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Perov et al.

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(54) **BIOCHIP SCANNER DEVICE**

(75) Inventors: **Alexander Perov**, Troitsk (RU); **Alexander I. Belgovskiy**, Mayfield Heights, OH (US); **Andrei D. Mirzabekov**, Darien, IL (US)

(73) Assignee: **The University of Chicago**, Chicago, IL (US)

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(52) **U.S. Cl.** **250/461.2**; 250/459.1
(58) **Field of Search** 250/461.2, 461.1, 250/459.1

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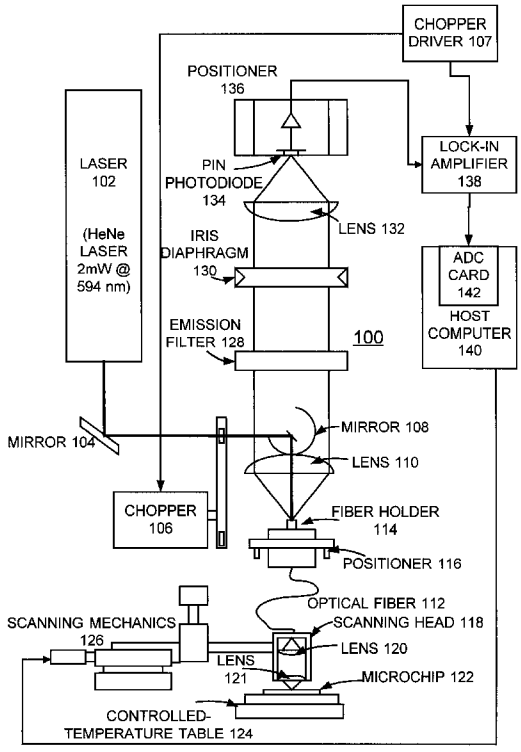
Primary Examiner—Constantine Hannaher
Assistant Examiner—Albert Gagliardi
(74) *Attorney, Agent, or Firm*—Joan Pennington

(57) **ABSTRACT**

A biochip scanner device used to detect and acquire fluorescence signal data from biological microchips or biochips and method of use are provided. The biochip scanner device includes a laser for emitting a laser beam. A modulator, such as an optical chopper modulates the laser beam. A scanning head receives the modulated laser beam and a scanning mechanics coupled to the scanning head moves the scanning head relative to the biochip. An optical fiber delivers the modulated laser beam to the scanning head. The scanning head collects the fluorescence light from the biochip, launches it into the same optical fiber, which delivers the fluorescence into a photodetector, such as a photodiode. The biochip scanner device is used in a row scanning method to scan selected rows of the biochip with the laser beam size matching the size of the immobilization site.

