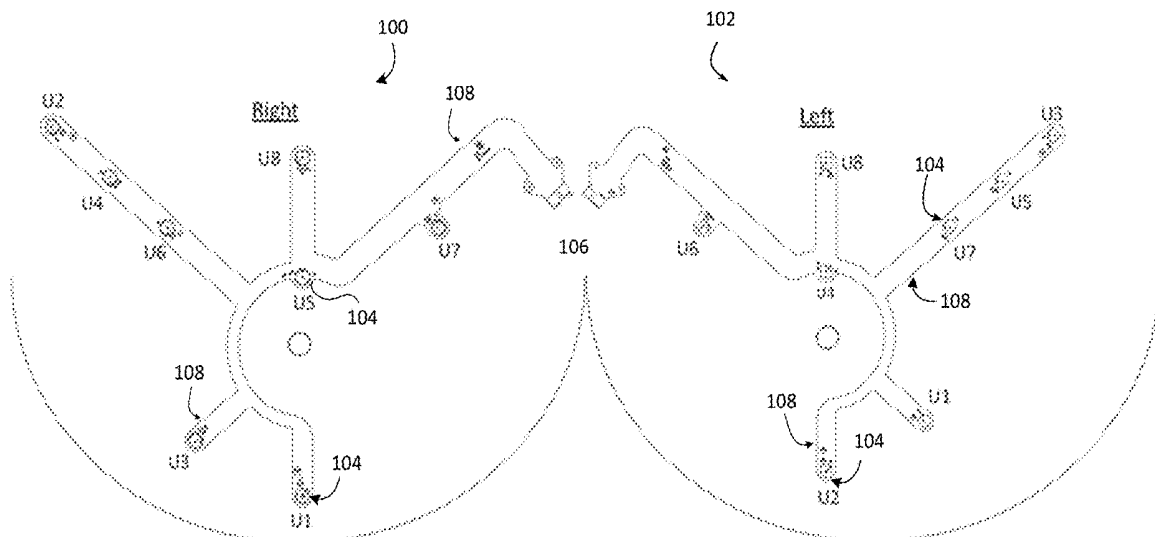




US 20200037949A1

(19) **United States**(12) **Patent Application Publication**
Subbhuraam(10) **Pub. No.: US 2020/0037949 A1**(43) **Pub. Date: Feb. 6, 2020**(54) **SYSTEMS AND METHODS FOR ANALYZING
SKIN SURFACE TEMPERATURE RHYTHMS
TO MONITOR HEALTH CONDITIONS***G16H 50/50* (2006.01)*G06N 3/08* (2006.01)(52) **U.S. CL.**CPC *A61B 5/4312* (2013.01); *A61B 5/6823*
(2013.01); *A61B 5/015* (2013.01); *A61B*
5/7264 (2013.01); *A61B 5/7275* (2013.01);
G06N 3/08 (2013.01); *A61B 5/002* (2013.01);
A61B 5/4857 (2013.01); *G16H 50/20*
(2018.01); *G16H 50/50* (2018.01); *A61B*
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TX (US)**(21) Appl. No.: **16/530,894**(22) Filed: **Aug. 2, 2019****Related U.S. Application Data**(60) Provisional application No. 62/714,033, filed on Aug.
2, 2018.**Publication Classification**(51) **Int. Cl.***A61B 5/00* (2006.01)*A61B 5/01* (2006.01)*G16H 50/20* (2006.01)(57) **ABSTRACT**

Systems, methods, and devices for utilizing predictive analytic analysis of circadian rhythm fluctuations to monitor breast wellness are disclosed. A wearable device may comprise a plurality of temperature sensors placed at predetermined positions on a subject. A set of temperature data collected from the wearable device over a period of time may be utilized to extract a plurality of non-linear features indicative of variability in temperature data. Classifier systems, including predictive models filter the non-linear features, and the filtered features may be used in a predictive model to determine a breast tissue classification.



