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(54) **METHOD OF MEASURING SUPERFICIAL CHEMICAL SPECIES AND APPARATUS FOR MEASURING THE SAME**

VERFAHREN ZUR MESSUNG VON OBERFLÄCHLICHEN CHEMISCHEN SPEZIES UND MESSGERÄT DAFÜR

PROCÉDÉ DE MESURE DES ESPÈCES CHIMIQUES SUPERFICIELLES ET APPAREIL DE MESURE

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EP 1 719 448 B1

Description

TECHNICAL FIELD

[0001] The present invention relates to a method of measuring a blood flow in a biological surface or the like by conducting a spectral analysis of a light reflected from the biological surface to which a white light is irradiated. The present invention also relates to an apparatus for measuring the same.

BACKGROUND ART

[0002] Conventional diagnosis of skin cancer etc. has been made by pathological analysis, e.g., seeing the color of the skin, touching the skin by hand and/or taking a living tissue as a sample therefor, Observation by taking a living tissue sample, however, creates a painful burden to the patient, and can cause metastasis thereof if it is virulent cancer. Thus, it is not desirable to take a living tissue sample.

[0003] As a solution, a noninvasive test method has heretofore been proposed, wherein the color of the skin surface at respective positions is split so that a light of a wavelength specific to a predicted pathological change is detected through a plurality of filters, displaying the reflection intensity thereof as a two-dimensional image. An apparatus for measuring and displaying such spectroscopic images of colors are disclosed in patent document 1, for example.

[0004] The conventional measuring methods and apparatuses, however, have problems that there are many errors in detecting a pathological change since an image is obtained by choosing a wavelength characteristic of a specific color in accordance with an intended purpose, and then filtering the same; and that the measuring apparatuses become too complex since they use a plurality of filters.

> Patent document 1: Japanese Un-examined Patent Publication No. 2000-356552

[0005] Patent US5784162 discloses a method for imaging applicable to medical diagnostics. which comprises the steps of:

> collecting spectra independently and simultaneously from each point (e.g. pixel) of a sample using the cervical smear prepared for a Papanicolaou smear test performed to diagnose a cervical cancer;
> conducting a principal component analysis of the spectral data to obtain the principal components 1-20;
> obtaining black and white images from the principal components; and deriving concentrations of substances that identify cancerous cells from the principal components 10 and 13.

[0006] Moreover, patent WO03043492 discloses a method for spectroscopic tissue examination; the received spectrum is transformed to scalar coefficients, which are correlated to the susceptibility of the mammal to develop a certain disease.

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0007] An object of the present invention is to provide a method for processing skin surface observation measurement data that can solve the above-mentioned problem, and respond to various pathological changes with less detection errors thereof. It is another object of the present invention to provide a measuring apparatus used for that purpose that has a simple structure, eliminating the need for any filters.

MEANS FOR SOLVING THE PROBLEMS

[0008] A method of measuring a biological surface according to the invention is defined in claim 1. An apparatus according to the invention is defined in claim 3.

[0009] According to the above measuring method, since all the spectra reflected from each position of the biological surface used as a sample are detected to allow them to undergo statistical data processing, no filter is needed. Further, since the condition of a biological surface is measured and displayed by comprehensive analysis of a wide range of data, it is effective to decrease errors in detecting pathological changes.

[0010] Since the multivariate analysis is conducted with a basic wavelength band of light used for data processing ranging from 500-600nm and 500-850nm, it is effective for observing, for example, diabetic peripheral vascular obstruction syndrome or the post-transplant condition of a transplanted skin, enabling errors in detecting pathological changes to be lessened.

[0011] Since the multivariate analysis is conducted with a basic wavelength band of light used for data processing ranging from 500-600nm and 700-780nm, not only a melanin amount in the skin such as a mole, but also a cancer hidden in the mole can be detected.

[0012] Specifically, as the multivariate analysis is conducted to calculate the score with respect to an eigenvector corresponding to melanin, melanin amount can be predicted using a calibration curve, thus enabling a patient to undergo treatment before pathological change occurs.

[0013] Still further, as the multivariate analysis is conducted with a basic wavelength band of light used for data processing ranging from 500-600nm, 500-850nm and 700-780nm, it is effective for detecting a superficial cancer cell, for example.

[0014] Furthermore, since a light-sensitive substance is administered to a biological surface for treatment of a cancer; and the multivariate analysis is conducted with

a basic wavelength band of light used for data processing ranging from 500 to 600nm, 500 to 850nm and 700 to 780nm, further including a wavelength band specific to said light-sensitive substance, it is possible to observe the position of the cancer as well as the therapeutic effect by the light-sensitive substance having an absorption band in this wavelength band.

[0015] Still further, the multivariate analysis is conducted with a basic wavelength band of light used for data processing ranging from 700nm or above. Since such light is eye-safe one, it is possible, for example, to observe a blood flow and a relative amount of oxygenated hemoglobin and reduced hemoglobin on retina at the back of the eye.

[0016] Moreover, since the multivariate analysis is conducted with a basic wavelength band of light used for data processing ranging from 500 to 600nm, and 700 to 780 nm, to measure a moment-to-moment change of spectral information from subcutaneous peripheral blood vessels, it is possible to detect pathological changes such as hyperlipemia and abnormal glucose tolerance.

[0017] Also, the foregoing data measuring apparatus is the one that enables the implementation of the above-mentioned measuring method, eliminating the need for a filter which the conventional apparatuses would require, thus simplifying the structure of the apparatus.

[0018] Still moreover, according to the foregoing data measuring apparatus, the apparatus is combined with an optical fiber, and thus a white light irradiation part integral with a reflection condensing part is separable from a spectroscopic-analysis part. The apparatus structured as above enables the provision of an apparatus applicable to the inspection at the time of intraoral, craniotomy or abdominal operation, etc, as well as a measuring apparatus that enables easy inspection of a digestive organ, a respiratory organ and a wall surface of a blood vessel in combination with a conventional alimentary system endoscope, a respiratory system endoscope or a vascular catheter.

THE EFFECT OF THE INVENTION

[0019] According to the present invention, there can be provided a measuring method that can respond to various pathological changes with less detection errors thereof. Further, the measuring apparatus therefor does not need any filter, thus simplifying the structure of the apparatus.

BEST MODE FOR CARRYING OUT THE INVENTION

[0020] Next is a description of preferred embodiments of the present invention. First, a measuring apparatus of the present invention will be explained with reference to Fig. 1 and Fig. 2, In Fig. 1, numeral 1 designates a stage on which a sample S is placed, while numeral 2 designates a white light source. A spectroscope 4 provided with a slit 3 is provided above the stage 1.

[0021] The spectroscope 4 is an imaging spectroscope equipped with a transmission grating. The light reflected from one line of a sample is allowed to pass through the slit 3, and then separated (split) by the spectroscope 4 to thereby form an image on an acceptance surface of a CCD camera 5. In other words, X axis of the acceptance surface of the CCD camera 5 corresponds to a position of the sample on the one line, while the light is separated into a spectrum in the direction of Y axis thereof.

[0022] The structure of the spectroscope 4 is illustrated in detail in Fig. 2. The spectroscope 4 comprises the slit 3 composed of a slit body 3a and a lens 4a for focusing light. The spectroscope 4 further comprises two lenses 4a, 4c and a prism 4b of a transmission grating type provided therebetween. The camera 5 is equipped with a photo-multiplier 5a to raise sensitivity so that it can sense even a weak light.

[0023] Since the structure of the optical portion of this measuring apparatus is as described above, spectral data from one line of the sample S can be obtained on one frame of the CCD camera. The data are inputted into a data processing equipment 6. Then, the stage is moved a minute distance to thereby obtain subsequent one-line spectral data on a next frame of the CCD camera, which are then sent to the data processing equipment 6.

[0024] By repeating this operation, a spectral data of a two-dimensional field can be obtained. In reality, the data can be obtained by the CCD camera 5 synchronously with a substantially continuous movement of the stage 1 by a mechanism such as an adjusting means 7 for sweeping in a direction perpendicular to the one line of the surface of the sample, corresponding to the above-mentioned X axis.

[0025] Moreover, since the measuring apparatus is combined with an optical fiber, a white light irradiation part integral with a reflection condensing part is separated from a spectroscopic-analysis part. Thus, it is possible to measure a visceral condition observable via the optical fiber as well as a skin surface condition.

[0026] The apparatus structured as above is applicable to the inspection at the time of intraoral, craniotomy or abdominal operation, enabling easy inspection of a digestive organ, a respiratory organ and a wall surface of a blood vessel in combination with a conventional alimentary system endoscope, a respiratory system endoscope or a vascular catheter,

[0027] Next, a method of processing the data obtained as above is explained in detail. Whilst the size of a minute region of a sample to be detected is determined by the slit 3a and the magnification of the object lens 4a the S/N ratio of the spectral data is improved by taking the average of the spectral data of four adjacent minute regions.

[0028] Thus, the spectral data obtained in each position is plotted to a spectral multi-dimensional space. For example, if the wavelength of the obtained data is 500nm to 600nm, it is divided by a minimum resolution of 5nm, and then absorbance (in arbitral unit) at respective wavelengths are determined, thus plotting one point against

one position in the 20-dimensional space divided thus way.

