(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification:
A61B 5/00 (2006.01)   *A61B 5/16* (2006.01)
A61B 5/01 (2006.01)

(21) International Application Number:
PCT/CA2008/001007

(22) International Filing Date: 29 May 2008 (29.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/932,102   29 May 2007 (29.05.2007)   US

(71) Applicants and
(72) Inventors: MOTT, Christopher [CA/CA]; 306 - 2490 Stephens Street, Vancouver, British Columbia V6K 3W9 (CA). DUMONT, Guy [CA/CA]; 302 - 1328 Marinaside Crescent, Vancouver, British Columbia V6Z 3B3 (CA). BOIVIN, Diane [CA/CA]; 6575 Des Ecores, Montreal, Quebec H2G 2J8 (CA). MOLLICONE, Daniel [CA/US]; 510 South 44th Street, Philadelphia, Pennsylvania 19104 (US).

(74) Agents: RATTRAY, Todd A. et al.; 480 - The Station, 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,

[Continued on next page]

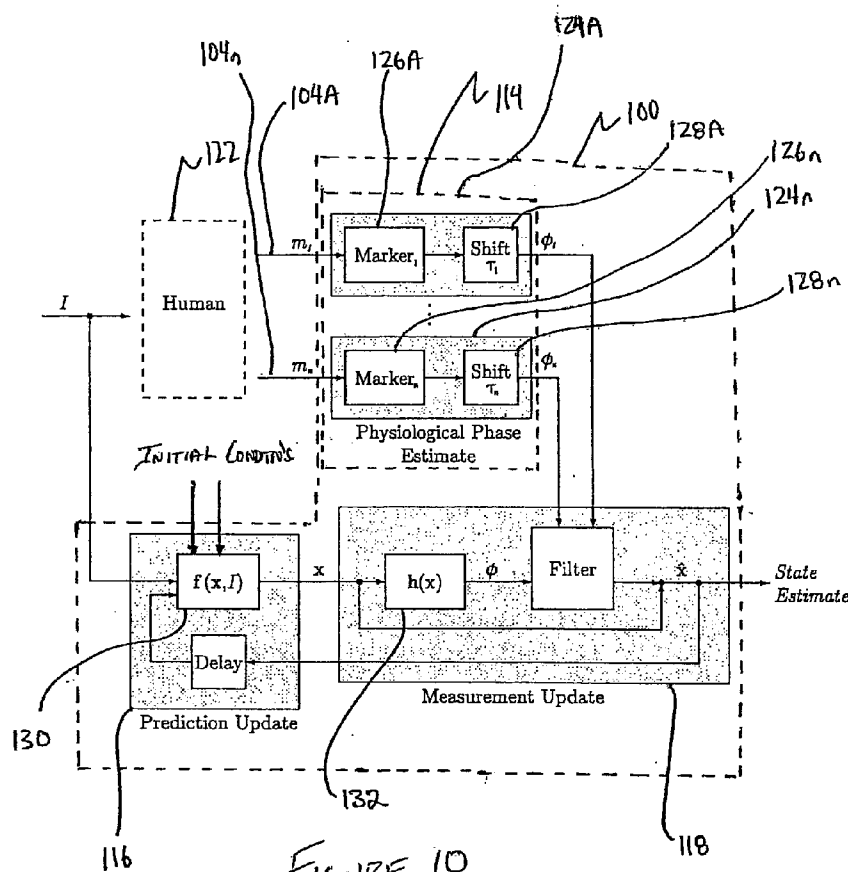(54) Title: METHODS AND SYSTEMS FOR CIRCADIAN PHYSIOLOGY PREDICTIONS

FIGURE 10

(57) Abstract: Systems and methods are provided for predicting a circadian state of an individual. The methods comprise: providing a state-space model representative of the response of the circadian state to light stimulus, the model comprising at least one state variable representative of a probability distribution function (PDF) of a phase offset of the circadian state of the individual; and using the model to estimate an updated PDF of the phase offset, wherein using the model to estimate the updated PDF of the phase offset comprises performing a Bayesian estimation process commencing with an initial PDF of the phase offset and iterating toward the updated PDF of the phase offset.

WO 2008/144908 A1

NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

METHODS AND SYSTEMS FOR CIRCADIAN PHYSIOLOGY PREDICTIONS

Related Applications

5   [0001] This application claims the benefit of the priority of US application No. 60/932,102 filed 29 May 2007 which is hereby incorporated herein by reference.

Technical Field

[0002] The invention relates to systems and methods for tracking the state of a

10   subject's circadian physiology. Particular embodiments provide state estimation systems and methods which combine mathematical models of circadian physiology, measurements of incident light, and measurements of physiological parameters to generate statistical estimates of circadian states.

15   Background

[0003] The word "circadian" is derived from the Latin words *circa*, meaning about, and *dies*, or day and refers to processes with 24 hour rhythms. Circadian physiological rhythms are present in organisms across the animal and plant kingdoms. Circadian rhythms are thought to be driven by an internal pacemaker which maintains a

20   self-regulating oscillation with a 24 hour period. Recent research has revealed the molecular structures which form the core of the human circadian pacemaker. The pacemaker serves as a central timing mechanism which synchronizes the rhythms of a wide array of physiological systems.

25   *Circadian Pacemaker Mechanism*

[0004] Daily fluctuations in human physiology, such as sleeping and body temperature changes, have long been observed; however, it was not until the 1970s that strong experimental evidence of the existence in humans of an endogenous circadian pacemaker emerged. Subsequently, in the 1990s the molecular basis of a

30   central human circadian pacemaker was identified. More specifically, research indicates that a molecular clock located in the suprachiasmatic nucleus (SCN) in the hypothalamus region of the brain maintains an approximate 24 hour rhythm. While evidence of additional peripheral oscillators exists, such as in the liver, the SCN pacemaker is believed to play the central role in regulating circadian timing signals for

35   other physiological systems.

