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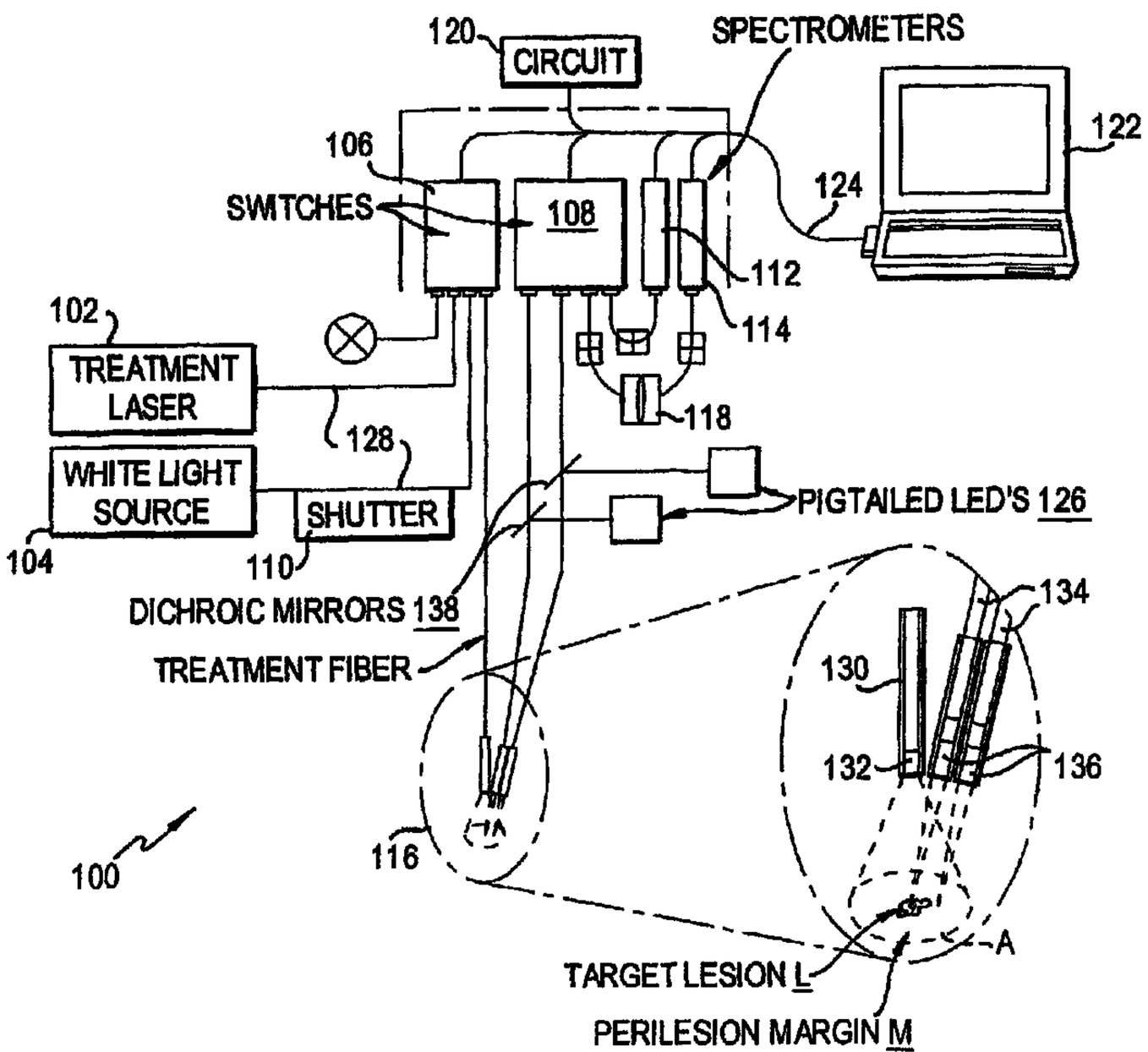
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(54) Title: PHOTODYNAMIC THERAPY WITH SPATIALLY RESOLVED DUAL SPECTROSCOPIC MONITORING



(57) Abrégé/Abstract:
An instrument for photodynamic therapy applies treatment light from a dye laser, white light, and ultraviolet fluorescence excitation light from an LED onto a lesion and surrounding areas in a time-multiplexed manner. The reflected white light is analyzed in a spectrometer to determine a correction for the dynamic optical spectral properties of the patient's tissue. Light emitted by fluorescence from the lesion and the surrounding areas is analyzed in another spectrometer, and the results are corrected in a computer, using the correction. An optical switch has been developed for the instrument, using a bistable solenoid and a sled.

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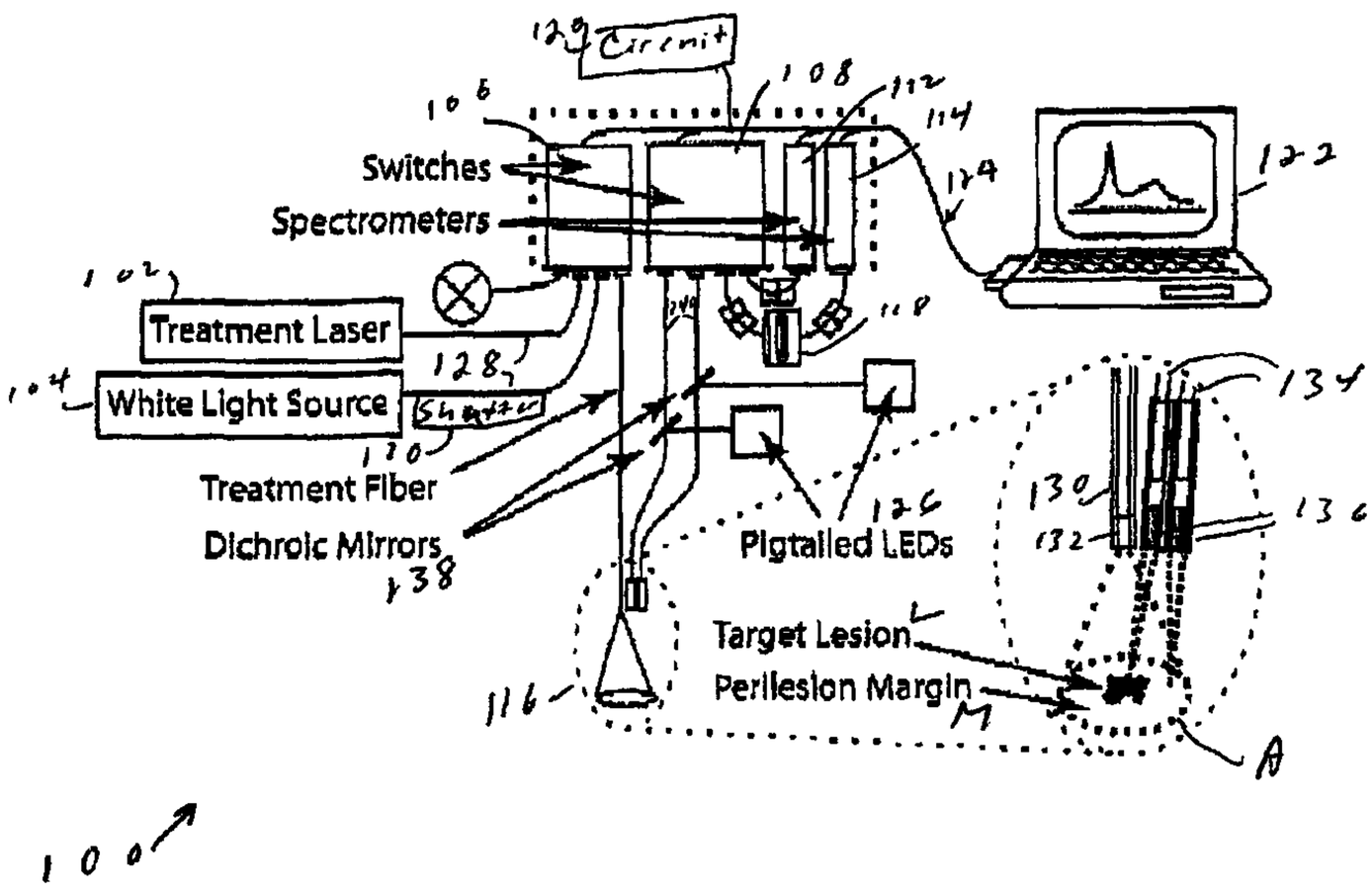
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[Continued on next page]

(54) Title: PHOTODYNAMIC THERAPY WITH SPATIALLY RESOLVED DUAL SPECTROSCOPIC MONITORING



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PHOTODYNAMIC THERAPY WITH SPATIALLY RESOLVED DUAL SPECTROSCOPIC MONITORING

Reference to Related Application

[0001] The present application claims the benefit of U.S. Provisional Patent Application No. 60/583,786, filed June 30, 2004, whose disclosure is hereby incorporated by reference in its entirety into the present disclosure.

Statement of Government Interest

[0002] The research leading to the present invention was supported by the Roswell Park Cancer Institute/NIH under Grant No. P01 CA55719. The government has certain rights in the invention.

