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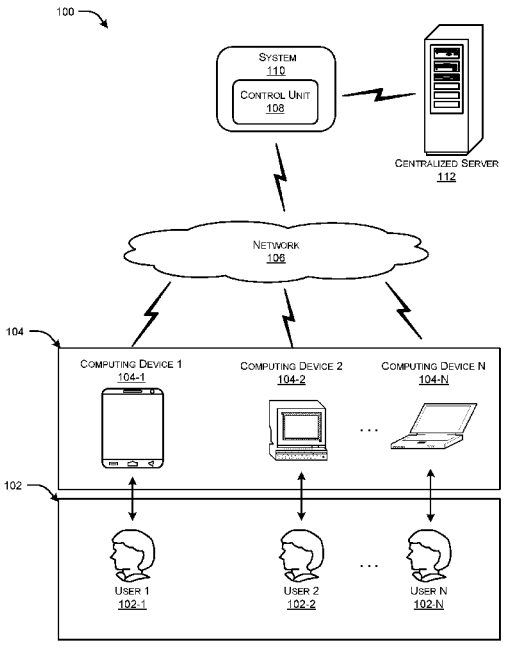

FIG. 1A

(57) Abstract: The present disclosure provides a system (200) for rapid diagnosis of malignant lesions from biopsy tissue. The system comprises table-top platform (202) integrated with microsensors (206) and electronic modules for label-free and rapid phenotyping of extracted biopsy tissues using multiple modalities for a quick diagnosis, and to identify the margin for use inside the operation room. A multiple logistic regression model takes all the physical parameters measured as input variables to accurately predict the diagnosis. The electrical resistivity, thermal conductivity and mechanical stiffness of the extracted biopsy tissues are measured and used for performing the diagnostic delineation. The computations are performed on-board and the entire system can be controlled and actuated using a smart-phone.

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APPARATUS AND SYSTEM FOR RAPID DIAGNOSIS OF MALIGNANT LESIONS

TECHNICAL FIELD

[0001] The present disclosure relates, in general, to a micro-electro-mechanical system (MEMS)-based system and more specifically, relates to a portable table-top tool for the rapid diagnosis of malignant lesions from the biopsy tissue for use in the operation room.

BACKGROUND

[0002] Background description includes information that may be useful in understanding the present disclosure. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed disclosure, or that any publication specifically or implicitly referenced is prior art.

[0003] Cancer is a major non-communicable disease with the global burden in 2018 rising to 18.1 million cases with 9.6 million deaths. According to the International Agency for Research on Cancer (IARC) one-in-five men and one-in-six women worldwide will develop cancer during their lifetime. Breast cancer is the second most prevalent cancer by incidence and fifth most by mortality for both sexes taken together. In India, breast cancer is the most common cancer in women accounting for 14% of all cases in women. The challenge, with a disease like cancer, is the need to improve diagnosis and staging. Additionally, a significant improvement in the standard of care provided through better prognosis while not substantially increasing the cost incurred by the patients will be useful. Even though medical technologies have significantly advanced in the last decade, disease screening and intra-operative techniques have remained largely unchanged.

[0004] Current cancer diagnostic methods involve lab tests like blood tests, complete blood count, urine analysis and tumour markers, diagnostic imaging like transmission, reflection and emission imaging and types of tumour biopsies like endoscopic, skin, bone marrow, fine needle aspiration, excisional or incisional biopsy. With respect to pre-operative margin assessment within the operation room, the number of techniques and technologies available are presently very limited.

[0005] The standard technique is the frozen section biopsy which is a pathological laboratory procedure for a quick examination and microscopic analysis of excised tissue. But this technique still involves sending the biopsy tissue out of the operation room and into the pathology labs. The surgeons then wait for the results to arrive, which may take from 30 min to 2 hr. To assess a conservative margin around the tumour this must be carried out on

multiple samples around the suspected lesion site as well as the surrounding lymph nodes. This adds to the time of diagnosis as well as the operation. Apart from this technique, the surgeons also make use of the pre-surgery scan reports, visual cues such as colour, texture, consistency of the tissue to assess the margin between cancerous and normal tissue.

[0006] Conventional techniques though accurate and standardized, are limited in their application inside an operation room owing to the time taken and the requirement of sample preparation such as paraffinization, sample sectioning, chemical treatment, antibody addition, imaging, etc. Some additional known limitations include difficulty in identifying the progression from premalignancy to early malignancy, false negatives necessitating a second biopsy, and low sensitivity from frozen samples requiring re-excision/re-operation. Physical properties of breast tissues such as its electrical, thermal, and mechanical properties hold the key for such a label-free diagnosis.

[0007] Several technologies have been developed that aims to improve the diagnostic accuracy of sampled tissue. Some of these are micro RNA analysis, computer-aided morphometric analysis, Raman spectroscopic analysis of tissues, etc. These techniques are however limited by the availability of equipment, which are at times bulky, require trained personnel, high test costs, and inter-personal variability in the interpretation of the results. Considering the challenge of developing a portable platform for analysing the physical properties of tissues in a label-free manner, micro-electro-mechanical systems (MEMS) present an interesting way forward, as a solution, because of their miniature size and versatility. MEMS consist of electrical and mechanical components ranging from few micro-meters to a few hundred micro-meters.

[0008] MEMS-based devices are broadly classified as actuators or sensors. MEMS-based devices have been used for several biomedical applications such as guided tissue biopsy, artificial skin, microfluidics point-of-care bioassays, etc. Few groups have used MEMS-based piezoresistive micro-cantilevers to study the mechanical properties of breast tissue sections. Flexible sensors for electro-mechanical characterization of breast tissue sections by augmenting an atomic force microscope (AFM) probe has also yielded interesting results. These studies were limited by the fact that they measured from tissue sections of micrometer dimensions which require separate preparation steps. Additionally, the requirement for bulky equipment like AFM, the fragility of the micro-cantilevers, and the use of a costly tool such as micromanipulators limits the system to be translated into a portable tool.

[0009] Till now only a few studies have reported the measurement of the physical properties of tissue samples using a portable cancer diagnosis tool. The results are obtained from only few subjects e.g., dead tissue samples: three normal and three invasive ductal carcinomas. Further, the measurements were carried out only in the Z-direction while the anisotropy of the tissues and the coupling factors between the properties were not considered. Thus, there are no commercially available tools that can be used inside the operation room to perform rapid phenol typing of core biopsy or any form of excised breast tissue.

[0010] Therefore, there is a need in the medical industry to provide a portable tool that can be placed inside the operation room for rapid phenol typing of extracted biopsy tissue to delineate between cancer and normal to guide margin assessment for minimal relapse surgical outcomes.

OBJECTS OF THE PRESENT DISCLOSURE

[0011] Some of the objects of the present disclosure, which at least one embodiment herein satisfies are as listed herein below.

[0012] It is an object of the present disclosure to provide for a system that can freshly extracted biopsy tissue during surgery.

[0013] It is an object of the present disclosure to provide for a system that facilitates elimination of the need for any sample preparation steps e.g., sectioning or staining.

[0014] It is an object of the present disclosure to provide for a system that makes the diagnostic process faster.

[0015] It is an object of the present disclosure to provide for a system that facilitates real-time detection of cancerous tissue that can be scaled-up to include other parameters such as age, sex, body mass index, smoking status, menstrual status etc to improve the prediction accuracy of the system.

[0016] It is an object of the present disclosure to provide for a system that permits the delineation of a normal and malignant tissue without the need for a paired adjacent confirmed normal tissue.

SUMMARY

[0017] The present disclosure relates, in general, to a micro-electro-mechanical system (MEMS)-based system and more specifically, relates to a portable table-top tool for the rapid diagnosis of malignant lesions from the biopsy tissue for use in the operation room.

[0018] In an aspect, the present disclosure provides for a system for determining cancerous tissues. The system may include a platform that may include a plurality of microsensors, wherein each microsensor may be operatively coupled to an indenter configured to probe a tissue in a combination of linear and angular directions, a sample holder to hold the tissue coupled to a rotational mechanism, a control unit operatively coupled to the plurality of microsensors and the rotational mechanism, the control unit comprising a processor, wherein the processor may execute a set of executable instructions that are stored in a memory, upon execution of which, the processor may cause the system to: receive from the plurality of microsensors, a first set of signals corresponding to a plurality of parameters associated with a plurality of properties of the tissue, extract from the received first set of signals, a first set of attributes pertaining to parameters associated a plurality of properties of the tissue, compare the extracted first set of attributes with a predefined set of parameters associated with the properties of a normal tissue, and based on the comparison, determine whether the tissue may be cancerous or normal and if cancerous, identify margin of malignancy in the tissue.

[0019] In an embodiment, the control unit may be coupled to the rotational mechanism, wherein the control unit may rotate the sample holder in any or a combination of horizontal and vertical direction.

[0020] In an embodiment, the plurality of microsensors may detect surface and bulk measurements of the physical properties of the tissue at any room and elevated temperatures to capture the effects of anisotropy in the tissue.

[0021] In an embodiment, determination of the properties of the tissue may be any or a combination of a stored tissue and freshly extracted biopsy tissue during surgery.

[0022] In an embodiment, the plurality of microsensors may be housed in a sensor module, said sensor module may be detachable from the platform, and communicatively coupled to the control unit through any or a combination of wired and wireless network.

[0023] In an embodiment, the control unit may be communicatively coupled to a computing device associated with a user.

[0024] In an embodiment, the control unit is configured to self train based on a machine learning module coupled to a logistic regression module.

[0025] In an embodiment, the control unit may be further configured to model and fit the collected data on-the-fly using scaling laws to assess the extent of disorder in the tissue and apply the model parameters for delineation.

[0026] In an embodiment, each microsensor may include at least one microheater at the centre surrounded by one or more resistance temperature devices (RTD), one or more interdigitated electrodes, at least an embedded piezoelectric or piezoresistive layer formed over a diaphragm to simultaneously measure electrical, thermal, and mechanical properties of the tissue.

[0027] In an aspect, the present disclosure provides for a method for fabricating a microsensor. The method may include the steps of depositing a dielectric layer of a predefined thickness on top of a substrate, forming a photoresist on the dielectric layer and patterning of the dielectric layer, patterning with one or more predefined metal elements and the photoresist, wherein the patterning of the dielectric layer with the one or more predefined metal elements and the photoresist may form a patterned structure, performing a first wet etching of the patterned substrate, patterning a plurality of trenches for thermal isolation through photolithographic exposure, performing a second dry etching of the substrate after a second patterning of the plurality of trenches, and performing ion etching on the patterned substrate to create through-holes on the plurality of trenches.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The following drawings form part of the present specification and are included to further illustrate aspects of the present disclosure. The disclosure may be better understood by reference to the drawings in combination with the detailed description of the specific embodiments presented herein.

[0029] FIG. 1A illustrates exemplary network architecture in which or with which proposed system may be implemented, in accordance with an embodiment of the present disclosure.

[0030] FIG. 1B illustrates an exemplary architecture of the system/ centralised server in accordance with an exemplary embodiment of the present disclosure.

[0031] FIGs. 2A-2F illustrate an exemplary representation of portable table-top platform, according to an embodiment of the present disclosure.

[0032] FIGs. 3A-3D illustrate a schematic view of the indenter, according to an embodiment of the present disclosure.

[0033] FIGs. 4A-4E illustrate an exemplary representation of a modular sensor, according to an embodiment of the present disclosure.

[0034] FIGs. 5A-5C illustrate the fabrication process of the electro-thermal sensor, according to an embodiment of the present disclosure.

[0035] FIGs. 6A-6B illustrate the block diagram of the electronic modules incorporated inside the platform, according to an embodiment of the present disclosure.

[0036] FIG. 7 illustrates a schematic view of the main controller PCB, according to an embodiment of the present disclosure.

[0037] FIG. 8 illustrates the schematic view of the graphical user interface (GUI) for calibrating, controlling, and acquiring and displaying data from the system, according to an embodiment of the present disclosure.

[0038] FIG. 9 illustrates flow diagram of the multiple logistic regression process, according to an embodiment of the present disclosure.

[0039] FIGs. 10A-10C illustrate a graphical representation of different measurements between cancer and normal tissues, according to an embodiment of the present disclosure.

[0040] FIG. 11 illustrates exemplary representations of temperature-dependent bulk and surface resistivity measurements in accordance with embodiments of the present disclosure.

[0041] FIG. 12 illustrates exemplary representations of experimental analysis through thermal conductivity measurement in accordance with embodiments of the present disclosure.

[0042] FIG. 13 illustrates exemplary representations of regression analysis in accordance with embodiments of the present disclosure.

[0043] FIG. 14 illustrates exemplary representations of model fitting of experimental data in accordance with embodiments of the present disclosure.

[0044] FIG. 15 illustrates exemplary representations of a process flow for designing a mechanical sensing layer in accordance with embodiments of the present disclosure.

DETAILED DESCRIPTION

[0045] The following is a detailed description of embodiments of the disclosure depicted in the accompanying drawings. The embodiments are in such detail as to clearly communicate the disclosure. However, the amount of detail offered is not intended to limit the anticipated variations of embodiments; on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the present disclosure as defined by the appended claims.

[0046] If the specification states a component or feature "may", "can", "could", or "might" be included or have a characteristic, that particular component or feature is not required to be included or have the characteristic.

[0047] As used in the description herein and throughout the claims that follow, the meaning of "a," "an," and "the" includes plural reference unless the context clearly dictates

otherwise. Also, as used in the description herein, the meaning of "in" includes "in" and "on" unless the context clearly dictates otherwise.

[0048] The use of any and all examples, or exemplary language (e.g., "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non – claimed element essential to the practice of the invention.

[0049] As illustrated in FIG. 1A, in a network implementation, a user (102) may be associated with one or more computing devices (104-1, 104-2, 104-3...104-N) (also referred collectively as computing devices 104 and individually as computing device 104). The user (102) may be doctors, health officials, system operators, technicians, nurses and the like.

[0050] In an embodiment, the system (110) may include a plurality of microsensors and a plurality of electronic hardware devices operatively coupled to a platform. Each microsensor may be further operatively coupled to an indenter configured to probe a tissue in a combination of linear and angular directions. In an exemplary embodiment, the linear and angular directions may include x,y, z and θ but not limited to the like. The system (110) may also include a sample holder to hold the tissue, the sample holder coupled to a rotational mechanism. The system (110) may include a control unit (108) operatively coupled to the plurality of microsensors and the rotational mechanism. The control unit (110) may receive from the plurality of microsensors, a first set of signals corresponding to a plurality of parameters associated with a plurality of properties of the tissue and then extract from the received first set of signals, a first set of attributes pertaining to parameters associated a plurality of properties of the tissue. The control unit (108) may then compare the extracted first set of attributes with a predefined set of parameters associated with the properties of a normal tissue and based on the comparison, the control unit may determine whether the tissue may be cancerous or normal. In an exemplary embodiment, the predefined set of parameters associated with the properties of a normal tissue may include properties such as electrical, thermal, and mechanical properties but not limited to the like.

