(19) NL Octrooicentrum

(11) **2009124**

(12)C **OCTROOI**

(21) Aanvraagnummer: **2009124**

(22) Aanvraag ingediend: **05.07.2012**

(51) Int.Cl.:
A61B 1/04 (2006.01) ***A61B 1/00*** (2006.01)
A61B 1/05 (2006.01) ***A61B 1/06*** (2006.01)
A61B 5/0215 (2006.01)

(43) Aanvraag gepubliceerd:
-

(47) Octrooi verleend:
07.01.2014

(45) Octrooischrift uitgegeven:
15.01.2014

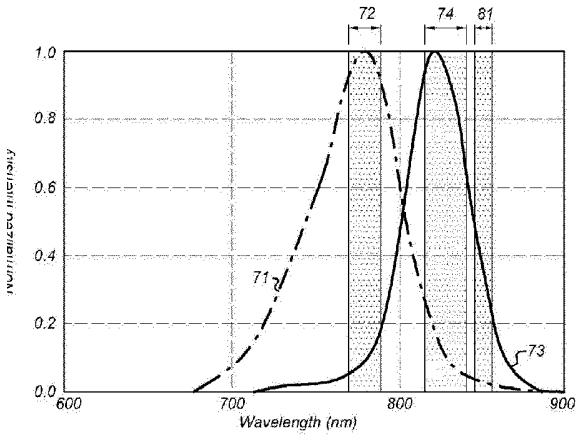
(73) Octrooihouder(s):
Quest Photonic Devices B.V.
te Middenmeer.

(72) Uitvinder(s):
Richard Johannes Cornelis Meester
te Middenmeer.

(74) Gemachtigde:
Dr. R. Jorritsma c.s. te Den Haag.

(54) **Method and device for detecting fluorescence radiation.**

(57) The invention provides a method for detecting fluorescence radiation from a fluorescence agent, the method comprising
- emitting light at an excitation wavelength range (72) for causing fluorescence radiation emission in the fluorescence agent, said fluorescence radiation having a fluorescence wavelength profile (73);
- detecting light at a first fluorescence wavelength range (74) as a first detection signal (S1);
- detecting light at a second fluorescence wavelength range (81, 91) as a second detection signal (S2);
- numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal (S1), the second detection signal (S2), and the fluorescence wavelength profile (73).



NL C 2009124

Method and device for detecting fluorescence radiation

Field of the invention

[0001] The invention relates to a method for detecting fluorescence radiation from a fluorescence agent using a probe such as an endoscope tip, to an endoscope tip suitable to perform said method, and to an endoscope system configured to perform said method. The invention also relates to an optical system comprising a camera and lens forming a probe other than an endoscope.

Background of the invention

[0002] In fluorescence imaging applications, a fluorescence dye or other fluorescence substance is applied as a labelling agent in an (internal) body part. With light at a specific wavelength (the excitation wavelength) from a light source such as a laser or LED, the fluorescence agent is excited. As a result, fluorescence light at a secondary wavelength is emitted by the agent. This light is sampled by an imaging sensor, such as a CCD sensor, of a probe to obtain a fluorescence signal. Especially when the probe must detect the fluorescence light through skin and tissue, the signal to noise ratio can be low. High gain usually needs to be applied to get a suitable signal level. In addition, scattering of fluorescence photons in tissue further reduces the signal to noise ratio.

[0003] This effect is usually overcome by using long integration times to increase the number of photons reaching the imaging sensor and therefore increasing the fluorescence signal and the signal to noise ratio.

[0004] Besides fluorescence radiation, the sensor also picks up so-called background radiation that is not caused by the excited fluorescence agent. Since the aim of fluorescence imaging is to view only the light emitted from the fluorescence agent, this background radiation should be separated from the measured fluorescence signal.

[0005] In some cases, the background signal is suppressed by applying a threshold criterion to the sensor signal. In real time systems during surgery however with varying light conditions this is no viable solution. The threshold level is varying and

hence the background signal can be higher than the threshold level, rendering the threshold useless, or the total background and fluorescence signal can be lower than the threshold, removing both the fluorescence and background signal.

Object of the invention

[0006] It is an object of the invention to provide a method and device for fluorescence imaging that overcomes at least one of the mentioned drawbacks.

Summary of the invention

[0007] The invention provides a method for detecting fluorescence radiation from a fluorescence agent, the method comprising

- emitting light at an excitation wavelength range for causing fluorescence radiation emission in the fluorescence agent, said fluorescence radiation having a fluorescence wavelength profile;
- detecting light at a first fluorescence wavelength range as a first detection signal;
- detecting light at a second fluorescence wavelength range as a second detection signal;
- numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal, the second detection signal, and the fluorescence wavelength profile.

[0008] By measuring at two different fluorescence wavelength ranges, and using knowledge of the fluorescence emission distribution curve at least in those ranges, the influence from the background radiation to the measured signal can be numerically reduced or practically eliminated. Thus, the signal to noise (fluorescence-to-background) ratio is advantageously improved.

[0009] In an embodiment according the invention, the method further comprises

- generating a fluorescence image based on the third detection signal;
- showing said fluorescence image on a display.

[0010] In an embodiment according the invention, the method further comprises

- detecting visible light as a fourth detection signal;

- merging the fluorescence image with an image based on the fourth detection signal.

[0011] This way an image is obtained containing both visible details and the fluorescence radiation. The position of the fluorescence agent is thus easier to determine, and the fluorescence image will be easier to interpret.

[0012] In an embodiment according the invention, the detected light (fluorescence and/or visible light) is captured via a single incident light entry surface, so that the respective detection signals are spatially aligned.

[0013] In an embodiment according the invention, the method comprises applying a numerical criterion to determine if a pixel in a measured fluorescence image contains essentially only background radiation and, if said numerical criterion is satisfied, removing or darkening the pixel in the measured fluorescence image. That way, detected radiation that appears to be fluorescence but is in fact background radiation can be removed from a measured image, so that only the fluorescence radiation remains. The fluorescence radiation is what the operator of the method is typically primarily interested in. The criterion to numerically determine if a pixel comprises essentially only background radiation can be provided in different ways. For example, the criterion may be that the background radiation may comprise no more than 80%, 90%, or 95% of the total measured radiation, as indicated by the action of determining the separation of background radiation and fluorescence radiation.

[0014] In an embodiment according the invention, numerically determining the third detection signal comprises calculating the difference of the first detection signal and the second detection signal. In particular, numerically determining the third detection signal can comprise evaluating (S1 - S2) / (1 - x), wherein S1 represents a detection signal in the first fluorescence range , S2 represents a detection signal in the second fluorescence range, and x is the calculated ratio of light emitted in the first florescence wavelength range and light emitted in the second fluorescence wavelength range according to the fluorescence wavelength profile.

[0015] In an embodiment according the invention, the second fluorescence wavelength range is at a wavelength range where the fluorescence wavelength

profile has a normalized value of at least 0.2. In an embodiment according the invention, the second fluorescence wavelength range is at a wavelength range where the fluorescence wavelength profile has a normalized value that is less than 0.2.

[0016] In an embodiment according the invention, the light at the excitation wavelength is emitted from an endoscope tip, and the detectors are comprised in said endoscope tip. In an alternative embodiment, the light at the excitation wavelength is emitted from a light source external to a fluorescence measuring probe (such as the mentioned endoscope tip). In any system, the light at the first and/or the second fluorescence wavelength ranges may be detected using a prism based camera system.

[0017] The invention also provides a measurement device for measuring fluorescence radiation from a fluorescence agent having a fluorescence wavelength profile, the device comprising

- a wavelength separation device configured to receive incident light originating from the agent and to separate said light into a plurality of channels;
- at least two imaging sensors connected to at least two respective channels of the plurality of channels, wherein the first channel is configured for transmitting light at a first fluorescence wavelength range, from which the respective sensor will generate a first detection signal, and the second channel is configured for light at a second fluorescence wavelength range, from which the respective sensor will generate a second detection signal;
- a processing device configured for numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal, the second detection signal, and the fluorescence wavelength profile.

[0018] In an embodiment according the invention, the measurement device is configured for use as an endoscope tip, wherein the wavelength separation device is a dichroic prism assembly. The device may be further provided with fibers for transmitting excitation light to excite the fluorescence agent. The dichroic prism assembly can have at least three channels, the third channel being configured for transmitting light at a visible wavelength range, from which the respective sensor

can generate a fourth signal representative of the visible environment of the endoscope tip.