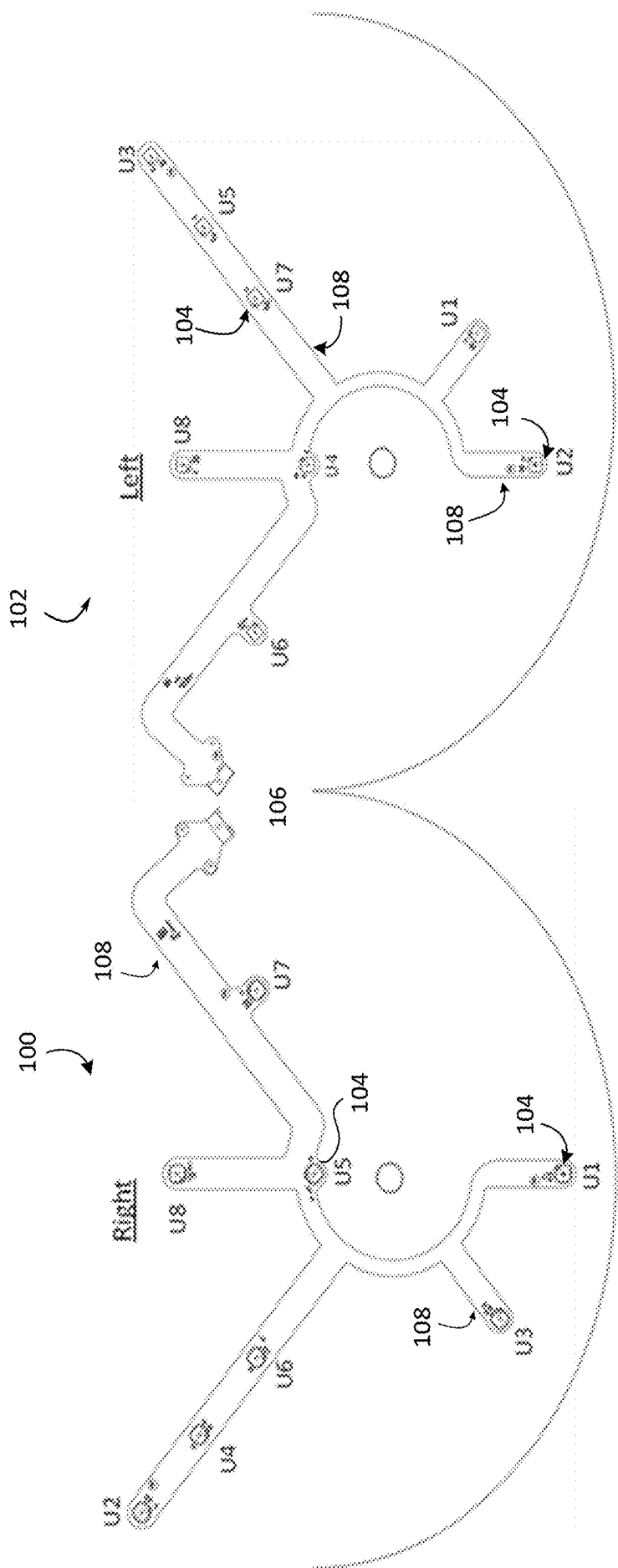


FIG. 1

Array Size 3

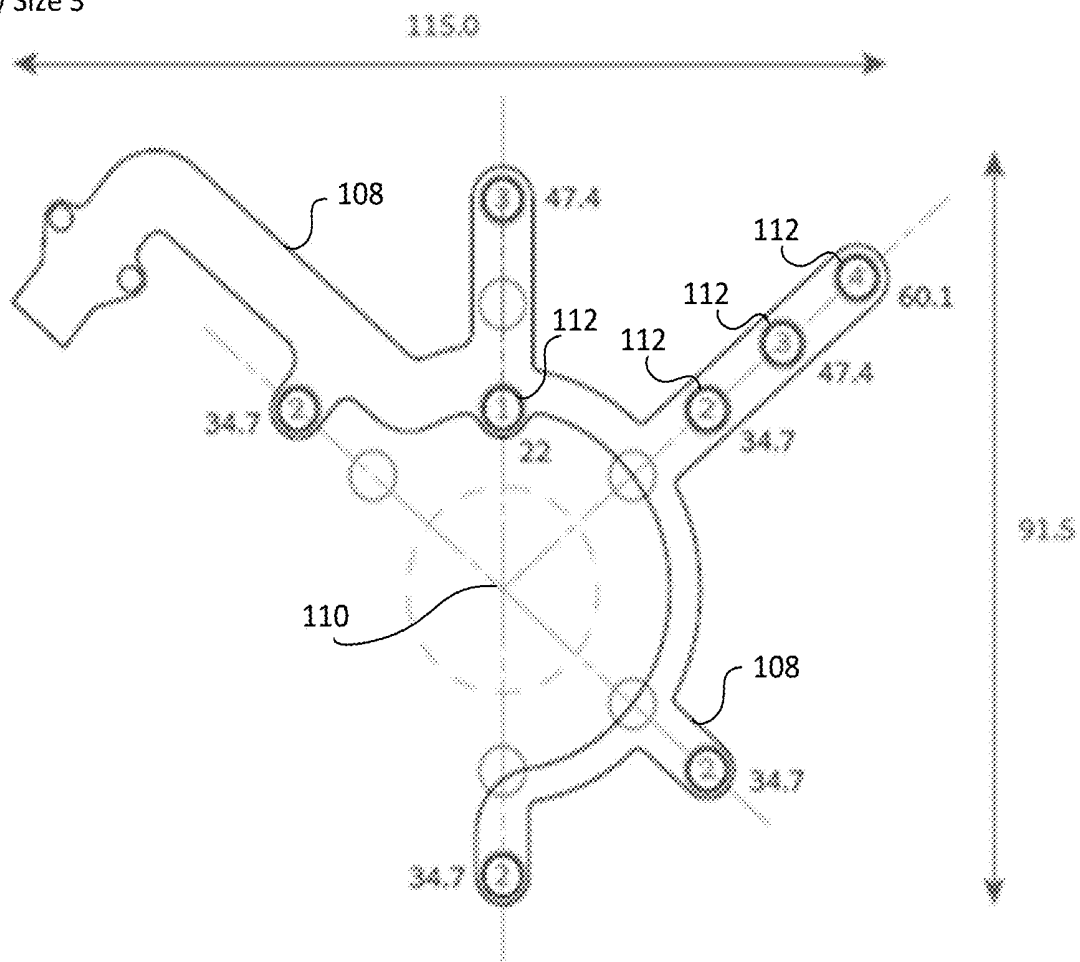


FIG. 2A

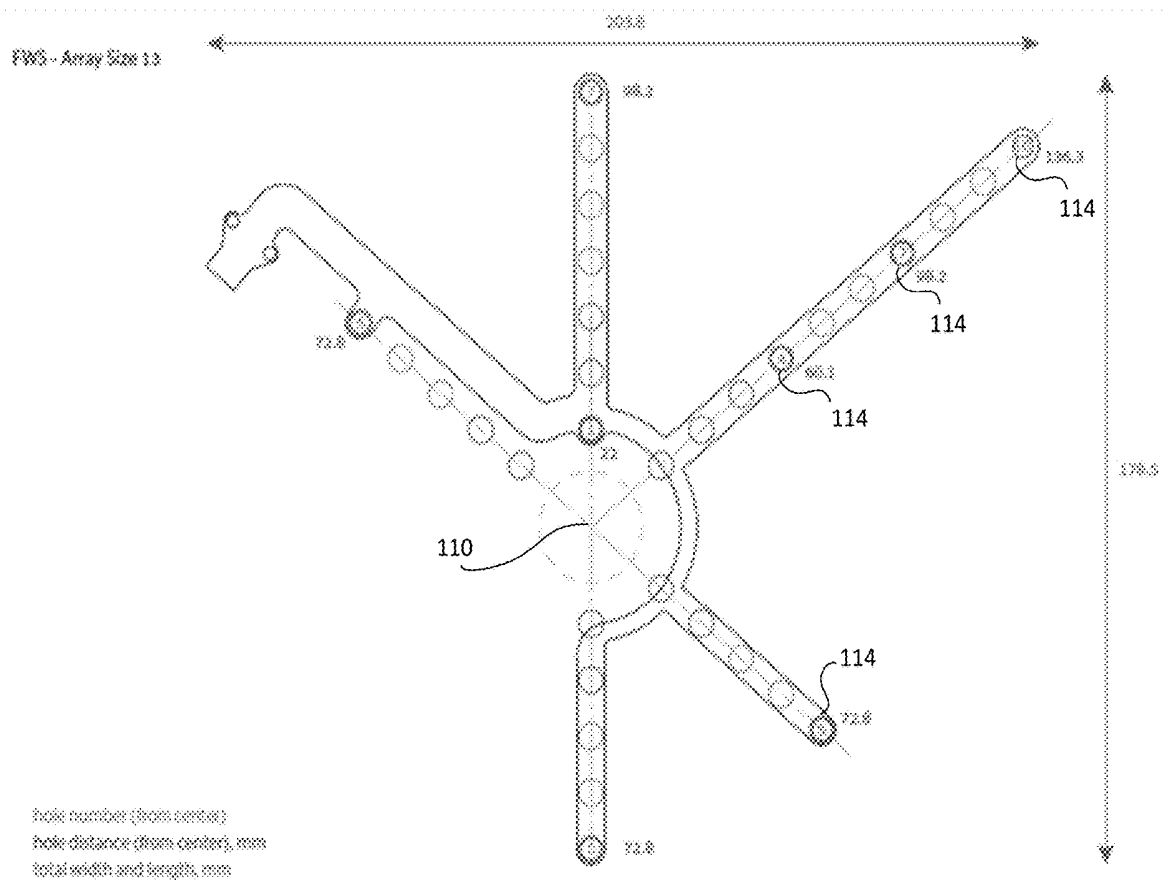
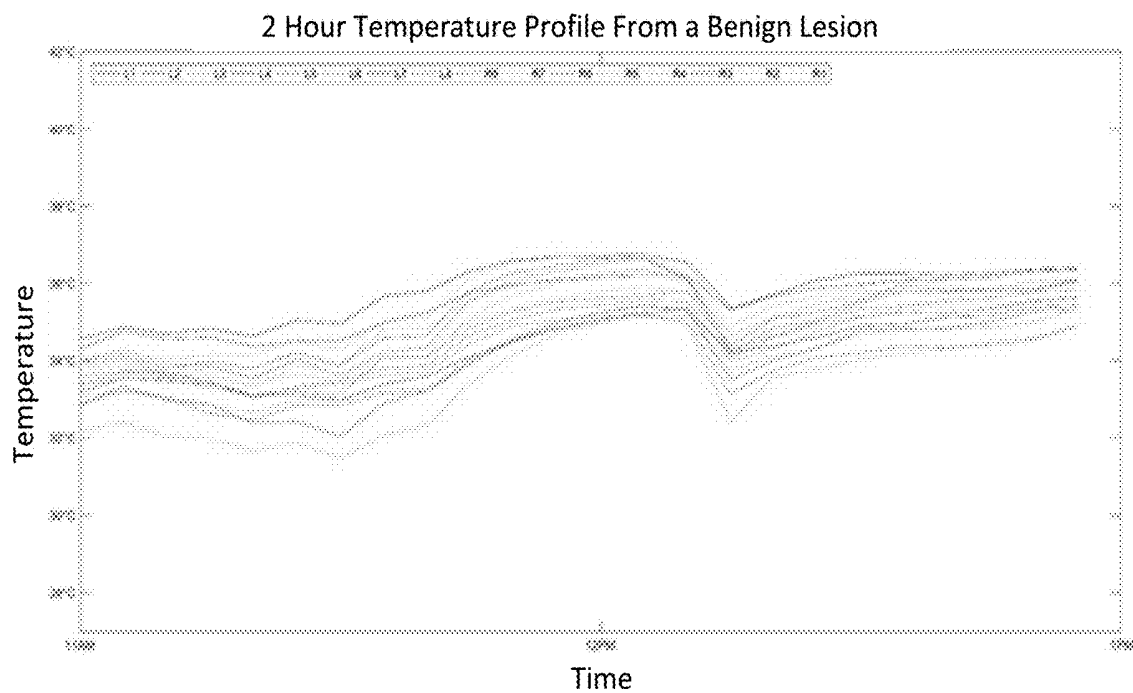
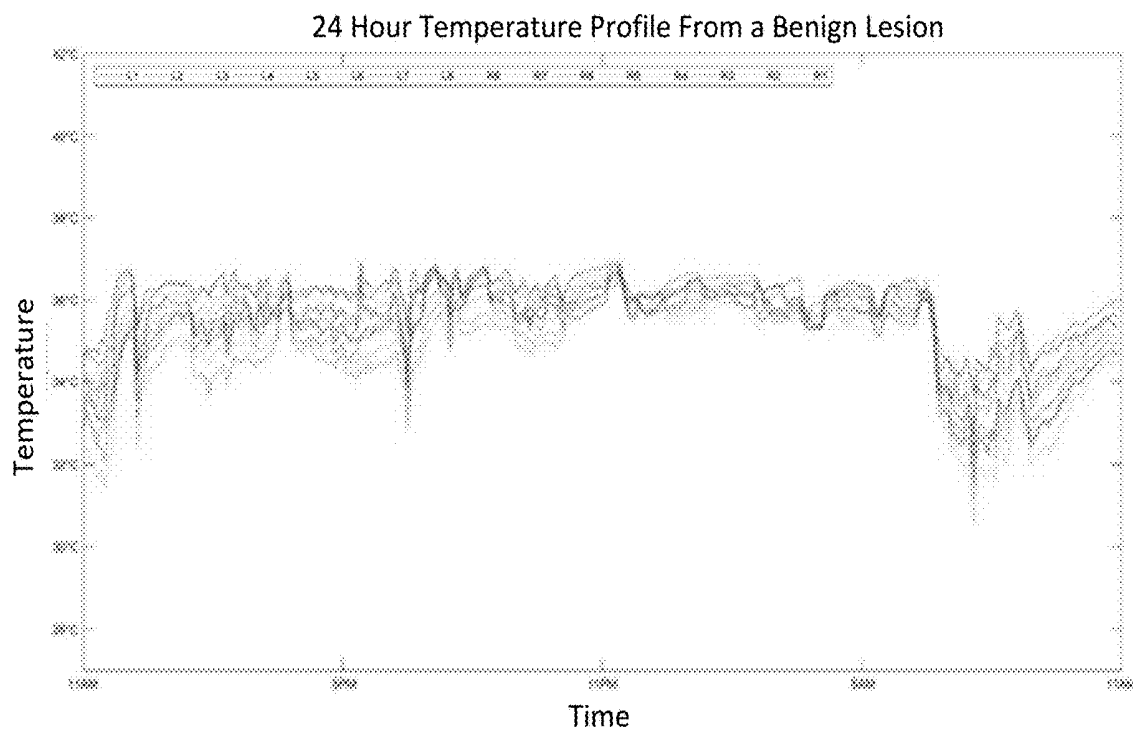