[0005] Although the circadian pacemaker has an intrinsic period close to 24 hours, precise synchronization to the external environment is maintained by external stimuli referred to as "zeitgebers" (from German *zeit* (time) and *geber* (giver)). For most organisms, including humans, the strongest known zeitgeber is light. The daily

SUBSTITUTE SHEET (RULE 26)

transitions between light and dark caused by the earth's rotation relative to the sun create a strong environmental stimulus to which organisms naturally synchronize.

[0006] Synchronization of the circadian pacemaker to light occurs through photoreceptors in the retina which have a neural pathway to the SCN that is distinct from the neural pathway of the visual system. Signals arriving to the SCN modify both the phase and amplitude of the pacemaker's oscillations. The duration, intensity, timing of light exposure relative to circadian phase and the pattern of light exposure are all factors which have been observed to influence an organism's circadian pacemaker.

[0007] Studying the effects of circadian rhythms is generally not as straight forward as considering 24 hour physiological oscillations. Daily patterns of physical activity and sleep-wake also generally occur on a 24 hour schedule, so it is desirable to distinguish between behavior-induced rhythms (e.g. body temperature rising during the day because of walking) and endogenously driven rhythms (e.g. body temperature rising based on internal circadian thermoregulatory signals).

[0008] Two predominant experimental techniques for isolating circadian effects are referred to as the "forced desynchrony" and "constant routine" protocols. Both occur in time isolation laboratories. The forced desynchrony technique forces an individual's sleep and wake schedules to desynchronize from their internal circadian pacemaker. The constant routine technique eliminates sleep/wake effects by keeping individuals awake in a constant environment for more than 24 hours. Based on studies conducted with these protocols, a number of relationships between the circadian pacemaker and various physiological systems has been identified. Non-limiting examples of physiological systems that are, or may be ,effected by, or otherwise related to, the circadian pacemaker include: core body temperature (CBT), hormonal melatonin concentration, hormonal cortisol concentration, rate of cell proliferation, the cardiac regulatory system, chemoreceptive respiratory feedback system and cognitive performance (alertness).

Indirect Measurement of Circadian State

[0009] Since the human central circadian pacemaker mechanism is inaccessibly located in the brain, its state cannot be measured directly. Some researchers have attempted to indirectly measure a subject's circadian state by inferring the subject's circadian state from measurements of downstream physiological systems. A complication arising out of such indirect inference is that systems with an observable circadian modulation, such as CBT and melatonin secretion for example, are also

responsive to other physiological systems and/or environmental stimulus. From the perspective of attempting to infer a subject's circadian state, such physiological systems and/or environmental stimulus are considered to mask the circadian contribution to the observed physiological system. Accordingly, most indirect

5   measurements of a subject's circadian state require methods to "demask" the circadian signal components of an observable system from the other, non-circadian components. Two demasking approaches which have been used in the past involve: physical elimination of time-varying exogenous stimulus; and extraction of exogenous factors using signal processing techniques. Laboratory protocols associated with holding all

10   exogenous stimuli constant may be referred to as"constant routine" techniques. Signal processing methods for extracting exogenous factors may be referred to as "purification" techniques.

The Constant Routine Technique

15   **[0010]** CBT and hormonal melatonin levels are two physiological systems that tend to exhibit consistent and observable circadian rhythms. However, CBT also responds to physical activity, posture, ambient temperature, and sleep and melatonin secretion is also responsive to ambient light exposure. A constant routine demasking procedure developed by Czeisler (Czeisler, C., J. Allan, S. Strogatz, E. Ronda, R. Sanchez, C.

20   Rios, G. Freitag, G. Richardson, and R. Kronauer, Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science 233:4764, 667–671; 1986 (Czeisler 1986)) attempts to minimize such confounding effects on CBT and melatonin levels, by placing subjects in a strictly controlled laboratory environment. To reduce the effects of sleep-wake transitions and posture

25   changes, the Czeisler technique typically involves: keeping subjects awake for long periods of time (e.g. up to 40 hours) in a semi-recumbent position; setting light exposure to a low level (e.g. to 10 lux); introducing meals at regular intervals (e.g. one hour intervals); and limiting physical activity.

[0011] During the constant routine technique, CBT may be measured continuously

30   and the circadian contribution to the CBT (a roughly sinusoidal oscillation with an amplitude of approximately 2°C) may be monitored. The timing of the minimum of this approximately sinusoidal CBT oscillation typically occurs between 4:00 AM and 5:00 AM and is may be used as an indicator of the circadian state of a subject. The natural circadian melatonin cycle includes an onset in secretion approximately at one's

35   typical sleep time. The timing of this onset is driven by the circadian pacemaker; however, melatonin secretion is also affected by exposure to ambient light. The dim

light conditions of the constant routine technique facilitate measurement of the Dim
Light Melatonin Onset (DLMO) time.

[0012] The constant routine technique is currently accepted as a state of the art
method for experimentally assessing the circadian state of a subject and is the primary
method by which data have been collected about the circadian-phase-shifting effects
of light. Despite the success of the constant routine technique, its application is
limited to laboratory environments and often involves subject discomfort (e.g. having
to be awake for 40 hours).

The Purification Technique

[0013] The "purification" demasking approach is another method of circadian state
estimation which attempts to use signal analysis techniques to remove masking
contributions from observed physiological phenomena (i.e. to extract the circadian
contribution from the observed physiological phenomena). Typically, purification
techniques attempt to avoid the restrictive physical constraints of the constant routine
technique. Physical activity and sleep represent two well known masking factors
associated with the observable phenomena of CBT. Consequently, prior art
purification methods have focused on the separation of the effects physical activity
and sleep contributions to CBT from the circadian component contribution to CBT. In
contrast to the constant routine technique, participants in purification studies have
been allowed to follow regular sleep/wake schedules with free ambulatory movement
during waking periods.

