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(54) Title: BLOOD LOSS VOLUME PREDICTION FROM ARTERIAL WAVEFORM

(57) Abstract: Techniques for monitoring blood loss in a subject animal includes collecting arterial pressure waveform measurements during an observation period spanning several heartbeats. The measurements are processed to extract one or more blood pressure features. A value of at least one objective blood loss metric for the subject animal is output by providing the blood pressure features as input to one or more machine learning (ML) models. The output is presented at a device. The ML models are trained on historical instances. Each instance includes historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination experiment. The historical measurements are associated with a historical objective blood loss metric value determined from directly-measured blood loss during the experiment.

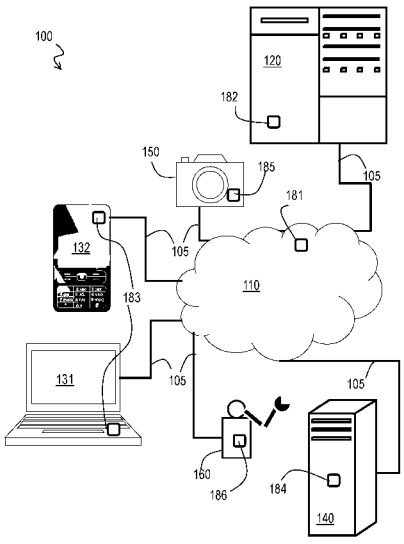


FIG. 1A

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BLOOD LOSS VOLUME PREDICTION FROM ARTERIAL WAVEFORM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of Provisional Appln. 63/532,529, filed August 14, 2023, the entire contents of which are hereby incorporated by reference as if fully set forth herein, under 35 U.S.C. §119(e).

STATEMENT OF GOVERNMENTAL INTEREST

[0002] Under paragraph 1(a) of Executive Order 10096, the conditions under which this invention was made entitle the Government of the United States, as represented by the Secretary of the Army, to an undivided interest therein on any patent granted thereon by the United States. This and related patents are available for licensing to qualified licensees.

BACKGROUND

[0003] Hemorrhagic shock is a type of shock that is caused by heavy blood loss, which can be caused by internal or external bleeding. Hemorrhagic shock can be life threatening and needs to be treated as a medical emergency. Hemorrhagic shock can be characterized by class: Class 1 represents volume loss up to 15% of total blood volume; Class 2 represents volume loss from 15% to 30% of total blood volume; Class 3 represents volume loss from 30% to 40% of total blood volume; and Class 4 represents volume loss over 40% of total blood volume. In the acute phase of traumatic hemorrhagic shock, the therapeutic priority is to stop the bleeding. As long as such bleeding is not controlled, the physician must manage fluid resuscitation, vasopressors, and blood transfusion to prevent or treat acute coagulopathy of trauma.

[0004] Compensatory Reserve Metric (CRM) for trauma victims suffering from hypovolemia (decreased circulating blood volume) is a single health indicator value that ranges from 100% for healthy individuals, down to 0% at hemodynamic decompensation - when the body can no longer compensate for blood loss. However, identifying the point of

decompensation needed for developing CRM can be subjective, often relying on qualitative observations made by the patient.

[0005] Canines, horses and other animals operating in hazardous situations, such as search and rescue or battlefield conditions, can also suffer from hemorrhagic shock and should be monitored for the severity of blood volume loss.

SUMMARY

[0006] Techniques are provided for determining quantitative metrics predictive of hemorrhagic shock based on objective measurements from arterial waveform sensors monitoring a subject, such as a human or other animal. The arterial waveforms can be obtained in any known manner, including obtained via an indwelling arterial cannula transducer and displayed on a monitor providing a beat-to-beat estimate of the systolic, diastolic, and mean arterial pressures (MAPs), or from optical transmission or electrical voltage measurements.

[0007] These techniques are based on machine learning on animal training data sets obtained through controlled exsanguination of laboratory animals, including animals that are surrogates for humans.

[0008] In a first set of embodiments, a method for monitoring blood loss in a subject animal includes collecting arterial pressure waveform measurements of the subject animal. The arterial pressure waveform measurements are collected by a pressure waveform sensor during an observation period spanning several heartbeats. The method also includes processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features. The method further includes outputting a value of at least one objective blood loss metric for the subject animal by providing the one or more extracted blood pressure features as input to one or more machine learning (ML) models. Still further the method includes presenting the value of the at least one objective blood loss metric. The one or more machine learning models are trained on multiple historical instances. Each instance includes historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination

experiment. The historical arterial pressure waveform measurements are associated with at least one historical objective blood loss metric value determined from directly-measured blood loss during the laboratory exsanguination experiment.

[0009] In some embodiments of the first set, the at least one objective blood loss metric includes a blood loss volume metric (BLVM) based on a ratio of a shed blood volume over a maximum shed blood volume that the subject animal can survive. In some of these embodiments, the at least one objective blood loss metric includes a hemorrhage area (HemArea) or mean arterial pressure area (MAPArea) or both derived from the BLVM.

[0010] In some embodiments of the first set, the at least one objective blood loss metric includes a percent estimated blood loss (PEBL) based on a ratio of a shed blood volume over a total blood volume for the subject animal. In some of these embodiments, the total blood volume for the subject animal is based on a height or weight, or both, and a species of the subject animal.

[0011] In some embodiments of the first set, the one or more machine learning models include an ensemble bagged trees model. In some of these embodiments, wherein the ensemble bagged trees model includes about eight to twelve blood pressure features as input and eight to 12 leaf nodes as output.

[0012] In some embodiments of the first set, the one or more blood pressure features are selected from a group including: peak-to-peak interval; area under a systolic rise; area under a trace from a systolic maximum to a start of a next beat subtracted by a pressure at a first inflection point and normalized by a number of samples in a single arterial pressure waveform; a duration of the systolic rise; or an area under a trace of a systolic decay.

[0013] In some embodiments of the first set, the method also includes handling or treating the subject animal based on the value of the at least one objective blood loss metric.

[0014] In some embodiments of the first set, the method also includes collecting additional arterial pressure waveform measurements based on the value of the at least one objective blood loss metric for the subject animal.

[0015] In other sets of embodiments, a computer readable medium or apparatus or system is configured to perform the steps of one or more of the above methods.

[0016] Still other aspects, features, and advantages are readily apparent from the following detailed description, simply by illustrating a number of particular embodiments and implementations, including the best mode contemplated for carrying out the invention. Other embodiments are also capable of other and different features and advantages, and its several details can be modified in various obvious respects, all without departing from the spirit and scope of the invention. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Embodiments are illustrated by way of example, and not by way of limitation, in the figures of the accompanying drawings in which like reference numerals refer to similar elements and in which:

[0018] FIG. 1A is a block diagram that illustrates an example of a computer-based system, used according to an embodiment;

[0019] FIG. 1B is a block diagram that illustrates an example of a sensor to use in computer system of Fig. 1A, according to an embodiment.

[0020] FIG. 1C is a plot that illustrates an example of raw output from a blood pressure waveform sensor, used as input according to an embodiment.

[0021] FIG. 1D is a plot that illustrates an example of derived features of a blood pressure waveform sensor, used as input according to an embodiment.

[0022] FIG. 2A is a block diagram that illustrates a training set, used according to an embodiment;

[0023] FIG. 2B is a block diagram that illustrates an example automatic process for machine learning values for uncertain parameters of a chosen model, according to an embodiment;

[0024] FIG. 3A is a block diagram that illustrates an example of a decision tree to be trained, according to various embodiments;

[0025] FIG. 3B is a block diagram that illustrates an example neural network to be trained, according to various embodiments;

[0026] FIG. 3C is a plot that illustrates example activation functions used to combine inputs at any node of a neural network, according to various embodiments;

[0027] FIG. 4A is a flowchart that illustrates an example of a method to train a machine learning (ML) model, including any neural network deep learning (DL) model, according to various embodiments;

[0028] FIG. 4B is a flowchart that illustrates an example of a method to use a trained ML or DL model, according to various embodiments;

[0029] FIG. 5 is a plot that illustrates examples of time series of mean arterial pressure (MAP) of input waveforms from a canine and time series output of two models, each trained to predict compensatory reserve measurement (CRM) as a blood loss metric, according to some embodiments;

[0030] FIG. 6 is a plot that illustrates examples of time series of mean arterial pressure (MAP) of input waveforms from a canine and a time series of training values for a blood loss volume metric (BLVM) and a prediction of BLVM from a trained ML model, according to an embodiment;

[0031] FIG. 7 is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output BLVM, according to various embodiments;

[0032] FIG. 8 is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output percent estimated blood loss (PEBL), according to various embodiments;

[0033] FIG. 9A is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output hemorrhage area (HemArea), according to various embodiments;

[0034] FIG. 9B is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output BVLM that is then used to HemArea, according to various embodiments;

[0035] FIG. 10A is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output mean arterial pressure area (MAParea), according to various embodiments;

[0036] FIG. 10B is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output MAP that is then used to derive MAParea, according to various embodiments;

[0037] FIG. 11 is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output TinyMAParea, according to various embodiments;

[0038] FIG. 12 is a block diagram that illustrates a computer system upon which an embodiment of the invention may be implemented;

[0039] FIG. 13 illustrates a chip set upon which an embodiment of the invention may be implemented; and

[0040] FIG. 14 is a diagram of exemplary components of a mobile terminal (e.g., cell phone handset) for communications, which is capable of operating in the system, according to one embodiment.

DETAILED DESCRIPTION

[0041] A method and apparatus are described for outputting an objective metric of blood loss in animals, including humans. In the following description, for the purposes of explanation, numerous specific details are set forth in order to provide a thorough understanding of the present invention. It will be apparent, however, to one skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known structures and devices are shown in block diagram form in order to avoid unnecessarily obscuring the present invention.

1. Computer based system

[0042] FIG. 1 is a block diagram that illustrates an example of a computer-based system, used according to an embodiment. The system includes a network 110 of interconnected communication devices using wired or wireless single channel or multichannel connections 105. User devices such as laptop 131 and mobile device 132 are connected to the network using one or more wired or wireless single channel or multichannel connections 105. One or more server nodes 120, often at different locations, also using one or more connections 105, provide services for devices connected to the system 100, and store data in one or more

special storage nodes 140, often at different locations, also using one or more connections 105. In addition, in some systems, one or more sensors 150 (such as digital cameras, telescopes, laser and radar detectors, medical imagers, patient vital signs monitors, etc.) respond to physical phenomena with signals that are converted to data transmitted over connections 105 to other devices in the system 100. In addition, in some systems, one or more actuators 160 (such as assembly line robots, 2D and 3D printers, lasers, radiation sources, etc.) produce physical phenomena in response to signals received as data transmitted over connections 105 from other devices in the system 100. Each of these components include one or more software modules that operate the device and communicate with other devices in the systems, as represented by the module 181 for the network 110, module 182 for server(s) 120, module 183 for user device laptop 131 or mobile device 132, module 184 for storage node(s) 140, module 185 for sensor 150, and module 186 for actuator 160. The software modules 181, 182, 183, 184, 185 and 185 are collectively referenced herein as software modules 180.

[0043] Although processes, equipment, and data structures are depicted in FIG. 1 as integral blocks in a particular arrangement for purposes of illustration, in other embodiments one or more processes or data structures, or portions thereof, are arranged in a different manner, on the same or different hosts, in one or more databases, or are omitted, or one or more different processes or data structures are included on the same or different hosts.

2. Blood pressure monitoring

[0044] FIG. 1B is a block diagram that illustrates an example of a sensor 151 to use in computer system 100 of FIG. 1A, according to an embodiment. One or more sensors 151 are embodiments of sensor 150 depicted in FIG. 1A. Sensors 151 monitor a physical state of a subject animal, such as canine subject 190, and communicates data to computer system 130, such as laptop 131 or mobile device 132 or remote server 140, or some combination. Although canine subject 190 is depicted for purposes of illustration, canine subject 190 is not part of system 100. Any set of one or more sensors that monitors a condition of an animal subject may be used as sensors 151. In various embodiments, sensors 151 include an

indwelling arterial cannula pressure transducer or external pressure cuff, or photo optic sensors and components for an oximeter that non-invasively measures blood oxygenation (SpO_2) level variations and pulse from the photoplethysmography waveform, or electrical voltage transducer that measures heartrate. In the illustrated embodiments, the sensors 151 measure directly (e.g., using the cannula or pressure cuff) or indirectly (e.g., using pulse rate) an arterial pressure waveform.

[0045] The computing device 130 includes a blood loss metric prediction module 187 that includes one or more data structures that hold data that indicates one or more machine learning (ML) or deep learning (DL) models that have been previously trained on a training set, as described in more detail below. The output of module 187 is the value of each of one or more blood loss metrics, selected from those described in more detail below, after each of one or more blood pressure pulses detected by sensors 151.

[0046] FIG. 1C is a plot that illustrates an example of raw data from a blood pressure waveform sensor, used as input according to an embodiment. The horizontal axis indicates time in arbitrary units and the vertical axis indicate pressure in arbitrary units. The pressure waveform revers to the time evolution of pressure over several pressure pulses. Each pressure pulse includes a systolic upstroke, a systolic peak pressure, and post peak features that include a systolic decline, a dicrotic notch, a diastolic runoff to an minimum pressure called an end diastolic pressure.

[0047] FIG. 1D is a plot that illustrates an example of derived features of a blood pressure waveform sensor, used as input according to an embodiment. As illustrated in FIG. 1D, the height and width of these arterial pressure waveform pulses can vary over time based on changing conditions of the subject. The time average of a pressure waveform pulse from the beginning of the systolic upstroke until the end diastolic pressure is called the mean arterial pressure (MAP). As shown in FIG. 1D, the value of MAP for the first pulse is less than the value of MAP for the second pulse. The MAP is one feature of a blood pressure pulse waveform. Other features fall into types or categories listed in Table 1.

Table 1. Candidate blood pressure waveform feature types.

Feature Category	Description	Examples*	Quantity
Base features	Feature calculated using simple mathematical manipulation of the landmarks of the BP beat	Peak to peak interval, Pulse area, average pressure of the systolic phase, ratio of the systolic to diastolic, slope at the half rise between the pulse foot and systolic peak	42
Normalization by number of samples in a window	Base features are normalized by dividing the number of samples in a window	**[0010]** iastolic area divided by the number of samples in a window between the pulse foot and the end of the waveform	11
Normalization by number of samples in the entire signal	Base features are normalized by dividing the number of samples in the entire signal	Systolic decent area divided by the number of samples in the signal where the systolic decent area was calculated from	201
NODIA features	Base features are normalized by subtracting the	Mean of the systolic decent subtracted by the waveform value of the inflection point	20

	waveform value at the inflection point	where the mean of the systolic decent was calculated from	
Normalization by the width of the heartbeat pulse	Base features are normalized by dividing the width of the pulse	Pulse pressure divided by the width of the waveform where the pulse pressure was calculated from	6
Normalization by the width of the entire signal	Base features are normalized by dividing the width of the entire signal	Systolic area divided by the width of the signal where the systolic was calculated from	6
Variability (Heartbeats)	The standard deviation of the base features over a window of 20 heartbeats	Variability of the ratio between the waveform value of the systolic point and the diastolic point	95
Variability (Time)	The standard deviation of the base features over a window of 20 seconds	Variability of the average slope between the pulse foot and the systolic peak	95

Simple Delta-Change	Base features normalized by subtracting the mean value of the window from the mean of the baseline	Simple Delta-Change of the peak to peak interval	475
Complex Delta-Change (Heartbeats)	Base features normalized by subtracting the mean value of a shifting window of heartbeats from the mean of the baseline	Complex Delta-Change (20 heartbeats) of the area of the region between the pulse foot and the half rise between the pulse foot and the systolic peak	475
Complex Delta-Change (Time)	Base features normalized by subtracting the mean value of a shifting window of time from the mean of the baseline	Complex Delta-Change (20 seconds) of the systolic area	475

3. Machine Learning Overview

[0048] In general, machine learning (ML) involves one or more models M each with fixed parameters P that relates input variables X to outputs of interest (aka results) Y. This relationship is represented by Equation 1.

$$Y = M(P, X) \quad (1)$$

Machine learning learns the values of parameters P that best relate the input variables X to output of interest Y based on training data with known values for X and Y. In most cases, Machine Learning (ML)/Artificial Intelligence(AI) is automatically learning the values for the parameters P that are constant while using model M on multiple different instances of input data X. The model M can be a physical model that attempts to capture known mechanisms that relate X to Y, or can be purely statistical, wherein no mechanism is implied or enforced, or some combination.

[0049] FIG. 2A is a block diagram that illustrates a training set 200, used according to an embodiment. As shown in FIG. 2A, The training data set 200 includes values of both input X 202 and output Y 204 for each instance 201 of multiple experimental and or historical instances and usually has many more instances than the number of parameters P to be learned. The input X 202 can be a single value, such as binary or rational value, a complex number with real and imaginary parts, or a vector of values for multiple input features, such as a time series of values for a feature or values for a set of different features, or a matrix of values, such as 2 dimensional (2D) set of time series for different features, or an image, 3 dimensional (3D) sets of images at different slices from a medical scanner or at different times in a video stream, or 4D sets of images at different slices and times, or even higher dimensional matrices. The output Y 204 can likewise be a value, vector or matrix of dimension the same or different from the dimensions of input X 202.

[0050] Various learning approaches are known and fall into three categories. In supervised learning, the computer is presented with example inputs and their desired outputs, given by a "teacher", and the goal is to learn a general rule that maps inputs to outputs. In unsupervised learning, no labels are given to the learning algorithm, leaving it on its own to find structure in its input. Unsupervised learning can be a goal in itself (discovering) or a means towards an end (feature learning). In reinforcement learning, a computer program interacts with a dynamic environment in which it must perform a certain goal (such as driving a vehicle or playing a game against an opponent). As it navigates its problem space, the program is provided feedback that's analogous to rewards, which it tries to maximize.

[0051] FIG. 2B is a block diagram that illustrates an example automatic process for learning values for uncertain parameters P 212 of a chosen model M 210, according to an embodiment. The model M 210 can be a Boolean model for a result Y of one or more binary values, each represented by a 0 or 1 (e.g., representing FALSE or TRUE respectively), a classification model for membership in two or more classes (either known classes or self-discovered classes using cluster analysis), other statistical models such as multivariate regression or neural networks, or a physical model, or some combination of two or more such models. A physical model differs from the other purely data-driven models because a physical model depends on mathematical expressions for known or hypothesized relationships among physical phenomena. When used with machine learning, the physical model includes one or more parameterized constants, such as propagation loss coefficients, that are not known or not known precisely enough for the given purpose.

[0052] During training depicted in FIG. 2B, the model 210 is operated with current values 212 of the parameters P, including one or more uncertain parameters of P (initially set arbitrarily or based on order of magnitude estimates) and values of the input variables X 202 from an instance 201 of the training set 200. The values 218 of the output Y_M from the model M, also called simulated measurements, are then compared to the values 220 of the known result output variables Y 204 from the corresponding instance 201 of the training set 200 in the parameters values adjustment module 230.

[0053] The parameters values adjustment module 230 implements one or more known or novel procedures, or some combination, for adjusting the values 212 of the one or more uncertain parameters of P based on the difference between the values of Y_M 218 and the values of Y 204. The difference between Y_M 218 and Y 204 can be evaluated using any known or novel method for characterizing a difference, including least squared error, maximum entropy, fit to a particular probability density function (pdf) for the errors, e.g., using *a priori* or *a posterior* probability. The model M 210 is then run again with the updated values 212 of the uncertain parameters of P and the values of the input variables X from a different instance 201 of the training set 200. The updated values 218 of the output Y_M from the model M 210 are then compared to the values of the known output variables Y 204 from

the corresponding instance of the training set 200 in the next iteration of the parameter values adjustment module 230.

[0054] The process of FIG. 2B continues to iterate until some stop condition is satisfied. Many different stop conditions can be used. The model can be trained by cycling through all or a substantial portion of the training set. In some embodiments, a minority portion of the training set 200 is held back as a validation set. The validation set is not used during training, but rather is used after training to test how well the trained model works on instances that were not included in the training. The performance on the validation set instances, if truly randomly withheld from the instances used in training, is expected to provide an estimate of the performance of the learned model in producing Y_M when operating on target data X with results Y that are not already known. Typical stop conditions include one or more of a certain number of iterations, a certain number of cycles through the training portion of the training set, producing differences between Y_M and Y less than some target threshold, producing successive iterations with no substantial reduction in differences between Y_M, or not substantial differences in the values of the uncertain parameters P, or errors in the validation set less than some target threshold, among others.

[0055] One type of model 210 is the well-known and long-used regression analysis, in which the variability in the output Y is associated with variability of each of one or more candidate input variables. In regression analysis, the output Y is a linear or non-linear combination of the inputs with coefficients of each input constituting the learned parameters P.

[0056] Another type of model 210 is a decision tree model. A decision tree model is an algorithm that is considered to be basically a decision tree, i.e., a sequence of queries or tests that are done adaptively, so the outcome of previous tests can influence the tests performed next. FIG. 3A is a block diagram that illustrates an example of a decision tree 300 to be trained, according to various embodiments. Start at the root node 301. This is an ensemble made up of many instances of the training set. Certain values of the known outputs Y 204 are considered to be in a category to be detected, such as one of two or more classes, or a narrow range of a broad range of possible output values Y. An "impurity" metric of the node indicates how many instances are outside one category of instances. The root node ensemble

has, by definition, many instances of multiple categories and has a high impurity level. For each input feature Xi of the input parameters X of each instance, the algorithm finds the potential split (threshold *Ti*) that minimizes the sum of the node impurities in the two child nodes; and from these splits for all input features, the algorithm chooses the one threshold T_1 for the one feature X_1 that gives the overall minimum. This threshold test is depicted in FIG. 3A as branch test 302a based on input feature X_1.