FIG. 2B

**FIG. 3A****FIG. 3B**

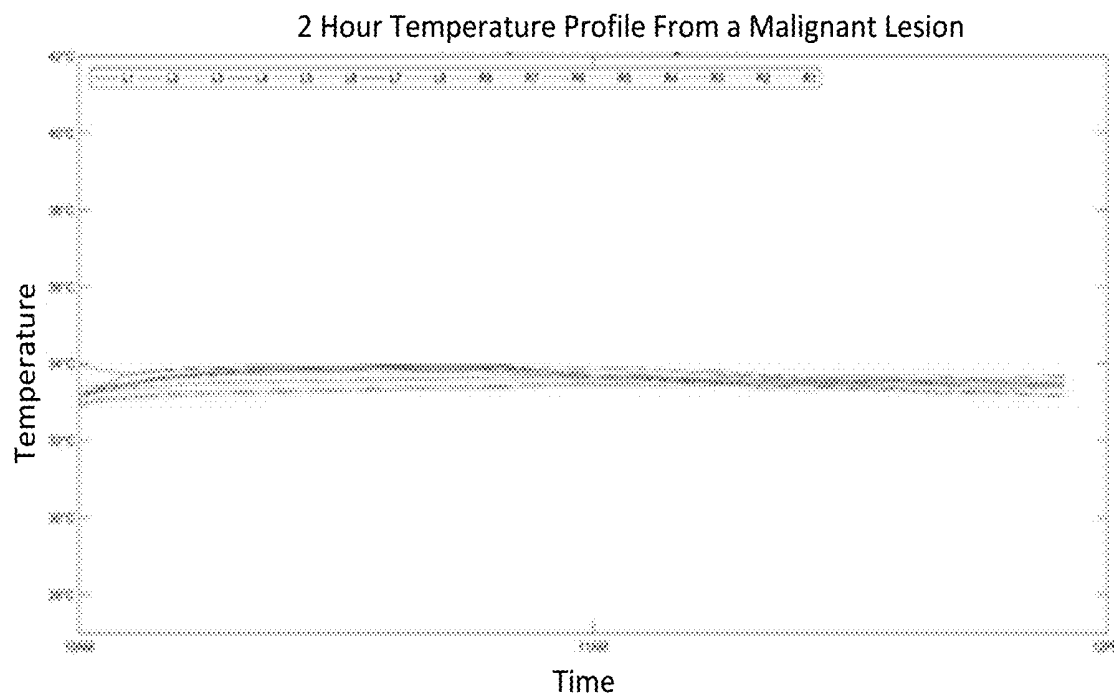


FIG. 4A

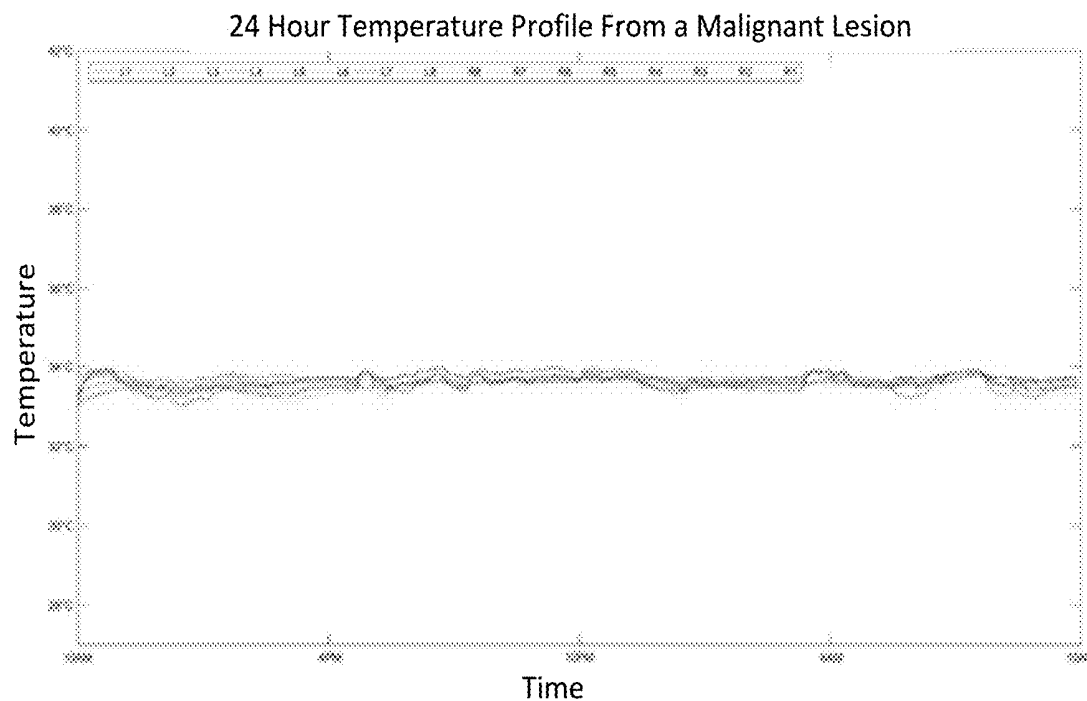


FIG. 4B

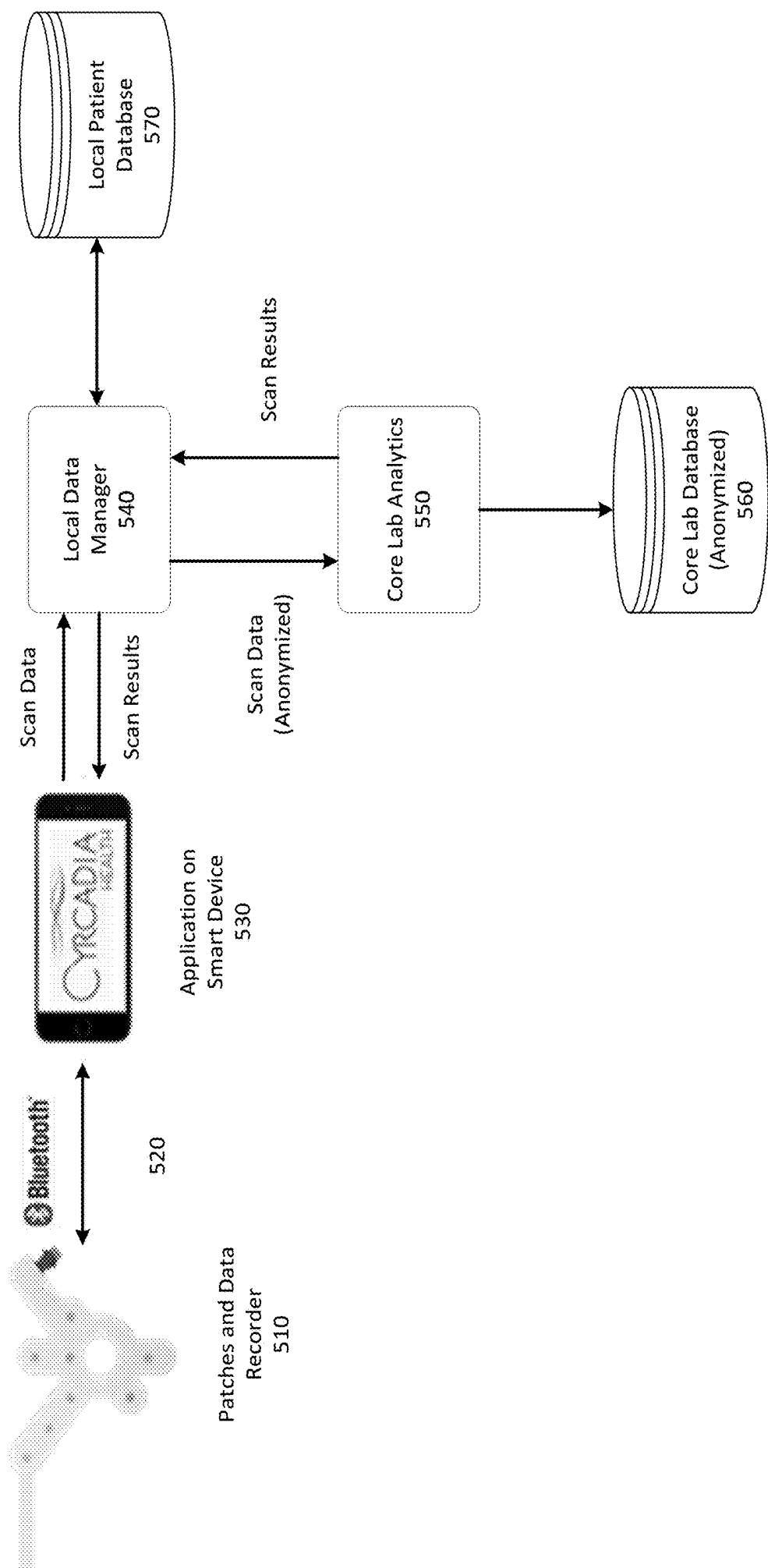
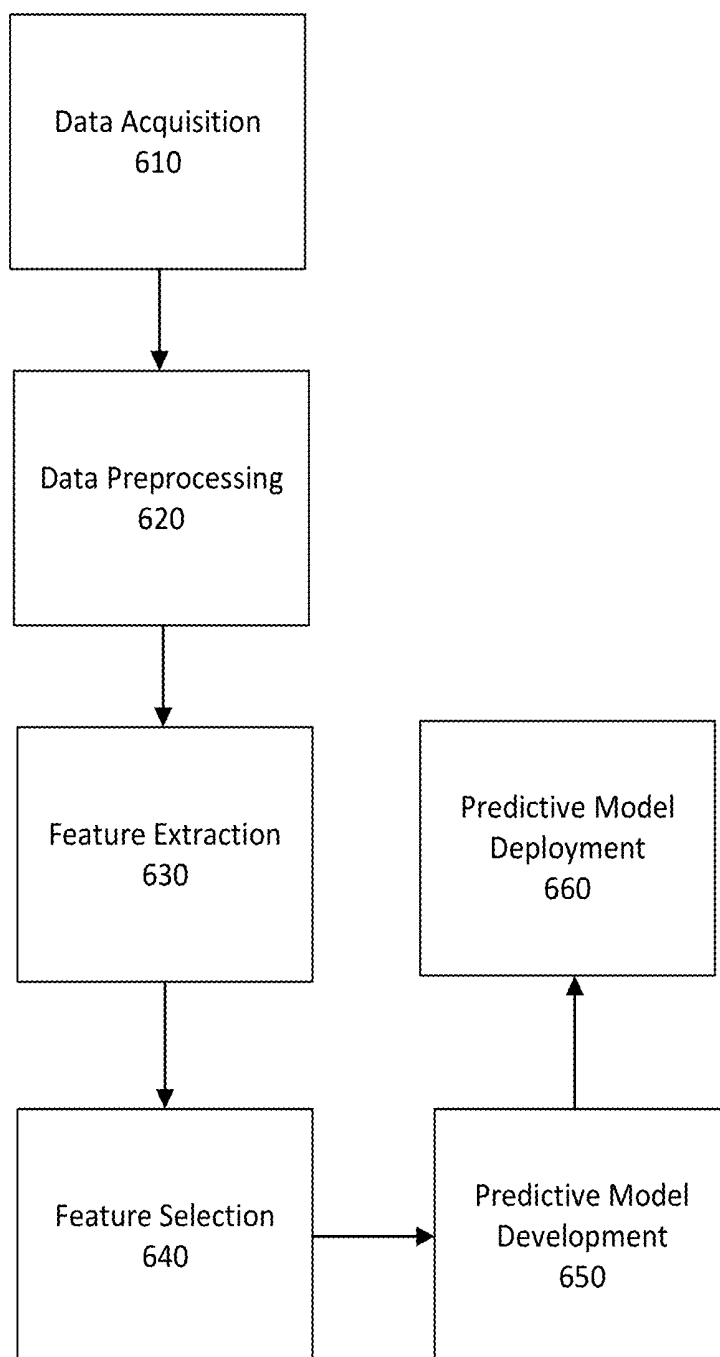