[0029] For example, assuming that the size of a sample is 0.01 square millimeter, and the minute region to be detected is 0.01 square millimeter, then the spectral data from 10,000 minute regions are obtained. For example, when the data of four minute regions are averaged for the purpose of improving a S/N ratio, then the number of the data finally obtained is 2,500. These 2,500 spectral data are plotted to the above-mentioned 20-dimensional spectral space.

[0030] Next, a direction where variance of the 2,500 points becomes the greatest in the 20-dimensional spectral space is determined as the first principal component, using, for example, the technique of multivariate analysis, such as principal component analysis (PCA), thus making that direction the eigenvector of the first principal component. Then, each plotting point is projected on a space orthogonal to the first eigenvector to determine the second principal component, thus making the same the eigenvector of the second principal component. In this way, the third to the nth principal components, and the third to the nth eigenvectors are determined according to the same procedure

[0031] Thus, the eigenvectors of the first, second and third principal components are determined, respectively, while the aforesaid 2,500 plotted data are projected on each of the eigenvectors. In other words, the component in the direction of each eigenvector is determined. The magnitude of the component is called a score The score in the direction of each eigenvector is plotted to each position of a sample on a gray scale or in colors according to the value of each score, thus displaying the same in a two-dimensional expression.

[0032] Fig. 3 shows a spectral absorption characteristic of human blood, A horizontal axis denotes a wavelength of light while a vertical axis denotes absorbance (in arbitrary unit). In Fig. 3, one of the two graphs shows the absorption spectrum of oxygenated hemoglobin, while the other thereof shows the absorption spectrum of reduced hemoglobin.

[0033] The characteristic difference between the two absorption spectra lies in that there are two peaks in the absorption spectrum of oxygenated hemoglobin, while one peak in that of reduced hemoglobin with regard to the form of peak between 500 nm and 600 nm. Another difference is noted between 700 nm and 800 nm where the absorption spectrum of oxygenated hemoglobin is flat, while the absorption spectrum of reduced hemoglobin has one peak.

[0034] Fig. 4 shows the value of each eigenvector component relative us to a certain wavelength is shown when the normal skin as a sample is measured, using a wavelength band from 500 nm to 600 nm.

[0035] The eigenvector component corresponding to the first principal component shows a total average of the 2,500 spectrums. The eigenvector component corresponding to the second principal component shows a spectrum corresponding to the total amount of hemoglobin, and that of the third principal component shows a difference spectrum of the oxygenated hemoglobin spectrum and the reduced hemoglobin spectrum.

[0036] Figs. 5(a) and 5(b) are each two-dimensional representation of the scores of the second and third principal components with the scores in respective positions being related to positions of measurement in the sample. As seen from Fig. 5 (a) and Fig. 5 (b), the relative levels of oxygenated hemoglobin and reduced hemoglobin as well as the blood total amount of a portion where a blood capillary is present was detected by the measuring apparatus of the invention.

[0037] Fig. 6 (a) and Fig. 6 (b) also show the two-dimensional representation thereof as observed with a larger spectral region (i.e., from 500 nm to 850 nm). Fig. 6 (a) shows the score of the second principal component, while Fig. 6 (b) that of the third principal component. Like in Fig. 5, a portion where a blood capillary is present was detected.

[0038] For example, when circulation of the blood to the capillary vessel is sluggish such as in dialectical peripheral vascular obstruction syndrome, the eigenvector corresponding to the second principal component will take the form of the difference spectrum of oxygenated hemoglobin and reduced hemoglobin, and thus more reduced hemoglobin will be observed in a portion where the blood is stagnating (not shown).

[0039] Further, when the skin is successfully implanted after a skin transplant operation, then the blood will be flowing into the capillary vessel on the skin, so that the post-transplant condition of the skin can be sensed by detecting the presence of hemoglobin therein.

[0040] Figs.7 and 8 show a second embodiment where a portion including lentigo is measured. The result of measurement using a wavelength band from 500 nm to 600 nm is shown in Fig.7, while the result of measurement using a wavelength band from 700 nm to 780 nm is shown in Fig. 8.

[0041] Fig. 7 is a two-dimensional representation of the score values of the second principal component with a wavelength band from 500 nm to 600 nm. As is seen therefrom, much hemoglobin is detected around the lentigo, while the lentigo portion strongly absorbs light and thus shows a low value.

[0042] Fig. 8 is a two-dimensional representation of the score values of the third principal component with a wavelength band from 700 nm to 780 nm. Reduced hemoglobin makes a large contribution to this component. Fig. 8 demonstrates that a lot of reduced hemoglobin is present around the lentigo.

[0043] For example, in some disease states, new blood vessels grow and concentrate around a tumor if there is a malignant melanoma so that hemoglobin around the tumor increases, and thus the image of the second principal component for a wavelength band from 500nm to 600nm is clearly different from that in the case of lentigo.

[0044] Moreover, due to a lot of oxygenated hemoglobin being present in new blood vessels, the score values of the images of the second and third principal components are clearly different from that in the case of lentigo, for a wavelength band from 700nm to 780nm.

[0045] Melanin (not shown) is one of the main components that are deposited in a skin surface layer to determine the color of the skin. Deposition of a large amount of melanin produces a spot or a lentigo. Since a portion with a lentigo has lots of melanin and light of a short wavelength is easy to be absorbed, light does not reach a dermis where blood vessels are present. Moreover, an absorption characteristic specific to melanin is also observed.

[0046] Although many researches on the melanin concentration using a spectroscopic method have been conducted since 1980s, they have remained in the discussions on chromatic coordinate parameter or melanin index, and have not yet reached concentration quantification.

[0047] In order to measure the concentration of melanin, visible-range absorption spectrum from the skin was first analyzed using the technique of the multivariate analysis of the present invention, to thereby determine the eigenvector corresponding to melanin, while a calibration curve was drawn as shown in Fig.9, using a skin model made of melanin and collagen.

[0048] By using this calibration curve, the melanin concentration in arbitrary portion can be predicted from the score value thereof.

[0049] As for a third embodiment, the score of the second principal component when using a sample having a cancer cell and the wavelength band from 500nm to 600nm is shown in Fig. 10(a), while that of the third principal component is shown in Fig. 10 (b). The score of the second principal component when using the wavelength band from 500nm to 800nm is shown in Fig. 11, while the score of the third principal component when using the wavelength band from 700nm to 780nm is shown in Fig. 12, respectively.

[0050] Since vascular growth occurs around a cancer cell and hence hemoglobin increases there, the score of the second principal component in the periphery of the cancer cell becomes large, as can be observed from Fig. 10 (a) and Fig. 11.

[0051] Also, vascular growth occurs around a cancer cell and hence oxygenated hemoglobin increases while reduced hemoglobin decreases relatively. Accordingly, as shown in Fig. 10 (b), comparatively a large amount of oxygenated hemoglobin was present around a cancer cell, and the score of the third principal component was high. Moreover, as shown in Fig. 12, it can be observed that the score of the third principal component in the case of using wavelength band from 700nm to 780nm decreased around a cancer cell.

[0052] According to the method of the present invention one example is shown that verifies the therapeutic effect on cancer when using talaporfin as a light-sensitive substance. It is known that talaporfin as a light-sensitive substance is accumulated into a macrophage around a cancer cell, and that if a light of a certain wavelength (intrinsic absorption region) specifically absorbed by talaporfin is irradiated thereto, active oxygen is generated at the time of decomposition of talaporfin, thus killing a cancer cell while clogging a new blood vessel, thereby providing an effective medical treatment for cancer. This is called Photo Dynamic Therapy (PDT).

[0053] Fig. 13 shows the score of the second principal component for the wavelength band from 500nm to 800nm when the sample having a cancer cell of the third embodiment underwent the above-mentioned treatment, while Fig. 14 shows the score of the third principal component for the wavelength band from 500nm to 600nm, respectively.

[0054] As can be seen from Figs. 13 and 14, it was demonstrated that hemoglobin was present around a cancer cell, and that it was rich in reduced hemoglobin. That is, it was demonstrated that the flow in oxygenated hemoglobin-rich new blood vessels was inhibited.

[0055] On the other hand, since the intrinsic absorption region of tissue-bonded talaporfin is in a range of from 660nm to 670nm (center wavelength: 664nm), the result of analysis using a wavelength band including that wavelength is shown in Fig. 15. Fig. 15 is a diagram showing the score of the third principal component, with a wavelength band from 600nm to 700nm.

[0056] It can be observed from Fig. 15 that talaporfin disappeared in the cancer cell, but remained a little in the peripheral portion thereof.

[0057] From the result, not only the therapeutic effect on cancer can be confirmed, but also the completeness of the treatment to cause talaporfin remaining around the cancer cell to disappear can be confirmed.

[0058] Fig. 16 shows a change of quantity of talaporfin with time from the administration of talaporfin to post-PDT.

