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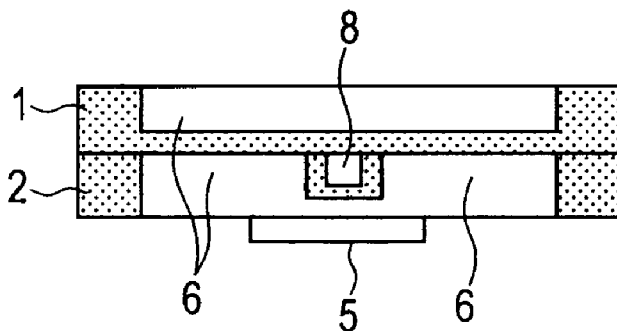
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(54) Title: FLUID PATH DEVICE

FIG. 3



(57) Abstract: In a fluid path device having a minute fluid path and a plurality of heaters arranged along the fluid path, the fluid path device is formed by, direct bonding or anodic bonding of one substrate and another substrate in which the fluid path is formed on a bonding surface, the plurality of heaters is formed on a surface different from the bonding surface of any one of the substrates, and the substrate formed with the heater has, between the heaters, a region where thermal conductivity is smaller than the substrate. According to the device, a fluid path having a heater can be formed inexpensively, heat conduction from the heater to the fluid path is good, each thermal operation of a plurality of heaters provided in a single fluid path is not interfered, and a temporally high-speed temperature history can be formed irrespective of movement of a fluid.

DESCRIPTION

FLUID PATH DEVICE

Technical Field

[0001]The present invention mainly relates to a fluid path device which applies a temperature change to a liquid flowed in a fluid path to create a reaction.

Background Art

[0002]In conventional laboratory tests, reagents of ml level to μ l level are required for chemical analysis, reagent preparation, chemical synthesis, and reaction detection. However, recently, in a test at a test tube level, a minute reaction field is formed by applying a lithographic process and a thick film process technique, whereby a test at nl level can be performed. As a technique for realizing a laboratory test utilizing the minute reaction field by a miniaturized and automated apparatus in a unified manner, a micro total analysis system (μ -TAS) technology has been developed. The μ -TAS technology is applied to, for example, medical testing and diagnostics such as genetic testing, chromosomal test, and cytoscropy, biotechnology, testing of a small amount of environmental substances, rearing environment research of farm products, and genetic testing of farm products.

[0003]In a conventional test, reagents are mainly treated by techniques of laboratory technicians, and since a test process is often complex, a skilled operation of apparatuses is required. However, if the process is automated by introducing the μ -TAS technology, a laboratory test with high reproducibility can be realized regardless of a technique of an operator. Further, by virtue of the μ -TAS technology, automation, speeding up, high accuracy, low cost, swiftness, and reduction of environmental impact are realized, and a large effect is expected to be obtained.

[0004] In a fluid path device introduced with the μ -TAS technique, in addition to a fluid path through which a reaction liquid is passed, a processing section for inducing, in a reaction field, heating, cooling, drying, or applied voltage required according to the usage of the device is generally installed.

[0005] For example, as an example of utilizing a reaction field according to heating, there is a device which performs polymerase chain reaction (PCR). In order to analyze nucleic acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), these nucleic acids are required to be amplified to a required amount. A PCR reaction method is one of methods of amplifying nucleic acid. DNA is constituted of molecules constituted of a double strand in which four kinds of bases are connected, and the double strand is unraveled at a high temperature (for example, near 95°C) to be separated into single strands. Thereafter, when the temperature is lowered (for example, near 55°C), the single strands return to the double strand again. If a large amount of primer (single strand DNA having a sequence of the upstream of an intended base sequence that is desired to be especially amplified) is compounded in an atmosphere in which temperature is raised and lowered, primer is bonded to a specific complementary portion in many unraveled double strands to form a double strand when the temperature is lowered. A base sequence that forms a Watson-Crick base pair with a certain sequence to form a double strand is referred to as a sequence complementary to the certain sequence, and the mechanism that the complementary sequences are bonded to each other and single strands become a double strand is referred to as hybridization. Subsequently, temperature is set to an intermediate temperature (for example, near 70°C), and a DNA synthetase and four kinds of bases are compounded in a

solution, whereby each unravelled strand is synthesized, from a portion to which a primer is bonded as a base point, with a complementary strand to extend a double strand. Those sequential operations are repeated, whereby DNA and RNA can be amplified.

