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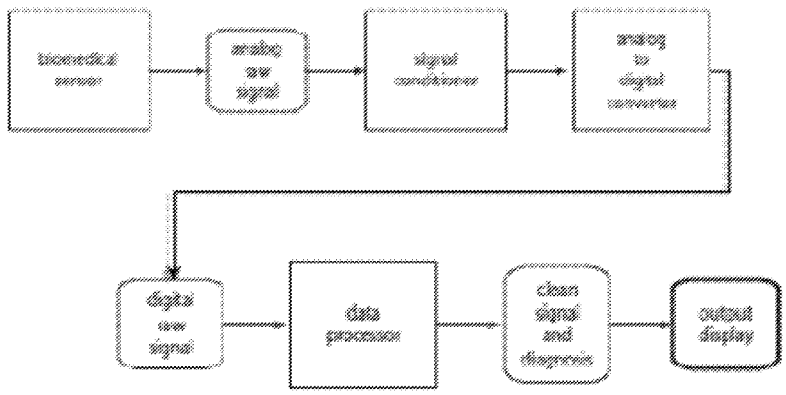
(54) **Title**: PROCESSING PHYSIOLOGICAL SENSOR DATA USING A PHYSIOLOGICAL MODEL COMBINED WITH A PROBABILISTIC PROCESSOR

FIG. 1



(57) **Abstract**: A pulse oximeter system comprises a data processor configured to perform a method that combines a sigma point Kalman filter (SPKF) or sequential Monte Carlo (SMC) algorithm with Bayesian statistics and a mathematical model comprising a cardiovascular model and a plethysmography model to remove contaminating noise and artifacts from the pulse oximeter sensor output and measure blood oxygen saturation, heart rate, left-ventricular stroke volume, aortic pressure and systemic pressures.

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TITLE

Processing Physiological Sensor Data Using a Physiological Model Combined with a Probabilistic Processor

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a PCT of U.S. Application Serial No. 61/171,802, filed 22 April 2009 and U.S. Application Serial No. 12/640,278, filed 17 December 2009.

BACKGROUND

Field of the Invention

The present invention relates generally to apparatus and methods for processing physiological sensor data and specifically to a pulse oximeter comprising a data processing system. The data processing system improves the accuracy of blood oxygen saturation and heart rate measurements made by the pulse oximeter and can be used to estimate stoke volume, cardiac output, and other cardiovascular and respiratory parameters.

Description of Related Art

Biomedical monitoring devices such as pulse oximeters, glucose sensors, electrocardiograms, capnometers, fetal monitors, electromyograms, electroencephalograms, and ultrasounds are sensitive to noise and artifacts. Typical sources of noise and artifacts include baseline wander, electrode-motion artifacts, physiological artifacts, high-frequency noise, and external interference. Some artifacts can resemble real processes, such as ectopic beats, and cannot be removed reliably by simple filters.

The influence of multiple sources of contaminating signals often overlaps the frequency of the signal of interest, making it difficult, if not impossible, to apply conventional filtering. Severe artifacts such as occasional signal dropouts due to sensor movement or large periodic artifacts are also difficult to filter in real time. Biological sensor hardware can be equipped with a computer comprising software for post-processing data and reducing or rejecting noise and artifacts. Current filtering

techniques typically use some knowledge of the expected frequencies of interest where the sought-after physiological information should be found, and do not contain a mathematical model describing either the physiological processes that are measured or the physical processes that measure the signal.

Adaptive filtering has been used to attenuate artifacts in pulse oximeter signals corrupted with overlapping frequency noise bands by estimating the magnitude of noise caused by patient motion and other artifacts, and canceling its contribution from pulse oximeter signals during patient movement. Such a time correlation method relies on a series of assumptions and approximations to the expected signal, noise, and artifact spectra, which compromises accuracy, reliability and general applicability.

Biomedical filtering techniques based on Kalman and extended Kalman techniques offer advantages over conventional methods and work well for filtering linear systems or systems with small nonlinearities and Gaussian noise. These filters, however, are not adequate for filtering highly nonlinear systems and non-Gaussian/non-stationary noise. Therefore, obtaining reliable biomedical signals continue to present problems, particularly when measurements are made in mobile, ambulatory and physically active patients.

Existing data processing techniques, including adaptive noise cancellation filters are unable to extract information that is hidden or embedded in biomedical signals and may also discard some potentially valuable information.

BRIEF SUMMARY OF THE INVENTION

The present invention fills a need in the art for biomedical monitoring devices capable of accurately and reliably measuring physiological parameters made in mobile, ambulatory and physically active patients. The present invention also provides for the processing of data measured by a biomedical monitoring device to extract additional information from a biomedical sensor signal to measure additional physiological paramaters. For instance, pulse oximeters are currently used to

measure blood oxygen saturation and heart rate. A pulse oximetry signal, however, carries additional information that is extract using the present invention to estimate additional physiological parameters including left-ventricular stroke volume, aortic blood pressure, and systemic blood pressure.

One embodiment described herein is a pulse oximeter system comprising a data processor configured to perform a method that combines a sigma point Kalman filter (SPKF) or sequential Monte Carlo (SMC) algorithm with Bayesian statistics and a mathematical model comprising a cardiovascular model and a plethysmography model to remove contaminating noise and artifacts from the pulse oximeter sensor output to measure blood oxygen saturation, heart rate, left-ventricular stroke volume, aortic blood pressure, systemic blood pressure, and total blood volume.

Another embodiment is an electrocardiograph comprising a data processor performing a method combining a SPKF or SMC algorithm with Bayesian statistics and a mathematical model comprising a cardiovascular model including heart electrodynamics, electronic/contractile wave propagation and a model to remove contaminating noise and artifacts from electrode leads and sensor output to produce electrocardiograms.

The computational model includes variable state parameter output data that corresponds to a physiological parameter being measured to mathematically represent a current physiological state for a subject. The physiological parameter being measured is, most preferably, directly represented by a variable state parameter such that the value for the state parameter at time t is equal to an estimated value for the physiological parameter at time t. The estimated value of the physiological parameter being measured (estimated) may also correspond directly to (*i.e.* be equal to) the value of the model parameter at time t or the estimated value for the physiological parameter may be calculated from a state parameter, a model parameter, or a combination of one or more state and/or model parameters.

SPKF or SMC is used to generate a reference signal in the form of a first probability distribution from the model's current (time = *t*) physiological state. The reference signal probability distribution and a probability distribution generated from a measured signal from a sensor at a subsequent time (time = *t+n*) are convoluted using Bayesian statistics to estimate the true value of the measured physiological parameter at time = *t+n*. The probability distribution function may be discrete or continuous, and may identify the probability of each value of an unidentified random variable (discrete), or the probability of the value falling within a particular interval (continuous).

BRIEF DESCRIPTION OF THE DRAWINGS:

FIG. 1 is a flow chart showing the path of information flow from a biomedical sensor to a data a processor and on to an output display according to one embodiment of the invention.

FIG. 2 is a flow chart showing inputs, outputs, and conceptual division of model parts for a dynamic state-space model (DSSM).

FIG. 3 is a block diagram showing mathematical representations of inputs, output and conceptual divisions of the DSSM shown in FIG. 2.

FIG. 4 is a mathematical representation of the process of dual estimation.

FIG. 5 is a schematic diagram showing the process steps involved in a dual estimation process.

FIG. 6 is a mathematical representation of the process of joint estimation.

FIG. 7 is a schematic diagram showing the process steps involved in a joint estimation process.

FIG. 8 is a flow chart showing the components of a DSSM used for pulse oximetry data processing.

FIG. 9 is a flow chart showing examples of parameter inputs and outputs for a DSSM used for pulse oximetry data processing.

FIG. 10 is a flow chart showing the components of a DSSM used for electrocardiography data processing.

FIG. 11 is a chart showing input sensor data and processed output data from a data processor configured to process pulse oximetry data.

FIG. 12 is a chart showing input sensor data and processed output data from a data processor configured to process pulse oximetry data under a low blood perfusion condition.

FIG. 13 is a chart showing noisy non-stationary ECG sensor data input and processed heart rate and ECG output for a data processor configured to process ECG sensor data.

FIG. 14 is a chart showing input ECG sensor data and comparing output data from a data processor according to the present invention with output data generating using a Savitzky-Golay FIR data processing algorithm.

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 shows an example of a top-level schematic for data processing according to the present invention. A biomedical sensor, usually associated with a biomedical monitoring device, normally produces a raw analog output signal that is converted to a raw digital output signal. The analog to digital conversion may also be accompanied by signal filtering or conditioning. Digital signals are received by a data processor configured to process the digital data and produce a processed (or clean) signal comprising an estimated true value for the physiological parameter being measured. The processed signal is then displayed, for example, in the form of an electronic, hard copy, audible, visual, and/or tactile output. The output may be used, for example, by a user to monitor a patient, by a user for self monitoring, or by a user as biofeedback process.

The data processor shown in **FIG. 1** is configured to receive, as input data, digital signals from one or more biomedical sensors, and enter the data into a dynamic state-space model (DSSM) integrated with a processor engine. The integrated DSSM/Processor engine produces transformed output data that corresponds to a physiological parameter measured by the biomedical sensor(s), in the form of an estimated true value for the physiological parameter. The processor engine may operate in a dual estimation mode (a dual estimation engine) or in a joint estimation mode (a join estimation engine). The output may include additional outputs corresponding to physiological parameters not measured by the physiological

sensor(s), diagnostic information, and a confidence interval representing the probability that the output estimated value(s) for the physiological parameter(s) is accurate. The data transformation process performed by the data processor may be used to remove artifacts from the input data to produce output data having higher accuracy than the input data and/or to extract information from the input data to generate output data estimating the values for physiological parameters that are not otherwise measured or reported using data from the sensor(s).

Mathematical and Computational Models

A mathematical model or a computer model, as used herein, involves the use of dependent state parameters and independent, variable, or constant model parameters in a mathematical representation of physiological processes that give rise to a physiological parameter being measured and processes through which sensor data is detected.

A mathematical model may include model and/or state parameters that correspond directly to physiological parameters including vital signs such as oxygen saturation of blood (SpO_2), heart rate (HR), respiratory rate (RR), and blood pressure (BP) that can be directly measured; physiological parameters not directly measured such as total blood volume (TBV), left-ventricular stroke volume (SV), vasomotor tone (VT), autonomous nervous system (ANS) tone, and stroke volume (SV); and hemoglobin-bound complexes, concentrations of metabolic intermediates, and concentrations of drugs present in one or more tissues or organs.

A mathematical model may also use mathematical representations of physiological observations that do not correspond directly to any physiological process, such as mathematical representations of signals obtained from sensor data or empirically fitting a mathematical equation to data collected from a physiological source.

While the scope of a mathematical model used in the context of the present invention cannot possibly encompass every single process of human physiology, it should have the capacity to interpret the measured observable(s). For instance, if the intent

is to process electrocardiography (ECG) signals, a model describing the generation and propagation of electrical impulses in the heart should be included.

The fusion of two or more biomedical signals follows the same principle. For instance, if the intent is to measure blood pressure waves and electrocardiogram signals simultaneously, the use of a heart model describing both the electrical and mechanical aspects of the organ should be used. Initially, the model may also accept manual data input as a complement to data from sensors. Nonlimiting examples of manually entered data include food consumption over time vital signs, gender, age, weight, and height.