[0059] Since talaporfin has a characteristic absorption band at 664nm, the feature of this characteristic absorption band will appear in the second principal component if principal component analysis is performed with a wavelength band from 600nm to 700nm.

[0060] If the spectrums in all the observing places are projected onto the direction of the second principal component, the value obtained will serve as an index of talaporfin concentration. Fig. 16 shows the change of the amount of talaporfin with time, using the magnitude of the index thereof

[0061] The drawings indicate that on a color scale, the warmer (the colder) the color is, the more (the less) talaporfin is present. It can be seen that soon after the administration by intravenous injection, talaporfin is increasingly accumulated around a cancer cell over timer, due to its affinity for cancer.

[0062] It is a well-known fact that after PDT (to a potion of cancer encircled by a dashed line in Fig. 16(f)) the tetrapyrrole ring of talaporfin is broken so that the 664nm

absorption peak disappears. It is to be noted that such fact is exactly reflected in Fig. 16(f).

[0063] When principal component analysis is performed with a wavelength band from 500nm to 600nm, the third principal component can be interpreted as a difference spectrum of an oxygenated hemoglobin spectrum and a reduced hemoglobin spectrum. Therefore, it follows that the larger (the smaller) the score of the third principal component is, the larger (smaller) amount of oxygenated (reduced) hemoglobin is relatively present.

[0064] Fig. 17 shows the change of the score of the third principal component with time. The drawings indicate that the warmer (the colder) the color is, the more oxygenated (reduced) hemoglobin is present. It can be seen that the vicinity of the cancer cell has more oxygenated hemoglobin as compared with the surrounding thereof.

[0065] This is in agreement with a clinical condition that the growth of new blood vessels occurs around a cancer cell. It is assumed that after PDT (to a potion of cancer encircled by a dashed line in Fig. 17 (f)), blood vessels in the portion are clogged, so that the amount of reduced hemoglobin relatively increases around the cancer cell. It is to noted that such fact is exactly reflected in Fig. 17 (f).

[0066] According to a further method one example is shown that measures the amounts of hemoglobin and oxygenated hemoglobin in diagnosing the bloodstream on retina at the back of the eye. In the conventional diagnosis of the bloodstream on retina at the back of the eye, strong visible light is irradiated to the back of the eye to take an image thereof so as to make a diagnosis from the image, which, however, creates a painful burden to a test subject. Moreover, it often leads to erroneous diagnosis to make a diagnosis using a photograph of a surface only.

[0067] According to this method the two-dimensional display according to the blood flow of the fundus of the eye is obtained, and thus it is possible to observe where the test subject has an abnormality and how serious it is Since visible light is too strong to open an eye, the present invention features the use of an eye-safe light of a near-infrared region of 700nm or above The scores of the second and third principal components are used for imaging, like the foregoing examples.

[0068] According to a further method, one example is shown that detects blood fluidity failure that causes organ microcirculation failure in the multiple risk-factor syndrome essentially consisting of hyperlipemia, abnormal glucose tolerance, obesity, insulin resistance syndrome, etc., through the analysis of change of the score of the second principal component with time.

[0069] The measurement is performed in such a manner that a part of a test subject's body such as his/her upper arm is compressed by a tourniquet to temporarily stop the flow of blood, and then loosen the tourniquet to thereby measure moment-to-moment change of the score of the principal component having an eigenvector indicative of a spectrum showing total amount of hemoglobin or a difference spectrum of oxygenated hemoglobin and reduced hemoglobin.

[0070] For example, in the wavelength band of 500 nm to 600 nm, the score of the second principal component indicates a relative amount of oxygenated hemoglobin and reduced hemoglobin, and thus the score takes a negative value when the flow of blood is temporarily stopped by the compression.

[0071] When the tourniquet is loosened, then the blood will flow out and the total amount of hemoglobin and the relative amount of oxygenated hemoglobin will increase. At that moment, if there is no blood fluidity failure, blood flow volume will be recovered promptly, but if there is, it will take time, thus making it possible to detect the presence of absence of failure

[0072] Fig. 18 shows a moment-to-moment change of the score of the second principal component with respect to five test subjects, using a wavelength band of 500nm to 600nm. The graph of Fig.18 is standardized so that the score of the second principal component may vary between 0 and 1.

[0073] Fig. 19 shows the time taken for the standardized score of the second principal component to rise to 50%, 70% and 90%. Test subject A is a type II diabetic (fasting glucose level: 200 mg/dl), while the others are normal subjects (fasting glucose level: 95 mg/dl). It can be seen therefrom that the test subject A has a 90% rise time longer than the others.

[0074] Fig. 20 shows the time obtained from a moment-to-moment change of the score of the second principal component, in the wavelength band of 500nm to 850nm, using the same method as the above-mentioned. As can be also seen therefrom, the test subject A has a 90% rise time greater than the others. Thus way, blood fluidity failure can be easily detected through the observation of the moment-to-moment change of the score of the second principal component

[0075] Moreover, since oxygenated hemoglobin will begin to flow into capillary vessels if the skin begins to be successfully implanted after a skin transplant operation, moment-to-moment change of the skin implantation condition can be known by observing change of the score of the second principal component over time, using the same method as the above-mentioned method.

BRIEF DESCRIPTION OF THE DRAWINGS

[0076]

Fig. 1 is a schematic diagram showing a measuring apparatus in accordance with the present invention.
Fig. 2 is a schematic diagram showing the structure of a spectroscope mounted in the measuring apparatus of the present invention.
Fig. 3 is a graph showing spectral absorption characteristics of human blood.
Fig. 4 is a graph showing components of eigenvec-

tors corresponding to respective principal components calculated from the spectra from the normal skin.

Fig. 5 is a two-dimensional representation of images of the score values from the normal skin measured by the apparatus of Fig. 1 with a wavelength band of from 500 nm to 600 nm according to the first embodiment of the invention.

Fig. 6 is a two-dimensional representation of images of the score values from the normal skin measured by the apparatus of Fig. 1 with a wavelength band of from 500 nm to 850 nm according to the first embodiment of the invention.

Fig. 7 is a two-dimensional representation of images of the score values of the second principal component from the skin including lentigo measured by the apparatus of Fig- 1 with a wavelength band of from 500 nm to 600 nm according to the second embodiment of the invention.

Fig. 8 is a two-dimensional representation of images of the score values of the third principal component from the skin including lentigo measured by the apparatus of Fig. 1 with a wavelength band of from 700 nm to 780 nm according to the second embodiment of the invention.

Fig. 9 is a graph showing relationship between a melanin concentration and a score in the direction of an eigenvector corresponding to melanin.

Fig. 10 is a two-dimensional representation of images of the score values from the skin having a cancer cell measured by the apparatus of Fig. 1 with a wavelength band of from 500 nm to 600 nm according to the third embodiment of the invention.

Fig. 11 is a two-dimensional representation of images of the score values from the skin having a cancer cell measured by the apparatus of Fig. 1 with a wavelength band of from 500 nm to 800 nm according to the third embodiment of the invention.

Fig. 12 is a two-dimensional representation of images of the score values from the skin having a cancer cell measured by the apparatus of Fig. 1 with a wavelength band of from 700 nm to 780 nm according to the third embodiment of the invention.

Fig. 13 a two-dimensional representation of images of the score values of the second principal component from the skin having a cancer cell after PDT treatment, measured by the apparatus of Fig. 1 with a wavelength band from 500nm to 800nm according to the fourth embodiment of the invention.

Fig. 14 a two-dimensional representation of images of the score values of the third principal component from the skin having a cancer cell after PDT treatment, measured by the apparatus of Fig. 1 with a wavelength band from 500nm to 600nm according to the fourth embodiment of the invention.

Fig. 15 a two-dimensional representation of images of the score values of the third principal component, measured by the apparatus of Fig. 1 with a wavelength band from 600nm to 700nm according to the fourth embodiment of the invention.

Figs. 16a to 16f are diagrams showing the change of amount of talaporfin with time from the administration of talaporfin to post-PDT.

Figs. 17a to 17f are diagrams showing the change of the score of the third principal component with time from the administration of talaporfin to post-PDT, with a wavelength band of from 500nm to 600nm.

Fig. 18 is a graph showing the change of the score of the second principal component with time measured by the apparatus of Fig. 1 with a wavelength band from 500nm to 600nm according to the sixth embodiment of the invention.

Fig. 19 is a table showing the time taken for the score of the second principal component measured by the apparatus of Fig. 1 with a wavelength band from 500nm to 600nm to rise to 50%, 70% and 90%.

Fig. 20 is a table showing the time taken for the score of the second principal component measured by the apparatus of Fig. 1 with a wavelength band from 500nm to 850nm to rise to 50%, 70% and 90%.