[0014] Waterhouse has developed statistical methods of purification utilizing data
from activity sensors. One method involves categorizing activity during waking and
sleep periods and then calculating an associated temperature effect from each activity
category (Waterhouse, J., D. Weinert, D. Minors, S. Folkard, D. Owens, G. Atkinson,
D. Macdonald, N. Sytnik, P. Tucker, and T. Reilly, A comparison of some different
methods for purifying core temperature data from humans. Chronobiology
International 17:4, 539–566; 2000 (Waterhouse 2000A)). A second method uses a
linear regression based on direct mean scores from activity sensors
(Waterhouse2000a). Recent developments in purification-based methods have
introduced some basic thermoregulatory models (Weinert, D., A. Nevill, R.
Weinandy, and J. Waterhouse, The development of new purification methods to assess
the circadian rhythm of body temperature in mongolian gerbils. Chronobiology
International 20:2, 249–270; 2003).

- 5 -

[0015] While results using purification techniques have been shown to be comparable to constant routine techniques in some cases (Waterhouse, J., S. Kao, D. Weinert, B. Edwards, G. Atkinson, and T. Reilly, Measuring phase shifts in humans following a simulated time-zone transition: Agreement between constant routine and purification methods. Chronobiology International 22(5), 829–858; 2005), there remains contention among experts about the accuracy of purification approaches relative to constant routine techniques. A significant limitation of the statistical purification approach is that during periods of significant desynchrony between sleep-wake times and circadian phase, linear methods to separate the two effects from CBT data are inherently unreliable.

Actigraphy

[0016] Another approach to indirectly measuring the circadian state of an individual is referred to as actigraphy and is based on the assumption that there is a direct correlation between an individual's rest-activity rhythm and their sleep-wake rhythm and thus their circadian state. Actigraphy involves recording of rest-activity patterns using sensors which record gross physical movement. Typically, actigraphs are implemented using wrist-worn accelerometers.

[0017] Actigraphy has been used to indirectly measure the circadian state of cancer patients for timing the delivery of chronomodulated chemotherapy drugs. The type of circadian variation present in actigraph measurements has also been shown to provide an indicator of 'health status' of cancer patients. Actigraphy appears attractive for use in field applications, since it is portable and generally non-invasive. However, studies to date have yet to produce strong evidence demonstrating the link between actigraphy and more direct physiological systems known to be correlated to circadian state (e.g. CBT or melatonin). Actigraphy-based techniques have been applied only to individual's following a regular diurnal schedule. As such, confounding factors such as inter-individual variations in circadian phase, differences in behavioral patterns, and irregular schedules, such as arise with shift-work or the like, limit the accuracy and precision of actigraphy-based techniques.

Modeling and Predicting Circadian Dynamics

[0018] An alternative to measurement of observable physiological phenomena and using such physiological measurements to estimate an individual's circadian state involve the use of predictive models of circadian pacemaker physiology. Mathematical models describing the dynamic response of the circadian pacemaker

- 6 -

have been used to predict the behavior of the circadian pacemaker under specific light exposure scenarios.

Mathematical Models of Circadian State

[0019] The most widely accepted model of the circadian pacemaker was developed by Kronauer et al in 1987 based on observations of dose-response relationships between light exposure and circadian phase shifts. Kronauer inferred from experimental data that the model should have both a self-regulating oscillator component representing the internal circadian pacemaker, and a light input response component representing the pathway from light in the eye to a synchronizing input on the oscillator. Subsequent discovery of the molecular functionality of the circadian pacemaker has supported the general physiological basis of the Kronauer model. A refined version of the Kronauer model (the Kronauer-Jewett model) was published in 1999 (Jewett, M., D. Forger, and R. Kronauer, Revised limit cycle oscillator model of human circadian pacemaker. Journal of Biological Rhythms 14:6, 493–499; 1999 (Jewett 1999b)).

[0020] Figure 1 represents a schematic, block-diagram depiction of the Kronauer-Jewett model 10, which comprises a dynamic model including a circadian pacemaker component 12 and a physiological marker component 14 for comparison to a measurable physiological parameter. In the prior art Kronauer-Jewett model 10 of Figure 1, the measurable physiological parameter is the subject's CBT. Circadian pacemaker component 12 of the Kronauer-Jewett model 10 receives a light input I together with a set of initial conditions x_{init}, $x_{c\ init}$ and n_{init} corresponding to its state variables x, x_c and n and uses this information together with its model equations to generate output state variables x, x_c. Typical profiles of output state variables x, x_c are shown in Figure 2. It may be observed that output state variables x, x_c are approximately sinusoidal in shape with a period of approximately 24 hours and that output state variables x, x_c are approximately 90° out of phase with one another.

[0021] Physiological marker component 14 of the Kronauer-Jewett model 10 incorporates a minimizer component 16. Minimizer component 16 receives the output state variable x and returns a time at which output state variable x is a minimum x_{min}. As shown in Figure 2, the minimum x_{min} (also referred to as a nadir of the state variable x) occurs once every period of output state variable x or approximately once every 24 hours. The time at which output state variable x is a minimum x_{min} is referred to Figures 1 and 2 as $\phi_{min}\{x\}$.

[0022] The Kronauer-Jewett model 10 also incorporates the experimentally determined observation that the time $\phi_{min}\{x\}$ that the state variable x is a minimum x_{min}

is correlated to the time of the CBT minimum CBT_{min}. The time that physiological marker component 14 predicts to be the time of CBT_{min} is referred to in Figure 1 as $\phi_{min}\{CBT\}$. As can be seen by observation of summing junction 18, the Kronauer-Jewett model 10 incorporates the experimentally determined relationship that the time $\phi_{min}\{CBT\}$ typically occurs 0.8 hours after the time $\phi_{min}\{x\}$. Physiological marker component 14 of the Kronauer-Jewett model 10 outputs the time $\phi_{min}\{CBT\}$ of the CBT minimum CBT_{min} which in turn permits comparison of the Kronauer-Jewett model 10 to measured CBT values. Since the time $\phi_{min}\{x\}$ that the state variable x is a minimum x_{min} is only output once every approximately 24 hours, it follows that physiological marker component 14 only outputs the time $\phi_{min}\{CBT\}$ of the CBT minimum CBT_{min} once every approximately 24 hours.

