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(54) Title: NON-INVASIVE PASSIVE INTERSTITIAL FLUID COLLECTOR

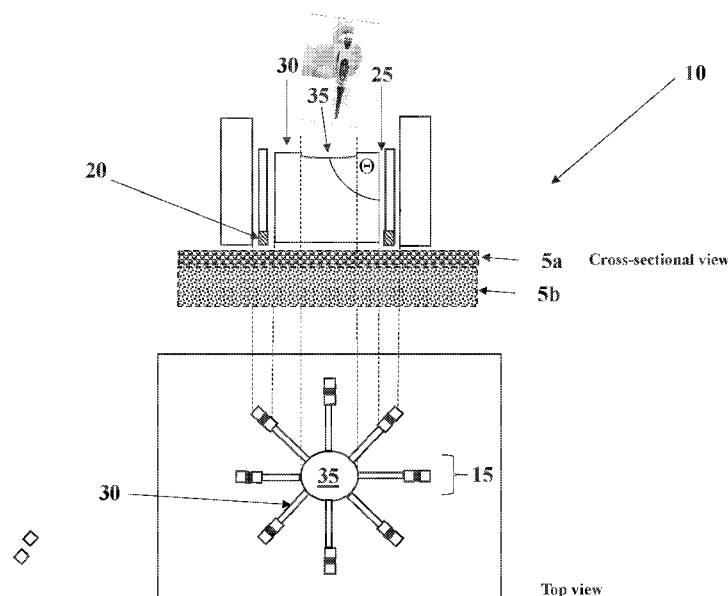


FIGURE 2a

(57) Abstract: A microfluidic device for non-invasively and passively accessing interstitial fluid from a patient includes a substrate containing multiple vertical micro channels therethrough, wherein at a first end of each of the multiple vertical micro channels a microheater is formed for controllably ablating a portion of dry dead skin cells to access the interstitial fluid; and wherein at a second end of each of the multiple vertical micro channels is a horizontal micro channel for receiving accessed interstitial fluid from a vertical micro channel and guiding the accessed interstitial fluid to a common collection port.

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NON-INVASIVE PASSIVE INTERSTITIAL FLUID COLLECTOR**Applicant/Assignee: Georgetown University****CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] The present application claims the benefit of priority to similarly titled U.S. Provisional Patent Application Serial No. 62/414,448 filed on October 28, 2016 which is incorporated herein by reference in its entirety.

BACKGROUND**Field of the Embodiments**

[0002] The present embodiments generally relate to the collection of bodily fluids for clinical testing and more particularly to devices and processes for the collection of interstitial fluid from an individual.

Description of Related Art

[0003] Blood is by far the most popular and physician-accepted choice of bodily fluid for use in clinical testing, primarily because blood is the circulating fluid that surrounds all tissue and organs and potentially collects metabolic by-products and biomarkers from both normal and diseased areas. Changes in the concentrations of specific plasma proteins have been associated with disease processes, leading to well-accepted clinical applications. The human body, however, is composed of a host of different fluids such as, urine, cerebral spinal fluid (CSF), saliva, tears, and sweat, each containing a wide variety of proteins and clinically-relevant biomarkers as discussed in J.A. Loo, et al., "Comparative Human Salivary and Plasma Proteomes", *J Dent Res.* 89(10), 1016, 2010.

[0004] Interestingly, one bodily fluid that is commonly disregarded or omitted from the list of testable bodily fluids is interstitial fluid (ISF), which also surrounds all living tissue and organs and contains constituents of the blood that are typically size excluded to being < 60kDa. Thus, clinical testing of ISF provides a completely new body fluid for diagnostic applications that has not seen any extensive use. This is mainly due to the collection methods currently available – the suction blister method described in J. Kool et al., "Suction blister fluid as a potential body fluid for biomarker proteins", *Proteomics*, 7(20), 3638, 2007 (hereafter "suction method") and the cantharide-induced skin blister method as discussed in M. Brunner, et al., "Direct assessment of

peripheral pharmacokinetics in humans: comparison between cantharides blister fluid sampling, in vivo microdialysis and saliva sampling”, *Br J Clin Pharmacol.*, 46(5), 425, 1998 (hereafter “blister method”), both interestingly considered as non-invasive.

[0005] Referring to prior art **Figures 1A** and **1B**, the suction method involves the application of vacuum suction on the skin surface for at least 2 hours, resulting in the epidermis slowly becoming detached from the underlying dermis. The resulting induced blister fills with interstitial fluid that can be collected by piercing the blister with a syringe needle to draw the ISF. A variant of using a suction pump is to raise suction blisters using syringes, which can take more than 2 hours to produce. Although these procedures are considered as being painless, at worst causing itching and discomfort, the resulting wounds typically heal in 7 to 10 days without forming any scars. However, some subjects can develop hyperpigmentation at the wound sites that can last for months or longer.

[0006] The blister method for obtaining ISF samples relies on the toxic reaction of cantharide on the skin to generate sub-epidermally located skin blisters. Cantharides are blistering agents made from the powdered, dried bodies of *Lytta vesicatoria*, or the blister beetle. The principle component of cantharide is cantharidin, the blistering agent shown to potentially cause adverse effects. For this reason, it has been included in a list of "problem drugs". However, when compounded properly and applied in the clinic topically by medical personnel familiar with its effects and uses, cantharidin can be safely and effectively used to treat some benign skin lesions like warts. In order to collect ISF, the cantharides are impregnated onto a dermal patch and adhered to the skin for 12 hours. The resulting blister fluid can be aspirated into a syringe by puncturing the blister with a fine needle, similar to the collection strategy used in the suction method.

[0007] An even more invasive approach to collect ISF is to use micro-needles to draw the ISF as described in the article by A.V. Romanyuk et al. entitled “Collection of Analytes from Microneedle Patches,” *Anal Chem.* 2014 Nov 4; 86(21): 10520–10523 (“Romanyuk et al.”).

[0008] Obviously, the methods above used to harvest interstitial fluid are uncomfortable, time-consuming, and intrusive, and a blood draw would likely seem to provide a simpler course.

[0009] Accordingly, a less invasive and more efficient device and process for collecting ISF would be welcome by both patients and the clinical community.

SUMMARY OF EMBODIMENTS

[0010] A first exemplary embodiment includes a microfluidic device for non-invasively and passively accessing interstitial fluid from an individual, the microfluidic device including: a substrate containing multiple vertical micro channels therethrough, wherein at a first end of each of the multiple vertical micro channels a microheater is formed for controllably ablating a portion of the dry dead skin cells to access the interstitial fluid; and further wherein at a second end of each of the multiple vertical micro channels is a horizontal micro channel for receiving accessed interstitial fluid from a vertical micro channel and guiding the accessed interstitial fluid to a common collection port.