Field of the Invention

[0003] The present invention is directed to photodynamic therapy (PDT) and more particularly to a method and apparatus for accurate, real-time determination of a therapeutic dose delivered by photodynamic therapy.

Description of Related Art

[0004] The accurate, real-time determination of therapeutic dose delivered by photodynamic therapy (PDT) is an area of active research and clinical importance. Photosensitizer evolution, including photobleaching and photoproduct formation, and accumulation of endogenous porphyrins provide attractive implicit dose metrics, as these processes are mediated by similar photochemistry as dose deposition and report cellular damage, respectively. Reflectance spectroscopy can similarly report blood volume and hemoglobin oxygen saturation.

[0005] However, the accuracy of known techniques is still not sufficient. In particular, living human tissue has dynamic optical properties which may reduce the accuracy.

Summary of the Invention

[0006] It is an object of the invention to provide real-time *in vivo* determination of photodynamic therapy dose metrics and tissue optical properties.

[0007] It is another object to correct for the dynamic optical properties of tissue.

[0008] To achieve the above and other objects, the present invention is directed to an apparatus for real-time determination of photodynamic therapy dosimetry *in vivo,* employing measurements of fluorescence emission spectra corrected for the effects of dynamic tissue optical properties using white light diffuse reflectance. This system accurately measures photosensitizer photobleaching, photoproduct formation, and tissue oxygenation, all of which are useful as dose metrics.

[0009] Compact instrumentation is developed that controls delivery and monitoring of PDT dose. In at least one embodiment, the instrumentation provides 405 nm fluorescence excitation light to two spatially-resolved points on the skin, delivered through fiber-pigtailed LEDs terminated with GRIN microlenses. One point is located inside the PDT target lesion and the other in the perilesion margin. The fluorescence spectra generated from sensitizer, photoproducts, autofluorescence, and various endogenous porphyrins are measured from both points, concurrently with excitation. Emission spectra from these points are corrected for the effects of tissue optical properties with division by white light reflectance spectra delivered through the treatment fiber. Spectral fitting reports fluorophore concentrations and blood oxygenation. This instrumentation employs multimode fiber switches and time multiplexing to deliver the treatment beam at 635 nm, fluorescence excitation beam at 405 nm, and white light interrogation beam while monitoring the aforementioned dose metrics with a pair of thermoelectrically cooled spectrometers.

[0010] The present invention can provide real-time determination of photodynamic therapy dosimetry *in vivo* during PDT treatment. The fluorescence spectra and white light reflectance are measured from each point during brief interruption of the treatment beam. Emission spectra are corrected for the effects of tissue optical properties with division by white light reflectance spectra, and spectral fitting is used to accurately characterize photosensitizer photobleaching, photoproduct formation, blood volume, and tissue oxygenation, all of which are useful as dose metrics.

Brief Description of the Drawings

[0011] Preferred embodiments of the invention will be set forth in detail with reference to the drawings, in which:

[0012] Fig. 1 is a schematic diagram showing an instrument according to a first preferred embodiment of the invention;

[0013] Fig. 2 is a timing chart showing a timing of operation of the instrument of Fig. 1;

[0014] Fig. 3 is a schematic diagram showing an instrument according to a second preferred embodiment of the invention;

[0015] Figs. 4A and 4B show a 1x2 fiber optic switch usable in the embodiment of Fig. 1 or that of Fig. 3;

[0016] Figs. 5A-5C show variations of the fiber terminations in the switch of Figs. 4A and 4B;

[0017] Fig. 6 shows a 2x2 fiber optic switch based on the fiber optic switch of Figs. 4A and 4B;

[0018] Figs. 7A and 7B show a variation of the switch of Figs. 4A and 4B with a filter which can be moved into or out of the light beam;

[0019] Figs. 8A and 8B show a further modification of the switch of Figs. 4A and 4B;

[0020] Fig. 9 is a perspective view showing a bulkhead used in the switch of Figs. 8A and 8B;

[0021] Fig. 10 shows an instrument according to a third preferred embodiment of the present invention; and

[0022] Fig. 11 shows an alternative fiber coupler usable with the embodiment of Fig. 10.

Detailed Description of the Preferred Embodiments

[0023] Preferred embodiments of the present invention will be set forth in detail with reference to the drawings, in which like reference numerals refer to like elements or operational steps throughout.

[0024] An instrument according to a first preferred embodiment of the present invention is shown in Fig. 1 as 100. As shown, the instrument includes a treatment laser (such as a dye laser) 102, a white light source (such as a tungsten halogen or xenon lamp) 104, fiber optic switches 106, 108, a shutter 110, two thermoelectrically cooled spectrometers 112, 114, an optical probe 116, an optical filter 118, circuitry 120, housings (not shown), and a computer 122. The computer 122 and the spectrometers 112, 114 communicate through a USB cable connection 124. Each of the spectrometers 112, 114 has reserved auxiliary (AUX) pins on its on-board circuitry. The AUX pins are connected to the LEDs 126, shutter 110, and fiber optic switches 106, 108 via external circuitry 120. Transistor-transistor logic (TTL) pulses transmit from the AUX pins to the circuitry 120.

[0025] In a delivery arm of the instrument 100, the white light source 104 and treatment laser 102 are coupled via fibers 128 into the 2x1 fiber optic switch 106. The output of this switch 106 is coupled via a fiber 130 to part of the optical probe 116 and is terminated with a microlens 132.

[0026] In the detection arm, two more optical fibers 134 terminated with microlenses 136 are in the probe. Each of the two fibers 134 is directed to a housing (not shown) with a dichroic optical filter 138. The reflection path of the filter housing contains an LED 126, and the transmission path contains a secondary optical fiber 140. The secondary optical fibers 140 are connected to the 2x2 optical switch 108. One of the two outputs of the 2x2 switch 108 is directed to the first spectrometer 112, and the

second output is directed to the optical filter 118 and then to the second spectrometer 114.

[0027] The treatment area *A* includes two regions, a target lesion region *L* and a perilesion margin region *M*.

[0028] The computer 122 determines which of two states the first fiber optic switch 106 is in and the state of the white light shutter 110. Depending on the states of the switch 106 and shutter 110, the light is blocked, white light is transmitted through the treatment fiber 130, or laser light from the treatment laser 102 is transmitted though the treatment fiber 130. Light transmitted through the treatment fiber 130 is directed onto the treatment area *A,* comprising both the lesion region *L* and the perilesion region *M*. The treatment areas may have different optical, chemical or physiological properties.

[0029] Light emitted or reflected from the area *A* is collected by the two optical fibers 134 terminated with microlenses 136. One of the optical fibers 134 collects primarily from the target lesion region *L,* and the other fiber 134 collects primarily from the perilesion margin region *M*. Light may also be generated by the LEDs 126 in the detection arm. Light generated by the LEDs 126 will be reflected off the dichroic mirror 138 and transmitted through the optical fibers 134 and directed through the microlenses 136 onto the corresponding treatment regions *L, M*. Light omitted or reflected from these regions will be collected by the fibers 134 and directed onto the dichroic mirror 138. Light that is at a different wavelength from the LED sources 126 will be transmitted through the filter 138. Light transmitted through the secondary fibers 140 is directed into the 2x2 optical switch 108. Depending on the state of the 2x2 optical switch 108, light from either of the two secondary detection fibers 140 can

be directed either through another optical filter 118 followed by a spectrometer 114 or directly into a spectrometer 112.

[0030] Up to three measurements can be made for each of two spatially resolved locations during photodynamic therapy. The laser source is used as a treatment beam. Light from this source is directed into the treatment area and activates photoactive drugs within that area.

[0031] Treatment beam excited fluorescence can be measured. Some of the absorbed laser light may be emitted as fluorescence. By directing collected light through the filtered path of the system before the spectrometer, the fluorescent signal can be evaluated without the spectrometer being optically saturated by the treatment laser. Therefore, with the first switch transmitting the laser and the second switch directing light collected from the treatment area region of interest, spatially resolved fluorescence from that region can be measured.

[0032] In measuring 405 nm excited fluorescence, the fluorescent signals of interest are highly excited by light emitted by the LED sources. By using the first fiber switch and shutter to stop the laser and white sources and using pulses to turn on the LED source, the 405 nm light can be directed onto either treatment region of interest, and excited fluorescence can be collected through that same path and directed by the 2x2 fiber switch directly to the non-filtered spectrometer path. Therefore, a spatially resolved measurement of fluorescence can be made.

[0033] The reflected spectrum of a white light source provides information about tissue optical properties, blood volume, and blood oxygenation. White light can be directed through the first optical switch on the treatment area, and the reflected signal can be collected by the detection arm. Either of the two fibers in the detection path can be directed into the non-filtered spectrometer, and the spatially resolved white

light reflectance can be measured. The computer 122 receives detection signals for all types of reflected light and uses the reflected white light to correct the detection signals for the dynamic optical properties of the tissue, particularly the spectral reflectivity.

[0034] During the measurements listed, data are transmitted from the spectrometers into the computer, where characteristics about the treatment regions are stored and analyzed. Analysis of the data from these measurements can be fed back into the system to control the timing of the measurements and the treatment.