Non-physiological models may be included in and/or coupled to the DSSM in cases where non-biomedical signals are measured. For instance, one may use non-biomedical measurements to enhance or complement biomedical measurements. A non-limiting example is the use of accelerometer data to enhance motion artifact rejection in biomedical measurements. In order to accomplish this, the physiological model is extended to describe both measurements, which may include, in this example, cardiovascular circulation at rest, at different body postures (standing, supine, etc), and in motion.

Dynamic State-Space Model

FIG. 2 and FIG. 3 show schematics of a dynamic state-space model (DSSM) used in the processing of data according to the present invention. The DSSM comprises a process model **F** that mathematically represents physiological processes involved in generating one or more physiological parameters measured by a biomedical sensor and describes the state of the subject over time in terms of state parameters. This mathematical model optimally includes mathematical representations accounting for process noise such as physiologically caused artifacts that may cause the sensor to produce a digital output that does not produce an accurate measurement for the physiological parameter being sensed. The DSSM also comprises an observational model **H** that mathematically represents processes involved in collecting sensor data measured by the biomedical sensor. This mathematical model optimally includes

mathematical representations accounting for observation noise produced by the sensor apparatus that may cause the sensor to produce a digital output that does not produce an accurate measurement for a physiological parameter being sensed. Noise terms in the mathematical models are not required to be additive.

While the process and observational mathematical models may be conceptualized as separate models, they are normally integrated into a single mathematical model that describes processes that produce a physiological parameter and processes involved in sensing the physiological parameter. That model, in turn, is integrated with a processing engine within an executable program stored in a data processor that is configured to receive digital data from one or more sensors and to output data to a display or other output formats.

FIG. 3 provides mathematical descriptions of the inputs and outputs corresponding to **FIG. 2**. Initially, values for state parameters, preferably in the form of a state vector $\mathbf{x}_k$, are received by the DSSM together with input model parameters W_k. Process noise $\mathbf{v}_k$ and observation noise n_k are also received by the DSSM, which updates the state parameter vector and model parameter vector and produces an output observation vector $\mathbf{y}_k$. Once the model is initialized, the updated state vector $\mathbf{x}_{k+1}$, updated model parameters $\mathbf{W}_{k+1}$, and time-specific sensor data are used as input for each calculation for subsequent iterations, or time steps.

The DSSM is integrated in a dual estimation processing engine or a joint estimation processing engine. The most favored embodiment makes use of a DSSM built into a Sigma point Kalman filter (SPKF) or Sequential Monte Carlo (SMC) processing engine. Sigma point Kalman filter (SPKF), as used herein, refers to the collective name used for derivativeless Kalman filters that employ the deterministic sampling based sigma point approach to calculate approximations of the optimal terms of the Gaussian approximate linear Bayesian update rule, including unscented, central difference, square-root unscented, and square-root central difference Kalman filters.

SMC and SPKF processing engines operate on a general nonlinear DSSM having the form:

$$\mathbf{x}_k = \mathbf{f}(\mathbf{x}_{k-1}, \mathbf{v}_{k-1}; \mathbf{W}) \quad (1)$$

$$\mathbf{y}_k = \mathbf{h}(\mathbf{x}_k, \mathbf{n}_k; \mathbf{W}) \quad (2)$$

A hidden system state, $\mathbf{x_k}$, propagates over time index, **k**, according to the system model, **f**. The process noise is $\mathbf{v_{k-1}}$, and **W** is the vector of model parameters. Observations, $\mathbf{y_k}$, about the hidden state are given by the observation model **h** and $\mathbf{n_k}$ is the measurement noise. When **W** is fixed, only state estimation is required and either SMC or SPKF can be used to estimate the hidden states.

Unsupervised Machine Learning

Unsupervised machine learning, sometimes referred to as system identification or parameter estimation, involves determining the nonlinear mapping:

$$y_k = g(x_k ; w_k) \quad (3)$$

where xk is the input, yk is the output, and the nonlinear map g(.) is parameterized by the model parameter vector **W**. The nonlinear map, for example, may be a feed-forward neural network, recurrent neural network, expectation maximization algorithm, or enhanced Kalman filter algorithm. Learning corresponds to estimating **W** in some optimal fashion. In the preferred embodiment, SPKF or SMC is used for updating parameter estimates. One way to accomplish this is to write a new state-space representation

$$w_{k+1} = w_k + r_k \quad (4)$$

$$d_k = g(x_k ; w_k) + e_k \quad (5)$$

where w_k correspond to a stationary process with identity state transition matrix, driven by process noise r_k. The desired output d_k corresponds to a nonlinear observation on w_k.

Dual Estimation Engine for Estimation of State and Model Parameters

The state and parameter estimation steps may be coupled in an iterative dual-estimation mode as shown in **FIGs. 4 and 5**. This formulation for a state estimator operates on an adaptive DSSM. In the dual estimation process, states $\mathbf{x_k}$ and

parameters **W** are estimated sequentially inside a loop. When used in a data processor for a pulse oximeter, the current state $\mathbf{x_k}$ from pulse oximeter sensor input $\mathbf{y_k}$. States $\mathbf{x_k}$, and parameters **W** are estimated sequentially inside a loop. Parameter estimates are passed from the previous iteration to state estimation for the current iteration. Several different implementations or variants of the SMC and SPKF methods exist, including the sigma-point, Gaussian-sum, and square-root forms. The particular choice may be influenced by the application.

The current estimate of the parameters $\mathbf{W_k}$ is used in the state estimator as a given (known) input, and likewise the current estimate of the state $\mathbf{x_k}$ is used in the parameter estimator. This results in a step-wise stochastic optimization within the combined state-parameter space.

The flow chart shown **FIG. 5** provides a summary of the steps involved in dual estimation process. Initial probability distributions for state and model parameters are provided to the DSSM to produce an initial probability distribution function (first PDF or prior PDF) representing the initial state. Data for a time t_1 from a sensor (new measurement) and the initial PDF are combined using a Bayesian statistical process to generate a second, posterior PDF that represents the state at the time of the measurement for the first sensor data. Expectation values for the second PDF are calculated, which may represent the most likely true value. Expectation values may also represent, for instance, the confidence interval or any statistical measure of uncertainty associated with the value. Based upon the expectation values, usually but not necessarily the values for state parameters having the highest probability of being correct, updated state parameters for time t_1 are combined with sensor data for time t_1 to update the model parameters for time t_2 in the DSSM by the process shown in **FIG. 4**. The expectation values are also fed into the DSSM as the state, in the form of a vector of state parameters (new PDF) as shown in **FIG. 4**. Once the state parameters and model parameters for the DSSM are updated to time t_1, the process is repeated with timed data for time t_2 to produce updated parameters for time t_2 and so forth. The time interval between time steps is usually constant such that time

points may be described as *t*, *t*+*n*, *t*+2*n*, etc. If the time interval is not constant, then the time may be described using two or more time intervals as *t*, *t*+*n*, *t*+*n*+*m*, etc.

Joint Estimation Engine for Estimation of State and Model Parameters

The state and parameter estimation steps may also be performed in a simultaneous joint-estimation mode as shown in **FIGs. 6 and 7**. The calculated variables for the state parameters and model parameters of the physiological model are concatenated into a single higher-dimensional joint state vector:

$$X = \left[x_k^T \; w_k^T \right]^T \tag{6}$$

where $\boldsymbol{x}_k$ are the state parameters and $\boldsymbol{w}_k$ the model parameters. The joint state space is used to produce simultaneous estimates of the states and parameters.

The flow chart shown **FIG. 7** provides a summary of the steps involved in dual estimation process. The process is similar to that shown for dual estimation in **FIG. 5**, with the exception that model and state parameters are not separated into two separate vectors, but are represented together in a single vector. The process is initiated by entering a vector representing initial state and model parameter value distributions into the DSSM and producing an initial first PDF. The first PDF is combined with sensor data (new measurement) for time t_1 in a Bayesian statistical process to generate a second, posterior PDF that represents the state and model parameters at time t_1. Expectation values for the second PDF are calculated, which may represent the most likely true value. Expectation values may also represent, for instance, the confidence interval or any statistical measure of uncertainty associated with the value. Based upon the expectation values, updated state and model parameters for time t_1 are entered into the DSSM by the process shown in **FIG. 6**. Once the state parameters and model parameters for the DSSM are updated to time t_1, the process is repeated with timed data for time t_2 to produce updated parameters for time t_2 and so forth.

Compared to dual estimation, both state and parameters are concatenated into a single vector that is transformed by the dynamic state-space model. Hence, no

machine learning step is necessary in order to update model parameters. Joint estimation may be performed using a sequential Monte Carlo method or sigma-point Kalman method. These may take the form of unscented, central difference, square-root unscented, and square-root central difference forms. The optimal method will depend on the particular application.

Sequential Monte Carlo Methods

SMC methods estimate the probability distributions of all the model unknowns by propagating a large number of samples called probability particles in accordance with the system models (typically nonlinear, non-Gaussian, non-stationary) and the rules of probability. Artifacts are equivalent to noise with short-lived probability distributions, also called non-stationary distributions. The number of simulated particles scales linearly with computational power, with ≥100 particles being reasonable for real time processing with presently available processors. The system model describes pertinent physiology and the processor engine uses the system model as a "template" from which to calculate, using Bayesian statistics, posterior probability distribution functions (processed data). From this, the expectation values (*e.g.* the mean) and confidence intervals can be estimated **FIG. 7**. The combination of SMC with Bayesian Statistics to calculate posterior probability distribution functions is often referred to as a Particle Filter.

SMC process nonlinear and non-Gaussian problems by discretizing the posterior into weighted samples, or probability particles, and evolving them using Monte Carlo simulation. For discretization, Monte Carlo simulation uses weighted particles to map integrals to discrete sums:

$$p(\mathbf{x}_k|\mathbf{y}_{1:k}) \approx \hat{p}(\mathbf{x}_k|\mathbf{y}_{1:k}) = \sum_{i=1}^{n} \delta(\mathbf{x}_k - \mathbf{x}_k^{(i)}) \quad (7)$$

where the random samples $\{x(i);\ i = 1, 2,...,N\}$, are drawn from $p(x_k|y_{1:k})$ and $\delta(.)$ is the Dirac delta function. Expectations of the form

$$E[\mathbf{g}(\mathbf{x}_k)] = \int \mathbf{g}(\mathbf{x}_k) p(\mathbf{x}_k|\mathbf{y}_{1:k}) d\mathbf{x}_k \quad (8)$$

can be approximated by the estimate:

$$E[\mathbf{g}(\mathbf{x}_k)] \approx \hat{E}[\mathbf{g}(\mathbf{x}_k)] = \frac{1}{N}\sum_{i=1}^{N}\mathbf{g}(\mathbf{x}_k^{(i)}) \tag{9}$$

if the distribution has finite support. As N approaches infinity, the estimate converges to the true expectation.