[0023] The Kronauer-Jewett circadian pacemaker model 10 has been used with differential-equation-solving algorithms to generate simulations predicting the phase shift of the circadian pacemaker, starting from known initial conditions $(x_{init}, x_{c\ init}, n_{init})$, in response to a given light exposure pattern (I). This predictive capability has been successfully used to design of experimental protocols and confirm experimental observations of circadian phase shifts in a laboratory context. Despite the apparent usefulness of the Kronauer-Jewett model 10, it has not actually been widely applied in broader contexts -- e.g. outside of an experimental laboratory environment.

[0024] A number of drawbacks have tended to limit widespread adoption of the prior art Kronauer-Jewett model 10 as a general modeling framework. By way of non-limiting example, such limitations include: (i) the circadian phase of the subject is not presented as a continuous variable which can be monitored (e.g. as an output of model 10) or updated (e.g. as an initial condition of model 10); (ii) the correlation between the circadian phase and physiological marker 14 is not defined in a statistical manner (i.e. Kronauer-Jewett model 10 does not incorporate statistical uncertainties); and (iii) the Kronauer-Jewett model 10 only specifies a correlation to CBT and not to other physiologically observable phenomena.

Alertness Models

[0025] One use of circadian physiology models is in the field of human alertness modeling and prediction. Human alertness may also be referred to as human performance. Current models of human alertness incorporate both a sleep-related component and a circadian component; however, most of the widely used human-alertness models assume a fixed circadian phase – e.g. a series of sinusoidal

- 8 -

harmonics with a predetermined and constant phase. With such constant phase assumption, scenarios in which the actual circadian phase of a subject may be non-stationary, e.g. shift work or transmeridian travel, cannot be accurately modeled. Some human-alertness models incorporate the potential for changing circadian phase.

5   One such human-alertness model uses a version of the Kronauer model for accommodating variations in the circadian phase (Jewett, M. and R. Kronauer (1999). Interactive mathematical models of subjective alertness and cognitive throughput in humans. Journal of Biological Rhythms 14:6, 588–597; 1999 (Jewett 1999a)). Another such human-alertness model uses a "rule of thumb" for shifting the circadian

10   phase in response to time-zone changes – e.g. a constant rate of change of the circadian phase until the subject is entrained to the new time zone (Akerstedt, T., S. Folkard, and C. Portin, Predictions from the three process model of alertness. AVIATION SPACE AND ENVIRONMENTAL MEDICINE March 75:3, Suppl., A75–A83; 2004).The lack of dynamic circadian modeling has been identified as a

15   general need in the context of human alertness prediction.

[0026] One of the challenges in applying a human-alertness model incorporating a detailed dynamic circadian pacemaker model to real world scenarios is that current simulation methods require precise specification of initial conditions and complete knowledge of light levels during the course of the simulation. In uncontrolled

20   environments, such as in an actual workplace or in almost any scenario outside of a laboratory, it is difficult to assess both the circadian phase and ambient light levels for a specific individual. It may be this reason that the Kronauer-Jewett model 10 has found application in simulating laboratory environment scenarios, where circadian phase and light levels can be controlled, but has not been widely used in operational

25   scenarios. This inability to apply circadian predictions to real world environments may be partially responsible for the fact that despite a well-established model of the circadian pacemaker, it remains difficult for scientists to provide definitive advice concerning specific circadian adjustment countermeasures.

[0027] There is a general desire for systems and methods for predicting a belief in or

30   probability of the circadian state of a subject which may overcome or ameliorate some of the aforementioned issues with the prior art.

Brief Description of the Drawings

[0028] In drawings which depict non-limiting embodiments of the invention:

35   Figure 1 schematically depicts the prior art Kronauer-Jewett model for circadian phase estimation in response to changes in light exposure;

Figure 2 depicts typical curves of the state variables (x, x_c) of the Figure 1 Kronauer-Jewett model;

Figure 3 is a schematic illustration of a system for estimating a belief in a circadian phase according to a particular embodiment of the invention;

Figure 4 schematically illustrates a system model which incorporates a modified version of the Figure 1 Kronauer-Jewett model and which is suitable for use in the Figure 3 circadian phase estimation system;

Figure 5 is a graphical relationship between the state variables (x, x_c) of the Figure 1 Kronauer-Jewett model and the state variables (A, ϕ) of the Figure 4 modified Kronauer-Jewett model;

Figures 6A and 6B respectively depict plots showing the phase angle θ and the phase offset ϕ for the cases of a constant phase offset ϕ and for the case of a shift in phase offset ϕ;

Figures 7A and 7B respectively depict plots showing how the continuous phase offset estimates compare to the Kronauer-Jewett nadir-reference phase offset estimates for the case where the phase offset is relatively constant (i.e. where a subject has entrained to particular pattern of sleep and light exposure) and for the case of a shift in phase offset;

Figure 8 a schematic depiction of the operation of the physiological phase estimator of the Figure 1 system according to a particular embodiment of the invention;

Figure 9 schematically depicts a method 200 of Bayesian filtering according to a particular embodiment of the invention;

Figure 10 is a more detailed schematic depiction of the Figure 1 estimation system;

Figure 11 schematically depicts a particle filtering method according to a particular embodiment of the invention;

Figures 12A, 12B, 12C and 12D respectively represent pseudocode procedures for implementing the prediction update, IMPORTANCE WEIGHT, RESAMPLE and MOVE blocks of the Figure 11 particle filtering method;

Figures 13A, 13B and 13C schematically depict an example of a Gaussian kernel replacement to reconstruct a continuous PDF from a particle distribution according to a particular embodiment of the invention;

Figure 14 shows a number of plots of simulated data relating to state variables in a first simulation scenario with a 24 point particle filter;

Figure 15 shows phase PDFs generated by a second simulation scenario with no noise;

Figure 16 shows phase PDFs generated by the second simulation scenario with process noise;

Figure 17 shows phase PDFs generated by the second simulation scenario with process noise and light input noise;

Figure 18 schematically depicts the light pattern used for third and fourth simulation scenarios;

Figure 19 shows phase PDFs generated by a third simulation scenario;

Figure 20 shows phase PDFs generated by a fourth simulation scenario;

Figure 21 is schematic illustration of an experimental phase prediction system according to a particular embodiment;

Figure 22A shows phase PDFs generated by the Figure 21 system for a human subject without incorporation of prior sleep history information;

Figures 23A, 23B and 23C respectively show the evolution of the phase PDFs of a human subject experiment in the cases of a Bayesian particle filter estimation without physiological measurement information (Figure 23A), a CBT measurement only (Figure 23B) and a Bayesian particle filter estimation with CBT measurement information (23C);

Figure 24 shows the Figure 23 phase PDFs at the conclusion of the human subject experiment; and

Figure 25 shows melatonin and cortisol measurements taken from an individual subject and shows the results of a Fourier curve-fitting technique used to obtain physiological feature PDFs according to a particular embodiment of the invention.