[0057] The result of the split of X_1 based on threshold T_1 give two child nodes, also called branch nodes. If a stop condition is not reached, each child node is split similarly in turn, as depicted in FIG. 3A as branch test 302b and 302c on input features X_2 and X_3, respectively, which may be different from input feature X_1. Either feature X_2 or X_3 may be the same as feature X_1, but with a different threshold T_2 from threshold T_1. The branching continues at deeper levels, such as branch test 202d among other test indicated by ellipsis, and any deeper levels indicated by additional ellipsis. If a stopping criterion is reached, then the tree stops growing and any node with no child node is called a leaf node. The leaf nodes indicate the classes or ranges output by the model and may be at the same branch level or a different branch levels. From each other. FIG. 3A depicts leaf nodes 304 representing putputs Class A, Class B, Class C and Class D plus zero or more classes indicated by ellipsis.

[0058] The training determines which input features serve as X_1, X_2 etc., and what are the corresponding thresholds T_1, T_2, etc., respectively. Bagging, also known as bootstrap aggregation, is an ensemble decision tree learning method that is commonly used to reduce variance within a noisy data set. In bagging, an ensemble for training a decision tree is a random sample of data in a training set selected with replacement—meaning that an individual instance 201 can be chosen for more than one ensemble. The different decision trees resulting from different ensembles are then combined. In some embodiments, described in more detail below, an ensemble bagged trees machine learning (ML) model was chosen as the model 210 for predicting, as model output Y_M, one or more canine blood loss metrics that are described in more detail below.

[0059] Deep learning (DL) refers to a subset of ML using one or more neural networks within the model 210. Deep learning is widely used in image processing and natural language

processing. FIG. 3B is a block diagram that illustrates an example neural network 200, according to various embodiments. A neural network 200 is a computational system, implemented on a general-purpose computer, or field programmable gate array, or some application specific integrated circuit (ASIC), or some neural network development platform, or specific neural network hardware, or some combination. The neural network is made up of an input layer 210 of nodes, at least one hidden layer 220, 230 or 240 of nodes, and an output layer 250 of one or more nodes. Each node is an element, such as a register or memory location, that holds data that indicates a value. The value can be code, binary, integer, floating point or any other means of representing data, including arrays of values in vectors or matrices. Values in nodes in each successive layer after the input layer in the direction toward the output layer is based on the values of one or more nodes in one or more previous layers. The nodes in one layer that contribute to the next layer are said to be connected to the node in the later layer. Connections 212, 223, 245 are depicted in FIG. 2A as arrows. The values of the connected nodes are combined at the node in the later layer and weighted using some activation function with scale and bias (also called weights) that can be different for each connection. Neural networks are so named because they are modeled after the way neuron cells are connected in biological systems. A fully connected neural network has every node at each layer connected to every node at any previous or later layer.

[0060] FIG. 3C is a plot that illustrates example activation functions used to combine inputs at any node of a neural network, according to various embodiments. These activation functions are normalized to have a magnitude of 1 and a bias of zero; but when associated with any connection can have a variable magnitude given by a weight and centered on a different value given by a bias. The values in the output layer 250 depend on the values in the input layer and the activation functions used at each node and the weights and biases associated with each connection that terminates on that node. The sigmoid activation function (dashed trace) has the properties that values much less than the center value do not contribute to the combination (a so called switch off effect) and large values do not contribute more than the maximum value to the combination (a so called saturation effect), both properties frequently observed in natural neurons. The *tanh* activation function (solid

trace) has similar properties but allows both positive and negative contributions. The *softsign* activation function (short dash-dot trace) is similar to the *tanh* function but has much more gradual switch and saturation responses. The rectified linear units (ReLU) activation function (long dash-dot trace) simply ignores negative contributions from nodes on the previous layer, but increases linearly with positive contributions from the nodes on the previous layer; thus, ReLU activation exhibits switching but does not exhibit saturation. In some embodiments, the activation function operates on individual connections before a subsequent operation, such as summation or multiplication; in other embodiments, the activation function operates on the sum or product of the values in the connected nodes. In other embodiments, other activation functions are used, such as kernel convolution.

[0061] An advantage of neural networks is that they can be trained to produce a desired output from a given input without knowledge of how the desired output is computed. There are various algorithms known in the art to train the neural network on example inputs with known outputs. Typically, the activation function for each node or layer of nodes is predetermined, and the training determines the weights and biases for each connection. A trained network that provides useful results, e.g., with demonstrated good performance for known results, is then used in operation on new input data not used to train or validate the network.

[0062] In some neural networks, the activation functions, weights and biases, are shared for an entire layer. This provides the networks with shift and rotation invariant responses. The hidden layers can also consist of convolutional layers, pooling layers, fully connected layers and normalization layers. The convolutional layer has parameters made up of a set of learnable filters (or kernels), which have a small receptive field. In a pooling layer, the activation functions perform a form of non-linear down-sampling, e.g., producing one node with a single value to represent two or more nodes in a previous layer. There are several non-linear functions to implement pooling among which max pooling is the most common. A normalization layer simply rescales the values in a layer to lie between a predetermined minimum value and maximum value, e.g., 0 and 1, respectively. A dropout layer improves

generalization and prevents overfitting by randomly disabling a proportion of neurons during training, encouraging the network to learn more robust features.

[0063] In some embodiments, described in more detail below, a neural network, i.e., a deep machine learning (DL) model, was chosen as the model 210 for predicting, as model output Y_M, one or more objective blood loss metrics that are described in more detail below. The training determines which input features serve as X, and what are the corresponding thresholds weights and biases applied to the connections at each node in each hidden layer.

4. Objective Blood loss monitoring system

[0064] Some embodiments of the invention are described here based on training data collected from six canines using machine learning (ML) technique and certain features of the arterial waveform to use as input X and various species independent, objective blood loss metrics to use as output Y as a substitute for the human subjective CRM. However, the invention is not limited to this embodiment. In other embodiments, more or fewer canines or other animal subjects or surrogates for human subjects, such as swine, are used in the training set, more or fewer or different features of the arterial waveform are used as input X, different objective metrics are used as output, and different ML or DL models are used to produce the output Y from the input X.

[0065] Hemorrhage (i.e, shedding blood, also simply called bleeding) can be risky to humans, canines and other service animals alike. One related risk is the risk of occult shock, which is generally defined as a state of tissue hypoperfusion despite normal macrocirculatory parameters. Both hemorrhage and occult shock may be associated with higher morbidity and mortality in animals. In turn, effective hemorrhage detection is critical for animal patient safety. Effective hemorrhage detection may require both time sensitivity (e.g., early detection) and patient specificity (e.g., identifying individual patient pathophysiological status). At a single instant in time, occult shock might be identified using static measures of legacy vital signs (e.g., heart rate, arterial blood pressure), urine characteristics (e.g., volume, specific gravity, color), and blood chemistry (e.g., systemic lactate concentration). Such approaches to occult shock often fail to be speedy and patient-specific when measures remain

in normal or near-normal ranges during phases of compensation, when measures contain significant inter-individual variability, and/or when measures provide little information for specific early diagnosis. Such issues likely result from measuring only parts (such as single snapshots in time) of a complex integrated cascade of inter-related physiological compensatory mechanisms that function to avoid reduced tissue oxygenation after significant blood losses.

[0066] In contrast to the single time, static approach, the inventors here use changes in one or more measured features over time. For example, changing features in the arterial pressure waveform help remediate the above issues based on static measurements, because the evolution of the arterial waveform contains information both about the individualized normal state of the subject and about the individualized integrated compensatory responses of the subject to blood loss. For example, a human patient's arterial waveform might be monitored over time using a sensor 151 such as a pulse oximeter, and data from that pulse oximeter can be analyzed by a computing device to identify hemodynamic decompensation specific to that subject. When implemented properly, as shown herein, this approach provides an earlier assessment with higher sensitivity and specificity to predict subject status compared to standard vital signs and other static hemodynamic and metabolic measurements. Indeed, the inventors here demonstrate that the temporal monitoring approach incorporates and recognizes differences in fully integrating all physiological compensatory mechanisms that protect against inadequate blood pressure regulation, systemic blood flow, and tissue oxygenation associated with hypovolemia.

[0067] Adding to the challenge for treating non-human animals, inventors have observed that improvements in the diagnosis and monitoring of human patients are not easily adapted to canine patients. Tests performed to attempt to analogize research data and machine learning techniques for humans and/or baboons on canines generally suggest poor correlations between the two. More broadly, in veterinary medicine, determination of volume status continues to be challenging. Veterinarians often rely on clinical judgment and surrogates to volume status and tissue perfusion, but this approach can waste significant intellectual capital in identifying when an animal patient is fully and not over-resuscitated.

As such, veterinarians often find themselves tasked with not only concentrating on the technical challenges of the emergent surgeries at hand, but also simultaneously needing to guide anesthesia and monitoring of their critical animal patients. This is particularly wasteful when veterinary teams tend to be relatively understaffed, less funded, and the like. For example, teams for military working dogs (e.g., those handling military working dog combat casualties) may have staffing and equipment limitations, forcing those teams to expend significant time and effort on tasks that are easier in the human context. This has significant consequences. For example, during Operation Iraqi Freedom and Enduring Freedom, trauma (including hemorrhagic shock) was a leading cause of death among military working dogs.

[0068] During experiments that serve as an example of the type of ML that can be performed on a larger sample set to train various models, adult (one to six-year-old) male purpose-bred laboratory canines from 30-50 kilograms (kg) were anesthetized, instrumented, and underwent a controlled hemorrhage through a catheter in a jugular artery or in either the left or right femoral artery (all canines were treated, allowed to recover, and happily adopted after this testing). Hemorrhage proceeded until one of two endpoints were reached: either a mean arterial pressure of 50 mmHg; or 40% blood volume removed. The study canines were held at this hypovolemic state for 45 minutes, then resuscitated. During this process, arterial waveform data from baseline through to hemorrhage and resuscitation was collected at one thousand samples per second (kilohertz, kHz, later down sampled to 500 samples per second, hertz, Hz)

[0069] One of many discoveries during this testing was that the compensatory reserve measurement (CRM) used for humans (that is, a 0 to 1 value calculated from the difference of a value of 1 and the ratio of the current pressure being experienced in a lower body negative pressure (LBNP) chamber to the maximum pressure experienced in the study) was somewhat unhelpful when analyzing canine hemorrhage. Animals cannot answer the subjective questions used in determining CRM, such as degree or temporal onset of symptoms. Similar limitations occur when the human is unconscious or otherwise gives uncalibrated responses to subjective observations. During the baseline readings collected from the canines, the CRM for the canines was on average 0.41 +/- 0.12. Indeed, during

hemorrhage, the CRM reached a minimum value more quickly than the mean arterial pressure (MAP) and the CRM decreased by 75% at the minimum, whereas the mean arterial pressure (MAP) had only decreased by 26% at the same time point. The CRM and MAP both rise in the 45 minute phase of constant maximum total blood loss before resuscitation.

[0070] Various objective blood loss metrics to use as ML outputs Y, were developed for this work. An objective analog for CRM was developed called a Blood Loss Volume Metric (BLVM), calculated as given by Equation 2a.

$$BLVM = 1 - \frac{Shed\ blood\ volume(t)}{Maximum\ ShedHemorrhaged\ Blood\ Volume} \quad (2a)$$

[0071] Another objective blood loss metric developed for this work to use as ML output Y is hemorrhage area (HemArea), which is calculated as the integral of the blood loss volume curve versus the time during hemorrhage, as given by Equation 2b.

$$HemArea = \sum BLVM \times \Delta t \quad (2b)$$

[0072] Another objective blood loss metric developed for this work to use as ML output Y is percent estimated blood loss (PEBL), which gives a percentage of the total blood volume of a subject which is estimated from an animal's weight or weight and height for different species, calculated as given by Equation 1c.

$$PEBL = \frac{Hemorrhage\ Volume\ (t)}{Total\ Blood\ Volume} \quad (2c)$$

Note, that the blood loss was measured during the experiments on the six subject canines, so that the values of these metrics over time could be determined precisely for the Y values in the training set. These metrics track the actual measured blood loss over time very well, compared to CRM or MAP, as will be shown in more detail below.

[0073] Another objective blood loss metric developed for this work is mean arterial pressure area (MAPArea, also called BAP_Burden) which is the area under a MAP trace over time given by Equation 2d.

$$MAParea = \sum MAP(t) \times \Delta t \quad (2d)$$

[0074] Another objective metric for analyzing the mean pressure experienced by an animal in their baseline region was the MAP burden, calculated by taking the mean MAP from the baseline region and subtracting that value from the MAP at a later time t. This normalized MAP value is then multiplied by the time between the MAP at the point of interest and the following MAP time. These normalized integral slices may then be cumulatively summed to calculate the total integral accumulation of the animal, as given by Equation 2d. High MAP is not a health issue so the high MAP area doesn't matter. So TinyMAParea is defined relative to a starting MAP (MAP(baseline)) so only MAPs below that are included, as given by Equation 2e.

$$TinyMAParea = \sum [MAP(t) - MAP(baseline)] \times \Delta t \quad (2e)$$

[0075] FIG. 4A is a flowchart that illustrates an example of a method 400 to train a machine learning (ML) model, including any neural network deep learning (DL) model, according to various embodiments. Although steps are depicted in FIG. 4A, and in subsequent flowchart FIG. 4B, as integral steps in a particular order for purposes of illustration, in other embodiments, one or more steps, or portions thereof, are performed in a different order, or overlapping in time, in series or in parallel, or are omitted, or one or more additional steps are added, or the method is changed in some combination of ways .

[0076] In step 401, arterial pressure waveforms, such as depicted in FIG. 1C, are collected simultaneously with calibrated measurements of blood volume shed during exsanguination experiments on multiple animals of a species related to whatever subject animal is to be monitored using machine learning models. In the example embodiment, described below, the species is canines. In other embodiments, other experiments are performed on other species, such as horses, or, as a human analog, ape or swine species. In the example exsanguination experiments, the arterial waveforms are collected during a pre-bleeding phase, followed by a

time duration of constant bloodletting through an artery of the experimental animal, with collected blood volume measured, through to a degree of maximum blood loss from which the experimental animal can survive. The maximum blood loss can be determined by total volume shed being 40% of the estimated total volume of the animal based on its species and size (e.g., height or weight or both) or a MAP of about 50 millimeters of Mercury (mmHg). The animal is maintained at this constant level of maximum survivable blood loss for a period, such as 45 minutes, as the body tries to recover from the blood volume loss. This period is called the shock hold period. Then the animal is resuscitated, during which time the arterial pressure waveform may or may not be measured.

[0077] A time series of pressure is obtained covering multiple pressure pulses associated with heartbeats. Time resolution is much higher than a heart rate that is about 1 to 4 beats per second (hertz, Hz) in most animals, so that detection of blood pressure variation during one beat and variability beat to beat can be detected. Thus, the sampling rate is selected in a range from 100 hertz (Hz) to 1000 Hz. In various embodiments, various forms of processing of the arterial waveform data collected during the study were performed for best accuracy. For example, to meet the particular needs of the models and tools used in the study, the arterial waveform data was down sampled to twenty-second-long samples with overlaps of 10 seconds (ultimately processed into ten second intervals) and smoothed using a finite impulse response window lowpass filter (specifically, using a moving mean with a window of 500 samples). Inflection points were identified in this data by specifically identifying, for a given waveform, a pulse foot, a systolic peak, a half-rise between the pulse foot and the systolic peak, a first inflection point, and an end of the waveform segment. When a waveform segment lacked an inflection point, the half-drop between the systolic peak and the following pulse foot was calculated. Such approaches are optional and largely tools-related, but underscore the type of training that might be advantageous in implementation.

[0078] Thus step 401 illustrates historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination experiment.

[0079] In step 403, time series of values for multiple candidate features of arterial pressure waveforms are determined. As shown in FIG. 1D, mean arterial pressure (MAP) over the pressure waveform for a single beat is one example of a candidate feature. Observations have shown that MAP is quite variable and does not closely map the blood volume shed during an exsanguination experiment. Thus, other features are derived from the pressure waveform for each heartbeat or variations between two or more successive heartbeats. In this way dozens to hundred to thousands of features can be defined to capture characteristics of beat to beat variability in a pressure waveforms that can be considered as inputs X to a ML model, including any DL model. In various embodiments, the various combinations of the candidate features listed in Table 2 are determined or derived from the measured pressure waveforms. Thus step 403 includes, processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features.

[0080] In step 405, a subset of the candidate features of arterial pressure waveforms are selected based on their expected or estimated relevance to indicating blood loss. In some embodiments, this is done by inputting the values of the measured blood loss and the corresponding values of the candidate features into a Minimum Redundancy Maximum Relevance (MRMR) Algorithm. The MRMR algorithm finds a ranked set of features that is mutually and maximally dissimilar and can represent the response variable effectively in order from most relevant to least relevant, without redundancy. For example, using canine bloodletting data, the most relevant features are: peak-to-peak interval; area under a trace of a systolic rise; area under a trace from a systolic maximum to a start of a next beat subtracted by a pressure at a first inflection point and normalized by a number of samples in a single arterial pressure waveform; a duration of the systolic rise; and, an area under a trace of a systolic decay. In other embodiments, more or fewer pressure waveform features are included. Thus step 405 includes processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features. An advantage of selecting candidate features in steps 403 and 405 rather than putting the waveform directly into a statistical model such as the decision tree or a neural network, is that the resulting highly weighted inputs provide a physiological understanding of what about the waveform is

driving the predictions. Such an understanding is lacking in purely statistical models on the original input waveform.

[0081] In step 407, a time series of values for one or more objective blood loss metrics are determined for the time durations of the exsanguination experiments. Objective blood loss metrics outperform CRM and include a blood loss volume metric (BLVM) based on a ratio of a shed blood volume over a maximum shed blood volume that the subject animal can survive, as expressed in Equation 1a, above; a hemorrhage area (HemArea) using Equation 1b or mean arterial pressure area (MAPArea) or both derived from the BLVM using Equation 1b and Equation 1d, respectively; and a percent estimated blood loss (PEBL) based on a ratio of a shed blood volume over a total blood volume for the subject animal using Equation 1c.

[0082] Thus, step 407 includes associating historical arterial pressure waveform measurements with values of at least one historical objective blood loss metric determined from directly-measured blood loss during the laboratory exsanguination experiment.

[0083] In step 409, a training set of multiple historical instances is generated. Each historical instance includes, for one or more times during an exsanguination experiment, input (X) values for at least five highest ranked features and output (Y) value(s) for at least one blood loss metric.

[0084] In step 411, one or more ML or DL models or some combination of models are selected to be trained using the training data. For example, in some embodiments a regression model is selected for which training determines the coefficients of linear or higher powers of the input parameters. In some embodiments a decision tree model is used. In some embodiments bootstrap aggregation (baffing) is used for a decision tree model. In some embodiments, a neural network DL model is used. Routines to implement and train all these models are available, for example, in MATLAB™ available from MATHWORKS™ of Natick, Massachusetts.

[0085] In step 413, one or more models are trained for each instance of multiple instances from training set. For example 80% of the training set is used to establish values for the uncertain parameters P of the selected model or models, e.g., using MATLAB™. Thus, in

step 411, the one or more machine learning models are trained on a plurality of historical instances.

[0086] In step 415, the one or more trained models are validated using training set instances not used during training, e.g., using the 20% of the training set not used in step 413. Moreover, to avoid bias from this arterial waveform data, a Leave One Subject Out (LOSO) approach was employed during testing of the trained machine learning model. For the six canines of the example experiment described below, this process was performed six times, where each subject was held out for blind test while the rest of the data was used for training. For example, an ML model was trained with canines one to five followed by blind testing on all the different rounds of canine 6, resulting in an unbiased BLVM prediction for that subject. That BLVM prediction was then smoothed and used in a linear regression, as described above

[0087] In step 417, the one or more trained and validated models are installed into blood loss metric prediction module 187, depicted in FIG. 1B, and the ML/DL model training process ends. For example, the computing device may receive the trained machine learning model and/or may generate the trained machine learning model by providing, to a machine learning model, training data. The trained machine learning model may be trained to identify hemorrhage based on training data indicating, for each of a plurality of canine patients, an arterial waveform and an indication of whether the corresponding canine patient was undergoing a hemorrhage. The training data may comprise, for example, arterial waveform information such as a peak-to-peak interval, an area under the curve of a systolic rise, an area from a systolic maximum to a start of a next beat subtracted by a pressure at a first inflection point and normalized by a number of samples in the arterial waveform, a duration of a systolic rise, and/or a calculated area under a curve of systolic delay.

[0088] FIG. 4B is a flowchart that illustrates an example of a method 450 to use a trained ML or DL model, according to various embodiments. In step 451, an arterial pressure waveform at next heartbeat pressure pulse is obtained from next subject of species, e.g., by operating sensor 151 to collect the data or receiving waveform data from local or remote storage either unsolicited or in response to a query. Thus step 451 includes collecting arterial

pressure waveform measurements of a subject animal, the arterial pressure waveform measurements collected by a pressure waveform sensor during an observation period spanning several heartbeats.. For example, the computing device may receive, via one or more sensors, arterial waveform data that indicates heart activity of a canine subject. The one or more sensors may comprise, for example, a pressure transducer and/or a pulse oximeter

[0089] In step 453, for the collected pulse, the values for each feature of the highest ranked features are calculated and used as inputs (X) for each of one or more trained models. Thus step 453 includes processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features. provide the arterial waveform data as input to the trained machine learning model. For example, the computing device may provide, as input to one or more input nodes of the trained machine learning model, the features derived from the arterial waveform data or the arterial waveform data itself.

[0090] In step 455, a value for an objective blood loss metric for that collected pulse is output Y from each of the one or more models in response to using the blood pressure features as input X. For example, one or more of BLVM, HemArea, MAParea and PEBL is output by the trained models. Thus step 455 includes outputting a value of at least one objective blood loss metric for the subject animal by providing the one or more extracted blood pressure features as input to one or more machine learning (ML) models. computing device may receive output from the trained machine learning model. For example, the computing device may receive, as output from one or more output nodes of the trained machine learning model, an indication of whether the arterial waveform data corresponds to a hemorrhage. The output may comprise and/or be based on indications of the BLVM, the PEBL, the HemAreaModel, the HemAreaCalc, the MAP-AreaModel, and/or the MAP-AreaCalc.