[0006] PTL 1 discloses a fluid path device having a plurality of temperature control areas with respect to a fluid path for the purpose of performing PCR reaction at high speed. In the fluid path device in PTL 1, the fluid path formed near a heating surface side is bent toward a counter-heating surface in a place between different temperature areas, and in the different temperature areas in which the fluid path is bent, the fluid path device has a groove-shaped air heat insulating layer on the heating surface side. The fluid path device is in contact with a plurality of heaters provided on the device side at each of a plurality of temperature areas and exchanges heat.

Citation List

Patent Literature

[0007] PTL 1: Japanese Patent Application Laid-Open No. 2008-253227

Summary of Invention

Technical Problem

[0008] A PCR reaction is normally a reaction form in which such a cycle of a temperature history that a plurality of setting temperatures is reciprocated is performed a plurality of times. In PTL 1, such a section is created that three kinds of temperatures corresponding to the respective stages of the PCR reaction are steadily maintained, and the fluid path is formed so that a liquid in the fluid path is reciprocated in the respective sections and then moved to the next temperature section, whereby a temperature change of the liquid is realized.

[0009] However, in the fluid path device in PTL 1, the heater

is not provided in the fluid path device but provided on a control device side, and the heater is in contact with the fluid path device, whereby heating is performed. Namely, in order to change a temperature of a liquid in the fluid path, heat transfer through a member constituting a fluid path wall surface is required, and there is a limit to changing temperatures of a plurality of temperature areas at high speed.

[0010] Accordingly, the present invention provides a device, which can form a temporally high-speed temperature history without depending on movement of a fluid. In order to provide the device, a plurality of problems should be solved simultaneously. Those problems include that a method of forming a fluid path having a heater is inexpensive, heat conduction from the heater to the fluid path is good, and each thermal operation of a plurality of heaters provided in a single fluid path is not interfered.

Solution to Problem

[0011] In order to solve the above problem, the present invention is characterized in that a heater and a fluid path are provided to be in vicinity to each other and constituted as an integrated device. Further, the present invention is characterized in that a metal resistor is patterned on a surface opposite to a surface of one substrate on which the fluid path is formed to provide a rear surface heater and that two substrates are integrated using a direct bonding method. Furthermore, the present invention is characterized in that a plurality of fluid paths is provided, and among wirings to heaters of the plurality of fluid paths, common wirings are used near a heat insulating layer.

Advantageous Effects of Invention

[0012] As described above, in the present invention, while a method the same as a method of manufacturing a device of a single fluid path is used, a manufacturing process

is not complicated, and a plurality of heaters is arranged, so that a temperature change in the fluid path can be induced effectively. Further, while the fluid path device has good thermal followability with respect to the fluid path, a thermal interference between a plurality of heaters can be suppressed.

[0013] Further features of the present invention will become apparent from the following description of exemplary embodiments with reference to the attached drawings.

Brief Description of Drawings

[0014] [Fig. 1] Fig. 1 is a top view of a fluid path device in a first embodiment of the present invention.

[Fig. 2] Fig. 2 is a bottom view of the fluid path device in the first embodiment of the present invention.

[Fig. 3] Fig. 3 is a cross-sectional view of the fluid path device in the first embodiment of the present invention.

[Fig. 4] Fig. 4 is a cross-sectional view of a fluid path device in a second embodiment of the present invention.

[Fig. 5] Fig. 5 is a top view of a fluid path device in a third embodiment of the present invention.

[Fig. 6] Fig. 6 is a bottom view of the fluid path device in the third embodiment of the present invention.

[Fig. 7] Fig. 7 is a cross-sectional view of the fluid path device in the third embodiment of the present invention.

[Fig. 8] Fig. 8 is a cross-sectional view of a fluid path device in a fourth embodiment of the present invention.

[Fig. 9] Fig. 9 is a cross-sectional view of a fluid path device in a fifth embodiment of the present invention.

