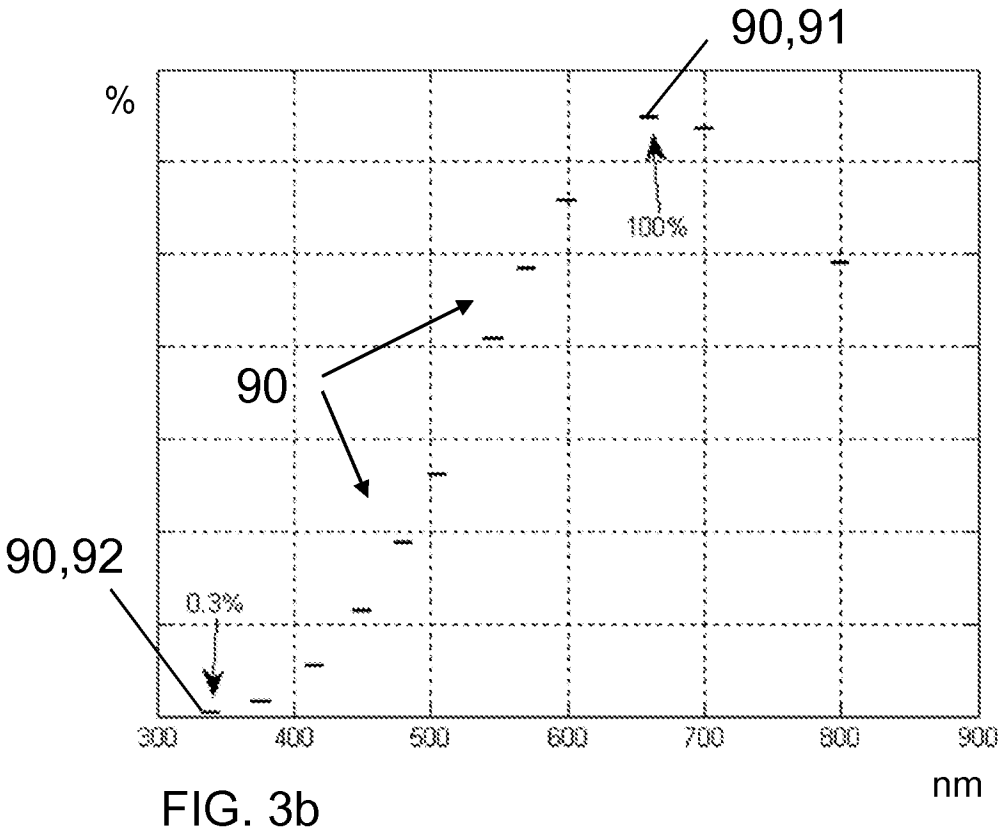
90,91
%
100%
90
90,92
0.3%
300 400 500 600 700 800 900
nm