[0019] The invention further provides an endoscope system comprising an endoscope tip as described above, and processing means for numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal, the second detection signal, and the fluorescence wavelength profile, as also described above.

[0020] The invention further provides a probe system comprising a fluorescence measurement device as described above, such as an open system fluorescence measurement device, and processing means for numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal, the second detection signal, and the fluorescence wavelength profile.

Brief description of the Figures

[0021] On the attached drawing sheets,

- figure 1 schematically shows light paths through a dichroic prism assembly;
- figure 2 schematically shows a perspective view of an extended dichroic prism assembly module according to an embodiment of the invention;
- figure 3 schematically shows a perspective view dichroic prism assembly for use in a fluorescence probe according to an embodiment of the invention;
- figures 4 and 5 schematically show cross sections of an endoscope tube comprising a dichroic prism assembly according to an embodiment of the invention;
- figure 6 schematically shows a perspective view of an endoscope tube according to an embodiment of the invention with part of the tube wall removed;
- figure 7 shows an excitation and fluorescence wavelength distribution;
- figures 8 and 9 show excitation and fluorescence wavelength distributions and light sampling wavelength ranges according to an embodiment of the invention;

- figures 10, 11, and 12 show further fluorescence wavelength distributions and light sampling wavelength ranges according to an embodiment of the invention; and
- figure 13 schematically shows a fluorescence measurement probe according to an embodiment of the invention.

Detailed description

[0022] Figure 1 schematically shows light paths through a dichroic prism assembly. An exemplary dichroic prism assembly configured to separate light into red R, green G, and blue B components will now be discussed to illustrate the functioning of such assembly. However, the invention is not limited to separation into R, G, and B. In reference to figures 7 - 12, other wavelengths will be discussed. It will be clear to a skilled person that a dichroic prism assembly is a light separation means which can be configured to separate light into arbitrary wavelengths.

[0023] Returning to the exemplary assembly of figure 1, light comprising red R, green G and blue B components enters the assembly through incident surface 19, shown here as the bottom surface of the assembly. The first transition surface 17, between the first 11 and second prisms 12 comprises a coating that is configured to reflect blue light and transmit red and green light. The blue component B is nearly totally reflected and, due to the shape of first prism 11, exits the first prism through the side where sensor 14 is attached. The applied coating can be a grated refraction index coating.

[0024] The green G and red R components pass through the first transition surface 17. The second transition surface 18, between the second 12 and third 13 prisms, is provided with a coating, for example another grated refraction index coating, that reflects red light but allows green light to pass. The red light is thus reflected at surface 18 and exits the second prism through the face on which the second sensor 15 is attached. The green light passes through second transition surface 18 and third prism 13 and exits through the face on which third sensor 16 is attached. Each of these paths through the prism assembly is known as a channel.

[0025] It is again noted that the invention is not limited to the exemplary R, G, and B separation. Any configuration of components can be used, as determined by the

reflection/transmission wavelength of the coating(s) used. For example, suitable coatings may be used that so that one channel includes light in the wavelength range of 400 to 650 nm (blue, green, and red), another light in the range 650 to 750 nm (red, near-infrared) and a third channel has light in the range 750 to 1000 nm (infrared). In addition, filters may be placed between the exit of the prism and the sensor.

[0026] Returning to the example of figure 1, the red, green, and blue, R, G, B, components are thus sampled by first, second and third detectors 14, 15, and 16. As mentioned before, these principles apply to any light components, not necessarily red, green and blue, provided that suitable coatings of surfaces 17 and 18 and material for prisms 11, 12, 13 is used.

[0027] Conventionally, air gaps are often used to provide a second transient surface 17 suitable for reflecting red light. According to the invention, also a grated refraction index coating may be used on any transient surface 17. Such a coating can be in principle applied for any wavelength. Such a coating removes the need for air gaps, which is advantageous since air gaps may be filled with dust when the module is cut.

[0028] Figure 2 schematically shows a perspective view of an dichroic prism assembly module 10, comprising three extended prisms 11, 12, 13. Vacuum bonding is performed by pressing the small uncut pieces together. In order to further fortify the bonding, a glass sheet 21 is attached to each side of the module (front and back). This sheet may later be removed, when the formed dichroic prism assembly for use in an endoscope is formed. The sheet can also remain in the formed dichroic prism assembly.

[0029] According to an embodiment of the invention, the dichroic prism assembly module 10, having at least one dimension unsuitable for use in an endoscope tip is cut along a cutting line 20. Figure 2 shows several examples of cutting lines 20. After cutting, at least one dichroic prism assembly 30 suitable for use in an endoscope tip is obtained. Repeated cuttings will yield a plurality of dichroic prism assemblies 30.

[0030] Figure 3 shows an example of an dichroic prism assembly 30 obtained by the described cutting process. The assembly 30 has width W, height H, and length L_2. Length L_2 is much smaller than the length L of the module 10 of which assembly 30

was a part. A typical value for L_2 is between 0.5 mm and 2 mm. Typical values for H are between 0.5 mm and 2 mm, and for W also between 0.5 mm and 2 mm.

[0031] In figure 4, a length-wise cross section of an endoscope tip according an embodiment of the invention is shown. The incident light that enters the endoscope tip along incident path 42 is transmitted through cover plate 50, focused by a lens 51 onto a dichroic prism assembly 52 according the invention. The assembly 52 may be obtained by the above described method of cutting a module 10. The assembly 52 is dimensioned to be suitable for use in an endoscope tip. The dimensions of the assembly 52 may be between 0.5 and 5 mm in each direction, preferably between 0.5 and 2mm or between 1 and 1.5 mm.

[0032] The dichroic prism assembly 52 is provided with sensors 53. These sensors may comprise Charge-Coupled Devices (CCDs). The sensors may also comprise a chip comprising means for determining a relative or absolute orientation, or rate of change of said orientation, of the endoscope tip. An example is a so-called gyro chip. The endoscope tip may also comprise processing means, for example for processing pixel data from the CCD. Connected to the sensors are signal wires 54 for carrying a signal from the sensor and/or chip in the sensor away from the endoscope tip, typically to an external signal processing device such as a PC or monitoring device.

[0033] In figure 5, a cross section of tube wall 44 is shown. The interior 45 comprises optical fibers 60 or bundles of fibers 60. These fibers may be used to transport light from an external light source, through the transparent front surface 45 to illuminate an area surrounding the endoscope tip. The reflecting light is then received via the first and second incident paths 42 and 43. Because two incident light paths are provided, the endoscope can be used for stereo imaging.

[0034] Figure 6 schematically shows a perspective view of an endoscope tube according the invention with part of the tube wall 44 removed, and without the fibers 60, lense 51 and cover surfaces 45 and 50.

[0035] The endoscopes according the invention are, however, not limited to endoscope tips with one incident paths 42 as shown in figures 4, 5 and 6. Endoscopes with two (e.g. for stereo applications) or three or more incident paths

can also be envisaged. Not all paths need to be provided with a dichroic prism assembly according the invention - only where the light needs to be separated into several components.

[0036] Figure 7 shows excitation 71 and emission 73 curves for Fluorescein Isothiocyanate (FITC). Many other fluorescence agents are available, such as Indocyanine Green (ICG), CW-800, Cy5, Cy5.5, etc., each with their respective excitation and emission curves. The x-axis shows the wavelength (in nanometres, nm) of the excitation or emission wavelength. FITC has a peak excitation wavelength of approximately 495 nm, and a peak fluorescence emission wavelength of approximately 521 nm. As excitation source typically a laser, LED, or other light source having a narrow emission profile 72 close to the peak excitation wavelength is used. In the present example, nearly monochromatic laser light at 488 nm is used as excitation source.

[0037] To measure the fluorescence, typically a narrow band filter is placed in the optical path of the detector to only sample the emission wavelength close to the top of emission, but away from the excitation wavelength. Furthermore the excitation source wavelength is blocked from reaching the sensor. In the present example, a filter having a bandwidth of approximately 30 nm is used around a central wavelength of approximately 530 nm.

[0038] In fluorescence endoscopy applications using an endoscope having an endoscope tip as shown in figures 4, 5, and 6, at least one but typically more fibers 60 emit light at the excitation wavelength. Other fibers may emit light in the visible range (e.g. white light), so that the endoscope can also register a visible image, for example to aid the operator of the endoscope in navigating. In case of open systems (see e.g. figure 13) the excitation wavelength and visible light can be supplied by any general illumination apparatus.