The optimal Bayesian solution can be outlined by the following recursive algorithm. Suppose the required PDF $p(\mathbf{x}_{k-1}|\mathbf{y}_{1:k-1})$ at time k-1 is available. In the prediction stage, the prior PDF at time k is obtained using the DSSM via the Chapman-Kolmogorov equation:

$$p(\mathbf{x}_k|\mathbf{y}_{1:k-1}) = \int p(\mathbf{x}_k|\mathbf{x}_{k-1})p(\mathbf{x}_{k-1}|\mathbf{y}_{1:k-1})\,d\mathbf{x}_{k-1} \tag{10}$$

The DSSM model describing the state evolution $p(\mathbf{x}_k|\mathbf{x}_{k-1})$ is defined by the system equation (1) and the known statistics of v_{k-1}. At time step k a measurement $\mathbf{y}_k$ becomes available, and this may be used to update the prior (updated stage) via Bayes' rule:

$$p(\mathbf{x}_k|\mathbf{y}_{1:k}) = \frac{p(\mathbf{y}_k|\mathbf{x}_k)p(\mathbf{x}_k|\mathbf{y}_{1:k-1})}{p(\mathbf{y}_k|\mathbf{y}_{1:k-1})} \tag{11}$$

where the normalizing constant

$$p(\mathbf{y}_k|\mathbf{y}_{1:k-1}) = \int p(\mathbf{y}_k|\mathbf{x}_k)p(\mathbf{x}_k|\mathbf{y}_{1:k-1})\,d\mathbf{x}_k \tag{12}$$

depends on the likelihood function $p(\mathbf{y}_k|\mathbf{x}_k)$ defined by the measurement model (equation 2) and the known statistics of $\mathbf{n}_k$.

It is not possible to sample directly from the posterior density function so importance sampling from a known proposal distribution $\pi(x_{0:k}|y_{1:k})$ is used. One may use sigma-point Kalman filters, for example, to generate the proposal.

The known distribution is introduced into Equation 5 to yield:

$$E[\mathbf{g}(\mathbf{x}_{0:k})] = \int \mathbf{g}(\mathbf{x}_{0:k})\frac{w_k(\mathbf{x}_{0:k})}{p(\mathbf{y}_{1:k})}\pi(\mathbf{x}_{0:k}|\mathbf{y}_{1:k})\,d\mathbf{x}_{0:k} \tag{13}$$

where the variables $w_k(x_{0:k})$ are unnormalized importance weights, which are written as $w_k(x_{0:k})= w_k$:

$$w_k(\mathbf{x}_{0:k}) = \frac{p(\mathbf{y}_{1:k}|\mathbf{x}_{0:k})p(\mathbf{x}_{0:k})}{\pi(\mathbf{x}_{0:k}|\mathbf{y}_{1:k})} \tag{14}$$

resulting in a weighted expectation:

$$E[\mathbf{g}(\mathbf{x}_{0:k})] \approx \hat{E}[\mathbf{g}(\mathbf{x}_{0:k})] = \sum_{i=1}^{N} \tilde{w}_k^{(i)} \mathbf{g}(x_{0:k}^{(i)}) \tag{15}$$

where $\tilde{w}_k^{(i)}$ are normalized importance weights:

$$\tilde{w}_k^{(i)} = w_k^{(i)} \Big/ \sum_{j=1}^{N} w_k^{(j)} \tag{16}$$

Importance sampling is made sequential by reiterating the Markov 1st order assumption, resulting in the assumption that the current state is not dependent on future observations:

$$\pi(\mathbf{x}_{0:k}|\mathbf{y}_{1:k}) = \pi(\mathbf{x}_{0:k-1}|\mathbf{y}_{1:k-1})\pi(\mathbf{x}_k|\mathbf{x}_{0:k-1}, \mathbf{y}_{1:k}) \tag{17}$$

and that observations are conditionally independent given the states:

$$p(\mathbf{x}_{0:k}) = p(\mathbf{x}_0)\prod_{j=1}^{k} p(\mathbf{x}_j|\mathbf{x}_{j-1}) \tag{18}$$

$$p(\mathbf{y}_{1:k}|\mathbf{x}_{0:k}) = \prod_{j=1}^{k} p(\mathbf{y}_j|\mathbf{x}_j) \tag{19}$$

A recursive estimate for the importance weights is:

$$w_k = w_{k-1}\frac{p(\mathbf{y}_k|\mathbf{x}_k)p(\mathbf{x}_k|\mathbf{x}_{k-1})}{\pi(\mathbf{x}_k|\mathbf{x}_{0:k-1}, \mathbf{y}_{1:k})} \tag{20}$$

which is called Sequential Importance Sampling (SIS). SIS suffers from degeneracy so that, over a few iterations, all but one of the importance weights will be zero, effectively removing a large number of samples. To remedy this, samples with low

importance weights may be eliminated while high importance samples may be multiplied. One way to accomplish this is Sampling-Importance Resampling (SIR), which involves mapping the Dirac random measure

$$\{x_k^{(i)}, \tilde{w}_k^{(i)}; i = 1,\ldots,N\} \tag{21}$$

into a measure with equal weights, 1/*N*:

$$\{x_k^{(i)}, \frac{1}{N}; i = 1,\ldots,N\} \tag{22}$$

A pseudo-code for a generic SMC (also called bootstrap filter or condensation algorithm) can be written as:

1. Importance sampling step. For $i = 1,\ldots,N$, do:

   i) sample $x_k^{(i)} \sim p(\mathbf{x}_k | x_{k-1}^{(i)})$

   ii) evaluate $w_k^{(i)} \sim w_{k-1}^{(i)} p(\mathbf{y}_k | x_k^{(i)})$

   iii) normalize $\tilde{w}_k^{(i)} = w_k^{(i)} / \sum_{j=1}^{N} w_k^{(j)}$

2. Importance resampling step

   i) eliminate or multiply samples $x_k^{(i)}$ according to weights $\tilde{w}_k^{(i)}$ to obtain *N* random samples approximately distributed according to $p(\mathbf{x}_k | \mathbf{y}_{1:k})$.

   ii) For $i = 1,\ldots, N$, set $w_k^{(i)} = \tilde{w}_k^{(i)} = N^{-1}$

3. Output

   i) any expectation, for instance: $\hat{\mathbf{x}}_k = E[\mathbf{x}_k | \mathbf{y}_{1:k}] \approx \frac{1}{N} \sum_{i=1}^{N} x_k^{(i)}$

SPKF may be used to approximate probability distributions. Assuming that *x* has a mean $\bar{\mathbf{x}}$ covariance $\mathbf{P}_x$, and dimension *L*, a set of 2*L*+1 weighted sigma-points, $S_i = \{w_i, \mathbf{X}_i\}$, is chosen according to:

$\mathbf{X}_0 = \bar{\mathbf{x}}$ $\qquad w_0^{(m)} = \frac{h^2 - L}{h^2}$

$$\mathbf{X}_i = \bar{\mathbf{x}} + (h\sqrt{\mathbf{P}_x})_i \quad i = 1,\ldots,L \qquad w_i^{(m)} = \frac{1}{2h^2} \quad i = 1,\ldots,2L$$

$$\mathbf{X}_i = \bar{\mathbf{x}} - (h\sqrt{\mathbf{P}_x})_i \quad i = L+1,\ldots,2L \qquad w_i^{(c)} = \frac{1}{4h^2} \quad i = 1,\ldots,2L$$

$$w_i^{(c)} = \frac{h^2-1}{4h^4} \quad i = 1,\ldots,2L \qquad (23)$$

where h is a scaling parameter. Each sigma-point is propagated through the DSSM to yield the posterior sigma-point set, $\mathbf{Y}_i$:

$$\mathbf{Y}_i = \mathbf{h}(\mathbf{f}(\mathbf{X}_i)), \; i = 0,\ldots,2L \qquad (24)$$

From this, the posterior statistics are calculated using a procedure resembling the linear Kalman filter. For instance, for the unscented Kalman filter case, a SPKF variant, the time-update equations are:

$$\mathbf{X}^x_{k|k-1} = \mathbf{f}(\mathbf{X}^x_{k-1}, \mathbf{X}^v_{k-1}, \mathbf{u}_{k-1}) \qquad (25)$$

$$\hat{\mathbf{x}}_k^- = \sum_{i=0}^{2L} w_i^{(m)} \mathbf{X}^x_{i,k|k-1} \qquad (26)$$

$$\mathbf{P}_{\mathbf{x}_k}^- = \sum_{i=0}^{2L} w_i^{(c)} (\mathbf{X}^x_{i,k|k-1} - \hat{\mathbf{x}}_k^-)(\mathbf{X}^x_{i,k|k-1} - \hat{\mathbf{x}}_k^-)^T \qquad (27)$$

and the measurement-update equations are:

$$\mathbf{Y}_{k|k-1} = \mathbf{h}(\mathbf{X}^x_{k|k-1}, \mathbf{X}^n_{k-1}) \qquad (28)$$

$$\hat{\mathbf{y}}_k^- = \sum_{i=0}^{2L} w_i^{(m)} \mathbf{Y}_{i,k|k-1} \qquad (29)$$

$$\mathbf{P}_{\tilde{\mathbf{y}}_k} = \sum_{i=0}^{2L} w_i^{(c)} (\mathbf{Y}_{i,k|k-1} - \hat{\mathbf{y}}_k^-)(\mathbf{Y}_{i,k|k-1} - \hat{\mathbf{y}}_k^-)^T \qquad (30)$$

$$\mathbf{P}_{\mathbf{x}_k \mathbf{y}_k} = \sum_{i=0}^{2L} w_i^{(c)} (\mathbf{X}^x_{i,k|k-1} - \hat{\mathbf{x}}_k^-)(\mathbf{Y}_{i,k|k-1} - \hat{\mathbf{y}}_k^-)^T \qquad (31)$$

$$\mathbf{K}_k = \mathbf{P}_{\mathbf{x}_k \mathbf{y}_k} \mathbf{P}_{\tilde{\mathbf{y}}_k}^{-1} \qquad (32)$$

$$\hat{\mathbf{x}}_k = \hat{\mathbf{x}}_k^- + \mathbf{K}_k(\mathbf{y}_k - \hat{\mathbf{y}}_k^-) \qquad (33)$$

$$\mathbf{P}_{\tilde{x}_k} = \mathbf{P}^{-}_{\tilde{x}_k} - \mathbf{K}_k \mathbf{P}_{\tilde{y}_k} \mathbf{K}_k^T \tag{34}$$

where *x*, *v* and *n* superscripts denote the state, process noise and measurement noise dimensions, respectively.

The mathematical structure for sequential Monte Carlo and SPKF represent two examples of a family of probabilistic inference methods exploiting Monte Carlo simulation and the sigma point transform, respectively, in conjunction with a Bayesian statistical process.

SPKF are generally inferior to SMC but are computationally cheaper. Like SMC, SPKF evolve the state using the full nonlinear DSSM, but represent probability distributions using a sigma-point set. This is a deterministic step that replaces the stochastic Monte Carlo step in the SMC. As a result, SPKF lose accuracy when posterior distributions depart heavily from the Gaussian form, such as with bimodal or heavily-tailed distributions, or with strong nonstationary distributions such as those caused by motion artifacts in pulse oximeters. For these cases SMC are more suitable.