Detailed Description

[0029] Throughout the following description, specific details are set forth in order to provide a more thorough understanding of the invention. However, the invention may be practised without these particulars. In other instances, well known elements have not been shown or described in detail to avoid unnecessarily obscuring the invention. Accordingly, the specification and drawings are to be regarded in an illustrative, rather than a restrictive, sense.

[0030] Systems and methods are provided for predicting a circadian state of an individual. The methods comprise: providing a state-space model representative of the

response of the circadian state to light stimulus, the model comprising at least one state variable representative of a probability distribution function (PDF) of a phase offset of the circadian state of the individual; and using the model to estimate an updated PDF of the phase offset, wherein using the model to estimate the updated PDF of the phase offset comprises performing a Bayesian estimation process commencing with an initial PDF of the phase offset and iterating toward the updated PDF of the phase offset. Systems may comprise processors suitably configured for carrying out the methods of the invention.

[0031] Figure 3 schematically depicts a circadian phase estimation system 100 according to a particular embodiment of the invention. System 100 estimates the circadian phase ϕ of an individual subject (not shown). In particular embodiments, the circadian phase ϕ estimates output by system 100 may comprise statistical information relating to the circadian phase ϕ – e.g. a probability distribution function (PDF) relating to the circadian phase ϕ. Such statistical information may express a belief or confidence interval in the circadian phase ϕ estimate.

[0032] In the illustrated embodiment, estimation system 100 receives light input information 102 which relates to the amount of light experienced by the individual subject. Light information 102 input to system 100 may be measured and/or controlled. System 100 may also receive one or more optional physiological inputs 104A ... 104n (collectively, physiological inputs 104). Physiological inputs 104 may be related to measurable physiological parameters. Physiological inputs 104 may comprise statistical information relating to the measurable physiological parameters – e.g. PDFs relating to the physiological parameters. In the illustrated embodiment, system 100 also receives one or more optional initial conditions 106A ... 106n (collectively, initial conditions 106). Initial conditions 106 may be estimated or measured. Initial conditions 106 may relate to state variables of a system model (not shown) used by estimation system 100. In addition to the circadian phase ϕ, estimation system may also output one or more optional other output(s) 110. Such other outputs 110 may be related to the state variables of the system model used by estimation system 100.

[0033] In the illustrated embodiment, estimation system 100 comprises a number of components, which include a system model 112, a physiological phase estimator 114, a prediction updator 116 and a measurement updator 118. For simplicity of the schematic illustration, system model 112, physiological phase estimator 114, prediction updator 116 and measurement updator 118 are shown as separate components. However, it will be appreciated by those skilled in the art that these

- 12 -

components of estimation system 100 may overlap one another in whole or in part. System model 112, physiological phase estimator 114, prediction updator 116 and measurement updator 118 are explained in more detail below.

[0034] Estimation system 100 may be implemented at least in part by one or more suitably configured controllers. In general, the type of controller used to implement system 100 may comprise or may otherwise be embodied by a wide variety of components. For example, such a controller may comprise one or more programmable processor(s) which may include, without limitation, embedded microprocessors, dedicated computers, groups of data processors or the like. Some functions of such a controller may be implemented in software, while others may be implemented with one or more hardware devices. The operation of such a controller may be governed by appropriate firmware/code residing and/or executing therein, as is well known in the art. Such a controller may comprise memory or have access to external memory.

[0035] The invention may also comprise methods of operating estimation system 100 to generate estimates of the circadian phase ϕ.

Modified Kronauer-Jewett Model

[0036] Model 112 of estimation system 100 (Figure 3) may be implemented using a modified version of the Kronauer-Jewett model 10.

[0037] As discussed above, the prior art Kronauer-Jewett model 10 (Figure 1) involves predicting the impact of light exposure I on the circadian parameters of an individual. The Kronauer-Jewett model 10 incorporates a modified Van der Pol oscillator which maintains a steady state oscillation with a stable amplitude and period and models the self-sustaining rhythm of circadian pacemaker 12. A light input term (B) may be incorporated into the oscillator to describe how light intensity I observed in the subject's retina causes changes in the circadian parameters (e.g. phase and/or amplitude). In particular embodiments, the modified Van der Pol oscillator of Kronauer-Jewett model 10 may be described by a pair of interacting state variables (x, x_c) described by the following non-linear equations:

$$\dot{x} = \frac{\pi}{12}\left[x_c + \mu\left(\frac{1}{3}x + \frac{4}{3}x^3 - \frac{256}{105}x^7\right) + B\right] \tag{1}$$

$$\dot{x}_c = \frac{\pi}{12}\left\{qBx_c - \left[\left(\frac{24}{\tau_x(0.99729)}\right)^2 + kB\right]x\right\} \tag{2}$$

where $\mu = 0.13$, $q = 1/3$, $\tau_x = 24.2$, $k = 0.55$, and B is a driving input due to light input I (Jewett1999b). As shown in Figure 2, the Kronauer-Jewett state variables x and x_c

- 13 -

typically follow trajectories which have shapes that are approximately sinusoidal with phases that differ by 90°.