[0011] A second exemplary embodiment includes a microfluidic device for non-invasively and passively accessing interstitial fluid from an individual, the microfluidic device including: a first layer formed of Kapton; a second layer formed of poly(dimethylsiloxane) (PDMS), wherein the first and second layer are bonded together; an array of vertical microchannels formed through the first and second layer; and an electrically controllable microheater formed at a Kapton end of each of the vertical microchannels.

BRIEF DESCRIPTION OF FIGURES

[0012] **Figures 1A and 1B** illustrate the results of prior art blister formation techniques used to collect ISF;

[0013] **Figures 2a and 2b** illustrate an exemplary embodiment of the present invention wherein a microheater and microchannel configuration with a collection reservoir which may be used to collect ISF;

[0014] **Figure 3** illustrates a first exemplary embodiment of the present invention wherein a microheater and microchannel configuration with a collection reservoir which may be used to collect ISF;

[0015] **Figures 4a and 4b** illustrate a second exemplary embodiment of the present invention wherein a microheater and microchannel configuration with a collection reservoir which may be used to collect ISF;

[0016] **Figures 5a to 5i** illustrate exemplary prior art micro-heater configurations for use with one or more of the exemplary embodiments described herein;

[0017] **Figure 6** illustrates an alternative micro-heater placement configuration within one or more of the exemplary embodiments described herein;

[0018] **Figure 7** illustrates the embodiment of **Figures 2a** and **2b** during use; and

[0019] **Figure 8** illustrates an alternative embodiment of the device using combinations of materials.

DETAILED DESCRIPTION

[0020] Current knowledge of the physiological and pathophysiological composition of interstitial fluid is mainly based on blood studies due to the relative ease of obtaining a blood sample. The study of the true composition of interstitial fluid is hindered by the relative difficulty in extracting or sampling it. Such difficulties are identified and discussed in articles by L. Ebah, “Extraction and Analysis of Interstitial Fluid, and Characterization of the Interstitial Compartment in Kidney Disease”, PhD Thesis, University of Manchester, 2012 and Romanyuk et al., both of which are incorporated herein by reference.

[0021] The present embodiments outline a simple, effective, and time efficient way to painlessly collect ISF from a patient. This device may be utilized to assess the presence of certain biomarkers in ISF using standard clinical methods including, but not limited to, mass spectrometry, liquid chromatography, etc. The device utilizes microfluidic technology to help in the transfer process of ISF from the skin surface to a collection port for subsequent aspiration by pipetting (see **Figure 2**). The ISF originates using, for example, thermal ablation micro-heaters **20**, situated on the device surface, or inset therein that will be placed in contact with the top layer of the skin containing dry, dead skin cells, or stratum corneum, **5a**. Multiple micro-heaters **20** may be activated simultaneously or in succession in order to harvest larger volumes of ISF, as needed, from lower layers of skin **5b**. **Figure 2a** illustrates cross-sectional and top views of an exemplary system **10** having 8 individual ablation/collection sites **15**. At each collection site **15**, there is a single microheater **20** flanked by two vertical micro-channels **30**. The microheaters and channels may be in various shapes and configurations, including rectangular, square, circular or combinations thereof. The dimensions of the vertical microchannels may be on the order of approximately 50-100 microns per side. The spatial separation distance between sites **15** can be determined, and varied, based on whether dermal trauma is indicated. The ISF resulting from the thermal ablation is transported through hydrophilic vertical micro-channels **25** by capillary action, and connected to approximately horizontal micro-channels **30** oriented substantially in the plane

of the device surface and ending at a common collection port **35**. Each vertical micro-channel **25** with a corresponding substantially horizontal micro-channel **30** is formed in the substrate with angle Θ therebetween. These generally planar micro-channels can be arranged in any way that maximizes collection, such as with a spoke-like configuration illustrated in **Figure 2a**. In **Figure 3**, the approximately horizontal micro-channels are oriented so as to be slightly inclined towards the central collection port **35** such that angle Θ is less than 90 degrees. In both configurations, the collection port **35** may be indented slightly to pool the ISF from the horizontal channels **30**, although such an indentation is not required.

[0022] Alternatively, **Figures 4a-4c** illustrate a system **100** having different collection geometries wherein multiple vertical micro-channels **125** simply terminate at a central collection area **135** and the ISF can be extracted from the central collection area **135** for analysis. The number of collection channels feeding the central collection area and the arrangement thereof is not limited. **Figures 4a** and **4b** show a configuration having a line of 10 separate collection channels **125** whereas **Figure 4c** shows a bottom view of a 12 x 3 array of collection channels **125**. In **Figure 4a**, the collection area **135** is shown as being formed so as to resemble a trough or bowl to better collect the ISF for extraction. This trough or bowl configuration of the central collection area **135** is not required.

[0023] The thermal ablation micro-heaters **20** function to ablate a microscopic portion of the stratum corneum containing dry, dead skin cells, the topmost layer of skin **5a**, so that the interstitium, part of lower layer **5b**, can be exposed, releasing ISF. The micro-heaters **20** are in close proximity to the skin surface, together with electrical components that control current to the micro-heaters **20**. Each micro-heater preferably comprises a pair of electrodes connected by a conductive pathway that is arranged, either by the use of a resistive material or by a serpentine conductive pathway, to provide sufficient resistance to the flow of electricity such that an effective amount of heat is produced so as to locally ablate an appropriate portion of the stratum corneum. Electrical connections may also be provided to each of the two electrodes to connect the micro-heating unit to a controller that controls the application of an electrical current source to the electrodes, thus providing for individualized control of heating on a per micro-heater **20**, per collection site **15** basis. In operation, the micro-heater **20** is pulsed with a suitable alternating or direct current to provide local ablation. Control of the duration and intensity of the heating pulse is preferably carried out to effect ablation of the desired area and depth. The micro-ablation

preferably occurs in a confined volume of the stratum corneum. By way of example only, an area having the dimensions of approximately $50\text{ }\mu\text{m} \times 50\text{ }\mu\text{m} \times 40\text{ }\mu\text{m}$ may be suitable for collection of an adequate amount of ISF. Alternative embodiments are contemplated wherein the individual micro-heaters may be for single-use, as compared to multiple use, such that when the individual micro-heater is used, the heating circuit is “blown” and may not be used again.