[0039] In an embodiment according the invention the endoscope tip is provided with a dichroic prism assembly 52 configured to split light into three wavelength ranges and provided with a respective sensor 14, 15, 16 for each of the three wavelength ranges. A first wavelength range may be a first fluorescence wavelength range. The second wavelength range may be a second fluorescence wavelength range (preferably not overlapping the first wavelength range, in any case not identical to

the first wavelength range) and the third wavelength range may be in the visible light range. As was mentioned before, by sensing the visible light in one channel, the endoscope can transmit a gray-scale image that may aid the operator of the endoscope. The use of the first and second fluorescence wavelength ranges will be discussed in reference to figures 8 and 9.

[0040] Figure 8 shows an example of an excitation wavelength range 72 (near the peak of the exemplary excitation curve 71), a first fluorescence wavelength range 74 near the peak of the fluorescence curve 73, and a second fluorescence wavelength range 81 In the example of figure 8, the first fluorescence wavelength range 74 overlaps with the emission curve near the peak value. That is, the normalized (i.e. the peak value corresponds to 1.0) emission intensity of the overlapped part of the fluorescence emission profile is between 0.6 and 1.0. The first fluorescence wavelength range is thus close to the peak of the emission profile 73 and may overlap with the peak wavelength, as is the case in figure 8. Other ranges 74 are also possible, for example overlapping parts of the emission curve 73 where the normalized intensity is between 0.4 and 1.0, between 0.5 and 1.0, and between 0.8 and 1.0.

[0041] In the example of figure 8, the second fluorescence wavelength range 81 overlaps with the emission curve 73 in an area where the normalized emission intensity is between 0.2 and 0.6. Other ranges 81 are also possible, for example overlapping parts of the emission curve 73 where the normalized intensity is between 0.2 and 0.4, between 0.2 and 0.6, between 0.2 and 0.8 and between 0.2 and 1.0.

[0042] In an embodiment according the invention, the first wavelength range 74 is closer to the peak emission wavelength than the second wavelength range 81.

[0043] Let S1 denote the signal detected by the sensor detecting light of the first wavelength range 74 and S2 denote the signal detected by the sensor detecting light of the second wavelength range 81 can be calculated. In an approximation, the background emission B is independent of the wavelength. The detectors will thus detect a combination of a wavelength independent background emission B and wavelength dependent fluorescence radiation P1 (averaged over the first wavelength range) and P2 (averaged over the second wavelength range). In formula form: S1 =

B + P1 and S2 = B + P2. In these formulas, the emissions are presented per unit of wavelength interval, to account for the differences in wavelength range widths.

[0044] Since the fluorescence emission curve 73 is known, the number of variables (B, P1, and P2) can be reduced from three to two. Based on the knowledge of the emission curve 73, P2 can be expressed as a fraction of P1 (considering that the first wavelength range is closer to the peak emission wavelength than the second range, so that P1 > P2), i.e. P2 = x P1, where x is a real number between 0 and 1.

[0045] Now the background radiation contribution B can be eliminated from the equations, to obtain for example the following expression for P1: P1 = (S1 - S2) / (1 - x). Thus, a third detection signal is obtained from which the background radiation is largely eliminated. in a further embodiment, the third detection signal is calibrated using known procedures so that a quantitative fluorescence measurement is obtained.

[0046] In figure 9, the second wavelength range 91 is chosen at a larger distance from the first wavelength range so that it can be said to overlap the tail of the emission distribution. It follows that the range 91 overlaps with a part of the emission curve having lower normalized intensity values, i.e. between 0.0 and 0.1. Other exemplary overlap ranges are between normalized intensity values 0.0 and 0.2, between 0.0 and 0.3, 0.0 and 0.4, etc. An advantage of obtaining the second fluorescence signal from the tail of the emission distribution is that the difference between S1 and S2 becomes larger and the division in the equation for P1 becomes numerically more stable since the denominator is closer to 1. However, a disadvantage is that the S2 signal may be considerably more noisy. It may be necessary to increase the integration time, which is not desirable in real-time applications.

[0047] Given a specific fluorescence agent and application, a skilled person will be able to determine whether the approach of figure 8 or of figure 9, both of which correspond to aspects of the invention, is more suitable.

[0048] As shown above, by performing calculations based on the first detection signal (S1), the second detection signal (S2) and knowledge of the fluorescence wavelength profile 73, a third detection signal (S3 = (S1-S2)/(1-x)) with an improved

fluorescence-to-background radiation ratio can be calculated as a function of S1, S2, and x.

[0049] Other numerical approaches may also be used. A very simple approach is to simply calculate the difference between the signal S1 at a fluorescence peak and the signal S2 corresponding to a wavelength where the fluorescence profile 73 has a lower fluorescence emission intensity (e.g. at a minimum intensity value in curve 73, or somewhere between the minimum and maximum value), that is S3 = S1 - S2. In areas where background emission is predominant, the term S2 - S1 will mostly cancel, whereas where fluorescence emission is predominant, S2 - S1 is positive. In yet another embodiment, the difference between S2 and S1 is normalized, e.g. using S3 = (S1 - S2) / (S1 + S2). In these simplified formulas, the fluorescence profile 73 is not explicitly present. However, the profile 73 is implicitly used, since the wavelength ranges S1 and S2 are chosen based on the known fluorescence profile 73.

[0050] Because the light arriving at the sensors follows a single incident light path 42 before being separated in the dichroic prism assembly 52, the detected images of all three sensors are completely aligned. By measuring fluorescence radiation at two separate frequencies for the same spatial location, due to the alignment, the background radiation can be accurately separated from the fluorescence radiation. Moreover, due to the alignment of the three sensors, the separated fluorescence radiation can be accurately superimposed on a visible light (grayscale) image of the surroundings of the endoscope or open lens system.

[0051] The detected data will typically be organized in a matrix form with rows and columns to present a digital picture comprising pixels. Each pixel corresponds to a direction of incident radiation. In one of many possible representations, pixels representing a low measured signal are dark and pixels representing a relatively high signal are bright. Based on the determined third detection signal, pixels comprising essentially only background radiation may be darkened. That way, the areas of the image representing fluorescence data will be more clearly visible, and a human operator will be better able to interpret the measurement data.

[0052] The shown image may be the third detection signal, or a post-processed (for example, normalized or calibrated) image based on the third detection signal. In an

embodiment, the third detection signal is merged with a visible light image, to create an image showing the visible surroundings overlaid with fluorescence data.

[0053] As has been shown, from the signals S1 and S2 a ratio of fluorescence to background radiation may be determined. For example, B can be expressed as B=(S2-xS1)/(1-x), so that the fluorescence to background radiation ratio can be expressed as P1/B = (S1-S2)/(S2-xS1). Using such a measure or any other estimate of the fluorescence and background fractions in the signal, there are many ways in which the criterion of "essentially only background radiation" for darkening pixels may be applied. The system can use a hard threshold, for example darkening all pixels with an estimated fluorescence fraction of less than 10% (i.e. 90% background radiation), or less than 20%, or less than 5%. In an alternative embodiment, the pixel is darkened by multiplying its original value with the determined fraction of fluorescence radiation. After such "soft mixing" the image may be re-normalized so that the areas with the most fluorescence radiation have high brightness. In yet another embodiment, the pixel value will be set proportional to the determined fraction of fluorescence radiation.

[0054] There are fluorescence agents that have multiple peaks in the fluorescence emission distribution. An exemplary distribution 120 having two peaks is schematically shown in figures 10, 11, and 12. According to embodiments of the invention, the first wavelength range 110, 111 can overlap with either emission peak, while the second wavelength range 111, 110, 112 can overlap with either other emission peak (ranges 111, and 110, respectively) or with the "valley" between the peaks (range 112). Using the principles as explained in reference to figures 8 and 9, the skilled person can separate background and fluorescence radiation based on measurements on at least two sampling channels.

[0055] While the exemplary embodiments discussed in reference to figures 8 through 12 show only two simultaneous sampling wavelength ranges (74, 81, 91, 110, 111, 112), the invention is not limited to just two simultaneous ranges. Three or more simultaneous ranges may be used. Such increased number of sampling ranges will increase the reliability of the background/fluorescence separation according the invention. In a particular embodiment, a probe is used with a dichroic prism assembly in the tip which has three channels, configured for three fluorescence sampling wavelengths. In yet another embodiment, the probe tip is

provided with two dichroic prism assemblies. However, in this embodiment care must be taken to align the measurements from the separate prism assemblies.