20 Claims, 5 Drawing Sheets



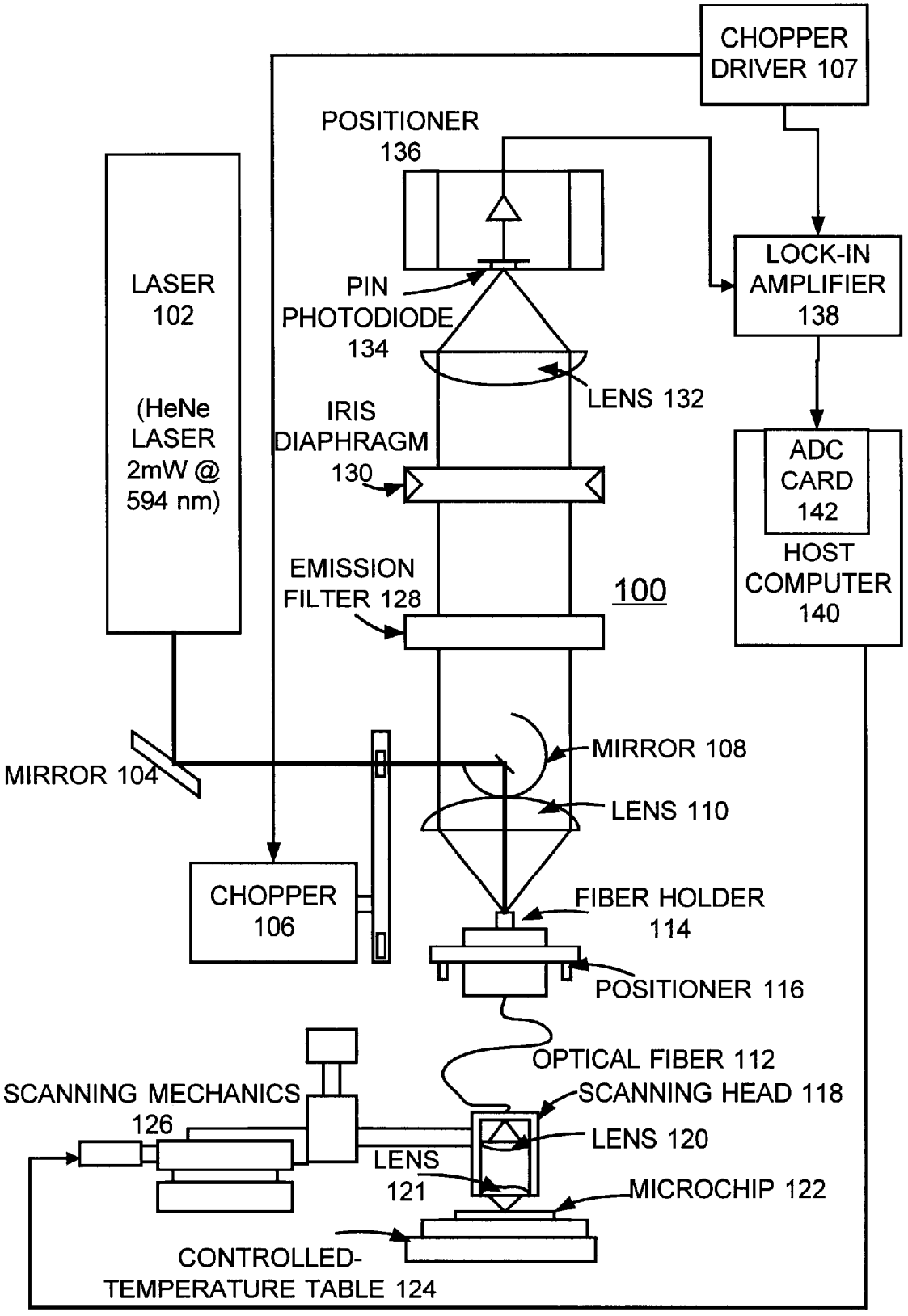

CHOPPER DRIVER 107
POSITIONER 136
LASER 102
(HeNe LASER 2mW @ 594 nm)
PIN PHOTODIODE 134
LOCK-IN AMPLIFIER 138
LENS 132
IRIS DIAPHRAGM 130
ADC CARD 142
HOST COMPUTER 140
EMISSION FILTER 128
100
MIRROR 104
MIRROR 108
LENS 110
CHOPPER 106
FIBER HOLDER 114
POSITIONER 116
OPTICAL FIBER 112
SCANNING MECHANICS 126
SCANNING HEAD 118
LENS 120
LENS 121
MICROCHIP 122
CONTROLLED-TEMPERATURE TABLE 124