[0035] An example of timing is shown in Fig. 2. The timing of the light source alternates among the laser, the white light source, and the LED (an ultraviolet source). The corresponding time periods for measurement are fluorescence from the laser, reflectance from the white light, and fluorescence from the LED. With those measurements, it is possible to correct for dynamic tissue optical characteristics.

[0036] A second preferred embodiment, using an optical probe, will now be described. An instrument according to the second preferred embodiment is shown in Fig. 3 as 300. Except as noted below, the instrument 300 can be constructed and used like the instrument 100.

[0037] The optical probe 302 is capable of two-point spatial resolution. A single or plurality of optical fibers 304 can be used in concert with either a single or plurality of MEMS (micro-electro-mechanical systems) scanning mirrors 306 in a housing 308 to scan the treatment area. At each location (pixel) in the scan analogous measurements to those above can be performed. Also, the delivery of the laser, white light, and LED sources may be delivered through the same optical probe that is doing the collection depending on switching configuration.

[0038] Either of the preferred embodiments can use a variety of switches, such as the following.

[0039] Several embodiments of large diameter multimode fiber switches (the switches 106 and 108 of Figs. 1 and 3) are provided, as illustrated in Figs. 4A through 9. The purpose of the switches is to control the flow of light through the system, as previously disclosed. In addition, some embodiments contain in-line filters which can be moved into or out of the path in order to control the light transmitted through the system.

[0040] Fig. 4A shows a top view of a 1x2 fiber optic switch 400 in which an optical fiber 402 is mounted on a translating sled 404 that can be translated by a linear actuator (bistable solenoid) 406 by applying a voltage from a voltage source 408 across electrical leads. In this embodiment using a bistable solenoid 406, a voltage pulse across one set of leads translates the sled 404 into a first position. Permanent magnets within the solenoid 406 latch the device in place so that it is stable and requires no additional electrical source to hold it in place. In this position, the fiber 402 is in close proximity to the fiber 412 and provides optical throughput from the fiber 402 to the fiber 412 (or vice versa). Application of a voltage pulse across a second set of leads (not shown) translates the sled 404 to a second position, as shown in Fig. 4B, where a second set of permanent magnets holds the sled 404 in place and throughput between the fiber 402 and a fiber 410 is obtained. A precision linear slide (not shown) holds the sled 404 very precisely in two dimensions to reduce fiber alignment errors otherwise imparted by the slop in the axle of the bistable solenoid 406.

[0041] Figs. 5A-5C show a magnified view of the sled 404 and the alignment of the optical fibers 402, 410, 412. In Fig. 5A, the fibers used have polished ends 502 and

are coupled by placing them in close proximity. In Fig. 5B, the fibers are terminated with lenses (GRIN lenses) 504 which collimate the beam and allow efficient coupling at spacing prohibitive for polished fiber coupling. An alternative embodiment of that shown in Fig. 5B would include traditional lenses or ball lenses. Fig. 5C shows a perspective view of the sled holding an optical fiber.

[0042] Fig. 6 shows a 2x2 switch 600 using the same base components as used for the 1x2 switches of Figs. 4A and 4B. In this embodiment, an interconnecting fiber 602 allows either of the two input fibers 604, 606 to be connected to either of the two output fibers 608, 610 by controlling the positions of the sleds 404 with two bistable solenoids 406. The basic 1x2 switch can be multiplexed together as in the 2x2 switch to increase number of channels that can be switched.

[0043] Figs. 7A and 7B show a removable in-line filter 702 incorporated into a 1x2 switch 700 based on the previous design. In this embodiment, a fiber 704 from the 1x2 switch is coupled to a second fiber 704 with lenses 706. A filter 702 mounted onto a sled 404 (as previously described) can then be translated into or out of the beam path using a solenoid 406. In this way, light transmitted through the system can be modified in intensity, spectral content, or polarization depending on filter choice. Fig. 7A shows this device with the filter not in the path of the light, and Fig. 7B shows this device with the filter in the path of the light. Again, a precision linear guide may be used to improve system repeatability and robustness.

[0044] Figs. 8A and 8B show an alternative 1x2 switch embodiment 800 in which two lens-terminated fibers 802, 804 are mounted in the switch 800 and aligned to the two input ends of a y-coupled fiber 806. Switching between throughput of fibers is accomplished by translating a bulkhead 808 with through holes 810. In Fig. 8A, the bulkhead 808 is in a first position, and light transmitted through a first fiber 802

travels through a through hole 810 in the bulkhead and is coupled into the output by the y-coupler 806. Light transmitted through the second fiber 804 is blocked by the bulkhead 808. Fig. 8B shows the device 800 after the bistable solenoid 406 is used to switch the position of the bulkhead 808. In this state, light transmitted through the first fiber 802 is blocked by the bulkhead 808, and light transmitted through the second fiber 804 is transmitted through a through hole 810 and is coupled into the output fiber by the y-coupler 806. A perspective view of the bulkhead 808 with through holes 810 is illustrated in Fig. 9. Similarly, this basic switch unit can be multiplexed to achieve a higher number of channels and can also have in-line filters incorporated for additional functionality.

[0045] Use of a precision linear slide to improve throughput repeatability and lifetime and inclusion of coupling optics to improve robustness separates this system from known prior art examples. No prior art incorporating y-couplers and bulkheads with through holes is known. Switches incorporating bistable solenoids can be purchased commercially from Fibersense & Signals Inc., San Jose, California, U.S.A.

[0046] Fig. 10 shows a third preferred embodiment of the invention. In the third preferred embodiment, the instrument 1000 can be constructed and used like the instrument 100 of Fig. 1, except that additional light sources, such as a fluorescence laser 1002, are coupled into the system and transmitted through the treatment fiber. Such additional sources may be coupled with multiplexed switches, as described above. In a variation of the third preferred embodiment, sources may be coupled into the system by butt-coupling multiple fiber sources into the treatment source. A known type of coupling is shown in Fig. 11 as 1100, in which input fibers 1102 are formed into a fiber bundle 1104 in a housing 1106 and tapered to form a taper region 1108 leading to the output fiber 1110. In this case, the source fibers used would have

smaller diameters than the treatment fiber, and the sources would be switched on and off, or shuttered on and off upstream of the coupling. In this way, multiple sources can be used to interrogate the target tissue without much added complexity. It is an advantage of this embodiment that the sources are transmitted to the tissue surface in the same geometry which simplifies computational analysis and interpretation of resulting measurements.

[0047] While preferred embodiments and variations thereon have been set forth above, those skilled in the art who have reviewed the present disclosure will readily appreciate that other embodiments can be realized within the scope of the invention. For example, wavelengths and other numerical values are illustrative rather than limiting. Therefore, the present invention should be construed as limited only by the appended claims.

We claim:

1. An instrument for performing photodynamic therapy on a region of interest on a living patient, the instrument comprising:

light sources for providing treatment light, broadband light and fluorescence excitation light;

first optics for causing the treatment light, the broadband light and the fluorescence excitation light to be incident on the region of interest, whereby the broadband light is reflected from the region of interest and the fluorescence excitation light causes the region of interest to emit fluorescence emission light;

second optics for receiving the reflected broadband light and the fluorescence emission light from the region of interest;

a first spectrometer for receiving the reflected broadband light from the second optics and for producing a signal representing a spectrum of the reflected broadband light;

a second spectrometer for receiving the fluorescence emission light from the second optics and for producing a signal representing a spectrum of the fluorescence emission light; and

a computer, receiving the signals from the first and second spectrometers, for correcting the spectrum of the fluorescence emission light in accordance with the spectrum of the reflected broadband light.

2. The instrument of claim 1, wherein the first optics comprise an optical switch for time-multiplexing the treatment light and the broadband light.

3. The instrument of claim 2, wherein the optical switch comprises:

a first optical fiber for supplying the treatment light to the optical switch;

a second optical fiber for supplying the broadband light to the optical switch;

a third optical fiber for selectively receiving the treatment light or the broadband light;

a sled for moving the third optical fiber to be in optical communication with the first optical fiber or the second optical fiber; and

a bistable solenoid for moving the sled.

4. The instrument of claim 3, wherein each of the first, second and third optical fibers comprises a polished fiber end.

5. The instrument of claim 3, wherein each of the first, second and third optical fibers is terminated by a lens.

6. The instrument of claim 5, wherein the lens is a gradient index lens.

7. The instrument of claim 2, wherein the optical switch comprises:

a first optical fiber for supplying the treatment light to the optical switch;

a second optical fiber for supplying the broadband light to the optical switch;

a Y coupler for selectively receiving the treatment light or the broadband light;

a bulkhead, having at least one through hole, for selectively blocking light from the first optical fiber or the second optical fiber to the Y coupler;

a sled for moving the bulkhead to block the light from the first optical fiber or the second optical fiber; and

a bistable solenoid for moving the sled.

8. The instrument of claim 2, wherein the optical switch time-multiplexes the treatment light, the broadband light and the fluorescence excitation light.

9. The instrument of claim 1, wherein the first optics comprise spatially resolving optics for causing the fluorescence excitation light to be incident on a plurality of locations in the region of interest.