FIG. 5

**FIG. 6**

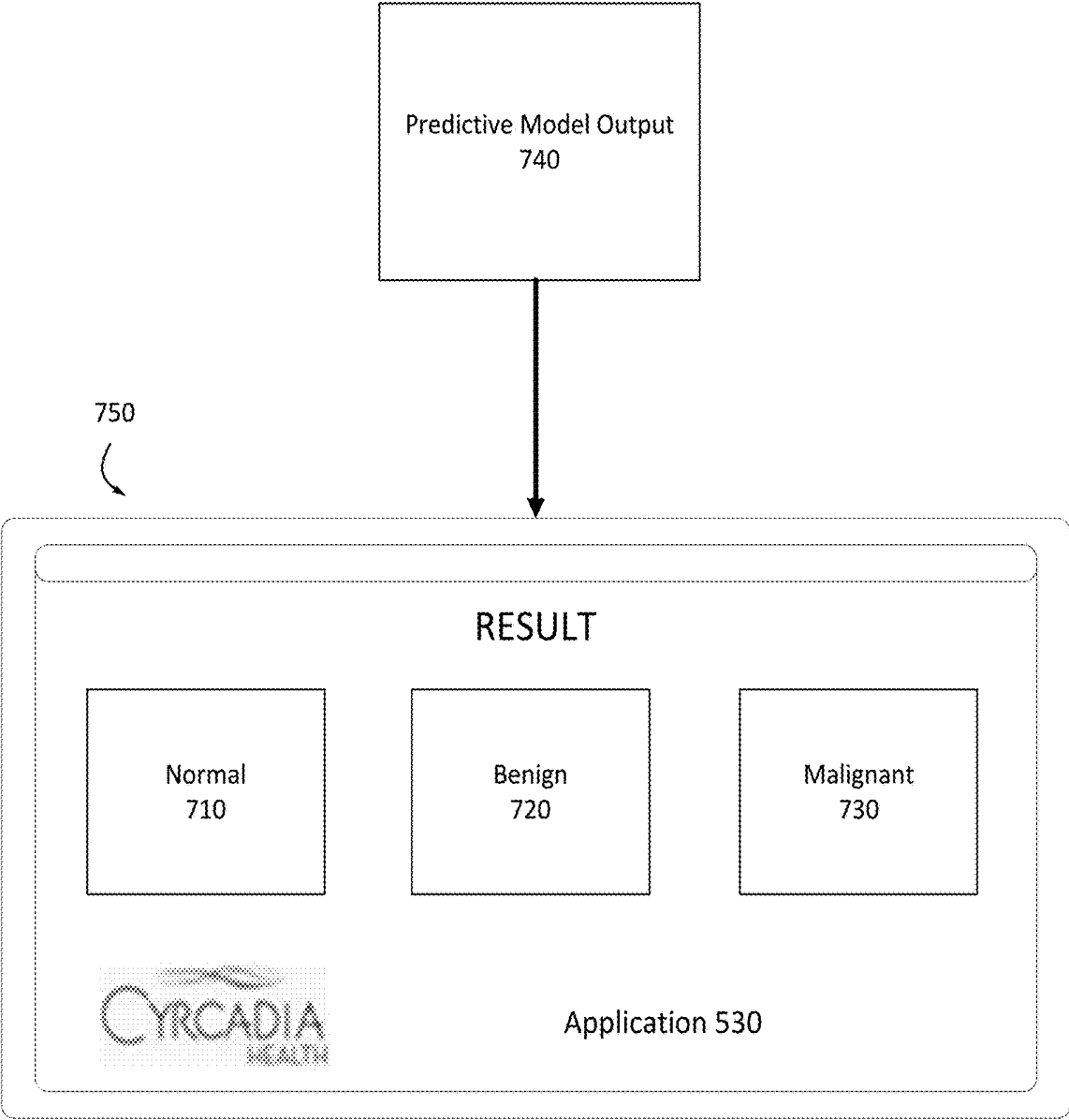


FIG. 7

SYSTEMS AND METHODS FOR ANALYZING SKIN SURFACE TEMPERATURE RHYTHMS TO MONITOR HEALTH CONDITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119(e) of Provisional U.S. Patent Application No. 62/714,033, filed Aug. 2, 2018, the contents of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates generally to devices for monitoring health conditions, and more particularly, devices for analyzing skin surface temperature to identify abnormal conditions.

BACKGROUND

[0003] Breast cancer refers to the erratic growth and proliferation of cells that originate in the breast tissue. The global impact of breast cancer is huge and is continually increasing. In most nations, the mortality rate is high primarily due to a lack of screening protocols, early detection technologies that are comfortable and radiation-free, and access to quality care. An affordable in-home breast health monitoring device that can efficiently diagnose the presence of early abnormal breast tissue changes without the need for trained professionals would go a long way toward improving survival rates.

Breast Cancer Screening Techniques

[0004] Many screening and diagnostic techniques based on ultrasound, X-rays, nuclear science, genetics, optics, pathology, and/or electrical characteristics have been or are being developed to detect breast cancer. The most commonly used modalities are Mammography, Breast Ultrasound, and Magnetic Resonance Imaging (MM).

[0005] Mammography uses low dose X-ray, high-contrast and high-resolution detectors, and an X-ray system designed specifically for imaging the breasts. In this procedure, the breast is gently compressed between two plates for a few seconds. Breast compression decreases the thickness of the breast tissue under study, and hence, improves the visibility of small lesions, reduces the radiation dose, enhances the image quality, and results in better immobilization of the breast. The compressed breast is exposed to X-rays. The attenuated X-ray photons pass through a grid, interact with an image receptor, and are then absorbed as a latent image on the recording devices. In the case of Film-Screen Mammography (FSM), the recording device is a film screen. The other clinical mammography technique is the Full Field Digital Mammography (FFDM) that uses digital detectors as the recording media.

[0006] Mammography is the current gold standard for imaging, but it is less sensitive in women with radiographically dense breasts, as dense tissues, which appear white on a mammogram, can hide tumors, which also appear white. Mammography is also limited by radiation exposure and compression discomfort.

[0007] Ultrasound imaging is based on the principle that when a sound wave strikes an object, it bounces back, passes through, or gets scattered. The scattered ultrasound waves vary depending on the density and bulk compressibility of

the object. In the case of breast tissue, at diagnostic imaging frequencies (<20 MHz), the structures that cause the strongest scattering include coarse calcium deposits followed by fibrous tissue. By measuring these scattered waves, it is possible to determine the distance, size, shape, consistency, and uniformity of the object. Thus, ultrasound is applied to detect changes in the appearance and function of organs, tissues, and abnormal masses such as tumors. In an ultrasound examination, the radiologist moves a hand-held transducer over the area of interest in the breast. The transducer directs inaudible, high-frequency sound waves into the breast tissues. The scattered sound waves are recorded by a sensitive microphone in the transducer. The recorded signals are displayed as 2D images on a computer. As the sensor is moved over the breast, continuous real-time images can be captured.

[0008] Like mammography, breast ultrasound is less accurate in detecting cancer in dense breasts and in detecting microcalcifications, and there may be degradation in the image quality of deep seated lesions in obese patients.

[0009] The third method, MRI, uses powerful magnetic fields and radio waves to create images of the breast. The MRI scanner is a tube surrounded by a giant circular superconductive magnet. During an MRI scan of the breast, the patient lies prone on the scanning table. The breast is inserted into a hole in the table, which contains coils that detect the magnetic signal. The magnet creates a strong magnetic field. When the body is immersed in such a static magnetic field, the protons of atomic material in the body (which are primarily hydrogen atoms mostly from water present in the body) become aligned with the magnetic field. When a rapidly alternating magnetic field at an appropriate resonant frequency in the Radio Frequency (RF) range is applied to the aligned protons, the orientation of the nuclear spins relative to the direction of the static magnetic field are changed. As a result, the nuclei make a transition from a lower energy state to a higher one by absorbing energy from the alternating magnetic field. When the alternating field is turned off, the nuclei return to the equilibrium state, emitting energy at the same frequency as was previously absorbed. The direction of the main magnetic field is referred to as the Z axis. Before the excitation by RF pulse, the amplitude in the Z axis is zero and the amplitude in the X-Y plane is maximal. During excitation, the amplitude in the Z axis slowly increases, while the amplitude in the X-Y plane slowly decreases. Therefore, there will be two forms of relaxation. First, the decay of the amplitude in Z axis is known as the T1 relaxation. Second, the re-growth of the amplitude in the X-Y plane is known as the T2 relaxation. Different tissues have different T1 and T2 relaxation rates. Conventional MRI images illustrate differences in T1 and T2 relaxation times of tissue water. The MRI image is fairly detailed and hence, tiny changes in the structure of tissue within the body can be detected.

[0010] MRI is limited by its inability to detect microcalcifications, long acquisition times, high costs, low specificity, and the fact that a contrast agent is required, which may affect benign lesions. It also requires patients to remain still during the scan as images are susceptible to motion artifacts. Scanning of patients with pacemakers, cochlear implants and certain other metallic foreign bodies is contraindicated due to the presence of high magnetic fields.