SPKF yields higher-order accuracy than the extended Kalman filter (EKF) and its related variants with equal algorithm complexity, $O(L^2)$. SPKF returns 2nd order accuracy for nonlinear and non-Gaussian problems, and 3rd order for Gaussian problems. EKF has only 1st order accuracy for nonlinear problems. Both EKF and SPKF approximate state distributions with Gaussian random variables (GRV). However, the EKF propagates the GRV using a single measure (usually the mean) and the 1st order Taylor expansion of the nonlinear system. The SPKF, on the other hand, decomposes the GRV into distribution moments (sigma points) and propagates those using the unmodified nonlinear system. SPKF implementation is simpler than EKF since it is derivativeless. That is, it uses the unmodified DSSM form, and therefore does not require lengthy Jacobian derivations.

The data processing method is also capable of prediction because the method can operate faster than real time measurements. At any given time during data processing, the measurement PDF, obtained either from SPKF or SMC, embodies all available statistical information up to that point in time. It is therefore possible to march the system model forwards in time, for instance, using the same sequential Monte Carlo method, to obtain deterministic or stochastic simulations of future signal trajectories. In this way, the future health status (physiological state) of a patient can be predicted with attached probabilities indicating the confidence of each prediction.

Noise Adaptation

The data processing method may benefit from a noise adaptation method if timed sensor data contains noise and/or artifact that changes its spectral qualities over time. That is, has a non-stationary probability distribution function. Here, a known algorithm such as the Robins-Monro or Annealing methods may be added to the data processing method in order to adapt the probability distribution functions of noise terms (stochastic terms) in the DSSM according to changing noise and artifact present in sensor data.

Output

In general, the output may include estimates of the true measured signals (*i.e.* processed data), and estimates of values for one or more physiological parameters measured by one or more sensors from which data was received, and estimates of values for one or more physiological parameters not measured by the sensors from which data was received (data extraction). A state parameter estimate is the processed data from the physiological sensor. Both noise and artifacts can be attenuated or rejected even though they may have very distinct probability distribution functions and may mimic the real signal. A model parameter estimate may be also used to produce a physiological parameter. For example, an estimate of total blood volume may be used to diagnose hemorrhage or hypovolemia; an estimate of tissue oxygen saturation may indicate poor tissue perfusion and/or hypoxia; estimates of glucose uptake in several tissues may differentiate between

diabetes mellitus types and severities; and estimates of carotid artery radius may be indicative of carotid artery stenosis.

EXAMPLES:

Pulse Oximeter with Probabilistic Data Processing

FIG. 8 shows the components of a DSSM suitable for processing data from a pulse oximeter model, including components required to describe processes occurring in a subject. **FIG. 9** illustrates the DSSM broken down into process and observation models, and including all input and output variables. Heart rate (*HR*), stroke volume (*SV*) and whole-blood oxygen saturation (SpO_2) are estimated from input noisy red and infrared intensity ratios (*R*). Radial (*P*w) and aortic (*P*ao) pressures are also available as state estimates.

In this example, the DSSM comprises the following function to represent cardiac output:

$$Q_{co}(t) = \bar{Q}_{co} \sum_{k=1}^{5} a_k \exp\left| \frac{-\left(t - b_k\right)^2}{c_k^2} \right| \tag{31}$$

wherein cardiac output *Q*co(t), is expressed as a function of heart rate (*HR*) and stroke volume (*SV*) and where Q_{CO} = (*HR* x *SV*)/60. The cardiac output function pumps blood into a Windkessel 3-element model of the vascular system including two state variables: aortic pressure, *P*ao, and radial (Windkessel) pressure, *P*w:

$$P_{ao,k+1} = \frac{1}{C_a R_p}\left((R_p + Z_o)Q_{co} - P_{ao,k}\right)\cdot \delta t + P_{ao,k} \tag{32}$$

$$P_{w,k+1} = P_{ao,k+1} + Z_o Q_{co} \tag{33}$$

*R*p and *Z*o are the peripheral resistance and characteristic aortic impedance, respectively. The sum of these two terms is the total peripheral resistance due to viscous (Poiseuille-like) dissipation:

$$Z_o = \sqrt{\rho / A C_t} \tag{34}$$

where ρ is blood density. The elastic component due to vessel compliance is a nonlinear function including thoracic aortic cross-sectional area, *A*:

$$A(P_{aa}) = A_{max}\left[\frac{1}{2} + \frac{1}{\pi}\arctan\left(\frac{P_{aa} - P_0}{P_1}\right)\right] \quad (35)$$

where *A*max, P_0 and P_1 are fitting constants correlated with age and gender:

$$A_{max} = (5.62 - 1.5(gender)) \cdot cm^2 \quad (36)$$

$$P_0 = (76 - 4(gender) - 0.89(age)) \cdot mmHg \quad (37)$$

$$P_1 = (57 - 0.44(age)) \cdot mmHg \quad (38)$$

The time-varying Windkessel compliance, *C*w, and the aortic compliance per unit length, *C*l, are:

$$C_w = lC_l = l\frac{dA}{dP_{aa}} = l\frac{A_{max}/(\pi P_1)}{1 + \left(\frac{P_{aa} - P_0}{P_1}\right)^2} \quad (39)$$

where *l* is the aortic effective length. The peripheral resistance is defined as the ratio of average pressure to average flow. A set-point pressure, *P*set, and the instantaneous flow:

$$R_p = \frac{P_{set}}{(HR \cdot SV)/60} \quad (40)$$

are used to provide compensation autonomic nervous system responses. The value for *P*set is adjusted manually to obtain 120 over 75 mmHg for a healthy individual at rest. The compliance of blood vessels changes the interactions between light and tissues with pulse. This is accounted for using a homogenous
photon diffusion theory for a reflectance or transmittance pulse oximeter configuration. For the reflectance case:

$$R = \frac{I_{ac}}{I_{dc}} = \frac{\Delta I}{I} = \frac{3}{2}\Sigma_s' K(\alpha, d, r)\Sigma_s'' \Delta V_a \quad (41)$$

for each wavelength. In this example, the red and infrared bands are centered at ~ 660 nm and ~ 880 nm. I denotes the detected intensities: total reflected (no subscript), and the pulsating (ac) and background (dc) components. *V*a is the arterial blood volume, which changes as the cross-sectional area of illuminated blood vessels, ΔA_w, changes as:

$$\Delta V_w \approx r \cdot \Delta A_w \tag{42}$$

where r is the source-detector distance. The tissue scattering coefficient, $\Sigma s'$, is assumed constant but the arterial absorption coefficient, Σa^{art}, depends on blood oxygen saturation, SpO_2:

$$\Sigma_a^{art} = \frac{H}{v_i}\left[SpO_2 \cdot \sigma_a^{100\%} + (1 - SpO_2) \cdot \sigma_a^{0\%}\right] \tag{43}$$

which is the Beer-Lambert absorption coefficient, with hematocrit, H, and red blood cell volume, v_i. The optical absorption cross sections for red blood cells containing totally oxygenated (HbO_2) and totally deoxygenated (Hb) hemoglobin are $\sigma_a^{100\%}$ and $\sigma_a^{0\%}$, respectively.

The function K(α,d,r) contains, along with the scattering coefficient, the wavelength, sensor geometry and oxygen saturation dependencies that alter the effective optical pathlengths:

$$K(\alpha, d, r) \approx \frac{e^{-\alpha r}}{1 + \alpha r} \tag{44}$$

The attenuation coefficient α is:

$$\alpha = \sqrt{3\Sigma_a(\Sigma_s + \Sigma_a)} \tag{45}$$

where Σ_a and Σ_s are whole-tissue absorption and scattering coefficients, respectively, which are calculated from Mie Theory.

Red and infrared K values as a function of SpO_2 may be represented by two linear fits:

$$\overline{K}_r \approx -4.03 \cdot SpO_2 - 1.17 \tag{46}$$

$$\overline{K}_{ir} \approx 0.102 \cdot SpO_2 - 0.753 \tag{47}$$

in mm^2. The overbar denotes the linear fit of the original function. The pulsatile behavior of ΔAw, which couples optical detection with the cardiovascular system model, is:

$$\Delta A_w = \frac{A_{w,\max}}{\pi} \frac{P_{w,1}}{P_{w,1}^2 + (P_{w,k+1} - P_{w,0})^2} \Delta P_w \quad (48)$$

with $P_{w,0}=(1/3)P_0$ and $P_{w,1}=(1/3)P_1$ to account for the poorer compliance of arterioles and capillaries relative to the thoracic aorta. Third and fourth state variables, the red and infrared reflected intensity ratios, R=Iac/Idc, are:

$$R_{r,k+1} = c\Sigma'_{s,r} \overline{K_r} \Sigma''_{a,r} \Delta A_w + R_{r,k} + v_r \quad (49)$$

$$R_{ir,k+1} = c\Sigma'_{s,ir} \overline{K_{ir}} \Sigma''_{a,ir} \Delta A_w + R_{ir,k} + v_{ir} \quad (50)$$

Here, ν are Gaussian-distributed process noises intended to capture the baseline wander of the two channels. The constant *c* subsumes all factors common to both wavelengths and is treated as a calibration constant. The observation model adds Gaussian-distributed noises, *n*, to R_r and R_{ir}:

$$\begin{bmatrix} y_{r,k} \\ y_{ir,k} \end{bmatrix} = \begin{bmatrix} R_{r,k} \\ R_{ir,k} \end{bmatrix} + \begin{bmatrix} n_{r,k} \\ n_{ir,k} \end{bmatrix} \quad (51)$$

A calibration constant *c* was used to match the variance of the real Iac/Idc signal with the variance of the DSSM-generated signal for each wavelength. After calibration, the age and gender of the patient was entered. Estimates for the means and covariances of both state and parameter PDFs were entered. **FIG. 11** plots estimates for a 15 s stretch of data. Photoplethysmographic waveforms (*A*) were used to extract heart rate (**B**), left-ventricular stroke volume (**C**), cardiac output (**D**), blood oxygen saturation (**E**), and aortic and systemic (radial) pressure waveforms (**F**). Results of processing pulse oximetry at low blood perfusion are shown in **FIG. 12**. Low signal-to-noise photoplethysmographic waveforms (**A**) were used to extract heart rate (**B**), left-ventricular stroke volume (**C**), blood oxygen saturation (**D**), and aortic and systemic (radial) pressure waveforms (**E**).

Electrocardiograph with Probabilistic Data Processing

FIG. 10 is a schematic of a dynamic state-space model suitable for processing electrocardiograph data, including components required to describe the processes

occurring in a subject. The combination of SPKF or SMC in state, joint or dual estimation modes can be used to filter electrocardiography (ECG) data. Any physiology model adequately describing the ECG signal can be used, as well as any model of noise and artifact sources interfering or contaminating the signal. One non-limiting example of such a model is the ECG signal generator proposed by McSharry (IEEE Transactions on Biomedical Engineering, 2003. **50**(3):289-294). Briefly, this model uses a sum of Gaussians with amplitude, center and standard deviation, respectively, for each wave (P, Q, R, S, T-, T+15) in an ECG. The observation model comprises the state plus additive Gaussian noise, but more realistic pink noise or any other noise distributions can be used.