10. The instrument of claim 9, wherein the spatially resolving optics comprise a plurality of optical fibers, each for directing a portion of the fluorescence excitation light onto one of the plurality of locations.

11. The instrument of claim 10, wherein each of the plurality of optical fibers in the spatially receiving optics is terminated by a lens.

12. The instrument of claim 11, wherein the lens is a gradient index lens.

13. The instrument of claim 10, wherein each of the plurality of optical fibers receives the reflected broadband light and the fluorescence emission light from said one of the plurality of locations and supplies the reflected broadband light and the fluorescence emission light to the second optics.

14. The instrument of claim 13, wherein the second optics comprise an optical switch for selectively applying the reflected broadband light and the fluorescence emission light from each of the plurality of optical fibers selectively to each of the first and second spectrometers.

15. The instrument of claim 9, wherein the spatially resolving optics comprise a scanning system for scanning the fluorescence excitation light onto the plurality of locations.

16. The instrument of claim 15, wherein the scanning system comprises at least one movable mirror.

17. The instrument of claim 1, wherein the second optics comprise a dichroic mirror for spectrally separating the fluorescence excitation light from the fluorescence emission light.

18. The instrument of claim 17, wherein the first optics apply the fluorescence excitation light to the region of interest by using the dichroic mirror.

19. An optical switch comprising:

a first optical fiber;

a second optical fiber;

a third optical fiber for selectively being in optical communication with the treatment light or the broadband light;

a sled for moving the third optical fiber to be in said optical communication with the first optical fiber or the second optical fiber; and

a bistable solenoid for moving the sled.

20. The switch of claim 19, wherein each of the first, second and third optical fibers comprises a polished fiber end.

21. The switch of claim 19, wherein each of the first, second and third optical fibers is terminated by a lens.

22. The switch of claim 21, wherein the lens is a gradient index lens.

23. An optical switch comprising:

a first optical fiber;

a second optical fiber;

a Y coupler for selectively being in optical communication with the first optical fiber or the second optical fiber;

a bulkhead, having at least one through hole, for selectively blocking light from the first optical fiber or the second optical fiber to the Y coupler;

a sled for moving the bulkhead to block the light from the first optical fiber or the second optical fiber; and

a bistable solenoid for moving the sled.

FIG. 1

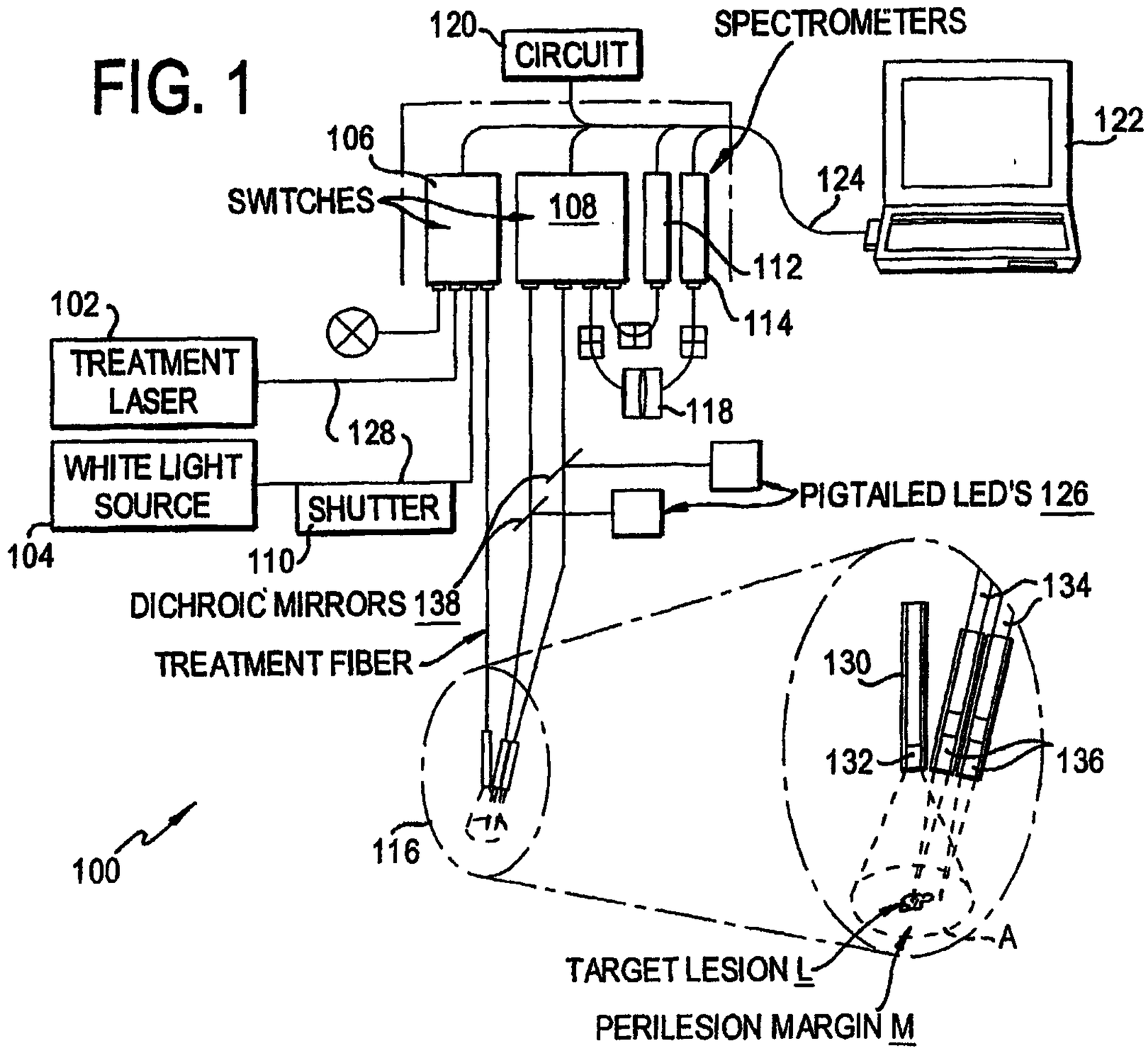

120
CIRCUIT
SPECTROMETERS
122
106
SWITCHES
108
124
112
114
102
TREATMENT LASER
128
118
WHITE LIGHT SOURCE
SHUTTER
PIGTAILED LED'S 126
104
110
DICHROIC MIRRORS 138
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TARGET LESION L
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FIG. 2