[0011] All three modalities require trained personnel to effectively interpret the images, and therefore, inter-observer

variabilities are prevalent. Nuclear medicine techniques are also limited by high cost and radiation exposure and are mostly used to detect cancer in high-risk patients. Again, there is clearly a need for adjunct modalities that are tissue density independent and radiation-free. Such adjunct techniques could reassure the doctors of their diagnostic predictions and also reduce the number of unwanted biopsies, thereby reducing healthcare cost and patient anxiety.

Circadian Rhythm Patterns in Cancerous Tissue

[0012] The circadian rhythm is a 24-hour cycle in the biochemical, physiological, or behavioral processes of living entities. It has been established that the circadian rhythm of skin surface temperature is altered in the presence of cancer. As cancer cells begin to divide more rapidly, new blood vessels must develop (angiogenesis) in the area of the tumor growth to provide nutrients to the increasing number of new cancer cells. Most of these new blood vessels found in malignancies lack smooth muscle, and hence, lack vascular receptivity and control by the autonomic nervous system. This leads to a more constant blood flow in the tumor area which gives rise to an altered circadian rhythm in the skin surface temperature.

[0013] Moreover, it is known that abnormal cellular division has a great appetite for proteins. It is highly believed that the proteins that would help the normal circadian clock PER1 and PER2 genes to maintain normal cellular processes, are extracted into the abnormal cellular division of cancer cells. The resulting effect is that the normal circadian pattern change which is enabled through the PER1 and PER2 processes is greatly reduced in all breast tissues. This change at the cellular level occurs much earlier than when the cancer can actually be felt on the surface or effectively captured by imaging. Thus, cancer cell activity falls outside the overall temporal harmony of the body. This unique relationship between thermo-circadian rhythm alterations and mitotic activity is an early indicator of tumor development, and could be helpful in cancer screening and diagnostic techniques. Commonly assigned U.S. Pat. Nos. 8,185,485, 8,226,572 and 8,231,542 disclose temperature sensor based solutions, but these solutions still require clinical services for applying the sensors and collecting and analyzing the data, as well as longer acquisition times.

SUMMARY

[0014] The disclosed systems, methods, and devices measure early circadian rhythm changes in the skin surface temperature to differentiate normal from abnormal breast tissue. An embodiment of the present invention comprises a wearable device comprising a plurality of temperature sensors placed at predetermined positions on the breast tissue of a subject. There may be 16 total sensors, with 8 sensors each on a left patch and a right patch of the device. The patches may be mirror images of each other, with temperature sensors positioned for placement on areas predominantly associated with breast cancer development.

[0015] In various embodiments, a computing device in communication with the wearable device comprises a processor and at least one memory in communication with the processor to at least receive a set of temperature data collected at the wearable device, extract a plurality of linear and non-linear features from the set of temperature data, apply at least one classifier system to filter the linear and

non-linear features, and utilize the filtered linear and non-linear features in a predictive model, such as a support vector machine, to determine a tissue classification.

[0016] In other embodiments, the classifier system includes a predictive model, such as a neural network. The classifier system may apply a statistical analysis to filter the linear and non-linear features. In another embodiment, the classifier system analyzes and ranks each feature according to a classifier. The tissue classification may further be based on data from predictive model training cases, or determined from the filtered non-linear features, and classifications may include benign, abnormal, and malignant tissues.

[0017] A key difference between the present invention and other breast cancer detection modalities is that the disclosed device utilizes dynamic measurement of the discrete temperature values from the breast over a relative period of time, e.g., two hours, in order to capture non-linear thermo-circadian rhythm alterations that can aid in detecting breast abnormalities early. The device is designed to be easily applied by a woman at home without the assistance or guidance of a physician or physician assistant. The device can be periodically used by a woman for self-examination. Since a woman can wear this wellness device years before having to undergo regular screening by modalities such as mammography and ultrasound, it enables a much earlier determination of any abnormal breast tissue changes and allows for subsequent clinical intervention.

[0018] Furthermore, the device is a tissue agnostic monitoring solution, meaning it can detect early changes in both fatty and dense tissues alike as it is based on analyzing cellular level changes and not breast images.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Various non-limiting embodiments are further described with reference to the accompanying drawings in which:

[0020] FIG. 1 illustrates the relative positioning of the thermal sensors on the left and right breasts of a subject in accordance with an embodiment of the present invention

[0021] FIGS. 2A and 2B illustrate different thermal sensor patch sizes, including the placement of temperature sensors on each patch.

[0022] FIGS. 3A and 3B illustrate recorded temperatures of a benign lesion over a period of 2 hours and 24 hours.

[0023] FIGS. 4A and 4B illustrate recorded temperatures of a malignant lesion over a period of 2 hours and 24 hours.

[0024] FIG. 5 illustrates a system architecture for capturing and analyzing the dynamic circadian temperature data, in accordance with embodiments of the present invention.

[0025] FIG. 6 illustrates the predictive analytics analysis process, in accordance with embodiments of the present invention.

[0026] FIG. 7 illustrates a graphical user interface for reporting the outcome of the predictive analytics analysis process, in accordance with embodiments of the present invention.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0027] Various aspects of the present disclosure described herein in are generally directed to devices, systems and methods for, among other things, utilizing predictive analytic analysis of skin surface temperature rhythms for moni-

toring breast wellness. It will be understood that the provided examples are solely for purposes of clarity and understanding and are not meant to limit or restrict the claimed subject matter or relevant portions of this disclosure in any manner.

[0028] FIG. 1 depicts a device in accordance with embodiments described herein, comprising of a pair of wearable, non-invasive, comfortable and reusable self-adhering breast patch holders **100** and **102**. Each patch is embedded with sensors **104**, labeled U1-U8, that can be worn under the bra to capture the dynamic circadian temperature changes within the breast tissue. The patches are wired through the holders **100** and **102** to connectors **106**, which may then be connected to a recorder (not shown) that collects the captured temperature data. The recorder unit may contain a battery to power the patches, a memory, and a low-energy Bluetooth transmission device, which can communicate the recorded data to an external computing device.

[0029] The wearable device is a contact active thermal analysis system that records a series of temperature values over a period of time, from each of the sensors on the device. In various embodiments described herein, the device comprises sixteen sensors **104** placed on the breast, eight on each side. In an exemplary embodiment, the device records temperature values from each of the sensors over a period of two hours, for example. It will also be appreciated that, in other embodiments, the device may record temperature values over different periods of time, from 2 to 24 hours, or up to 48 hours, although shorter acquisition times have better patient adoption, such that the device is more likely to be used, and are less likely to result in environmental interference and other fluctuations.

Patches

[0030] The sensor locations on the left patch may be a mirror image of the sensor locations on the right patch. The patches have a specific spatial alignment of thermal sensors based upon the predominance of breast cancer locations within a woman's breast (directly related to the National Tumor Registry's record of reported breast cancer occurrences) and the conformity over a specified area on the breast. The patches may be placed on the patient as per the placement in FIG. 1.

[0031] To ensure that the device can be used by women with various sizes of breast morphology, the patches may be available in different sizes. The patient can select the patch of the appropriate size based upon the traditional bra cup and chest size as shown in the following sizing charts of Table 1.

TABLE 1

Cup Size	Bra Size								
	32	34	36	38	40	42	44	46	48
A-	—	2	4	5	7	9	11	—	—
A+	1	3	5	6	8	10	12	—	—
B-	2	5	6	7	9	11	12	13	14
B+	3	6	7	8	10	12	13	—	—
C-	4	7	8	10	11	12	13	14	15
C+	5	8	10	11	12	13	14	—	—
D-	6	9	11	13	13	14	—	—	—
D+	7	10	12	—	—	—	—	—	—

TABLE 1-continued

	Length (at widest)	Width (at thickest part)
1	5 $\frac{3}{4}$ "	4"
2	6"	4 $\frac{1}{4}$ "
3	6 $\frac{1}{4}$ "	4 $\frac{1}{2}$ "
4	6 $\frac{1}{2}$ "	4 $\frac{3}{4}$ "
5	6 $\frac{3}{4}$ "	5"
6	7"	5 $\frac{1}{8}$ "
7	7 $\frac{1}{4}$ "	5 $\frac{1}{4}$ "
8	7 $\frac{1}{2}$ "	5 $\frac{1}{2}$ "
9	7 $\frac{3}{4}$ "	5 $\frac{3}{4}$ "
10	8"	5 $\frac{3}{4}$ "
11	8"	6"
12	8 $\frac{1}{4}$ "	6 $\frac{1}{2}$ "
13	8 $\frac{1}{2}$ "	6 $\frac{1}{2}$ "
14	8 $\frac{1}{2}$ "	6 $\frac{1}{2}$ "

[0032] FIGS. 2A and 2B illustrate two different patch sizes—#3 and #13 of Table 1—and the sensor placements on each patch size. The patch holders include a plurality of arms **108** extending radially from a central point, and each arm may comprise a plurality of holes in which a temperature sensor may be placed. Sensors may be placed into specific holes, which are labeled based on a distance from a central point **110** of the apparatus. For example, in FIG. 2A, hole **112** distances **1**, **2**, **3**, and **4** are respectively 22 mm, 34.7 mm, 47.4 mm, and 60.1 mm from a central point **110** of the device. In FIG. 2B, holes **114** distances **4**, **5**, **7**, and **10** are respectively 60.1 mm, 72.8 mm, 98.2 mm, and 136.3 mm from central point **110**. Although arm **108** length can vary depending on the patch size, the hole **112** distances may remain consistent throughout the various patch sizes (e.g., hole **1**, 22 mm from the center in FIGS. 2A and 2B). As noted above, the sensor placement for each patch holder **100** and **102** is based on patch size and the predominant locations of breast cancer.