[0091] In step 461, it is determined whether a criterion is satisfied for issuing a notification. For example, it is determined whether the objective blood loss metric indicates a loss of 5% or more for the subject animal so that a notification is warranted. In general, the computing device determines whether to transmit a notification based out the output received in step

455. If the computing device decides to transmit the notification, the method proceeds to step 463. In step 463 the notification with the value of the objective blood loss metric is issued, such as by sending a message or presenting the value on a display device. For example, the computing device may cause, based on the indication of whether the arterial waveform data corresponds to the hemorrhage, output of a notification. The indication of whether the arterial waveform data corresponds to the hemorrhage may indicate a prediction of oncoming decompensation. As another example, the computing device may predict, based on the indication of whether the arterial waveform data corresponds to the hemorrhage, total blood loss, such that the notification indicates the predicted total blood loss. Thus, step 461 and 463 include presenting the value of the at least one objective blood loss metric.

[0092] In step 465 it is determined whether there is another arterial pressure waveform pulse to obtain from the current subject animal. If so, control passes back to step 467 to collect the next waveform pulse of blood pressure from the same subject animal. Control then passes back to step 453 and following, described above, to process the next pulse and produce another output value for the objective blood loss metric.

[0093] If in step 465 it is determined there is not another arterial pressure waveform pulse to obtain from the current subject animal, the process ends for the current subject animal and control passes to step 471. In step 471 it is determined whether there is another animal of the same species to monitor blood loss using the trained ML/Dl models for that species. If so, control passes back to step 451 and following steps, described again, to process the pulses from the next subject animal and produce an output value of the objective blood loss metric for the next subject. If not, the process ends.

5. Objective blood loss monitoring system performance

[0094] An example blood loss monitoring system was developed and performance tested for canines. The blood pressure features found to be useful in modeling example blood loss metrics HemArea,, PEBL, BLVM are listed here. The meaning of these features can be inferred from the name and the categories listed in Table 1. For instance - Area_CC_Zeroed_ComplexDeltaChange would be the area from point C to C of successive

waveforms, zeroed to a baseline value and the feature is actually the delta change from a previous pair of waveforms.

Hem Area

Area_CC_Zeroed_ComplexDeltaChange

Ratio_BD_ComplexDeltaChange

BP_Area_Var_Norm_ComplexDeltaChangeTime

Ratios_ThirtyThree_Var_ComplexDeltaChangeTime

Interval_CC_Var_Time_Norm_ComplexDeltaChangeTime

Area_CD_Zeroed_Var_ComplexDeltaChange

Area_AA_Var_Time_Norm_ComplexDeltaChangeTime

sys_dec_area_norm_CB_Var_Norm_ComplexDeltaChange

Area_AA_Zeroed_ComplexDeltaChange

sys_area_nor_CB_ComplexDCTime

sys_rise_area_Var_Time_Norm_ComplexDeltaChangeTime

dia_area_norm_nodia_Var_Norm_ComplexDeltaChange

pp_area_Var_Time_Norm_ComplexDeltaChangeTime

sys_area_norm_CB_Var_Time_ComplexDCTime

pp_area_norm_Var_Time_Norm_ComplexDeltaChangeTime

Area_AA_Nodia_ComplexDeltaChange

IPA_ComplexDeltaChangeTime

pp_area_norm_nodia_CB_Var_Time_ComplexDeltaChange

Ratio_BC_Var_ComplexDeltaChange

PEBL

dia_area_norm_ComplexDeltaChange

Magnitude_BD_Var_Time_Norm_ComplexDeltaChange

Interval_AA_Var_Time

dia_area_nor_nodia_CB_Var_ComplexDCTime

Average_Slope_CC

slope_sys_Var_ComplexDeltaChangeTime

Average_Magnitude_BD_Nodia_Var

Interval_CD_ComplexDeltaChangeTime

BP_Area

Average_Magnitude_CD_Nodia_Var_Time_ComplexDeltaChangeTime

dia_area_norm_ComplexDeltaChangeTime

Area_CD_Var_Time

Average_Slope_AA

Average_Magnitude_BD_Var_Time_Norm_ComplexDeltaChange

sys_dec_area_nor_CB_Var_Time

avg_sys_rise_nodia_Var_Time_ComplexDeltaChange

Interval_AD

Area_AB_Var_Time

Average_Magnitude_AB_Nodia_Var_Time_Norm_ComplexDeltaChange

BLVM

Average_Magnitude_BB_Nodia_Var_Norm_ComplexDeltaChange

HRTPD_ComplexDeltaChange

dec_area_norm_nodia_CB_Var_Norm

Magnitude_CC

Average_Magnitude_AB_Var_Time_Norm_ComplexDeltaChange

sys_rise_area_nor_ComplexDeltaChange

slope_dia_Var

Interval_AA_Var_Norm_ComplexDeltaChangeTime

Average_Magnitude_AA_Var_Time_Norm_ComplexDeltaChange

Area_BC_norm_Var_Time_Norm

Interval_AB_Var_Time_ComplexDeltaChange

avg_dec_ComplexDeltaChange

Average_Magnitude_BD_Nodia_Var_Norm_ComplexDeltaChange

pp_area_norm_nodia_CB_Var_Time_Norm_ComplexDeltaChange

avg_dec_nodia

BP_Area_ComplexDeltaChangeTime

sys_dec_area_nor_Var_ComplexDeltaChange

Ratios_Fifty_Var_Time_ComplexDeltaChangeTime

t_dia

[0095] FIG. 5 is a plot that illustrates examples of time series of mean arterial pressure (MAP) of input waveforms from a canine and time series output of two models, each trained to predict compensatory reserve measurement (CRM) as a blood loss metric, according to some embodiments. The horizontal dimension indicates time in arbitrary units, with the measurement time before exsanguination occurring between time T561 and time T562, controlled constant hemorrhaging occurring between time T562 and time T563, and post-hemorrhage pre-resuscitation time occurring between time T563 and time T564. The right side vertical axis indicates pressure in mmHg for the mean arterial pressure (MAP) trace 501. The left side vertical axis indicates dimensionless fraction, for the compensatory reserve measurement (CRM) traces 502 and 503.

[0096] As stated earlier and shown by MAP trace 501 in which each point represents teh MAP value of a single heartbeat pressure pulse, MAP responds slowly to hemorrhaging and begins to rise even as blood loss remains constant after time T563. Thus MAP is a poor indication of objective blood loss.

[0097] CRM output by a bagged decision tree ML model is given by trace 502. It responds even more slowly than MAP to onset of hemorrhage and also rises even as blood loss remains constant after time T563. CRM output by a DL model is given by trace 503. It barely responds to onset of hemorrhage and also rises even before hemorrhage ceases. These aspects of the ML/DL models for CRM repeat for each canine subject left out of model training. The CRM using machine learning trace 502 was on average 0.88 ± 0.11 in the baseline region. During hemorrhage, the CRM using machine learning trace 502 dropped consistently but earlier than the mean arterial pressure waveform 402 dropped. Overall, the CRM using machine learning trace 502 had a wider operating range, with values spanning 0.45 to 0.95. Similarly, the CRM using deep learning trace 503 resulted in an average of 0.41 ± 0.12

during baseline. During hemorrhage, the CRM using deep learning trace 503 reached a minimum value earlier than the mean arterial pressure. The CRM traces were inconsistent after the minimum value was reached, and average values ranged from 0.30 to 0.45, which is a small dynamic range for monitoring physiological status.

[0098] Thus it was demonstrated that the subjective compensatory reserve measurement (CRM) used for humans (that is, a 0 to 1 value calculated from the difference of a value of 1 and the ratio of the current pressure being experienced in a lower body negative pressure (LBNP) chamber to the maximum pressure experienced in the study) was somewhat unhelpful when analyzing canine hemorrhage. During the baseline readings collected from the canines, the CRM for the canines was on average 0.41 +/- 0.12. Indeed, during hemorrhage, the CRM reached a minimum value more quickly than the mean arterial pressure: the CRM decreased by 75% at the minimum, whereas the mean arterial pressure had only decreased by 26% at the same time point.

[0099] The time to reach a minimum value was compared among the CRM ML trace 502, the CRM DL trace 503, and the MAP trace 501. The CRM ML trace 502 reached a minimum during hemorrhage approximately 9 minutes prior to the MAP trace 501; however, the CRM ML trace 502 exhibited significantly more variability. Moreover, the CRM DL trace 503 reached an initial minimum approximately 17 minutes earlier; however, the CRM DL trace 503 exhibits more variability. This variability is undesirable because, in practice, it means that it is unclear when a first minimum will be reached after baseline. Stated more bluntly, while use of CRM to identify hemorrhage appeared to be slightly better than use of MAP for the same purposes, its use was very unreliable and somewhat unpredictable (at least in respect to time) when applied to canines. The above results motivated the use of a different measurement -- the Blood Loss Volume Metric (BLVM) defined above.

[0100] FIG. 6 is a plot that illustrates examples of time series of mean arterial pressure (MAP) of input waveforms from a canine and a time series of training values for a blood loss volume metric (BLVM) and a prediction of BLVM from a trained ML model, according to an embodiment. The horizontal dimension and right side vertical axis are the same as in FIG.

5. The left side vertical axis indicates dimensionless fraction for the blood loss volume metric (BLVM)) traces 601 and 602. The MAP trace 603 is the same as MAP trace 501 in FIG. 5.

[0101] Here BLVM trace 602 is the measured blood loss for the training set for this particular canine subject and consequently clearly shows the desired aspects of constant high fraction before hemorrhaging start at time T562, constant linear decrease in fraction during constant exsanguination from time T562 to time T563, and constant low fraction in the post-hemorrhaging pre-resuscitation time from T563 to time T564.

[0102] BLVM trace 603 is the output of a bagged decision tree ML model trained on the other five canine subjects. The ML model output trace 602 is superior to the MAP trace 603/501 and the two CRM model output traces 502 and 503 by decreasing quickly after start of hemorrhaging at time T562, showing a relatively constant drop during constant hemorrhaging between time T562 and time T563, and being relatively flat at a low value with minimal rise after hemorrhaging stops at time T563 and before resuscitation at time T564.

[0103] The BLVM traces 601 and 602 in FIG. 6 depict a more ideal scenario, whereby a more objective measurement (BLVM) is used. The predicted BLVM trace 602 had a flatline behavior in the baseline region of the study, and dropped throughout the hemorrhage period. After hemorrhage, during the shock hold (post-hemorrhage and pre-resuscitation) , the predicted BLVM trace 602 ceased falling and returned to a flatline. This is precisely the result shown by the training set, directly measured BLVM trace 601, which is significantly less variable than the MAP trace 603. To briefly reiterate, the waveforms and analysis shown in FIG. 5 underscore one unexpected result of the processes described herein: the idea that the CRM developed for humans exhibits high variability when applied to canines during controlled hemorrhage/resuscitation, whereas the BLVM measurement was much preferred.

[0104] After all, while the CRM decreased more rapidly in the face of hemorrhage, the variability in the CRM would make it extremely difficult to apply in a clinical setting. There are a number of possible explanations for the lack of fit in this model. For example, the data used for the human CRM was derived from noninvasive arterial waveforms instead of direct arterial catheters (as used in the study of canines discussed herein). Moreover, and as

another example, the inherent variability in size and body conformation is significantly different between humans, baboons, and canines may play a factor. Additionally, and as yet another example, the canine spleen is well known to constrict in order to partially auto resuscitate in the face of hemorrhagic shock, which may affect results using CRM. In turn, approaches analyzing waveforms using, for example, the BLVM calculation method may be preferable when analyzing canines. Furthermore the development of CRM relied on subjective inputs based on human reports of symptoms and symptom onset that can only be estimated for a non-human animal or unconscious humans.

[0105] The result of this training process was a trained machine learning model that could predict, as an early indicator, oncoming decompensation in a hemorrhagic shock (e.g., a BLVM value) quickly and with an extremely high degree of accuracy. The performance of these models, detailed further below, was significantly faster than mere monitoring of mean arterial pressure. Indeed, the machine learning model could reach these quick and accurate results in a number of ways: for example, predicting accumulation of sliced pieces of the HemArea and the MAPBurden and/or by predicting individual slices of the HemArea and the MAPBurden and then using an accumulating sum of those predicted slices and comparing them to actual values. Regardless, one measure of effectiveness of the machine learning model was analyzing the time difference between mean arterial pressure began to drop during a hemorrhage and when the trained machine learning model had a response

[0106] FIG. 7 is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output BLVM, according to various embodiments. FIG. 7 shows how it was determined that the best-performing machine learning model for BLVM was one that used 10 features from arterial waveforms and a minimum decision tree leaf size (number of leaf nodes) of 8 (resulting in an $R^2$of 0.80). In the context of this analysis, BLVM ranges from 1 (no blood loss) to 0 (maximum blood loss). Closely favorable results, $R^2$of 0.79, are obtained for 12 leaf nodes.

[0107] FIG. 8 is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output percent estimated blood loss (PEBL), according to various embodiments. FIG. 8 shows model optimization results for PEBL (which ranges

from 0% (no blood loss) to 100% (total estimate blood loss)). In this context, the ideal PEBL model had 10 features with a leaf size of 12 and 20 features with a leaf size of 16, with both models having an $R^2$of 0.74. Closely favorable results ($R^2$of 0.73) are obtained for 10 features with a leaf size of 16.

[0108] HemArea and MAP area were each determined two ways. In a first approach (called direct modeling), predicting the tiny integral slices of the area under the MAP and blood loss were predicted at each time series time value to produce a time trace and then summing the values over the time slices. In general this gave lower R^2 values than the second approach. In a second approach (called derived), the area was calculation from the blood loss metric. In general this gave exceptionally good results with R^2 in the nineties. For HemArea the blood loss metric was BLVM. For MapArea, the blood loss metric was MAP. These metrics and MAPBurden and HemBurden in addition to MAP helped connect the metric to a physiological meaning.

[0109] FIG. 9A is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output hemorrhage area (HemArea), according to various embodiments. Directly modeling HemArea (the area between no blood loss and current blood loss across the time axis) gave poor results with R^2 values no higher than 0.39 for any combination of leaf size and number of features attempted.

[0110] FIG. 9B is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output BVLM that is then used to derive HemArea, according to various embodiments. Here performance was much better, indicating that the 5, 10, and 20 feature machine learning models had an R^2 of approximately 0.97, a significant increase over attempting to predict the HemArea as it is accumulating directly.

[0111] FIG. 10A is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output mean arterial pressure area (MAParea), according to various embodiments. Directly modeling MAParea (the area between baseline MAP and current MAP across the time axis) gave poor results with R^2 values no higher than 0.27 for any combination of leaf size and number of features attempted

[0112] FIG. 10B is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output MAP that is then used to derive MAParea, according to various embodiments. FIG. 10B shows excellent performance with the R^2 values averaging 0.99, 0.98, and 0.98 for the 5, 10, and 20 feature inputs for all leaf sizes attempted (4, 8, 12 and 16). Thus these can be modeled simply with a 5 input feature, 4 leaf bagged decision tree ML model, at least for the limited data set available in the example embodiments.

[0113] FIG. 11 is a chart that illustrates examples of goodness of fit (R^2) for several bagged decision tree ML models that output TinyMAParea, according to various embodiments. TinyMAParea could be estimated using ML models to predict that area directly or calculated from a MAP value.

[0114] Illustrative R^2 and root mean squared error (RMSE) results for each of the different aforementioned models are provided below in Table 2. As indicated by the above-referenced figures and the below table, the BLVM model with the best performance was using 5 features and a leaf size of 8, the best-performing PEBL model used 20 features with a leaf size of 12, the HemArea model directly predicting area under the curve as it increased had the best (but ppor) performance using 10 features and a leaf size of 4, the HemArea derived from BVLM had the best performance using 5 features and a leaf size of 12, the machine learning model for MAP-Area had its best (but still poor) performance using 10 features with a leaf size of 4, and the MAP-Area derived from BVLM had the best performing model with 5 features being used and a leaf size of 8.

TABLE 2

	R-Squared	**RMSE**
BLVM	0.795	0.157
PEBL	0.739	0.0768
HemAreaModel	0.391	1245113
HemAreaCalc	0.972	250559
MAP-AreaModel	0.249	35540

MAP-AreaCalc	0.990	5283

[0115] As already suggested above, the result of these models was significantly faster and more accurate analysis of arterial waveforms, including the ability to detect hemorrhage. Average results for predictions and ground truth calculation for each model, with the time axis normalized were also compared with good agreement. The difference between the mean arterial pressure response to hemorrhages and how much quicker or slower a respective prediction metric is were also compared. The MAP-Area had an average response to hemorrhage of 913.69 seconds before mean arterial pressure began to drop, the HemArea prediction metric responded to a hemorrhage, on average, 1008.35 seconds after the mean arterial pressure response, the PEBL responded to hemorrhage 1515.71 seconds after the mean arterial pressure response, the BLVM, on average, responded quicker than the MAP response by 1477.60 seconds, and PEBL had the quickest response to a hemorrhage in the canines. That said, while PEBL may have had the quickest response, all the prediction metrics responded to hemorrhage quicker than mean arterial pressure.

[0001] During the process of testing various canine subjects and training the machine learning models, for the purposes of accuracy, R^2 values and RMSE values were calculated for each canine at each round of study (keeping the LOSO process described above). These r-squared values and RMSE values are summarized below in Table 3 and Table 4.

TABLE 3

R-Squared	Round 1	Round 2	Round 3	Round 4	Round 5	Average
Canine 1	0.81	0.81	0.84	0.71	0.93	0.82
Canine 2	0.89	0.74	0.85	0.47	0.87	0.76
Canine 3	0.29	0.80	0.04	0.39	0.75	0.45
Canine 4	0.84	0.86	0.57	0.90	0.83	0.80

Canine 5	0.69	0.88	0.91	0.56	0.88	0.79
Canine 6	0.90	0.90	0.75	0.94	0.83	0.86
					Total Average	**0.75**

TABLE 4

RMSE	Round 1	Round 2	Round 3	Round 4	Round 5	Average
Canine 1	0.14	0.16	0.13	0.21	0.09	0.15
Canine 2	0.10	0.16	0.12	0.27	0.13	0.16
Canine 3	0.28	0.16	0.34	0.25	0.16	0.24
Canine 4	0.15	0.13	0.25	0.10	0.14	0.15
Canine 5	0.21	0.13	0.10	0.23	0.12	0.16
Canine 6	0.11	0.11	0.16	0.08	0.15	0.12
					Total Average	0.16

6. Computational Hardware Overview

[0116] FIG. 12 is a block diagram that illustrates a computer system 1200 upon which an embodiment of the invention may be implemented. Computer system 1200 includes a communication mechanism such as a bus 1210 for passing information between other internal and external components of the computer system 1200. Information is represented

as physical signals of a measurable phenomenon, typically electric voltages, but including, in other embodiments, such phenomena as magnetic, electromagnetic, pressure, chemical, molecular atomic and quantum interactions. For example, north and south magnetic fields, or a zero and non-zero electric voltage, represent two states (0, 1) of a binary digit (bit). Other phenomena can represent digits of a higher base. A superposition of multiple simultaneous quantum states before measurement represents a quantum bit (qubit). A sequence of one or more digits constitutes digital data that is used to represent a number or code for a character. In some embodiments, information called analog data is represented by a near continuum of measurable values within a particular range. Computer system 1200, or a portion thereof, constitutes a means for performing one or more steps of one or more methods described herein.

[0117] A sequence of binary digits constitutes digital data that is used to represent a number or code for a character. A bus 1210 includes many parallel conductors of information so that information is transferred quickly among devices coupled to the bus 1210. One or more processors 1202 for processing information are coupled with the bus 1210. A processor 1202 performs a set of operations on information. The set of operations include bringing information in from the bus 1210 and placing information on the bus 1210. The set of operations also typically include comparing two or more units of information, shifting positions of units of information, and combining two or more units of information, such as by addition or multiplication. A sequence of operations to be executed by the processor 1202 constitutes computer instructions.

[0118] Computer system 1200 also includes a memory 1204 coupled to bus 1210. The memory 1204, such as a random access memory (RAM) or other dynamic storage device, stores information including computer instructions. Dynamic memory allows information stored therein to be changed by the computer system 1200. RAM allows a unit of information stored at a location called a memory address to be stored and retrieved independently of information at neighboring addresses. The memory 1204 is also used by the processor 1202 to store temporary values during execution of computer instructions. The computer system 1200 also includes a read only memory (ROM) 1206 or other static storage

device coupled to the bus 1210 for storing static information, including instructions, that is not changed by the computer system 1200. Also coupled to bus 1210 is a non-volatile (persistent) storage device 1208, such as a magnetic disk or optical disk, for storing information, including instructions, that persists even when the computer system 1200 is turned off or otherwise loses power.

[0119] Information, including instructions, is provided to the bus 1210 for use by the processor from an external input device 1212, such as a keyboard containing alphanumeric keys operated by a human user, or a sensor. A sensor detects conditions in its vicinity and transforms those detections into signals compatible with the signals used to represent information in computer system 1200. Other external devices coupled to bus 1210, used primarily for interacting with humans, include a display device 1214, such as a cathode ray tube (CRT) or a liquid crystal display (LCD), for presenting images, and a pointing device 1216, such as a mouse or a trackball or cursor direction keys, for controlling a position of a small cursor image presented on the display 1214 and issuing commands associated with graphical elements presented on the display 1214.

[0120] In the illustrated embodiment, special purpose hardware, such as an application specific integrated circuit (IC) 1220, is coupled to bus 1210. The special purpose hardware is configured to perform operations not performed by processor 1202 quickly enough for special purposes. Examples of application specific ICs include graphics accelerator cards for generating images for display 1214, cryptographic boards for encrypting and decrypting messages sent over a network, speech recognition, and interfaces to special external devices, such as robotic arms and medical scanning equipment that repeatedly perform some complex sequence of operations that are more efficiently implemented in hardware.