[0056] The invention has been mainly described in reference to an endoscopy application utilizing an endoscope with a tip as shown in figures 4-6. In particular, the invention can be practised using an endoscope having a tip with integrated miniaturized dichroic prism assembly for wavelength separation. However, the invention may also be applied to other fluorescence probes, such as open systems comprising a lens.

[0057] Figure 13 shows an alternative probe 100 according the invention. The probe 100 has an elongated cylindrical body, comprising main part 101 and distal end or tip 102. The tip 102 is provided with a surface 104 for collecting incident radiation. The incident radiation comprising the fluorescence radiation to be measured will pass through a lens (not shown) in the tip and be collected in a plurality of optical fibers. The fibers will transport the light through the main part 101 of the probe towards a connected analysis unit 105. The analysis unit may comprise a wavelength separation unit, such as a dichroic prism assembly, and sensors with which the invention may be practised. An external light source (not shown) is used to excite the fluorescence agent.

[0058] The invention can thus be practiced using endoscopes or other types of probes such as open systems. The light for fluorescence agent excitation may be provided via the system (for example generated in or at least transported through fibers in an endoscope) or external (for example external to an open system probe) The endoscope or probe may comprise wavelength separation means (such as a dichroic prism assembly) at or near the site of incident radiation collection (i.e. in the tip) or in a connected analysis unit to which the incident radiation is transported (for example using optical fibers).

[0059] In the foregoing description of the figures, the invention has been described with reference to specific embodiments thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the scope of the invention as summarized in the attached claims.

[0060] In particular, combinations of specific features of various aspects of the invention may be made. An aspect of the invention may be further advantageously enhanced by adding a feature that was described in relation to another aspect of the invention.

[0061] It is to be understood that the invention is limited by the annexed claims and its technical equivalents only. In this document and in its claims, the verb "to comprise" and its conjugations are used in their non-limiting sense to mean that items following the word are included, without excluding items not specifically mentioned. In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

[0062] Aspects of the invention may also be understood from the following clauses.

[0063] Clause 1. Method for detecting fluorescence radiation from a fluorescence agent, the method comprising

- emitting light at an excitation wavelength range (72) for causing fluorescence radiation emission in the fluorescence agent, said fluorescence radiation having a fluorescence wavelength profile (73);
- detecting light at a first fluorescence wavelength range (74) as a first detection signal (S1);
- detecting light at a second fluorescence wavelength range (81, 91) as a second detection signal (S2);
- numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal (S1), the second detection signal (S2), and the fluorescence wavelength profile (73).

[0064] Clause 2. The method according to clause 1, further comprising

- generating a fluorescence image based on the third detection signal;
- showing said fluorescence image on a display.

[0065] Clause 3. Method according to clause 2, further comprising

- detecting visible light as a fourth detection signal;

- merging the fluorescence image with an image based on the fourth detection signal.

[0066] Clause 4. Method according to clause 2 or 3, wherein the detected light is captured via a single incident light entry surface, so that the respective detection signals are spatially aligned.

[0067] Clause 5. Method according to any of the previous clauses, wherein numerically determining the third detection signal comprises calculating the difference of the first detection signal (S1) and the second detection signal (S2).

[0068] Clause 6. Method according to clause 5, wherein numerically determining the third detection signal comprises evaluating (S1 - S2) / (1 - x), wherein S1 represents a detection signal in the first fluorescence range (74), S2 represents a detection signal in the second fluorescence range (81, 91), and x is the calculated ratio of light emitted in the first florescence wavelength range (74) and light emitted in the second fluorescence wavelength range (81, 91) according to the fluorescence wavelength profile (73).

[0069] Clause 7. Method according to any of the previous clauses, wherein the second fluorescence wavelength range is at a wavelength range (81) where the fluorescence wavelength profile (73) has a normalized value of at least 0.2.

[0070] Clause 8. Method according to any of the previous clauses 1-6, wherein the second fluorescence wavelength range is at a wavelength range (91) where the fluorescence wavelength profile (73) has a normalized value that is less than 0.2.

[0071] Clause 9. Method according to any of the previous clauses, wherein the light at the excitation wavelength is emitted from an endoscope tip, and the detectors are comprised in said endoscope tip

[0072] Clause 10. Method according to any of the previous clauses 1-8, wherein the light at the excitation wavelength is emitted from a light source external to the probe and the light at the first and/or the second fluorescence wavelength ranges are detected using a prism based camera system.

[0073] Clause 11. Measurement device for measuring fluorescence radiation from a fluorescence agent having a fluorescence wavelength profile (73), the device comprising

- a wavelength separation device (52, 30) configured to receive incident light originating from the agent and to separate said light into a plurality of channels;
- at least two imaging sensors connected to at least two respective channels of the plurality of channels, wherein the first channel is configured for transmitting light at a first fluorescence wavelength range (74), from which the respective sensor (14) will generate a first detection signal (S1), and the second channel is configured for light at a second fluorescence wavelength range (81, 91), from which the respective sensor (15) will generate a second detection signal (S2);
- a processing device configured for numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal (S1), the second detection signal (S2), and the fluorescence wavelength profile (73).

[0074] Clause 12. The device according to clause 11 configured for use as an endoscope tip, wherein the wavelength separation device is a dichroic prism assembly (52, 30).

[0075] Clause 13. The device according to clause 12 further provided with fibers (60) for transmitting excitation light to excite the fluorescence agent.

[0076] Clause 14. Endoscope tip according to clause 12 or 13, wherein the dichroic prism assembly (52, 30) has at least three channels, the third channel being configured for transmitting light at a visible wavelength range, from which the respective sensor (16) can generate a fourth signal representative of the visible environment of the endoscope tip.

[0077] Clause 15. Endoscope system comprising an endoscope tip according to any of the clauses 12 to 14 and processing means for numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal (S1), the second detection signal (S2), and the fluorescence wavelength profile (73).

[0078] Clause 16. Probe system comprising a device according to clause 11 and processing means for numerically determining a third detection signal with an improved fluorescence-to-background radiation ratio based on the first detection signal (S1), the second detection signal (S2), and the fluorescence wavelength profile (73).

Conclusies

Werkwijze voor het detecteren van fluorescentiestraling van een fluorescentiemiddel, the werkwijze omvattende
- het uitzenden van licht met een excitatiegolflengtebereik (72) om fluorescentiestralingsemissie te veroorzaken in het fluorescentiemiddel, welke fluorescentiestraling een fluorescentie golflengteprofiel (73) heeft;
- het detecteren van licht met een eerste fluorescentiegolflengtebereik (74) als een eerste detectiesignaal (S1);
- het detecteren van licht met een tweede fluorescentiegolflengtebereik (81, 91) als een tweede detectiesignaal (S2);
- het numeriek bepalen van een derde detectiesignaal met een verbeterde verhouding fluorescentie-tot-achtergrondstraling op basis van het eerste detectiesignaal (S1), het tweede detectiesignaal (S2) en het fluorescentie golflengteprofiel (73).

2. Werkwijze volgens conclusie 1, verder omvattende
- het genereren van een fluorescentiebeeld op basis van het derde detectiesignaal;
- het tonen van het fluorescentiebeeld op een weergeefinrichting.

3. Werkwijze volgens conclusie 2, verder omvattende
- het detecteren van zichtbaar licht als een vierde detectiesignaal;
- het bijeenvoegen van het fluorescentiebeeld met een beeld op basis van het vierde detectiesignaal.

4. Werkwijze volgens conclusie 2 of 3, waarbij het gedetecteerde licht ingevangen wordt via een enkel lichtinvangsoppervlak, zodat de respectievelijke detectiesignalen ruimtelijk met elkaar overeenstemmen.

5. Werkwijze volgens een van de vorige conclusies, waarbij het numeriek bepalen van het derde detectiesignaal het berekenen van het verschil tussen het eerste detectiesignaal (S1) en het tweede detectiesignaal (S2) omvat.

6. Werkwijze volgens claim 5, waarbij het numeriek bepalen van het derde detectiesignaal het evalueren van (S1 - S2) / (1-x) omvat, waarbij S1 het detectiesignaal van het eerste fluorescentiebereik (74), S2 het detectiesignaal van

het tweede fluorescentiebereik (81, 91), en x de berekende verhouding van licht uitgezonden in het eerste fluorescentiebereik (74) en licht uitgezonden in het tweede fluorescentiebereik (81, 91) volgens het fluorescentie golflengteprofiel (73) representeert.

7. Werkwijze volgens een van de voorgaande conclusies, waarbij het tweede fluorescentie golflengtebereik zich bevindt in een golflengtebereik (81) waar het fluorescentie golflengteprofiel (73) een genormaliseerde waarde van tenminste 0,2 heeft.