Circadian Rhythm Temperature Fluctuations

[0033] FIGS. 3A and 3B illustrate examples of automated readouts of the dynamic changes in temperature values from all of the sensors of two patch holders over a measured period of 2 and 24 hours, respectively, from a benign lesion in breast tissue. The distinct circadian rhythm being followed by all of the sensors is clearly illustrated in both examples. FIGS. 4A and 4B illustrate temperature changes from a malignant lesion in breast tissue over a similar time period of 2 and 24 hours, respectively. In benign or malignant tissue abnormalities, clear segments of time-phase metabolic change and thermo-circadian rhythm variation can be visualized as periods of thermistor temperature compression (amplitude and period) and differential (relative minima and maxima of sensors temperature).

[0034] As illustrated, the temperature fluctuations of the benign lesion over the depicted time period are greater than the malignant lesion measurements over a similar time period. In general, higher variations are seen in the thermal profile obtained from non-cancerous tissue. This is due, in part, because the superficial thermal pattern of the breast is related to metabolism and vascularization within the underlying tissues, thus resulting in significant temperature changes.

[0035] As discussed below, with further reference to FIGS. 5 and 6 the disclosed systems and methods utilize this temperature information with predictive models to analyze the observed circadian rhythm fluctuations and determine a

classification of the breast tissue from which skin surface temperatures have been recorded. In various embodiments, the models base predictions on temporal variations that occur at the early stages of tumor growth. In one embodiment, recorded data from the wearable device form a multidimensional time series dataset, with temperature values from 16 sensors over a two-hour time period. The predictive analytics framework utilizes data mining algorithms to capture subtle differences in the features derived from the recorded data

Predictive Analytics Framework

[0036] FIG. 5 illustrates an example system architecture for capturing and analyzing the dynamic circadian temperature data, in accordance with embodiments of the present invention. The system comprises a device, as described herein, to capture and record thermal data **510**, and an application in direct communication **520**, e.g., Bluetooth communication, with an application on a smart device **530**, such as a smart phone belonging to the patient/user on which the application has been downloaded. The application of the smart device **530** is in communication with a local data manager **540** to manage the processing, analysis, and storage of the scanned data. The local data manager may be hosted in a cloud, or one or more remote servers or computing devices in network communication with the smart device. In embodiments, the cloud may be local to a geographical region where the application **530** is used. The local data manager **540** receives temperature data from the application **530** and may store the data in a local patient database **570** on the smart device and/or send the data to a remote central core lab **550** for predictive analytics analysis. As discussed more substantially, with respect to FIG. 6, the core lab utilizes data mining algorithms and predictive models to analyze the temperature data and determine a condition of the analyzed tissue.

[0037] The core lab may be a remote server, in network communication with the local data manager, receiving the temperature data and performing additional processing of the received temperature data sets. The temperature data may also be anonymized prior to analysis at the core lab **550** to ensure user privacy. The core lab's predictive models and algorithms analyze the temperature data to determine a classification of the tissue, and the associated, anonymized data may be stored in the core lab database **560** for future reference and use. In embodiments, the predictive models may utilize classification algorithms, training modules, and previously collected temperature data to improve analysis and classification of received temperature data.

[0038] After the core lab **550** has analyzed the set of received temperature data, the results, which include a classification of the measured tissue, may be sent back to the local data manager **540**. From the local data manager **540** the information may be stored in a local patient database **570** and/or displayed to the user via the application **530**.

User Process

[0039] The following is a description of an exemplary process which may be followed by a user, in accordance with various embodiments implemented on the system architecture of FIG. 5. In the process, an application **530** installed on a computing device, such as a smartphone or other smart device, can wirelessly communicate **520** with

the recorder unit of the wearable device, in order to control the wearable device and receive data collected by the plurality of temperature sensors on the device patches. In embodiments, the application comprises additional modules containing information to educate a user about breast disease or use of the wearable device, data analysis modules, and options for ordering replacements and other parts of the wearable device.

[0040] When the wireless device patches are properly attached to the breasts, the user may initiate a connection, e.g., a Bluetooth connection, between the smart device and the wearable device via the application. In some embodiments, the connection may occur automatically upon placement of the wearable device on the user. In other embodiments, a Bluetooth connection and the loaded app may be required for the connection between the wearable device and application to occur automatically.

[0041] Once a connection **520** is established, the user may be notified through the application **530** about a test run. During the test, the firmware allows the temperatures from the sensors to stabilize for a period of time, e.g., one minute, and subsequently checks the sensor connections and temperature range. If the test run is successful, the user initiates the scan in the application **530**, and the application **530** sends the appropriate command to the recorder to start the scan. Once a scan is initiated, a signal will be sent to the recorder to start collecting data, and a timer will appear on the app counting backwards to zero illustrating to the user how much more time is required to complete the data collection process.

[0042] During the recording period, the user can proceed with normal daily activity. In embodiments, the data recording will continue even if the user moves away from, or out of range of the smart device. Once the timer hits zero in the app, the Bluetooth connection **520** will be revalidated. If the mobile device is still connected to the wearable device, transfer of data from the wearable to the app will commence. If the Bluetooth connectivity is not established, the user will be prompted to reestablish the connection between the wearable and the mobile device to send the data.

[0043] Once the application **530** receives the data, the data may be transferred to a back-end cloud environment—to a local database **570** for storage and also to a centralized core lab **550** for analysis. Once the data is received and transmitted to the back-end, an acknowledgement of the receipt of the data can be displayed on the smart device. There may also be a message indicating that the result will be transmitted back to the user and/or their physician/insurance provider, when available.

[0044] In the core lab **550**, the predictive model is used to analyze the data and obtain a result indicating the presence or absence of any abnormality. Once the data collection process is complete and the data has been transferred to the application successfully, the user may remove the patch holders and disconnect the data recorder.

Predictive Analytics Analysis

[0045] FIG. 6 illustrates the predictive analytics analysis for determining a measure of breast wellness from circadian rhythm temperature fluctuations. The following steps, described below in greater detail, illustrate the predictive analytics process:

[0046] Data Acquisition **610**

[0047] Data Preprocessing/Cleaning **620**

- [0048] Feature Extraction **630**
 [0049] Feature Selection **640**
 [0050] Predictive Model Development and Evaluation
650
 [0051] Model Deployment **660**

Data Acquisition **610**

[0052] To obtain temperature data from the wearable device, the associated data recorder on the device may comprise software to scan the temperature sensors on the device's patches at predetermined time intervals, e.g., every 10 seconds, and store the sensed data in a Flash Memory until the measurement cycle time, e.g., two hours, elapses. In an embodiment, the sensed data is stored in a structured read-only file (data.dat) in which all blocks have the same format. The size of this file is 124 kb. Unused records in a partial block are cleared to all zero's (0x00h). All unrecorded blocks contain all ones (0xFFh) and correspondingly have a checksum error. Table 2 below shows the format of data.dat for an example data file block. Each block of the file consists of a 16-byte header record (the first 16 bytes), up to 15 sample records (each record consists of one set of readings of the 16 sensors), followed by a 16-byte trailer record.

TABLE 2

Data.dat File Block Structure		
Block	Offset (bytes)	Record
N	0	16-byte Header Record
N	16	1st Sample Record - 8 right side sensors
N	32	1st Sample Record - 8 left side sensors
N		
N		
N	464	15th Sample Record - 8 right side sensors
N	480	15th Sample Record - 8 left side sensors
N	496	16-byte Trailer Record

[0053] The Header Record consists of the time stamp for the first sample record in the block, the measurement cycle (2 hours), record rate (10 seconds), number of records in the block (usually 15), total number of records (including this block), the record type, and a status byte (see Table 3 below). The Record Type byte is a binary value and indicates one of three block types; Recording 0x01, Stopped 0x02, Complete 0x04. The Status Byte indicates the dynamic status of the device and is represented by a binary value. Bit 7 is set by the recorder during active measurement cycle. In the last block of data after completion of measurement cycle bit 7 is set to 0.

TABLE 3

Sample Record Format									
Offset (bytes)	Sensor Data								
16 + (Rec#-1) * 32	2R	4R	6R	8R	1R	3R	5R	7R	
24 + (Rec#-1) * 32	1L	3L	5L	7L	2L	4L	6L	8L	

[0054] The Trailer Record contains the 14-byte User ID number followed by a 16-bit Checksum. The User ID is the ID of the user set in the application. Table 4 below shows the Trailer Record format.

TABLE 4

Trailer Record Format		
Offset (bytes)	Len (bytes)	Item
496	14	User ID
510	2	Checksum

Data Preprocessing **620**

[0055] Data preprocessing begins with converting the data file. At the end of every scan, the data.dat file described above is received by the app. The data.dat file is first converted to the .csv format for further analysis, then analyzed for outliers in the data set.

[0056] In embodiments, outliers may be handled in multiple steps. In a first step, rows with 511.9922 (or unrecorded blocks) are removed. In the second step, rows/temperature records beyond a particular threshold, such as a sample loss threshold are removed. For example, a 2 hour recording at a 10 second sampling rate will result in 720 samples. Sample loss is defined as any temperature record (set of 16 sensor values) with values <27C. Thus, any rows/temperature records with the defined sample loss are removed. Alternatively, the threshold may be defined such that only a maximum of 1 sample at a time can be bad (out of range or zeros), and overall, there can be only 3 bad samples. Beyond that, the data is rejected for analysis.

Feature Extraction **630**

[0057] The outlier-free selected dataset is then used to extract several features that could adequately describe the time-series data. The recorded temperature rhythms are non-linear in nature. Hence, both linear and non-linear features are extracted in order to capture the variability in the rhythms. The following 10 features are extracted from the data: Mean, Variance (Var), Approximation Entropy (ApEn), Fractal Dimension (FD), Second Order Moment (Cum_2), Short Hurst Exponent (SHE), Largest Lyapunov Exponent (LLE), Mobility (Mob), Wavelet Entropy (WEnt), and Permutation Entropy (PE). Mobility is the ratio of variance of the first derivative of the data to the variance of the data. Permutation entropy describes the complexity of a time series or signal, and takes into account non-linear behavior of the time series. The extracted features may be determined as follows.