[0121] Computer system 1200 also includes one or more instances of a communications interface 1270 coupled to bus 1210. Communication interface 1270 provides a two-way communication coupling to a variety of external devices that operate with their own processors, such as printers, scanners and external disks. In general the coupling is with a network link 1278 that is connected to a local network 1280 to which a variety of external devices with their own processors are connected. For example, communication interface

1270 may be a parallel port or a serial port or a universal serial bus (USB) port on a personal computer. In some embodiments, communications interface 1270 is an integrated services digital network (ISDN) card or a digital subscriber line (DSL) card or a telephone modem that provides an information communication connection to a corresponding type of telephone line. In some embodiments, a communication interface 1270 is a cable modem that converts signals on bus 1210 into signals for a communication connection over a coaxial cable or into optical signals for a communication connection over a fiber optic cable. As another example, communications interface 1270 may be a local area network (LAN) card to provide a data communication connection to a compatible LAN, such as Ethernet. Wireless links may also be implemented. Carrier waves, such as acoustic waves and electromagnetic waves, including radio, optical and infrared waves travel through space without wires or cables. Signals include man-made variations in amplitude, frequency, phase, polarization or other physical properties of carrier waves. For wireless links, the communications interface 1270 sends and receives electrical, acoustic or electromagnetic signals, including infrared and optical signals, that carry information streams, such as digital data.

[0122] The term computer-readable medium is used herein to refer to any medium that participates in providing information to processor 1202, including instructions for execution. Such a medium may take many forms, including, but not limited to, non-volatile media, volatile media and transmission media. Non-volatile media include, for example, optical or magnetic disks, such as storage device 1208. Volatile media include, for example, dynamic memory 1204. Transmission media include, for example, coaxial cables, copper wire, fiber optic cables, and waves that travel through space without wires or cables, such as acoustic waves and electromagnetic waves, including radio, optical and infrared waves. The term computer-readable storage medium is used herein to refer to any medium that participates in providing information to processor 1202, except for transmission media.

[0123] Common forms of computer-readable media include, for example, a floppy disk, a flexible disk, a hard disk, a magnetic tape, or any other magnetic medium, a compact disk ROM (CD-ROM), a digital video disk (DVD) or any other optical medium, punch cards, paper tape, or any other physical medium with patterns of holes, a RAM, a programmable

ROM (PROM), an erasable PROM (EPROM), a FLASH-EPROM, or any other memory chip or cartridge, a carrier wave, or any other medium from which a computer can read. The term non-transitory computer-readable storage medium is used herein to refer to any medium that participates in providing information to processor 1202, except for carrier waves and other signals.

[0124] Logic encoded in one or more tangible media includes one or both of processor instructions on a computer-readable storage media and special purpose hardware, such as ASIC 1220.

[0125] Network link 1278 typically provides information communication through one or more networks to other devices that use or process the information. For example, network link 1278 may provide a connection through local network 1280 to a host computer 1282 or to equipment 1284 operated by an Internet Service Provider (ISP). ISP equipment 1284 in turn provides data communication services through the public, world-wide packet-switching communication network of networks now commonly referred to as the Internet 1290. A computer called a server 1292 connected to the Internet provides a service in response to information received over the Internet. For example, server 1292 provides information representing video data for presentation at display 1214.

[0126] The invention is related to the use of computer system 1200 for implementing the techniques described herein. According to one embodiment of the invention, those techniques are performed by computer system 1200 in response to processor 1202 executing one or more sequences of one or more instructions contained in memory 1204. Such instructions, also called software and program code, may be read into memory 1204 from another computer-readable medium such as storage device 1208. Execution of the sequences of instructions contained in memory 1204 causes processor 1202 to perform the method steps described herein. In alternative embodiments, hardware, such as application specific integrated circuit 1220, may be used in place of or in combination with software to implement the invention. Thus, embodiments of the invention are not limited to any specific combination of hardware and software.

[0127] The signals transmitted over network link 1278 and other networks through communications interface 1270, carry information to and from computer system 1200. Computer system 1200 can send and receive information, including program code, through the networks 1280, 1290 among others, through network link 1278 and communications interface 1270. In an example using the Internet 1290, a server 1292 transmits program code for a particular application, requested by a message sent from computer 1200, through Internet 1290, ISP equipment 1284, local network 1280 and communications interface 1270. The received code may be executed by processor 1202 as it is received, or may be stored in storage device 1208 or other non-volatile storage for later execution, or both. In this manner, computer system 1200 may obtain application program code in the form of a signal on a carrier wave.

[0128] Various forms of computer readable media may be involved in carrying one or more sequence of instructions or data or both to processor 1202 for execution. For example, instructions and data may initially be carried on a magnetic disk of a remote computer such as host 1282. The remote computer loads the instructions and data into its dynamic memory and sends the instructions and data over a telephone line using a modem. A modem local to the computer system 1200 receives the instructions and data on a telephone line and uses an infra-red transmitter to convert the instructions and data to a signal on an infra-red a carrier wave serving as the network link 1278. An infrared detector serving as communications interface 1270 receives the instructions and data carried in the infrared signal and places information representing the instructions and data onto bus 1210. Bus 1210 carries the information to memory 1204 from which processor 1202 retrieves and executes the instructions using some of the data sent with the instructions. The instructions and data received in memory 1204 may optionally be stored on storage device 1208, either before or after execution by the processor 1202.

[0129] FIG. 13 illustrates a chip set 1300 upon which an embodiment of the invention may be implemented. Chip set 1300 is programmed to perform one or more steps of a method described herein and includes, for instance, the processor and memory components described with respect to FIG. 12 incorporated in one or more physical packages (e.g., chips). By way

of example, a physical package includes an arrangement of one or more materials, components, and/or wires on a structural assembly (e.g., a baseboard) to provide one or more characteristics such as physical strength, conservation of size, and/or limitation of electrical interaction. It is contemplated that in certain embodiments the chip set can be implemented in a single chip. Chip set 1300, or a portion thereof, constitutes a means for performing one or more steps of a method described herein.

[0130] In one embodiment, the chip set 1300 includes a communication mechanism such as a bus 1301 for passing information among the components of the chip set 1300. A processor 1303 has connectivity to the bus 1301 to execute instructions and process information stored in, for example, a memory 1305. The processor 1303 may include one or more processing cores with each core configured to perform independently. A multi-core processor enables multiprocessing within a single physical package. Examples of a multi-core processor include two, four, eight, or greater numbers of processing cores. Alternatively or in addition, the processor 1303 may include one or more microprocessors configured in tandem via the bus 1301 to enable independent execution of instructions, pipelining, and multithreading. The processor 1303 may also be accompanied with one or more specialized components to perform certain processing functions and tasks such as one or more digital signal processors (DSP) 1307, or one or more application-specific integrated circuits (ASIC) 1309. A DSP 1307 typically is configured to process real-world signals (e.g., sound) in real time independently of the processor 1303. Similarly, an ASIC 1309 can be configured to performed specialized functions not easily performed by a general purposed processor. Other specialized components to aid in performing the inventive functions described herein include one or more field programmable gate arrays (FPGA) (not shown), one or more controllers (not shown), or one or more other special-purpose computer chips.

[0131] The processor 1303 and accompanying components have connectivity to the memory 1305 via the bus 1301. The memory 1305 includes both dynamic memory (e.g., RAM, magnetic disk, writable optical disk, etc.) and static memory (e.g., ROM, CD-ROM, etc.) for storing executable instructions that when executed perform one or more steps of a

method described herein. The memory 1305 also stores the data associated with or generated by the execution of one or more steps of the methods described herein.

[0132] FIG. 14 is a diagram of exemplary components of a mobile terminal 1400 (e.g., cell phone handset) for communications, which is capable of operating in the system, according to one embodiment. In some embodiments, mobile terminal 1401, or a portion thereof, constitutes a means for performing one or more steps described herein. Generally, a radio receiver is often defined in terms of front-end and back-end characteristics. The front-end of the receiver encompasses all of the Radio Frequency (RF) circuitry whereas the back-end encompasses all of the base-band processing circuitry. As used in this application, the term "circuitry" refers to both: (1) hardware-only implementations (such as implementations in only analog and/or digital circuitry), and (2) to combinations of circuitry and software (and/or firmware) (such as, if applicable to the particular context, to a combination of processor(s), including digital signal processor(s), software, and memory(ies) that work together to cause an apparatus, such as a mobile phone or server, to perform various functions). This definition of "circuitry" applies to all uses of this term in this application, including in any claims. As a further example, as used in this application and if applicable to the particular context, the term "circuitry" would also cover an implementation of merely a processor (or multiple processors) and its (or their) accompanying software/or firmware. The term "circuitry" would also cover if applicable to the particular context, for example, a baseband integrated circuit or applications processor integrated circuit in a mobile phone or a similar integrated circuit in a cellular network device or other network devices.

[0133] Pertinent internal components of the telephone include a Main Control Unit (MCU) 1403, a Digital Signal Processor (DSP) 1405, and a receiver/transmitter unit including a microphone gain control unit and a speaker gain control unit. A main display unit 1407 provides a display to the user in support of various applications and mobile terminal functions that perform or support the steps as described herein. The display 1407 includes display circuitry configured to display at least a portion of a user interface of the mobile terminal (e.g., mobile telephone). Additionally, the display 1407 and display circuitry are configured to facilitate user control of at least some functions of the mobile terminal. An audio function

circuitry 1409 includes a microphone 1411 and microphone amplifier that amplifies the speech signal output from the microphone 1411. The amplified speech signal output from the microphone 1411 is fed to a coder/decoder (CODEC) 1413.

[0134] A radio section 1415 amplifies power and converts frequency in order to communicate with a base station, which is included in a mobile communication system, via antenna 1417. The power amplifier (PA) 1419 and the transmitter/modulation circuitry are operationally responsive to the MCU 1403, with an output from the PA 1419 coupled to the duplexer 1421 or circulator or antenna switch, as known in the art. The PA 1419 also couples to a battery interface and power control unit 1420.

[0135] In use, a user of mobile terminal 1401 speaks into the microphone 1411 and his or her voice along with any detected background noise is converted into an analog voltage. The analog voltage is then converted into a digital signal through the Analog to Digital Converter (ADC) 1423. The control unit 1403 routes the digital signal into the DSP 1405 for processing therein, such as speech encoding, channel encoding, encrypting, and interleaving. In one embodiment, the processed voice signals are encoded, by units not separately shown, using a cellular transmission protocol such as enhanced data rates for global evolution (EDGE), general packet radio service (GPRS), global system for mobile communications (GSM), Internet protocol multimedia subsystem (IMS), universal mobile telecommunications system (UMTS), etc., as well as any other suitable wireless medium, e.g., microwave access (WiMAX), Long Term Evolution (LTE) networks, code division multiple access (CDMA), wideband code division multiple access (WCDMA), wireless fidelity (WiFi), satellite, and the like, or any combination thereof.

[0136] The encoded signals are then routed to an equalizer 1425 for compensation of any frequency-dependent impairments that occur during transmission though the air such as phase and amplitude distortion. After equalizing the bit stream, the modulator 1427 combines the signal with a RF signal generated in the RF interface 1429. The modulator 1427 generates a sine wave by way of frequency or phase modulation. In order to prepare the signal for transmission, an up-converter 1431 combines the sine wave output from the modulator 1427 with another sine wave generated by a synthesizer 1433 to achieve the desired frequency of

transmission. The signal is then sent through a PA 1419 to increase the signal to an appropriate power level. In practical systems, the PA 1419 acts as a variable gain amplifier whose gain is controlled by the DSP 1405 from information received from a network base station. The signal is then filtered within the duplexer 1421 and optionally sent to an antenna coupler 1435 to match impedances to provide maximum power transfer. Finally, the signal is transmitted via antenna 1417 to a local base station. An automatic gain control (AGC) can be supplied to control the gain of the final stages of the receiver. The signals may be forwarded from there to a remote telephone which may be another cellular telephone, any other mobile phone or a land-line connected to a Public Switched Telephone Network (PSTN), or other telephony networks.

[0137] Voice signals transmitted to the mobile terminal 1401 are received via antenna 1417 and immediately amplified by a low noise amplifier (LNA) 1437. A down-converter 1439 lowers the carrier frequency while the demodulator 1441 strips away the RF leaving only a digital bit stream. The signal then goes through the equalizer 1425 and is processed by the DSP 1405. A Digital to Analog Converter (DAC) 1443 converts the signal and the resulting output is transmitted to the user through the speaker 1445, all under control of a Main Control Unit (MCU) 1403 which can be implemented as a Central Processing Unit (CPU) (not shown).

[0138] The MCU 1403 receives various signals including input signals from the keyboard 1447. The keyboard 1447 and/or the MCU 1403 in combination with other user input components (e.g., the microphone 1411) comprise a user interface circuitry for managing user input. The MCU 1403 runs a user interface software to facilitate user control of at least some functions of the mobile terminal 1401 as described herein. The MCU 1403 also delivers a display command and a switch command to the display 1407 and to the speech output switching controller, respectively. Further, the MCU 1403 exchanges information with the DSP 1405 and can access an optionally incorporated SIM card 1449 and a memory 1451. In addition, the MCU 1403 executes various control functions required of the terminal. The DSP 1405 may, depending upon the implementation, perform any of a variety of conventional digital processing functions on the voice signals. Additionally, DSP 1405 determines the background noise level of the local environment from the signals detected by microphone 1411

and sets the gain of microphone 1411 to a level selected to compensate for the natural tendency of the user of the mobile terminal 1401.

[0139] The CODEC 1413 includes the ADC 1423 and DAC 1443. The memory 1451 stores various data including call incoming tone data and is capable of storing other data including music data received via, e.g., the global Internet. The software module could reside in RAM memory, flash memory, registers, or any other form of writable storage medium known in the art. The memory device 1451 may be, but not limited to, a single memory, CD, DVD, ROM, RAM, EEPROM, optical storage, magnetic disk storage, flash memory storage, or any other non-volatile storage medium capable of storing digital data.

[0140] An optionally incorporated SIM card 1449 carries, for instance, important information, such as the cellular phone number, the carrier supplying service, subscription details, and security information. The SIM card 1449 serves primarily to identify the mobile terminal 1401 on a radio network. The card 1449 also contains a memory for storing a personal telephone number registry, text messages, and user specific mobile terminal settings.

[0141] In some embodiments, the mobile terminal 1401 includes a digital camera comprising an array of optical detectors, such as charge coupled device (CCD) array 1465. The output of the array is image data that is transferred to the MCU for further processing or storage in the memory 1451 or both. In the illustrated embodiment, the light impinges on the optical array through a lens 1463, such as a pin-hole lens or a material lens made of an optical grade glass or plastic material. In the illustrated embodiment, the mobile terminal 1401 includes a light source 1461, such as a LED to illuminate a subject for capture by the optical array, e.g., CCD 1465. The light source is powered by the battery interface and power control module 1420 and controlled by the MCU 1403 based on instructions stored or loaded into the MCU 1403.

7. Alternatives, Deviations and modifications

[0142] In the foregoing specification, the invention has been described with reference to specific embodiments thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention. The specification and drawings are, accordingly, to be regarded in an illustrative

rather than a restrictive sense. Throughout this specification and the claims, unless the context requires otherwise, the word "comprise" and its variations, such as "comprises" and "comprising," will be understood to imply the inclusion of a stated item, element or step or group of items, elements or steps but not the exclusion of any other item, element or step or group of items, elements or steps. Furthermore, the indefinite article "a" or "an" is meant to indicate one or more of the item, element or step modified by the article.

[0143] Notwithstanding that the numerical ranges and parameters setting forth the broad scope are approximations, the numerical values set forth in specific non-limiting examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements at the time of this writing. Furthermore, unless otherwise clear from the context, a numerical value presented herein has an implied precision given by the least significant digit. Thus, a value 1.1 implies a value from 1.05 to 1.15. The term "about" is used to indicate a broader range centered on the given value, and unless otherwise clear from the context implies a broader range around the least significant digit, such as "about 1.1" implies a range from 1.0 to 1.2. If the least significant digit is unclear, then the term "about" implies a factor of two, e.g., "about X" implies a value in the range from 0.5X to 2X, for example, about 100 implies a value in a range from 50 to 200. Moreover, all ranges disclosed herein are to be understood to encompass any and all sub-ranges subsumed therein. For example, a range of "less than 10" for a positive only parameter can include any and all sub-ranges between (and including) the minimum value of zero and the maximum value of 10, that is, any and all sub-ranges having a minimum value of equal to or greater than zero and a maximum value of equal to or less than 10, e.g., 1 to 4.

8. References

[0144] Each of the following references is hereby incorporated by reference as if fully set forth herein except for terminology that is inconsistent with that used herein.

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Feature Selection and the Effects of Subject Variability," Bioengineering, vol. 10, no. 5, Art. no. 5, May 2023, doi: 10.3390/bioengineering10050612.

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CLAIMS

What is claimed is:

1. A method for monitoring blood loss in a subject animal, the method comprising:

collecting arterial pressure waveform measurements of a subject animal, the arterial pressure waveform measurements collected by a pressure waveform sensor during an observation period spanning several heartbeats;

processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features;

outputting a value of at least one objective blood loss metric for the subject animal by providing the one or more extracted blood pressure features as input to one or more machine learning (ML) models; and

presenting the value of the at least one objective blood loss metric,

wherein the one or more machine learning models are trained on a plurality of historical instances, each instance including historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination experiment, said historical arterial pressure waveform measurements associated with at least one historical objective blood loss metric value determined from directly-measured blood loss during the laboratory exsanguination experiment.

2. The method as recited in claim 1, wherein the at least one objective blood loss metric includes a blood loss volume metric (BLVM) based on a ratio of a shed blood volume over a maximum shed blood volume that the subject animal can survive.

3. The method as recited in claim 2, wherein the at least one objective blood loss metric includes a hemorrhage area (HemArea) or mean arterial pressure area (MAPArea) or both derived from the BLVM.

4. The method as recited in claim 1, wherein the at least one objective blood loss metric includes a percent estimated blood loss (PEBL) based on a ratio of a shed blood volume over a total blood volume for the subject animal.

5. The method as recited in claim 4, wherein the total blood volume for the subject animal is based on a height or weight, or both, and a species of the subject animal.

6. The method as recited in claim 1, wherein the one or more machine learning models include an ensemble bagged trees model.

7. The method as recited in claim 6, wherein the ensemble bagged trees model includes about eight to twelve blood pressure features as input and eight to 12 leaf nodes as output.

8. The method as recited in claim 1, wherein the one or more blood pressure features are selected from a group including: peak-to-peak interval; area under a systolic rise; area under a trace from a systolic maximum to a start of a next beat subtracted by a pressure at a first inflection point and normalized by a number of samples in a single arterial pressure waveform; a duration of the systolic rise; or an area under a trace of a systolic decay.

9. The method as recited in claim 1, further comprises handling or treating the subject animal based on the value of the at least one objective blood loss metric.

10. The method as recited in claim 1, further comprises collecting additional arterial pressure waveform measurements based on the value of the at least one objective blood loss metric for the subject animal.

11. A non-transitory computer-readable medium carrying one or more sequences of instructions for monitoring blood loss in a subject animal, wherein execution of the one or more sequences of instructions by one or more processors causes the one or more processors to perform the steps of:

collecting arterial pressure waveform measurements of a subject animal, the arterial pressure waveform measurements collected by a pressure waveform sensor during an observation period spanning several heartbeats;

processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features;

outputting a value of at least one objective blood loss metric for the subject animal by providing the one or more extracted blood pressure features as input to one or more machine learning (ML) models; and

presenting the value of the at least one objective blood loss metric,

wherein the one or more machine learning models are trained on a plurality of historical instances, each instance including historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination experiment, said historical arterial pressure waveform measurements associated with at least one historical objective blood loss metric value determined from directly-measured blood loss during the laboratory exsanguination experiment.

12. An apparatus for monitoring blood loss in a subject animal, the apparatus comprising:

at least one processor; and

at least one memory including one or more sequences of instructions,

the at least one memory and the one or more sequences of instructions configured to, with the at least one processor, cause the apparatus to perform at least the following,

collecting arterial pressure waveform measurements of a subject animal, the arterial pressure waveform measurements collected by a pressure waveform sensor during an observation period spanning several heartbeats;

processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features;

outputting a value of at least one objective blood loss metric for the subject animal by providing the one or more extracted blood pressure features as input to one or more machine learning (ML) models; and

presenting the value of the at least one objective blood loss metric,

wherein the one or more machine learning models are trained on a plurality of historical instances, each instance including historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination experiment, said historical arterial pressure waveform measurements associated with at least one historical objective blood loss metric value determined from directly-measured blood loss during the laboratory exsanguination experiment.

13. A system for monitoring blood loss in a subject animal, the system comprising:

an arterial pressure waveform sensor configured to collect arterial pressure waveform measurements of a subject animal;

at least one processor; and

at least one memory including one or more sequences of instructions,

the at least one memory and the one or more sequences of instructions configured to, with the at least one processor, cause the apparatus to perform at least the following,

collecting arterial pressure waveform measurements of the subject animal during an observation period spanning several heartbeats;

processing the arterial pressure waveform measurements of the subject animal to extract one or more blood pressure features;

outputting a value of at least one objective blood loss metric for the subject animal by providing the one or more extracted blood pressure features as input to one or more machine learning (ML) models; and

presenting the value of the at least one objective blood loss metric,

wherein the one or more machine learning models are trained on a plurality of historical instances, each instance including historical arterial pressure waveform measurements for an animal of a related species over a historical observation period spanning a laboratory exsanguination experiment, said historical arterial pressure waveform measurements associated with at least one historical objective blood loss metric value determined from directly-measured blood loss during the laboratory exsanguination experiment.

14. The system as recited in claim 13, wherein the at least one objective blood loss metric includes a blood loss volume metric (BLVM) based on a ratio of a shed blood volume over a maximum shed blood volume that the subject animal can survive.

15. The system as recited in claim 14, wherein the at least one objective blood loss metric includes a hemorrhage area (HemArea) or mean arterial pressure area (MAPArea) or both derived from the BLVM.

16. The system as recited in claim 13, wherein the at least one objective blood loss metric includes a percent estimated blood loss (PEBL) based on a ratio of a shed blood volume over a total blood volume for the subject animal.

17. The system as recited in claim 16, wherein the total blood volume for the subject animal is based on a height or weight, or both, and a species of the subject animal.

18. The system as recited in claim 13, wherein the one or more machine learning models include an ensemble bagged trees model.