[Fig. 10] Fig. 10 is a bottom view of the fluid path device in a sixth embodiment of the present invention.

Description of Embodiments

[0015] A fluid path device according to the present invention will be described with reference to the following embodiments. The fluid path device according to the present invention includes a minute fluid path and a plurality of heaters arranged along the fluid path and can be used in a medical testing element, for example. Although the medical testing element is typified by μ -TAS, it is the general term for one used in, for example, medical testing and diagnostics, such as a DNA chip, a lab-on-a-chip, a microarray, and a protein chip.

First embodiment

[0016] Figs. 1 to 3 are views for explaining a fluid path device according to a first embodiment of the present invention. Fig. 1 is a front view of the fluid path device, Fig. 2 is a rear view of the fluid path device, and Fig. 3 is a cross-sectional view at 3-3 of Fig. 2. Reference numeral 1 is a substrate on a front surface side, reference numeral 2 is a substrate on a rear surface side, reference numeral 3 is a heater, reference numeral 4 is a wiring for driving the heater 3, reference numeral 5 is an electrode pad electrically connected to the fluid path device, reference numeral 6 is a heat insulating layer, reference numeral 7 is an introduction port through which reagents are taken in and out, and reference numeral 8 is a fluid path. The substrates 1 and 2 are formed of silicon (Si). A method of processing Si includes a method used in micro electro mechanical system (MEMS) technique, and processing is easily performed including a control of a processing shape. The fluid path 8 and the heat insulating layer 6 are produced by processing an Si substrate by anisotropic etching. The heater 3 is formed of platinum, and the wiring 4 and the electrode pad 5 are formed of gold.

[0017] In the present embodiment, a heater is provided on the substrate on the rear surface side and formed on the

rear surface side that is the opposite surface of the fluid path. Thus, the fluid path surface sides of both the substrates are flat except for the fluid path 8 and the heat insulating layer 6, and the substrates can be integrated by a direct bonding method. If the heater is formed on the front surface on the fluid path side so as to be more close to the fluid path, irregularities (concavities and convexities) according to a metal pattern occur. Thus, a gap according to a step occurs at a bonding interface in the bonding using the direct bonding, and this induces a leakage of a reagent through the fluid path, and the device does not function as a fluid path device. In this case, to bond both the substrates to each other, there is required such an additional process that an adhesion layer which can absorb the step is interposed, or the bonding interface is planalized by adding an insulating material, so that a manufacturing process is complicated. In the present embodiment, the heater is provided on the rear surface that is the opposite surface of the fluid path, whereby the flatness of the bonding interface can be maintained in the formation of the fluid path. Hence, the fluid path can be formed using the direct bonding, whereby the fluid path can be manufactured in a simple and inexpensive manner.

[0018] Si has an excellent thermal conductivity. The thermal conductivity is 168 [W/m·k], and this value reaches, indeed, about 800 times of 0.2 [W/m·k] of PDMS used in PTL 1. Accordingly, the present embodiment is different from PTL 1 in which the fluid path is required to approach the surface heated by the heater, and a heating capacity does not become insufficient even if the heater is formed on the opposite surface. Further, in comparison with PTL 1 having the heater provided separately from the fluid path device, in the present embodiment, since the heater formed on the rear

surface is integrated with the fluid path device, heat transfer efficiency is high. Those constitutions have an advantage for application of a temperature change at high speed.

[0019] Note that, since high efficiency characteristics of heat conduction act isotropically, when heating is performed using a plurality of heaters, the heaters influence each other due to their heating operation. The interinfluence between the heaters can be reduced by providing a thermal boundary between the heaters by the heating insulating layer 6. The heat insulating layer may not be provided on a route linearly connecting a plurality of heaters, and the position of the heat insulating layer defined by the term "between the heaters" is not limited especially as long as the heat insulating layer is provided on a route in a substrate on which heat from one heater is conducted to a portion to be heated by the other heater. The heat insulating layer may have any configuration as long as the thermal conductivity of the heat insulating layer is lower than the thermal conductivities of other substrate portions, and it is preferable that the heat insulating layer is made to become an air heat insulating layer by removing a substrate material in terms of ease of the creation and cost. The substrate material is removed, remaining a material near the fluid path 8, whereby the thermal conductivity in a lateral direction is limited according to reduction of an area of Si in a cross-sectional shape. In the present embodiment, as shown in Fig. 3, an opening penetrating completely except for the vicinity of the fluid path is formed in one substrate, and a recess is formed on the other substrate by etching in order to secure mechanical strength. After the penetrating opening is processed up to the vicinity of the fluid path, a fluid path portion is masked, and a penetrating