8. Werkwijze volgens een van de voorgaande conclusies, waarbij het tweede fluorescentie golflengtebereik zich bevindt in een golflengtebereik (91) waar het fluorescentie golflengteprofiel (73) een genormaliseerde waarde die minder dan 0,2 is.

9. Werkwijze volgens een van de voorgaande conclusies, waarbij het licht met de excitatiegolflengte uitgezonden wordt uit een endoscoopuiteinde, welk endoscoopuiteinde ook de detectors omvat.

10. Werkwijze volgens een van de voorgaande conclusies 1-8, waarbij het licht met de excitatiegolflengte uitgezonden wordt door een extern van een fluorescentiemeetinrichting voorziene lichtbron, en het licht van het eerste en/of het tweede fluorescentie golflengtebereik wordt gedetecteerd met een op prisma's gebaseerd camerasysteem.

11. Meetinrichting voor het meten van fluorescentiestraling van een fluorescentiemiddel met een fluorescentie golflengteprofiel (73), de inrichting omvattende

- een golflengtescheidingsinrichting (52, 30) ingericht om licht te ontvangen dat van het fluorescentiemiddel komt en om het licht te scheiden via een meervoudig aantal kanalen;
- tenminste twee beeldsensoren verbonden met tenminste twee respectieve kanalen van het meervoudig aantal kanalen, waarbij het eerste kanaal is ingericht om licht met een eerste fluorescentie golflengtebereik (74) door te sturen, waaruit de respectieve sensor (14) een eerste detectiesignaal (S1) genereert, en het tweede kanaal is ingericht om licht met een tweede fluorescentie golflengtebereik (81, 91)

door te sturen, waaruit de respectieve sensor (15) een tweede detectiesignaal (S2) genereert;
- een verwerkingsinrichting ingericht voor het numeriek bepalen van een derde detectiesignaal met een verbeterde verhouding van fluorescentie-tot-achtergrondstraling op basis van het eerste detectiesignaal (S1), het tweede detectiesignaal (S2), en het fluorescentie golflengteprofiel (73).

12. Inrichting volgens conclusie 11 ingericht voor gebruik als een endoscoopuiteinde, waarbij de golflengtescheidingsinrichting een dichroïde prismasamenstel (52, 30) is.

13. Inrichting volgens conclusie 12, verder voorzien van fibers (60) voor het doorsturen van excitatielicht om het fluorescentiemiddel te exciteren.

14. Endoscoopuiteinde volgens conclusie 12 of 13, waarbij het dichroïde prismasamenstel (52, 30) tenminste drie kanalen heeft, waarbij het derde kanaal is ingericht voor het doorsturen van licht met een golflengte in het zichtbare bereik, waaruit de respectieve sensor (16) een vierde detectiesignaal genereert dat de zichtbare omgeving van het endoscoopuiteinde representeert.

15. Endoscoopsysteem omvattende een endoscoopuiteinde volgens een van de conclusies 12-14 en verwerkingsmiddelen voor het numeriek bepalen van een derde detectiesignaal met een verbeterde verhouding fluorescentie-tot-achtergrondstraling op basis van het eerste detectiesignaal (S1), het tweede detectiesignaal (S2), en het fluorescentie golflengteprofiel (73).

16. Meetsysteem omvattende een inrichting volgens conclusie 11 en verwerkingsmiddelen voor het numeriek bepalen van een derde detectiesignaal met een verbeterde verhouding fluorescentie-tot-achtergrondstraling op basis van het eerste detectiesignaal (S1), het tweede detectiesignaal (S2), en het fluorescentie golflengteprofiel (73).