Claims

1. A method of measuring a skin surface which comprises the steps of

   irradiating a white light to said skin surface as a sample;
   detecting a spectrum of the white light reflected from two or more positions on said skin surface;
   plotting an absorbance of said spectrum to a spectral multi-dimensional space of light;
   conducting a multivariate analysis of a data on said spectral multi-dimensional space obtained from said two or more positions to obtain eigenvectors of at least first, second and third principal components;
   projecting the data of each position onto a direction of each eigenvector to display a magnitude thereof on a gray scale or in colors according to the magnitude, on a two-dimensional screen,

   characterized in determining by measuring means

   a total amount of hemoglobin from the second principal component,
   a difference in amount between oxygenated hemoglobin and reduced hemoglobin from the third principal component,
   or
   an amount of talaporfin from the second principal component, wherein the principal component analysis is performed with a wavelength band from 600 to 700 nm and talaporfin is pre-

administered to said skin.

2. The method of measuring a skin surface according to claim 1, for the determination of the total amount of hemoglobin and a difference in amount between oxygenated hemoglobin and reduced hemoglobin wherein said multivariate analysis is conducted with said spectrum of light having wavelength bands of from 500 to 600 nm or 500 to 850 nm.

3. An apparatus for measuring a skin surface comprising:

a means for irradiating a white light to said skin surface as a sample;
a means for detecting a spectrum of the white light reflected from two or more positions on said skin surface;
a means for plotting an absorbance of said spectrum to a spectral multi-dimensional space of light;
a means for obtaining eigenvectors of at least first, second and third principal components by conducting a multivariate analysis of data on said spectral multi-dimensional space obtained from said two or more positions;

and

a means for displaying a magnitude thereof on a gray scale or in colors according to the magnitude, on a two-dimensional screen by projecting the data of each position onto a direction of each eigenvector,

characterized in the apparatus being configured to determine

a total amount of hemoglobin from the second principal component,
a difference in amount between oxygenated hemoglobin and reduced hemoglobin from the third principal component,

or

an amount of talaporfin from the second principal component, wherein the principal component analysis is performed with a wavelength band from 600 to 700 nm and talaporfin is preadministered to said skin.

4. The apparatus for measuring a skin surface according to claim 4, wherein said means for irradiating a white light is provided integrally with a means for condensing reflection from two or more positions on said skin surface sample by combining them with an optical fibre.

Patentansprüche

1. Verfahren zur Messung einer Hautoberfläche, umfassend die folgenden Schritte:

Bestrahlen der Hautoberfläche mit einem weißen Licht als eine Probe;
Detektieren eines Spektrums des weißen Lichts, das von zwei oder mehreren Positionen auf der Hautoberfläche reflektiert wird;
Markieren einer Absorbanz des Spektrums auf einem spektralen multidimensionalen Lichtraum;
Ausführen einer multivariaten Analyse von Daten am spektralen multidimensionalen Raum, der von den zwei oder mehreren Positionen erreicht wird, um Eigenvektoren von mindestens ersten, zweiten und dritten Hauptkomponenten zu erreichen;
Projizieren der Daten jeder Position auf eine Richtung jedes Eigenvektors, um einen Wert davon auf einer Grauskala oder in Farben gemäß dem Wert, auf einem zweidimensionalen Bildschirm zu zeigen,
gekennzeichnet dadurch, mittels Messmitteln folgendes zu Bestimmen:

eine Gesamtmenge an Hämoglobin vom zweiten Hauptkomponent,
einen Unterschied der Menge zwischen oxidiertem Hämoglobin und reduziertem Hämoglobin vom dritten Hauptkomponent,
oder
eine Menge an Talaporfin vom zweiten Hauptkomponent, wobei die Hauptkomponentenanalyse mit einem Wellenlängenband von 600 bis 700 nm durchgeführt wird, und Talaporfin auf die Haut voraufgetragen wird.

2. Verfahren zur Messung einer Hautoberfläche nach Anspruch 1, zur Bestimmung der Gesamtmenge an Hämoglobin und eines Unterschieds der Menge zwischen oxidiertem Hämoglobin und reduziertem Hämoglobin, wobei die multivariate Analyse ausgeführt wird, indem das Lichtspektrum Wellenlängenbänder von 500 bis 600 nm oder 500 bis 850 nm aufweist.

3. Gerät zur Messung einer Hautoberfläche, umfassend:

ein Mittel zur Bestrahlung der Hautoberfläche mit einem weißen Licht als eine Probe;
ein Mittel zur Detektion eines Spektrums des weißen Lichts, das von zwei oder mehreren Positionen auf der Hautoberfläche reflektiert wird;
ein Mittel zur Markierung einer Absorbanz des Spektrums auf einem spektralen multidimensio-

nalen Lichtraum;
ein Mittel zur Erreichung von Eigenvektoren von mindestens ersten, zweiten und dritten Hauptkomponenten durch die Ausführung einer multivariaten Analyse von Daten am spektralen multidimensionalen Raum, der von den zwei oder mehreren Positionen erreicht wird;
und
ein Mittel zum Zeigen eines Werts davon auf einer Grauskala oder in Farben gemäß dem Wert, auf einem zweidimensionalen Bildschirm durch die Projizierung der Daten jeder Position auf eine Richtung jedes Eigenvektors,
dadurch gekennzeichnet, dass das Gerät ausgeformt ist, um folgendes zu Bestimmen:

eine Gesamtmenge an Hämoglobin vom zweiten Hauptkomponent,
einen Unterschied der Menge zwischen oxidiertem Hämoglobin und reduziertem Hämoglobin vom dritten Hauptkomponent,
oder
eine Menge an Talaporfin vom zweiten Hauptkomponent, wobei die Hauptkomponentenanalyse mit einem Wellenlängenband von 600 bis 700 nm durchgeführt wird, und Talaporfin auf die Haut voraufgetragen wird.

4. Gerät zur Messung einer Hautoberfläche nach Anspruch 4, wobei das Mittel zur Bestrahlung mit einem weißen Licht in einem Stück mit einem Mittel zum Verdichten der Reflexion von zwei oder mehreren Positionen auf der Hautoberflächenprobe durch das Kombinieren von diesen mit einem Lichtleiter versehen ist.

Revendications

1. Procédé de mesure d'une surface de peau, qui comprend les étapes consistant à:

irradier une lumière blanche sur ladite surface de peau en tant qu'un échantillon;
détecter un spectre de la lumière blanche réfléchie depuis deux ou plusieurs positions sur ladite surface de peau;
tracer une absorbance dudit spectre à un espace de lumière multidimensionnel et spectral;
effectuer une analyse multivariée de données sur ledit espace de lumière multidimensionnel et spectral obtenues à partir desdits deux ou plusieurs positions afin d'obtenir des vecteurs propres d'au moins les premier, deuxième et troisième composants principaux;
projeter les données de chaque position sur une direction de chaque vecteur propre pour afficher une magnitude de celles-ci sur une échelle de gris ou de couleurs en fonction de la magnitude, sur un écran à deux dimensions,
caractérisé par la détermination par des moyens de mesure
d'une quantité totale d'hémoglobine du deuxième composant principal,
d'une différence en quantité entre l'hémoglobine oxygénée et l'hémoglobine réduite du troisième composant principal,
ou
d'une quantité de talaporfine du deuxième composant principal, l'analyse du composant principal étant effectuée par une bande de longueur d'onde comprise entre 600 et 700 nm, et le talaporfine étant administré préalablement à ladite peau.

2. Procédé de mesure d'une surface de peau selon la revendication 1, pour la détermination de la quantité total d'hémoglobine et
d'une différence en quantité entre l'hémoglobine oxygénée et l'hémoglobine réduite, ladite analyse multivariée étant effectuée avec ledit spectre de la lumière ayant des bandes de longueurs d'onde comprises entre 500 à 600 nm ou comprises entre 500 à 850 nm.

3. Appareil de mesure d'une surface de peau, comprenant:

un moyen pour irradier une lumière blanche sur ladite surface de peau en tant qu'un échantillon;
un moyen pour détecter un spectre de la lumière blanche réfléchie depuis deux ou plusieurs positions sur ladite surface de peau;
un moyen pour tracer une absorbance dudit spectre d'un espace de lumière spectral et multidimensionnel;
un moyen pour obtenir des vecteurs propres d'au moins les premier, deuxième et troisième composants principaux en effectuant une analyse multivariée de données sur ledit espace spectral et multidimensionnel obtenu à partir desdits deux ou plusieurs positions,
et
un moyen destiné à afficher une magnitude de celles-ci sur une échelle de gris ou de couleurs en fonction de la magnitude, sur un écran à deux dimensions en projetant les données de chaque position sur une direction de chaque vecteur propre,
caractérisé en ce que l'appareil est configuré pour la détermination
d'une quantité totale d'hémoglobine du deuxième composant principal,
d'une différence en quantité entre l'hémoglobine oxygénée et l'hémoglobine réduite du troisième

composant principal,
ou
d'une quantité de talaporfine du deuxième composant principal, l'analyse du composant principal étant effectuée par une bande de longueur d'onde comprise entre 600 et 700 nm, et le talaporfine étant administré préalablement à ladite peau.

4. Appareil de mesure d'une surface de peau selon la revendication 4, dans lequel ledit moyen pour irradier une lumière blanche est pourvu intégralement d'un moyen pour faire condenser la réflexion à partir de deux ou plusieurs positions sur ledit échantillon de surface de peau en les combinant avec une fibre optique.