FIG. 1

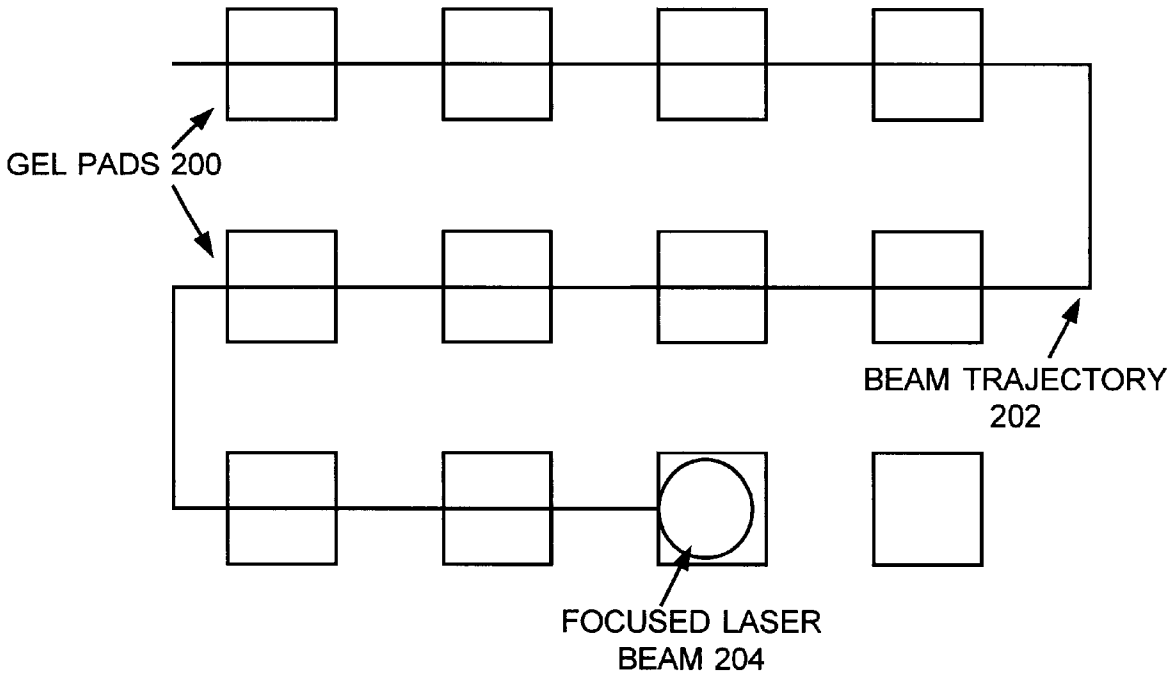


FIG. 2

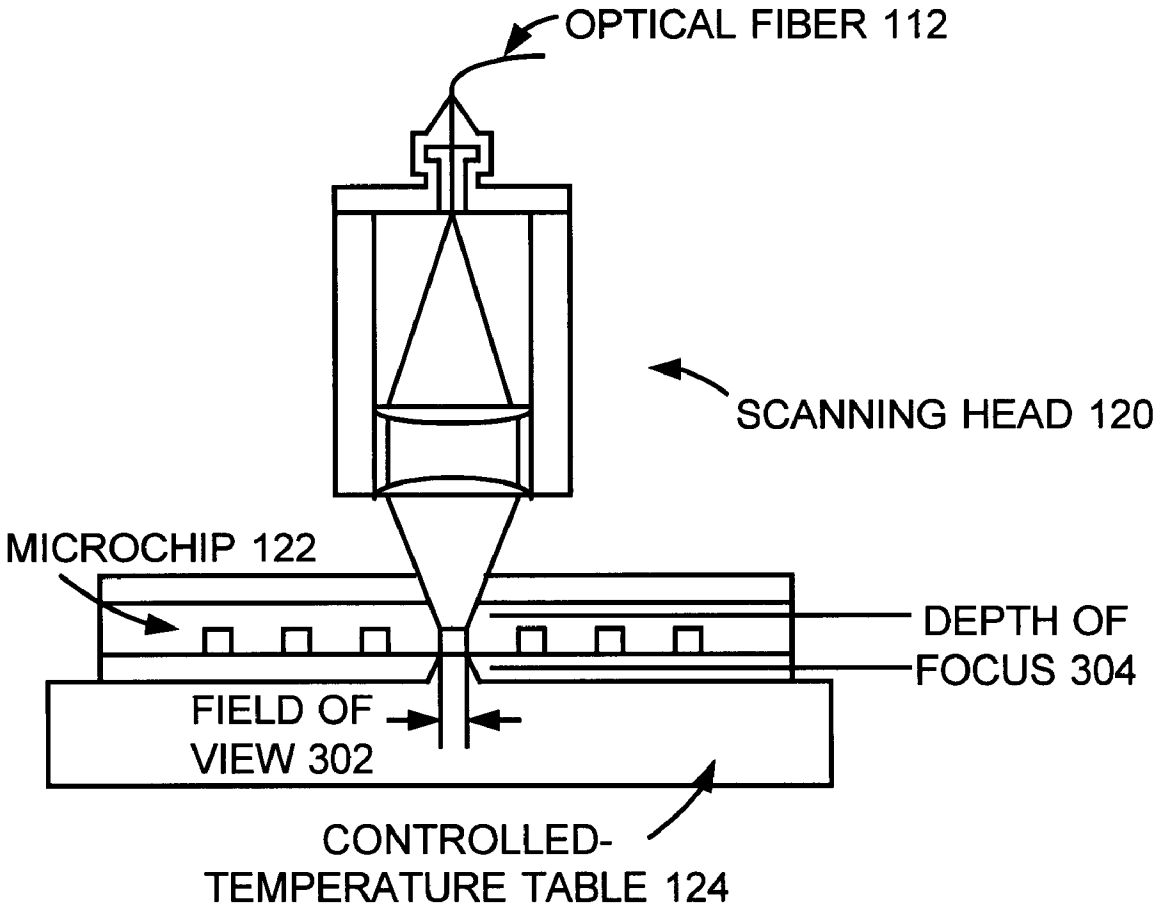
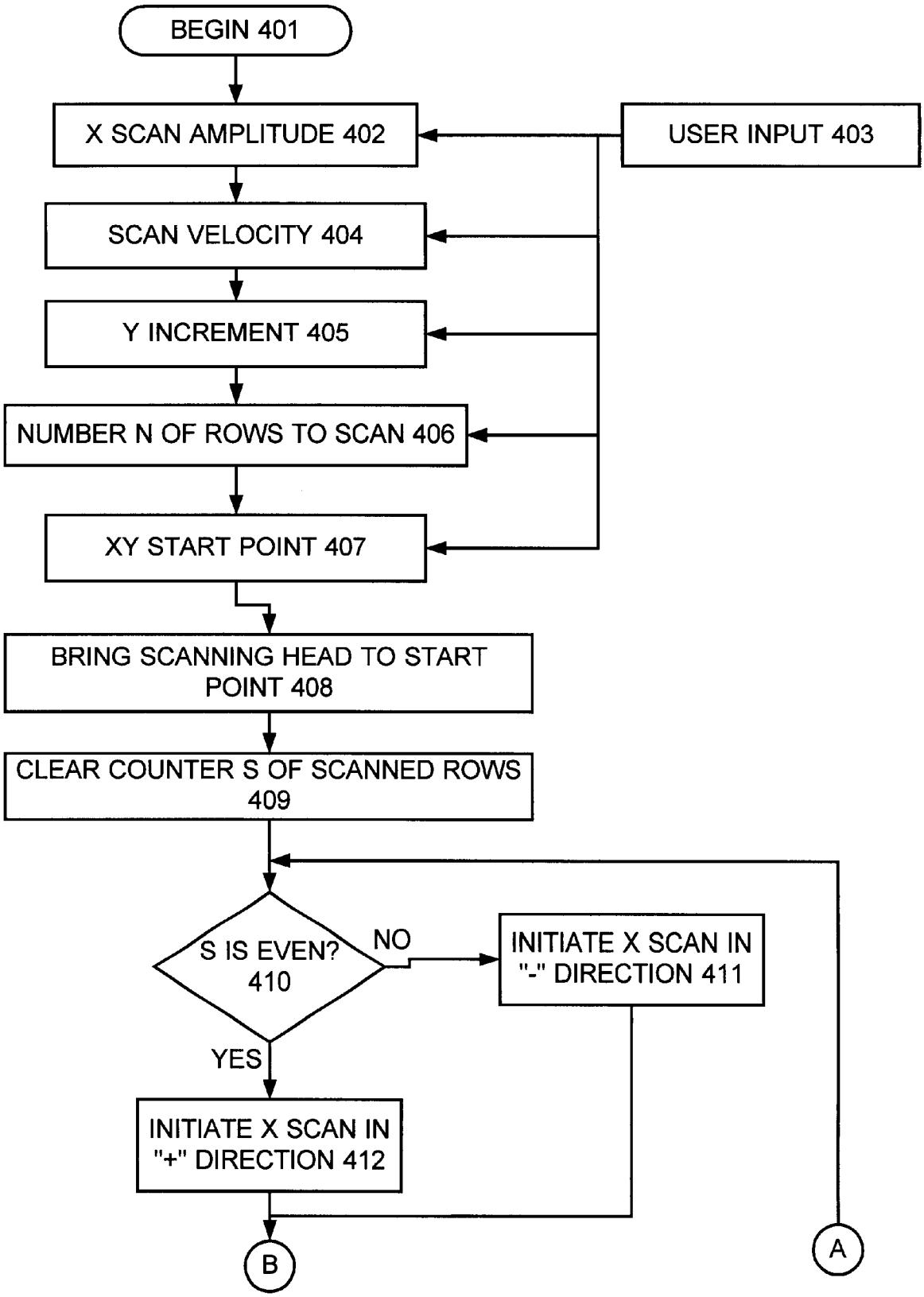