[0051] In an embodiment, the control unit may be coupled to the rotational mechanism to rotate the sample holder in any horizontal or vertical direction.

In an embodiment, the plurality of microsensors may detect surface and bulk measurements of the properties of the tissue at room and elevated temperatures to capture the effects of anisotropy in the tissue where determination of the properties of the tissue may be any or a combination of a stored tissue and freshly extracted biopsy tissue during surgery. In an

exemplary embodiment, the system can uniquely measure the surface and bulk electrical property of the tissue such as resistivity, impedance, and phase and the like at room as well as elevated tissue temperatures because of the specific construction of the sensor and the system, which serves as a novel modality for delineation.

[0052] In an exemplary embodiment, the plurality of microsensors may be housed in a sensor module that may be detachable from the platform and may be communicatively coupled to the control unit through any or a combination of wired and wireless network. In an exemplary embodiment, the first set of attributes extracted by the control unit (108) may be transmitted to the computing device (104) associated with the user (102). The control unit (108) may be further configured to self-train based on a machine learning module coupled to a logistic regression module.

[0053] In an exemplary embodiment, each microsensor may include at least one microheater at the centre surrounded by one or more resistance temperature devices (RTD).

[0054] In an implementation, the computing devices (104) coupled to the system (110) can be accessed by applications residing on any operating system, including but not limited to, AndroidTM, iOSTM, and the like. Examples of computing device (104) may include, but not limited to, any electrical, electronic, electro-mechanical or an equipment or a combination of one or more of the above devices such as mobile phone, smartphone, virtual reality (VR) devices, augmented reality (AR) devices, pager, laptop, a general-purpose computer, desktop, personal digital assistant, tablet computer, mainframe computer, or any other computing device, wherein the computing device may include one or more in-built or externally coupled accessories including, but not limited to, a visual aid device such as camera, audio aid, a microphone, a keyboard, input devices for receiving input from a user such as touch pad, touch enabled screen, electronic pen and the like. It may be appreciated that the computing device (104) may not be restricted to the mentioned devices and various other devices may be used. A smart computing device may be one of the appropriate systems for storing data and other private/sensitive information.

[0055] In an embodiment, the system (110) may be connected to one or more peripheral devices for providing the inputs related to the one or more health parameters, wherein the peripheral devices may include, but not limited to, a keyboard, a mouse, a touch pad, an image scanner, a touch screen and the like. Various other peripheral devices may also be used.

[0056] In an embodiment, the interface of the system (110) may display the at least one health information computed by the centralized server (112). The interface may be a

display screen or any medium for communicating the one or more inputs related to the health parameters of the user and for viewing the output or the computed health information.

[0057] FIG. 1B illustrates an exemplary architecture of the system (110)/ centralised server (112) in accordance with an exemplary embodiment of the present disclosure. The system (110) or the centralized server (112) may include one or more processors (122) that may be configured to receive from the plurality of microsensors, a first set of signals corresponding to a plurality of parameters associated with a plurality of properties of the tissue and extract from the received first set of signals, a first set of attributes pertaining to parameters associated a plurality of properties of the tissue such that the extracted first set of attributes may be compared with a predefined set of parameters associated with the properties of a normal tissue and based on the comparison, determine whether the tissue may be cancerous or normal.

[0058] The one or more processors (122) may be implemented as one or more microprocessors, microcomputers, microcontrollers, digital signal processors, central processing units, logic circuitries, and/or any devices that manipulate data based on operational instructions. Among other capabilities, the one or more processor(s) (122) may be configured to fetch and execute computer-readable instructions stored in a memory (124) of the centralized server (112). The memory (204) may store one or more computer-readable instructions or routines, which may be fetched and executed to create or share the data units over a network. The memory (124) may comprise any non-transitory storage device including, for example, volatile memory such as RAM, or non-volatile memory such as EPROM, flash memory, and the like.

[0059] The system (110) / centralized server (112) may also comprise an interface(s) (126). The interface(s) (126) may comprise a variety of interfaces, for example, interfaces for data input and output devices, referred to as I/O devices, storage devices, SCADA, Sensors and the like. The interface(s) (126) may facilitate communication of the centralized server (112) with various devices coupled to it. The interface(s) (126) may also provide a communication pathway for one or more components of the centralized server (112). Examples of such components include, but are not limited to, processing engine(s) (128) and database (120).

[0060] The one or more processors (122) may be implemented as a combination of hardware and programming (for example, programmable instructions) to implement one or more functionalities of the one or more processors (122). In examples described herein, such combinations of hardware and programming may be implemented in several different ways.

For example, the programming for the one or more processors (122) may be processor executable instructions stored on a non-transitory machine-readable storage medium and the hardware for the one or more processors (122) may comprise a processing resource (for example, one or more processors), to execute such instructions. In the present examples, the machine-readable storage medium may store instructions that, when executed by the processing resource, implement the one or more processors (122). In such examples, the system (110) / centralized server (112) may comprise the machine-readable storage medium storing the instructions and the processing resource to execute the instructions, or the machine-readable storage medium may be separate but accessible to the system / centralized server (112) and the processing resource. In other examples, the one or more processors (122) may be implemented by electronic circuitry.

[0061] In an aspect, the database (130) may be configured to store any data including, but not limited to, at least one of the properties associated with any or a combination of normal and cancerous tissue. In another aspect, the database (130) may comprise data that may be either stored or generated as a result of functionalities implemented by any of the components of the processor (122) or the processing engines (128).

[0062] In an exemplary embodiment, the processing engine(s) (128) may include a data acquisition engine (132), a logistic regression engine (134) and other engines (136), wherein the other engines (136) may further include, without limitation, input reminder engine, storage engine, or signal generation engine.

[0063] FIGs. 2A-2B illustrate an exemplary representation of a system with portable table-top platform, according to an embodiment of the present disclosure.

[0064] Referring to FIGs.2A and 2B, system (200) includes a MEMS-based multi-modal portable table-top platform (102) but not limited to it integrated with a plurality of microsensors (206) (also referred to as microsensors (206) hereinafter) and electronic modules for label-free and rapid phenol typing of breast biopsy tissues but not limited to it using multiple modalities for a quick diagnosis to determine whether an extracted biopsy tissue is cancerous or normal, and to identify the margin. The MEMS-based multi-modal table-top platform (202) can perform rapid label-free phenol typing of the fresh biopsy tissue in the X, Y, Z and θ directions to delineate between cancer and normal tissue. The platform leverages the differences in the physical properties of breast cancer tissues as compared to normal tissue, such as its electrical, thermal, and mechanical properties, in a label-free

manner to achieve rapid phenol typing of sample tissue to delineate whether it is cancer or normal tissue in short time e.g., under ten minutes.

[0065] In an embodiment, the universal tissue phenol typing platform (202) can be scaled and re-adopted to any solid tumour cancers. The universal solid tissue phenol typing platform based on electro-thermo-mechanical sensing modalities can be applied for studying a variety of diseases such as breast cancer, colon cancer, oral cancer, pancreatic cancer and the like. The system can be used with a wide variety of sample sizes ranging from several millimetres to several centimetres. The system internally calibrates the measured parameters according to the size of the sample tissue loaded. Delineation between cancer and normal tissue through multi-parametric surface and bulk measurements can take into account the anisotropy of the sample tissue to determine the nature of malignancy of the tissue.

[0066] In an embodiment, the platform can probe the tissue in the X, Y, Z directions using the respective indenters and has the flexibility of rotation of sample along the Z-axis with rotational control. It can perform surface and bulk measurements of the physical properties at room and elevated temperatures that enable the system to rightly capture the effects of anisotropy in the tissue. The system can perform rapid phenol typing directly on freshly extracted biopsy tissue during surgery thereby eliminating the need for any sample preparation steps e.g., sectioning or staining. This makes the process faster and more accurate as fresh tissues are used.

[0067] In an embodiment, a sensor module can be used in the system. The sensor module subsystem can be separately attached and removed from the overall system. This enables the use of a variety of sensors for probing the electrical, thermal, mechanical, chemical, and other physical properties of the tissue. The microsensor (206) is attached to the sensor module via an adaptor printed circuit board (PCB) and a sensor holder PCB but not limited to the like. The microsensors (206) in the sensor holder can be easily replaced because of the use of a slide fit contact that eliminates the need for soldering while ensuring ohmic contact.

[0068] In an embodiment, to account for the anisotropy in the tissue architecture, the system measures the surface and bulk electrical and thermal properties as well as the elastic/stiffness of the sample across the X, Y, and Z axes of the tissue with provision for rotation along the Z-axis. A multiple logistic regression engine (134) (interchangeably referred to as logistic regression model hereinafter) can be used to predict whether the sample is cancerous or normal by taking the surface and bulk electrical resistivity, thermal conductivity, their variation as a function of temperature of the tissue, and their ratios at

different tissue temperatures, and elasticity values at different temperatures as input variables to the model.

[0069] In other words, multiple logistic regression model can take all the physical parameters measured as input variables and are used to determine if the tissue is malignant or normal. All the computations are performed on-board and the entire system can be controlled and actuated using a smart-phone 104 or tablet-based application. The delineation between cancer and normal tissue can be determined from the result of a multiple logistic regression model that has all the measured physical parameters as inputs. This regression model can run real-time on the on-board electronics and can be scaled-up to include other parameters such as age, sex, body mass index, smoking status, menstrual status etc to improve the prediction accuracy of the system.

[0070] In another embodiment, on-board multiple logistic regression model can be used to accurately predict the diagnostic outcome, viz. whether the sample tissue is cancer or normal. The physical properties of the tissues include but are not limited to the electrical, thermal, mechanical, acoustic, and chemical properties. Leveraging this difference in property between cancer and normal tissue can pave the way for label-free diagnostics with no special sample preparation before testing with the system. The use of a pre-trained regression model for predicting the nature of the sample tissue (whether cancer or normal) permits the said delineation without the need for a paired adjacent confirmed normal tissue.

[0071] In another embodiment, compact, table-top platform (200) can be powered by regular alternating current (AC) supply as also battery-operated convenient for use inside an operation room, pathology labs, and in low resource settings. All the electronic modules for data acquisition, processing and display of results is integrated onto the platform 202 and can be controlled through the custom application running on the tablet personal computer (PC)204 or smartphone of the user. The data acquisition can be done on a standard micro controller, microprocessor or field programmable gate array (FPGA)-based electronic module but not limited to the like. The system (200) is designed for use inside the operation room to perform pre-operative margin assessment for surgery and also in pathology labs to aid in diagnosis.

[0072] FIGs. 2C-2F illustrate an exemplary representation of the portable table-top platform, according to an embodiment of the present disclosure.

[0073] Referring to FIGs. 2A-2F, the table-top platform (202) has an overall dimension of at least 205mm x 310mm x 165mm (L x W x H) but not limited to it. The tissue is placed on a removable metal tissue holder which can then be placed on a fixed rotary stage. The

rotary stage can rotate full 360 degrees with control on the degree of rotation. The rotary table is mounted directly on a NEMA17 stepper motor but not limited to it. The schematic view of the indenter is illustrated in FIGs. 3A-3D. The two indenters are placed diametrically opposite to each other with the tissue holder in the middle. Sensors are attached at the end of the indenters.

[0074] In an embodiment, by way of example and not as limitation, the indenters may be placed on a linear rail with rail block MGN9C. A closed-circuit timing belt system is made using GT2-16 tooth pulley placed directly on NEMA 17 motors and one idler pulley on the other side. A spring is used to tighten the timing belt. The combination of a timing belt, spring, and the length between two poles is designed in such a way that, even if the indenter gets stuck somewhere during the motion, the timing belt can take slip as a passive safety to the system and sensors. The timing belt is attached to the indenter using a 3D printed clamp. This arrangement constitutes the indenter subsystem. A similar indenter sub-system can be placed for probing the tissue in the Z-direction.

[0075] In another embodiment, by way of example and not as limitation the motors may be controlled by a 1/128 micro-step stepper motor driver. Stepper drivers may be placed on an Arduino computer numerical control (CNC) shield, the shield is then placed on an Arduino Nano microcontroller board. The motor motion is controlled using an android application installed on a tablet that communicates with the main Arduino Mega 2560 board which serves as the master controller. The platform can be powered from regular 230V AC signal. The switched mode power supply on-board converts it into 12V DC for use in the electronic modules inside. There is also provision for a battery for use in low resource settings or during power outage, if required.

[0076] In another embodiment, by way of example and not as a limitation, the tablet PC104 may run the android application for data capture, system control, and data visualization and can be either connected via universal serial bus (USB) cable or through Bluetooth/WiFi modules. The system is automated to approach the tissue, make sufficient and minimal contact required for measurements, cycle through increasing tissue temperature by heating with microheaters, record measurements for calculating electrical resistivity, thermal conductivity, and elasticity properties, once the start measurement command is given.

[0077] FIGs. 4A-4E illustrate an exemplary representation of a sensor module, according to an embodiment of the present disclosure. The sensor module attachment is designed in a modular fashion allowing for easy attachment and detachment from the indenter. The microsensor (206) is attached to the sensor module via an adaptor PCB and a

sensor holder PCB. The microsensor attaches to the sensor holder PCB and the adaptor PCB connects the sensor holder PCB and the sensor module attachment. This enables the system to use new and upgraded sensors as and when they need to be tested with samples. Only the sensor module attachment needs to be removed, attached to the new sensor, and re-attached.

[0078] In an embodiment, the microsensor (206) can be connected to the sensor holder PCB via solder-free slide fit contacts with the aim of easy replacement, as the sensor measures from biological samples it needs to be replaced for each new sample. The microsensor can be fabricated with different sensing materials such as platinum, aluminium, gold, nickel or any other metal with good conductivity for the electrodes and any material such as platinum, nichrome, and the like for the microheater and resistance temperature devices (RTDs).

[0079] FIGs. 5A-5C illustrate the fabrication process of the electro-thermal sensor, according to an embodiment of the present disclosure.

[0080] In an aspect, a method for fabricating the microsensors may include the steps of depositing a dielectric layer of a predefined thickness on top of a substrate, forming a photoresist on the dielectric layer and patterning of the dielectric layer, patterning with one or more predefined metal elements and the photoresist, wherein the patterning of the dielectric layer with the one or more predefined metal elements and the photoresist may form a patterned structure, performing a first wet etching of the patterned substrate, patterning a plurality of trenches for thermal isolation through photolithographic exposure, performing a second dry etching of the substrate after a second patterning of the plurality of trenches, and performing ion etching on the patterned substrate to create through-holes on the plurality of trenches.