FIG.1

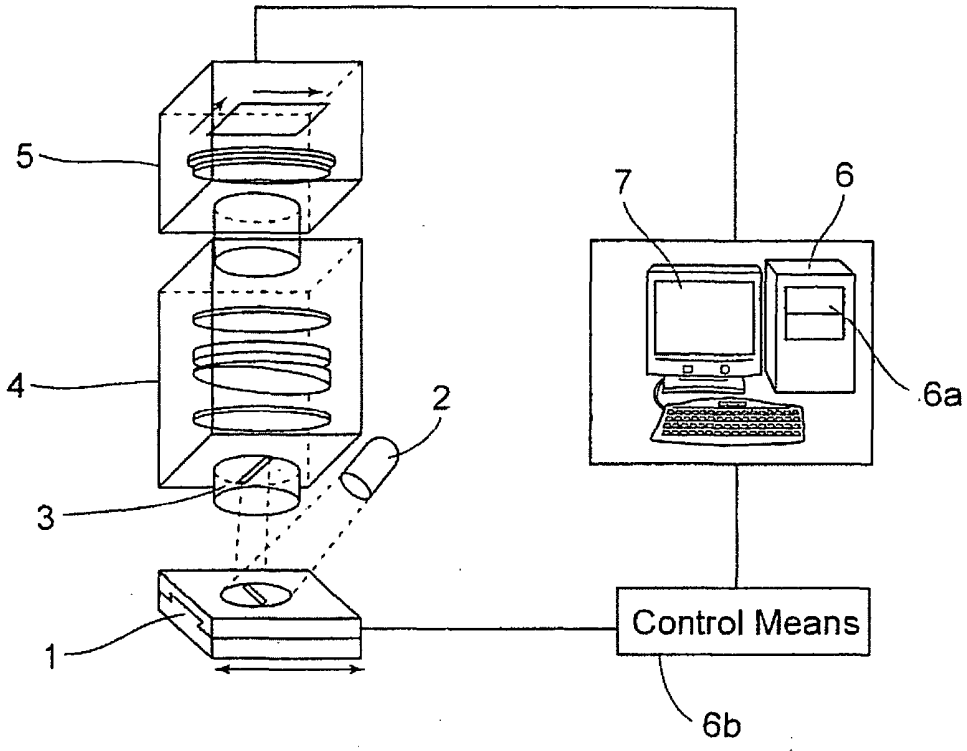


FIG.2

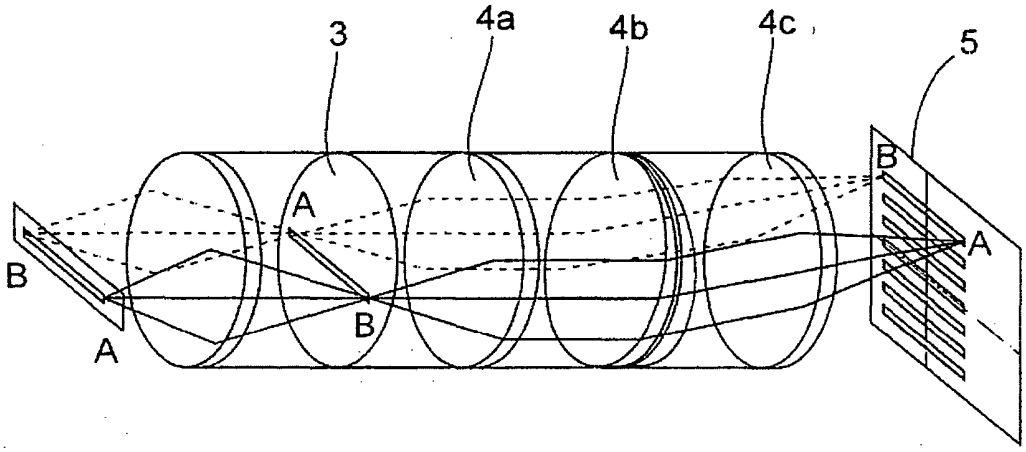


FIG.3

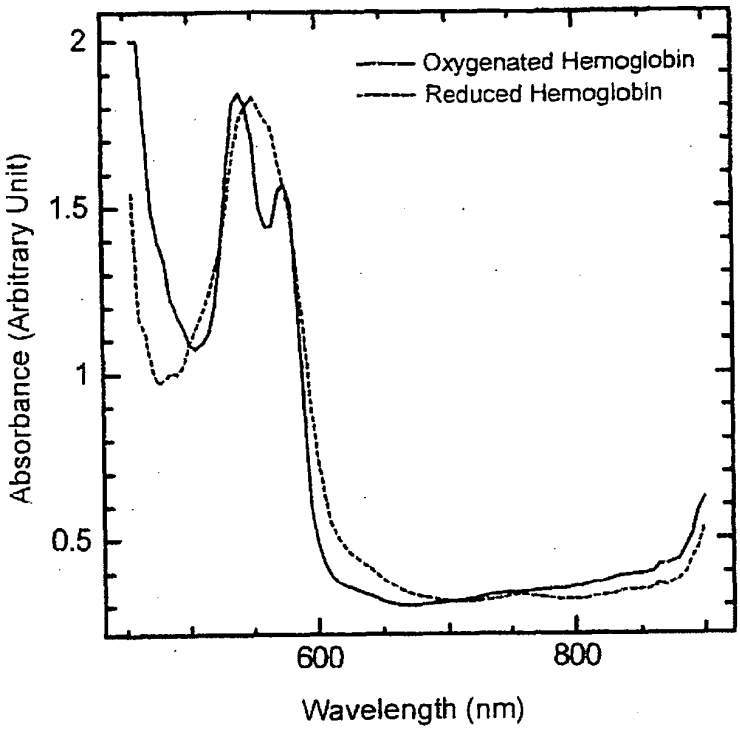

Oxygenated Hemoglobin
Reduced Hemoglobin
Absorbance (Arbitrary Unit)
2
1.5
1
0.5
600
800
Wavelength (nm)

FIG.4

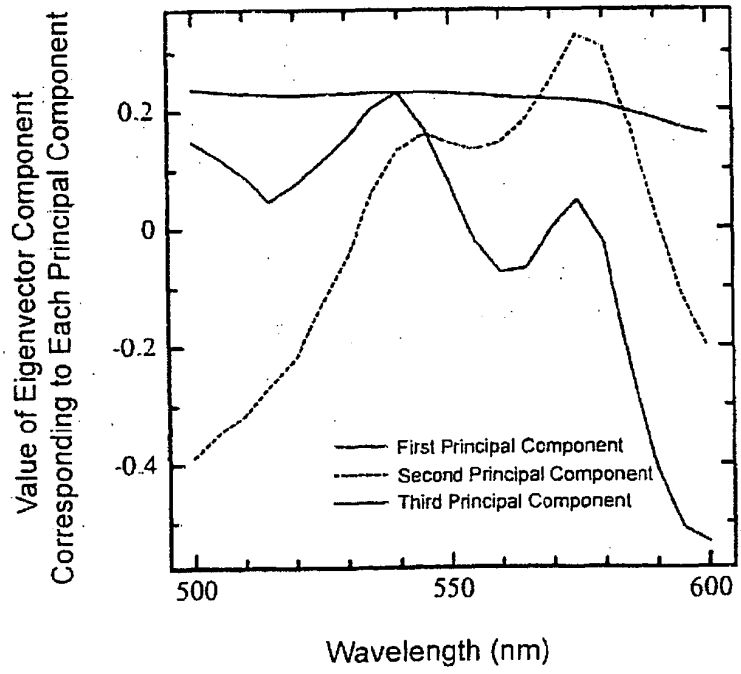

Value of Eigenvector Component Corresponding to Each Principal Component
0.2
0
-0.2
-0.4
First Principal Component
Second Principal Component
Third Principal Component
500
550
600
Wavelength (nm)

FIG.5a

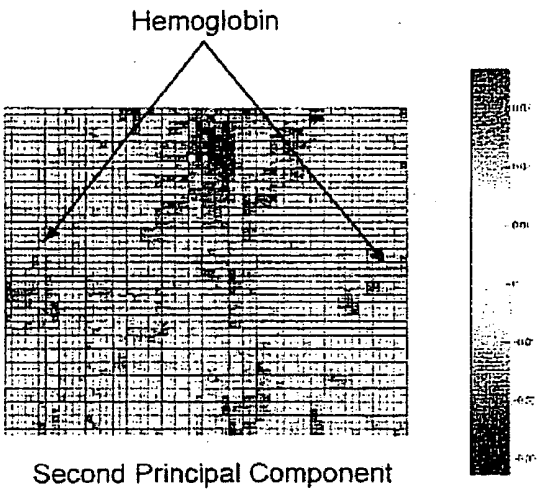
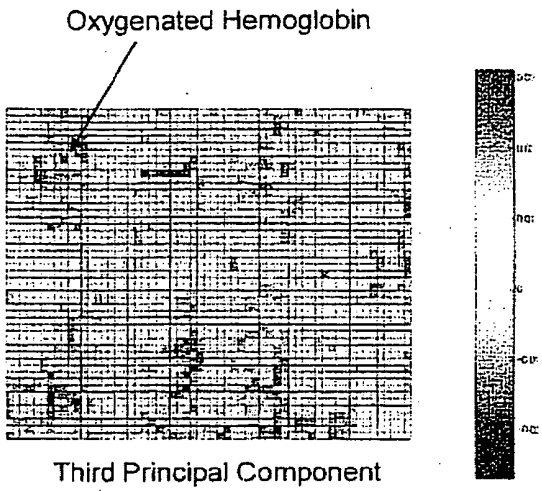