OPTICAL FIBER 112
SCANNING HEAD 120
MICROCHIP 122
DEPTH OF FOCUS 304
FIELD OF VIEW 302
CONTROLLED-TEMPERATURE TABLE 124

FIG. 3

FIG. 4A


BEGIN 401
X SCAN AMPLITUDE 402
USER INPUT 403
SCAN VELOCITY 404
Y INCREMENT 405
NUMBER N OF ROWS TO SCAN 406
XY START POINT 407
BRING SCANNING HEAD TO START POINT 408
CLEAR COUNTER S OF SCANNED ROWS 409
S IS EVEN? 410
NO
INITIATE X SCAN IN "-" DIRECTION 411
YES
INITIATE X SCAN IN "+" DIRECTION 412
B
A

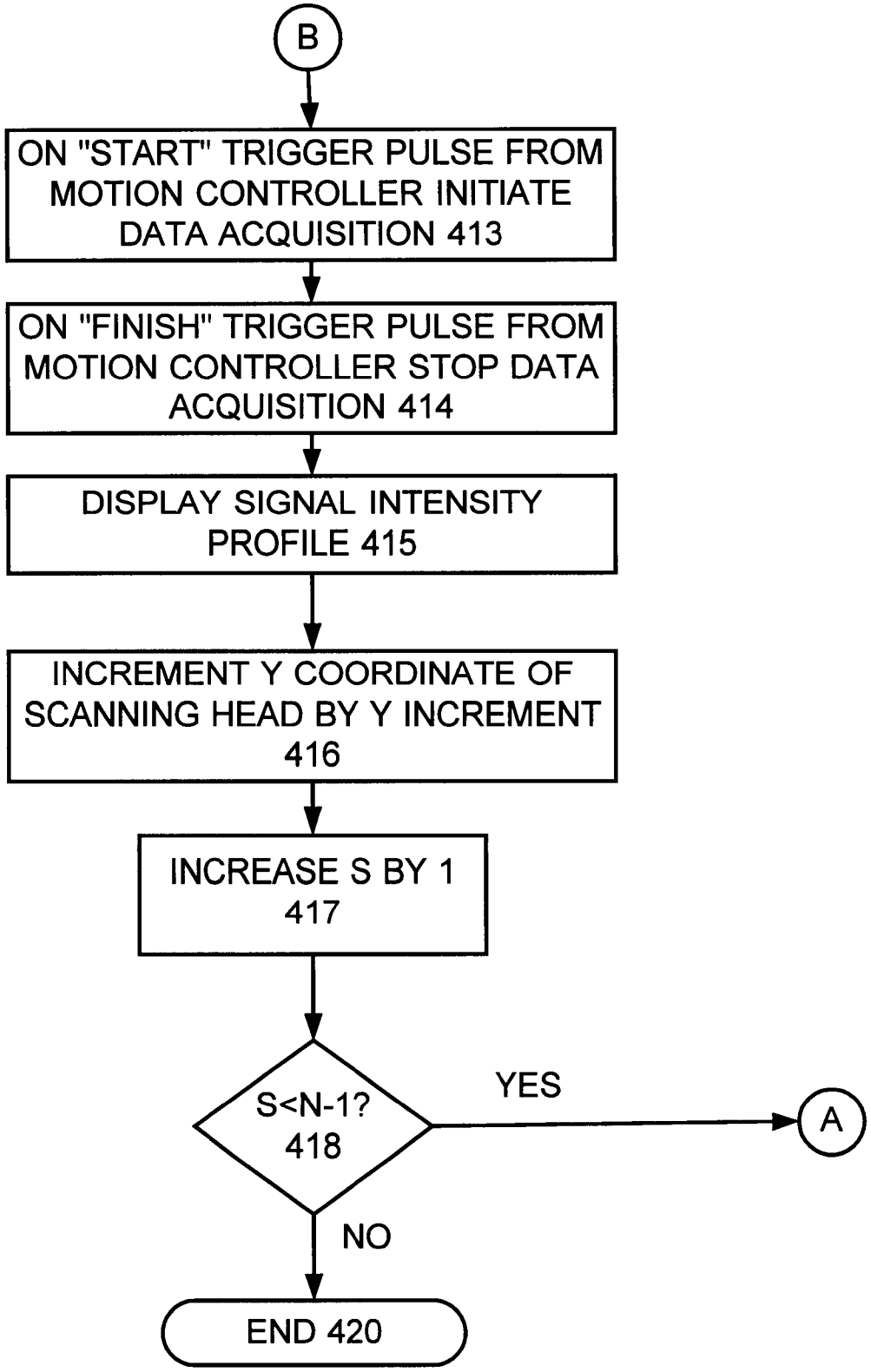

B
ON "START" TRIGGER PULSE FROM MOTION CONTROLLER INITIATE DATA ACQUISITION 413
ON "FINISH" TRIGGER PULSE FROM MOTION CONTROLLER STOP DATA ACQUISITION 414
DISPLAY SIGNAL INTENSITY PROFILE 415
INCREMENT Y COORDINATE OF SCANNING HEAD BY Y INCREMENT 416
INCREASE S BY 1 417
S<N-1? 418
YES
A
NO
END 420