portion is etched. In the present embodiment, since the penetrating heat insulating layer 6 is provided on a fluid path formation substrate, positional alignment between the fluid path and a processed portion is performed using a double-sided aligner which allows the positional alignment of masks on both surfaces.

[0020] When the fluid path is processed on the opposite substrate, a positional error at the time of bonding is added to the respective positional errors of the fluid path and the heat insulating layer, and therefore, it is preferable to process the fluid path and the penetrating heat insulating layer in a single substrate as in the present embodiment. It is preferable that the electrode pad 5 has a certain size or more in order to facilitate electrical connection. Thus, among the wirings connected to the heater 3, the wirings approaching the heat insulating layer are finely patterned, and the electrode pad 5 is arranged at a position where an area is available.

[0021] In the fluid path device of the present embodiment, a plurality of kinds of reagents is introduced in a minute channel fluid path, for example, and the fluid path device can be used for use in the amplification of DNA in the PCR reaction, and so on. In μ -TAS, a plurality of functional devices can be connected to be used. In the fluid path device described in the present embodiment, two reagents mixed with a primer corresponding to two test contents are introduced in a single fluid path. Both test reagents are separated from each other by a solution or a gas as a buffer so as not to mix with each other. The two reagents stop at positions on the two heaters in the fluid path. Thereafter, a voltage is applied to the two heaters, whereby the heaters generate heat, so that a desired temperature change required for the PCR reaction is applied to perform amplification reaction. In

comparison with a case where DNA is sequentially amplified in the reaction field using a single heater to be sent to the next device, the amplification operations to the two reagents are performed simultaneously using the two heaters, so that throughput can be enhanced. In the reaction of PCR, the conditions in which reaction efficiency is maximum may be different according to the amplified contents. The different conditions include a temperature, a time for keeping each temperature, and the keeping form. In such a case, since in the fluid path device of the present embodiment mutual thermal interference is suppressed by the heat insulating layer, control drivings independently of each other are performed, and good reaction can be produced. The heater 3 is formed of platinum, whereby temperature can be observed from a temperature coefficient of a resistance value. In order to observe temperature, the heater may not be formed of platinum and may be formed of any material as long as the heater includes a patterned metal film formed of a general metal. Although the contemporary PCR reaction of the two reagents has been described, one of the heaters is used as a temperature sensor, whereby not only the PCR reaction but also the PCR reaction and other functions such as a temperature monitor can be combined.

Second embodiment

[0022] Fig. 4 shows another embodiment of the fluid path device according to the present invention. In Fig. 4, when the heat insulating layer 6 of a fluid path formation substrate of the first embodiment is processed, the heat insulating layer 6 is processed using Si anisotropic etching as in the first embodiment. In the first embodiment, a series of processes from a masking operation to etching is repeated twice in order to penetrate the heat insulating layer around the fluid

path, and in the present embodiment, the process repeated twice can be collected into a single process, so that the process is simplified. The fluid path device of the present embodiment functions well as with the first embodiment.

Third embodiment

[0023] Figs. 5 to 7 show another embodiment of the fluid path device according to the present invention. Fig. 5 is a front view of the fluid path device. Fig. 6 is a rear view of the fluid path device. Fig. 7 is a view of a cross section (7-7 in Fig. 6) along the fluid path. In the drawings, reference numeral 11 is a front surface side substrate, reference numeral 12 is a rear surface side substrate, reference numeral 13 is a heater, reference numeral 14 is wiring, reference numeral 15 is an electrode pad, reference numeral 16 is a heat insulating layer, reference numeral 17 is an introduction port through which reagents are taken in and out, reference numeral 18 is a fluid path, reference numeral 19 is excitation light of fluorescence dye, and reference numeral 20 is fluorescence excited to emit light. The front surface side substrate 11 is formed of glass, and Tempax (registered trademark) is used therein. The rear surface side substrate 12 is formed of Si. The present embodiment is different from the first embodiment in that anodic bonding is used in a process of bonding both the substrates. As in the first embodiment, since the heater is arranged on the rear surface, a bonding surface of both the substrates is flat even if there is no additional work, and the substrates can be bonded well. The thermal conductivity of glass is, in quartz glass, for example, 1.9[W/m·k], and, naturally, this value is in single-digit larger than PDMS. Consequently, high speed drive of heat can be realized in comparison with the prior art. In the fluid path