[0081] Referring to FIGs. 5A-5C, by way of example and not as limitation, the working principle of the sensor is that the microheater at the centre can heat the tissue through a range of temperatures and the RTD around the microheater can sense the surface thermal conductivity from the tissue. The integrated interdigitated electrode (IDE) can measure the electrical properties of the tissue while at room temperature and while it is being heated. The same sensor mounted on the longitudinally opposite direction of the tissue on the tool can measure the bulk thermal and electrical properties of the sample. This sensor on the other end cannot be heated and the microheater can act as an RTD here. The same logic applies for the sensors mounted on the Z-direction.

[0082] In an embodiment, by way of example and not as a limitation, the sensor can be fabricated using a at least a 2-mask process. The active region of the chip may cover at least

1mm x 0.5mm and the overall chip size may be at least 10mm x 6mm. A 500μ thick silicon wafer can be used as the substrate but not limited to it. At least 1μ of silicon dioxide (SiO_2) is thermally grown on this wafer. This substrate is then patterned using standard photolithography techniques using Mask #1 to imprint the patterns for the microheater at the centre and the three RTDs around the microheater. When the microheater is not actively heated it may act as another RTD. For this, an image reversal lift-off process is used using AZ5214E positive photoresist (PR) but not limited to it.

[0083] In an embodiment, theSiO_2 deposited silicon wafer is first coated with PR, exposed with Mask #1, followed by reversal bake at 120°C and flood exposure but not limited to it. After development, at least 25nm of Titanium followed by at least 190 nm of Platinum may be sputter deposited onto this substrate. The titanium layer is used for better stiction of platinum onto the substrate. This step is followed by the lift-off process by immersing the wafer in acetone and isopropanol. After this step the metal patterns are formed on the substrate.

[0084] In an embodiment, the trenches may be created for thermal isolation of the microheater from the RTDs. For this, the metal patterned substrate may be coated with AZ4562 PR but not limited to it followed by photolithographic exposure with Mask #2 that forms the patterns for the trench. Following the development, the substrate is then dipped in hydrofluoric acid (HF) but not limited to it to remove the silicon dioxide underneath the trench area to make it pliable for dry etching. Deep reactive ion etching (DRIE) may be performed on this substrate to create through-holes on the trenches but not limited to it. By way of example and not as limitation, the photoresist may be then removed using piranha cleaning to get the final devices on the wafer. The wafer may be then diced into individual chips using automatic dicer.

[0085] In an exemplary embodiment, any type of sensor with a variety of sensing modalities conforming to the size of at least10mm x 6mm can be mounted on the sensor module connector and used for tissue phenotyping. The capability of performing the surface and bulk measurements at different elevated tissue temperatures through the microheater can be provided in the sensor design. This feature allows to correctly capture the tissue anisotropy as the effect of anisotropy becomes more prominent at elevated sample temperature owing to increased entropy.

[0086] In another embodiment, the detailed block diagram of the electronic subsystem is illustrated in FIG. 6A. The electronic subsystem communicates with the graphical user interface via the main controller PCB is illustrated in FIG 6B. In an embodiment, each sensor

can measure the various resistance values from the IDEs and RTDs. All the signal lines from the sensors in the X, Y and Z indenters are connected to the mux. Depending on the selected combination, pairs of resistances are selected and measured using an auto-ranging circuit. The resistance values which are then converted to digital form by the ADS1115 module. The digitized voltage value is converted to resistance value in the software and stored and displayed on the GUI. The tablet/smartphone in which the GUI runs is connected to the main controller card via the USB channel through a universal asynchronous receiver/transmitter (UART) protocol to send command for calibration, and actuation.

[0087] FIG. 7 illustrates a schematic view of the main controller PCB, according to an embodiment of the present disclosure.

[0088] In an embodiment, each sensor has eight logic lines for measuring the various resistance values from the IDEs and RTDs. The Arduino mega controller is provided with multiplexed sensor input, auto-ranging resistors, driving transistor, supply and ground. All the signal lines from the sensors in the X, Y and Z indenters are connected to the multiplexer. The 16:1 multiplexer module can be configured for connecting the different sensor signals and measuring them in multiplexed manner. The select lines go from the main controller Arduino which is in-turn controlled by the software running on the GUI. Depending on the selected combination, pairs of resistances are selected and measured using an auto-ranging circuit composed of a set of resistors calibrated to measure across a wide-range of resistance values. These resistance values appear as voltage values which are then converted to digital form by the ADS1115 module. The ADS1115 analog to digital converter (ADC) configured to convert the values read from the sensor with higher precision. The voltage driver circuit is configured for driving the microheater in the sensor with up to 12V input voltage.

[0089] In an embodiment, the digitized voltage value is converted to resistance value in the software and stored and displayed on the GUI. The tablet/smartphone 104 in which the GUI runs is connected to the main controller card via the USB channel through a universal asynchronous receiver/transmitter (UART) protocol. It can send commands for calibration, and actuation of the indenters, as well as for cycling through the measurements automatically once the start measurement command is given in the GUI. The controls e.g., calibrate, read, save etc. are shown in the GUI illustrated in FIG. 8. The GUI can be configured for calibrating, controlling, and acquiring and displaying data from the system.

[0090] In another embodiment, the heating of the microheater can be performed by providing the required voltage corresponding to the target temperature required through the driver circuit in the main controller card. The main controller card controls the

communications with the GUI i.e., sends and receives soft commands from the GUI, and also serves as a master for the smaller Arduino nano board that performs the motor control operations. The Arduino mega and Arduino nano within the main controller card act in a master-slave configuration over the second UART port of the Arduino mega.

[0091] FIG. 9 illustrates flow diagram of the multiple logistic regression process, according to an embodiment of the present disclosure.

[0092] In an embodiment, multiple logistic regression model can be used to provide result about the nature of the sample tissue as to whether it is cancer or normal. The logistic regression can be used for predicting binary outcomes. In the case of the present disclosure, the binary outcome can be whether the tissue under measurement in the platform is cancer or normal tissue. Multiple logistic regression model can take the following measured and computed variables as inputs to predict the outcome.

[0093] The measured and computed variables includes ratio of surface resistivity at 40^0C to the surface resistivity at room temperature ($\rho_{S,40}/\ \rho_{S,RT}$), ratio of bulk resistivity at 40^0C to the bulk resistivity at room temperature ($\rho_{B,40}/\ \rho_{B,RT}$), ratio of bulk resistivity to the surface resistivity at 40^0C. ($\rho_{B,40}/\ \rho_{S,\ 40}$), ratio of bulk resistivity to the surface resistivity at room temperature ($\rho_{B,RT}/\ \rho_{S,\ RT}$), bulk thermal conductivity (K_B), surface thermal conductivity (K_S), ratio of bulk to surface thermal conductivity (K_B/K_S), elasticity value computed at 40^0C (E_{40}), elasticity value computed at room temperature. (E_{RT}). The model can be pretrained and stored in the electronic module. The model evaluation can be performed on-board by inputting the measured and computed variables as above.

[0094] In addition to the above variables, the model can also be extended to include other parameters such as age, sex, body mass index (BMI), smoking status, menstrual status etc of the patient to improve the prediction accuracy. The tissue is placed on the tool and the start measurement command is given on the GUI. The tool makes a calibrated approach towards the tissue and makes sufficient and minimal contact required for measurement. This is ensured by monitoring the sudden drop in the resistance measured across the tissue. Once contact is made, the different signals from the sensors are measured at temperature ranges from room temperature 25 ^{0}C to 40 ^{0}C in steps of 5 ^{0}C. The peak temperature can be modified. After all the measurements are done, other variables are calculated on-board. These variables then input to the trained logistic regression model, the odds ratio value is calculated, and this value can be used to determine the diagnostic status of the tissue, namely whether it is cancerous or normal.

[0095] FIGs. 10A-10C illustrate a graphical representation of measurements between cancer and normal tissues, according to an embodiment of the present disclosure.

[0096] In an embodiment, a preliminary validation of the tool were performed by carrying out experiments with N=4 paired patient samples. The tissue samples were deparaffinised and rehydrated and used for measurement. These results show statistically significant delineation between cancer and normal tissues. Large scale clinical validation as well as experiments with animal models can also be performed.

[0097] In an embodiment, the results from the system with N=4 paired patient samples show significant difference between cancer and normal tissues.FIG.10Ashows the surface resistivity measurements between cancer and normal tissues at 25^{0}C and 35^{0}C. FIG. 10B shows the bulk resistivity measurements between cancer and normal tissue at the two temperatures and, FIG. 10C shows the surface and bulk thermal conductivity measurements between cancer and normal tissue. The results show a statistically significant difference between cancer and normal tissues.

[0098] FIG. 11 illustrates exemplary representations of temperature-dependent bulk and surface resistivity measurements in accordance with embodiments of the present disclosure. As illustrated, in an exemplary implementation, temperature-dependent bulk resistivity measurement for FFPE samples and formalin fixed samples and surface resistivity measurements for FFEE samples and formalin fixed samples using the proposed device are performed and analysed.

[0099] FIG. 12 illustrates exemplary representations of experimental analysis through thermal conductivity measurement in accordance with embodiments of the present disclosure. As illustrated, in an exemplary implementation, thermal conductivity measurement for FFPE samples and formalin fixed samples using the proposed device are performed and analysed.

[00100] FIG. 13 illustrates exemplary representations of regression analysis in accordance with embodiments of the present disclosure. As illustrated, in an exemplary implementation, regression analysis for combination of measurement parameters to serve as basis for logistic regression model is analysed.

[00101] FIG. 14 illustrates exemplary representations of model fitting of experimental data in accordance with embodiments of the present disclosure. As illustrated, in an exemplary implementation, results of model fitting of experimental data with scaling laws showing model fit parameters and critical temperature values in Table I and model fit parameters and cut off frequency values in Table II are depicted.

[00102] FIG. 15 illustrates exemplary representations of a process flow for designing a mechanical sensing layer in accordance with embodiments of the present disclosure. As illustrated, process flow and interfacing for combined electro-thermo-mechanical sensor with the contacts for the mechanical sensing layer is depicted. The process flow comprises the steps of depositing a silicon substrate, oxidising the silicon substrate, depositing a patterned bottom electrode, depositing and patterning an AIN piezoelectric layer, then depositing top electrodes at the top of the structure, depositing and window opening of PECVD oxide, coating photoresist and patterning for liftoff, depositing platinum or titanium and patterning of top structure, etching with backside oxide and DRIE diaphragm.

[00103] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive patent matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "includes" and "including" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refer to at least one of something selected from the group consisting of A, B, C ....and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc. The foregoing description of the specific embodiments will so fully reveal the general nature of the embodiments herein that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. Therefore, while the embodiments herein have been described in terms of preferred embodiments, those skilled in the art will recognize that the embodiments herein can be practised with modification within the spirit and scope of the appended claims.

[00104] While the foregoing describes various embodiments of the invention, other and further embodiments of the invention may be devised without departing from the basic scope thereof. The invention is not limited to the described embodiments, versions or examples, which are included to enable a person having ordinary skill in the art to make and use the

invention when combined with information and knowledge available to the person having ordinary skill in the art.

ADVANTAGES OF THE PRESENT DISCLOSURE

[00105] Some of the objects of the present disclosure, which at least one embodiment herein satisfies are as listed herein below.

[00106] The present disclosure provides for a system that can assess freshly extracted biopsy tissue during surgery.

[00107] The present disclosure provides for a system that facilitates elimination of the need for any sample preparation steps e.g., sectioning or staining.

[00108] The present disclosure provides for a system that makes the diagnostic process faster.

[00109] The present disclosure provides for a system that facilitates real-time detection of cancerous tissue that can be scaled-up to include other parameters such as age, sex, body mass index, smoking status, menstrual status etc to improve the prediction accuracy of the system.

[00110] The present disclosure provides for a system that permits the delineation of a normal and malignant tissue without the need for a paired adjacent confirmed normal tissue through the use of modelling based on scaling laws and multiple logistic regression.

We Claim:

1. A system for determining cancerous tissues, said system comprising:

a platform comprising:

a plurality of microsensors, wherein each microsensor is operatively coupled to an indenter configured to probe a tissue in a combination of linear and angular directions;

a sample holder to hold the tissue, said sample holder coupled to a rotational mechanism;

a control unit operatively coupled to the plurality of microsensors and the rotational mechanism, said control unit comprising a processor, wherein the processor executes a set of executable instructions that are stored in a memory, upon execution of which, the processor causes the system to:

receive from the plurality of microsensors, a first set of signals corresponding to a plurality of parameters associated with a plurality of properties of the tissue;

extract from the received first set of signals, a first set of attributes pertaining to parameters associated a plurality of properties of the tissue;

compare the extracted first set of attributes with a predefined set of parameters associated with the properties of a normal tissue;

based on the comparison, determine whether the tissue is cancerous or normal and if cancerous, identify margin of malignancy in the tissue.

2. The system as claimed in claim 1, wherein the control unit is coupled to the rotational mechanism, wherein the control unit rotates the sample holder in a rotational direction.

3. The system as claimed in claim 1, wherein the plurality of microsensors detects surface and bulk measurements of the physical properties of the tissue at room and elevated temperatures to capture the effects of anisotropy in the tissue.

4. The system as claimed in claim 1, wherein determination of the properties of the tissue is any or a combination of a stored tissue and freshly extracted biopsy tissue during surgery.

5. The system as claimed in claim 1, wherein the plurality of microsensors is housed in a sensor unit, said sensor unit is detachable from the platform, said sensor unit is communicatively coupled to the control unit through any or a combination of wired and wireless network.

6. The system as claimed in claim 1, wherein the control unit is communicatively coupled to a computing device associated with a user.

7. The system as claimed in claim 1, wherein the control unit is configured to self train based on a machine learning module coupled to a logistic regression module.

8. The system as claimed in claim 1, wherein the control unit is further configured to model and fit the collected data on-the-fly using scaling laws to assess the extent of disorder in the tissue and apply the model parameters for delineation.

9. The system as claimed in claim 1, wherein each microsensor comprises at least one microheater at the centre surrounded by one or more resistance temperature devices (RTD), one or more interdigitated electrodes, at least an embedded piezoelectric or piezoresistive layer formed over a diaphragm to simultaneously measure electrical, thermal, and mechanical properties of the tissue.

10. A method for fabricating a microsensor, said method comprising:

depositing a dielectric layer of a predefined thickness on top of a substrate;

forming a photoresist on the dielectric layer and patterning of the dielectric layer;

patterning with one or more predefined metal elements and the photoresist, wherein the patterning of the dielectric layer with the one or more predefined metal elements and the photoresist forms a patterned structure;

performing a first wet etching of the patterned substrate;

patterning a plurality of trenches for thermal isolation through photolithographic exposure;

performing a second dry etching of the substrate after a second patterning of the plurality of trenches; and,

performing ion etching on the patterned substrate to create through-holes on the plurality of trenches for thermal isolation from microheater.