FIG. 4B

BIOCHIP SCANNER DEVICE

RELATED APPLICATION

A related U.S. patent application Ser. No. 09/515,290 entitled "A PORTABLE BIOCHIP SCANNER DEVICE", by Alexander Perov, Alexei Sharonov and Andrei D. Mirzabekov is being filed on the same day as the present patent application.

CONTRACTUAL ORIGIN OF THE INVENTION

The United States Government has rights in this invention pursuant to Contract No. W-31-109-ENG-38 between the United States Department of Energy (DOE) and the University of Chicago representing Argonne National Laboratory.

FIELD OF THE INVENTION

The present invention relates to a biochip scanner device used to detect and acquire fluorescence signal data from biological microchips (biochips) and method of use.

DESCRIPTION OF THE RELATED ART

At the present time, biochips, after being incubated with a sample solution containing fluorescently labeled target molecules are assayed using either a microscope equipped with a charge coupled device (CCD) camera or a laser scanner. Regardless of the technique of fluorescence measurement used, all known biochip analyzers are high-resolution imaging instruments. This means that their output data is essentially a digital image of the chip composed of approximately 1000N elementary data points, where N represents the number of biochip immobilization sites. As a biochip user is typically interested in relative fluorescence intensities of the immobilization sites, an image as the output data format is highly redundant and requires further processing before the data can be analyzed. This may include signal integration over the immobilization sites, background subtraction, and normalization. The image processing is especially difficult in the case of analyzers based on wide-field microscopes, in which both the sensitivity and the image background are inherently non-uniform.

Due to the restraints on allowable working distance of the objective lens, currently available imaging biochip analyzers cannot be readily used with biochips mounted in an optical flow cell. This feature would be very desirable in order to facilitate the use of an experimental setup designed for multiple biochip use. Further high-resolution imaging requires the use of sophisticated electronic and optical components, which increase the instrument's complexity and cost.

A need exists for an improved mechanism to detect and acquire fluorescence signal data from biological microchips (biochips).

SUMMARY OF THE INVENTION

A principal object of the present invention is to provide a biochip scanner device used to detect and acquire fluorescence signal data from biological microchips (biochips) and method of use. Other important objects of the present invention are to provide such method and biochip scanner device substantially without negative effect; and that overcome some disadvantages of prior art arrangements.

In brief, a biochip scanner device used to detect and acquire fluorescence signal data from biological microchips (biochips) and method of use are provided. The biochip scanner device includes a laser for emitting a laser beam. A modulator, such as an optical chopper modulates the laser beam. A scanning head receives the modulated laser beam and a scanning mechanics coupled to the scanning head moves the scanning head relative to the biochip.

In accordance with features of the invention, an optical fiber delivers the modulated laser light to the scanning head. The scanning head serves for both focusing the excitation laser light onto the biochip and collecting the emitted fluorescence which is then delivered to a photodiode via the same optical fiber. The biochip scanner device is used in a row scanning method to scan selected rows of the biochip with the laser beam size matching the size of the immobilization sites.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention together with the above and other objects and advantages may best be understood from the following detailed description of the preferred embodiments of the invention illustrated in the drawings, wherein:

FIG. **1** is a schematic and block diagram illustrating a biochip scanner device in accordance with the preferred embodiment;

FIG. **2** is a diagram illustrating a method of scanning with the biochip scanner device in accordance with the preferred embodiment;

FIG. **3** is a diagram illustrating a field of view and depth of focus of a scanning head of the biochip scanner device in accordance with the preferred embodiment; and

FIGS. **4**A and **4**B together provide a flow chart illustrating a Row Scanning (RS) method of the preferred embodiment.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Having reference now to the drawings, in FIG. **1**, there is shown a biochip scanner device in accordance with the preferred embodiment generally designated by the reference character **100**. Biochip scanner device **100** is used to detect and acquire fluorescence signal data from biological microchips (biochips), such as oligonucleotide biochips.

In accordance with features of the invention, biochip scanner device **100** provides advantages over conventional fluorescence microscope equipped with a CCD camera. Biochip scanner device **100** provides much lower and considerably more uniform background. The detector field of view is limited to the focal spot of the laser beam on a microchip surface; as a result, the detector is substantially insensitive to all out-of-focus light. Biochip scanner device **100** provides essentially uniform and reproducible excitation and fluorescence-collection conditions. For each gel pad, the fluorescence is excited and detected under the same conditions; the same detector, the same optical path and the same excitation intensity. Biochip scanner device **100** uses a single-element photodetector that is significantly less expensive than a scientific-grade CCD camera. Biochip scanner device **100** employs a laser, such as a HeNe, diode-pumped solid state, and diode laser, that tend to be more reliable and consume significantly less power than microscopes using high-pressure arc lamps. Biochip scanner device **100** provides an improved data acquisition rate. Biochip scanner device **100** can be used to scan only the chip rows with the beam matching the size of the immobilization site instead of running a high-resolution scan of the entire chip surface. Biochip scanner device **100** allows real-time

data processing with the integral signal intensities being available for comparison and storage at the same rate as the rate of the chip being scanned.