FIG. 13 shows the results of processing a noisy non-stationary ECG signal. Heart rate oscillations representative of normal respiratory sinus arrhythmia are present in the ECG. The processor accomplishes accurate, simultaneous estimation of the true ECG signal and heart rate that follows closely the true values. The performance of the processor in a noise and artifact-corrupted signal is shown in **FIG. 14**. A clean ECG signal representing one heart beat (truth) was contaminated with additive noise and an artifact in the form of a plateau at R and S peaks (beginning at time = 10 s). Estimates by the processor remain close to the true signal despite the noise and artifact.

While a specific DSSMs and input and output parameters are provided for the purpose of describing the present method, the present invention is not limited to the DSSMs, sensors, biological monitoring devices, inputs, outputs, except as defined by the following claims.

CLAIMS

1. A method for processing sensor data from a biomedical monitoring device that measures a physiological parameter of a living subject to obtain an estimated value for the physiological parameter, said method comprising the steps of:

a) entering state parameters for a time t and model parameters for a time t into a dynamic state-space model to produce a first probability distribution function vector comprising state parameters for time *t+n*;

b) using the first probability distribution function vector and timed data obtained for time *t+n* from the sensor in a Bayesian statistical process to produce a second probability distribution function vector for state parameters for time *t+n*;

c) calculating probabilistic expectation values for the state parameters for time *t+n* from the second probability distribution function;

d) calculating updated model parameters for time *t+n+m* from the second probability distribution function vector for state parameters for time *t+n* and timed data obtained for time *t+n* from the sensor in an unsupervised machine learning operation; and

e) determining an estimated value for the physiological parameter for time *t+n* from probabilistic expectation values from the state and/or model parameters;

wherein:

the dynamic state-space model mathematically represents physiological processes that produce the measured physiological parameter and physical processes involved in measuring the physiological parameter, to produce a time dependent state representing a time dependent physiological state of the subject;

the state parameters for a time t entered into the dynamic state-space model in step a) are in the form of a state parameter probability distribution function produced from a sampling of the second probability distribution function calculated in step b) for an immediately preceding time t-n';

the model parameters for a time t entered into the dynamic state-space model in step a) are in the form of a model parameter probability distribution function produced from an unsupervised machine learning operation on data from the sensor for time t with the second probability distribution function vector for state parameters

in step b) for an immediately preceding time t-n'; and n, m, and n' are time intervals that may be the same of different.

2. The method of claim 1, further comprising the step of reporting the estimated value for the physiological parameter in a form that is visually, audibly, or tactilely comprehensible by a user.

3. The method of claim 1, wherein a state parameter or a model parameter of the dynamic state-space model corresponds directly to the estimated value for the measured physiological parameter.

4. The method of claim 1, wherein the estimated value for the measured physiological parameter determined in step (e) is performed by calculating the estimated value from a state parameter and/or a model parameter of the dynamic state-space model.

5. The method of claim 1, wherein generating the first probability distribution is performed using a Sequential Monte Carlo or Sigma Point Kalman Filter method.

6. The method of claim 5, wherein the Sigma Point Kalman Filter method is selected from the group consisting of unscented Kalman Filter, central difference Kalman Filter, square-root unscented Kalman Filter, square-root central difference Kalman Filter, and combinations thereof; and the Sequential Monte Carlo method is selected from the group consisting of an unscented Monte Carlo, central difference Monte Carlo, square-root unscented Monte Carlo, square-root central difference Monte Carlo method, Gaussian Sum Monte Carlo, Bayes Monte Carlo, Gaussian Mixture Sigma Point Monte Carlo, and combinations thereof.

7. The method of claim 1, wherein the dynamic state-space model comprises a state parameter or a model parameter corresponding to an additional physiological parameter not measured by the biomedical monitoring device and the method further

comprises calculating an estimated value for the additional physiological parameter not measured by said biomedical monitoring device.

8. The method of claim 7, wherein the biomedical monitoring device is a pulse oximeter and the additional physiological parameter not measured by the biomedical monitoring device is selected from left-ventricular stroke volume, heart rate, aortic pressure, systemic blood pressure, and total blood volume.

9. The method of claim 7, further comprising the step of reporting the estimated value for the additional physiological parameter in a form that is visually, audibly, or tactilely comprehensible by a user.

10. The method of claim 1, wherein the biomedical monitoring device is selected from the group consisting of a co-oximeter, a blood pressure monitor, an electrocardiograph, and a pulse oximeter.

11. A data processor configured to perform the method of claim 1.

12. A biomedical monitoring device comprising a data processor configured to perform the method of claim 1.

13. A method for processing sensor data from a biomedical monitoring device that measures a physiological parameter of a living subject to obtain an estimated value for the physiological parameter, said method comprising the steps of:

a) entering system and model parameters for a time t into a dynamic state-space model to produce a first probability distribution function vector comprising state and model parameters for time t+n;

b) using the first probability distribution function vector and timed data obtained for time t+n from the sensor in a Bayesian statistical process to produce a second probability distribution function vector for state and model parameters for time t+n;

c) calculating probabilistic expectation values for the state and model parameters for time t+n from the second probability distribution function; and

d) determining an estimated value for the physiological parameter for time t+n from probabilistic expectation values for the state and/or model parameters for time t+n

wherein:

the dynamic state-space model mathematically represents physiological processes that produce the measured physiological parameter and physical processes involved in measuring the physiological parameter, to produce a time dependent state representing a time dependent physiological state of the subject;

the state and model parameters for a time t entered into the dynamic state-space model in step a) are in the form of a probability distribution function produced from a sampling of expectation values calculated in step c) for an immediately preceding time t-n'; and

n and n' are time intervals that may be the same of different.

14. The method of claim 13, further comprising the step of reporting the estimated value for the physiological parameter in a form that is visually, audibly, or tactilely comprehensible by a user.

15. The method of claim 13, wherein a state parameter or a model parameter of the dynamic state-space model is equal to the estimated value for the measured physiological parameter.

16. The method of claim 13, wherein the estimated value for the measured physiological parameter determined in step (d) is performed by calculating the estimated value from s state parameter and/or a model parameter of the dynamic state-space model.

17. The method of claim 13, wherein generating the first probability distribution is performed using a Sequential Monte Carlo or Sigma Point Kalman Filter method.

18. The method of claim 17, wherein the Sigma Point Kalman Filter method is selected from the group consisting of unscented Kalman Filter, central difference Kalman Filter, square-root unscented Kalman Filter, square-root central difference Kalman Filter, and combinations thereof; and the Sequential Monte Carlo method is selected from the group consisting of an unscented Monte Carlo, central difference Monte Carlo, square-root unscented Monte Carlo, square-root central difference Monte Carlo method, Gaussian Sum Monte Carlo, Bayes Monte Carlo, Gaussian Mixture Sigma Point Monte Carlo, and combinations thereof.

19. The method of claim 13, wherein the model comprises a state parameter and/or a model parameter corresponding to an additional physiological parameter not measured by the biomedical monitoring device and the method further comprises calculating an estimated value for the additional physiological parameter not measured by said biomedical monitoring device.

20. The method of claim 19, wherein the biomedical monitoring device is a pulse oximeter and the physiological parameter not measured by the biomedical monitoring device is selected from left-ventricular stroke volume, heart rate, aortic pressure, systemic blood pressure, and total blood volume.

21. The method of claim 20, further comprising the step of reporting the estimated value for the additional physiological parameter in a form that is visually, audibly, or tactilely comprehensible by a user.

22. The method of claim 13, wherein the biomedical monitoring device is selected from the group consisting of a co-oximeter, a blood pressure monitor, an electrocardiograph, and a pulse oximeter.

23. A data processor configured to perform the method of claim 13.

24. A biomedical monitoring device comprising a data processor configured to perform the method of claim 14.

25. A method for processing data from a sensor of a biomedical monitoring device that produces an output value for a first physiological parameter based on an output of said sensor, said method comprising the steps of:

a) entering state parameters for a time t and model parameters for a time t into a dynamic state-space model to produce a first probability distribution function vector comprising state parameters for time *t+n*;

b) using the first probability distribution function vector and timed data obtained for time *t+n* from the sensor in a Bayesian statistical process to produce a second probability distribution function vector for state parameters for time *t+n*;

c) calculating probabilistic expectation values for the state parameters for time *t+n* from the second probability distribution function;

d) calculating updated model parameters for time *t+n+m* from the second probability distribution function vector for state parameters for time *t+n* and timed data obtained for time *t+n* from the sensor in an unsupervised machine learning operation; and

e) determining an estimated value for a second physiological parameter for time *t+n* from probabilistic expectation values from the state and/or model parameters;

wherein:

the biomedical monitoring device does not otherwise produce an output value for the second physiological parameter based on an output of said sensor

the dynamic state-space model mathematically represents physiological processes that produce the second physiological parameter and physical processes involved in measuring the second physiological parameter, to produce a time dependent state representing a time dependent physiological state of the subject;

the state parameters for a time t entered into the dynamic state-space model in step a) are in the form of a state parameter probability distribution function produced from a sampling of the second probability distribution function calculated in step b) for an immediately preceding time t-n';

the model parameters for a time t entered into the dynamic state-space model in step a) are in the form of a model parameter probability distribution function

produced from an unsupervised machine learning operation on data from the sensor for time t with the second probability distribution function vector for state parameters in step b) for an immediately preceding time t-n'; and n, m, and n' are time intervals that may be the same of different.

26. The method of claim 25, wherein generating the first probability distribution is performed using a Sequential Monte Carlo or Sigma Point Kalman Filter method.

27. The method of claim 26, wherein the Sigma Point Kalman Filter method is selected from the group consisting of unscented Kalman Filter, central difference Kalman Filter, square-root unscented Kalman Filter, square-root central difference Kalman Filter, and combinations thereof; and the Sequential Monte Carlo method is selected from the group consisting of an unscented Monte Carlo, central difference Monte Carlo, square-root unscented Monte Carlo, square-root central difference Monte Carlo method, Gaussian Sum Monte Carlo, Bayes Monte Carlo, Gaussian Mixture Sigma Point Monte Carlo, and combinations thereof.

28. A method for processing data from a sensor of a biomedical monitoring device that produces an output value for a first physiological parameter based on an output of said sensor, said method comprising the steps of:

a) entering system and model parameters for a time t into a dynamic state-space model to produce a first probability distribution function vector comprising state and model parameters for time t+n;

b) using the first probability distribution function vector and timed data obtained for time t+n from the sensor in a Bayesian statistical process to produce a second probability distribution function vector for state and model parameters for time t+n;

c) calculating probabilistic expectation values for the state and model parameters for time t+n from the second probability distribution function; and

d) determining an estimated value for a second physiological parameter for time t+n from probabilistic expectation values for the state and/or model parameters for time t+n

wherein:

the biomedical monitoring device does not otherwise produce an output value for the second physiological parameter based on an output of said sensor

the dynamic state-space model mathematically represents physiological processes that produce the measured physiological parameter and physical processes involved in measuring the physiological parameter, to produce a time dependent state representing a time dependent physiological state of the subject;

the state and model parameters for a time t entered into the dynamic state-space model in step a) are in the form of a probability distribution function produced from a sampling of expectation values calculated in step c) for an immediately preceding time t-n'; and

n and n' are time intervals that may be the same of different.

29. The method of claim 28, wherein generating the first probability distribution is performed using a Sequential Monte Carlo or Sigma Point Kalman Filter method.