FIG.5b



Wavelength Band 500nm ~ 600nm

FIG.6a

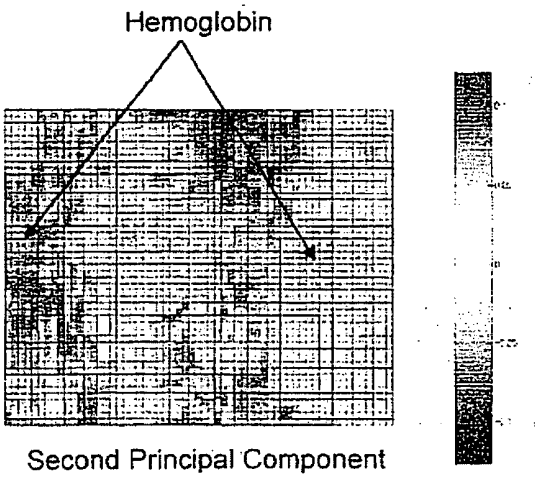
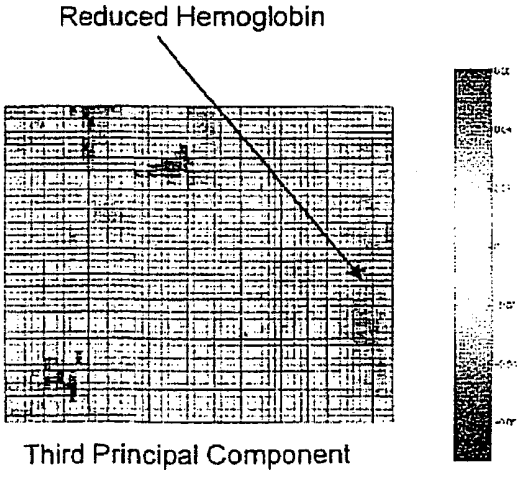
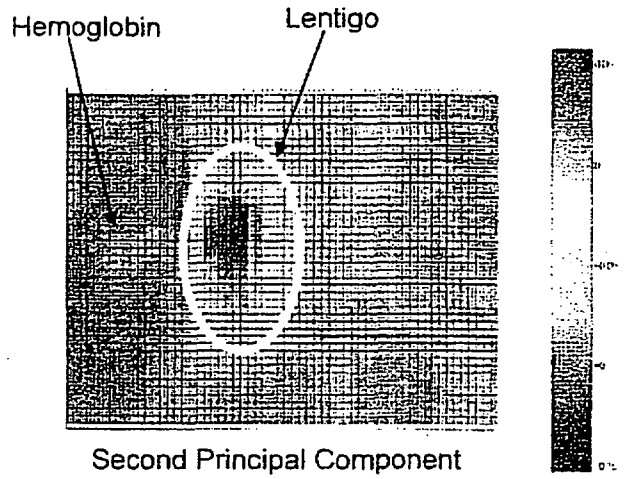


FIG.6b



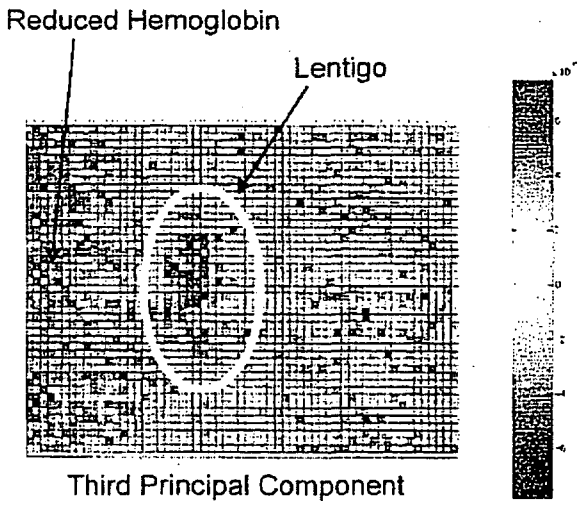
Wavelength Band 500nm ~ 850nm

FIG.7



Wavelength Band 500nm ~ 600nm

FIG.8



Wavelength Band 700nm ~ 780nm

FIG.9

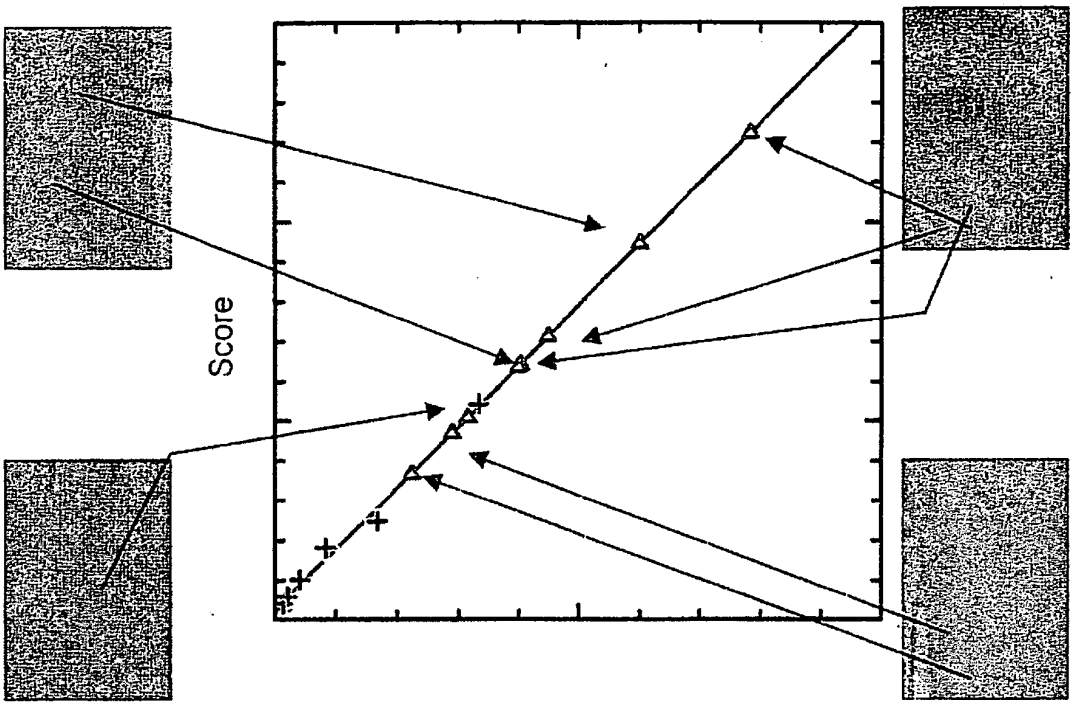


FIG.10a

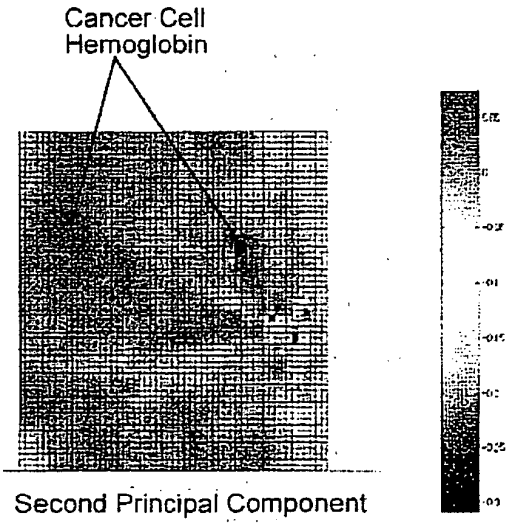
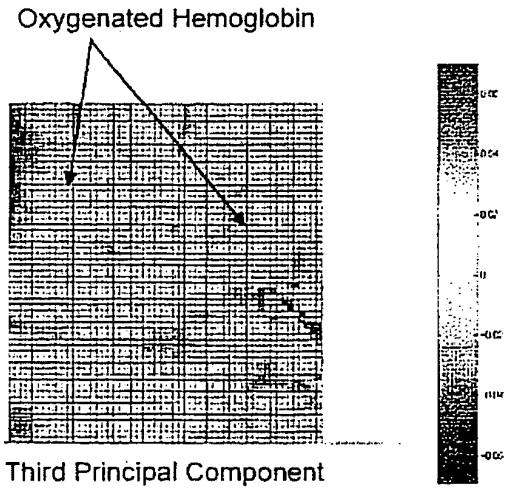
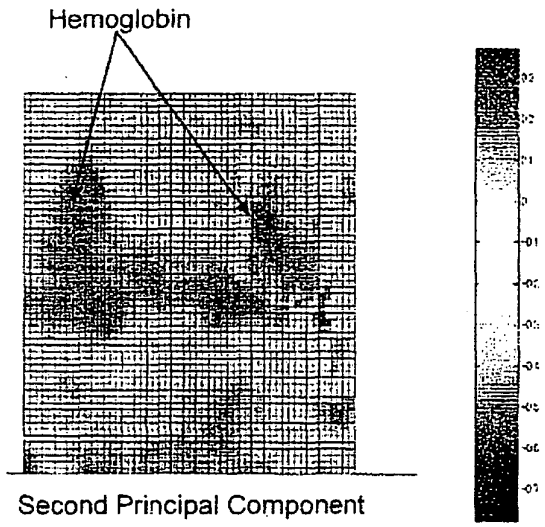