device of the present embodiment, since one substrate is formed of a transparent material, an optical operation can be performed in addition to heating of the fluid path. Since functions are separated for each surface so that the optical operation is performed from the front surface, and electrical connection is performed from the rear surface, different operations do not interfere with each other, and the degree of flexibility in layout is increased.

[0024] In the present embodiment, the PCR reaction is produced using a first heater to amplify DNA, and then heating is gradually performed by a second heater. Meanwhile, excitation light 19 is applied, and fluorescence 20 is observed, whereby a state in which DNA is changed from a double strand to a single strand is observed from brightness change of a fluorescent dye. The fluid path device of the present embodiment functions well when while the PCR reaction is performed, another temperature profile is given by the other heater.

Fourth embodiment

[0025] Fig. 8 shows another embodiment of the fluid path device according to the present invention. Fig. 8 shows a cross section including a heat insulating layer the same as the heat insulating layer shown in Fig. 7. In Fig. 8, reference numeral 21 is a front surface side substrate formed of quartz, reference numeral 22 is a rear surface side substrate formed of Si, and reference numeral 23 is a fluid path. In the present embodiment, quartz and Si are bonded by direct bonding. Since quartz has a good transmittance in a large wavelength region in comparison with general glass, it is suitable for optical operation and observation. As in the third embodiment, the fluid path device of the present embodiment can perform temperature operation and optical operation simultaneously.

Fifth embodiment

[0026] Fig. 9 shows another embodiment of the fluid path device according to the present invention in which a front surface side substrate is formed of quartz. While a laser beam 31 is collected by using a lens 32 from a transparent substrate side, the laser beam 31 is irradiated, and the laser beam 31 is absorbed in the fluid path to be converted into heat, whereby a reagent in the fluid path can be heated. A temperature state of the fluid path is monitored by observing a resistance value of a heater integrated with the rear surface. As in the third embodiment, in the present embodiment, a temperature profile well undergoing a transition along with time can be realized.

Sixth embodiment

[0027] Fig. 10 shows another embodiment of the fluid path device according to the present invention. Fig. 10 is a view in which a plurality of arranged fluid paths is observed from the rear surface side. Reference numeral 42 is a rear surface side substrate, reference numeral 43 is a heater, reference numeral 44 is a common wiring, reference numeral 45 is an electrode pad, and reference numeral 46 is a heat insulating layer.

[0028] In the present embodiment, among wirings to heaters for a fluid path, a plurality of wirings approaching a heat insulating layer is made in common. Consequently, the heat insulating layer can be expanded near the heater. According to the present embodiment, the size of the heat insulating layer which is one of the components of the present invention can be maximized, and the effects of the present invention can be maximized.

Reference Signs List

- [0029] 1 Substrate
2 Substrate
3 Heater
4 Wiring
5 Electrode pad

- 6 Heat insulating layer
- 7 Introduction port
- 8 Fluid path
- 19 Excitation light
- 20 Fluorescence
- 31 Laser beam
- 32 Lens

[0030] While the present invention has been described with reference to exemplary embodiments, it is to be understood that the invention is not limited to the disclosed exemplary embodiments. The scope of the following claims is to be accorded the broadest interpretation so as to encompass all such modifications and equivalent structures and functions.

[0031] This application claims the benefit of Japanese Patent Application No. 2011-056560, filed March 15, 2011, which is hereby incorporated by reference herein in its entirety.