[0024] Additional details regarding micro-heater configurations and details which may be used with one or more of the embodiments herein may be found in commonly owned and similarly titled U.S. Patent Nos. 6,887,202, 7,931,592, 8,568,315 and 9,332,937, which are incorporated herein by reference.

[0025] Exemplary prior art micro-heater configurations are shown in **Figures 5a-5i**. Although rectangular, serpentine micro-heaters are shown in the figures, the embodiments are not so limited. Further, variations to the placement of the micro-heaters with respect to the opening of the vertical microchannels is not limited to the configuration shown in the figures. That is, alternative configurations contemplate that instead of being inset within the substrate, some portion of the micro-heater may be layered on the substrate and thus be protruding therefrom as shown in **Figure 6**. Further, it is contemplated that the suspension may be achieved from a single side of the opening. Fabrication techniques and materials for suspending the heater across the opening of each vertical micro-channel are known to those skilled in the art. The following articles discuss suspended microheaters and the substance thereof is incorporated herein by reference: Hotovy et al., Gallium arsenide suspended microheater for MEMS sensor arrays, *Microsyst Technol* (2008) 14:629-635; Sidek et al., Effect of Heater Geometry on the High Temperature Distribution on a MEMS Micro-hotplate, 3rd Asia Symposium on Quality Electronic Design, IEEE 2011; Chau et al., Design and fabrication of a quasi-ordered nanoporous silicon membrane suitable for thermally induced drug release, *J. Micromech. Microeng.* 22 (2012) 085028 (14pp).

[0026] Using the embodiment from **Figures 2a-2b** as an example, **Figure 7** illustrates the configuration after the stratum corneum **5a** has been ablated by micro-heaters **20** to form micropores **40** therein and access the ISF **45**, which is shown by broken arrows. The ISF is drawn up through the vertical micro-channels **25** by capillary action.

[0027] For ease of fabrication and processing, the representative structure may be formed in poly(dimethylsiloxane) (PDMS) or Kapton (polyimide), but it is understood by one skilled in the

art that this is not the only material that can be used. PDMS channels may be formed using a molding process with high aspect ratio photoresist (SU-8) while Kapton can be chemically etched using patterned protective layers of metallic films. Laser processing may also be used for both PDMS and Kapton. In an alternative embodiment, the final device may be comprised of PDMS bonded with Kapton, where Kapton is the layer containing the microheaters and in contact with the skin, while the PDMS serves to transport the ISF upwards. Since PDMS is inherently hydrophobic, it is treated to render it hydrophilic. This may be accomplished by adding a nonionic organosilicone surfactant such as Silwet-77.

[0028] Alternatively, as shown in **Figure 8** an additional thin PDMS layer with openings for the microheater and microchannels can be added to the Kapton layer to provide a hydrophobic surface to aid in guiding ISF to the vertical microchannels from the skin. The result is that the microheaters **20** are very slightly recessed from the main surface of the device as shown, but are still well within heating reach of the skin. The thin PDMS layer may be on the order of 100 microns thick.

[0029] The following patents and patent applications, which are co-owned by the Applicant and include an overlapping inventor with the present application, are incorporated herein by reference in their entireties and variations to the present embodiments in accordance with one or more teachings therein are considered to be within the scope of these embodiments: USP 6,887,202, titled "Systems and Methods For Monitoring Health and Delivering Drugs Transdermally," USP 7,931,592, titled "Systems and Methods For Monitoring Health and Delivering Drugs Transdermally," USP 8,568,315, titled "Systems and Methods For Monitoring Health and Delivering Drugs Transdermally," USP 9,332,937, titled "Systems and Methods For Monitoring Health and Delivering Drugs Transdermally," US Pub. No. 2013-0289374, titled "Electrochemical Transdermal Glucose Measurement System Including Microheaters and Process For Forming," US Application Serial No. 13/835,696, titled "Microfluidic Systems For Electrochemical Transdermal Glucose Sensing Using a Paper-Based or Other Wicking Substrate," US Application Serial No. 13/834,199, titled "Microfluidic Systems For Electrochemical Transdermal Analyte Sensing Using a Capillary-Located Electrode," and US Application Serial No. 15/226,475, titled "Apparatus and Method For Delivery of Antimicrobial During a Transdermal Sampling and Delivery Process."

CLAIMS

1. A microfluidic device for non-invasively and passively accessing interstitial fluid from an individual, the microfluidic device comprising:

a substrate containing multiple vertical micro channels therethrough, wherein at a first end of each of the multiple vertical micro channels a microheater is formed for controllably ablating a portion of the dry dead skin cells to access the interstitial fluid; and

further wherein at a second end of each of the multiple vertical micro channels is a horizontal micro channel for receiving accessed interstitial fluid from a vertical micro channel and guiding the accessed interstitial fluid to a common collection port.

2. The microfluidic device of claim 1, wherein an angle between each of the multiple vertical micro channels and a corresponding horizontal micro channel is less than 90 degrees.

3. The microfluidic device of claim 1, wherein the device is formed in poly(dimethylsiloxane) (PDMS) or Kapton (polyimide).

4. The microfluidic device of claim 1, wherein the device is formed of both poly(dimethylsiloxane) (PDMS) and Kapton (polyimide).

5. The microfluidic device of claim 4, wherein the first end of each of the multiple vertical microchannels containing the microheaters is formed of Kapton and the second end of each of the multiple vertical micro channels, the horizontal micro channels and the common collection port are PDMS.

6. The microfluidic device of claim 5, wherein the PDMS is treated to make it hydrophilic.

7. The microfluidic device of claim 6, wherein the PDMS is treated by adding a nonionic organosilicone surfactant.

8. The microfluidic device of claim 7, wherein the nonionic organosilicone surfactant is Silwett-77.

9. The microfluidic device of claim 1, wherein the multiple vertical microchannels, multiple horizontal microchannels and the common collection port are arranged in a spoke and wheel configuration, wherein the multiple horizontal microchannels end at the common collection port.

10. The microfluidic device of claim 1, wherein the microheaters are formed in-line with the first end of each of the multiple vertical microchannels at a circumference of an opening at the first end of each of the multiple vertical microchannels.