[0058] Mean: The mean μ is the average value of the time series A. It is calculated as follows (N is the number of observations)

$$\text{Mean} = \frac{1}{N} \sum_{i=1}^N A_i$$

[0059] Variance (Var): The variance is a representation of the power of how far the time series fluctuates from its mean. The variance is defined as

$$\text{Var} = \frac{1}{N-1} \sum_{i=1}^N [A_i - \mu]^2$$

[0060] Approximate Entropy (ApEn): Approximate Entropy is a measure of complexity, and it quantifies the unpredictability of fluctuations in a time series. ApEn is scale invariant and assigns a nonnegative number to a time series, with larger values corresponding to more irregularity in the data. Let the time series A_N have N measurements $TS(1), TS(2) \dots TS(N)$. To calculate approximate entropy $ApEn(A_N, m, r)$, two parameters are chosen first – m , which specifies the pattern length, and r defines the criterion of similarity. Let $p_m(i)$ denote a pattern of m measurements starting at measurement i within the series A_N . Two patterns $p_m(i)$ and $p_m(j)$ are considered similar if the difference between any pair of corresponding measurements in both patterns is less than r . Let P_m denote the set of all patterns of length m within A_N beginning at measurements 1 to $N-m+1$. The correlation integral is defined by

$$C_m^m(r) = \frac{n_{im}(r)}{N - m + 1}$$

[0061] Where $n_{im}(r)$ is the number of patterns similar to $p_m(i)$. The correlation integral is calculated for each pattern in P_m . Let $C_m(r)$ be the mean of all these $C_i^m(r)$ values. Approximate Entropy is defined as the natural logarithm of the relative occurrence of repetitive patterns of length m compared to repetitive patterns of length $m+1$ as below

$$ApEn(A_N, m, r) = \ln \left[\frac{C_m(r)}{C_{m+1}(r)} \right]$$

[0062] Fractal Dimension (FD): FD is another measure of series complexity and the presence of transients in time series data. Let $\{a_1, a_2, a_3, \dots a_N\}$ indicate a N dimensional time series. The first step is to form k new time series A_k^m defined as follows

$$A_k^m = \left\{ a[m], a[m+k], a[m+2k], \dots, a \left[m + \text{int} \left(\frac{N-m}{k} \right) \cdot k \right] \right\}$$

[0063] Where k indicates the discrete time interval between points, and $m=1, 2, \dots, k$ represents the initial time value. The next step is to calculate the length of each new time series as follows:

$$L(m, k) = \frac{\left(\sum_{i=1}^{\text{int} \left(\frac{N-m}{k} \right)} a[m+ik] - a[m+(i-1)k] \right) \frac{N-1}{\text{int} \left(\frac{N-m}{k} \right) \cdot k}}{k}$$

[0064] Mean value of the curve length $L(k)$ is then calculated for each k by averaging $L(m, k)$ for all m . FD is defined as the slope of the line that fits (least squares linear best fit) $\log(L(k))$ and

$$\log \left(\frac{1}{k} \right).$$

[0065] Second Order Cumulant (Cum_2): Let $\{a_1, a_2, a_3, \dots a_N\}$ indicate a N dimensional time series. Its second order moment is defined as

$$m_2^a(i) = E[a(n)a(n+i)]$$

[0066] Where $E[.]$ indicates the expectation operator. Using moments, the second order cumulant is calculated as

$$\text{Cum}_2^a = m_2^a(i)$$

[0067] Short Hurst Exponent (SHE): The Hurst exponent is a numerical estimate of the predictability of a time series. It is used to determine if the time series is more, less, or equally likely to increase if it has increased in previous steps. It is defined as

$$SHE = \frac{\log \left(\frac{R}{S} \right)}{\log(T)}$$

[0068] Where T is the duration of the time series and R/S is the corresponding value of rescaled range. R is the difference between the maximum and minimum deviation from the mean and S is the standard deviation.

[0069] Largest Lyapunov Exponent (LLE): LLE is an indicator of chaos in the system. It defines the average rate by which two neighboring trajectories diverge or separate from one another. Consider two nearby points in a space as x_0 and $x_0 + \Delta x$ that are a function of time. Each of these points will generate an orbit of its own. The separation between the two orbits Δx is a function of the location of the initial value and has the form $\Delta x(x_0, t)$. The mean exponential rate of divergence of these two orbits is measured as follows

$$\lambda = \lim_{t \rightarrow \infty} \frac{1}{t} \ln \frac{|\Delta x(x_0, t)|}{|\Delta x|}$$

[0070] LLE is the maximum positive value of λ . A positive LLE indicates the existence of chaos in that system.

[0071] Mobility (MOB): Mobility is the square root of variance of the first derivative of the data A_N divided by the variance of the data A_N .

$$Mob = \sqrt{\frac{\text{Var} \left(\frac{dA}{dt} \right)}{\text{Var}(A)}}$$

[0072] Wavelet Entropy (WEnt): Shannon entropy is a measure of the spectral complexity of the time series. Let the power in each frequency in the time series be denoted by p_f . Shannon entropy is calculated as the sum of the entropy over the entire frequency range as given by

$$WEnt = \sum_f p_f \log \left[\frac{1}{p_f} \right]$$

[0073] Permutation Entropy (PE): Permutation entropy describes the complexity of a time series or signal and takes

into account the non-linear behavior of the time series. It considers the temporal order of the measurements in the time series data into account and helps determine any couplings between time series. Large values indicate more randomness in the time series. Given a time series A_N , an embedding procedure is first used to form vectors with embedding dimension m and lag l . For m different embedding dimensions, there will be $m!$ possible permutations (order pattern) π . Let $C(\pi_i)$ be the count of the occurrences of the order pattern $(\pi)_i$ where $i=1, 2, \dots, m!$. The relative frequency of $C(\pi_i)$ is given by $p(\pi)=C(\pi_i)/(N-(m-1)l)$. The permutation entropy is defined as:

$$PE = \sum_{m=1}^{m!} p(\pi) \ln p(\pi)$$

[0074] The following algorithm may be adopted to extract the features: Calculate the first feature of all the temperature readings obtained from the first sensor, and repeat for the remaining sensors. Each calculation should be stored in a matrix, i.e., a Feature Matrix.

[0075] For each remaining feature, calculate the feature from the temperature readings of each sensor, and append the values to the stored Feature Matrix. At the end of the calculations, the Feature Matrix should be the size of $1 \times (\# \text{ of sensors} \times \# \text{ of features})$. In an example of 16 sensors and 10 features, the Feature Matrix would have a size of 1×160 . In an exemplary embodiment, features in the Feature Matrix are named Mean1, Mean2, [. . .], Mean16, Var1, Var2 . . . Var16 etc., wherein the appending numbers 1, 2 [. . .], 16 indicate the sensor numbering).

Feature Selection 640

[0076] The main idea of feature selection is to choose a subset of features and eliminate the irrelevant ones from the dataset. Obtaining a smaller set of representative features and retaining the optimal salient characteristics of the data not only decreases the processing time but also leads to more compactness of the models learned, better generalization, and comprehensibility of the mined results. There are two basic feature subset selection techniques: (i) Filter Methods, in which the selection of features is independent of the classifier used, and (ii) Wrapper Methods, in which the features are selected using the classifier.

[0077] Filter methods rely on general characteristics of the data to evaluate and to select the feature subsets. Filters are usually used as a pre-processing step since they are simple and fast. A widely-used filter method for medical data is to apply a univariate criterion separately on each feature. In this work, the t-test was applied on each feature and the resulting p-value (or the absolute values of t-statistics) was compared for each feature as a measure of how effective it is at separating groups.

[0078] The Wrapper Method uses a classifier to perform classification using every possible feature subset and selects the feature subset that gives the best classification accuracy. This method is deemed to be an optimal way to improve a classifier's performance since both learning a classifier and selecting features use the same bias. Since a classifier is built as many times as the number of feature subsets generated, computationally intensive classifiers should not be considered.

[0079] Sequential feature selection is one of the most widely used wrapper technique. This method selects a subset of features by sequentially adding (forward search) or removing (backward search) until certain stopping conditions are satisfied. In this work, forward sequential feature selection in a wrapper fashion may be used to find important features. More specifically, since the typical goal of classification is to minimize the Misclassification Error (MCE), the feature selection procedure performs a sequential search using the MCE of a classifier on each candidate feature subset as the performance indicator for that subset. The training set is used to select the features and to fit the classifier, and the test set is used to evaluate the performance of the finally selected feature. During the feature selection procedure, to evaluate and to compare the performance of each candidate feature subset, stratified 10-fold cross-validation can be applied to the training set. In stratified ten-fold cross validation, the dataset is split into ten approximately equally sized disjoint subsets. The subsets are selected in a way that the proportion of benign to malignant samples is the same in all, i.e., stratified. In each fold or iteration, nine subsets are used for ranking the features. The process is repeated 10 times and the final feature subset selected.

Data Mining/Predictive Model Development 650

[0080] The final step in the predictive analytic analysis software is developing the predictive model that can classify the input data into one of the two classes—presence of thermal anomaly/absence of thermal anomaly. A predictive model is the best combination of selected features and classifiers that can present the highest classification accuracy, sensitivity and specificity for the studied dataset. Classifier performance depends greatly on the characteristics of the data to be classified. There is no single classifier that works best on all given problems. Hence, several classifiers may be evaluated to understand which classifier performed effectively.

[0081] Usually for classification tasks, supervised learning is preferred. In this type of learning, during the training phase, both the features (input) and the corresponding class label (pathology/output) are presented to help the classifier learn the relationship between the input and output. After training, only the features of the test data are presented. The classifier then automatically predicts the unknown class label with the help of the knowledge gained during the training phase. Evaluated classifiers include Bayes Net (BN), Naïve Bayes (NB), Radial Basis Function Neural Network (RBFNN), Sequential Minimal Optimization (SMO), Naïve Bayes Tree (NBTree), Decision Tree (DT), and Adaboost and Bagging meta-classifiers. A few other classifiers like Back Propagation Neural Network (BPNN), Probabilistic Neural Network (PNN), Support Vector Machine (SVM), Gaussian Mixture Model (GMM), and Fuzzy Equivalence (FEQ) have also been evaluated.