19. The system as recited in claim 18, wherein the ensemble bagged trees model includes about eight to twelve blood pressure features as input and eight to 12 leaf nodes as output.

20. The system as recited in claim 13, wherein the one or more blood pressure features are selected from a group including: peak-to-peak interval; area under a systolic rise; area under a trace from a systolic maximum to a start of a next beat subtracted by a pressure at a first inflection point and normalized by a number of samples in a single arterial pressure waveform; a duration of the systolic rise; or an area under a trace of a systolic decay.

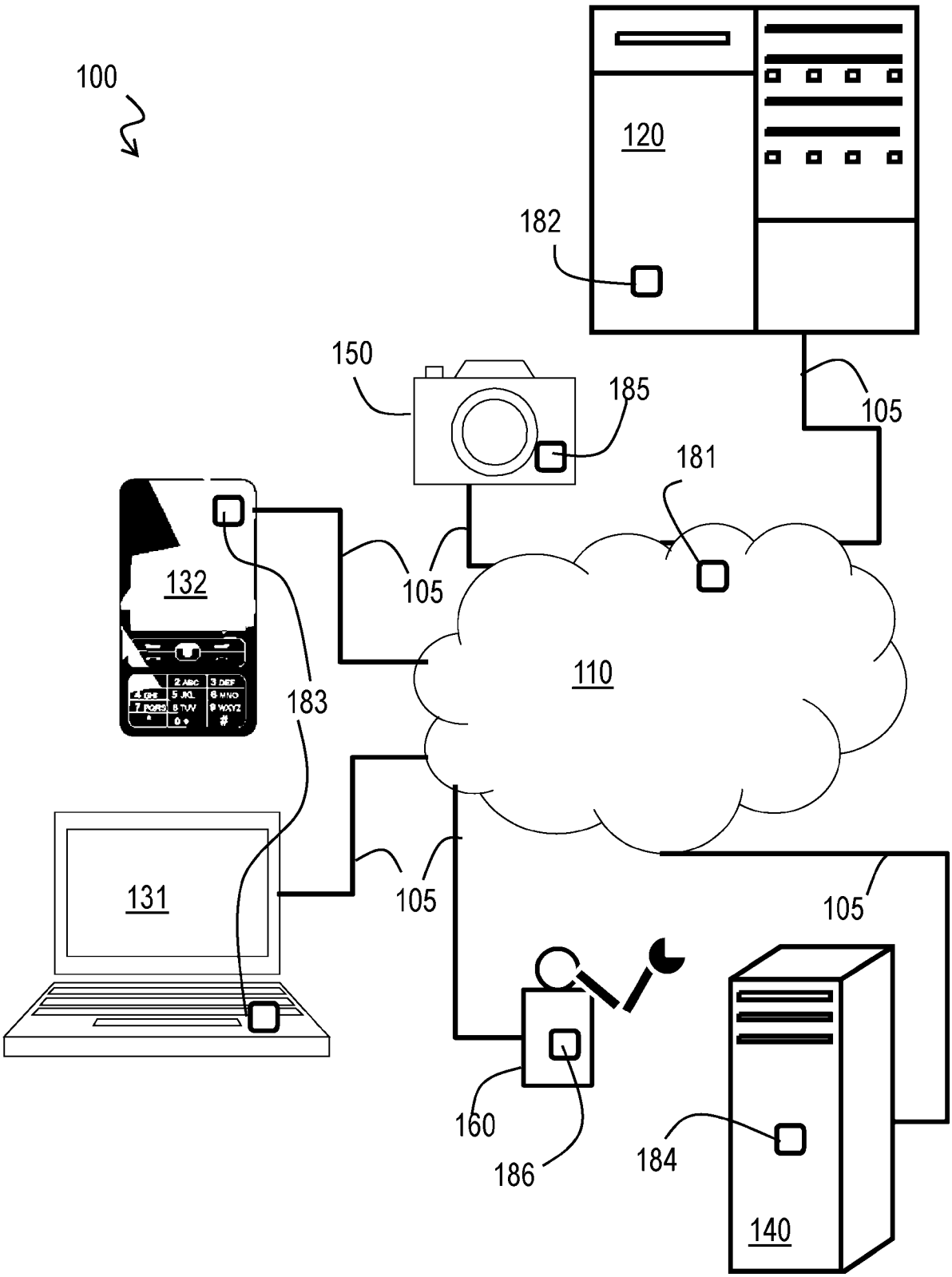

100
120
182
150
185
105
181
132
105
110
183
131
105
105
160
186
184
140

FIG. 1A

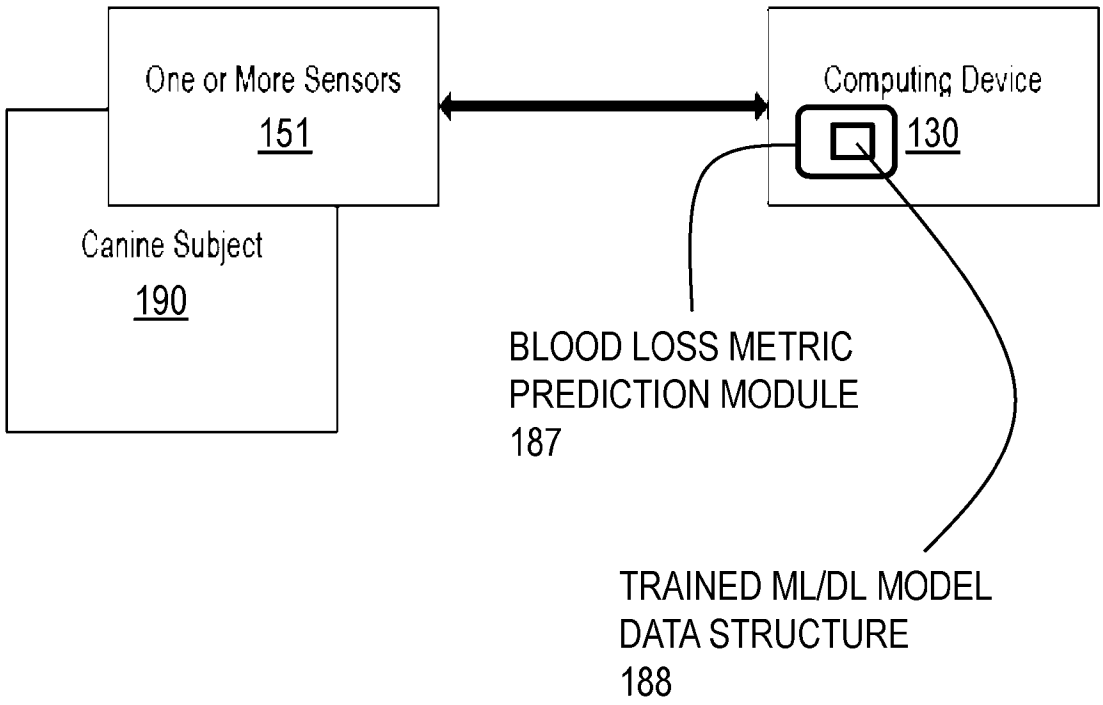

One or More Sensors
151
Canine Subject
190
Computing Device
130
BLOOD LOSS METRIC
PREDICTION MODULE
187
TRAINED ML/DL MODEL
DATA STRUCTURE
188

FIG. 1B

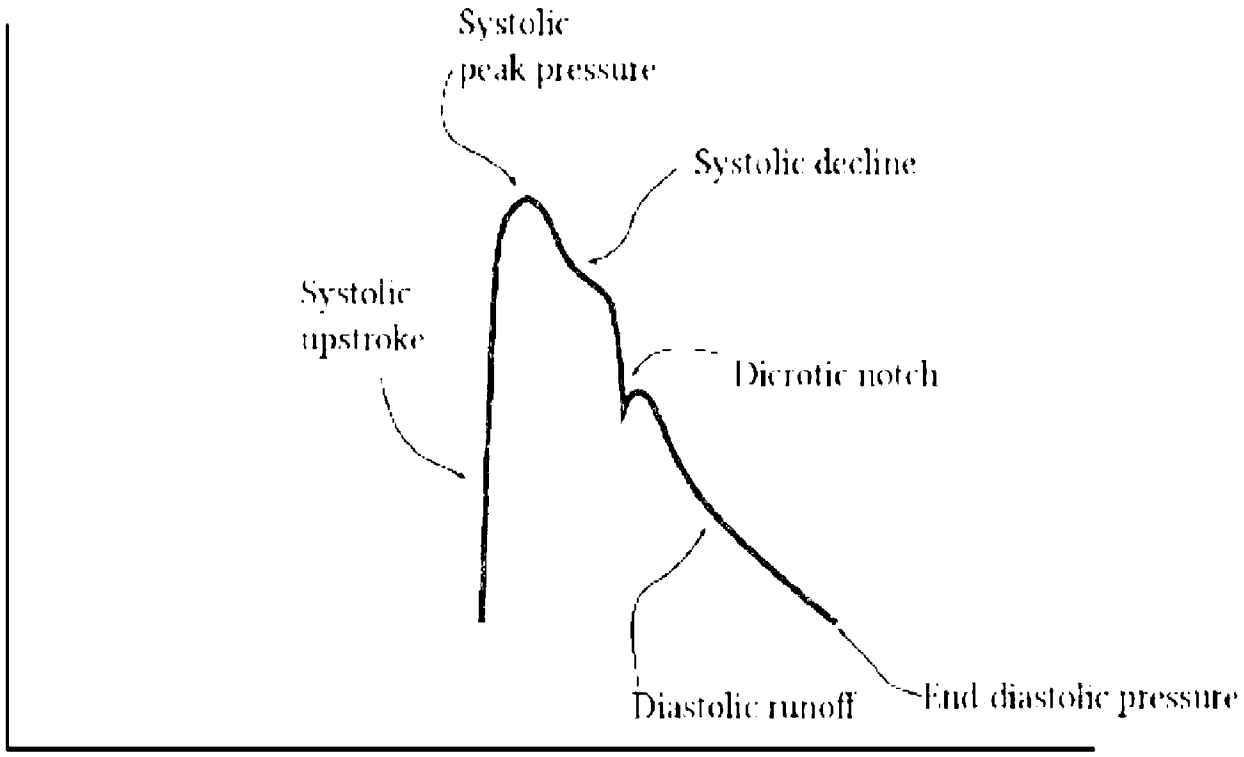

Systolic
peak pressure
Systolic decline
Systolic
upstroke
Dicrotic notch
Diastolic runoff
End diastolic pressure

FIG. 1C

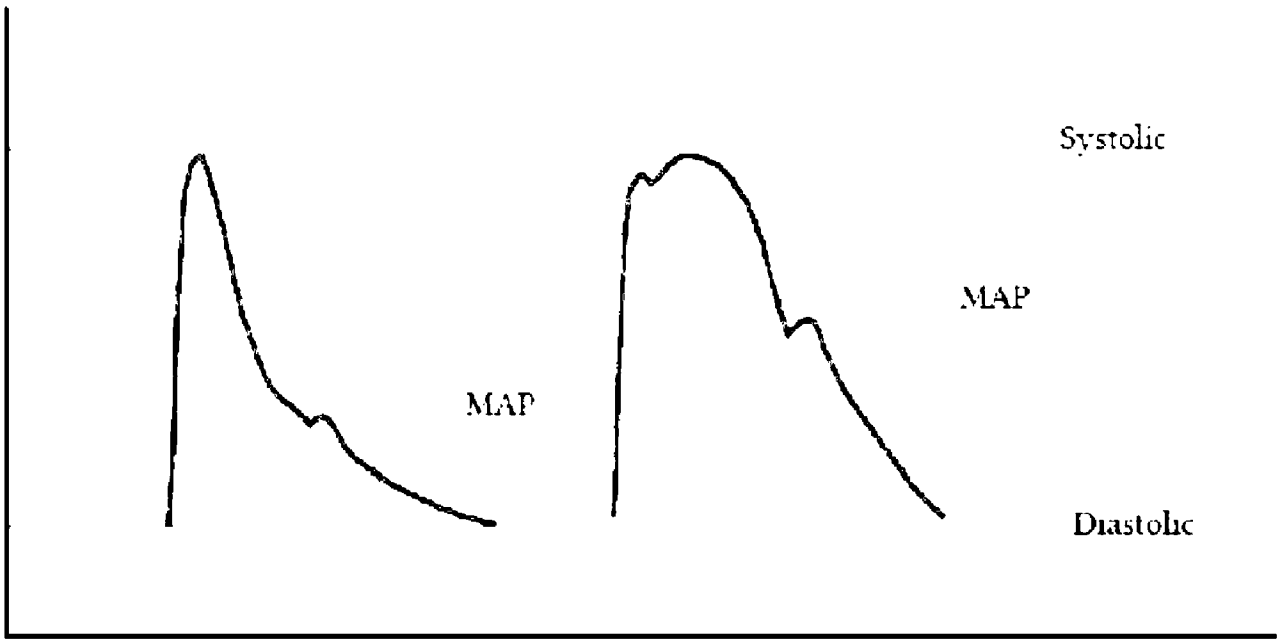

Systolic
MAP
MAP
Diastolic

FIG. 1D

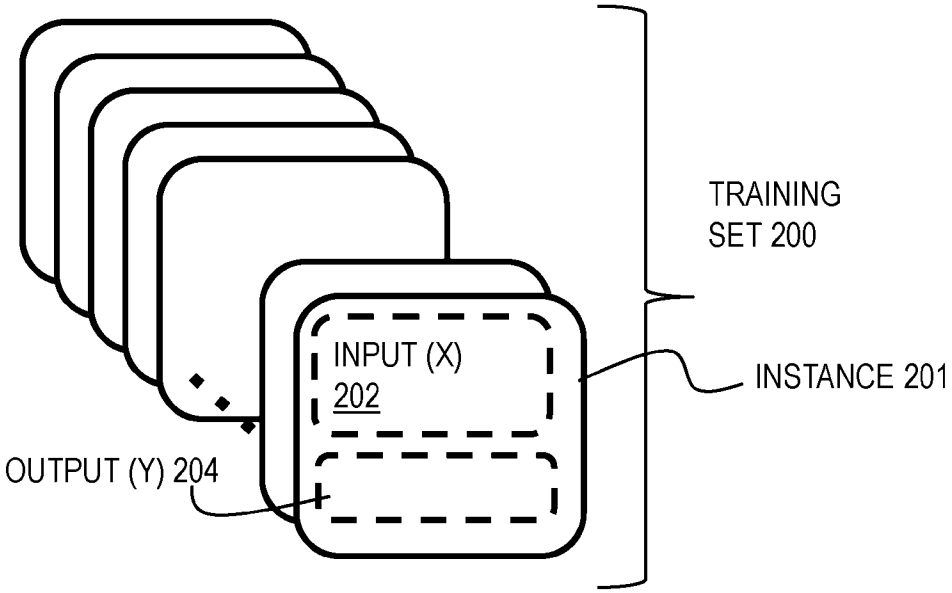


FIG. 2A

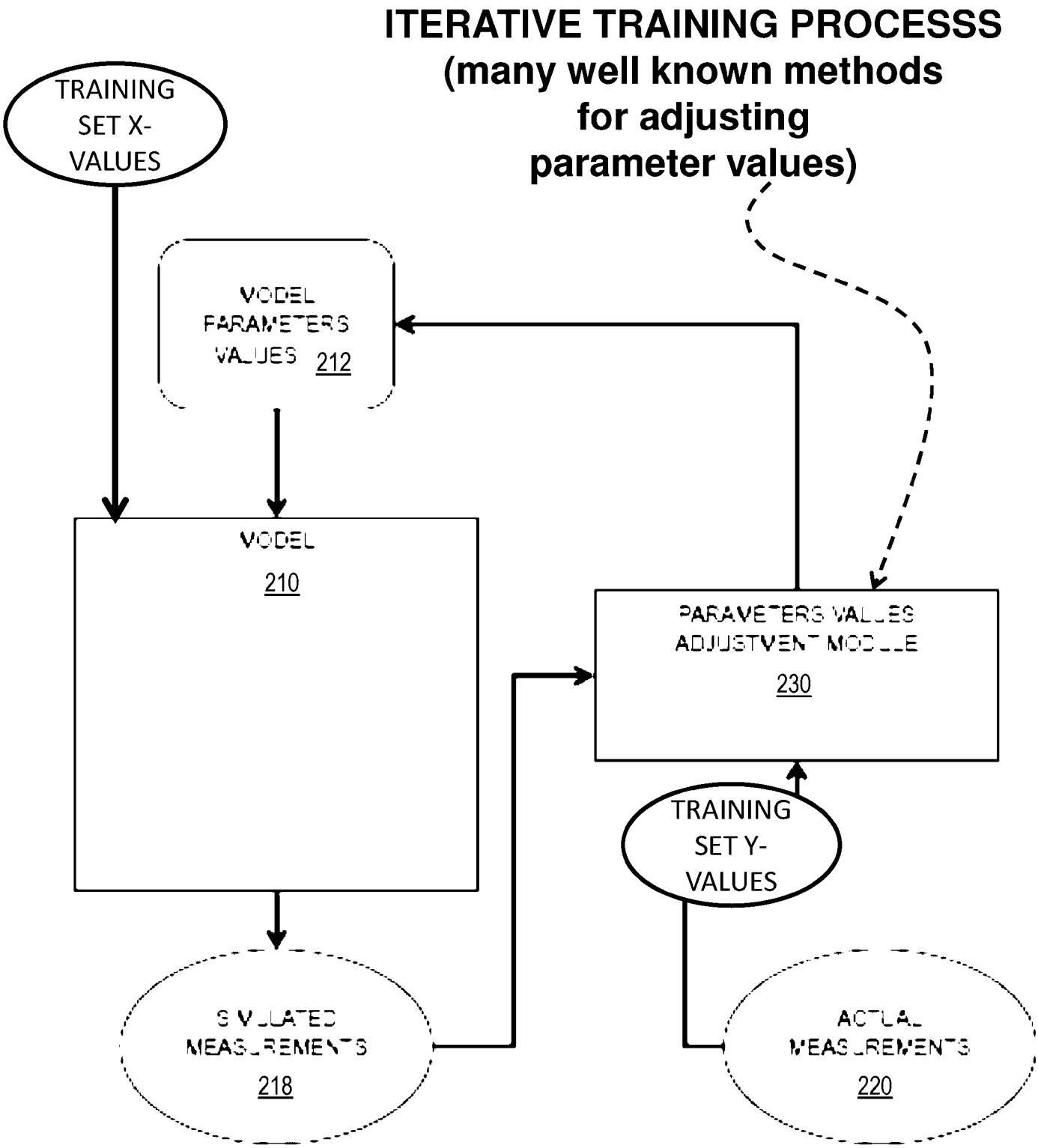

ITERATIVE TRAINING PROCESSS
(many well known methods
for adjusting
parameter values)
TRAINING SET X-VALUES
MODEL PARAMETERS VALUES 212
MODEL 210
PARAMETERS VALUES ADJUSTMENT MODULE 230
TRAINING SET Y-VALUES
SIMULATED MEASUREMENTS 218
ACTUAL MEASUREMENTS 220

FIG. 2B

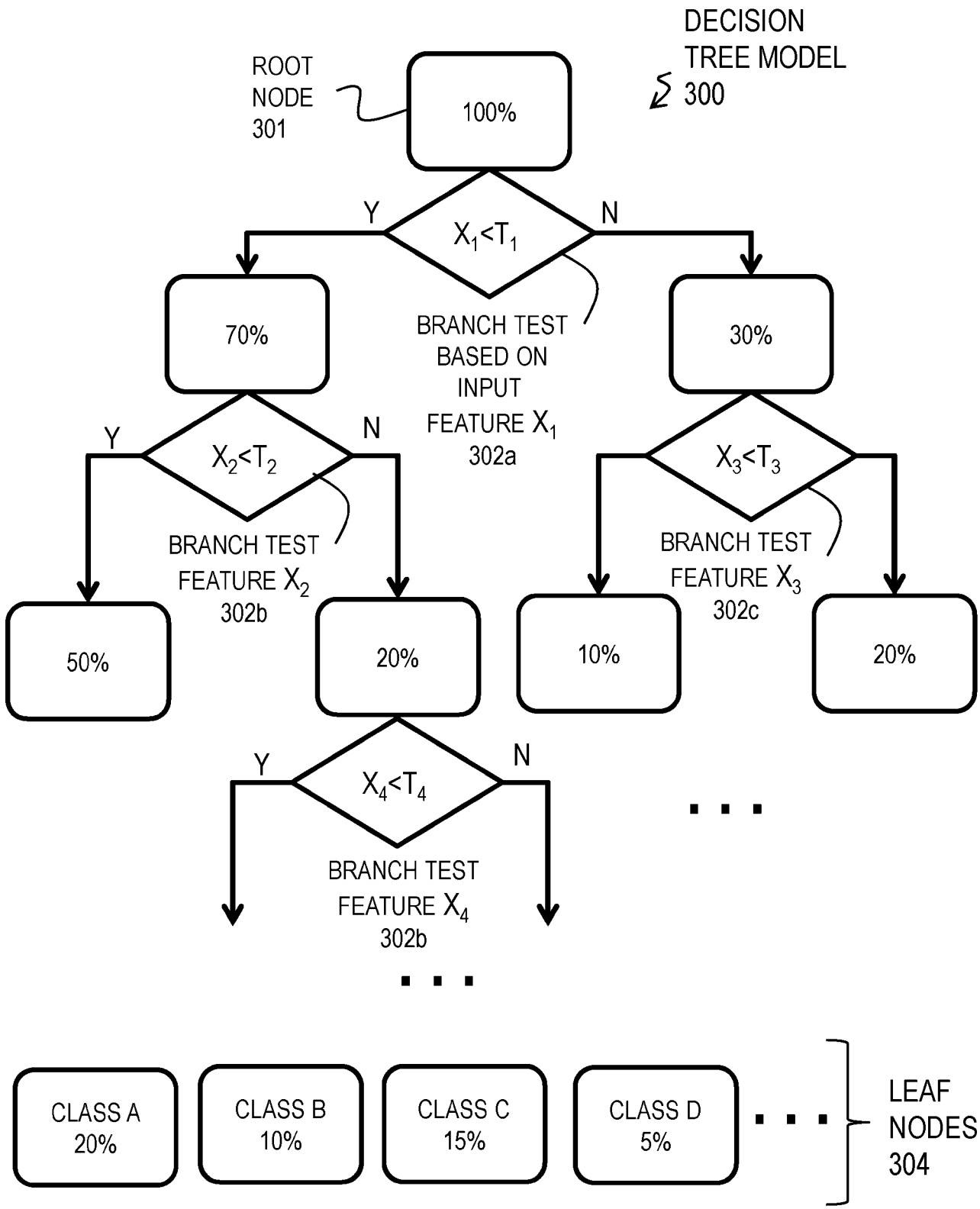

DECISION TREE MODEL 300
ROOT NODE 301
100%
Y
$X_1<T_1$
N
BRANCH TEST BASED ON INPUT FEATURE X_1 302a
70%
30%
Y
$X_2<T_2$
N
BRANCH TEST FEATURE X_2 302b
$X_3<T_3$
BRANCH TEST FEATURE X_3 302c
50%
20%
10%
20%
Y
$X_4<T_4$
N
BRANCH TEST FEATURE X_4 302b
CLASS A 20%
CLASS B 10%
CLASS C 15%
CLASS D 5%
LEAF NODES 304