11. The microfluidic device of claim 1, wherein the microheaters are formed in-line with the first end of each of the multiple vertical microchannels and at least a portion thereof is suspended across an opening at the first end of each of the multiple vertical microchannels.
12. The microfluidic device of claim 1, wherein the microheaters are formed so as to protrude from the first end of each of the multiple vertical microchannels at a circumference of an opening at the first end of each of the multiple vertical microchannels.
13. A microfluidic device for non-invasively and passively accessing interstitial fluid from an individual, the microfluidic device comprising:
 - a first layer formed of Kapton;
 - a second layer formed of poly(dimethylsiloxane) (PDMS), wherein the first and second layer are bonded together;
 - an array of vertical microchannels formed through the first and second layer; and
 - at least one electrically controllable microheater formed at a Kapton end of each of the vertical microchannels.
14. The microfluidic device of claim 13, wherein a PDMS end of each vertical microchannel is fluidically connected to an approximately horizontal microchannel for directing interstitial fluid to a collection port.
15. The microfluidic device of claim 13, wherein the PDMS is treated to make it hydrophilic.
16. The microfluidic device of claim 15, wherein the PDMS is treated by adding a nonionic organosilicone surfactant thereto.
17. The microfluidic device of claim 16, wherein the nonionic organosilicone surfactant is Silwett-77.
18. The microfluidic device of claim 13, further comprising a third layer formed of PDMS over a portion of the Kapton layer, but excluding each of the at least one electrically controllable microheater and each of the vertical microchannels.
19. The microfluidic device of claim 13, wherein at least a portion of the electrically controllable microheaters is suspended across an opening at the Kapton end of each of the vertical microchannels.
20. The microfluidic device of claim 13, wherein the microheaters are formed so as to protrude from the Kapton end of each of the vertical microchannels at a circumference of an opening at the Kapton end of each of the vertical microchannels.