[0082] Stratified ten-fold cross validation technique was employed to build and evaluate these classifiers i.e. the dataset was split into 10 subsets. Nine subsets were used for training, and the remaining subset was used for testing to get the performance measures like accuracy, sensitivity, and specificity. The process was repeated nine more times and the final performance measure was taken as the average of measures obtained in all ten iterations. Since the wrapper method was used for feature selection in embodiments described herein, several combinations of feature subsets

and classifiers were evaluated as part of the feature selection step described earlier to select the best feature set-classifier combination (also known as the predictive model).

[0083] The final feature set-classifier combination that presented high accuracy of prediction: Mean7, WEnt7, PE1, ApEn9, ApEn5, Var16, Cum2_16, PES, SHE1, Var13, Cum2_13, PE9, PE4, WEnt3, FD1, ApEn16, Cum2_14, Var14, ApEn8 in the SVM classifier with Radial Basis Function kernel.

Model Deployment 660

[0084] The previous five steps are carried out on a historical dataset that has the pathology information to train the classifier. The end result of those steps is a trained predictive model that has the knowledge of classifying if a new patient data has any abnormality in the breast tissue or not. In this model deployment phase, this predictive model is used for new patient data classification. First, the new dataset is examined for the presence of any loose sensors or if the data collection was incomplete (by checking for the presence of out of range or zero values). If the data is usable, the features that were determined the best during the model development process are extracted from the patient data. Then, these features are fed into the trained predictive model which determines the presence or absence of breast abnormalities.

[0085] The output of the predictive algorithm 740 is a result, which is indicative of a tissue classification and may be displayed to a user through a graphical user interface 750 of the application. In embodiments, the output may indicate whether the results are normal 710, benign 720 or malignant 730. FIG. 7 illustrates these possible tissue classifications in a simplified graphical user interface. These results can be reported to a health care practitioner to gauge overall breast wellness and support further treatment decisions.

[0086] The techniques described above may be embodied in, and fully or partially automated by, code modules executed by one or more computers or computer processors. The code modules may be stored on any type of non-transitory computer-readable medium or computer storage device, such as hard drives, solid state memory, optical disc, a cloud, and/or the like. The processes and algorithms may be implemented partially or wholly in application-specific circuitry. The results of the disclosed processes and process steps may be stored, persistently or otherwise, in any type of non-transitory computer storage such as, e.g., volatile or non-volatile storage.

[0087] The various features and processes described above may be used independently of one another, or may be combined in various ways. All possible combinations and sub-combinations are intended to fall within the scope of this disclosure.

[0088] Conditional language used herein, such as, among others, “can,” “could,” “might,” “may,” “e.g.,” and the like, unless specifically stated otherwise, or otherwise understood within the context as used, is generally intended to convey that certain embodiments include, while other embodiments do not include, certain features, elements, and/or steps. Thus, such conditional language is not generally intended to imply that features, elements and/or steps are in any way required for one or more embodiments or that one or more embodiments necessarily include logic for deciding, with or without author input or prompting, whether these features, elements and/or steps are included or are to be performed in any particular embodiment. The terms “comprising,”

“including,” “having,” and the like are synonymous and are used inclusively, in an open-ended fashion, and do not exclude additional elements, features, acts, operations, and so forth. Also, the term “or” is used in its inclusive sense (and not in its exclusive sense) so that when used, for example, to connect a list of elements, the term “or” means one, some, or all of the elements in the list.

[0089] While certain example embodiments have been described, these embodiments have been presented by way of example only, and are not intended to limit the scope of the inventions disclosed herein. Thus, nothing in the foregoing description is intended to imply that any particular feature, characteristic, step, module, or block is necessary or indispensable. Indeed, the novel methods and systems described herein may be embodied in a variety of other forms; furthermore, various omissions, substitutions and changes in the form of the methods and systems described herein may be made without departing from the spirit of the inventions disclosed herein. The accompanying claims and their equivalents are intended to cover such forms or modifications as would fall within the scope and spirit of certain of the inventions disclosed herein.

What is claimed:

1. A system for classifying breast tissue comprising:
 - a wearable device comprising a plurality of temperature sensors placed at predetermined positions on a subject;
 - a computing device comprising a processor and at least one memory in communication with the processor, the at least one memory storing instructions thereon that, when executed by the processor, causes the computing device to at least:
 - receive a set of temperature data collected at the wearable device, the set of temperature data indicative of readings from each of the plurality of temperature sensors over a period of time;
 - extract a plurality of linear and non-linear features from the set of temperature data, the non-linear features indicative of variability in the temperature data over the period of time;
 - apply at least one classifier system to filter the plurality of linear and non-linear features; and
 - utilize the filtered plurality of linear and non-linear features in a predictive model to determine a tissue classification.
2. The system of claim 1, wherein the wearable device comprises sixteen temperature sensors.
3. The system of claim 1, wherein the period of time is twenty-four hours or less.
4. The system of claim 3, wherein the period of time is two hours.
5. The system of claim 1, wherein the features include at least one of: Mean, Variance (Var), Approximation Entropy (ApEn), Fractal Dimension (FD), Second Order Moment, Short Hurst Exponent (SHE), Largest Lyapunov Exponent (LLE), Mobility (Mob), Wavelet Entropy (WEnt), and Permutation Entropy (PE).
6. The system of claim 1, wherein further comprising instructions that cause the computing device to at least:
 - analyze the set of temperature data to identify and remove outliers prior to extracting the linear and non-linear features.
7. The system of claim 1, wherein the classifier system applies a statistical analysis to each of the extracted linear and non-linear features.

8. The system of claim 1, wherein the classifier system analyzes and ranks each linear and non-linear feature according to a classifier.

9. The system of claim 8, wherein the classifier is at least one of: Bayes Net (BN), Naïve Bayes (NB), Radial Basis Function Neural Network (RBFNN), Sequential Minimal Optimization (SMO), Naïve Bayes Tree (NBTree), Decision Tree (DT), and Adaboost and Bagging meta-classifiers.

10. The system of claim 1, wherein the predictive model includes a neural network.

11. The system of claim 1, wherein the tissue classification is normal, benign, or malignant.

12. A method for classifying breast tissue comprising:
receiving, from a wearable device, a set of temperature data indicative of readings from each of the plurality of temperature sensors over a period of time, wherein the wearable device comprises a plurality of temperature sensors placed at predetermined positions on a subject;
extracting a plurality of linear and non-linear features from the set of temperature data, the non-linear features indicative of variability in the temperature data over the period of time;
applying at least one classifier system to filter the plurality of linear and non-linear features; and
utilizing the filtered plurality of linear and non-linear features in a predictive model to determine a tissue classification.

13. The method of claim 12, wherein the predetermined positions are areas predominantly associated with breast cancer.

14. The method of claim 12, wherein the period of time is twenty-four hours or less.

15. The method of claim 12, wherein the features include at least one of: Mean, Variance (Var), Approximation Entropy (ApEn), Fractal Dimension (FD), Second Order Moment, Short Hurst Exponent (SHE), Largest Lyapunov Exponent (LLE), Mobility (Mob), Wavelet Entropy (WEnt), and Permutation Entropy (PE).

16. The method of claim 12, wherein the at least one classifier system applies a classifier to the linear and non-linear features, wherein the classifier is at least one of: Bayes Net (BN), Naïve Bayes (NB), Radial Basis Function Neural

Network (RBFNN), Sequential Minimal Optimization (SMO), Naïve Bayes Tree (NBTree), Decision Tree (DT), and Adaboost and Bagging meta-classifiers.

17. The method of claim 12, wherein the predictive model includes a neural network.

18. The method of claim 12, wherein the at least one classifier system utilizes a wrapper method or a filter method.

19. The method of claim 12, wherein the tissue classification is normal, benign, or malignant.

20. A device for analyzing temperature changes in breast tissue to determine a suspect condition, comprising:
a pair of patches comprising a plurality of temperature sensors on each patch;
a recorder to record temperature from each of the plurality of temperature sensors over a period of time; and
a transmission device for communicating the recorded temperatures to a computing device for determining a breast tissue classification.

21. The device of claim 20, wherein there are eight temperature sensors on each patch.

22. The device of claim 20, wherein the temperature sensors are placed on locations predominantly associated with breast cancer.

23. The device of claim 20, wherein the period of time is two hours.

24. The device of claim 20, wherein the transmission device communicates recorded temperatures to the computing device via Bluetooth.

25. The device of claim 20, wherein the computing device is in communication with one or more computing modules to determine the breast tissue classification by at least:

extracting a plurality of linear and non-linear features from the recorded temperatures, the non-linear features indicative of variability in the temperature data over the period of time;

applying a classifier system to filter the plurality of linear and non-linear features; and

utilizing the filtered plurality of linear and non-linear features in a predictive model to determine a tissue classification.

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专利名称(译)	用于分析皮肤表面温度节律以监测健康状况的系统和方法		
公开(公告)号	US20200037949A1	公开(公告)日	2020-02-06
申请号	US16/530894	申请日	2019-08-02
发明人	SUBBHURAAM, VINITHA SREE		
IPC分类号	A61B5/00 A61B5/01 G16H50/20 G16H50/50 G06N3/08		
CPC分类号	A61B5/015 A61B5/0008 A61B5/6823 G16H50/50 A61B5/002 A61B5/7275 A61B5/4312 G06N3/08 G16H50/20 A61B5/7264 A61B5/4857 A61B5/01 A61B5/6805 A61B5/7267 A61B2562/0271 A61B5/0091 G01K13/002 G16H50/30		
优先权	62/714033 2018-08-02 US		
外部链接	Espacenet USPTO		

摘要(译)

公开了用于利用昼夜节律波动的预测分析分析来监测乳房健康的系统，方法和设备。可穿戴设备可包括放置在对象上的预定位置处的多个温度传感器。在一段时间内从可穿戴设备收集的一组温度数据可用于提取指示温度数据变化性的多个非线性特征。包括预测模型的分器系统对非线性特征进行滤波，并且可以在预测模型中使用滤波后的特征来确定乳房组织的分类。