Biochip scanner device **100** includes a laser **102** emitting a wavelength matching the excitation band maximum of a particular flurophore. In one embodiment, laser **102** is a 2 mW He—Ne laser emitting at 594 nm, which falls close to the absorption maximum of the popular fluorescent label, "Texas Red". For example, a He—Ne laser model 05 LYR 173 sold by Melles Griot of Irvine, Calif. can be used for laser **102**. It should be understood that other lasers could be used for laser **102**. The sensitivity of biochip scanner device **100** can be improved by using a red or infrared diode laser **102** as the excitation source. A red or infrared diode laser is more compact and more reliable than a He—Ne laser.

The laser beam is directed by a first mirror **104** and then is modulated by an optical chopper **106**. A chopper driver **107** drives the optical chopper **106**. In particular, this can be a chopper set at a frequency of 4.3 kHz. It should be understood that other techniques could be used to achieve intensity modulation of the excitation laser light. For example, in the case of a diode laser, the light intensity can be modulated by driving the laser with a periodic train of current pulses with a period corresponding to the desired modulation frequency. A mirror **108** and lens **110** then focus the laser beam into an optical fiber **112** supported by a fiber holder **114** and an X-Y-Z theta-phi positioner **116**. The optical fiber delivers the laser beam, excitation light to a miniature scanning head **118**. Scanning head **118** contains a first lens **120** and a second objective lens **121**. The scanning head **118** is moved relative to a microchip **122**.

Examples parts that can be used to form the biochip scanner device **100** are provided in the following; however, it should be understood that various other components could be used. A mirror part number 05D51OBD.1 sold by Newport of Irvine, Calif. can be used for mirror **104**. Chopper **106** and chopper driver **107** can be implemented with an optical chopper model 3501 sold by New Focus of Santa Clara, Calif. A mirror part number BRP-5-A sold by Newport of Irvine, Calif. can be used for mirror **108**. A lens part number PAC070 sold by Newport of Irvine, Calif. can be used for lens **110**. A lens part number PAC510 sold by Newport of Irvine, Calif. can be used for the first lens **120** of the scanning head **118**. A lens part number 350340B-00 sold by Geltech of Orlando, Fla. can be used for the objective lens **121** of the scanning head **118**. The fiber optic X-Y-Z theta-phi positioner **116** can be implemented with a part number M-FPR2-C1 sold by Newport of Irvine, Calif. An optional fiber patchcord part number F-MCC-T-OPT-10-10 sold by Newport of Irvine, Calif. can be used.

A controlled-temperature table **124** supports the microchip **122**. Scanning mechanics **126** is coupled to the scanning head **118** to move the scanning head **118** in both X and Y directions, under computer control, to perform scanning of the biochip **122**. A manual stage allows adjustments of the scanning head position in the Z direction perpendicular to the focal plane. Scanning head **118** includes for example, an objective lens **121** with a 3 mm working distance and acceptance angle of approximately 77°, focusing the excitation light onto the spot that is roughly equivalent to a gel pad in size, so as to excite most of the label in an immobilization site simultaneously.

A novel feature of the biochip scanner device **100** is that the objective lens **121** used for both focusing the excitation beam and collecting the fluorescent signal is located in a miniature remote scanning head **118** linked to the rest of the optical path elements by the optical fiber **112**. Accordingly, the fiber **112** is used for transmitting both the excitation beam and the fluorescence signal to and from the scanning head, respectively. This feature considerably simplifies the scanner design, because other optical path elements can be stationary. The fluorescence light emerging from the fiber **112** at the fiber holder **114** has a divergence much greater than that of the original laser beam. As a result, the diameter of the fluorescence beam after the collimating lens **110** is about 3 cm, which means that the small deflection mirror **108** used for coupling the excitation beam into the fiber **112** will block only a small fraction of the fluorescence flux.

After passing through the lens **110**, the fluorescence beam passes through an emission interference filter **128** and an iris diaphragm **130**. The emission interference filter **128** is a filter that rejects all light except fluorescent light. A second lens **132** is used to focus the filtered light onto a silicon photodiode **134** that is equipped with a low-noise pre-amplifier and supported by a positioner **136**. The output of the photodiode pre-amplifier is further amplified and demodulated by a lock-in amplifier **138**. The lock-in amplifier **138** is phase-locked to the chopper driver reference signal, to provide improved signal-to-noise ratio. The output of the lock-in amplifier **138** is a DC voltage that is proportional to the intensity of the fluorescence signal. The output of the lock-in amplifier **138** is digitized by an analog-to-digital converter (ADC) card **142** and then processed by a host computer **140**.

The same lens part number PAC070 sold by Newport of Irvine, Calif. as used for lens **110** can be used for lens **132**. A filter part number 645RDF72 sold by Omega Optical of Brattleboro, Vt. can be used for emission filter **128**. Iris diaphragm **130** can be implemented with a part number M-ID-1.5 sold by Newport of Irvine, Calif. A photoreceiver model 2001 sold by New Focus of Santa Clara, Calif. can be used for PIN photodiode **134**. A lock-in amplifier model **5105** sold by EG&G Instruments of Princeton, N.J. can be used for lock-in amplifier **138**. The ADC card **142** can be implemented with a data acquisition card number PCI-MIO-16XE-50 sold by National Instruments of Austin, Tex. The scanning mechanics **126** can be implemented with X-Y scanning stage sold by Newport of Irvine, Calif.