30. The method of claim 29, wherein the Sigma Point Kalman Filter method is selected from the group consisting of unscented Kalman Filter, central difference Kalman Filter, square-root unscented Kalman Filter, square-root central difference Kalman Filter, and combinations thereof; and the Sequential Monte Carlo method is selected from the group consisting of an unscented Monte Carlo, central difference Monte Carlo, square-root unscented Monte Carlo, square-root central difference Monte Carlo method, Gaussian Sum Monte Carlo, Bayes Monte Carlo, Gaussian Mixture Sigma Point Monte Carlo, and combinations thereof.

DRAWINGS:

FIG. 1

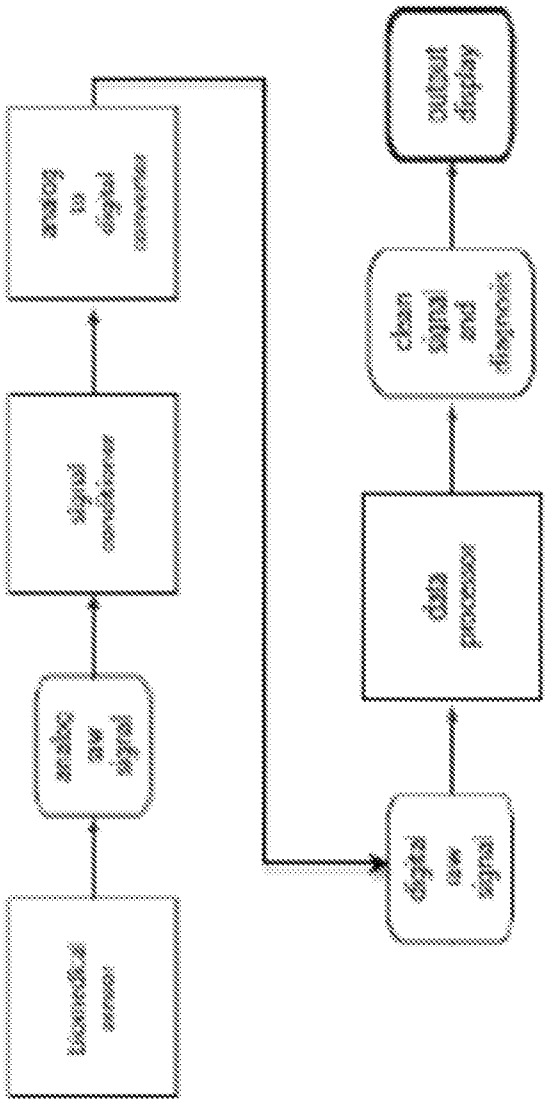


FIG. 2

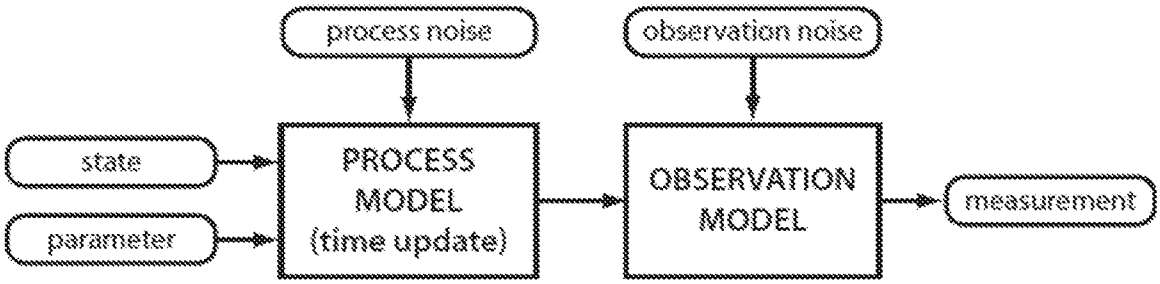

process noise
observation noise
state
parameter
PROCESS MODEL (time update)
OBSERVATION MODEL
measurement

FIG. 3

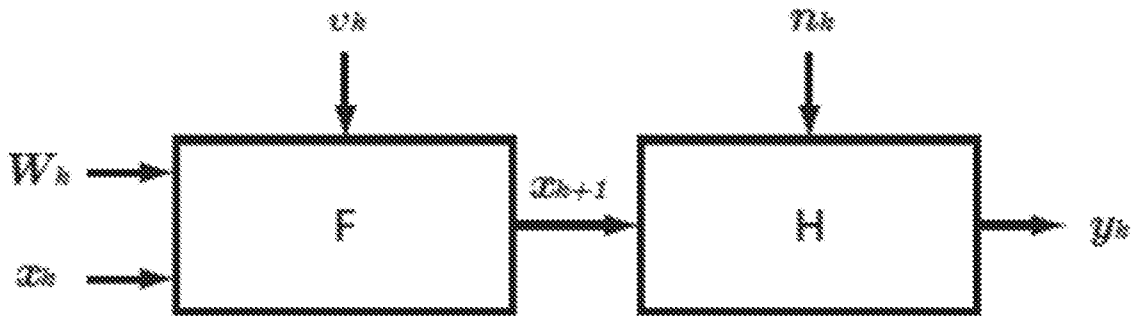


FIG. 4

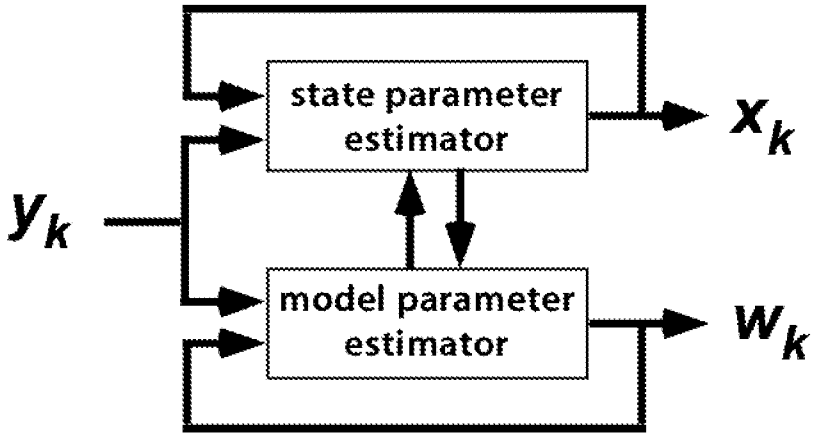

state parameter estimator
model parameter estimator
y_k
x_k
w_k

FIG. 5

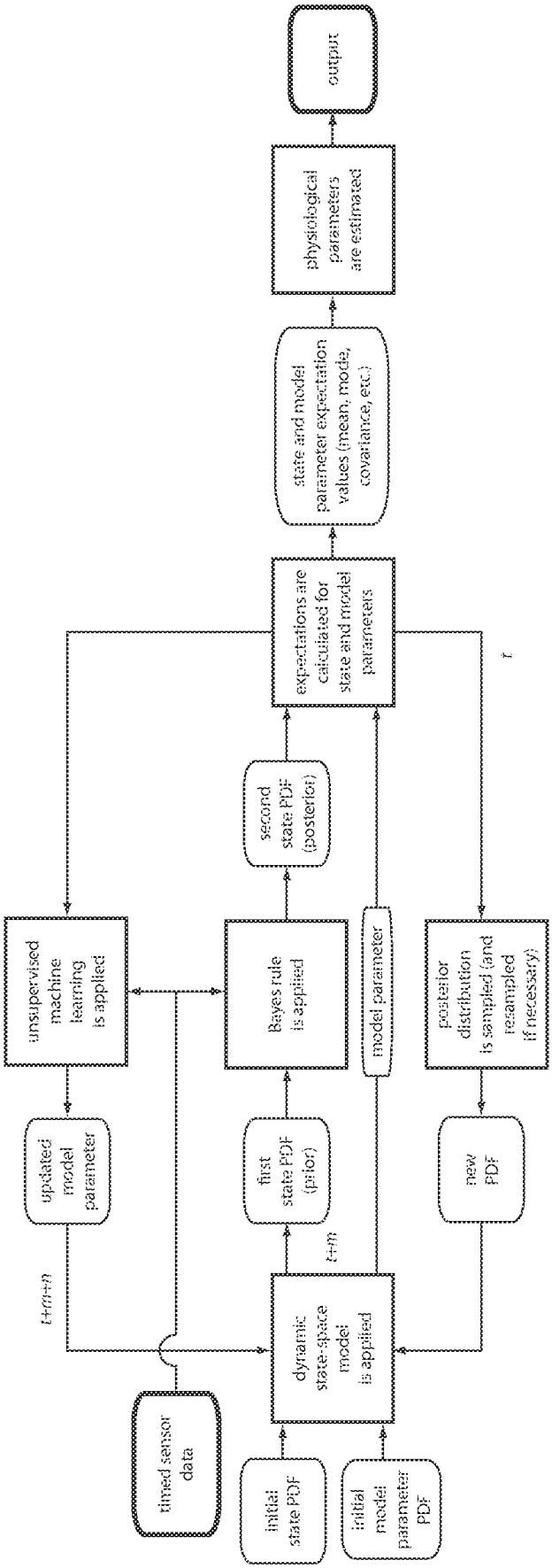

output
physiological parameters are estimated
state and model parameter expectation values (mean, mode, covariance, etc.)
expectations are calculated for state and model parameters
second state PDF (posterior)
unsupervised machine learning is applied
Bayes rule is applied
model parameter
posterior distribution is sampled (and resampled if necessary)
updated model parameter
first state PDF (prior)
new PDF
t+m+n
t+m
t
dynamic state-space model is applied
timed sensor data
initial state PDF
initial model parameter PDF

FIG. 6

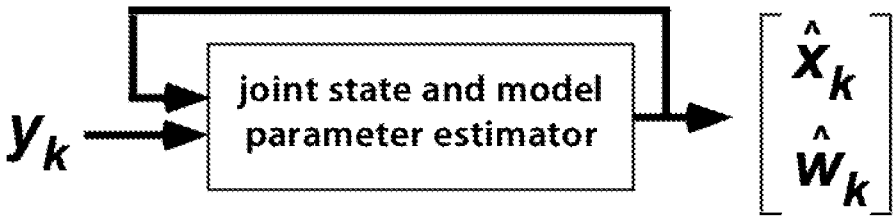


FIG. 7

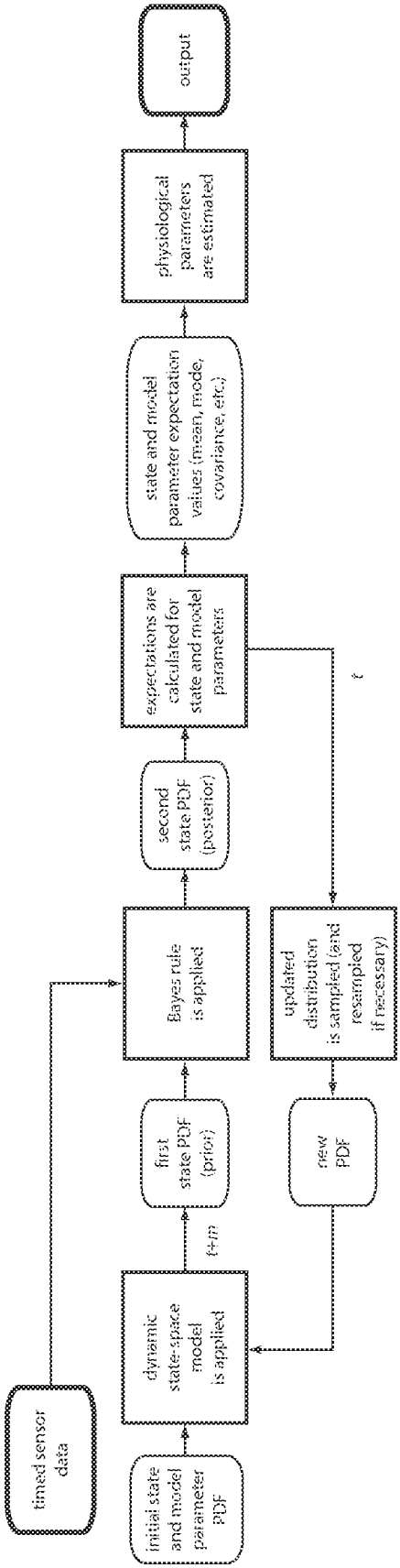

output
physiological parameters are estimated
state and model parameter expectation values (mean, mode, covariance, etc.)
expectations are calculated for state and model parameters
second state PDF (posterior)
Bayes rule is applied
first state PDF (prior)
dynamic state-space model is applied
timed sensor data
initial state and model parameter PDF
t+m
updated distribution is sampled (and resampled if necessary)
new PDF
t