FIGURE 1B – PRIOR ART

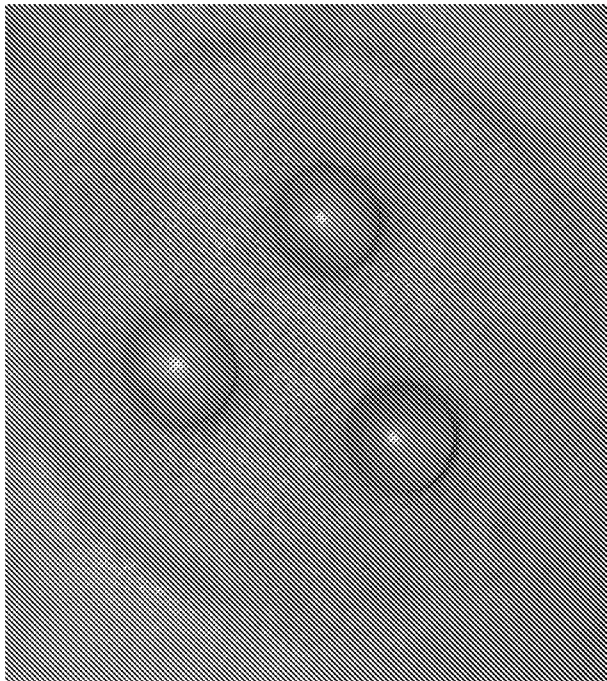


FIGURE 1A – PRIOR ART

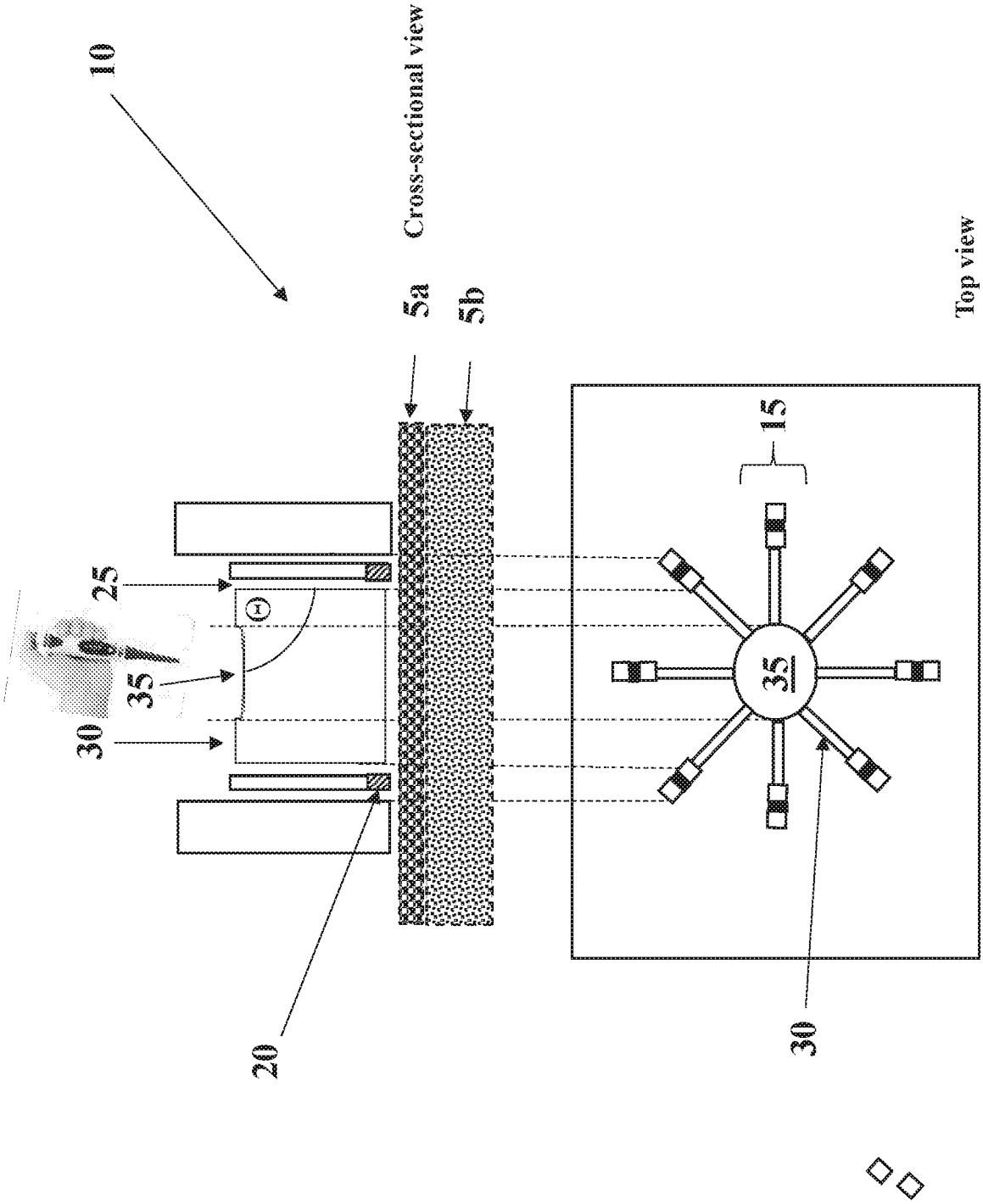
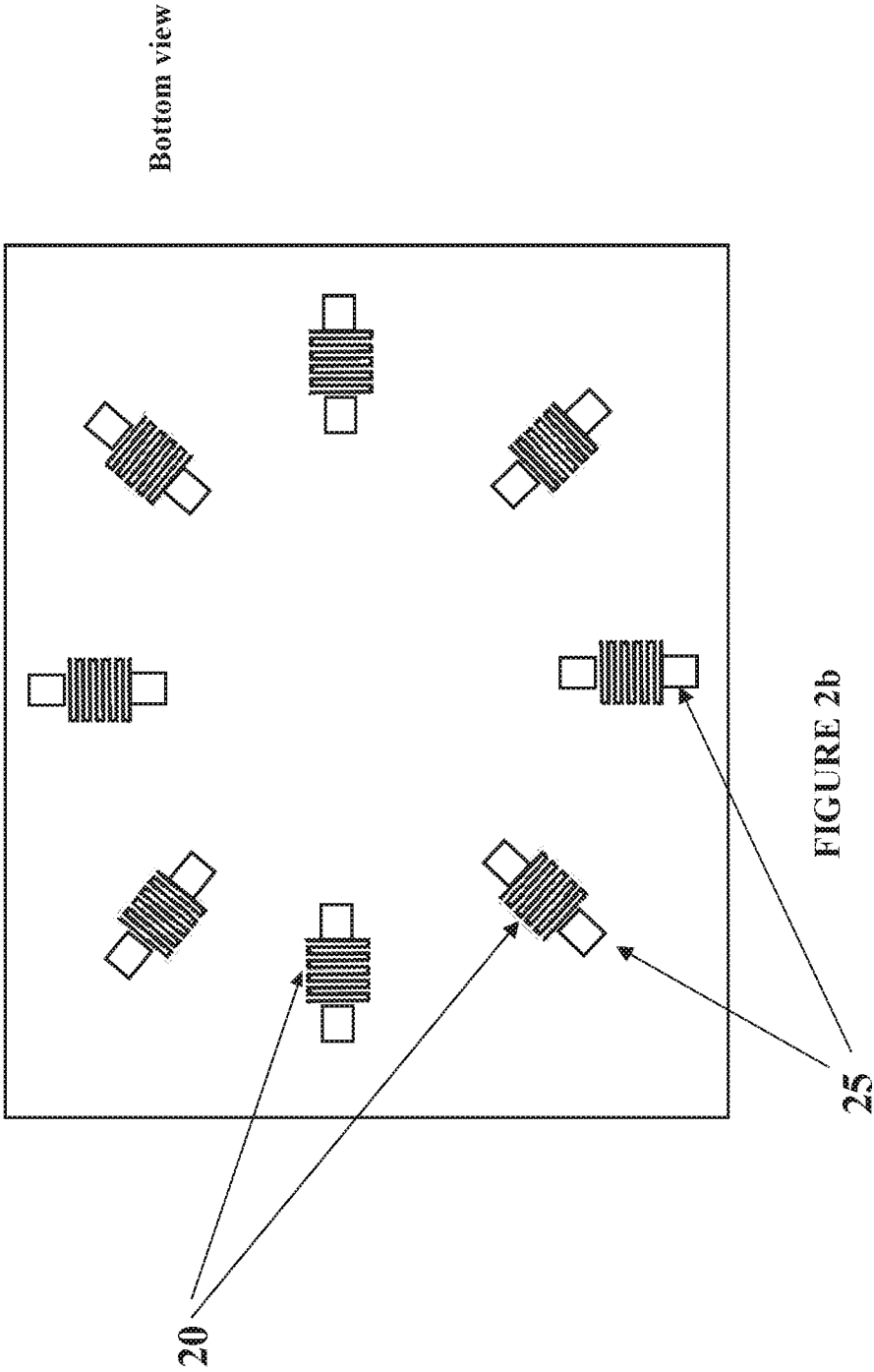