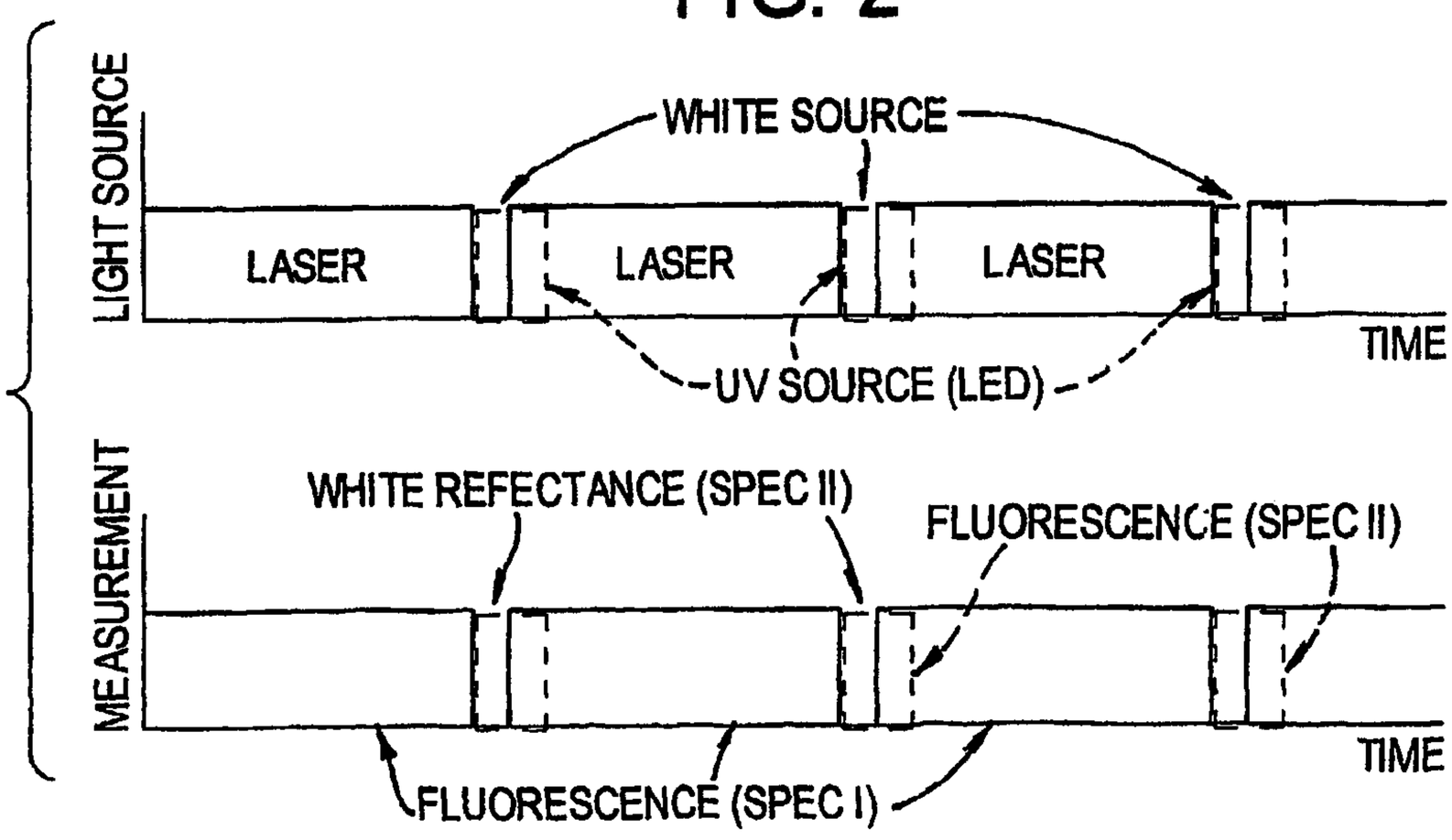
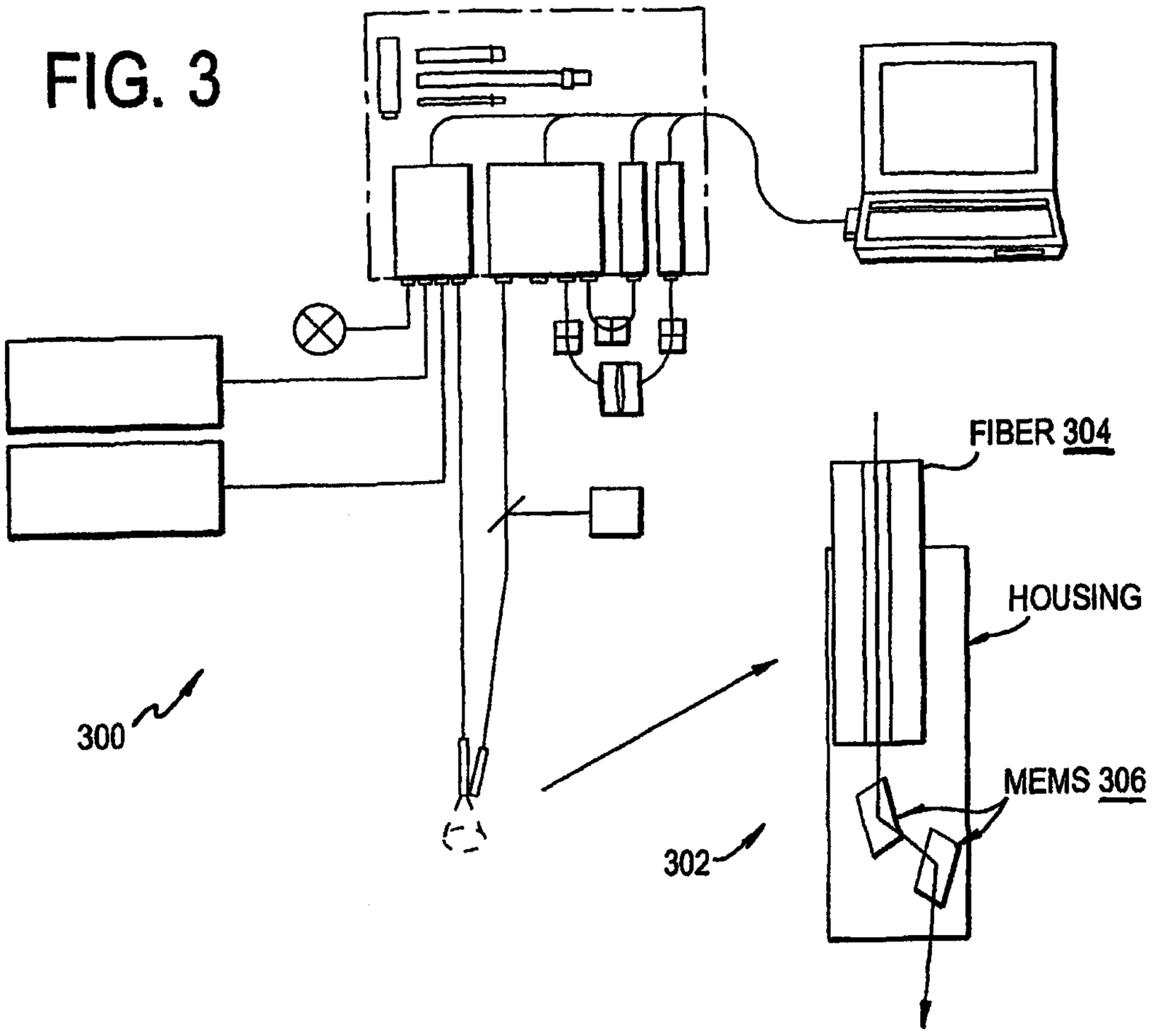

LIGHT SOURCE
WHITE SOURCE
LASER
LASER
LASER
TIME
UV SOURCE (LED)
MEASUREMENT
WHITE REFECTANCE (SPEC II)
FLUORESCENCE (SPEC II)
TIME
FLUORESCENCE (SPEC I)