[0038] In the Kronauer-Jewett model 10, the response (α) of the human eye to light may be modeled first by a logarithmic function:

$$\alpha = \alpha_0 \left(\frac{I}{9500} \right)^p \tag{3}$$

where I is the ambient light intensity in units of lux, $\alpha_0 = 0.05$ and $p=0.5$ (Jewett1999b).

[0039] A second component of the Kronauer-Jewett model 10 is a dynamic filter which relates the parameter α to the driving light-input variable (B) used in state variable equations (1) and (2). In accordance with the Kronauer-Jewett model 10, this dynamic filter may be provided by:

$$\dot{n} = 60\left[\alpha(1-n) - \beta n \right] \tag{4}$$

$$B = G\alpha(1-n)(1-mx)(1-mx_c) \tag{5}$$

where $\beta=0.0075$ and $G=19.875$ (Jewett1999b). Equation (4) models a filter (n) acting upon (α) and equation (5) models the modulation of the light-input variable (B) by the current state (x, x_c) of the circadian pacemaker and the filter (n).

[0040] The Kronauer-Jewett model 10 also comprises a physiological circadian phase marker 14 which, as discussed above, provides an estimate of the time $\phi_{min}\{CBT\}$ of the subject's minimum core body temperature CBT_{min}. In accordance with the Kronauer-Jewett model 10, the estimated time $\phi_{min}\{CBT\}$ of the subject's minimum core body temperature CBT_{min} is based on the corresponding time $\phi_{min}\{x\}$ of the minimum (nadir) x_{min} of the state variable x. More particularly, as shown by summing junction 16 in Figure 1, the estimated time $\phi_{min}\{CBT\}$ of the subject's minimum core body temperature CBT_{min} is obtained from the corresponding time $\phi_{min}\{x\}$ of the state variable minimum x_{min} according to:

$$\phi_{min}\{CBT\} = \phi_{min}\{x\} + 0.8 hours \tag{6}$$

[0041] System model 112 of estimation system 100 (Figure 3) may be implemented using the modified version of the prior art Kronauer-Jewett model 10. Figure 4 schematically depicts a modified Kronauer-Jewett model 112A which may be used to implement system model 112 (Figure 3) in particular embodiments. In particular embodiments, modified Kronauer-Jewett model 112A (Figure 4) involves modifying the prior art Kronauer-Jewett model 10 (Figure 1) by: applying non-linear state transformation to circadian pacemaker 12 of the prior art Kronauer-Jewett model 10

- 14 -

(Figure 1); modifying physiological marker 14 of the prior art Kronauer-Jewett model 10 to provide a physiological phase estimator 114 (Figure 3) capable of accommodating probability distributions (rather than point estimates) and capable of optionally relating the output of model 112 to multiple physiological inputs 104 which may include physiological inputs other than CBT. Modified Kronauer-Jewett model 112A is explained in more detail below.

Parameter Transformation of Circadian Pacemaker Model

[0042] The Kronauer-Jewett model 10 is a widely accepted characterization of a subject's circadian state and the responsiveness of the circadian state to light inputs. The Kronauer-Jewett model 10 suffers from the fact that phase and amplitude of the subject's circadian state are not accessible as state variables. Instead, the Kronauer-Jewett model 10 requires that the circadian amplitude be defined as a nonlinear function of the state variables (x, x_c) and the circadian phase be defined by physiological marker component 14 in relation to the nadir x_{min} of the state variable x. As a consequence of these definitions, the location of the nadir x_{min} of the state variable x provides the reference point for connecting the circadian phase predicted by the Kronauer-Jewett model 10 to the circadian phase observable from measurement of the subject's CBT as described above in equation (6).

[0043] In accordance with particular embodiments of the invention, this limitation of the prior art Kronauer-Jewett model 10 may be overcome by providing modified Kronauer-Jewett model 112A (Figure 4) with a state transformation T which maps the Kronauer-Jewett state variables (x, x_c) into directly useful states (ϕ, A). Modified Kronauer-Jewett model 112A of Figure 4 may be more fully understood by examining the properties of the Kronauer-Jewett state variables (x, x_c) and deriving the transformation T and its inverse transformation T^{-1}.

Characteristics of Kronauer-Jewett state variables (x, x_c)

[0044] The differential equations (1), (2), (4) used in the Kronauer-Jewett model 10 comprise three states (x, x_c, n). As discussed above, the state variables (x, x_c) interact to create a modified Van der Pol oscillator which self-oscillates at a period of approximately 24 hours. Both x and x_c follow nearly sinusoidal trajectories, in which the phase of the state variable x_c lags the phase of the state variable x by approximately 90°. The state variable n is part of a light input system.

[0045] In an approximately 24 hour period of the state variables (x, x_c), the prior art Kronauer-Jewett model 10 uses a single reference point (i.e. the time $\phi_{min}\{x\}$ of the

- 15 -

nadir x_{min} of the state variable x) to define the phase of the circadian pacemaker. For example, for an individual with sleep occurring regularly between 12:00am and 8:00am, simulations of the Kronauer-Jewett model 10 will tend to show that the nadir x_{min} of the state variable x occurs at a time $\phi_{min}\{x\}$ around 4.3h (4:22am), and in real experiments subjects will have a CBT minimum CBT_{min} occurring at a time $\phi_{min}\{CBT\}$ of approximately 5.1h (5:06am) as described above in equation (6). Based on a variety of experiments with different light exposure settings, the Kronauer-Jewett model 10 has been refined so that the time $\phi_{min}\{x\}$ of the nadir x_{min} maintains a constant time shift (0.8 hours) relative to the time $\phi_{min}\{CBT\}$ observed for the CBT nadir CBT_{min}.