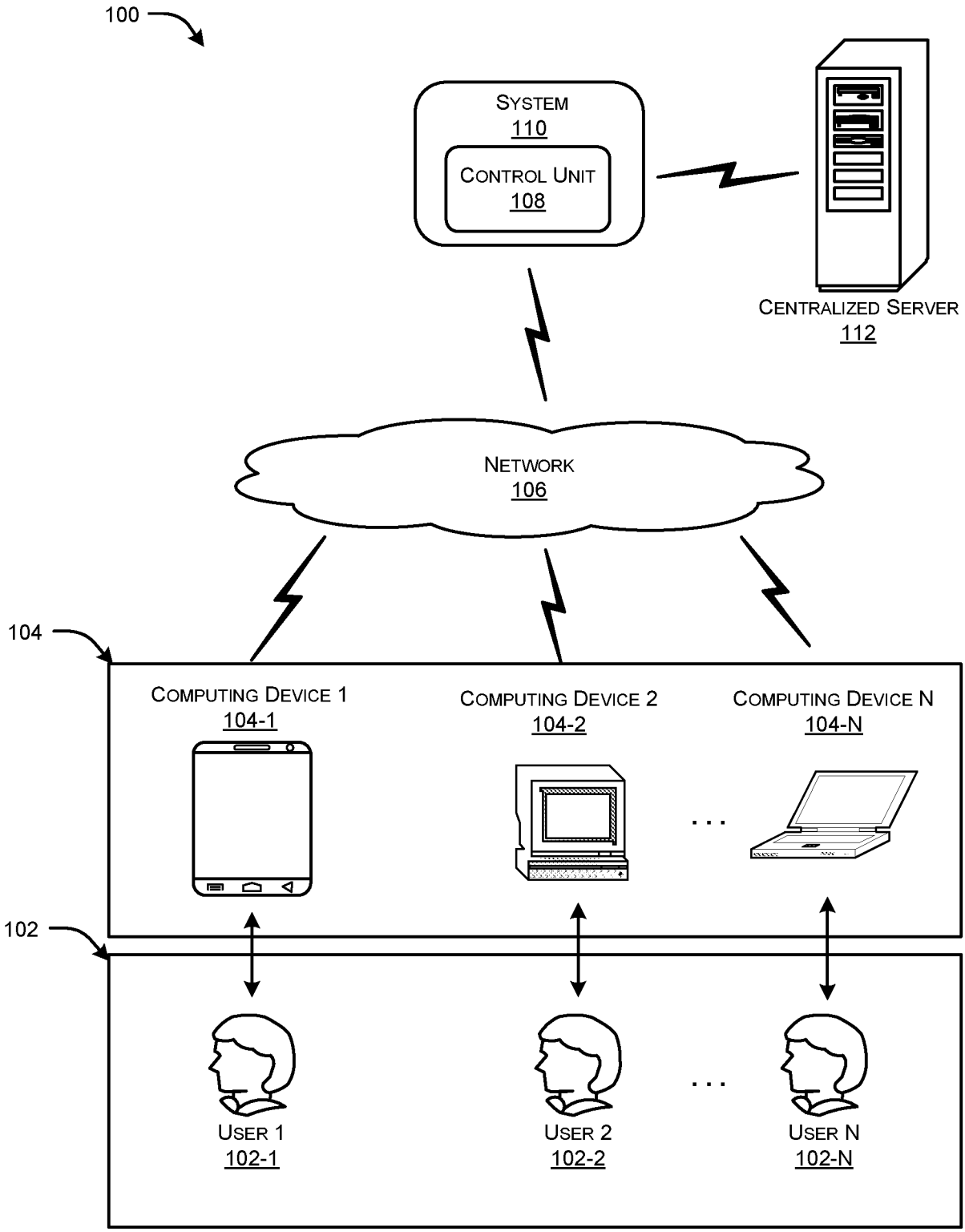
100
SYSTEM
110
CONTROL UNIT
108
CENTRALIZED SERVER
112
NETWORK
106
104
COMPUTING DEVICE 1
104-1
COMPUTING DEVICE 2
104-2
COMPUTING DEVICE N
104-N
102
USER 1
102-1
USER 2
102-2
USER N
102-N

FIG. 1A

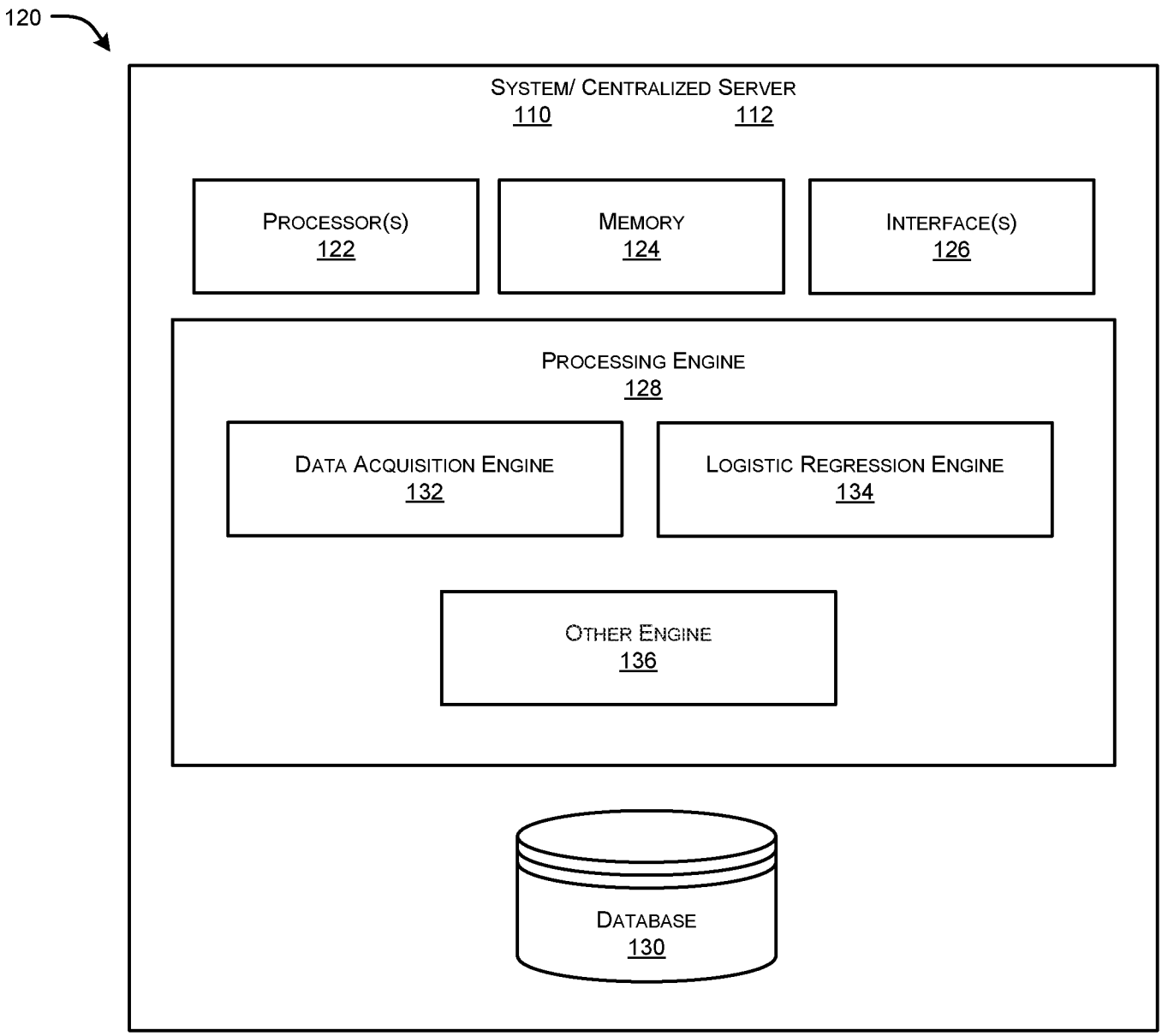
120
SYSTEM/ CENTRALIZED SERVER
110
112
PROCESSOR(S)
122
MEMORY
124
INTERFACE(S)
126
PROCESSING ENGINE
128
DATA ACQUISITION ENGINE
132
LOGISTIC REGRESSION ENGINE
134
OTHER ENGINE
136
DATABASE
130