FIG.10b



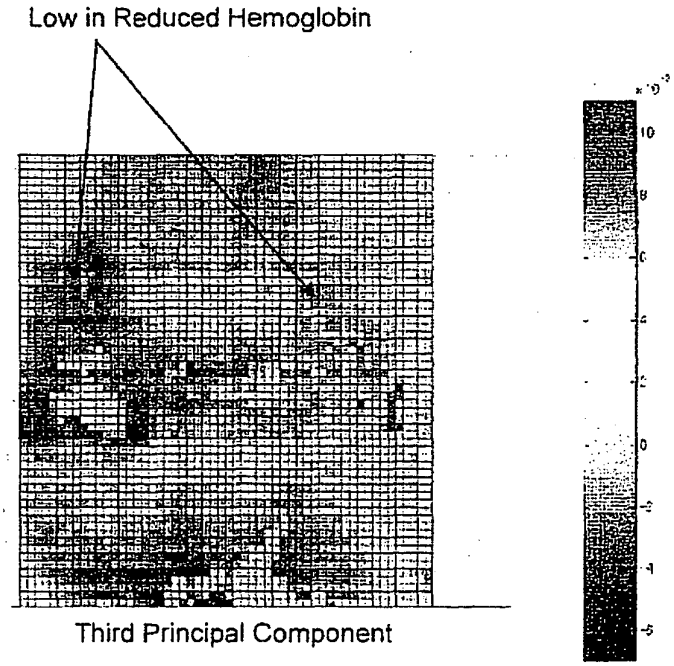
Wavelength Band 500nm ~ 600nm

FIG.11



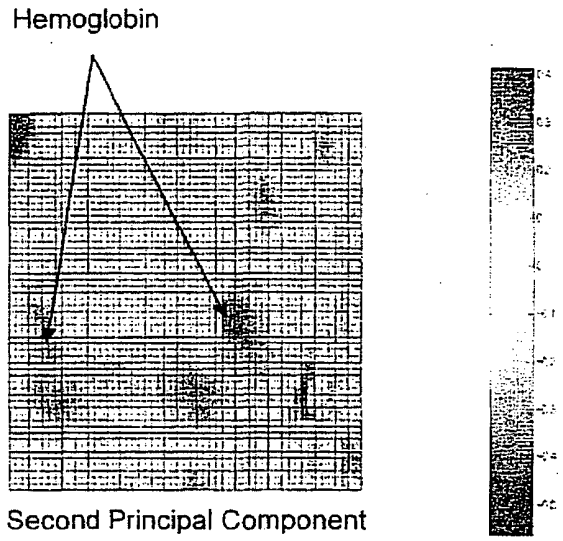
Wavelength Band 500nm ~ 800nm

FIG.12



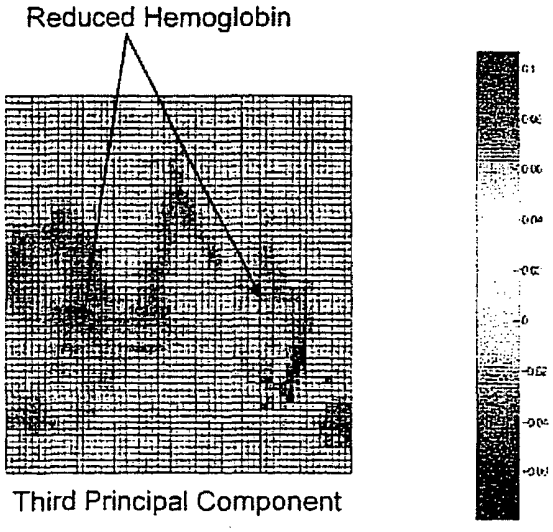
Wavelength Band 700nm ~ 780nm

FIG.13



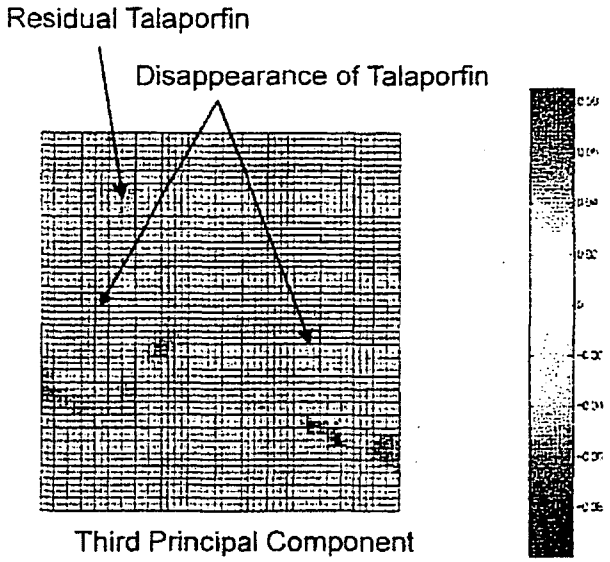
Wavelength Band 500nm ~ 800nm

FIG.14

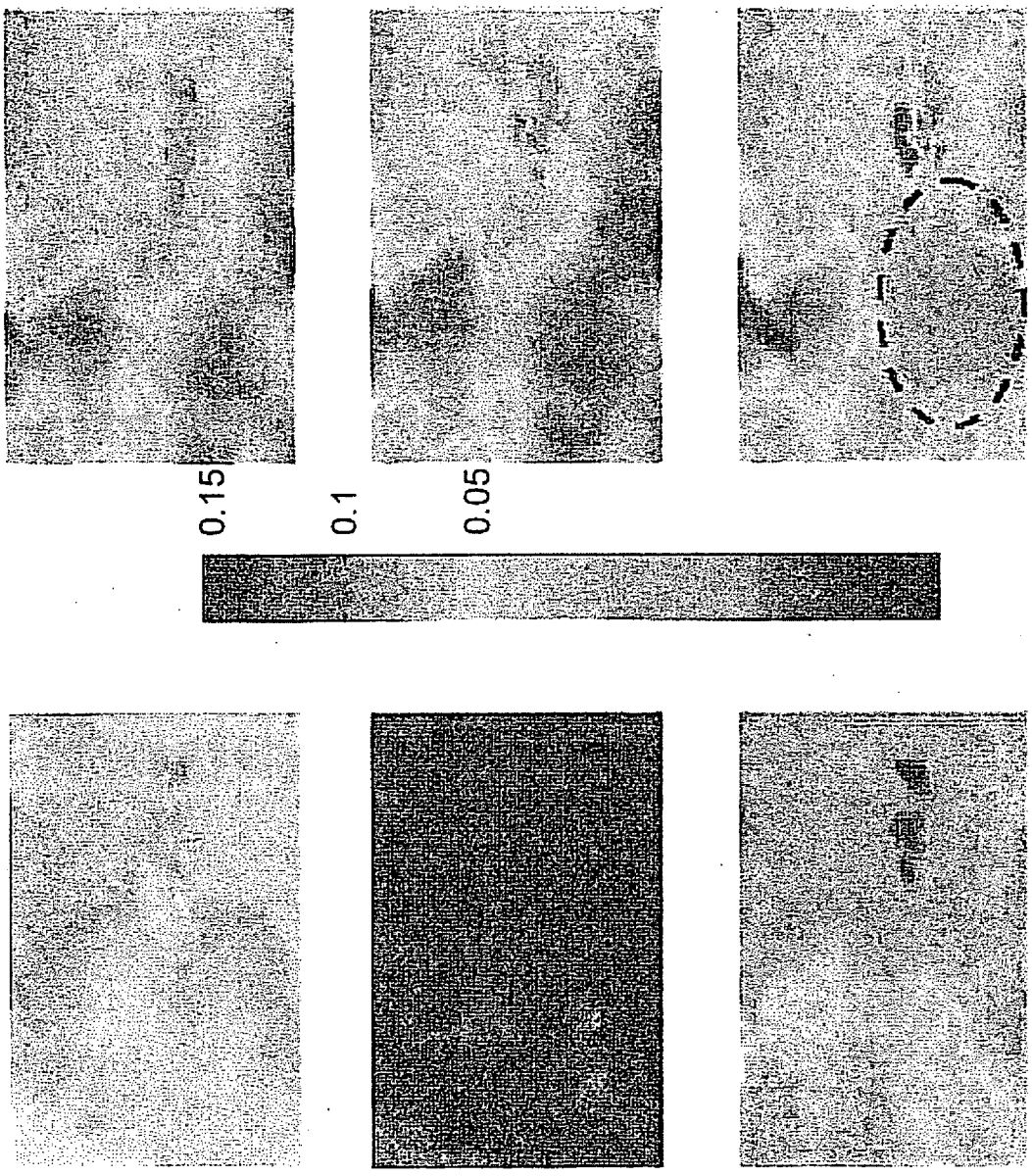


Wavelength Band 500nm ~ 600nm

FIG.15



Wavelength Band 600nm ~ 700nm


0.15
0.1
0.05

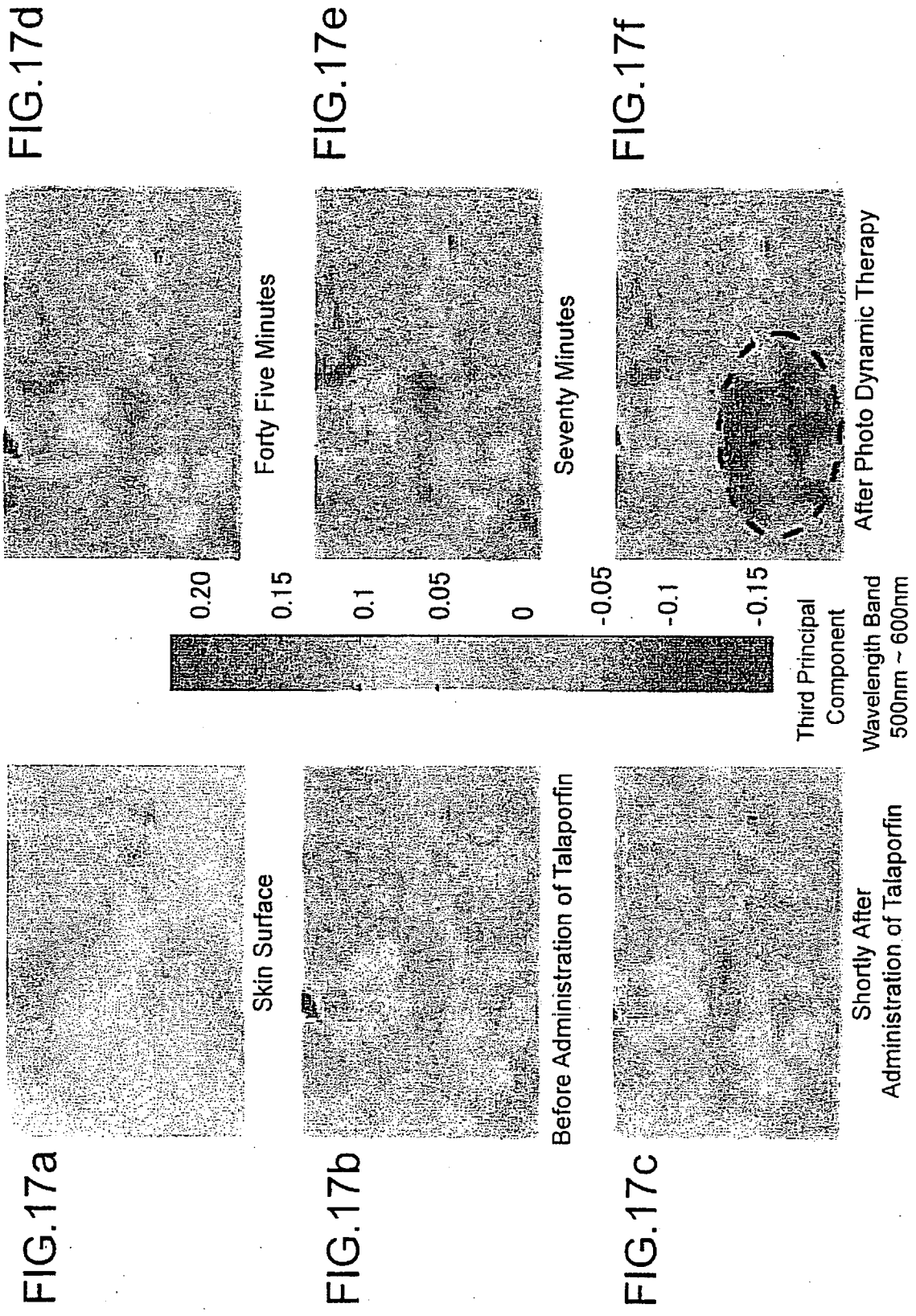


FIG.17a
Skin Surface
FIG.17b
Before Administration of Talaporfin
FIG.17c
Shortly After Administration of Talaporfin
FIG.17d
Forty Five Minutes
FIG.17e
Seventy Minutes
FIG.17f
After Photo Dynamic Therapy
0.20
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
Third Principal Component
Wavelength Band 500nm ~ 600nm

FIG.18

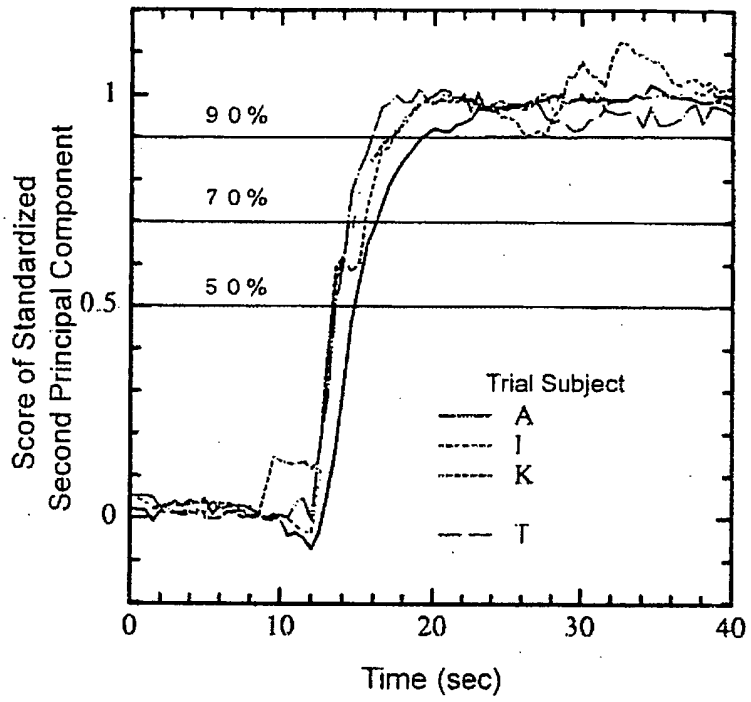


FIG.19

Trial Subject	Age	50%	70%	90%
A	64	4.5sec	6sec	9sec
T	62	3.5sec	4.5sec	6 sec
I	56	3sec	5sec	7sec
N	28	4sec	4.5sec	7sec
K	24	2sec	3sec	5.5sec

FIG.20