FIG. 3b

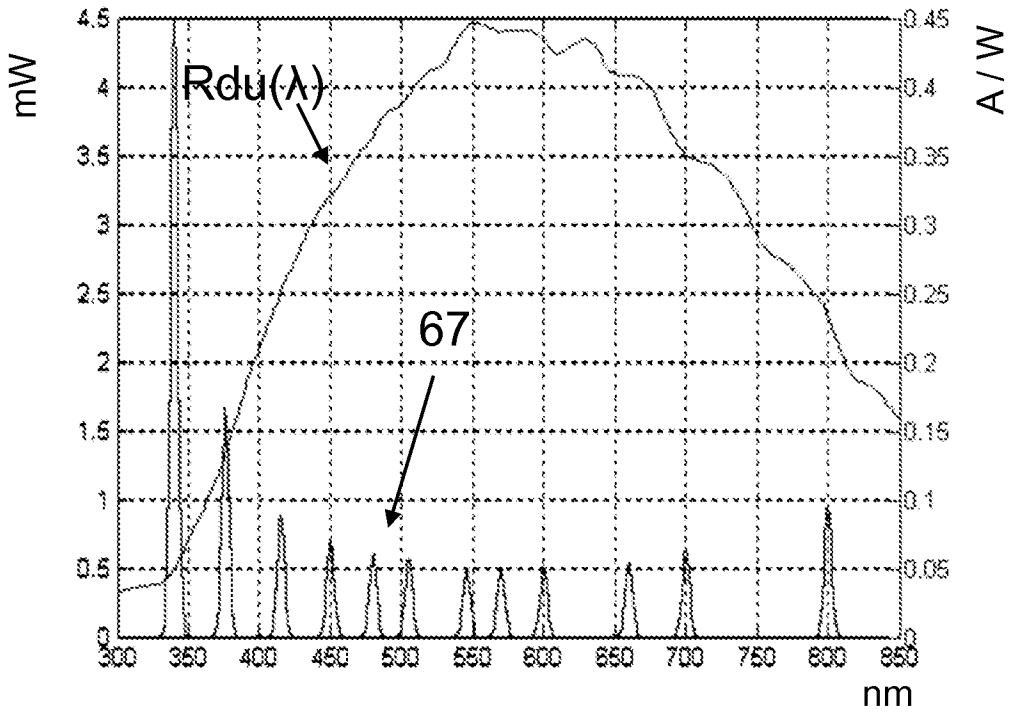

FIG. 4a

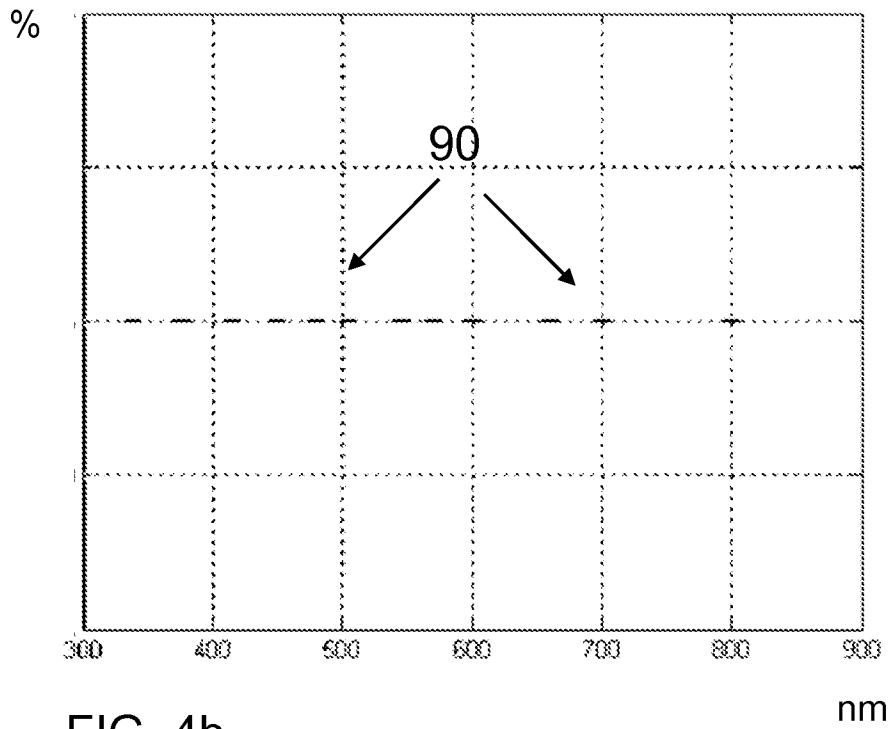

FIG. 4b

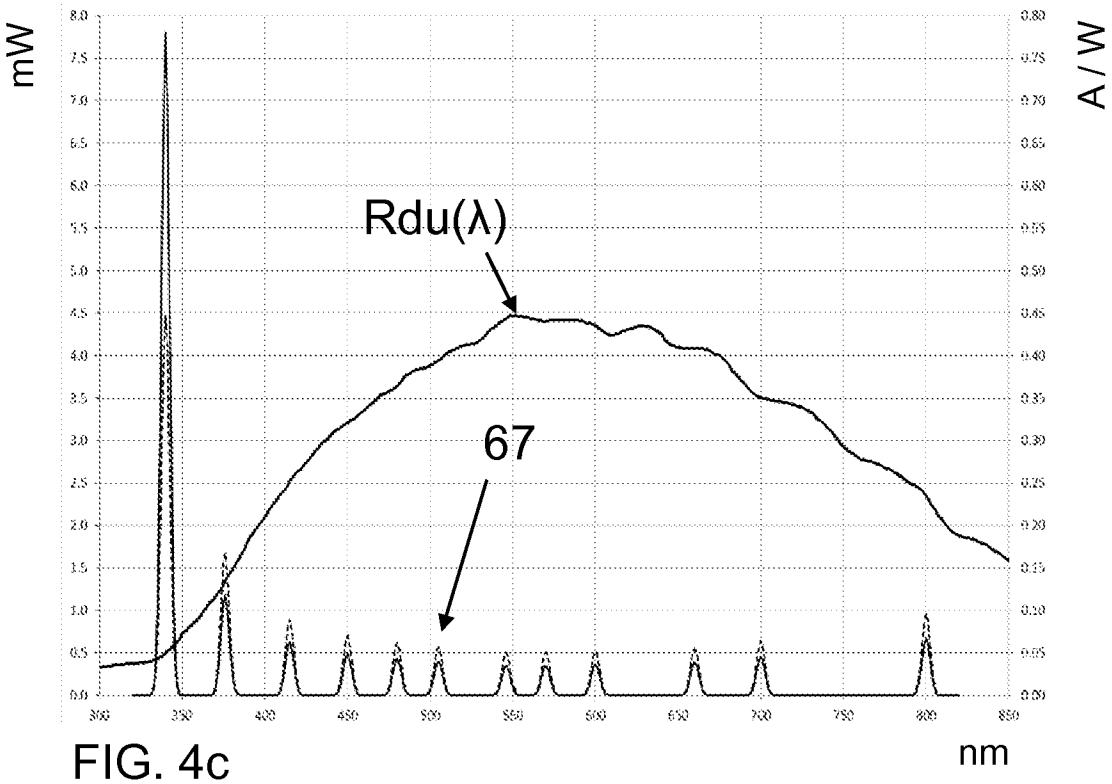

FIG. 4c

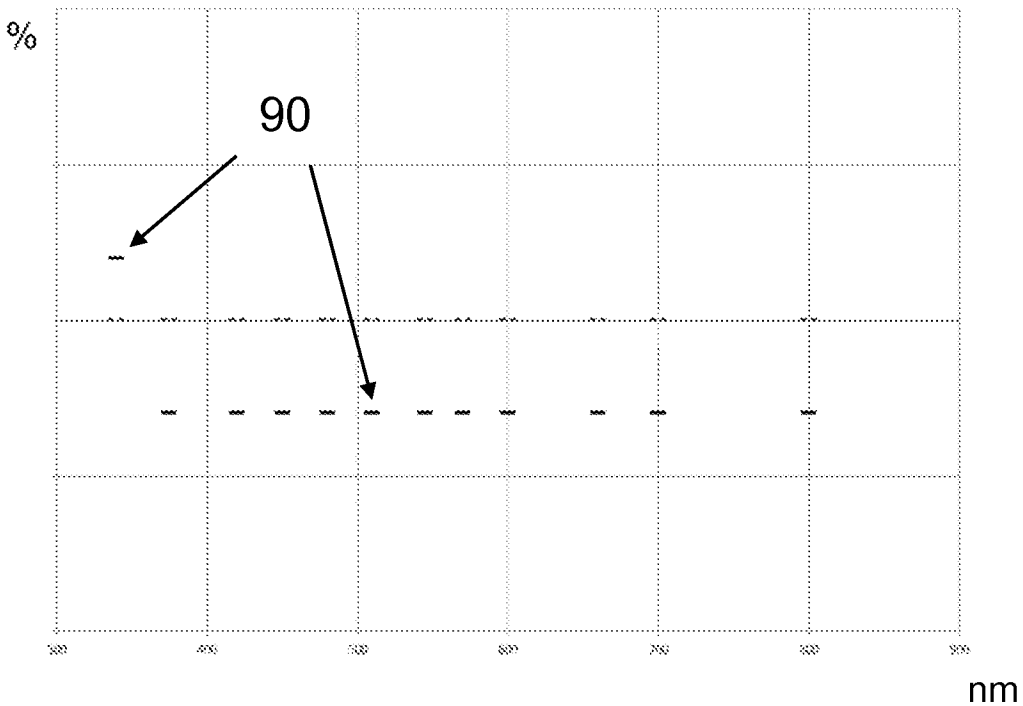

FIG. 4d

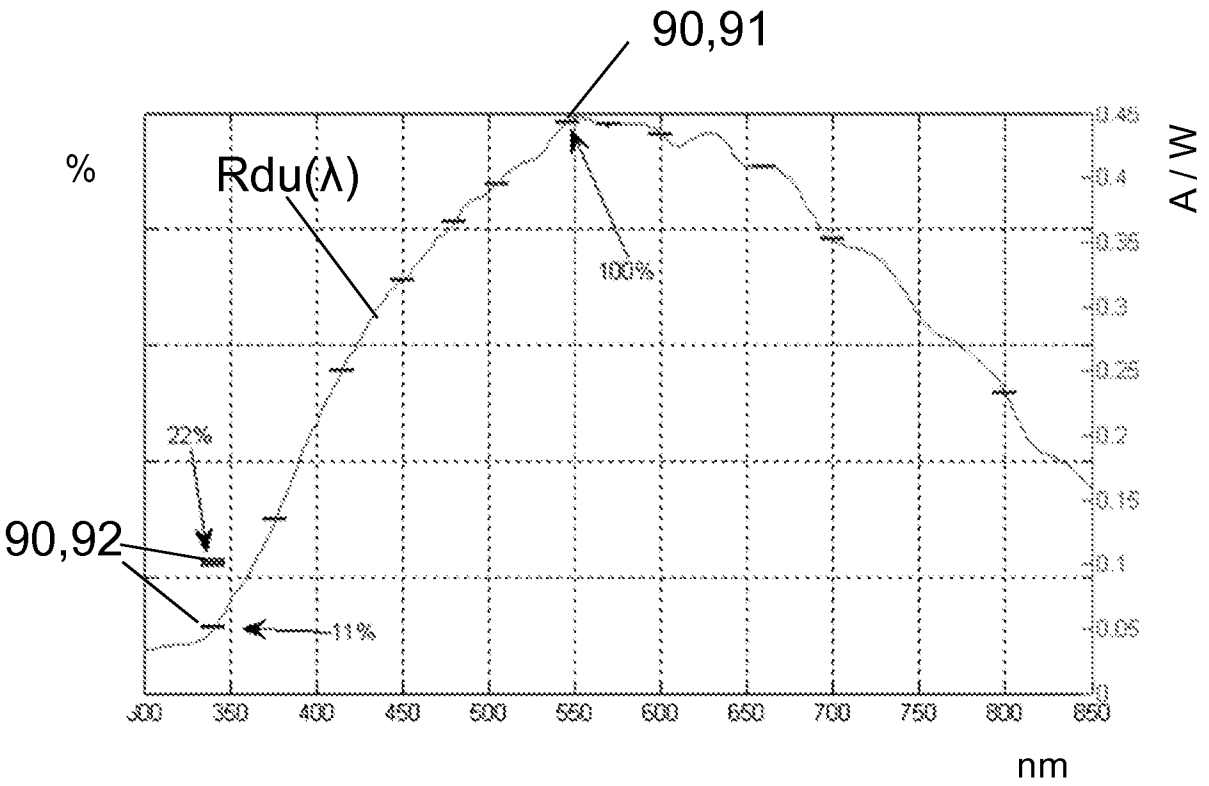
90,91
%
Rdu(λ)
100%
22%
90,92
11%
A / W
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
300
350
400
450
500
550
600
650
700
750
800
850
nm

FIG. 5

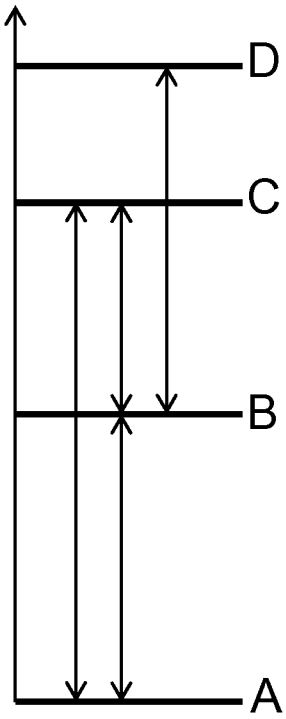

FIG. 6a

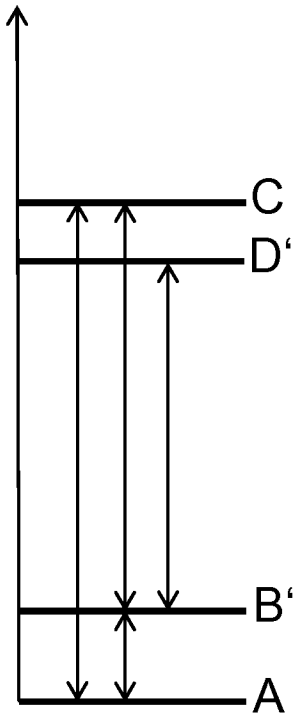

FIG. 6b

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061677

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N21/25 G01J3/02
ADD.

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)
G01N G01J

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 Y	US 4 681 454 A (BREEMER JOHANNES [NL]) 21 July 1987 (1987-07-21) column 1, line 10 - line 16 column 3, line 58 - line 62 column 6, line 17 - line 26	1,2,7-10 3-6, 11-15
Y	US 2008/094616 A1 (TANAKA TOSHIHIKO [JP]) 24 April 2008 (2008-04-24) paragraph [0115] figure 2	3-6, 11-15
A	US 2008/094631 A1 (JUNG WAYNE D [US] ET AL) 24 April 2008 (2008-04-24) paragraph [0392] - paragraph [0393] paragraph [0396]	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"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

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"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
23 September 2011	18/10/2011

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061677

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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