FIG. 1B

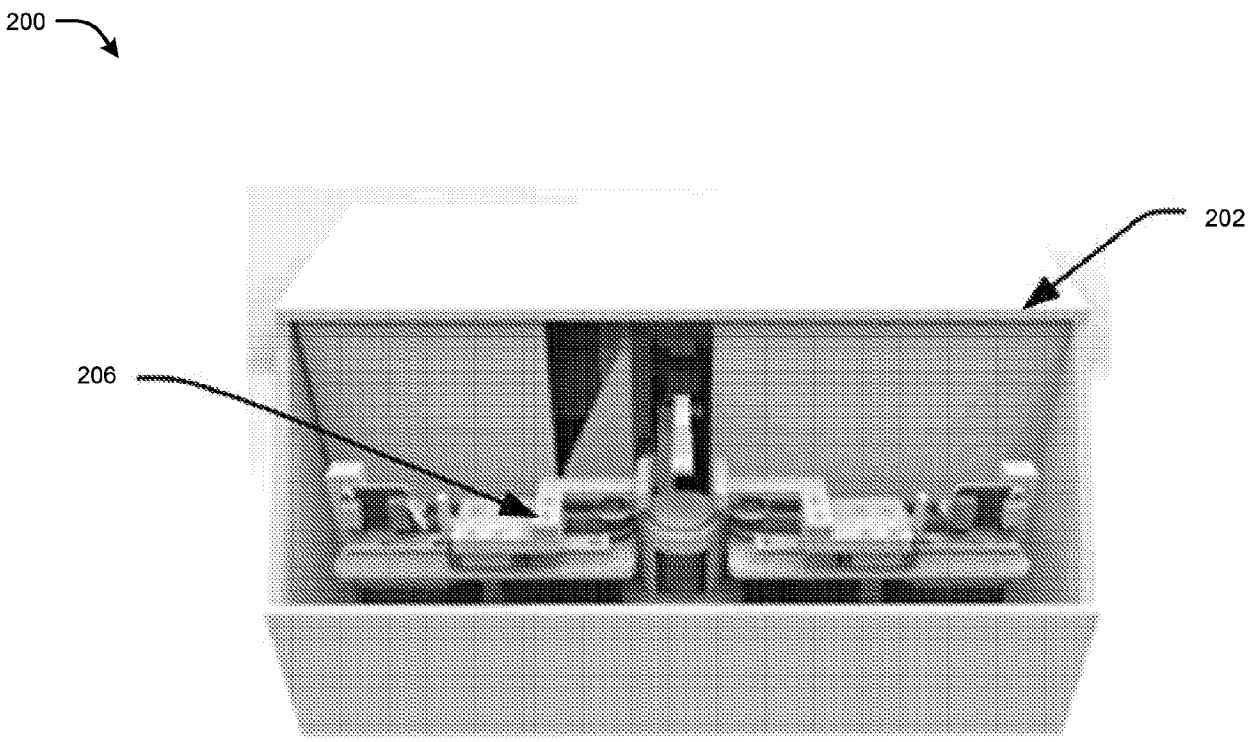

FIG. 2A

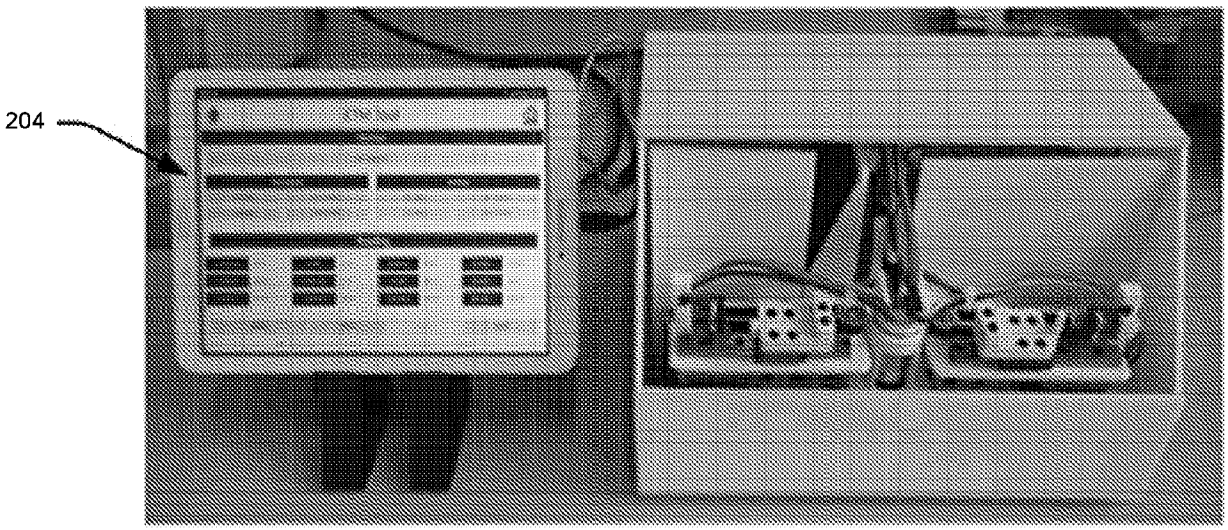

FIG. 2B

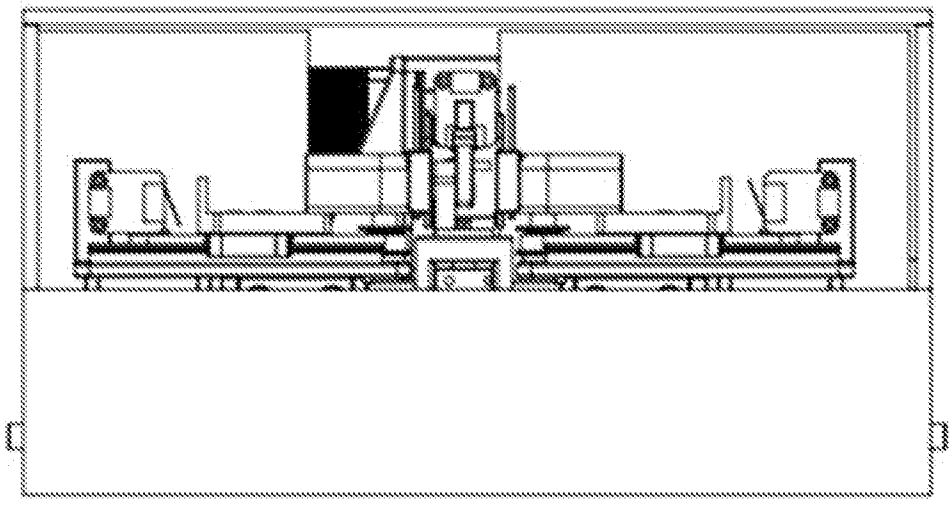

FIG. 2C

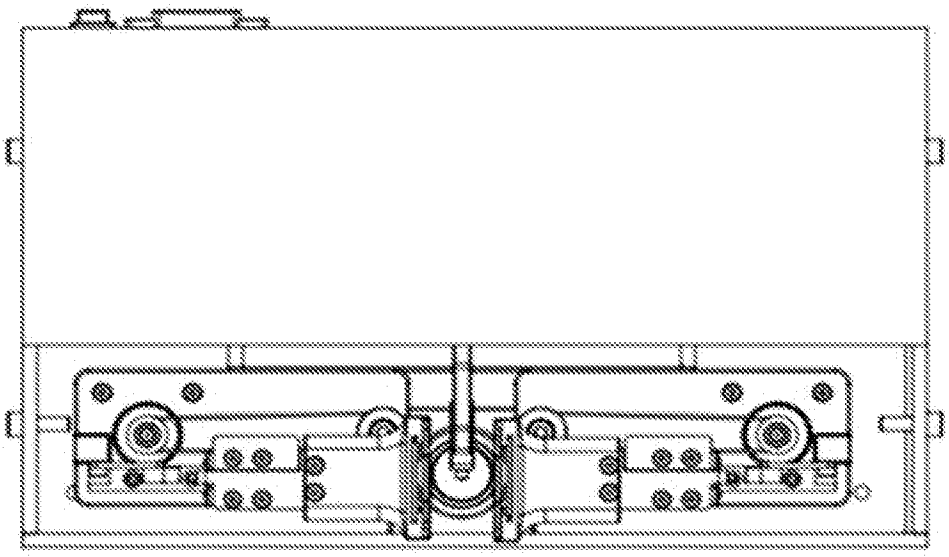

FIG. 2D

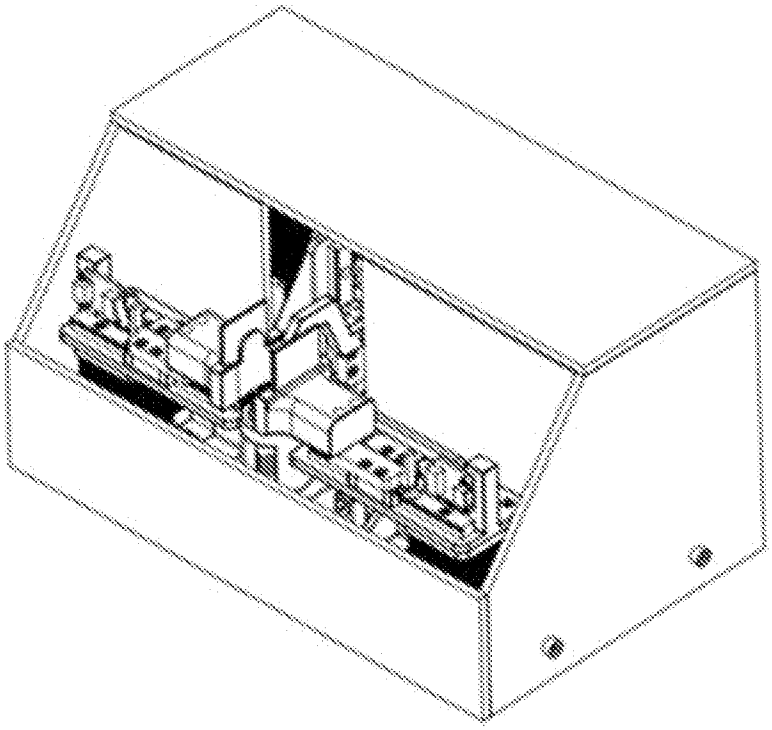

FIG. 2E

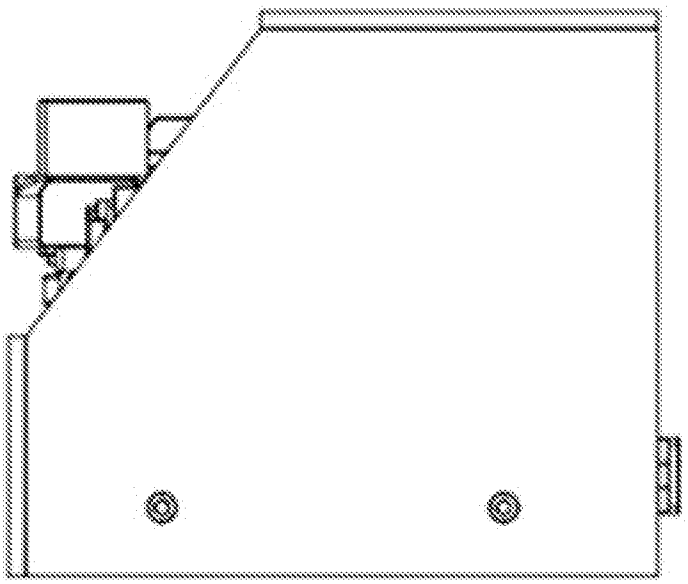

FIG. 2F

300

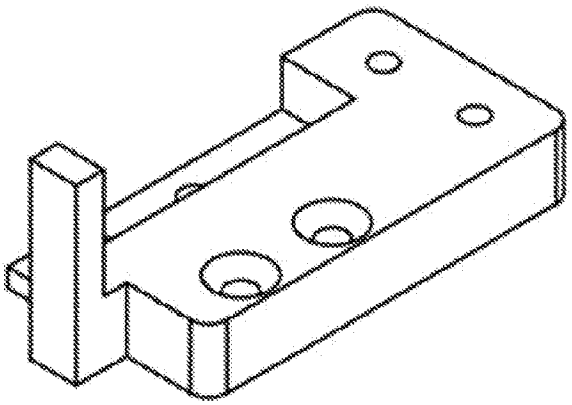

FIG. 3A

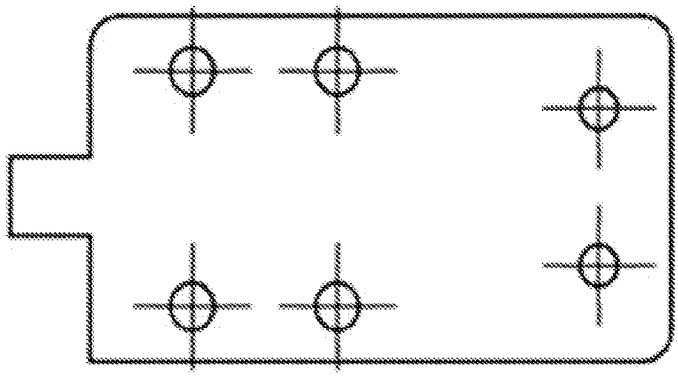

FIG. 3B

FIG. 3C

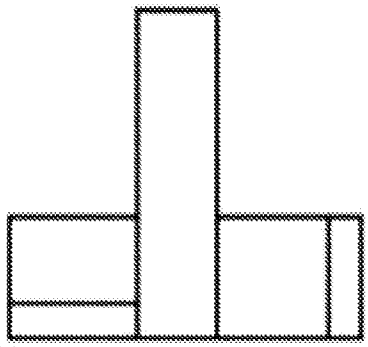

FIG. 3D

400

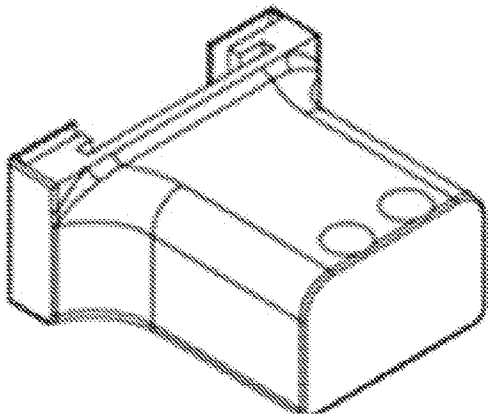

FIG. 4A

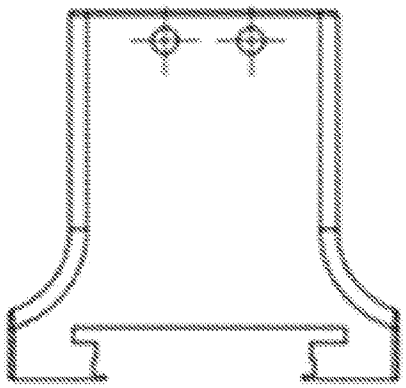

FIG. 4B

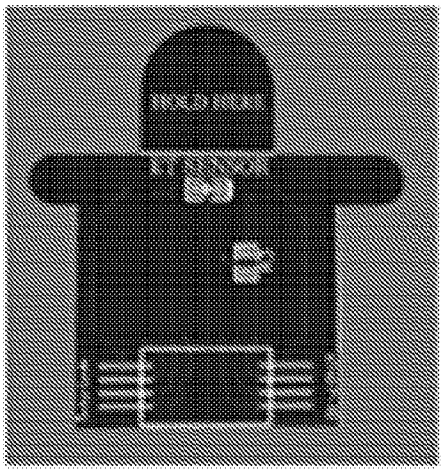

FIG. 4C

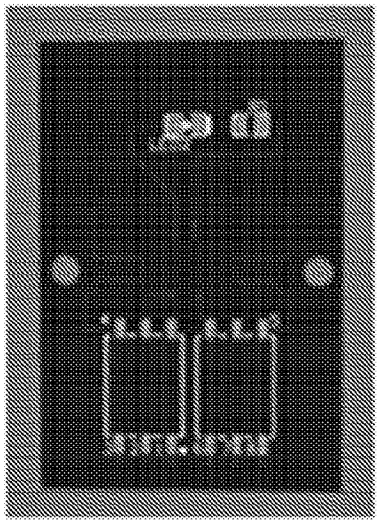

FIG. 4D

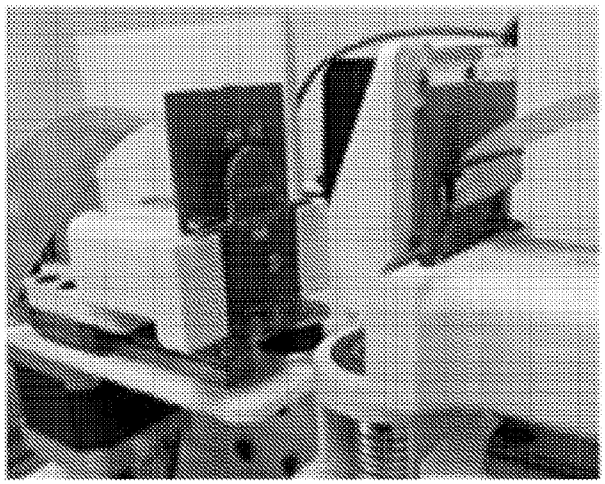

FIG. 4E

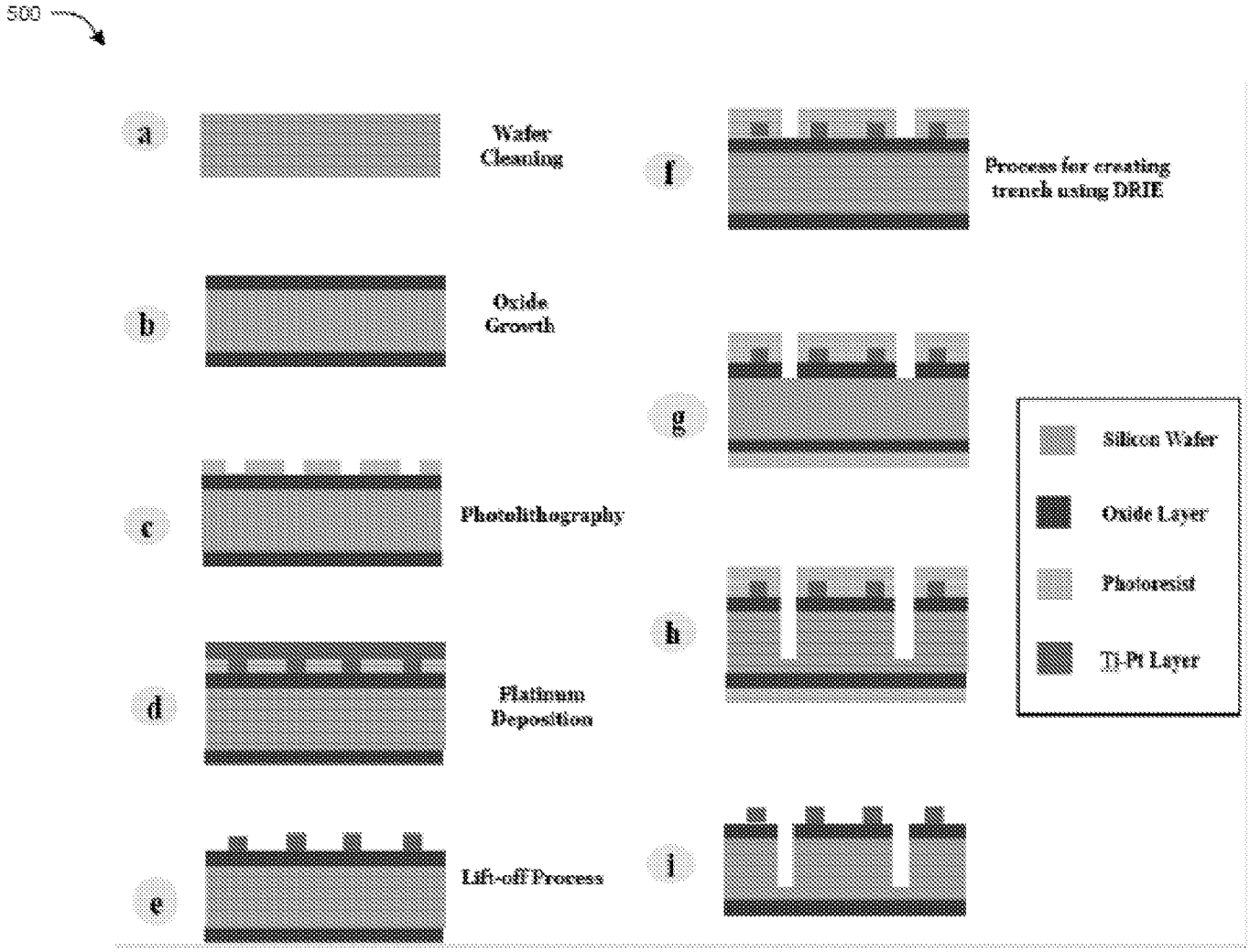
500
a
Wafer Cleaning
b
Oxide Growth
c
Photolithography
d
Platinum Deposition
e
Lift-off Process
f
Process for creating trench using DRIE
g
h
i
Silicon Wafer
Oxide Layer
Photoresist
Ti-Pt Layer