FIG. 8

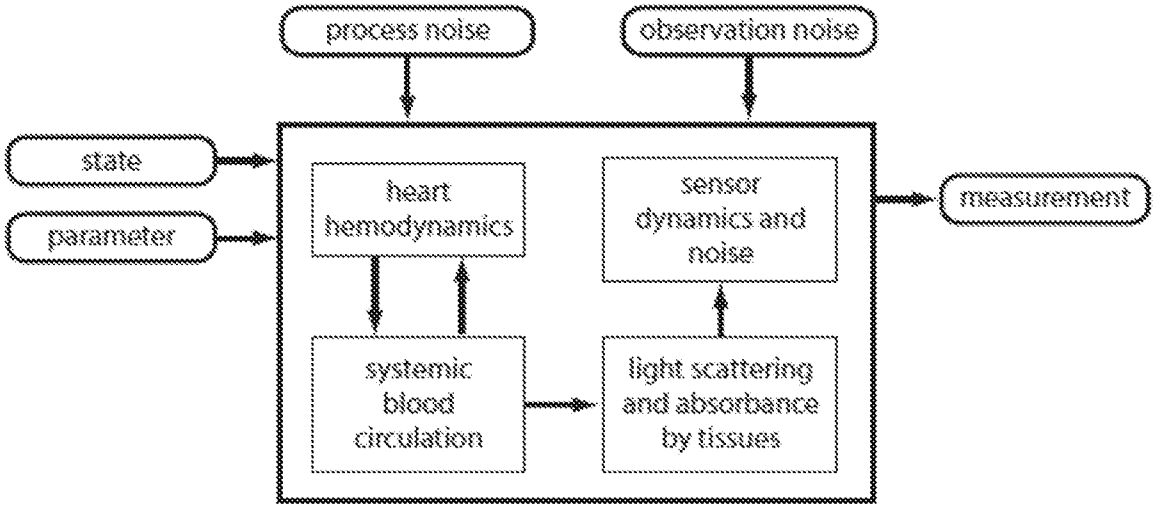

process noise
observation noise
state
parameter
heart hemodynamics
sensor dynamics and noise
measurement
systemic blood circulation
light scattering and absorbance by tissues

FIG. 9

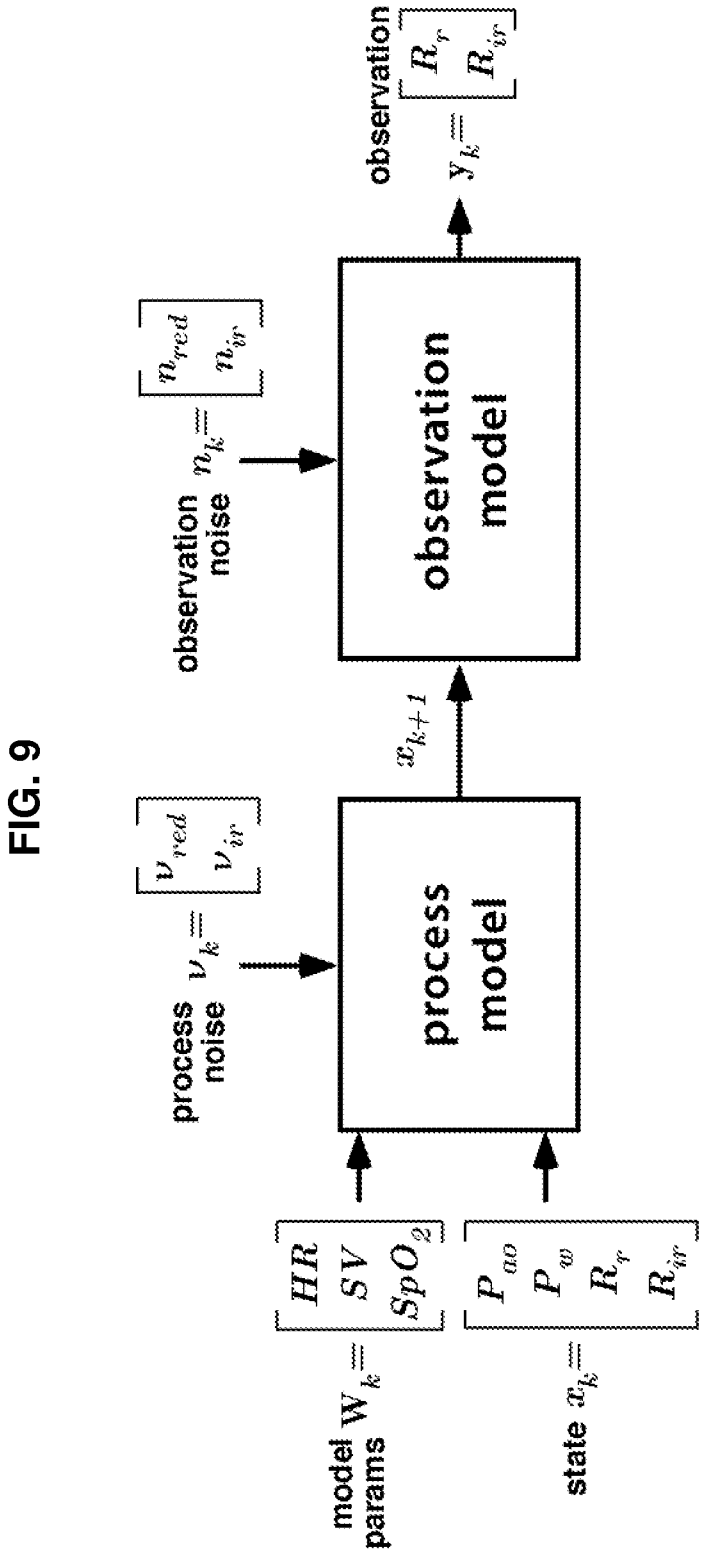

observation
R_r
R_{ir}
y_k
observation noise
n_k
n_{red}
n_{ir}
observation model
x_{k+1}
process noise
v_k
v_{red}
v_{ir}
process model
model params
W_k
HR
SV
SpO_2
state
x_k
P_{ao}
P_w
R_r
R_{ir}

FIG. 10

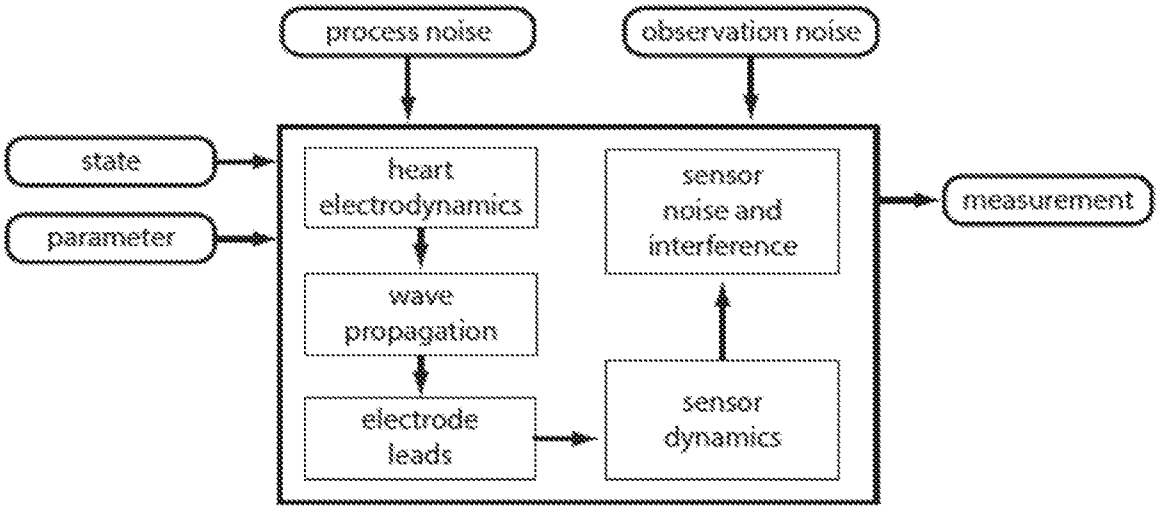

process noise
observation noise
state
parameter
heart electrodynamics
wave propagation
electrode leads
sensor noise and interference
sensor dynamics
measurement