[0046] This nadir-phase-reference method of the Kronauer-Jewett model 10 presents a number of limitations in the context of a circadian estimation system 100 (Figure 3). Firstly, the Kronauer-Jewett model 10 only outputs one phase prediction every approximately 24 hours – i.e. one time $\phi_{min}\{x\}$ in the Figure 1 illustration corresponding to each nadir x_{min} of the state variable x. This single phase prediction permits only one physiological marker output (i.e. one time $\phi_{min}\{CBT\}$ in the Figure 1 illustration) every approximately 24 hours. A second limitation of the Kronauer-Jewett nadir-phase-reference method relates to the lack of an inverse relationship from which the system's state variables (x, x_c, n) can be updated to match a given circadian phase and amplitude. Typically, in prior art applications, the initial conditions for Kronauer-Jewett simulations are assigned on the basis of a look-up table of values for typical situations (e.g. for a habitual schedule of 8h sleep and 16h awake in 160 lux the initial conditions at the onset of sleep time may be set to $x = -0.17$, $x_c=-1.22$, and $n=0.50$ (Jewett1999b)).

Parameter transformation to new state variables (ϕ, A)

[0047] In particular embodiments of the invention, the modified Kronauer-Jewett model 112A (Figure 4) comprises a transformation T for creating new phase and amplitude states (ϕ, A) based on Kronauer-Jewett states (x, x_c). Since Kronauer-Jewett states (x, x_c) are continuously updated (e.g. once every time step in a discrete-time context), the transformed phase and amplitude states (ϕ, A) of modified Kronauer-Jewett model 112A are similarly continuously updated. Transformation T may be based on an understanding of the Kronauer-Jewett state variables (x, x_c). As shown in Figure 1, the Kronauer-Jewett state variables (x, x_c) typically follow near-sinusoidal trajectories with a relatively constant phase difference. If the Kronauer-Jewett state variables (x, x_c) are considered to be (x, y) coordinates on a Cartesian plane, then they describe a near-circular locus. Figure 5 shows the Figure 2 data points transposed into

- 16 -

(x, y) coordinates. The near-circular (x, y) plot shown in Figure 5 may be described in a polar coordinate system using amplitude A and phase angle θ, where the amplitude A is the distance of the vector from the origin to the point (x, x_c) and the angle θ is measured from the horizontal axis as shown in Figure 5. The Kronauer-Jewett state variables (x, x_c) may be transformed to provide the amplitude A and the phase angle θ according to:

$$A = \sqrt{x^2 + x_c^2} \qquad (7)$$

$$\theta = \tan^{-1}\left(\frac{x}{x_c}\right) + \begin{cases} 0 \text{ if } x_c > 0 \text{ and } x > 0 \text{ (quadrant I)}, \\ \pi \text{ if } x_c < 0 \text{ (quadrant II or III)}, \\ 2\pi \text{ if } x_c > 0 \text{ and } x < 0 \text{ (quadrant IV)}, \end{cases} \qquad (8)$$

With these definitions, as time increases the point (x, x_c) follows a near-circular trajectory with a period of 24 hours and the angle θ increases from 0 to 2π radians. Together, equations (7) and (8) may be defined to be a transform T. The inverse transform T^{-1} may be accomplished according to:

$$x = A\sin(\theta) \qquad (9)$$

$$x_c = A\cos(\theta) \qquad (10)$$

[0048] In practice, it is most meaningful to describe the circadian system in terms of a phase offset ϕ which reflects the phase shift relative to a defined reference phase, rather than in terms of a phase angle θ which reflects the continually moving angle from 0 to 2π. The following relationship may be used to define the phase offset ϕ (in units of hours) based on the phase angle θ:

$$\theta = \omega(t + t_0) - \phi\frac{2\pi}{24} \qquad (11a)$$

or

$$\phi = \frac{24}{2\pi}\left(\omega(t + t_0) - \theta\right) \qquad (11b)$$

where ω represents a baseline frequency, t_0 is a baseline offset parameter measured in hours from midnight (i.e. midnight=0 hours) and t represents the current time measured in hours from midnight. Since the baseline frequency ω corresponds to a constant 24 hour day (i.e. $\omega=2\pi/24$), equation (11) can be rewritten as:

$$\phi = t + t_0 - \frac{24}{2\pi}\theta \qquad (12)$$

- 17 -

In accordance with the definition of the phase offset ϕ in equation (11) and (12), the phase offset ϕ represents the difference between the phase angle term $24\theta/2\pi$ and time variable t in units of hours.

[0049] Referring to equation (12), if an individual follows a consistent 24 light exposure schedule, then the time t will vary between 0 hours and 24 hours and the phase angle θ will vary between 0 and 2π over the same period. This situation is depicted in the plots of Figure 6A. Because of the corresponding changes in time t and phase angle θ over a period, the term $\frac{24}{2\pi}\theta$ will increase at the same rate as t, so the

difference $t - \frac{24}{2\pi}\theta$ will be relatively constant. This constant phase offset ϕ is shown in

the lower plot of Figure 6A. Alternatively, if an individual experiences a shift in light exposure (as is shown in the plots of Figure 6B), then the phase angle θ will vary by a different amount over a 24 hour period – i.e. an amount different than 0 to 2π.

Consequently, the term $\frac{24}{2\pi}\theta$ of equation (12) will increase or decrease relative to the

time t and a change in the phase offset ϕ will occur. In the circumstance shown in the lower plot of Figure 6B, the phase offset ϕ is increasing.

[0050] The equation (12) baseline offset term t_0 may be treated as a calibration constant, as it shifts the mean value of the phase offset ϕ. In particular embodiments, to determine the appropriate calibration value t_0, a comparison is made between the phase offset ϕ estimated using equation (12) and the transformation T (Figure 4 and equations (7) and (8)) to the phase offset ϕ estimated using the Kronauer-Jewett nadir-reference method described above. For consistency, the phase offset ϕ of the modified model (i.e. estimated using equation (12)) may be calibrated to match the phase offset ϕ estimated using the Kronauer-Jewett nadir-reference method. Since the Kronauer-Jewett nadir-phase-reference method provides only a single reference point every approximately 24 hours (i.e. at the nadir x_{min} of the state variable x) and the phase offset ϕ estimated using equation (12) provides continuous values, a variety of calibration methods may be used to select the baseline offset term t_0.