FIG. 3A

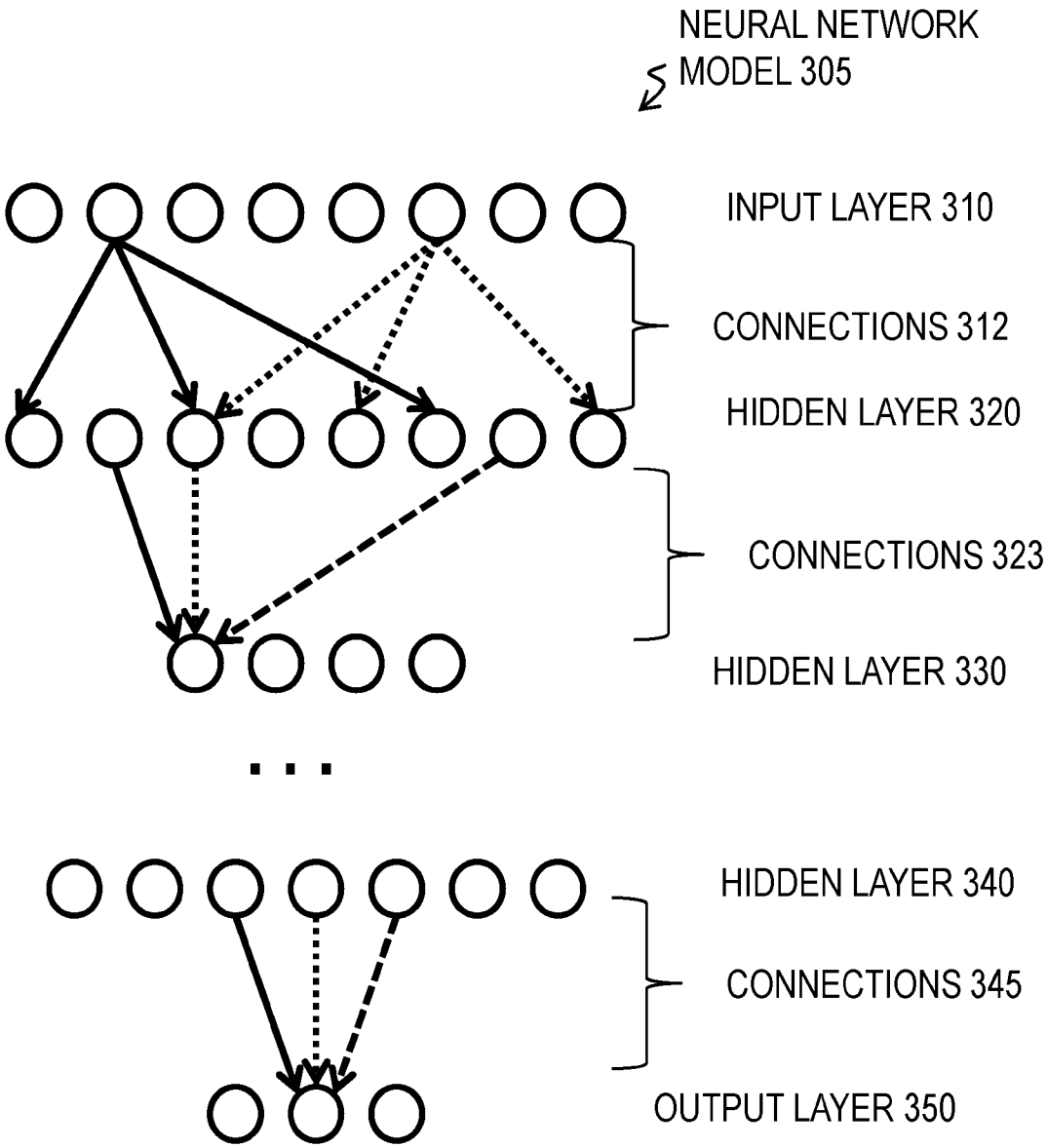

NEURAL NETWORK
MODEL 305
INPUT LAYER 310
CONNECTIONS 312
HIDDEN LAYER 320
CONNECTIONS 323
HIDDEN LAYER 330
HIDDEN LAYER 340
CONNECTIONS 345
OUTPUT LAYER 350

FIG. 3B

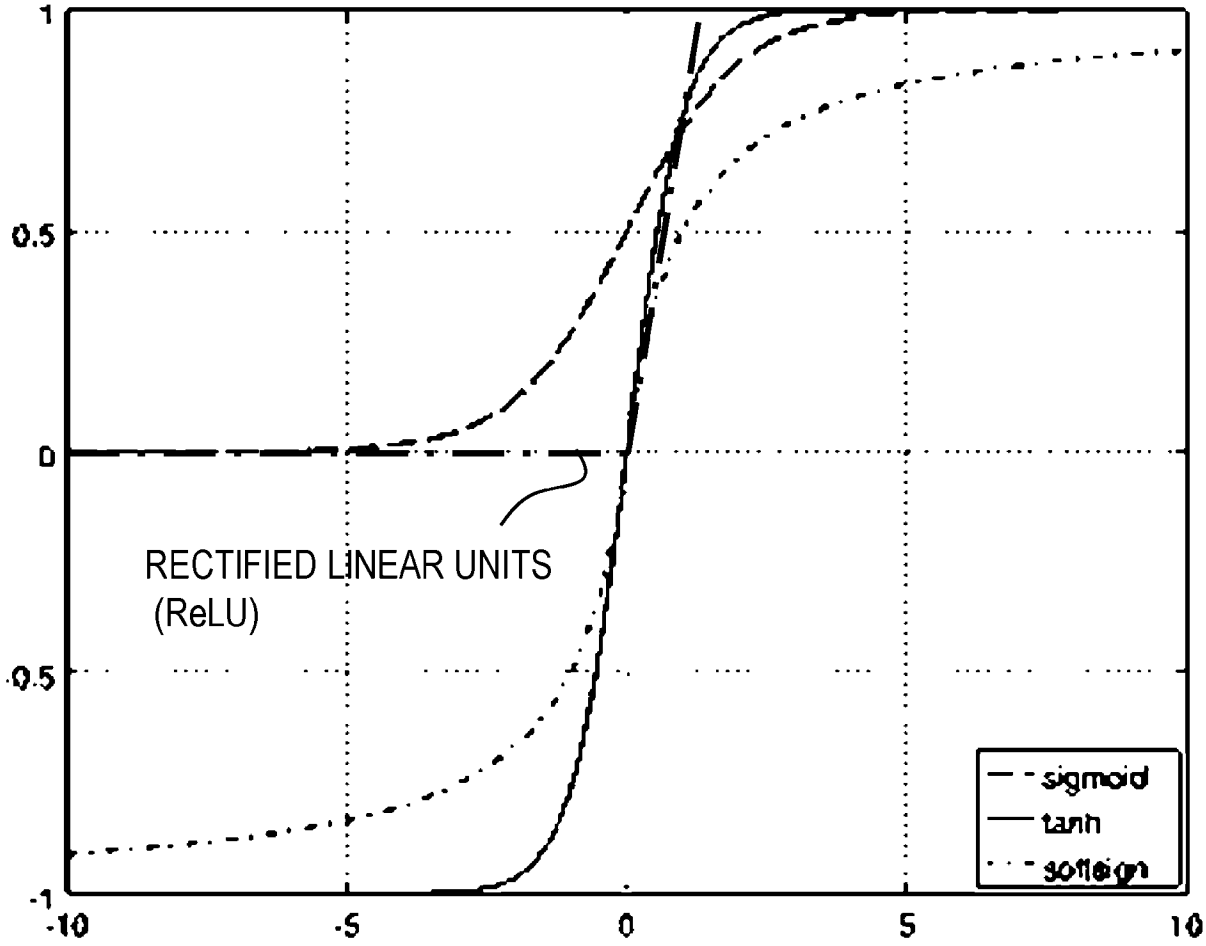

1
0.5
0
-0.5
-1
-10
-5
0
5
10
RECTIFIED LINEAR UNITS
(ReLU)
sigmoid
tanh
softsign

FIG. 3C

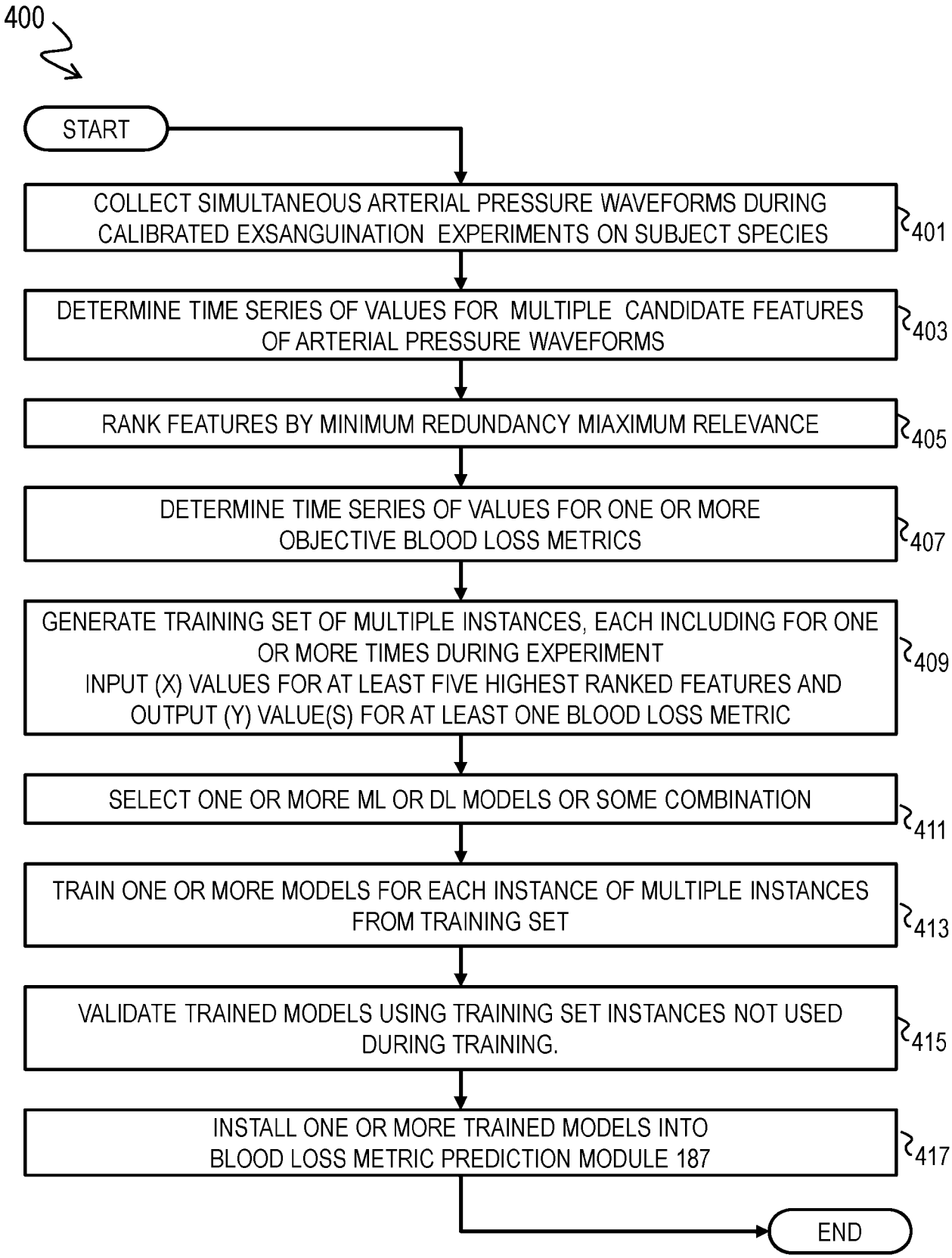

400
START
COLLECT SIMULTANEOUS ARTERIAL PRESSURE WAVEFORMS DURING CALIBRATED EXSANGUINATION EXPERIMENTS ON SUBJECT SPECIES
401
DETERMINE TIME SERIES OF VALUES FOR MULTIPLE CANDIDATE FEATURES OF ARTERIAL PRESSURE WAVEFORMS
403
RANK FEATURES BY MINIMUM REDUNDANCY MIAXIMUM RELEVANCE
405
DETERMINE TIME SERIES OF VALUES FOR ONE OR MORE OBJECTIVE BLOOD LOSS METRICS
407
GENERATE TRAINING SET OF MULTIPLE INSTANCES, EACH INCLUDING FOR ONE OR MORE TIMES DURING EXPERIMENT
INPUT (X) VALUES FOR AT LEAST FIVE HIGHEST RANKED FEATURES AND
OUTPUT (Y) VALUE(S) FOR AT LEAST ONE BLOOD LOSS METRIC
409
SELECT ONE OR MORE ML OR DL MODELS OR SOME COMBINATION
411
TRAIN ONE OR MORE MODELS FOR EACH INSTANCE OF MULTIPLE INSTANCES FROM TRAINING SET
413
VALIDATE TRAINED MODELS USING TRAINING SET INSTANCES NOT USED DURING TRAINING.
415
INSTALL ONE OR MORE TRAINED MODELS INTO BLOOD LOSS METRIC PREDICTION MODULE 187
417
END

FIG. 4A

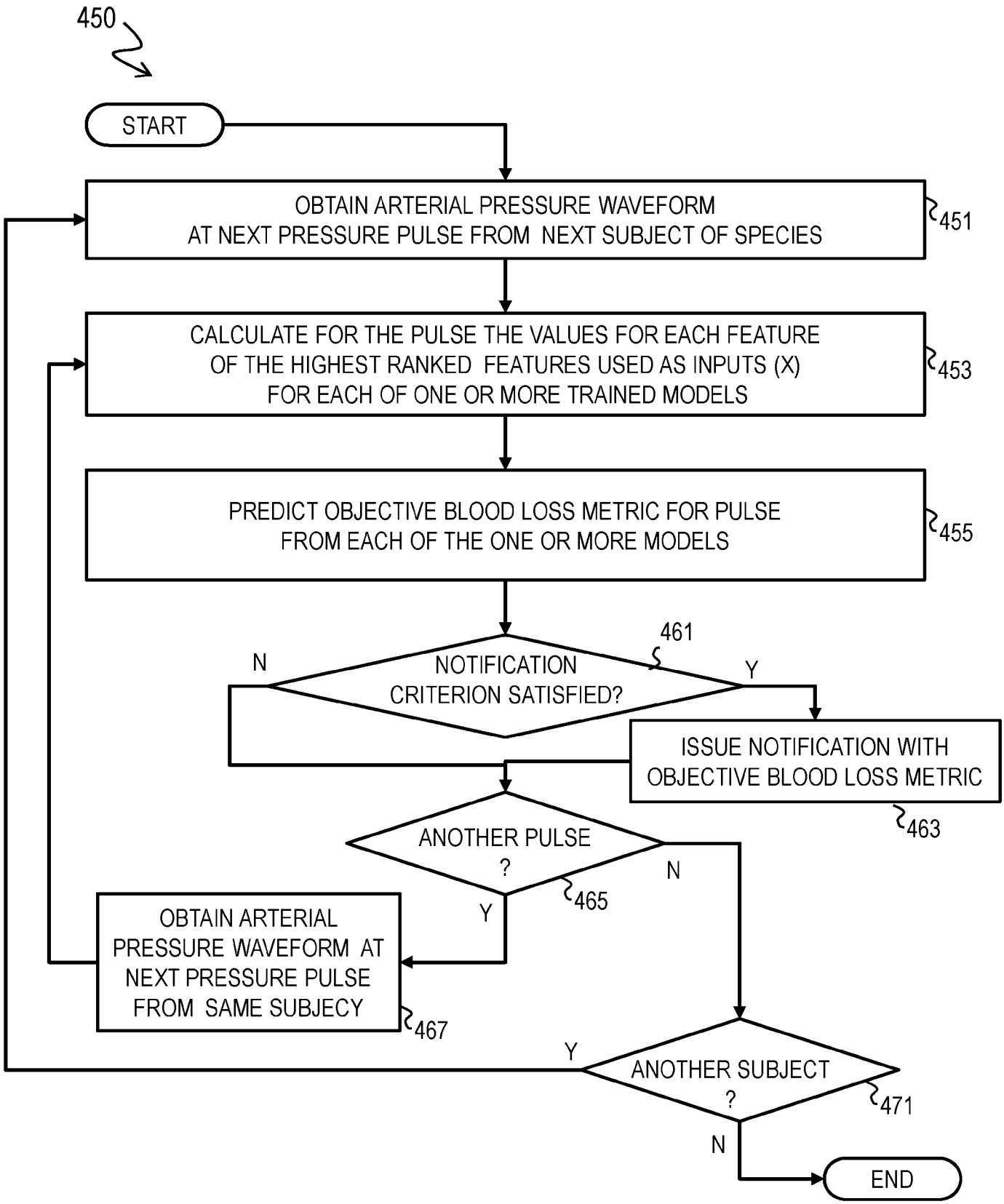

450
START
OBTAIN ARTERIAL PRESSURE WAVEFORM AT NEXT PRESSURE PULSE FROM NEXT SUBJECT OF SPECIES
451
CALCULATE FOR THE PULSE THE VALUES FOR EACH FEATURE OF THE HIGHEST RANKED FEATURES USED AS INPUTS (X) FOR EACH OF ONE OR MORE TRAINED MODELS
453
PREDICT OBJECTIVE BLOOD LOSS METRIC FOR PULSE FROM EACH OF THE ONE OR MORE MODELS
455
461
NOTIFICATION CRITERION SATISFIED?
N
Y
ISSUE NOTIFICATION WITH OBJECTIVE BLOOD LOSS METRIC
463
ANOTHER PULSE ?
465
N
Y
OBTAIN ARTERIAL PRESSURE WAVEFORM AT NEXT PRESSURE PULSE FROM SAME SUBJECY
467
ANOTHER SUBJECT ?
471
Y
N
END

FIG. 4B

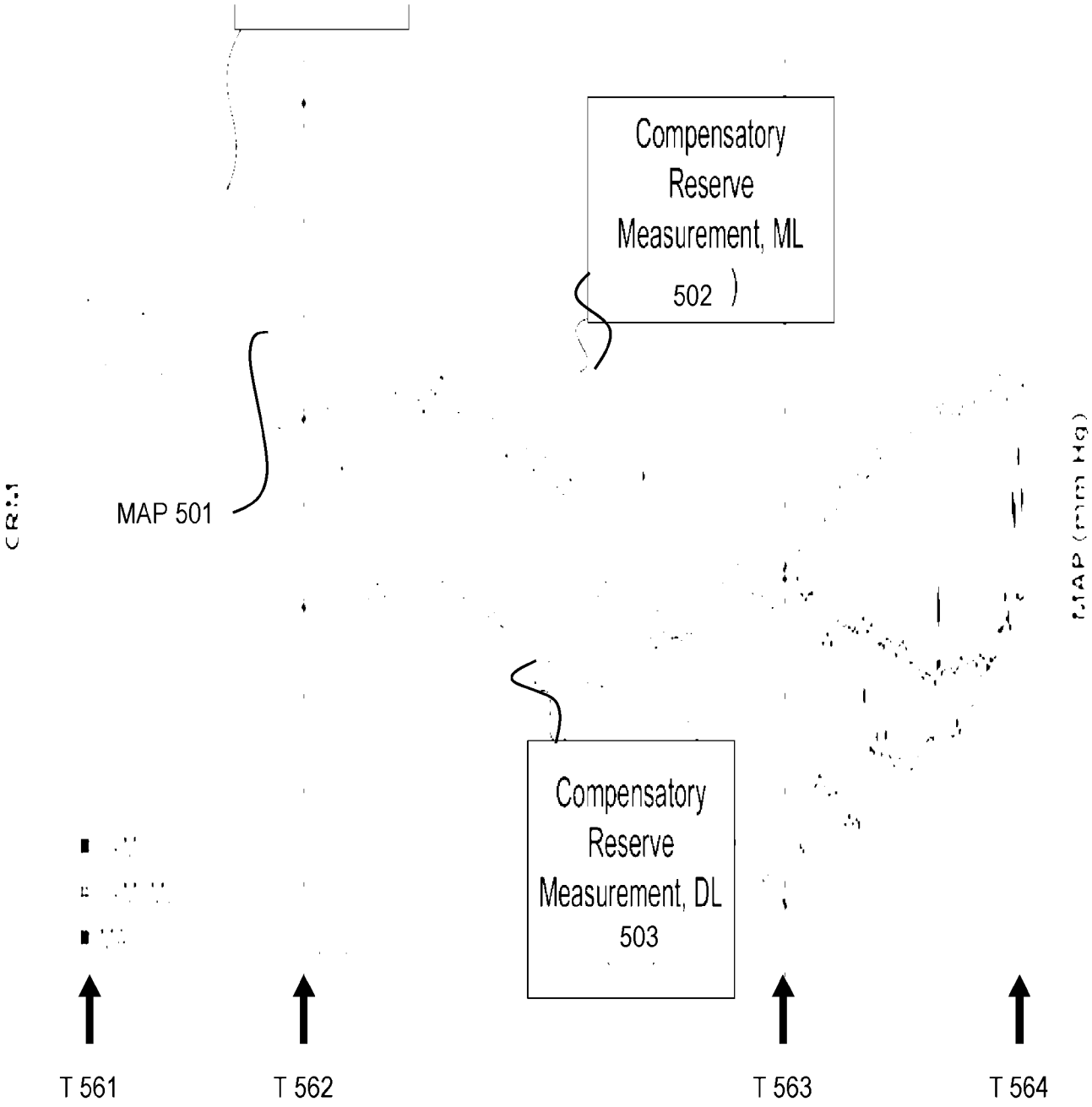

Compensatory Reserve Measurement, ML
502
MAP 501
Compensatory Reserve Measurement, DL
503
T 561
T 562
T 563
T 564