FIG. 5A

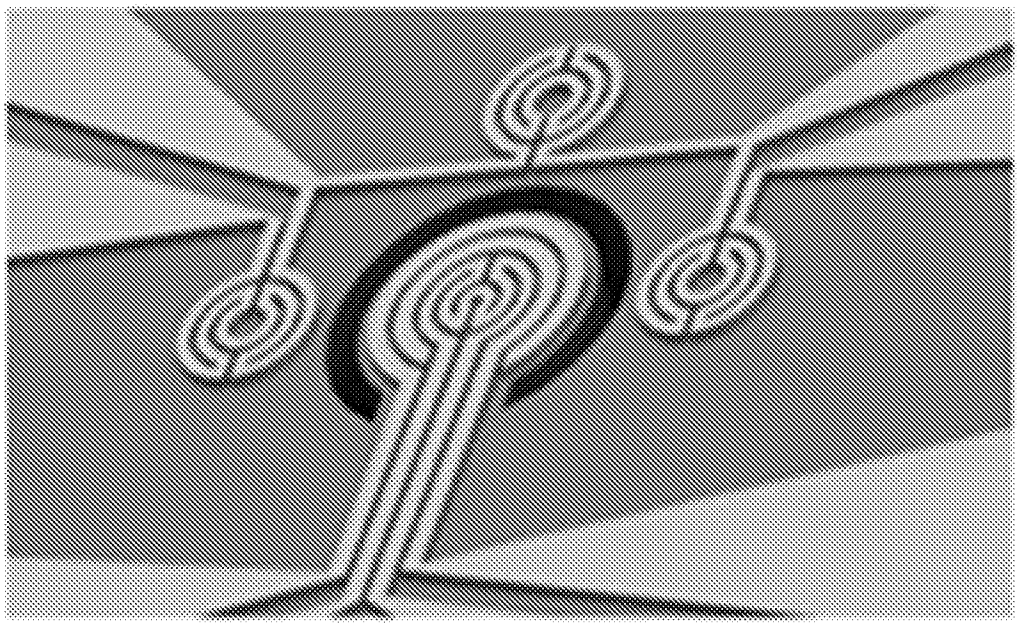

FIG. 5B

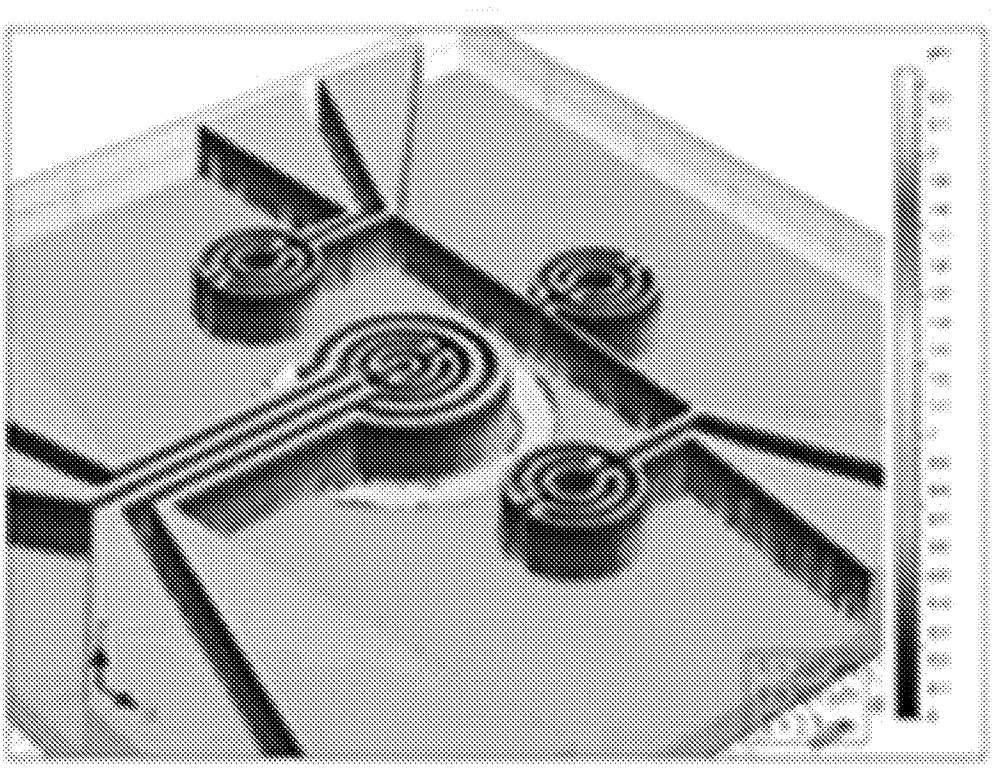

FIG. 5C

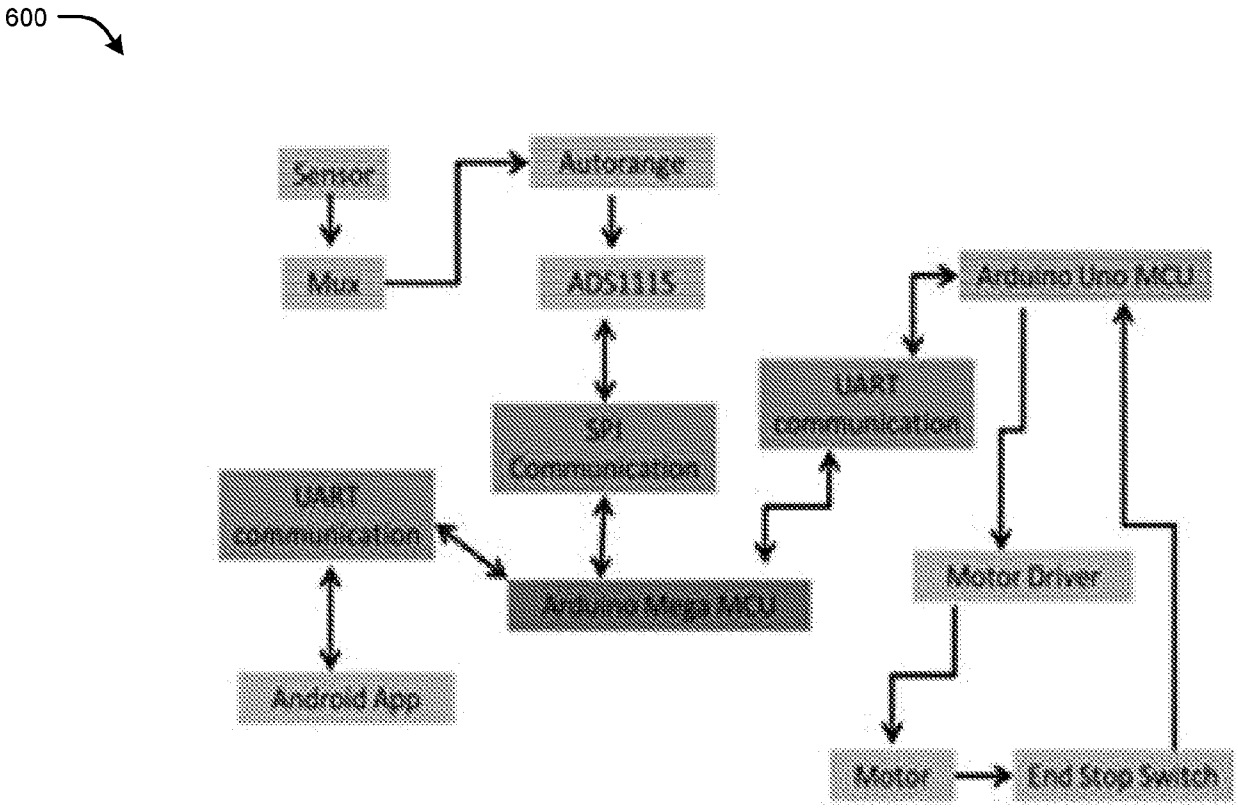
600
Sensor
Autorange
Mux
AD51115
Arduino Uno MCU
UART communication
SPI Communication
UART communication
Arduino Mega MCU
Motor Driver
Android App
Motor
End Stop Switch