Fig 1

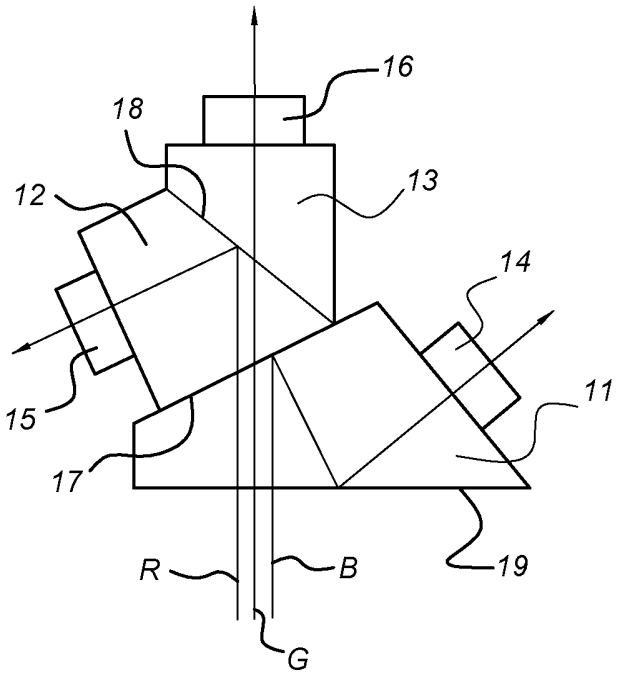


Fig 2

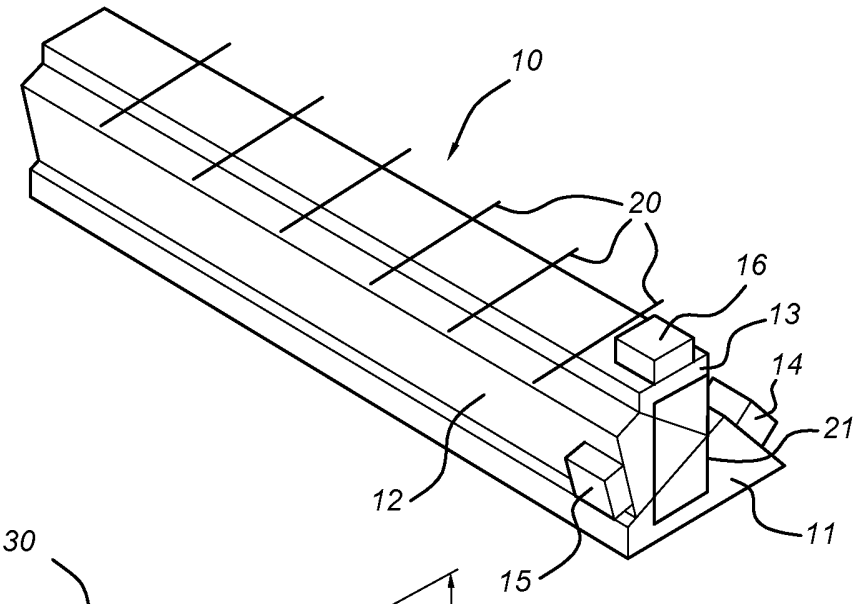


Fig 3

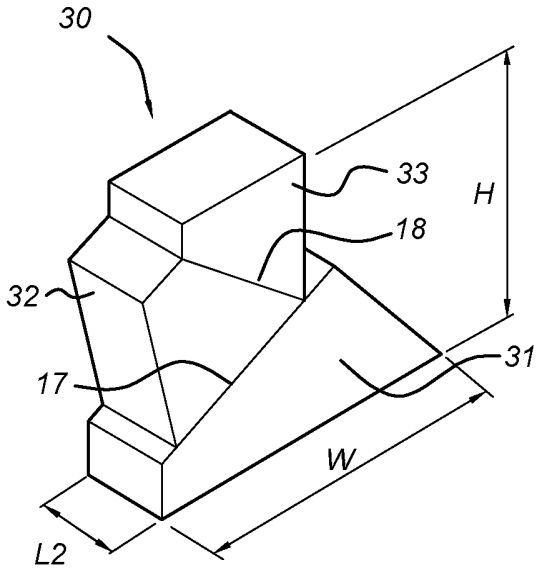


Fig 4

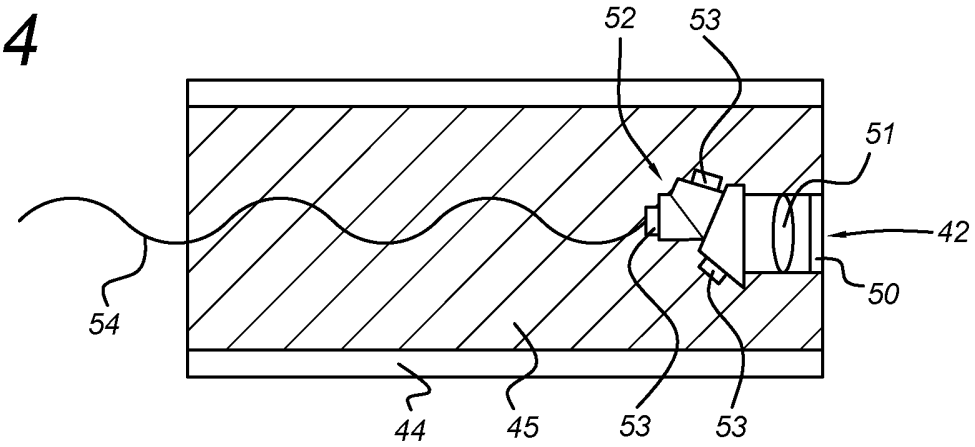


Fig 5

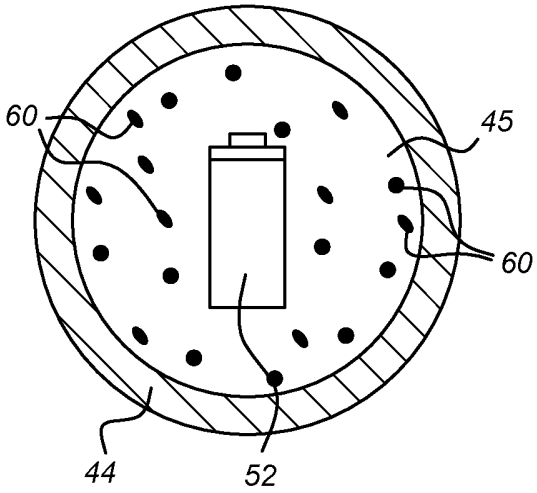


Fig 6

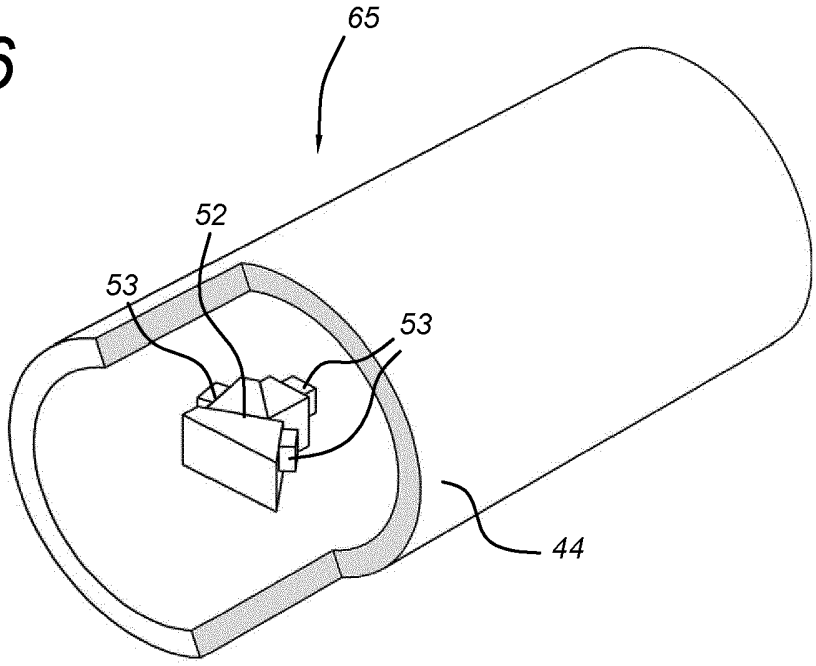


Fig 7

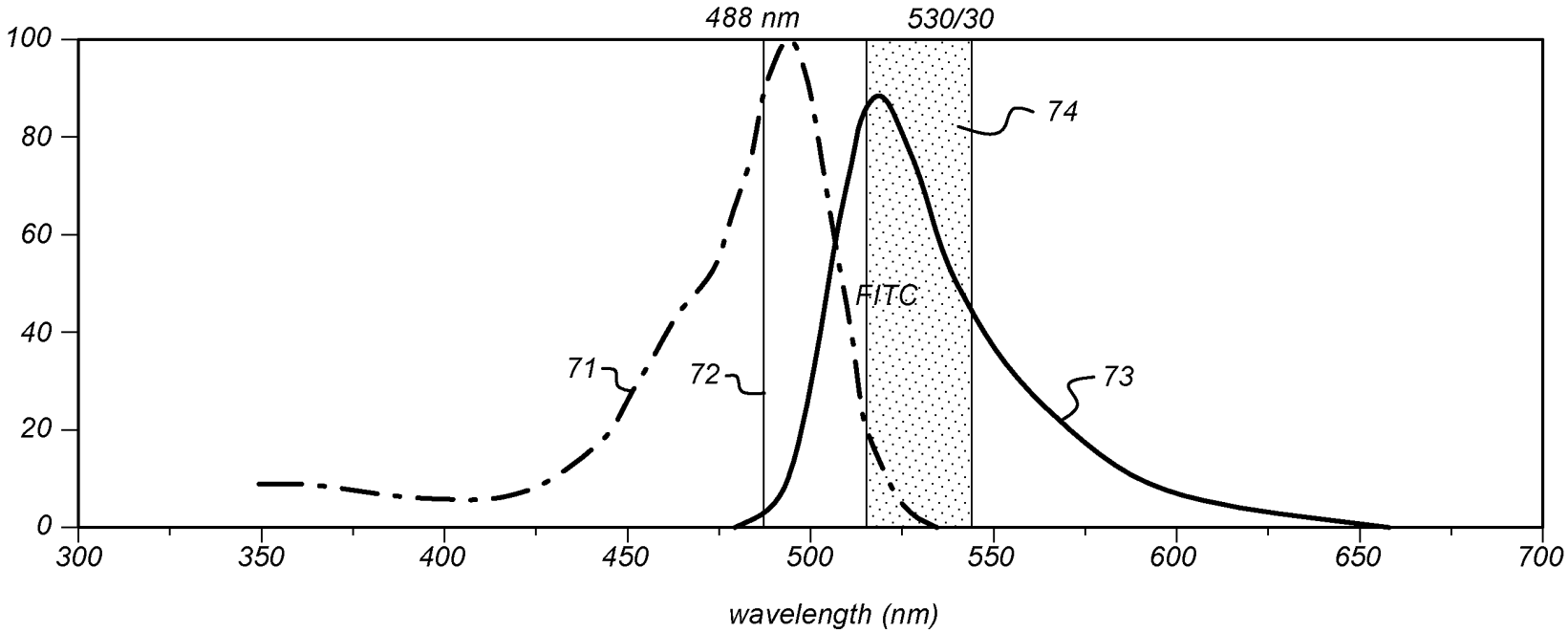

488 nm
530/30
100
80
60
40
20
0
74
FITC
71
72
73
300
350
400
450
500
550
600
650
700
wavelength (nm)