CLAIMS

- [1] A fluid path device comprising a fluid path and a plurality of heaters arranged along the fluid path, characterized in that the fluid path device being formed by bonding, one substrate and another substrate in which the fluid path is formed on a bonding surface, by direct bonding or anodic bonding, wherein the plurality of heaters is formed on a surface different from the bonding surface of any one of the substrates, and wherein the substrate having the heater has, between the heaters, a region where thermal conductivity is smaller than the substrate.
- [2] The fluid path device according to claim 1, wherein the region with the small thermal conductivity is formed in a substrate formed with the fluid path.
- [3] The fluid path device according to claim 2, wherein that a bonding method is anodic bonding.
- [4] The fluid path device according to claim 2, wherein a bonding method is direct bonding.
- [5] The fluid path device according to claim 4, wherein the substrate is formed of Silicon.
- [6] The fluid path device according to claim 3 or 4, wherein the substrate is formed of Silicon and glass.
- [7] The fluid path device according to claim 4, wherein the substrate is formed of Silicon and quartz.
- [8] The fluid path device according to claim 1, wherein a heater is a patterned metal film.
- [9] The fluid path device according to claim 1, wherein a plurality of fluid paths is arranged, and wirings arranged between a plurality of heaters and connected to the heaters are made in common.
- [10] The fluid path device according to claim 1, wherein the region with the thermal conductivity smaller than the substrate is a region from which a substrate material

is removed.

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FIG. 1

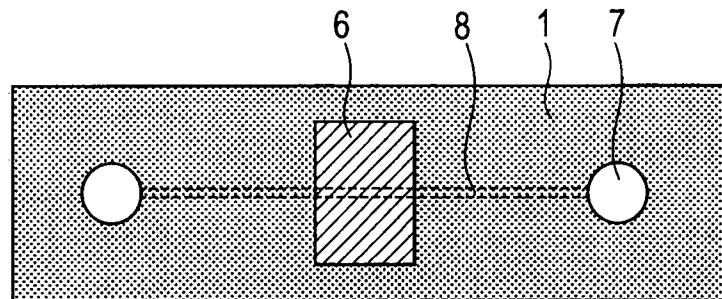


FIG. 2

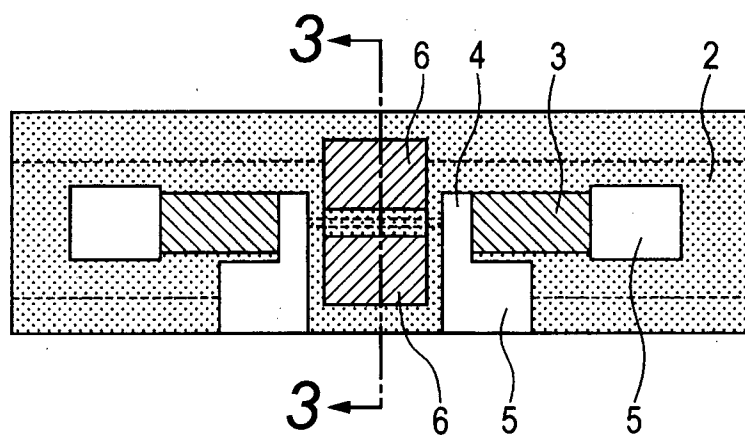
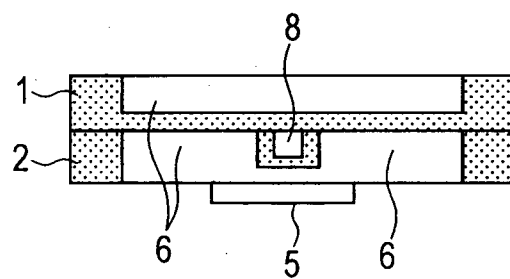