FIG. 6A

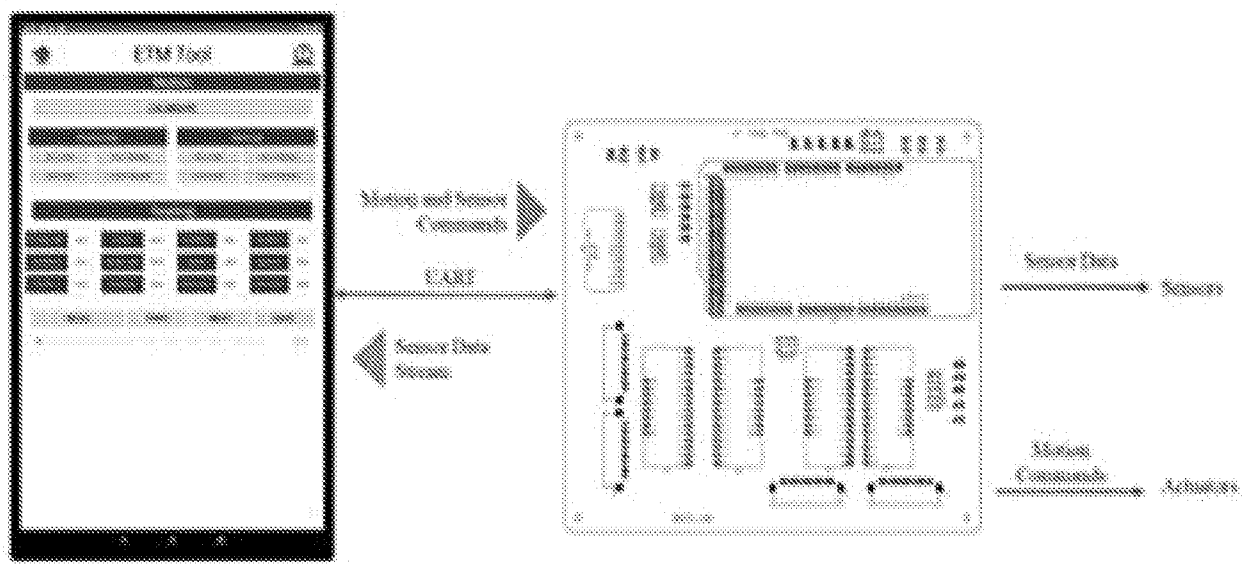

FIG. 6B

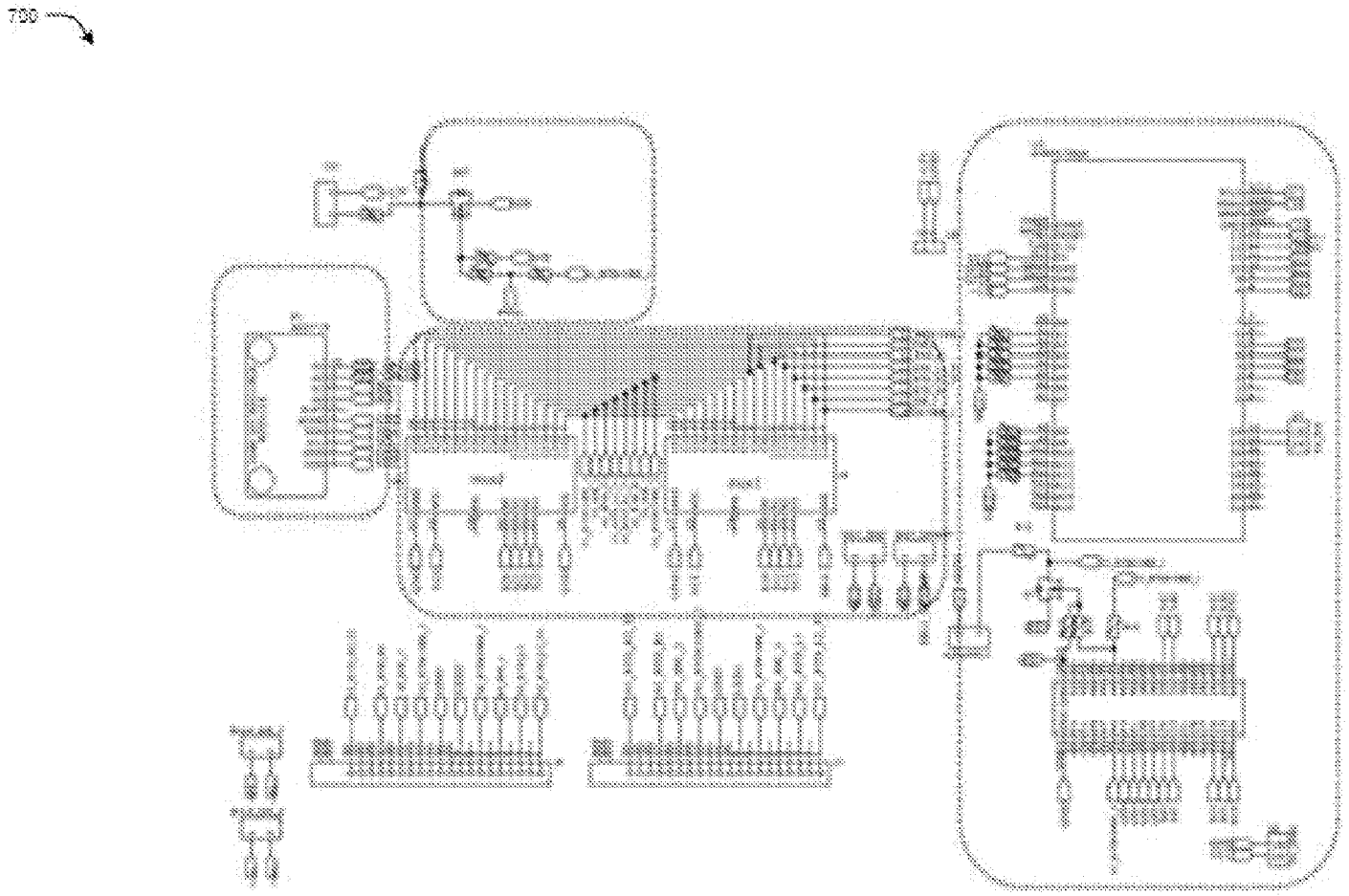

FIG. 7

800

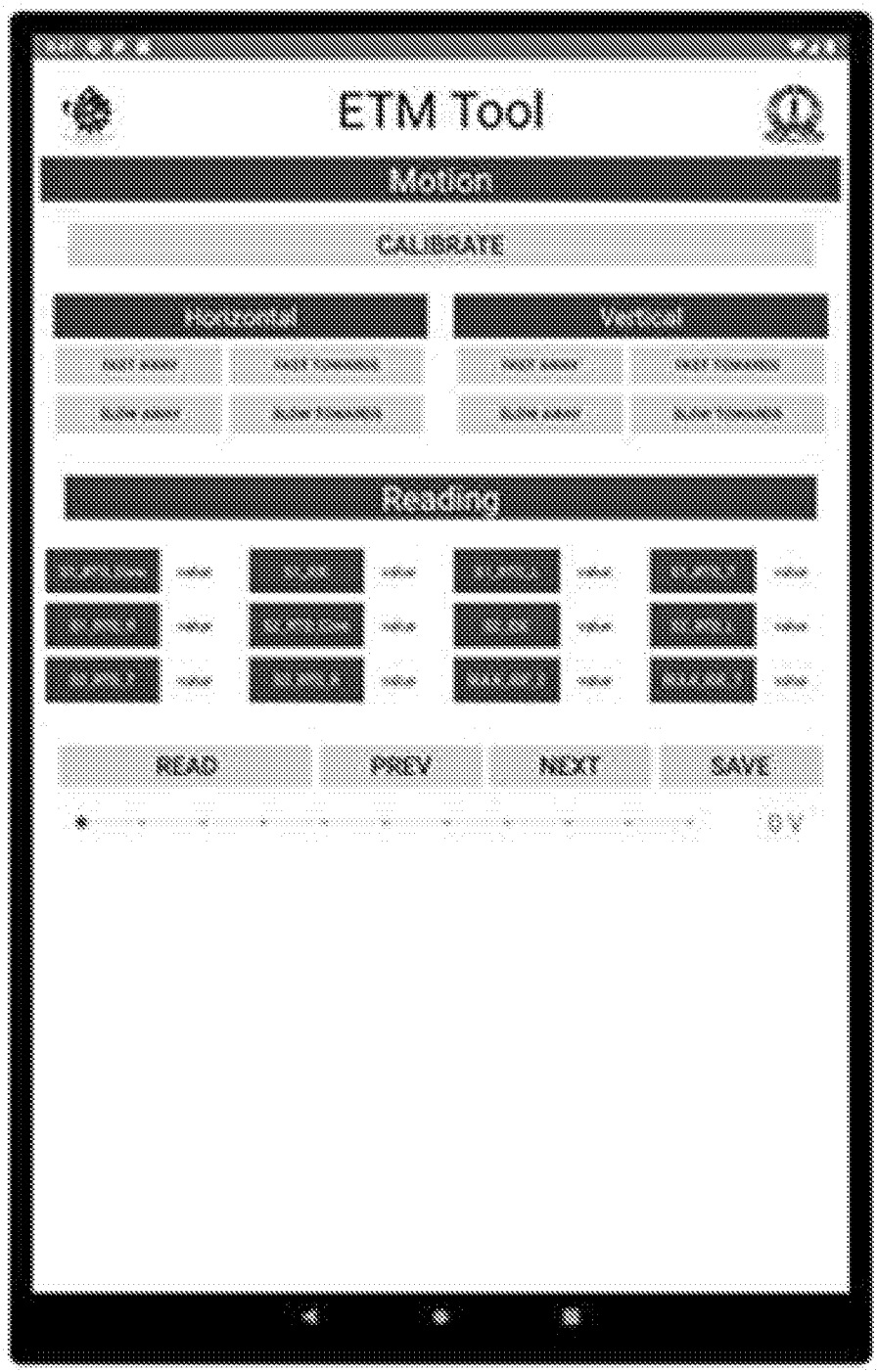

FIG. 8

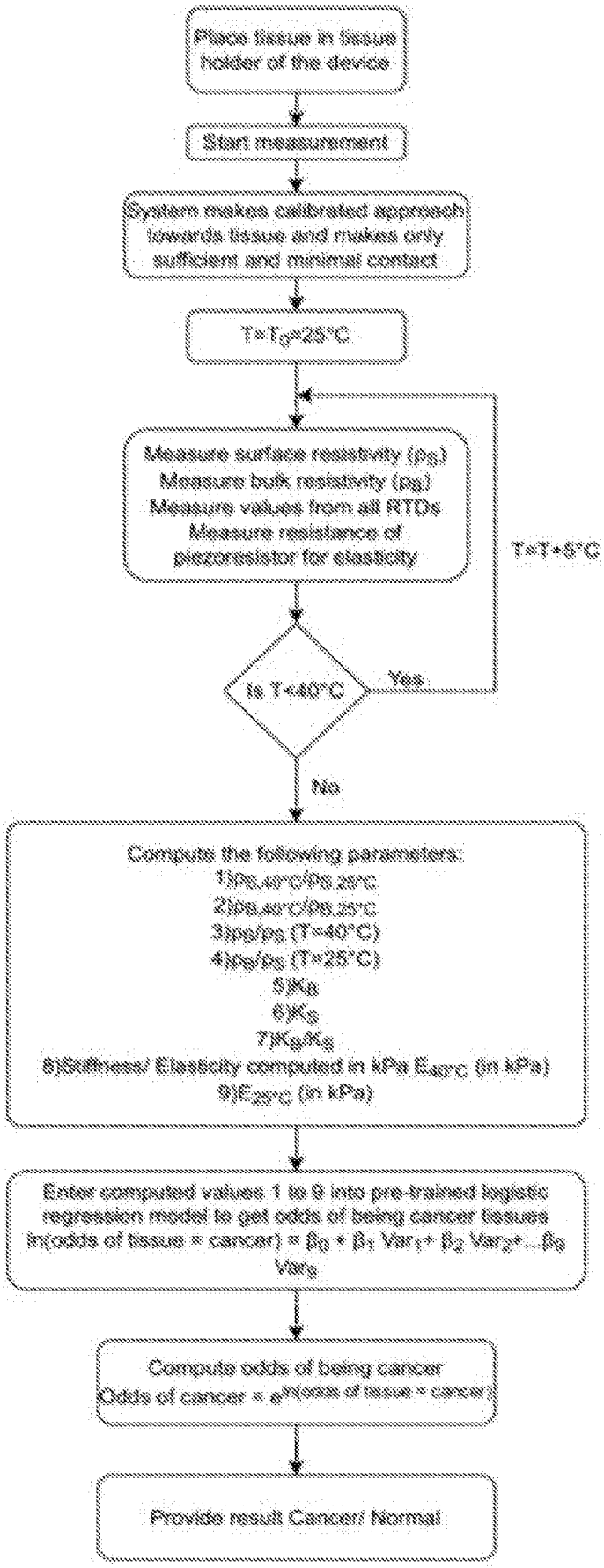
Place tissue in tissue holder of the device
Start measurement
System makes calibrated approach towards tissue and makes only sufficient and minimal contact
T=T0=25°C
Measure surface resistivity (ρS)
Measure bulk resistivity (ρB)
Measure values from all RTDs
Measure resistance of piezoresistor for elasticity
T=T+5°C
Is T<40°C
Yes
No
Compute the following parameters:
1)ρS,40°C/ρS,25°C
2)ρB,40°C/ρB,25°C
3)ρS/ρB (T=40°C)
4)ρS/ρB (T=25°C)
5)KS
6)KB
7)KS/KB
8)Stiffness/ Elasticity computed in kPa E40°C (in kPa)
9)E25°C (in kPa)
Enter computed values 1 to 9 into pre-trained logistic regression model to get odds of being cancer tissues
ln(odds of tissue = cancer) = β0 + β1 Var1+ β2 Var2+...β9 Var9
Compute odds of being cancer
Odds of cancer = e^(Odds of tissue = cancer)
Provide result Cancer/ Normal

FIG. 9

1000

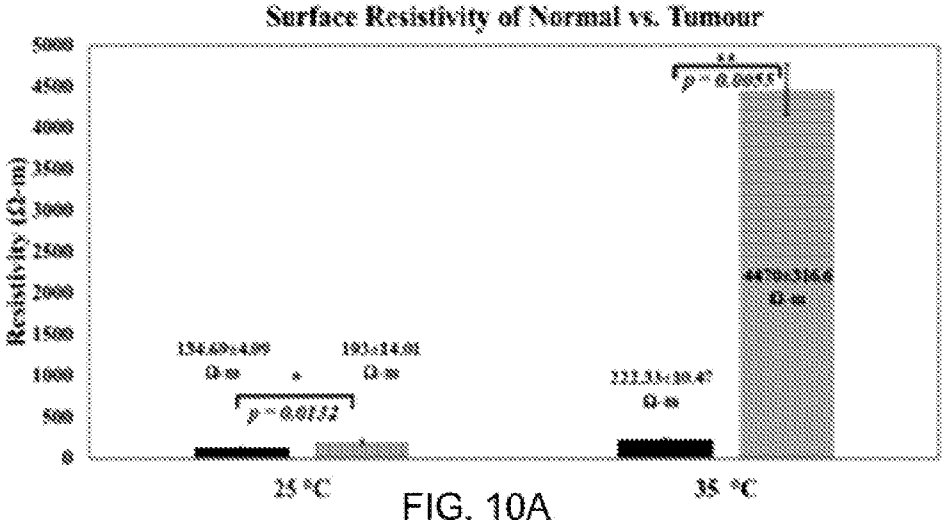

FIG. 10A

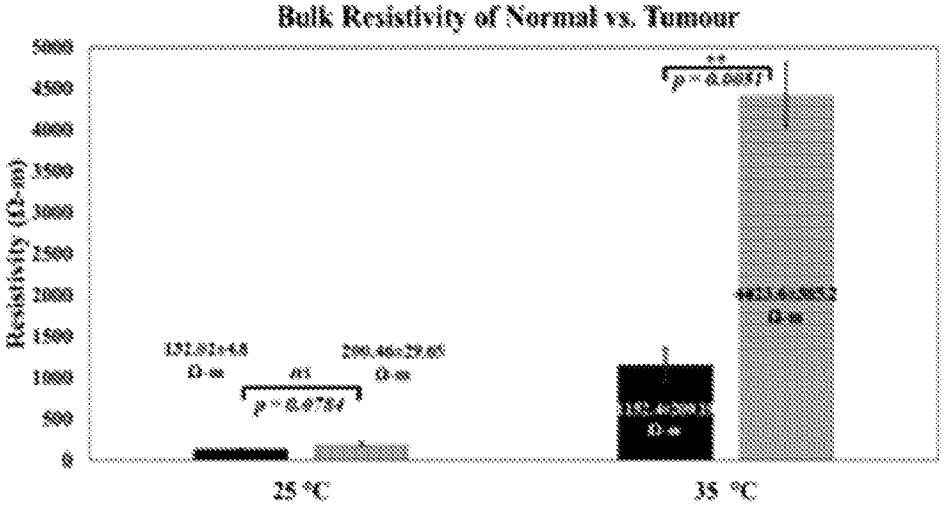

FIG. 10B

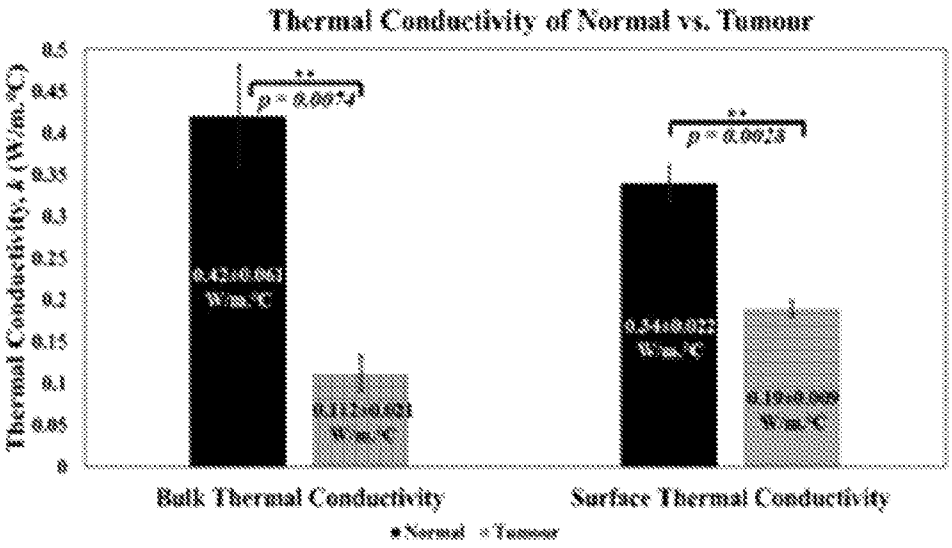

FIG. 10C

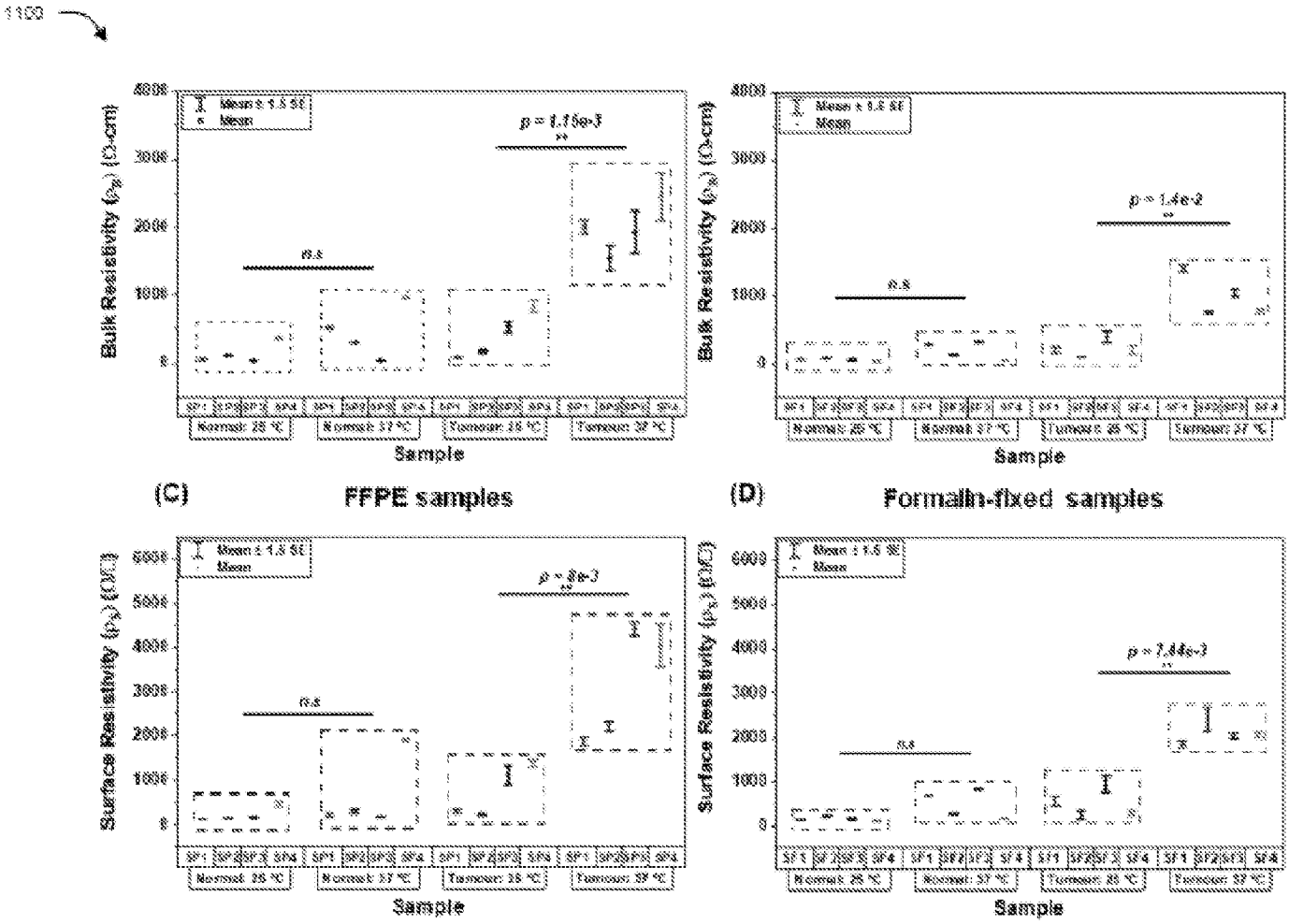
1100
Bulk Resistivity (ρ_B) (Ω-cm)
Surface Resistivity (ρ_S) (Ω/□)
Sample
(C) FFPE samples
(D) Formalin-fixed samples