FIG. **2** illustrates a method of scanning with the biochip scanner device **100** in accordance with the preferred embodiment. An innovative method called Row Scanning (RS) is used with the biochip scanner device **100**. In the RS method, a row of a biochip is scanned with a beam of a size that matches the immobilization site. An advantage of the RS method of the preferred embodiment where the length of time to accumulate the data is a consideration is that the RS method allows for real-time data processing, so that the integral signal intensities can be available for comparison and storage at the same rate that the chip **122** is being scanned. On the other hand, a reduction in scanning velocity can allow the sensitivity and dynamic range of the biochip scanner device **100** to be comparable with that of more expensive, conventional systems. Using the RS method provides a flexible and reliable way to relax hardware characteristics such as bandwidth, analog-to-digital conversion rate, optical resolution, and scanning mechanics parameters, depending upon the constraint of a particular user's needs, without sacrificing sensitivity and dynamic range of the biochip scanner device **100**.

FIG. **3** illustrates a field of view **302** and a depth of focus **304** with the scanning head **118** of the biochip scanner device **100** in accordance with the preferred embodiment. Referring also to FIG. **2**, the laser beam size substantially matches the gel pads **200** or immobilization site.

FIGS. **4**A and **4**B together provide a flow chart illustrating the Row Scanning (RS) method of the preferred embodiment starting at a block **401**. The area to be scanned is limited to essentially the rows of the biochip array. Each row is scanned in a single pass of the laser beam while the laser beam size is matched to the immobilization site. At the same rate of the chip being scanned, the amplitudes of the fluorescence peaks are recorded. As a result, the amplitudes of the fluorescence peaks recorded give the integral signal intensities, which are most relevant to biochip applications. Since the scanner implementing the RS technique generates data that requires minimum, if any off-line processing, it is inherently suitable for high-rate data acquisition, which, in the same time, can be realized at slower scanning speeds. Or on the other hand, the reduction in scanning speed allows the sensitivity and dynamic range of the inexpensive biochip scanner device **100** to be comparable with that of more expensive, conventional systems.

An X scan amplitude as indicated in a block **402** is received from a user input at block **403**. Other received user inputs include scan velocity, Y increment, number N of rows to scan and XY start point, respectively indicated at blocks **404**, **405**, **406**, and **407**. The scanning head **118** is brought to the start point as indicated in a block **408**. Then counter S is cleared of scanned rows as indicated in a block **409**. Checking whether S is even is performed as indicated in a decision block **410**. When not even, the X scan is initiated in the "−" direction as indicated in a block **411**. Otherwise, when even the X scan is initiated in the "+" direction as indicated in a block **412**. Continuing with FIG. **2**B following entry point B, on a start trigger pulse from the motion controller, data acquisition is initiated as indicated in a block **413**. On a finish trigger pulse from the motion controller, data acquisition is stopped as indicated in a block **414**. The signal intensity profile is displayed as indicated in a block **415**. The Y coordinate of the scanning head is incremented by the Y increment as indicated in a block **416**. S is increased by 1 as indicated in a block **416**. Next X is compared to the number of rows to scan, S<N−1, as indicated in a decision block **418**. When S is less than N-1, then the sequential operations return to decision block **410** in FIG. **4**A. Otherwise, the sequential operations end as indicated in a block **420**.

A practical evaluation of the biochip scanner device **100** of the preferred embodiment has shown that compact photodiodes **134** and low-power lasers **102** can provide the performance characteristics necessary for reliable detection of fluorescence at the level of 100,000 fluorescent molecules/gel pad. This sensitivity could be further improved by using a red and/or an infrared diode laser **102** as an excitation source. Assuming a 100 μm gel pad size, a 200 μm space between adjacent gel pads, biochip scanner device **100** can provide an effective acquisition rate of about 29 immobilization sites per second. This is an improvement over conventional systems.

While the present invention has been described with reference to the details of the embodiments of the invention shown in the drawing, these details are not intended to limit the scope of the invention as claimed in the appended claims.

What is claimed is:

1. A biochip scanner device, said biochip scanner device for quantifying a plurality of linear arrays of substantially separated, dimensionally uniform fluorescent targets, said arrays located at known positions on a plain support of a biochip; said biochip scanner device comprising:

a laser for emitting a laser beam of excitation radiation;

a modulator for modulating said laser beam;

a scanning head for receiving said modulated laser beam; said scanning head for focusing said laser beam of excitation radiation into a focal spot; said focal spot having a selected size substantially equal to a size of said substantially separated, dimensionally uniform fluorescent targets; and

a scanning mechanics coupled to said scanning head for moving said scanning head relative to the biochip for directing said laser beam focal spot for sequentially illuminating said fluorescent targets one at a time; said laser beam focal spot causing substantially entire excitation of each said illuminated fluorescent target; and for sequentially collecting fluorescence of each said illuminated fluorescent target.

2. A biochip scanner device as recited in claim **1** wherein said scanning head includes an objective lens for focusing said modulated laser beam into said focal spot.

3. A biochip scanner device as recited in claim **2** wherein said scanning head for sequentially collecting fluorescence of each said illuminated fluorescent target has a field of view substantially equal to size of said fluorescent target.