FIGURE 2a



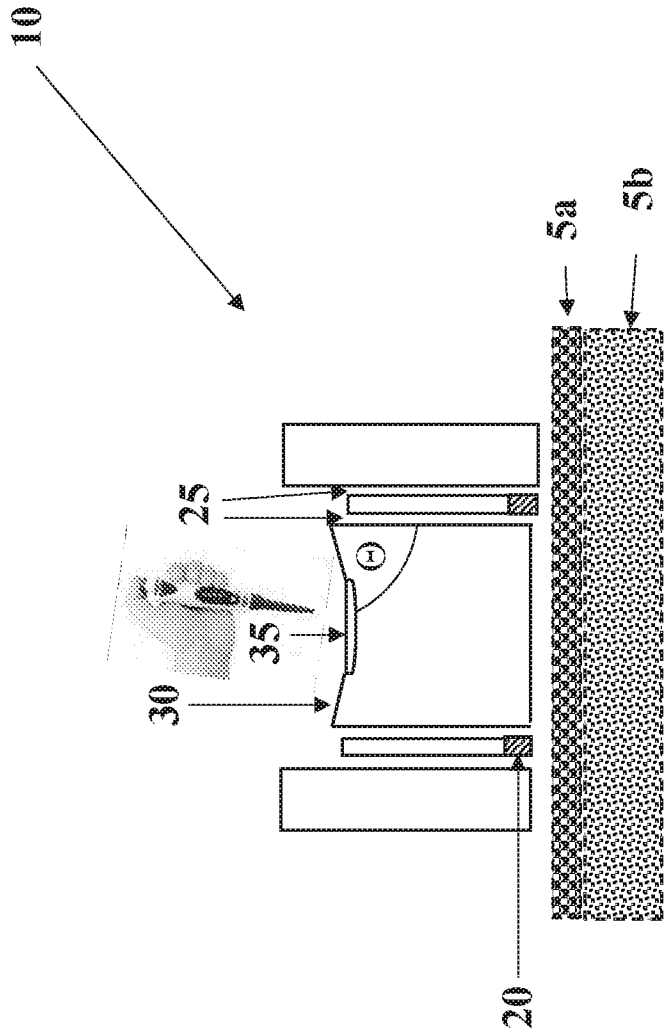


FIGURE 3

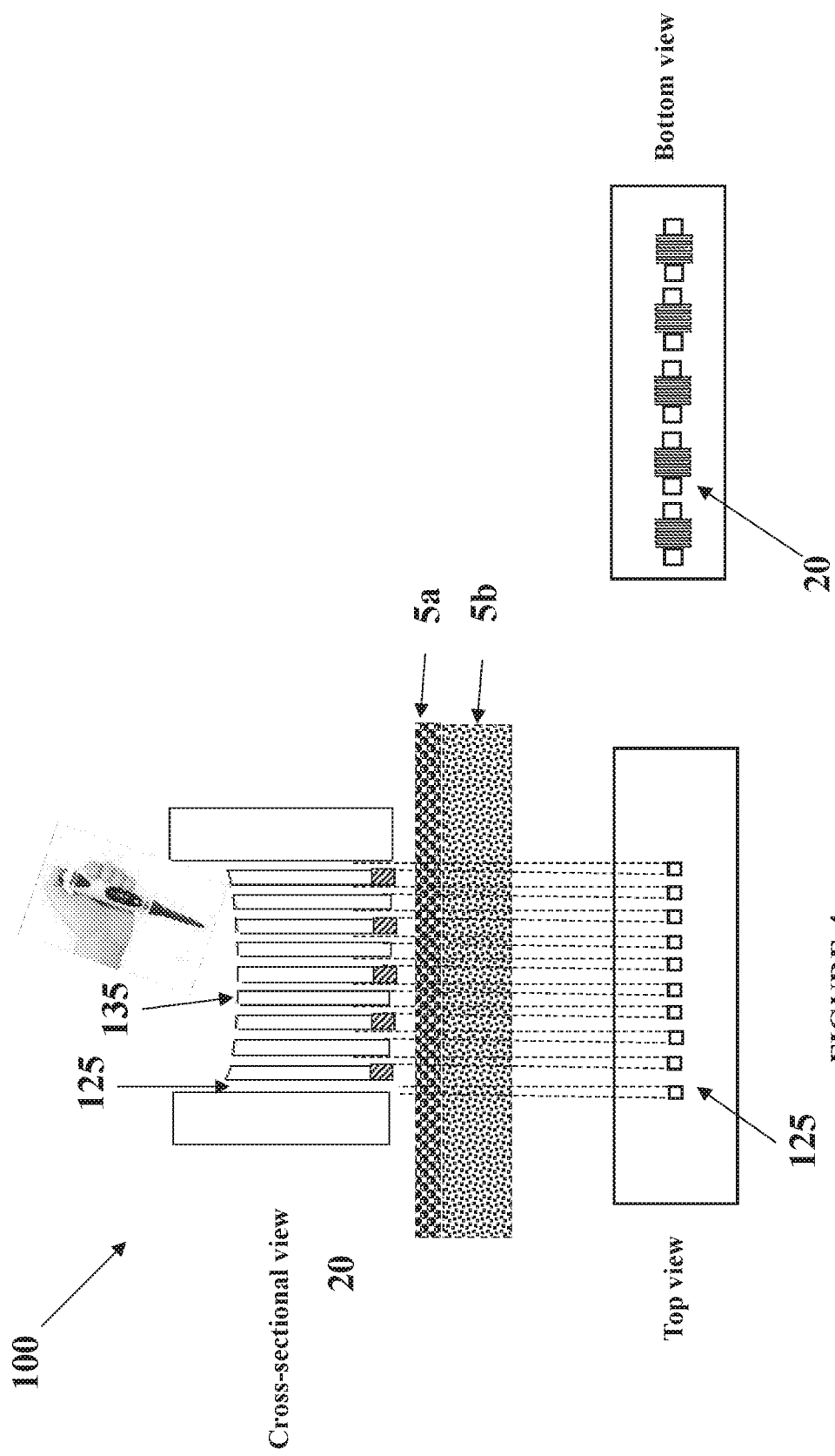


FIGURE 4a

FIGURE 4b

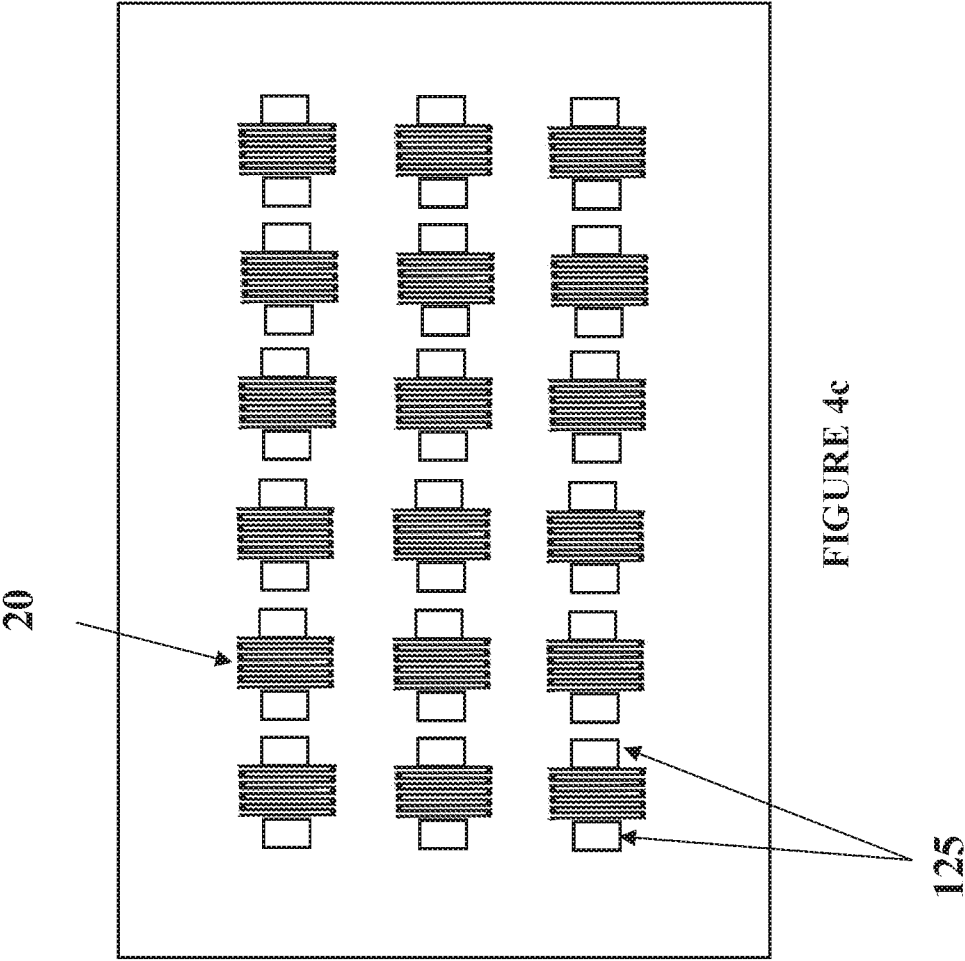


FIGURE 4c

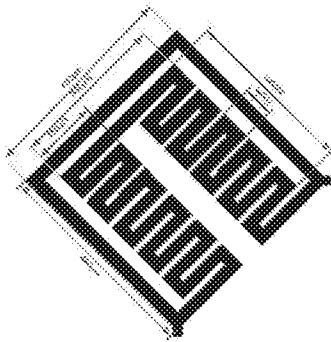


FIGURE 5a — Prior Art

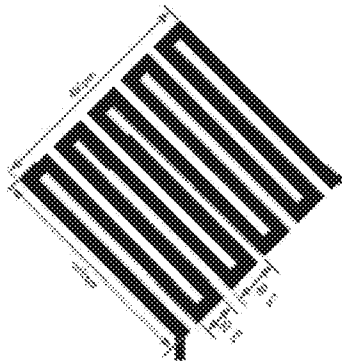


FIGURE 5b — Prior Art

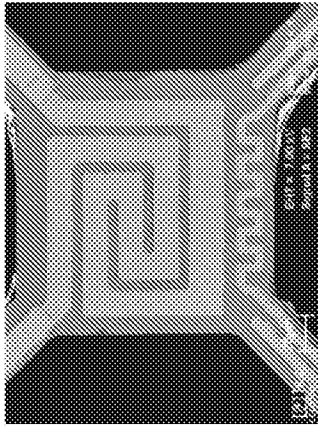


FIGURE 5c — Prior Art

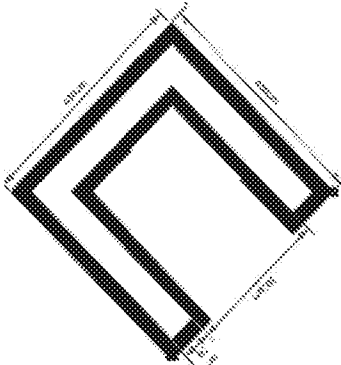


FIGURE 5d — Prior Art

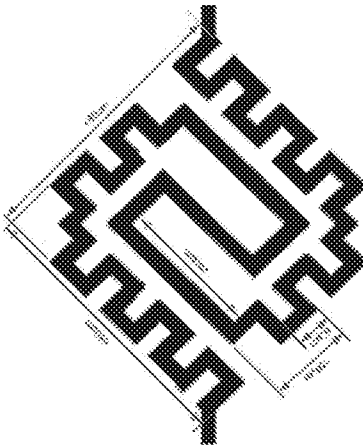


FIGURE 5e — Prior Art

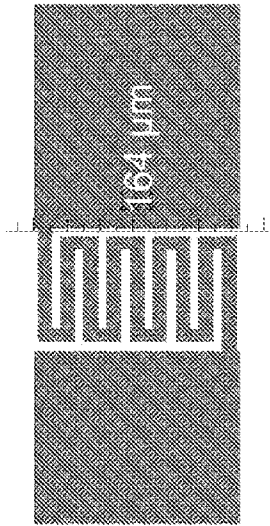


FIGURE 5f — Prior Art

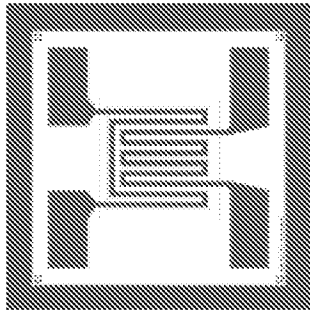


FIGURE 5g — Prior Art

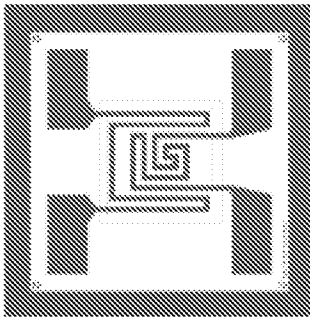