FIG. 5

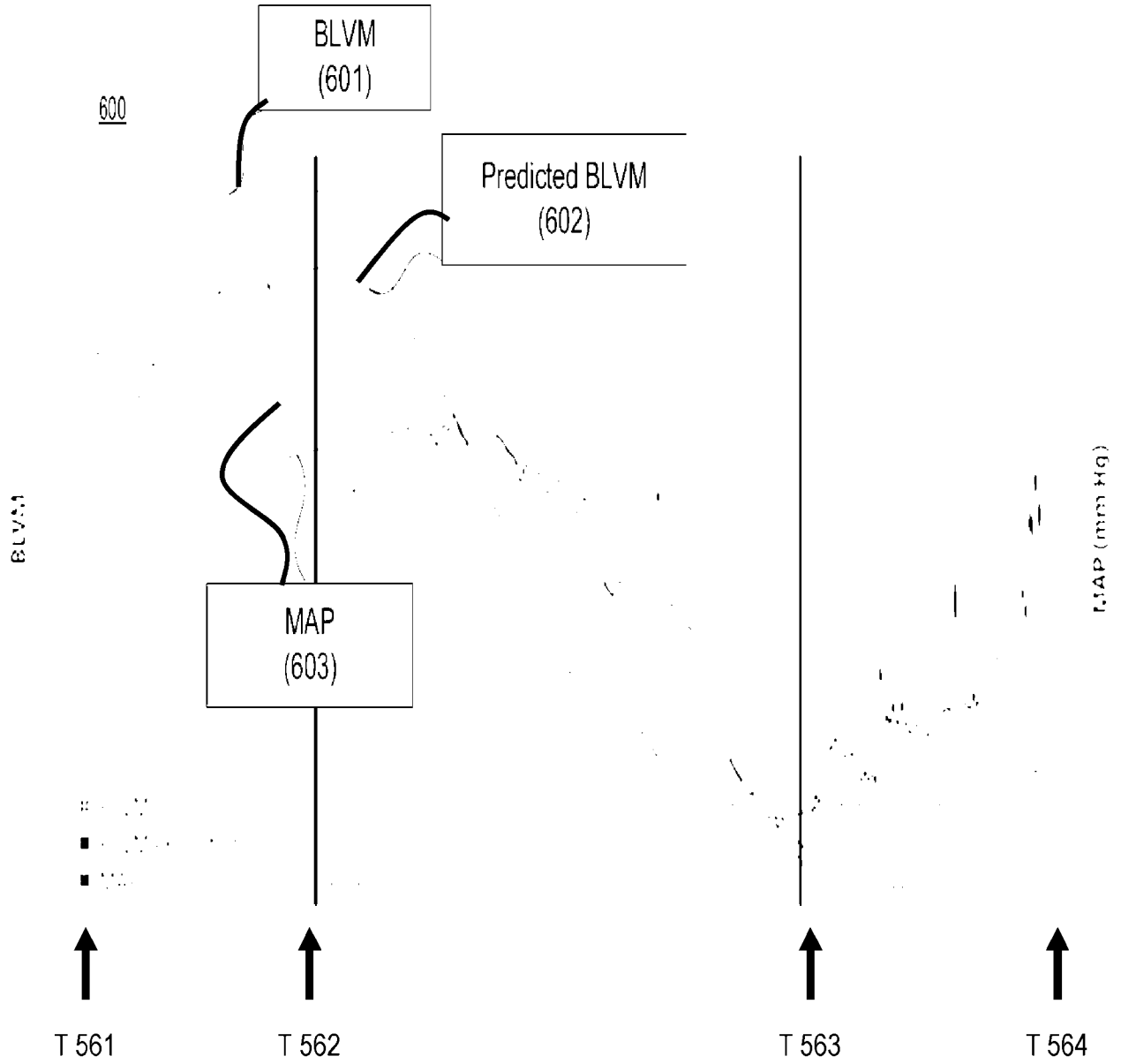


FIG. 6

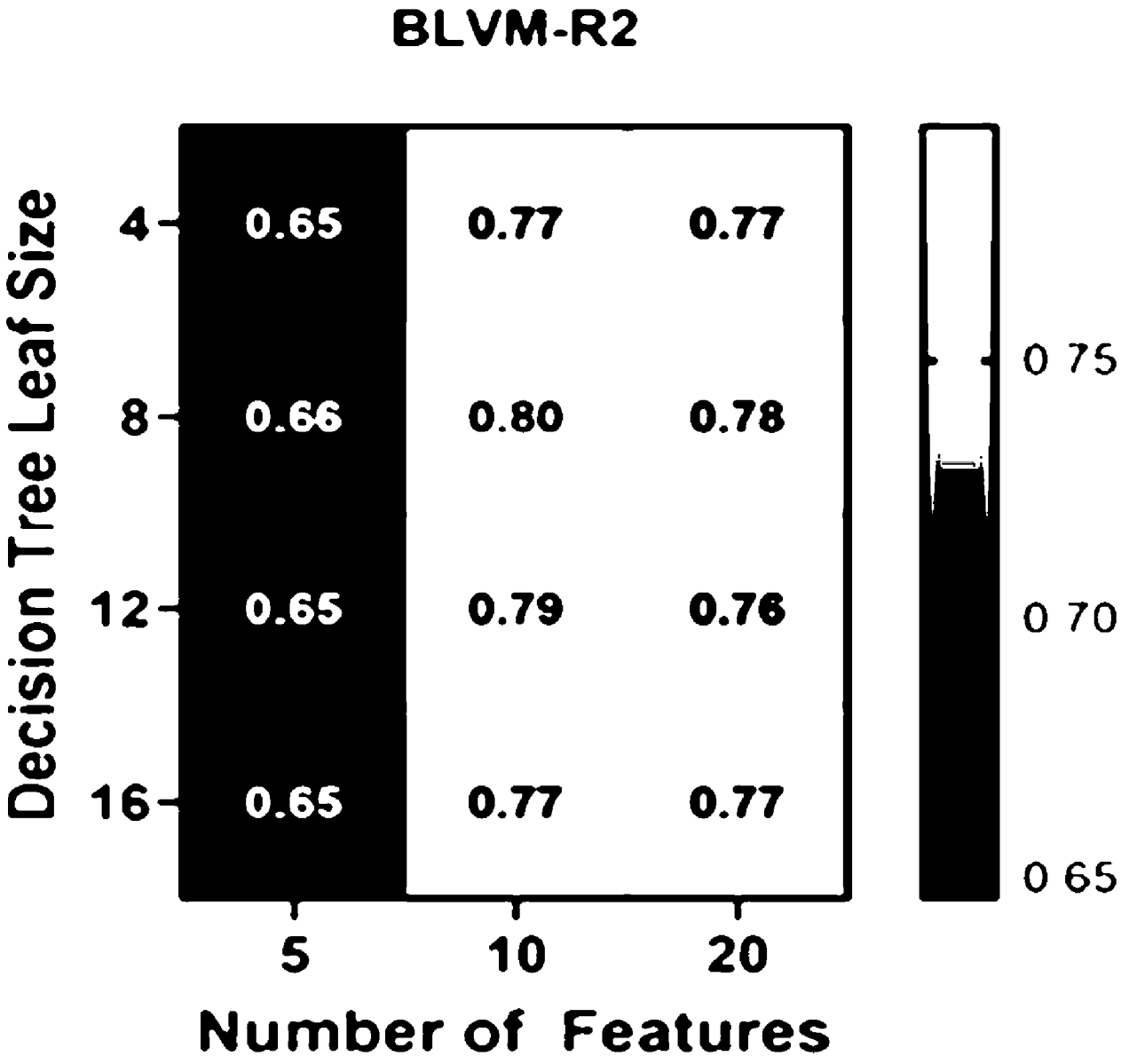

BLVM-R2
Decision Tree Leaf Size
4
8
12
16
0.65
0.77
0.77
0.66
0.80
0.78
0.65
0.79
0.76
0.65
0.77
0.77
5
10
20
Number of Features
0 75
0 70
0 65

FIG. 7

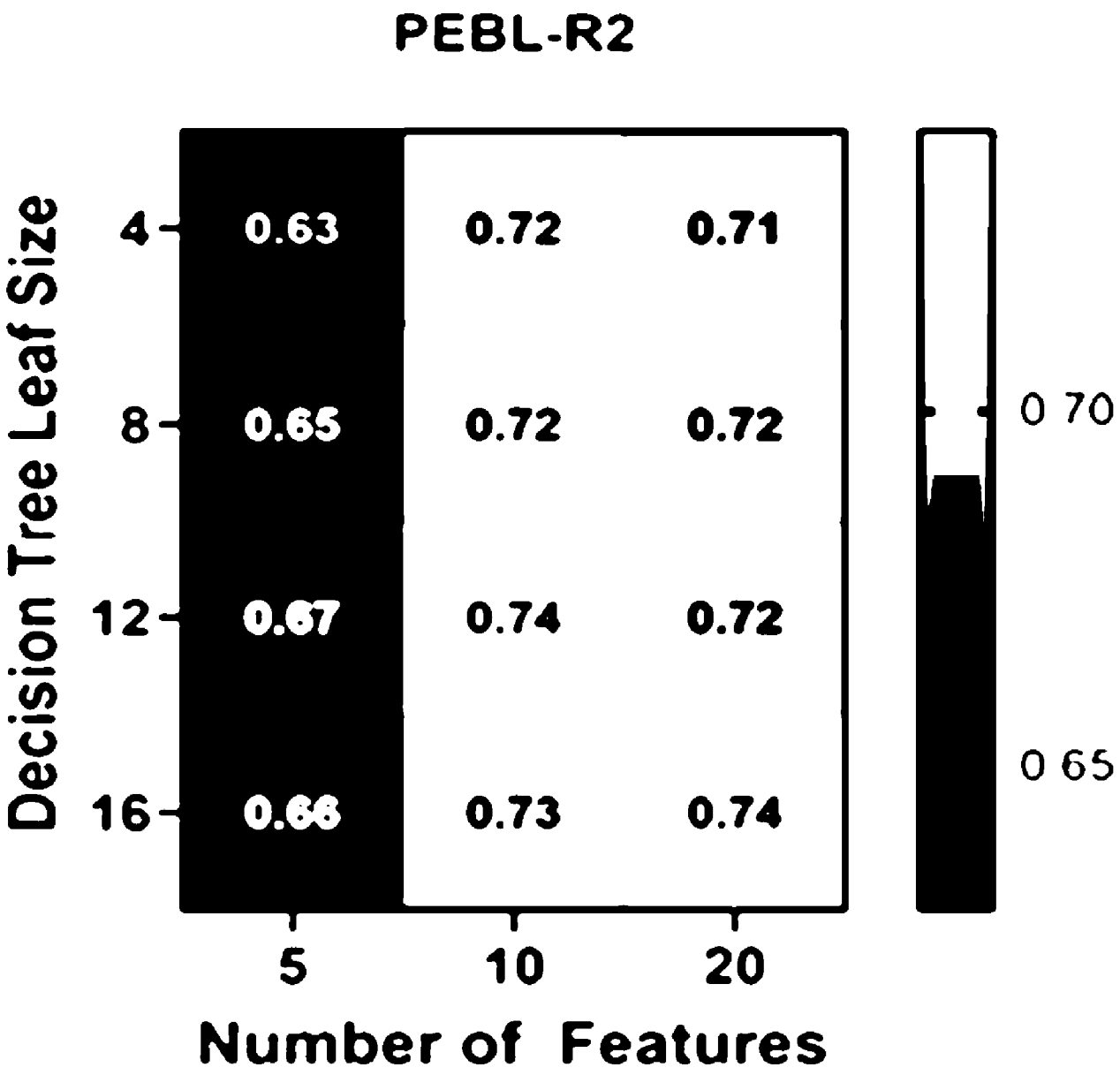

PEBL-R2
Decision Tree Leaf Size
4
8
12
16
0.63
0.72
0.71
0.65
0.72
0.72
0.67
0.74
0.72
0.66
0.73
0.74
5
10
20
Number of Features
0 70
0 65

FIG. 8

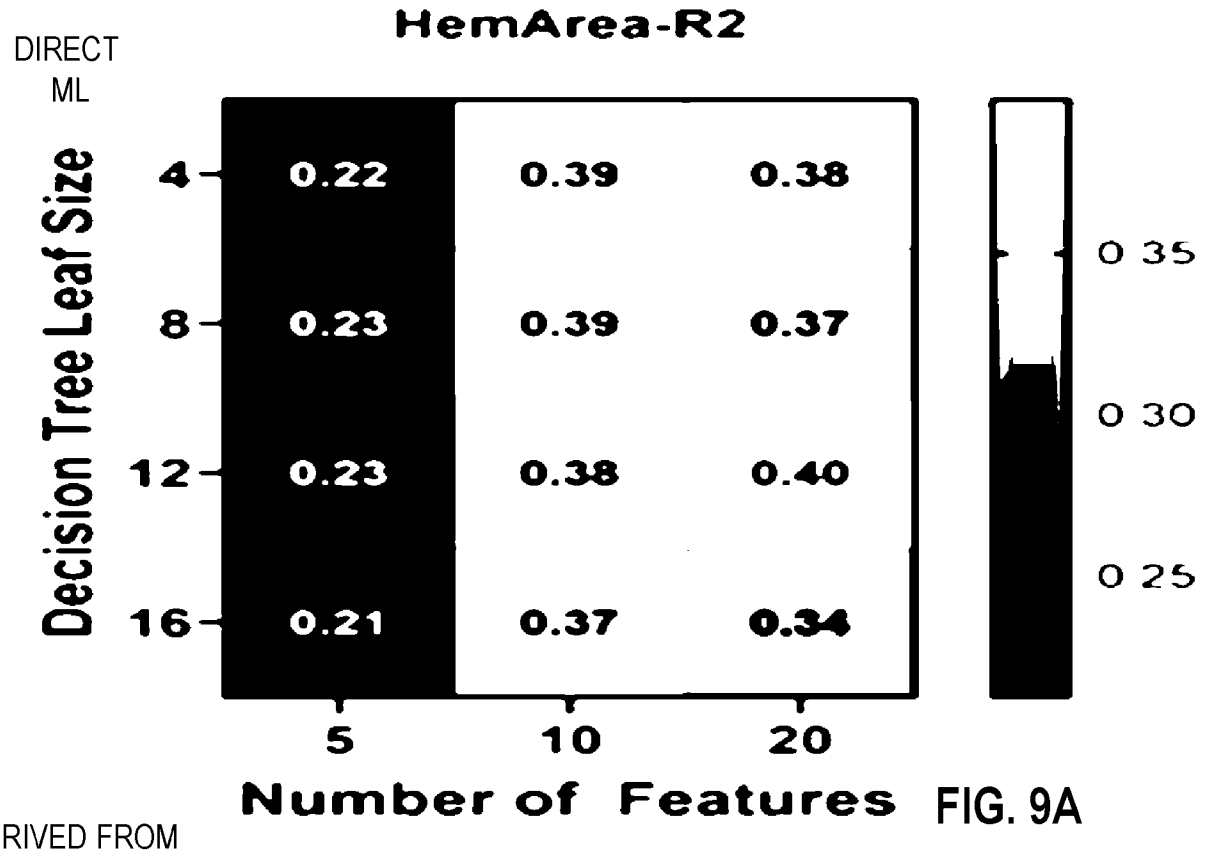

HemArea-R2
DIRECT ML
Decision Tree Leaf Size
4
8
12
16
0.22
0.39
0.38
0.23
0.39
0.37
0.23
0.38
0.40
0.21
0.37
0.34
5
10
20
Number of Features
0 35
0 30
0 25

FIG. 9A

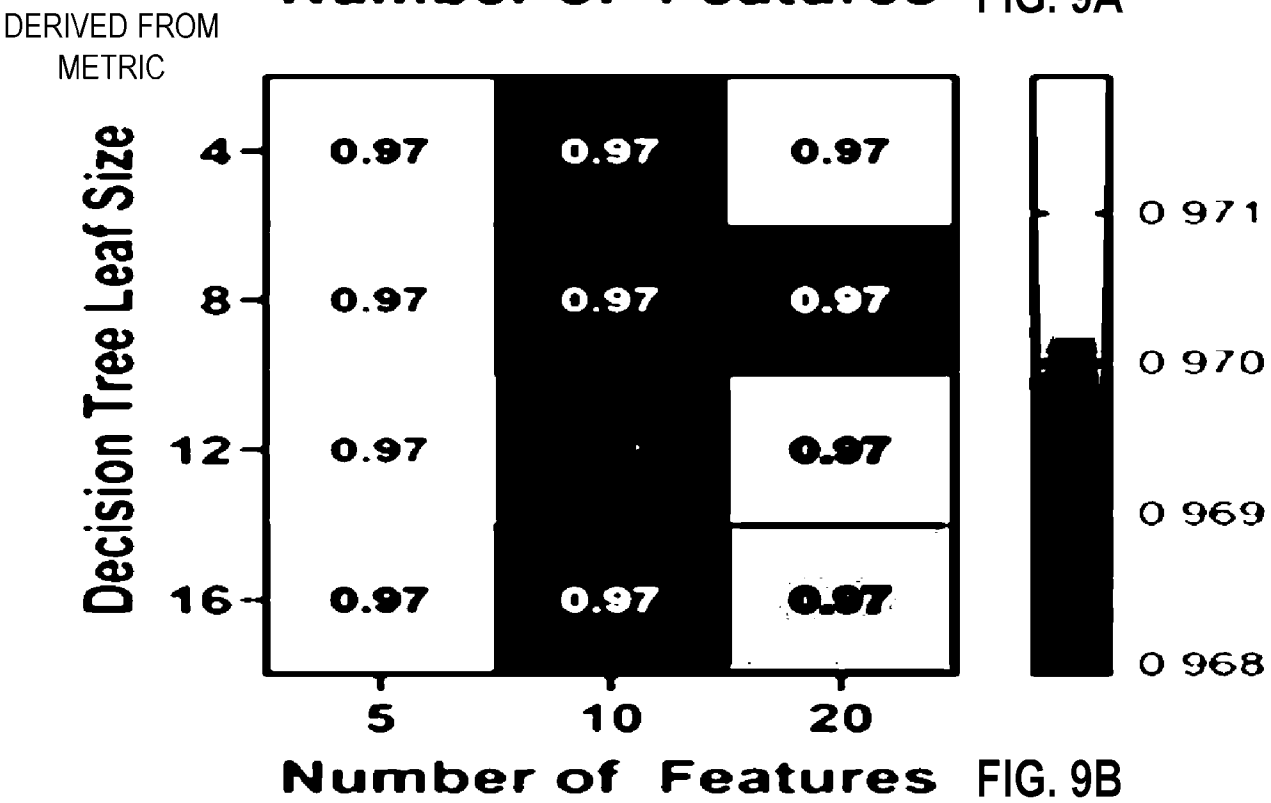

DERIVED FROM METRIC
Decision Tree Leaf Size
4
8
12
16
0.97
0.97
0.97
0.97
0.97
0.97
0.97
0.97
0.97
0.97
0.97
0.97
5
10
20
Number of Features
0 971
0 970
0 969
0 968