FIG. 3



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FIG. 4

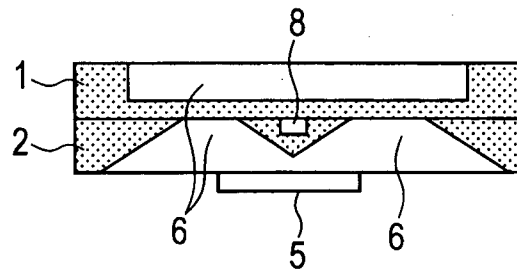


FIG. 5

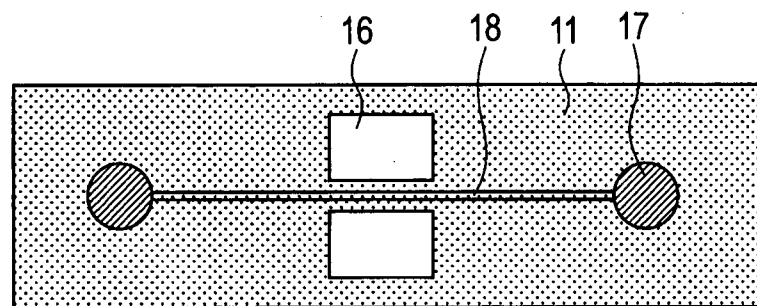
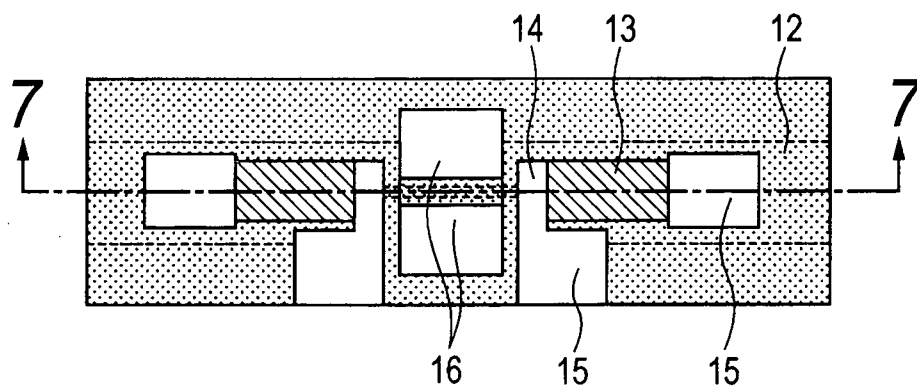