Trial Subject	Age	50%	70%	90%
A	64	5.5 sec	7 sec	12 sec
T	62	4 sec	5 sec	6.5 sec
I	56	5 sec	6 sec	8 sec
N	28	4 sec	5 sec	7 sec
K	24	4 sec	5 sec	6.5 sec

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- JP 2000356552 A **[0004]**
- US 5784162 A **[0005]**
- WO 03043492 A **[0006]**

专利名称(译)	测量表面化学物质的方法和测量表面化学物质的装置		
公开(公告)号	EP1719448B1	公开(公告)日	2012-08-29
申请号	EP2005719396	申请日	2005-02-22
[标]申请(专利权)人(译)	学校法人早稻田大学		
申请(专利权)人(译)	早稻田大学		
当前申请(专利权)人(译)	早稻田大学		
[标]发明人	ICHIKAWA FUMIHIKO		
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IPC分类号	A61B5/00 A61B10/00 G01N21/17 A61B5/103		
CPC分类号	A61B5/0059 A61B5/0075 A61B5/444		
优先权	2004047987 2004-02-24 JP		
其他公开文献	EP1719448A1 EP1719448A4		
外部链接	Espacenet		

摘要(译)

一种处理皮肤表面观察测量数据的方法，该测量数据能够解决各种疾病并减少疾病检测中的错误，并且提供一种不需要具有简单结构的过滤器的测量装置。该测量装置包括将白光作为样品施加到生物表面的装置，检测从生物表面上的多个位置反射的白光的光谱的装置，绘制上述光谱的吸光度的装置对于光谱多维空间，一种对从多个位置获得的光谱多维空间中的数据进行多变量分析以确定至少第一，第二和第三主成分的特征向量的方法，以及'在各个特征向量方向上的各个位置处投射数据，以在灰度级或与幅度对应的颜色的二维显示屏上显示它们的大小;以及该装置的测量方法。

FIG.1

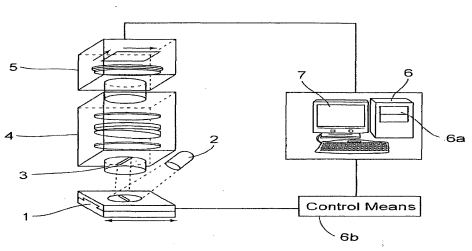

FIG.2