Fig 8

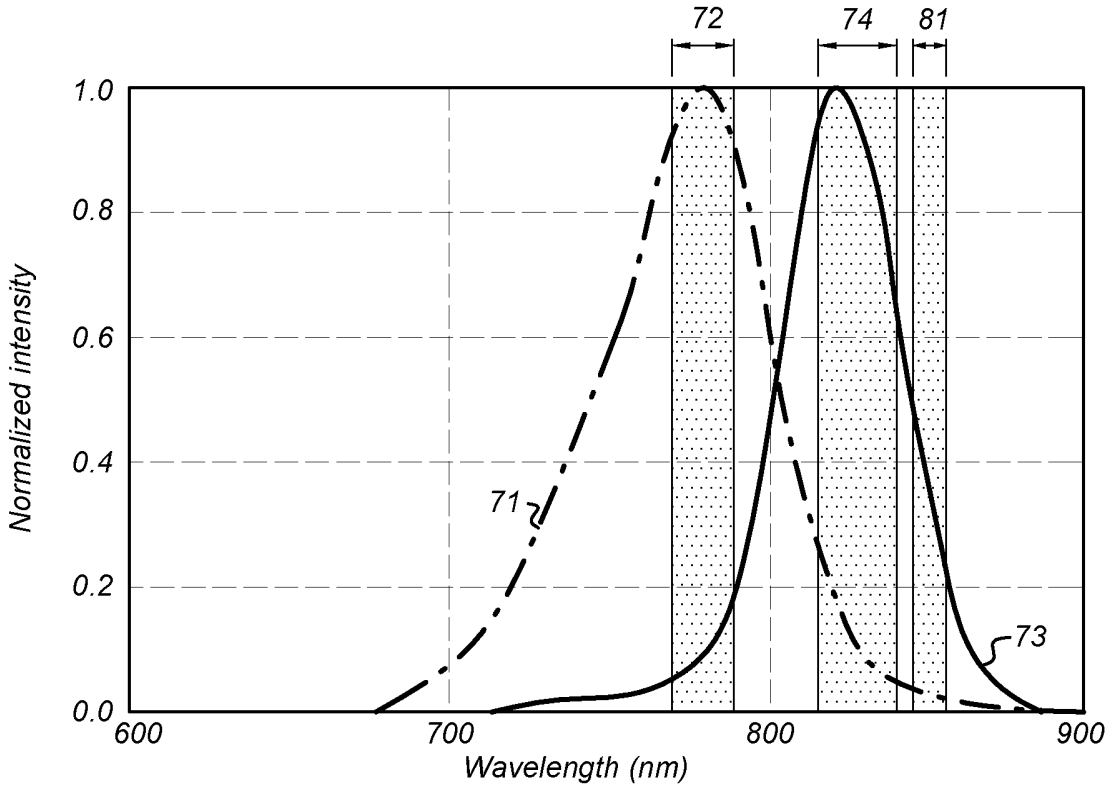

72
74
81
1.0
0.8
0.6
0.4
0.2
0.0
Normalized intensity
71
73
600
700
800
900
Wavelength (nm)

Fig 9

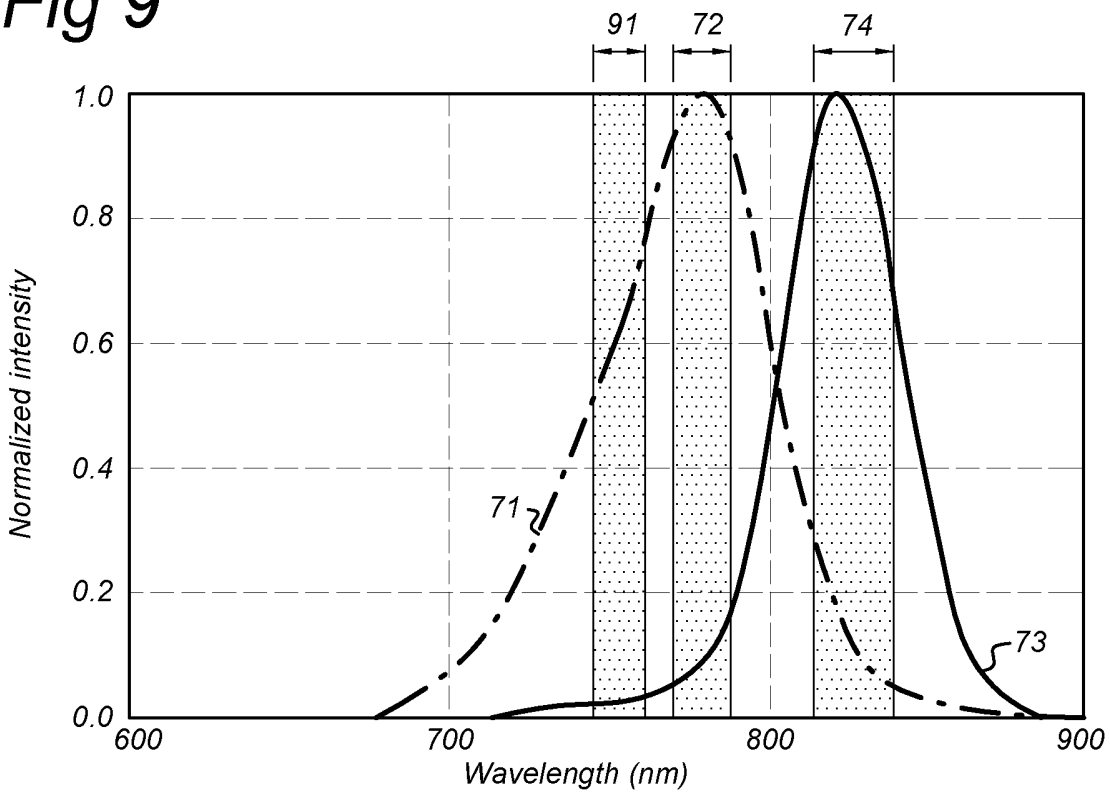

91
72
74
1.0
0.8
0.6
0.4
0.2
0.0
Normalized intensity
71
73
600
700
800
900
Wavelength (nm)

Fig 10

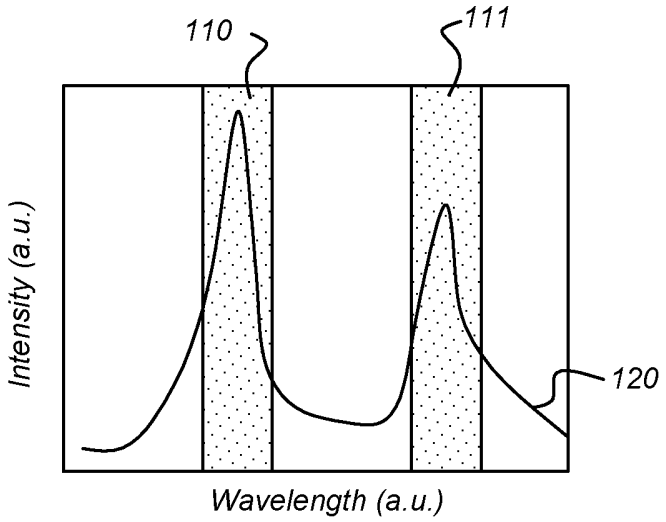


Fig 11

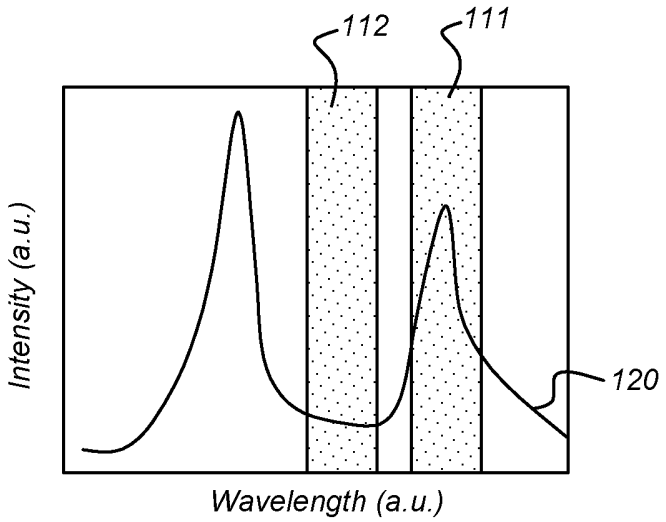


Fig 12

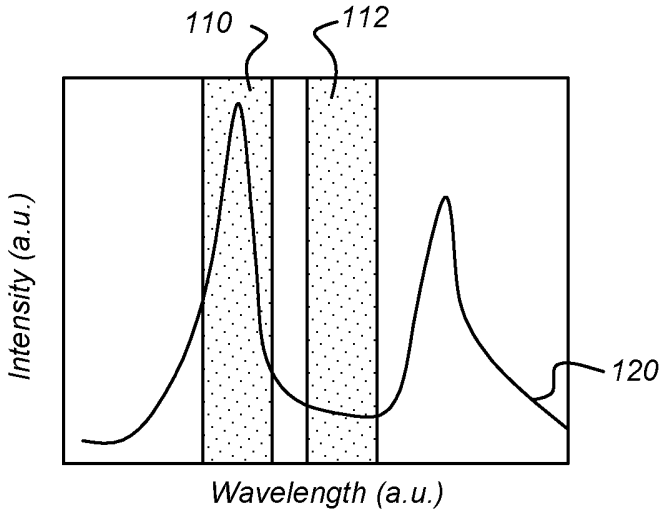
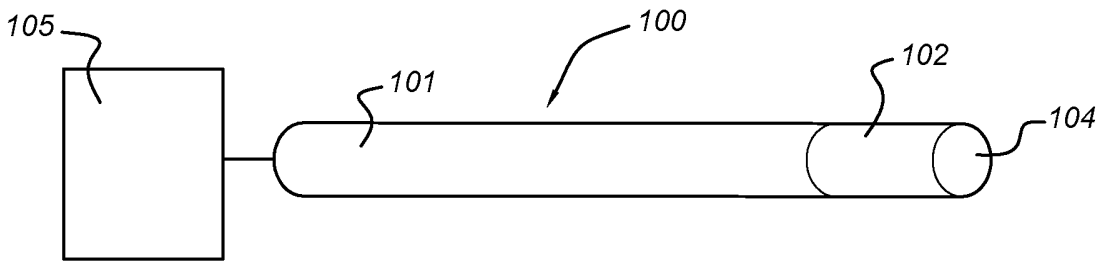