FIG. 11

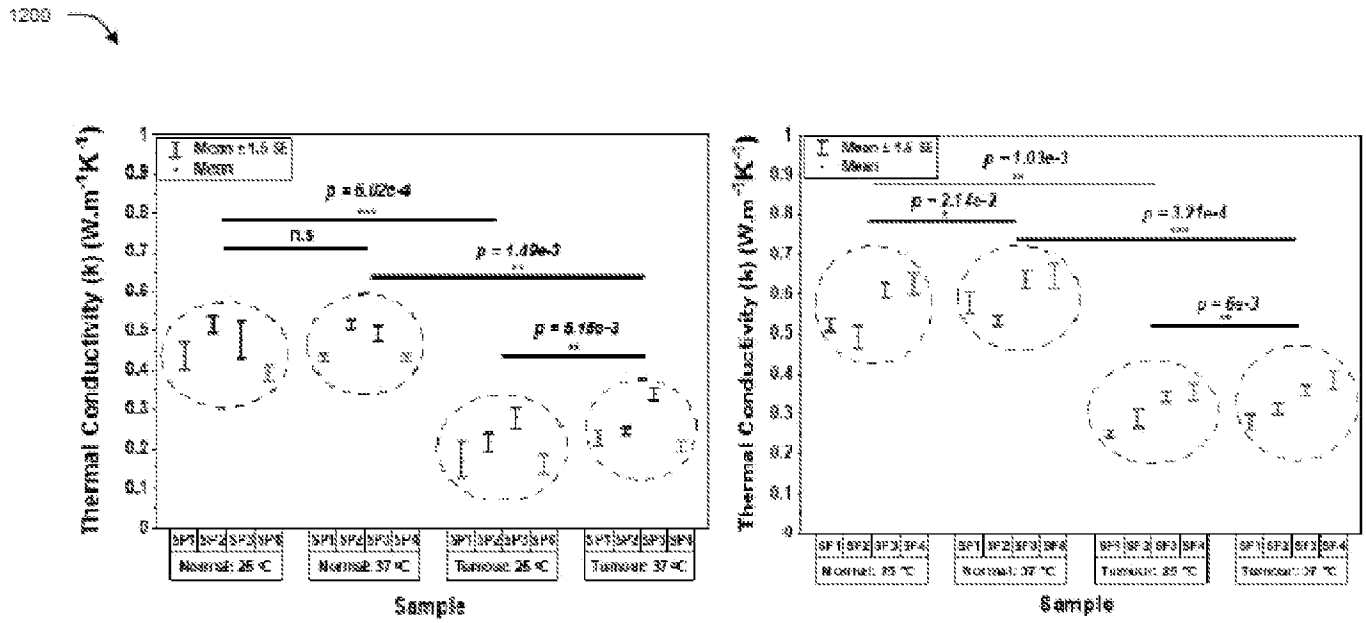
1200
Thermal Conductivity (k) (W.m⁻¹K⁻¹)
Sample
Normal: 25 °C
Normal: 37 °C
Tumour: 25 °C
Tumour: 37 °C

FIG. 12

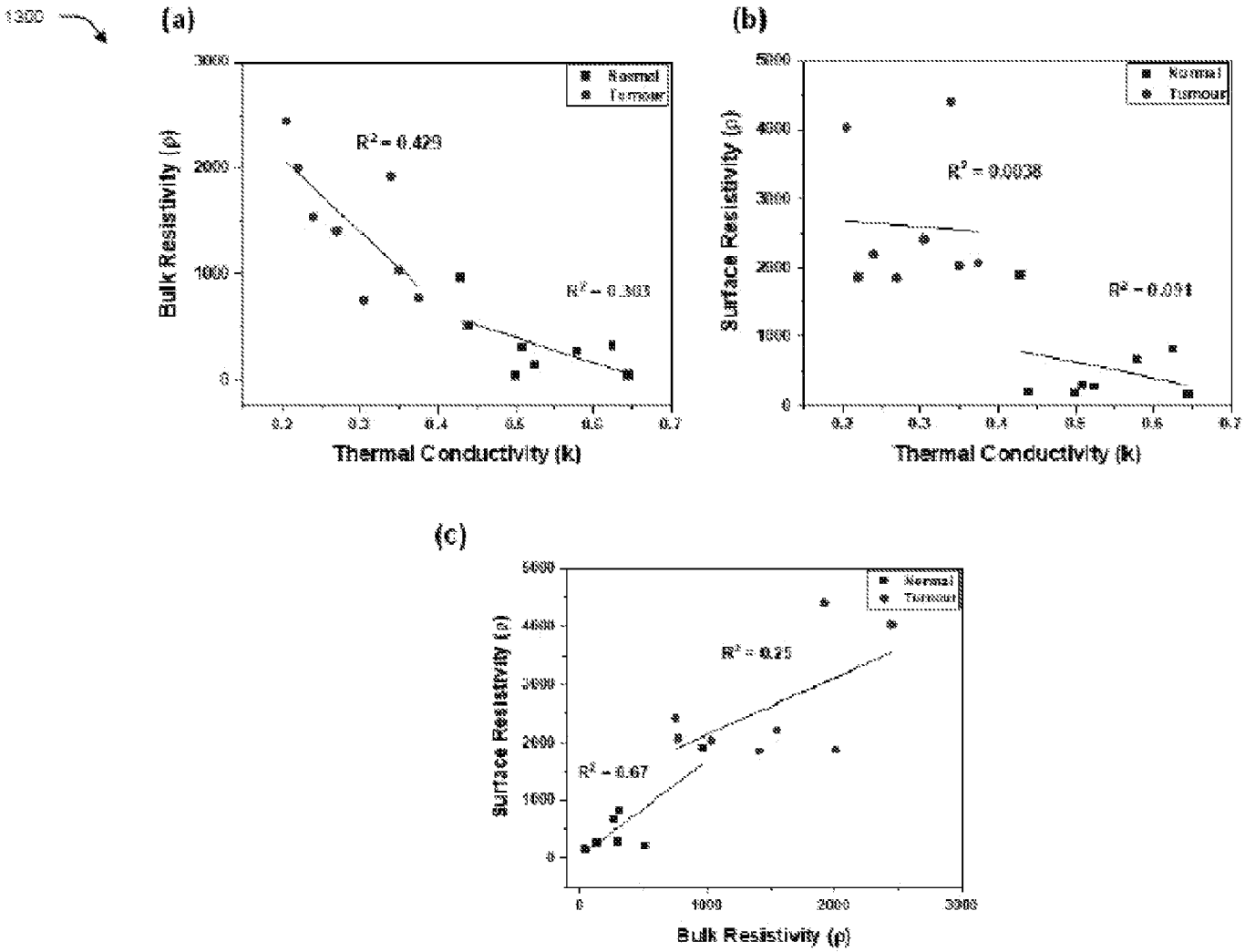
1300
(a)
Bulk Resistivity (ρ)
Thermal Conductivity (k)
Normal
Tumour
R² = 0.429
R² = 0.383
(b)
Surface Resistivity (ρ)
Thermal Conductivity (k)
Normal
Tumour
R² = 0.0038
R² = 0.091
(c)
Surface Resistivity (ρ)
Bulk Resistivity (ρ)
Normal
Tumour
R² = 0.25
R² = 0.67

FIG. 13

1400

Table I

MODEL FIT PARAMETERS AND CRITICAL TEMPERATURE VALUES

SAMPLE	GEM MODEL									
	ADJACENT NORMAL					TUMOR				
	T_C(°C)	A	s_l^*	s_u^*	R-square value	T_C(°C)	A	s_l^*	s_u^*	R-square value
S1	46.6	1.6	3.01	9.1e-71	0.96	37.2	1.45e-3	0.5	9.1e-71	0.99
S2	38.5	3.6	0.49	9.1e-71	0.96	37.7	3.35e-3	0.47	9.1e-71	0.98
S3	37.6	2.1	0.83	9.1e-71	0.96	41.7	2.97e-4	0.75	9.1e-71	0.96
S4	56.8	8.0	0.23	9.1e-71	0.93	37.2	8.52e-3	0.28	9.1e-71	0.96

Table II

MODEL FIT PARAMETERS AND CUTOFF FREQUENCY VALUES

SAMPLE	SCALING LAW MODEL							
	ADJACENT NORMAL				TUMOR			
	B	x	f_c (Hz)	R-square value	B	x	f_c (Hz)	R-square value
S1	1	0.23	1005032	0.84	1	0.5	3100	0.81
S2	1	0.33	8510	0.98	1	0.49	7360	0.96
S3	1	0.23	829153	0.91	1	0.25	577890	0.89
S4	1	0.28	59000	0.98	1	0.37	13022	0.99

FIG. 14

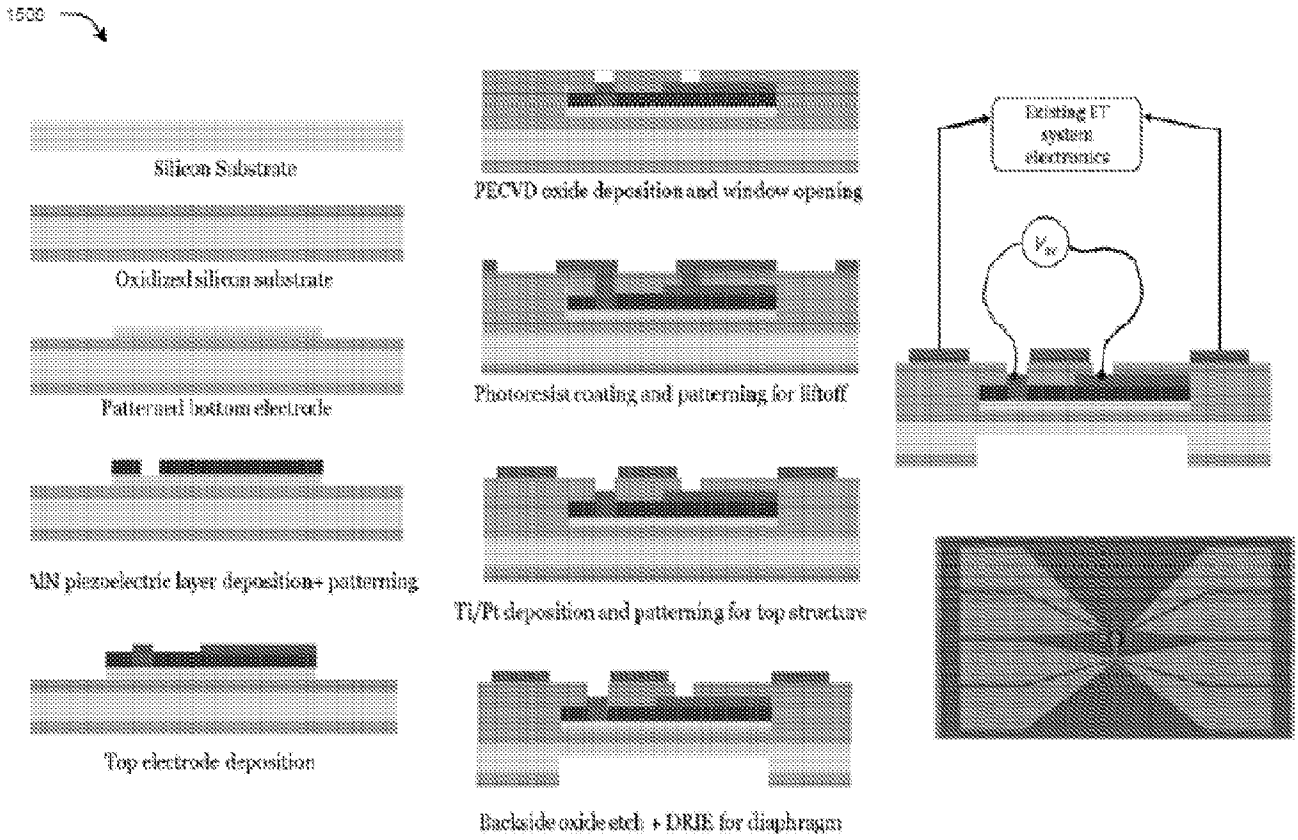
1500
Silicon Substrate
Oxidized silicon substrate
Patterned bottom electrode
AlN piezoelectric layer deposition+ patterning
Top electrode deposition
PECVD oxide deposition and window opening
Photoresist coating and patterning for liftoff
Ti/Pt deposition and patterning for top structure
Backside oxide etch + DRIE for diaphragm
Existing ET system electronics
V_{ac}

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/055611

A. CLASSIFICATION OF SUBJECT MATTER
A61B5/00,A61B90/00,G16H10/40 Version=2021.01

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)

A61B, G16H

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

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

Databases: PatSeer, IPO Internal Database
Keywords: Sensor, Mems

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP2689254A2 (ANPAC BIO-MEDICAL SCIENCE CO., LTD.) 29 JANUARY 2014 (29-01-2014) (Paragraphs [0053]; [0239 - 0240] and claims (1-10; 18; 52-54))	1-10

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07-10-2021	07-10-2021
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Sudhir Kumar Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/055611

Citation	Pub.Date	Family	Pub.Date
EP 2689254 A2	29-01-2014	CA 2831223 A1	27-09-2012
		US 2014017670 A1	16-01-2014