4. A biochip scanner device as recited in claim **1** includes an optical fiber delivering said modulated laser beam to said scanning head and collecting said fluorescence from said scanning head for each said illuminated fluorescent target.

5. A biochip scanner device as recited in claim **1** includes an emission interference filter coupled to said scanning head for receiving and filtering said fluorescence from each said illuminated fluorescent target.

6. A biochip scanner device as recited in claim **1** includes a photodiode for detecting said fluorescence from each said illuminated fluorescent target.

7. A biochip scanner device as recited in claim **1** includes a single-element photodetector for detecting said fluorescence from each said illuminated fluorescent target.

8. A biochip scanner device as recited in claim **7** wherein said single-element photodetector includes a preamplifier and further includes a lock-in amplifier coupled to said photodetector, said lock-in amplifier for amplifying a photodetector signal at a modulating frequency of said modulator.

9. A biochip scanner device as recited in claim **8** wherein said lock-in amplifier provides a DC signal proportional to an intensity of said fluorescence; and includes an analog-to-digital converter (ADC) for digitizing said DC signal; and a computer for processing said digitized DC signal.

10. A biochip scanner device as recited in claim **1** wherein said laser includes a low-power He—Ne laser and wherein said modulator includes an optical chopper.

11. A biochip scanner device as recited in claim **1** wherein said laser includes one of a red or infrared diode laser and wherein said modulator includes a current driver providing a periodic train of current pulses with a period corresponding to a desired modulation frequency.

12. A method of using a biochip scanner device, said biochip scanner device for quantifying a plurality of linear arrays of substantially separated, dimensionally uniform fluorescent targets, said arrays located at known positions on a plain support of a biochip; said method comprising the steps of:

defining a number of linear segments for scanning; at least some of said segments passing along a number of said linear arrays of fluorescent targets;

focusing a laser beam of excitation radiation into a focal spot; said laser beam focal spot substantially matching a size of said fluorescent targets; and

sequentially scanning each of said defined linear segments; directing said laser beam focal spot and sequen-

tially illuminating predefined ones of said fluorescent targets one at a time within each of said defined linear segments; said laser beam focal spot causing substantially entire excitation of each said illuminated fluorescent target;

sequentially collecting fluorescence of each said illuminated fluorescent target and quantifying an intensity of said collected fluorescence of each said illuminated fluorescent target; and

recording said fluorescence intensity of each said illuminated fluorescent target.

13. A method as recited in claim **12** includes the step of digitizing said fluorescence intensity utilizing an analog-to-digital converter; and processing said digitized DC signal utilizing a computer.

14. A method as recited in claim **13** wherein the step of sequentially collecting fluorescence of each said illuminated fluorescent target and quantifying an intensity of fluorescence of each said illuminated fluorescent target includes the steps of coupling said collected fluorescence of each said illuminated fluorescent target to a photodiode and amplifying a photodiode signal with a lock-in amplifier at a modulating frequency of a modulator for quantifying said intensity of fluorescence of each said illuminated fluorescent target.

15. A method as recited in claim **12** wherein the step of sequentially scanning each of said defined linear segments includes the step of providing a scanning head coupled to an optical fiber for receiving a modulated laser beam; utilizing said scanning head for focusing a laser beam of excitation radiation into a focal spot, said laser beam focal spot substantially matching a size of said fluorescent targets; directing said laser beam focal spot and sequentially illuminating predefined ones of said fluorescent targets one at a time within each of said defined linear segments; said laser beam focal spot causing substantially entire excitation of each said illuminated fluorescent target; and said scanning head for transmitting said collected fluorescence peaks to said optical fiber.

16. A biochip scanner device, said biochip scanner device for quantifying a plurality of linear arrays of substantially separated, dimensionally uniform fluorescent targets, said arrays located at known positions on a plain support of a biochip; said biochip scanner device comprising:

a laser for emitting a laser beam of excitation radiation;

a modulator for modulating said laser beam;

a scanning head for receiving said modulated laser beam; said scanning head for focusing said laser beam of excitation radiation into a focal spot; said focal spot having a selected size substantially equal to a size of each said substantially separated, dimensionally uniform fluorescent targets;

a scanning mechanics coupled to said scanning head for moving said scanning head relative to the biochip for directing said laser beam focal spot for sequentially illuminating said fluorescent targets one at a time; said laser beam focal spot causing substantially entire excitation of each said illuminated fluorescent target; and for sequentially collecting fluorescence of each said illuminated fluorescent target;

a photodetector for detecting said collected fluorescence of each said illuminated fluorescent target from the biochip; and

an optical fiber for delivering said modulated laser beam to said scanning head and said optical fiber for delivering said collected fluorescence of each said illuminated fluorescent target to said photodetector.

17. A biochip scanner device as recited in claim **16** further includes an emission interference filter coupled to said optical fiber for filtering said collected fluorescence of each said illuminated fluorescent target.

18. A biochip scanner device as recited in claim **16** wherein said modulator includes an optical chopper and wherein said photodetector includes a photodiode and a lock-in amplifier for amplifying a photodiode signal at a modulating frequency of said optical chopper.

19. A biochip scanner device as recited in claim **18** wherein said lock-in amplifier provides a DC signal proportional to an intensity of said collected fluorescence of each said illuminated fluorescent target.

20. A biochip scanner device as recited in claim **16** wherein said scanning head includes an objective lens for focusing said modulated laser beam of excitation radiation into a focal spot and for collecting said fluorescence of each said illuminated fluorescent target.

* * * * *