FIG. 11

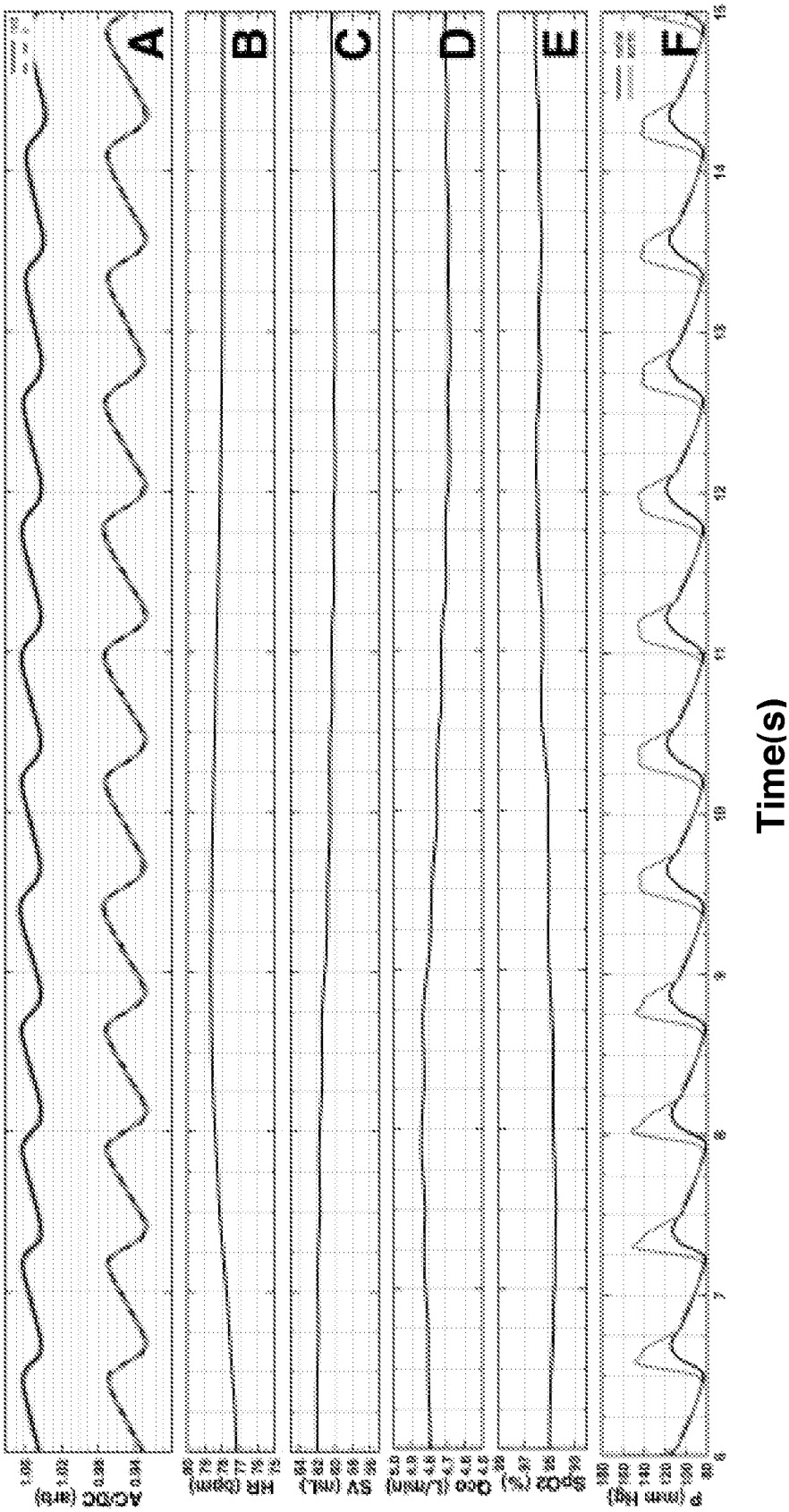


FIG. 12

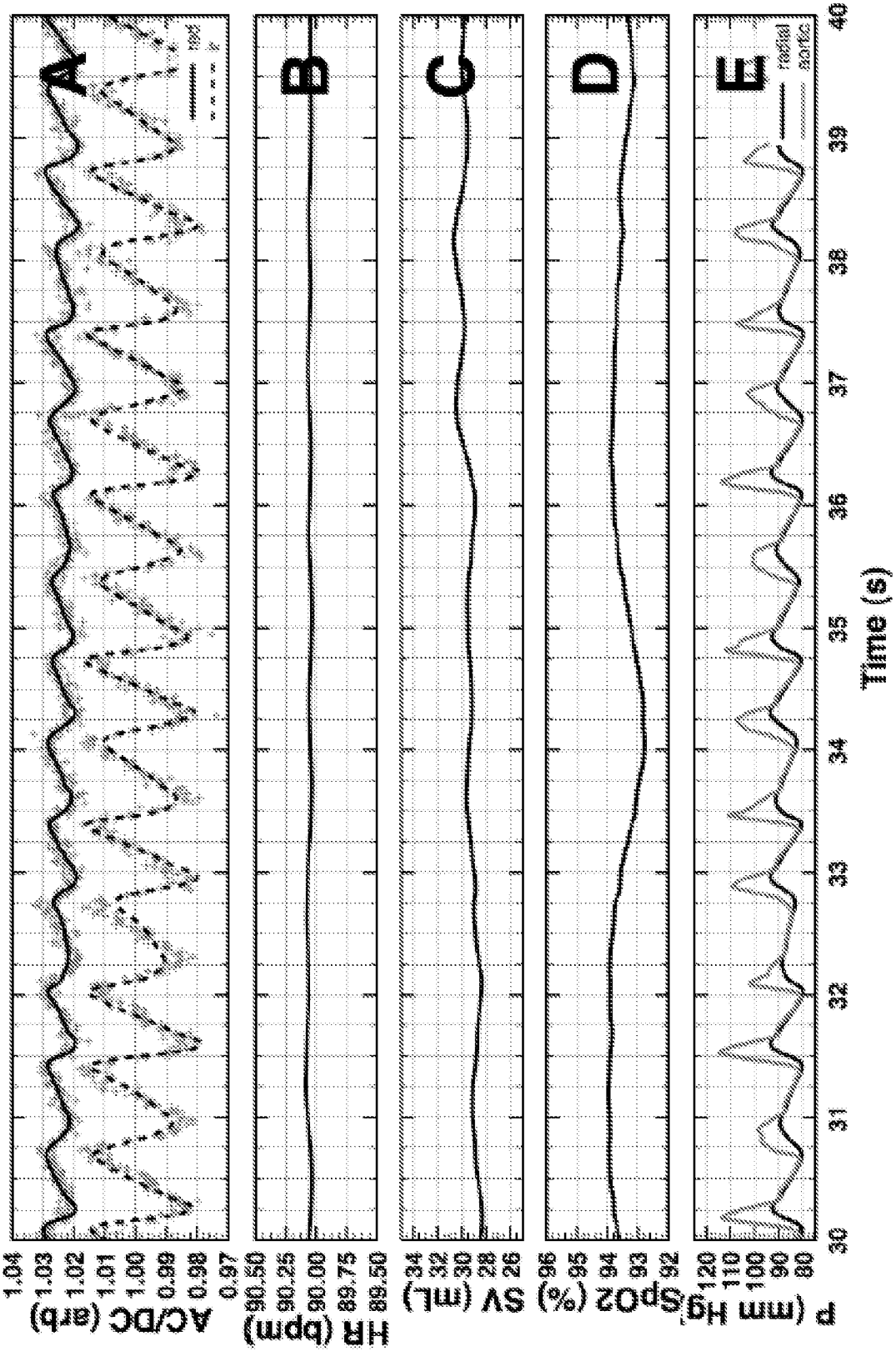

A
B
C
D
E
AC/DC (arb)
HR (bpm)
SV (mL)
SpO2 (%)
P (mm Hg)
Time (s)
red
ir
radial
aortic

FIG. 13

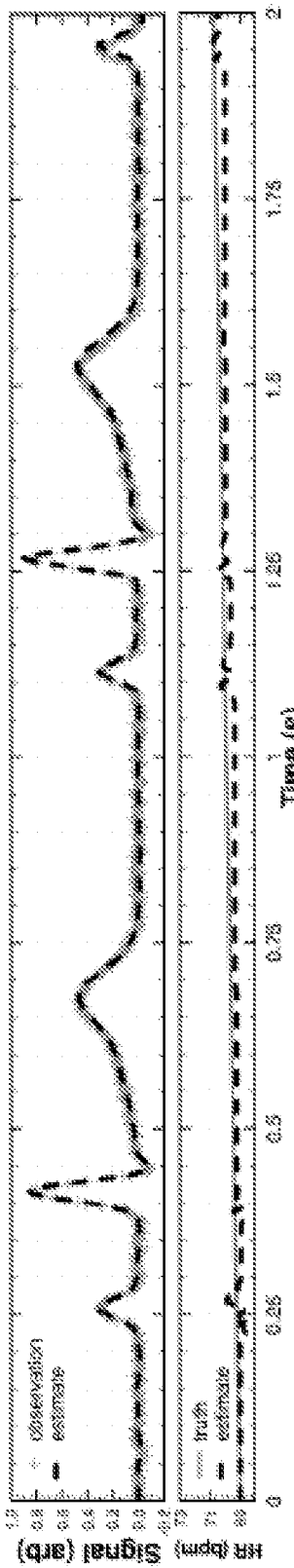
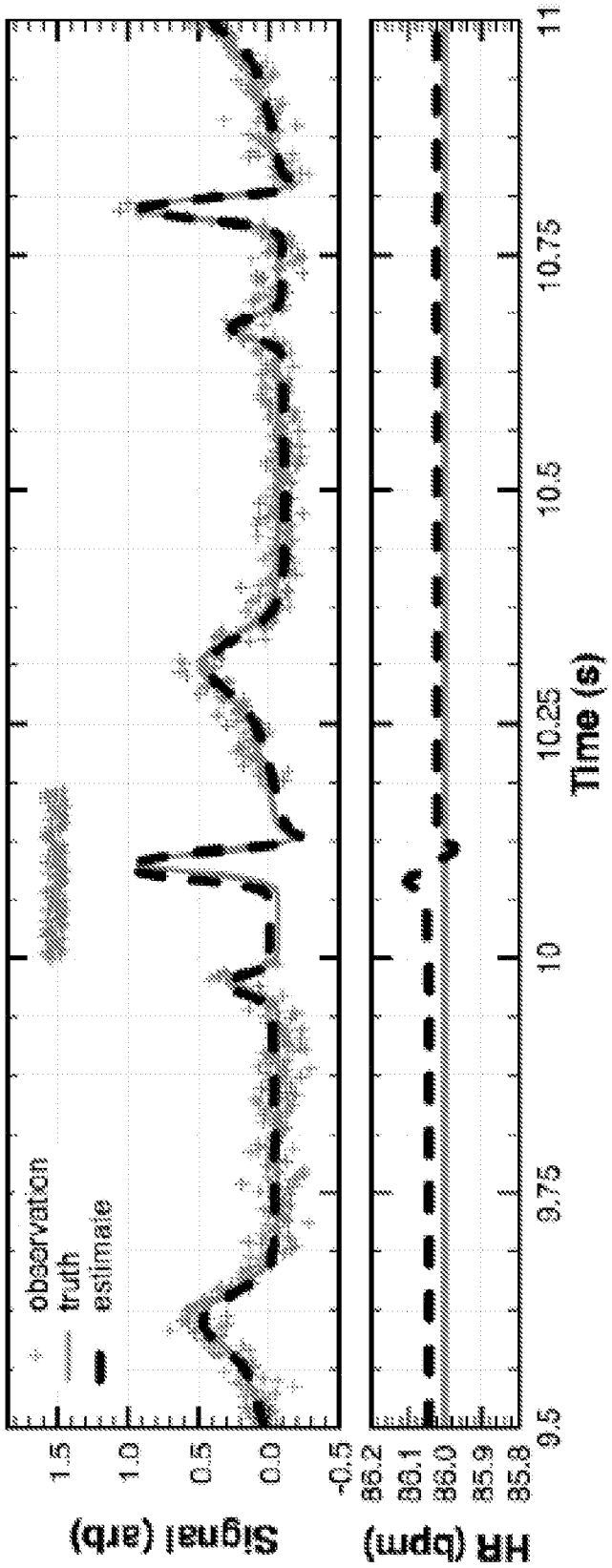

observation
estimate
Signal (arb)
truth
estimate
HR (bpm)
Time (s)
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2

FIG. 14


observation
truth
estimate
Signal (arb)
1.5
1.0
0.5
0.0
-0.5
HR (bpm)
86.2
86.1
86.0
85.9
85.8
9.5
9.75
10
10.25
10.5
10.75
11
Time (s)