FIGURE 5h — Prior Art

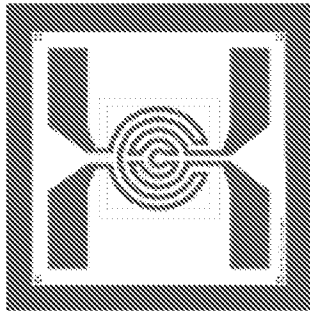


FIGURE 5i — Prior Art

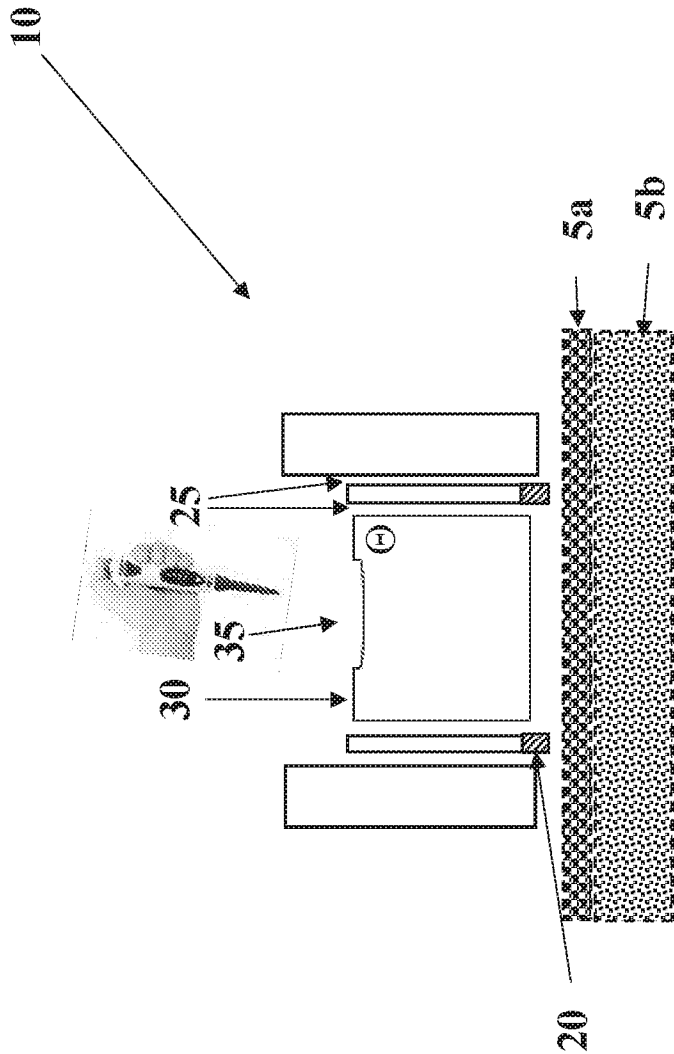


FIGURE 6

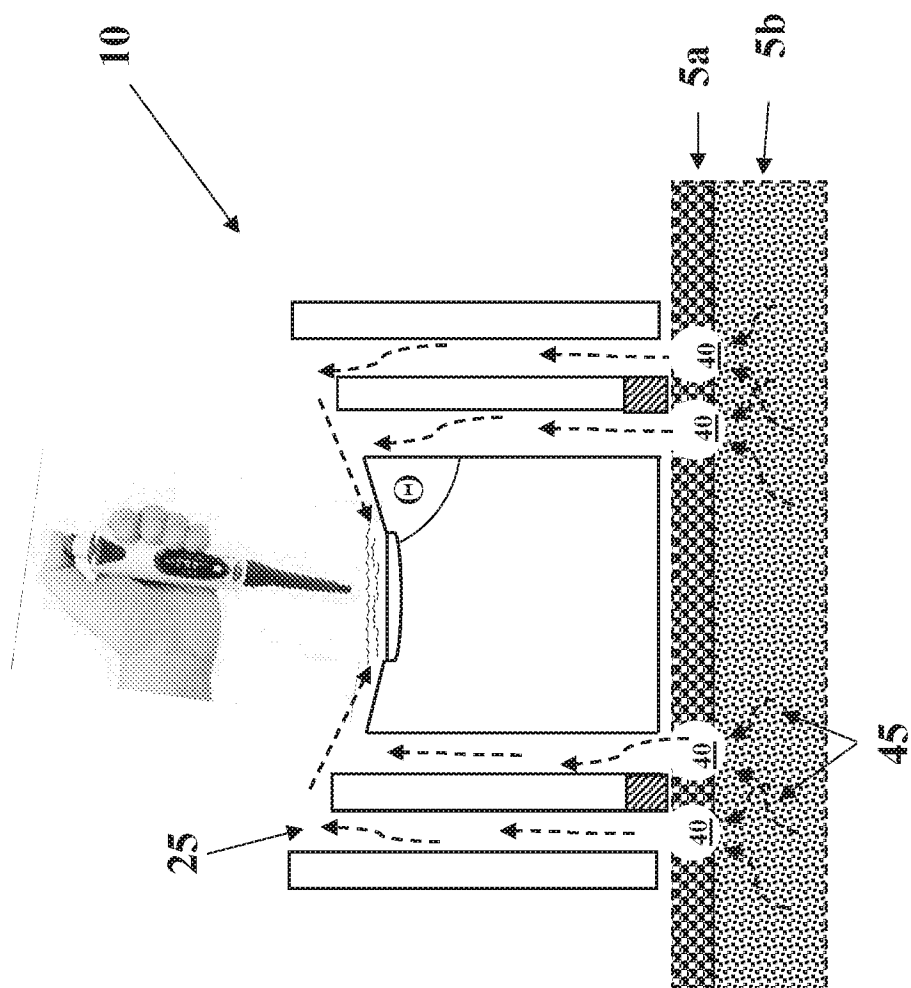


FIGURE 7

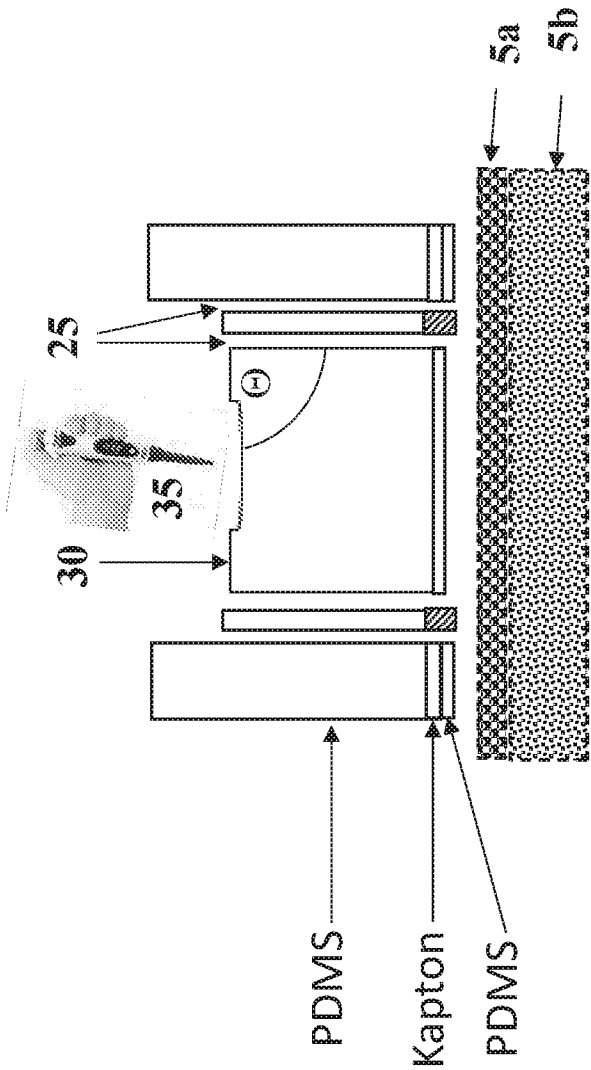


FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/57614

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61B 5/145, 5/1477, 5/1491 (2017.01)

CPC - A61B 5/1451, 5/14514, 5/1477, 5/1491, 5/6801, 5/6833

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)

See Search History document

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

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/0025000 A1 (SCIENCE APPLICATIONS INTERNATIONAL CORPORATION et al.) 23 January 2014; figure 7; paragraphs [0063], [0081]-[0082], [0171]; claim 1	1-20
A	US 2013/0123595 A1 (CURRIE, J et al.) 16 May 2013; figure 4; paragraphs [0048]-[0049], [0057], [0065], [0068], [0076], [0084], [0175]	1-20
A	US 2002/0010412 A1 (EPPSTEIN, J) 24 January 2002; figure 1; paragraphs [0002], [0055], [0057]; claim 35	1-12
A	US 2011/0178380 A1 (CHOWDHURY, D) 21 July 2011; figure 2a; paragraphs [0027]-[0030], [0036]; claim 1	1-20
A	US 2008/0121045 A1 (COLE, M et al.) 29 May 2008; paragraphs [0008], [0036]	13-20

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA/

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