Fig 13



SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE	KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
	P6041079NL
Nederlands aanvraag nr. **2009124**	Indieningsdatum **05-07-2012**
	Ingeroepen voorrangsdatum
Aanvrager (Naam) **Quest Photonic Devices B.V.**	
Datum van het verzoek voor een onderzoek van internationaal type **06-10-2012**	Door de Instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr. **SN 58897**

I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven)

Volgens de internationale classificatie (IPC)

A61B1/04 **A61B1/00** **A61B1/05**
A61B1/06 **A61B5/0215**

II. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimumdocumentatie

Classificatiesysteem	Classificatiesymbolen
IPC	**A61B**

Onderzochte andere documentatie dan de minimum documentatie, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

III.	☐ **GEEN ONDERZOEK MOGELIJK VOOR BEPAALDE CONCLUSIES**	(opmerkingen op aanvullingsblad)
IV.	☐ **GEBREK AAN EENHEID VAN UITVINDING**	(opmerkingen op aanvullingsblad)

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2009124

A. CLASSIFICATIE VAN HET ONDERWERP
INV. A61B1/04 A61B1/00 A61B1/05 A61B1/06 A61B5/0215
ADD.

Volgens de Internationale Classificatie van octrooien (IPC) of zowel volgens de nationale classificatie als volgens de IPC.

B. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte miminum documentatie (classificatie gevolgd door classificatiesymbolen)
A61B

Onderzochte andere documentatie dan de mimimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden)
EPO-Internal, WPI Data

C. VAN BELANG GEACHTE DOCUMENTEN

Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	US 2002/062061 A1 (KANEKO MAMORU [JP] ET AL) 23 mei 2002 (2002-05-23) * alineas [0051] - [0053], [0062] - [0071], [0087] - [0095], [0150] - [0169]; figuren 1,11,12 * -----	1-5,7,11
X	US 7 722 534 B2 (CLINE RICHARD W [CA] ET AL) 25 mei 2010 (2010-05-25) * kolom 4, regel 42 - regel 51 * * kolom 6, regel 20 - kolom 9, regel 13 * * kolom 10, regel 50 - kolom 11, regel 22 * * kolom 12, regel 18 - kolom 14, regel 7 * * kolom 20, regel 58 - kolom 21, regel 59 * * kolom 23, regel 3 - kolom 24, regel 12; figuren 1-4,6-9,17 * ----- -/--	1,2,4, 8-16

[X] Verdere documenten worden vermeld in het vervolg van vak C.

[X] Leden van dezelfde octrooifamilie zijn vermeld in een bijlage

° Speciale categorieën van aangehaalde documenten

"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft

"D" in de octrooiaanvrage vermeld

"E" eerdere octrooi(aanvrage), gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven

"L" om andere redenen vermelde literatuur

"O" niet-schriftelijke stand van de techniek

"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur

"T" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bezwarend is voor de octrooiaanvrage, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding

"X" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur

"Y" de conclusie wordt als niet inventief beschouwd ten opzichte van de combinatie van deze literatuur met andere geciteerde literatuur van dezelfde categorie, waarbij de combinatie voor de vakman voor de hand liggend wordt geacht

"&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie

Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid	Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type
15 april 2013	

Naam en adres van de instantie	De bevoegde ambtenaar
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rick, Kai

3

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2009124

C.(Vervolg). VAN BELANG GEACHTE DOCUMENTEN

Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
A	US 2008/027286 A1 (XIE TIANYU [JP]) 31 januari 2008 (2008-01-31) * alineas [0113] - [0135]; figuren 9,10 * -----	1-16
A	DE 10 2009 024943 A1 (WOM WORLD OF MEDICINE AG [DE]) 16 december 2010 (2010-12-16) * alineas [0003], [0007] - [0015], [0019], [0024] - [0028], [0056] - [0061], [0065] - [0073]; figuren 1-6 * -----	1-16

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Informatie over leden van dezelfde octrooifamilie

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2009124

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)	Datum van publicatie
US 2002062061 A1	23-05-2002	US 6422994 B1	23-07-2002
		US 2002062061 A1	23-05-2002
US 7722534 B2	25-05-2010	DE 60122894 T2	15-03-2007
		EP 1301118 A2	16-04-2003
		EP 1731087 A2	13-12-2006
		JP 4133319 B2	13-08-2008
		JP 2004504090 A	12-02-2004
		JP 2005046634 A	24-02-2005
		US 2002035330 A1	21-03-2002
		US 2005065406 A1	24-03-2005
		US 2008228037 A1	18-09-2008
		US 2010198010 A1	05-08-2010
		US 2010210904 A1	19-08-2010
		WO 0207587 A2	31-01-2002
US 2008027286 A1	31-01-2008	EP 1795111 A1	13-06-2007
		JP 4610970 B2	12-01-2011
		JP 2006075189 A	23-03-2006
		US 2008027286 A1	31-01-2008
		WO 2006028023 A1	16-03-2006
DE 102009024943 A1	16-12-2010	DE 102009024943 A1	16-12-2010
		EP 2440119 A1	18-04-2012
		US 2012268573 A1	25-10-2012
		WO 2010142672 A1	16-12-2010

WRITTEN OPINION

File No.	Filing date *(day/month/year)*	Priority date *(day/month/year)*	Application No.
SN58897	05.07.2012		NL2009124

International Patent Classification (IPC)
INV. A61B1/04 A61B1/00 A61B1/05 A61B1/06 A61B5/0215

Applicant
Quest Photonic Devices B.V.

This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the application
- ☐ Box No. VIII Certain observations on the application

	Examiner
	Rick, Kai

Application number

WRITTEN OPINION

NL2009124

Box No. I Basis of this opinion

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the application as filed.

   ☐ filed together with the application in electronic form.

   ☐ furnished subsequently for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	6
	No:	Claims	1-5, 7-16
Inventive step	Yes:	Claims	6
	No:	Claims	1-5, 7-16
Industrial applicability	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1 US 2002/062061 A1 (KANEKO MAMORU [JP] ET AL) 23 mei 2002 (2002-05-23)

D2 US 7 722 534 B2 (CLINE RICHARD W [CA] ET AL) 25 mei 2010 (2010-05-25)

2 Document D1 (the references in parentheses applying to this document) relates to a method for detecting fluorescence radiation from a fluorescence agent, the method comprising emitting light at an excitation wavelength range for causing fluorescence radiation emission in the fluorescence agent (Para. 87), said fluorescence radiation having a fluorescence wavelength profile detecting light at a first fluorescence wavelength range as a first detection signal (Para. 88); detecting light at a second fluorescence wavelength range as a second detection signal (Para. 89)and numerically determining a third detection signal with an improved fluorescence-to- background radiation ratio based on the first detection signal, the second detection signal, and the fluorescence wavelength profile (Para. 90, 161 and 162).

Thus all structural features mentioned in or derivable from present claim 1 are known from D1. In this context it is to be noted that also at least document D2 (e.g. col. 10, l. 50 to col. 11, l. 22) of the search report discloses all features of the above mentioned claim 1. Present **claim 1** thus **lacks novelty.** The same objection applies mutatis mutandis to corresponding apparatus **claim 11**.

3 Further **dependent claims 2-5, 7-10 and 12-16** contain either features known per se from the prior art or being slight constructional changes which come within the scope of the customary practice followed by persons skilled in the art. The applicant should in particular refer to the following passages:

- claim 2 see D1, Para. 90 and 94;
- claim 3 see D1, Para. 95;
- claim 4 see D1, Ref. **32**, Para. 62 and Fig. 1;
- claim 5 see D1, Para. 165;
- claim 7 see D1, Para. 161 and Fig. 12;

- claim 8 see D2, col. 7, l. 15-20;

- claim 9 see D2, col. 4, l. 42-46;

- claim 10 and 12-14 see D2, col. 12, l. 50-51 ,Figs. 1 and 9;

- claim 15 and 16 see D2, col. 23, l. 18-26.

Thus also claims 2-5, 7-10 and 12-16 do not meet the requirements with respect to novelty.

4 However the combination of the features of dependent **claim 6**, is neither known from, nor rendered obvious by, the available prior art.