FIG. 3



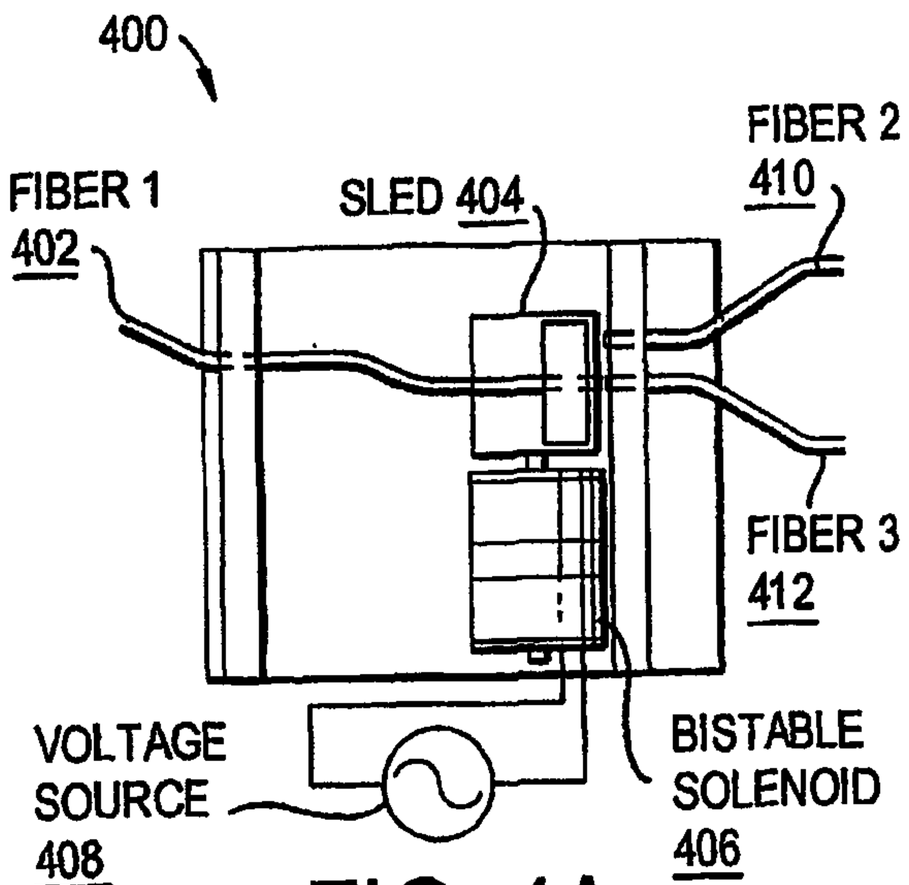


FIG. 4A

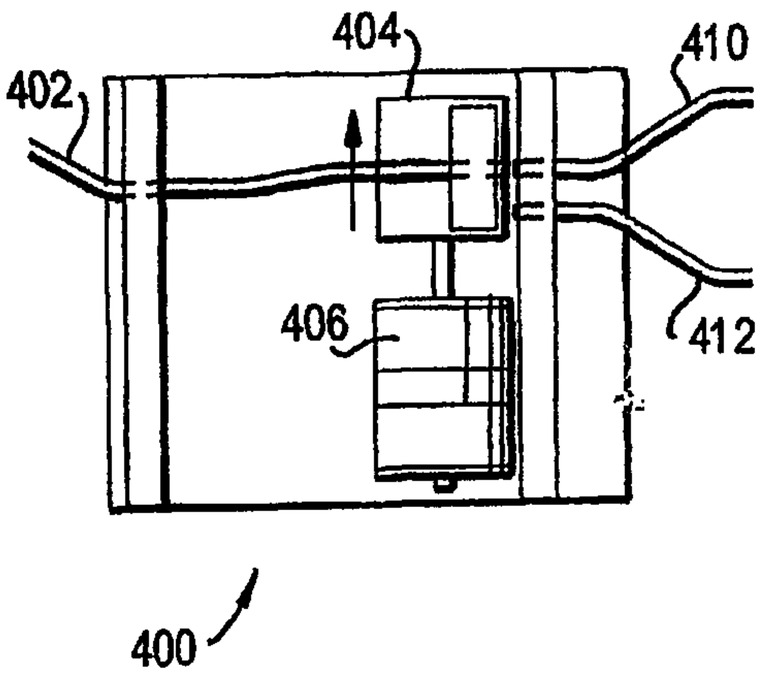


FIG. 4B

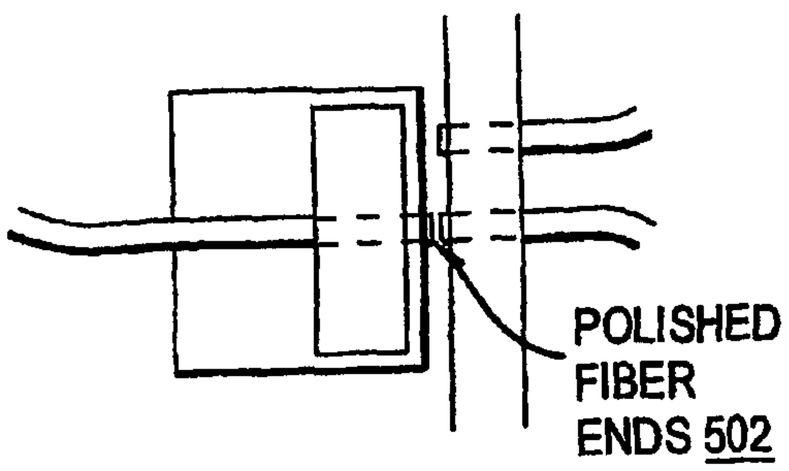


FIG. 5A

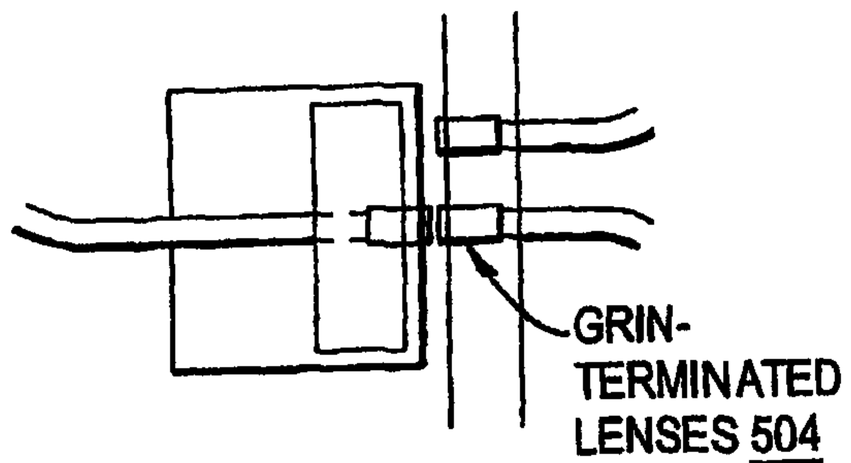


FIG. 5B

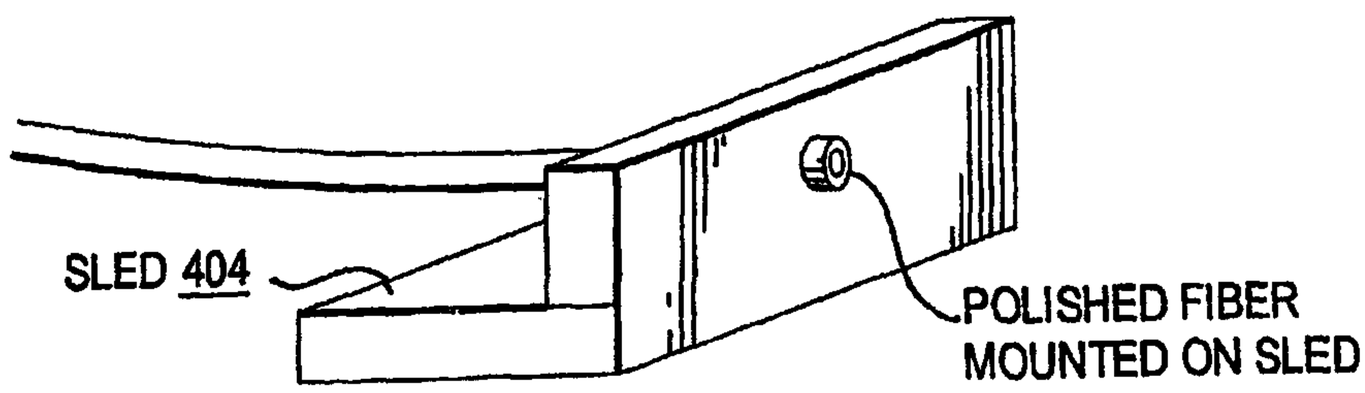


FIG. 5C

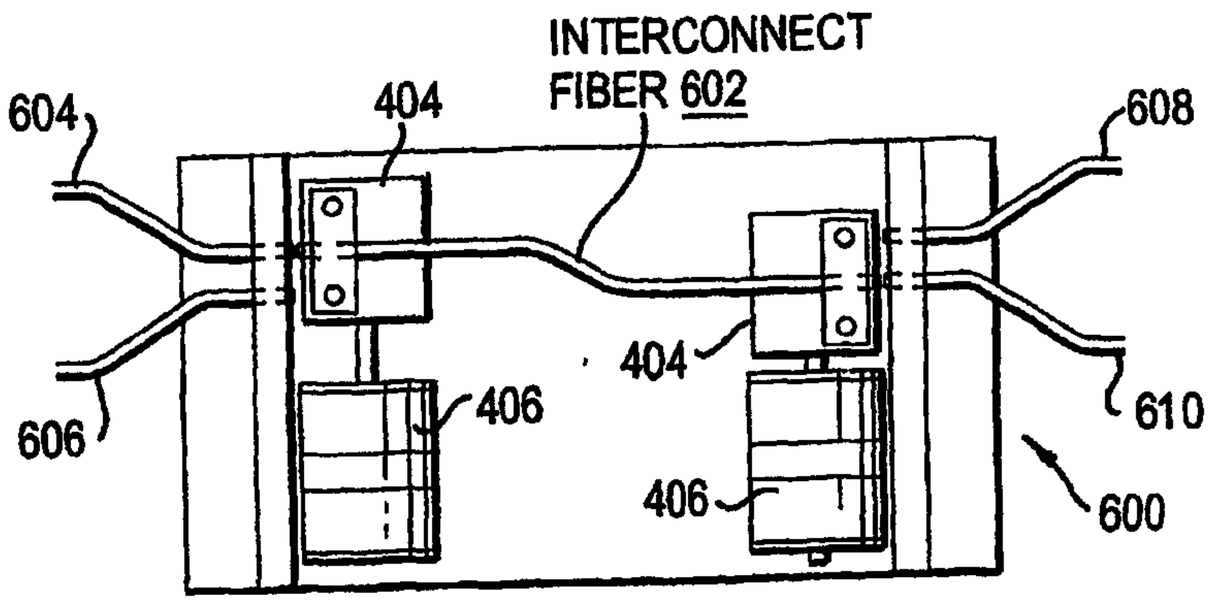


FIG. 6

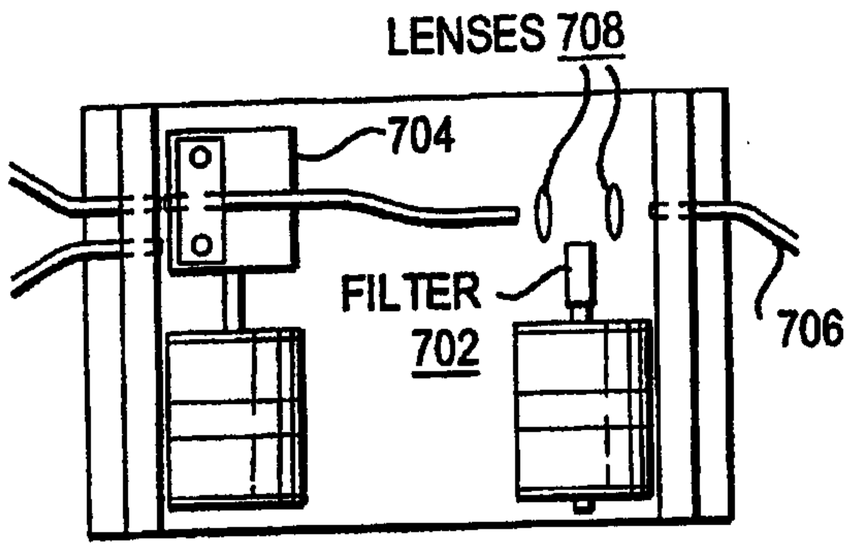


FIG. 7A

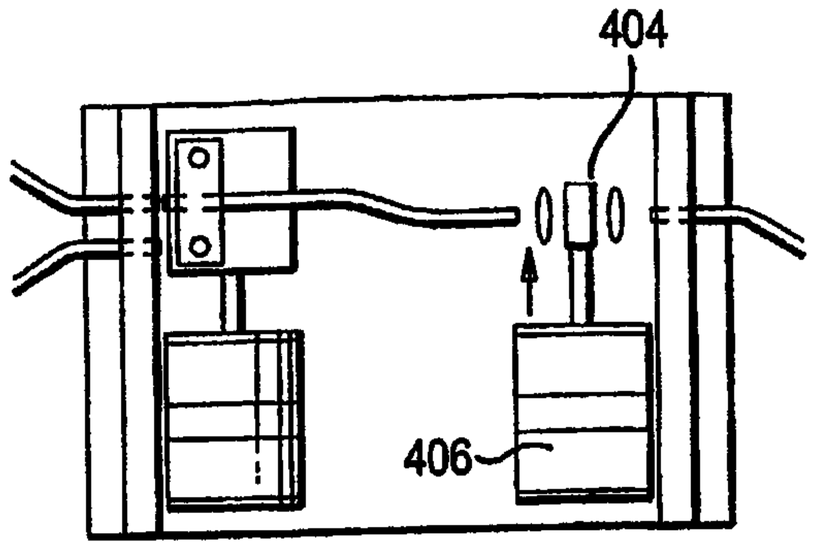