FIG. 6



3 / 4

FIG. 7

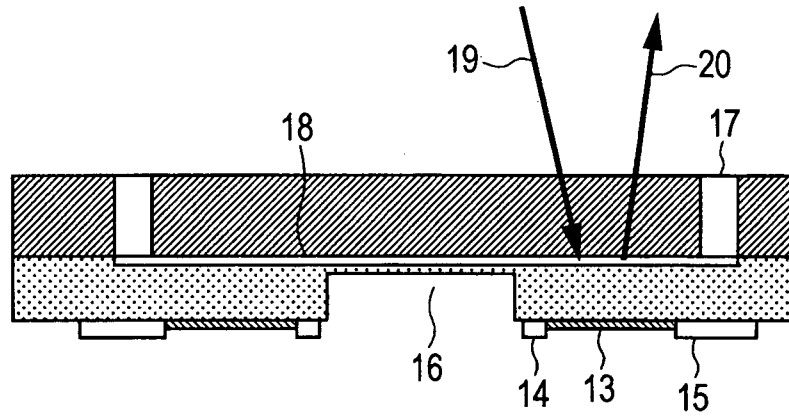


FIG. 8

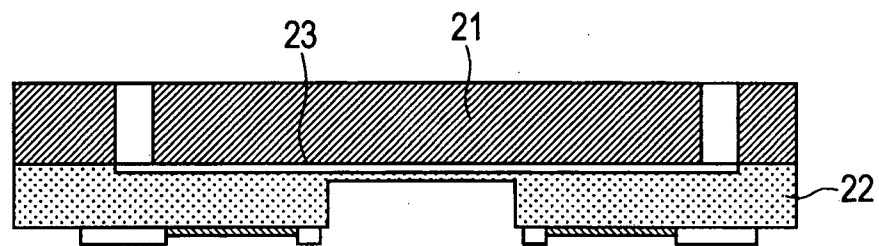


FIG. 9

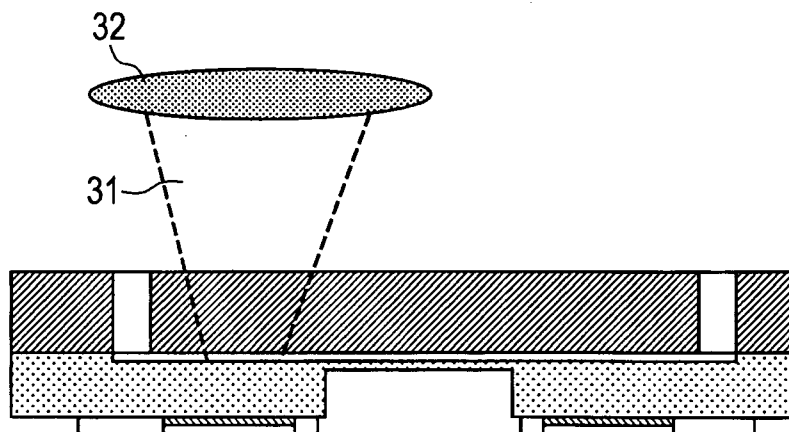
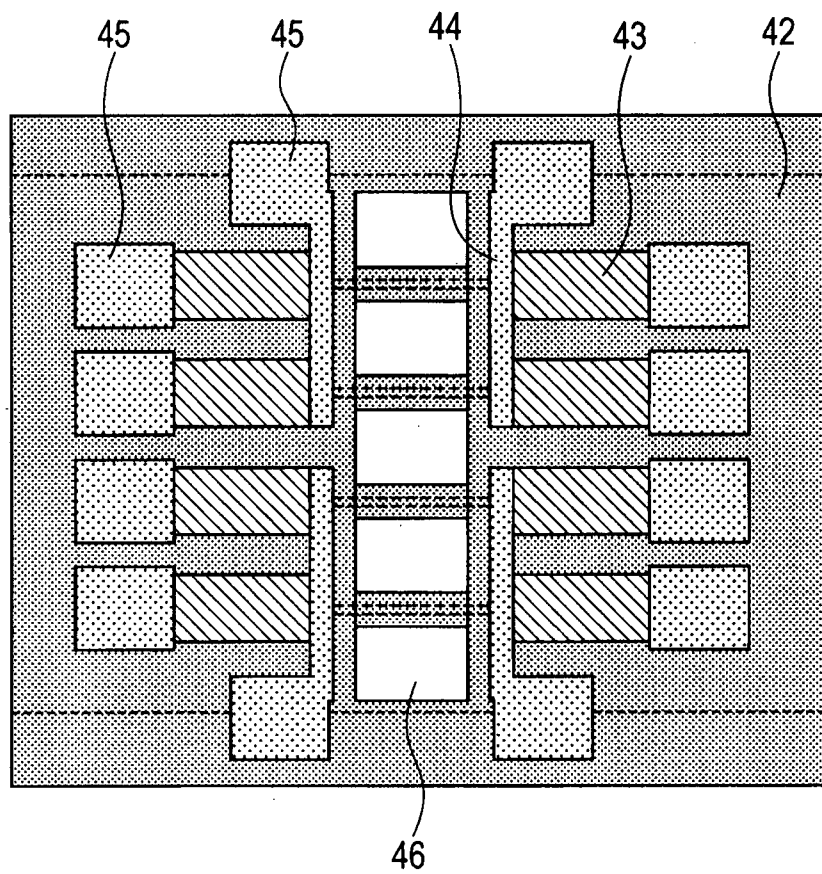


FIG. 10



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2012/055887

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. G01N35/00 (2006.01) i, G01N35/08 (2006.01) i, G01N37/00 (2006.01) i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. G01N35/00-37/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
 Published unexamined utility model applications of Japan 1971-2012
 Registered utility model specifications of Japan 1996-2012
 Published registered utility model applications of Japan 1994-2012

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2005-40784 A (CITIZEN WATCH CO., LTD) 2005.02.17, 【 0 0 9 1 】 - 【 0 0 9 3 】 & US 2005/0006372 A1	1-10
Y	JP 2007-268490 A (Fujifilm Corporation) 2007.10.18, 【 0 0 5 8 】, 【 0 0 5 9 】, 【 0 0 6 1 】 (No Family)	1-10
Y	WO 2007/099736 A1 (KONICA MINOLTA MEDICAL & GRAPHIC, INC.) 2007.09.07, [0032], [0040] (No Family)	1-10

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Date of the actual completion of the international search

18.04.2012

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