FIG. 9B

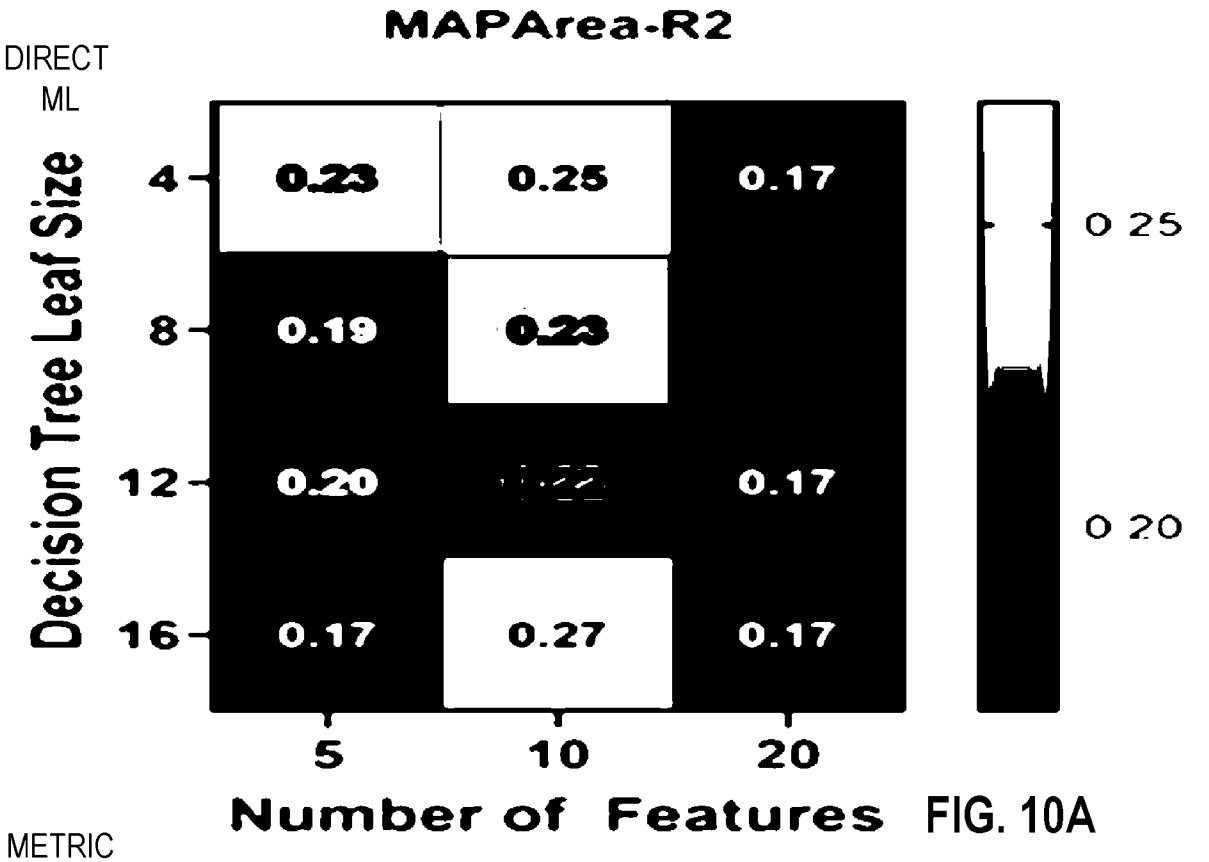


FIG. 10A

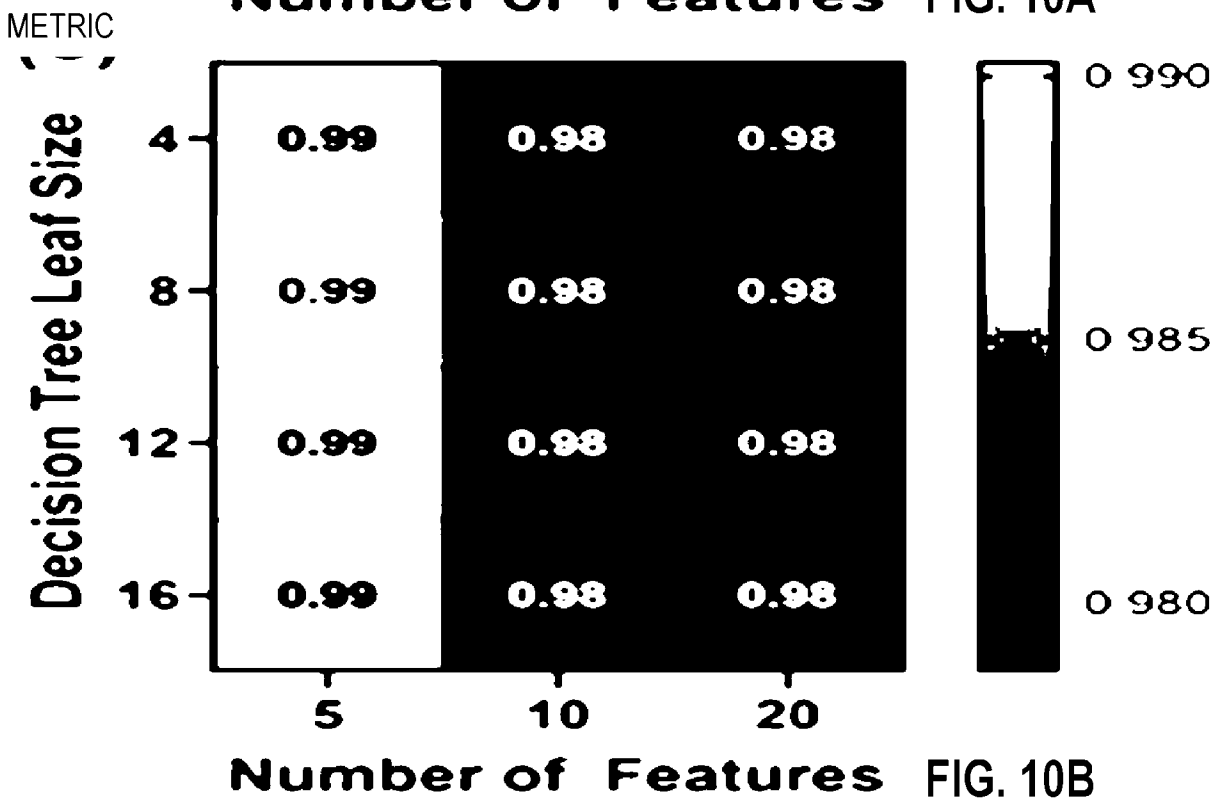


FIG. 10B

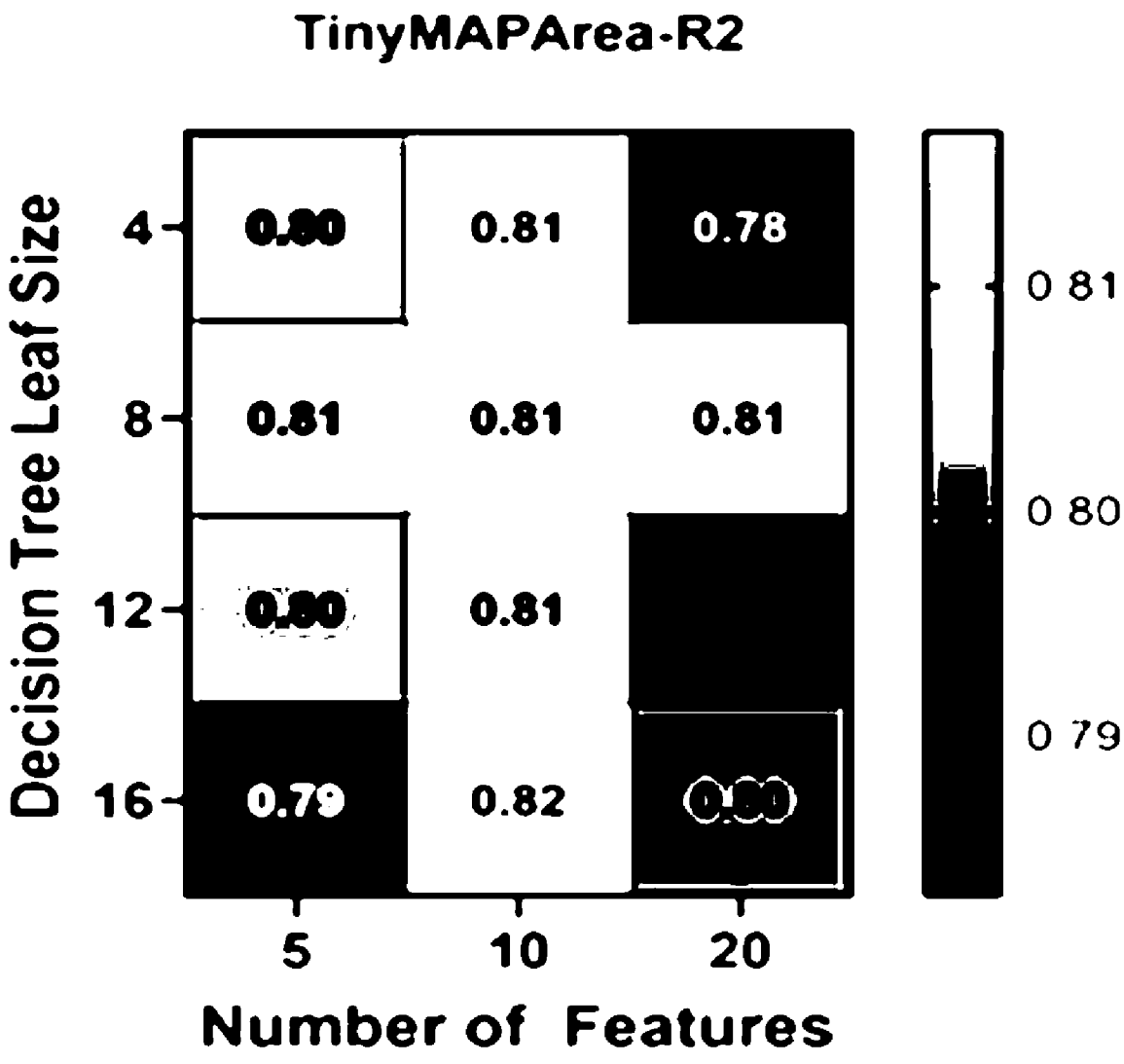

TinyMAPArea-R2
Decision Tree Leaf Size
4
8
12
16
0.80
0.81
0.78
0.81
0.81
0.81
0.80
0.81
0.79
0.82
5
10
20
Number of Features
0 81
0 80
0 79

FIG. 11

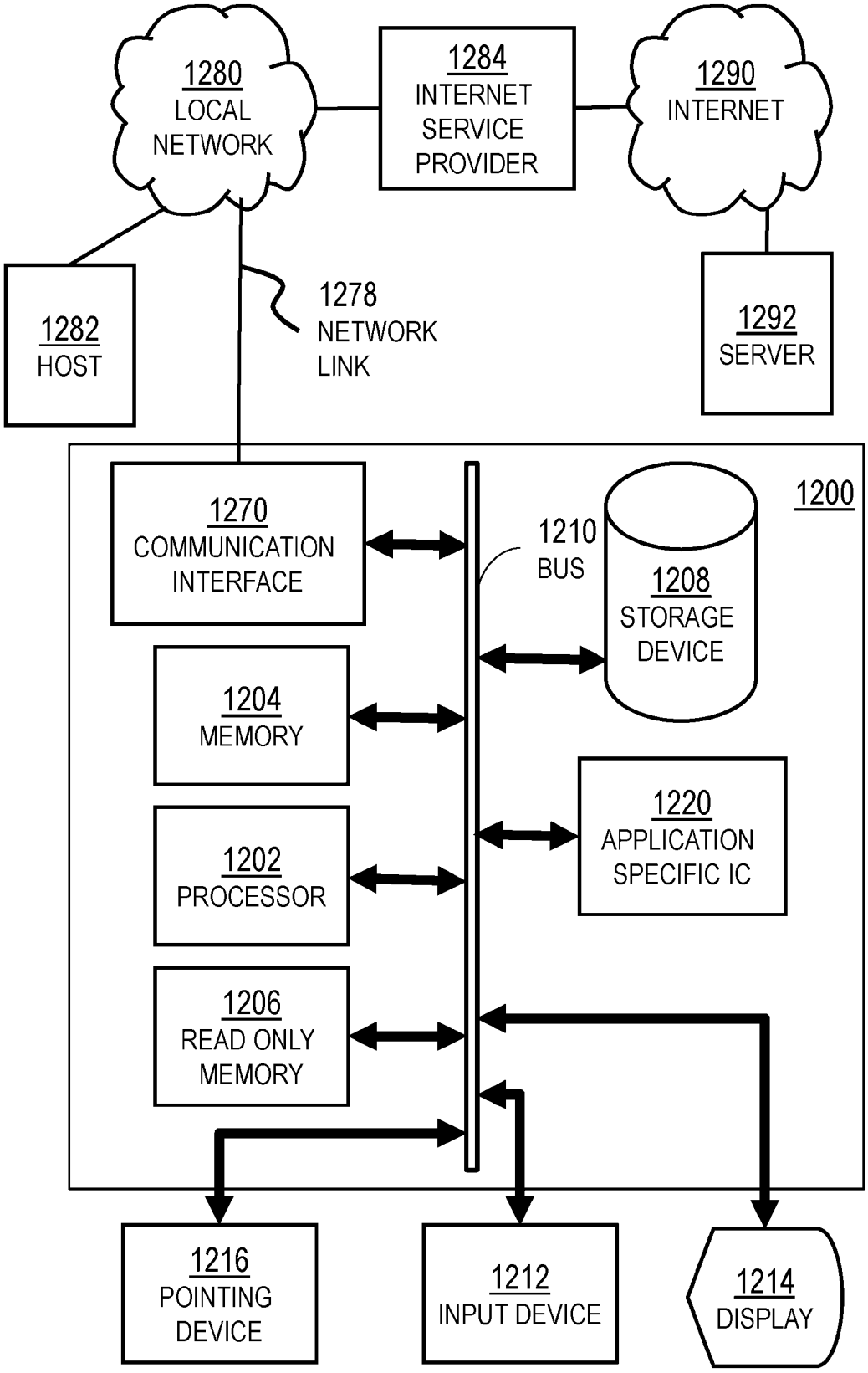

1280
LOCAL
NETWORK
1284
INTERNET
SERVICE
PROVIDER
1290
INTERNET
1282
HOST
1278
NETWORK
LINK
1292
SERVER
1200
1270
COMMUNICATION
INTERFACE
1210
BUS
1208
STORAGE
DEVICE
1204
MEMORY
1220
APPLICATION
SPECIFIC IC
1202
PROCESSOR
1206
READ ONLY
MEMORY
1216
POINTING
DEVICE
1212
INPUT DEVICE
1214
DISPLAY

FIG. 12

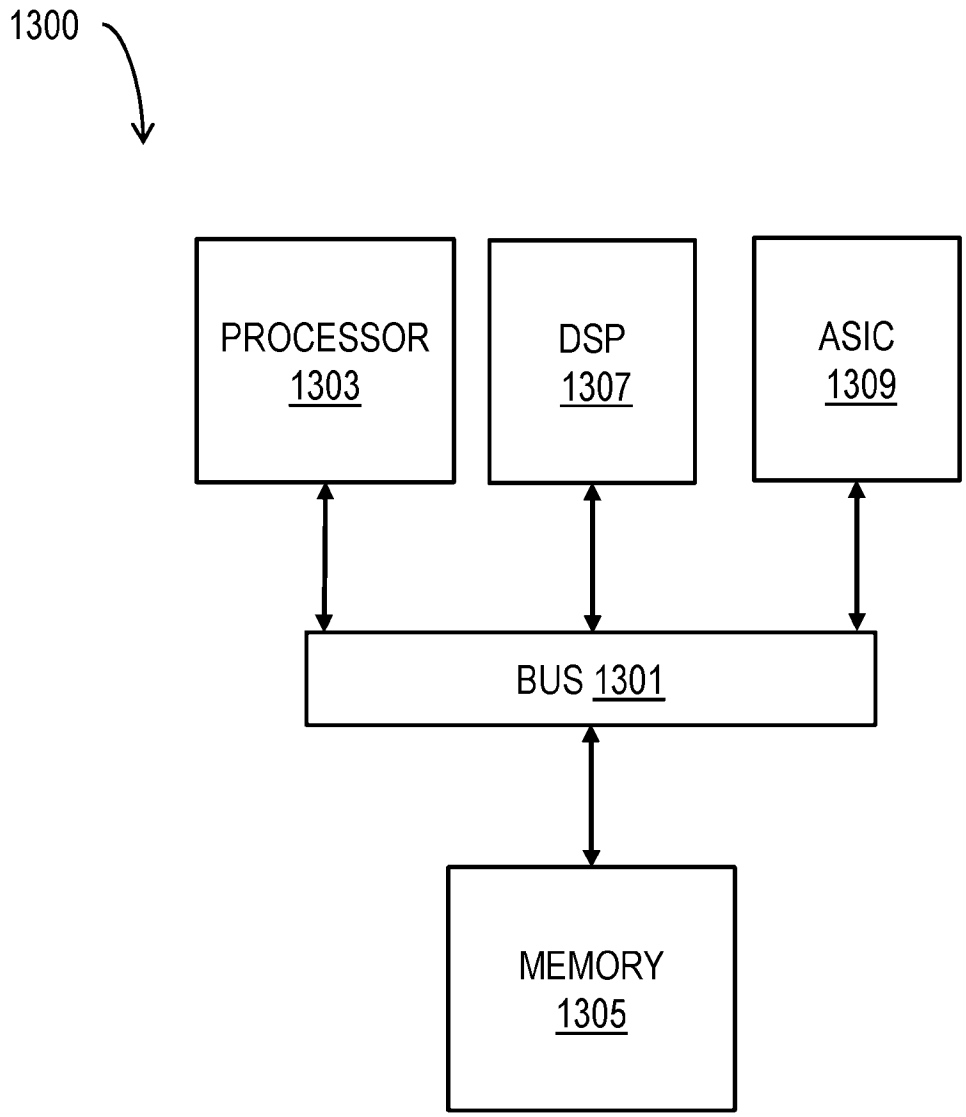
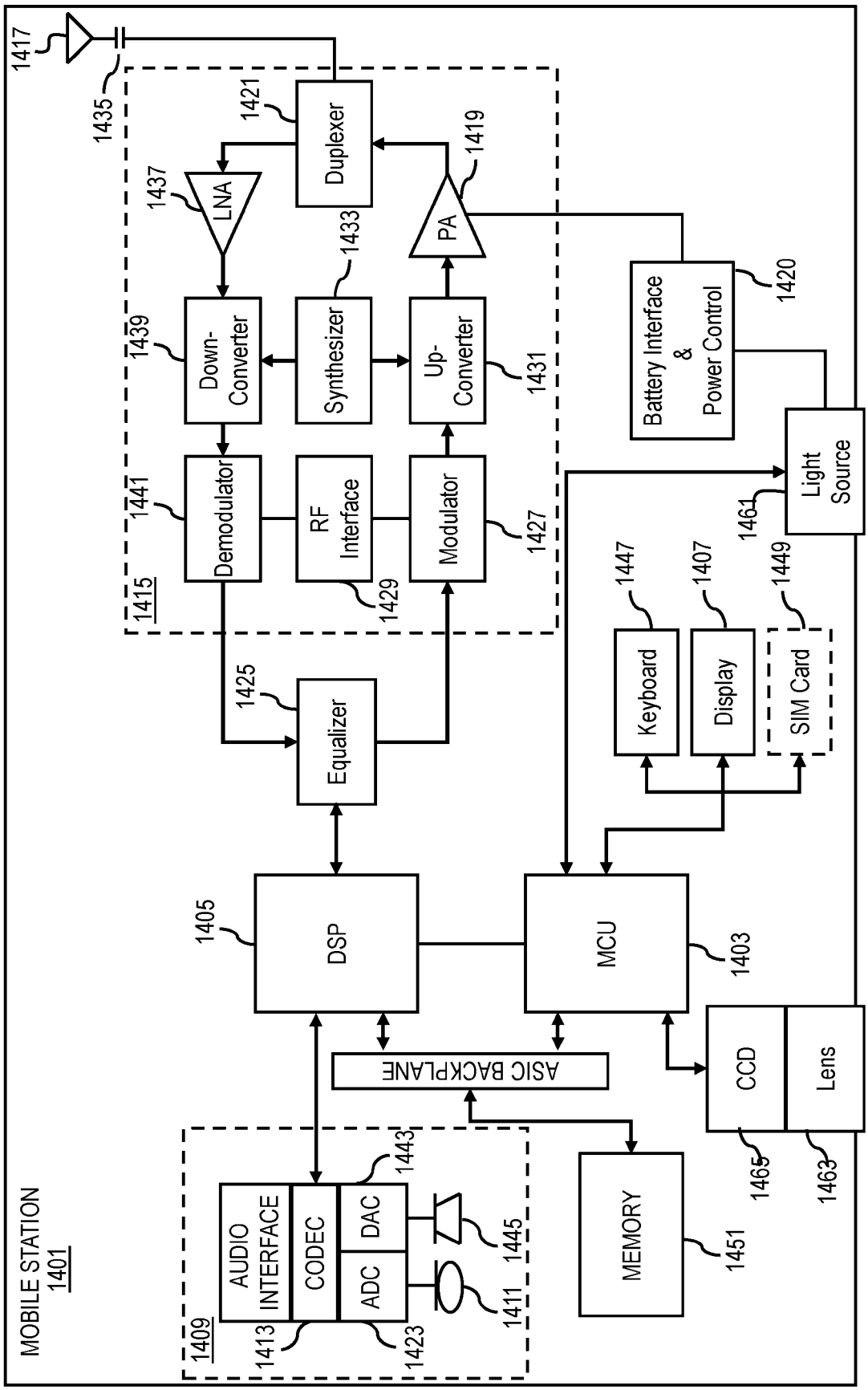


FIG. 13

FIG. 14


MOBILE STATION
1401
1417
1435
1421
Duplexer
1419
1437
LNA
PA
1433
1439
Down-Converter
Synthesizer
Up-Converter
1431
1420
Battery Interface & Power Control
1441
Demodulator
RF Interface
Modulator
1427
1415
1429
Light Source
1461
1425
Equalizer
1447
Keyboard
1407
Display
1449
SIM Card
1405
DSP
MCU
1403
ASIC BACKPLANE
CCD
Lens
1465
1463
1409
AUDIO INTERFACE
CODEC
DAC
ADC
1443
1445
1411
1413
1423
MEMORY
1451

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 24/42257

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61B 5/02, G06N 3/02, G06N 20/20, G06N 20/00, G06N 3/045 (2024.01)
ADD. A61B 8/06 (2024.01)

CPC - INV. A61B 5/02042, A61B 5/02108, G06N 3/02, G06N 20/20, G06N 20/00, G06N 3/045
ADD. A61B 8/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0287753 A1 (Parlikar et al.), 20 November 2008 (20.11.2008), entire document	1, 4-13 and 16-20
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A		2-3 and 14-15
Y	US 2012/0136224 A1 (Najarian et al.), 31 May 2012 (31.05.2012), entire document	1, 4-13 and 16-20
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A		2-3 and 14-15
Y	US 2019/0008427 A1 (Gauss Surgical, Inc.), 10 January 2019 (10.01.2019), entire document	4-5 and 16-17
Y	US 2019/0279111 A1 (ZestFinance, Inc), 12 September 2019 (12.09.2019), entire document	6-7 and 18-19
Y	US 2018/0289288 A1 (UNIVERSITY OF MARYLAND AT COLLEGE PARK et al.), 11 October 2018 (11.10.2018), entire document	8 and 20
A	US 2023/0148876 A1 (Medici Technologies LLC), 18 May 2023 (18.05.2023), entire document	1-20
A	US 2011/0319724 A1 (Cox), 29 December 2011 (29.12.2011), entire document	1-20

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

* Special categories of cited documents:
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"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
08 November 2024	NOV 27 2024
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300