FIG. 7B

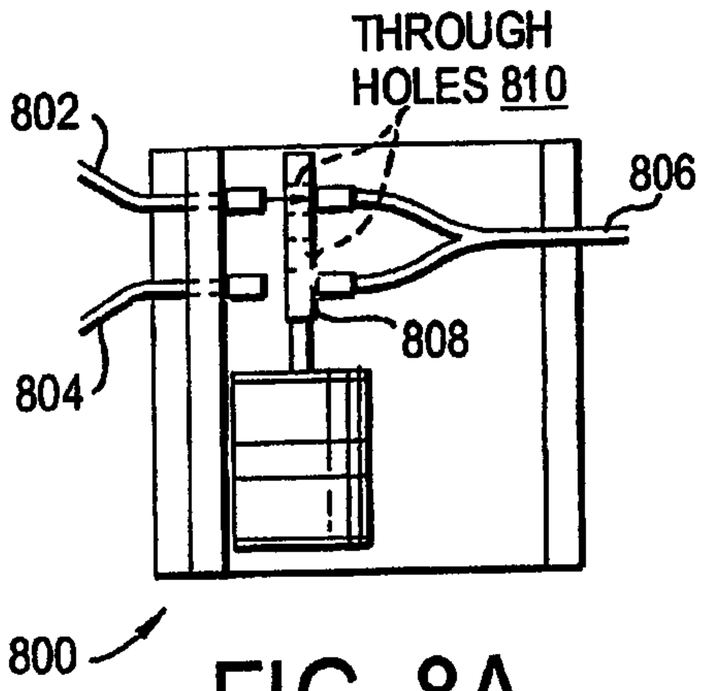


FIG. 8A

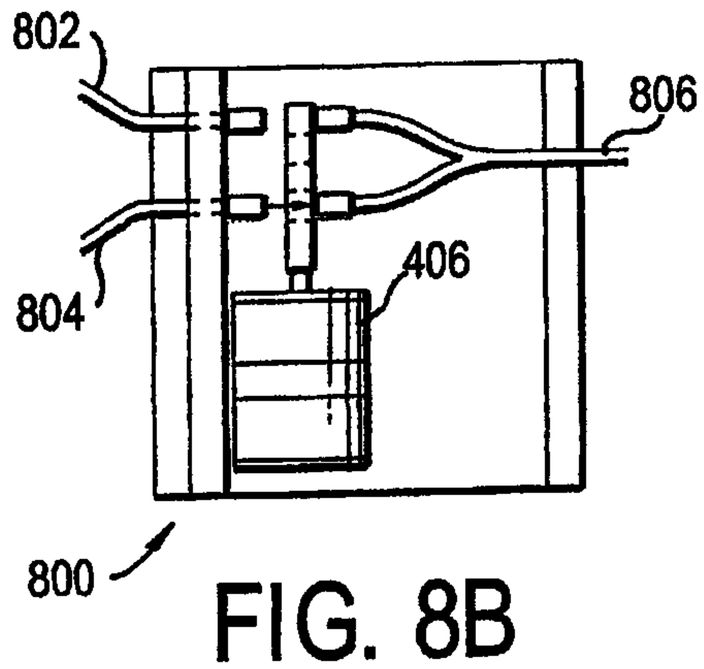


FIG. 8B

FIG. 9

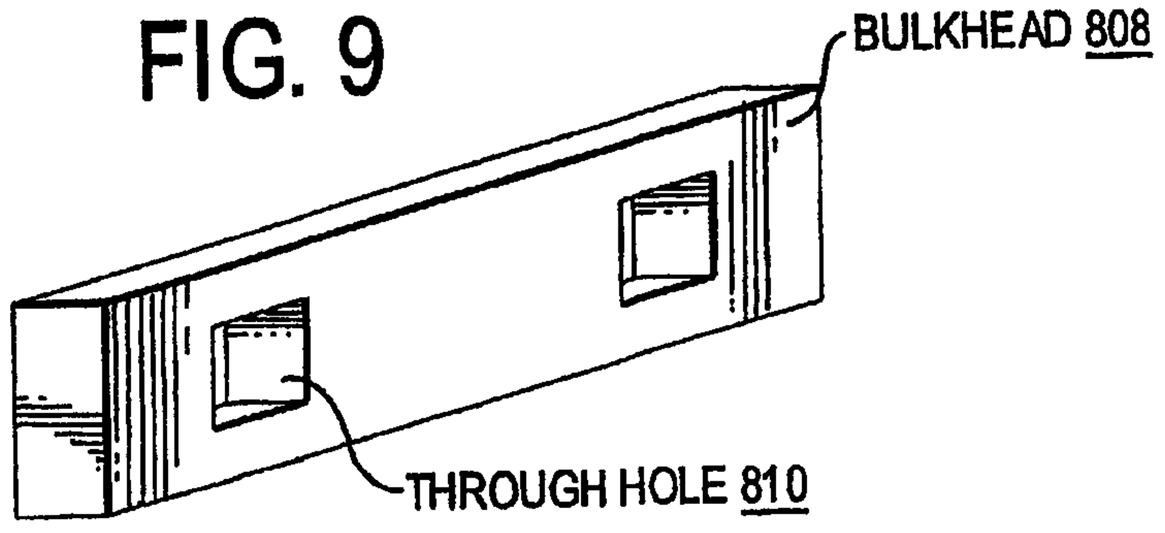


FIG. 10

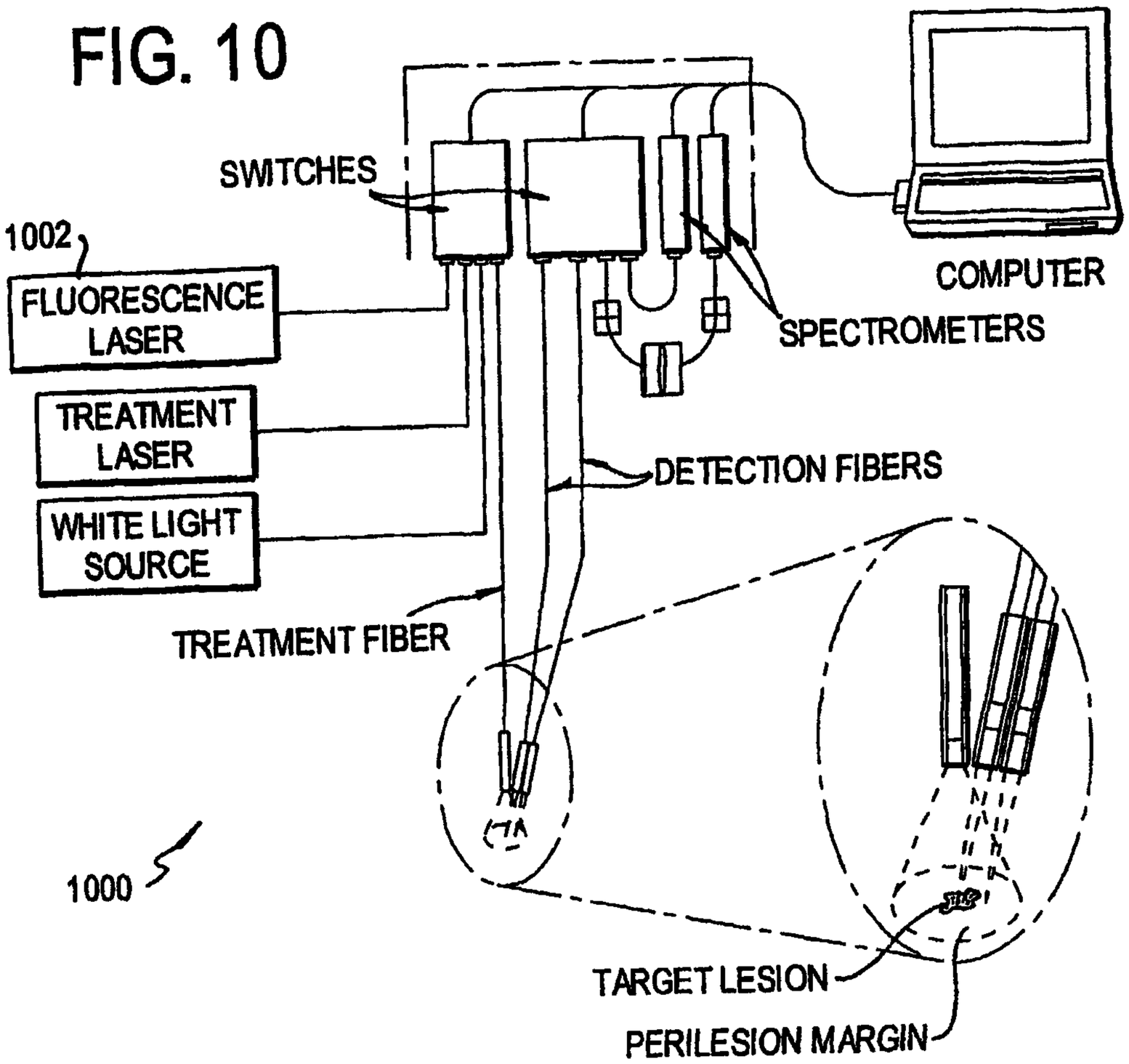
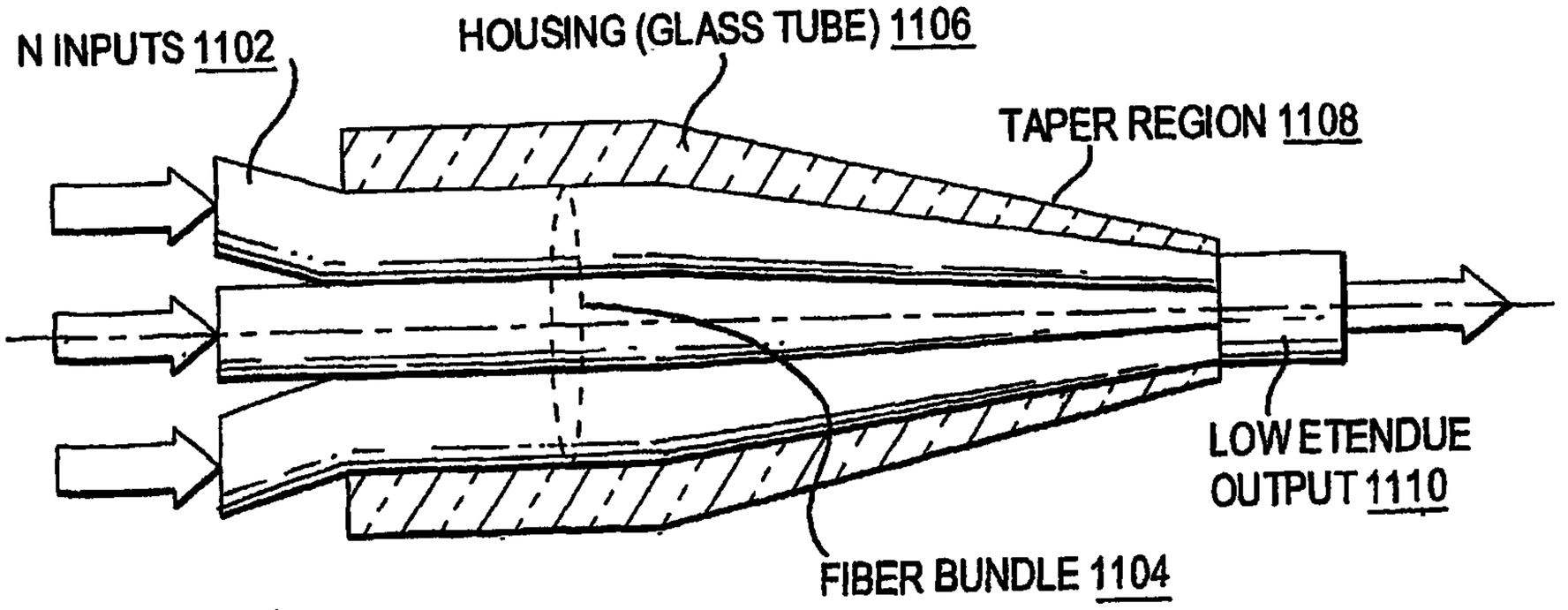
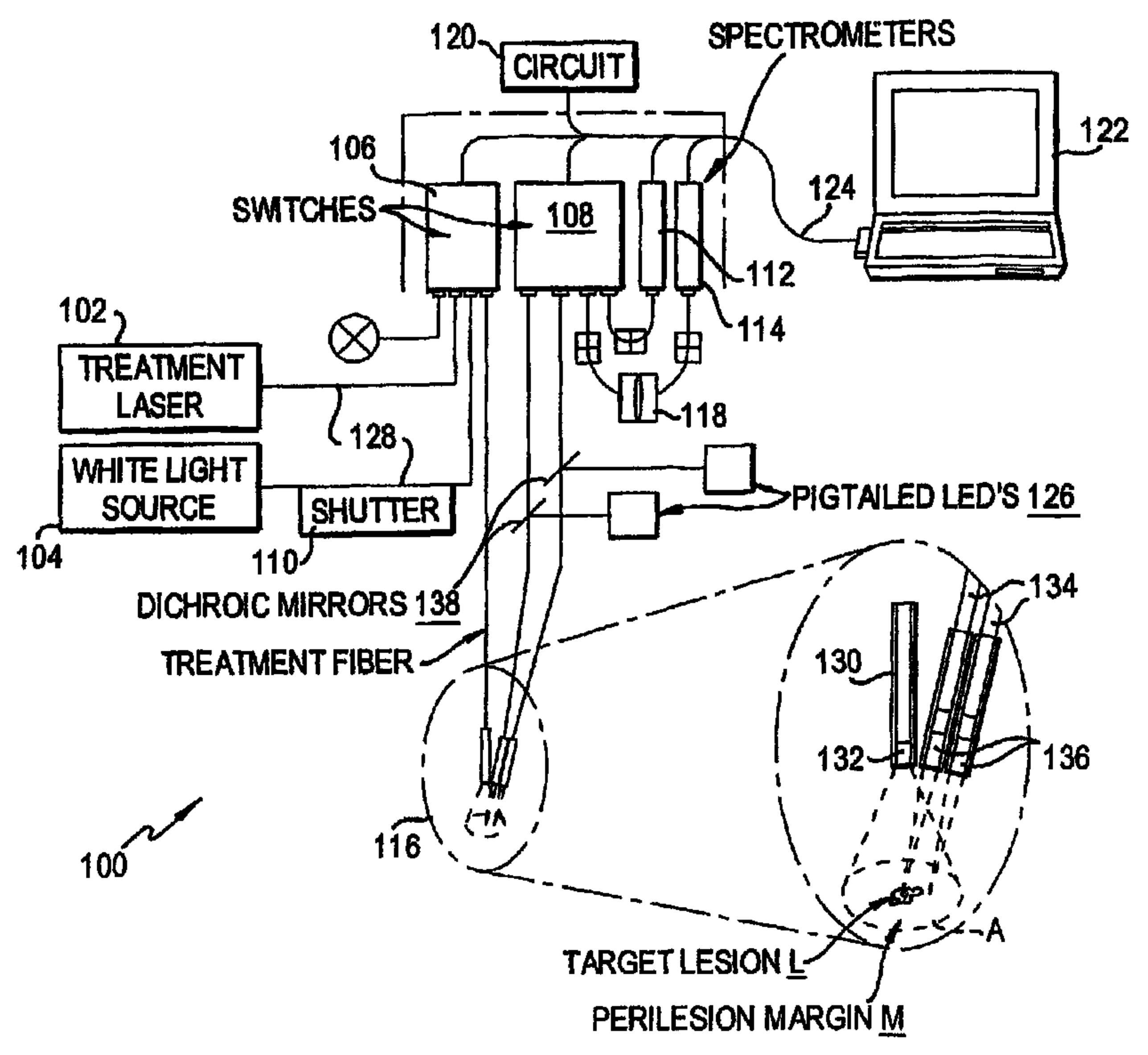

SWITCHES
1002
FLUORESCENCE LASER
TREATMENT LASER
WHITE LIGHT SOURCE
COMPUTER
SPECTROMETERS
DETECTION FIBERS
TREATMENT FIBER
1000
TARGET LESION
PERILESION MARGIN

FIG. 11


N INPUTS 1102
HOUSING (GLASS TUBE) 1106
TAPER REGION 1108
LOW ETENDUE OUTPUT 1110
FIBER BUNDLE 1104


120
CIRCUIT
SPECTROMETERS
122
106
SWITCHES
108
124
112
114
102
TREATMENT LASER
118
128
WHITE LIGHT SOURCE
SHUTTER
PIGTAILED LED'S 126
104
110
DICHROIC MIRRORS 138
134
TREATMENT FIBER
130
132
136
100
116
7A
A
TARGET LESION L
PERILESION MARGIN M