[0051] In one particular embodiment, calibration involves adjusting the baseline offset term t_0, such that the 24 hour mean of the equation (12) phase offset estimate ϕ matches the phase estimate ϕ at the time of x_{min} predicted using the Kronauer-Jewett nadir-reference method – i.e. if the time of x_{min} occurs at 4:00h, then t_0 is chosen such that the 24 hour mean of the equation (12) phase offset estimate ϕ will equal 4:00h. In an alternative embodiment, calibration involves adjusting the baseline offset term t_0 of

the equation (12) phase offset estimate ϕ such that the values of the equation (12)
phase offset estimate ϕ exactly match the phase estimates ϕ predicted by the
Kronauer-Jewett nadir-reference method at the reference points corresponding to the
nadir x_{min} of the state variable x. In the description that follows, unless otherwise

5   stated, it is assumed that the calibration technique of matching the mean of the
equation (12) phase estimate ϕ is used to obtain the baseline offset term t_0.

[0052] Using the 24 hour mean of the equation (12) phase offset ϕ, a specific
calibration value for the baseline offset term t_0 was determined from a simulation of
modified Kronauer-Jewett model 112A (Figure 4) under conditions which are

10   considered to involve a standard sleep schedule and light exposure scenario. More
particularly, the simulation involved repeated days comprising an eight hour sleep
episode (at a light level of 0 Lux) followed by a sixteen hour awake episode (at a
constant light level of 150 Lux) until modified Kronauer-Jewett model 112A achieved
steady state conditions. In accordance with this simulation, the value of t_0 which

15   causes the mean of the equation (12) phase offset estimate ϕ to match the phase offset
estimates ϕ predicted using the Kronauer-Jewett nadir-reference method was
determined to be $t_0 = 17.1$ hours. Accordingly, the resulting calibrated version of
equation (12) may be rewritten as:

$$\phi = t + 17.1 - \frac{24}{2\pi}\theta \tag{13}$$

20   where θ is given by equation (8). Phase offset estimates ϕ based on equation (12)
and/or equation (13) may be referred to herein as phase offset estimates ϕ obtained
using continuous phase estimation in contrast to phase offset estimates ϕ obtained
using the Kronauer-Jewett nadir-reference method. In addition, unless specifically
stated otherwise, references in the remainder of this description to phase should be

25   understood to refer to phase offset ϕ – i.e. the word offset may be dropped without
loss of generality.

[0053] Figures 7A and 7B respectively depict plots showing how the continuous
phase estimates compare to the Kronauer-Jewett nadir-reference phase estimates for
the case where the phase is relatively constant (i.e. where a subject has entrained to

30   particular pattern of sleep and light exposure) and for the case of a phase shift. In each
of Figures 7A and 7B: the upper plots represent the state variable x and the circled
points in the upper plots represent the nadirs x_{min} of the state variable x; the middle
plots represent the continuous phase estimates ϕ and the circled points in the middle
plots represent the phase estimates ϕ obtained using Kronauer-Jewett nadir-reference

35   method at the nadirs x_{min} of the state variable x; and the lower plots represent a

difference Δ between the continuous phase estimates ϕ and the circled points in the middle plots represent the phase estimates ϕ obtained using Kronauer-Jewett nadir-reference method.

[0054] Figure 7A shows that Δ fluctuates within each 24 hour period (due to the fact that the Van der Pol equations (1) and (2) are not perfectly sinusoidal) but that Δ is less than about ±0.5 hours for the case of entrained phase offset. The amplitude of this fluctuation is considered sufficiently small to obtain reasonably accurate phase estimates as explained in more detail below. In the plots of Figure 7B, the individual's sleep pattern is delayed by six hours from the entrained rhythm. This results in a six hour shift in the circadian phase ϕ as shown in the middle Figure 7B plot. The lower Figure 7B plot shows that Δ exhibits a small positive bias during phase transition, but that this bias disappears once the phase ϕ entrains to its new value. This bias is a transient effect which does not significantly impact phase estimates.

[0055] Referring back to modified Kronauer-Jewett model 112A of Figure 4, it may be observed that modified Kronauer-Jewett model 112A incorporates a transform component T which transforms the Kronauer-Jewett state variables (x, x_c) into transformed state variables (A, ϕ). In the above-described embodiment, transform component T may be implemented using equation (9) and one of equations (12) or (13). Modified Kronauer-Jewett model 112A also comprises an inverse transform component T^{-1} which transforms initial conditions (A_{init}, ϕ_{init}) into Kronauer-Jewett initial conditions $(x_{init}, x_{c\ init})$. In the above-described embodiment, inverse transform component T^{-1} may be implemented using equations (9) and (10).

State-space Model

[0056] It is convenient for the purposes of the Bayesian estimation methods described below to re-cast the modified Kronauer-Jewett model 112A into a state-space form. State-space models are defined by a state vector **x** that contains the time varying properties of the system, a state transition function (also referred to as a state propagation function) that describes how the state vector evolves in time, and an output function that describes how the states can be observed. We may define a state vector **x** which includes the three state variables of the modified Kronauer-Jewett model 112A:

$$\mathbf{x} = \begin{bmatrix} A \\ \phi \\ n \end{bmatrix} \tag{14}$$

- 20 -

where A is circadian amplitude, ϕ is circadian phase, and n is the light filter state. For the case of a discrete-time system, the state vector x and its states evolve at incremental time intervals (also referred to as time steps) with sampling period T. This discrete-time formulation may be described according to:

$$\mathbf{x}_k = \mathbf{x}(t) \quad \text{where } t = t_0 + kT, \; k \in N \tag{15}$$

[0057] In addition to the state vector x, state-space models comprise a state transition function and an output function. For discrete-time systems, the general state transition function may be written:

$$\mathbf{x}_{k+1} = \mathbf{f}(\mathbf{x}_k, \mathbf{u}_k, \mathbf{v}_k) \tag{16}$$

where $\mathbf{x}_k$ is the current state vector at time step k, $\mathbf{u}_k$ is a measured input, $\mathbf{v}_k$ is an unmeasured input, and $\mathbf{x}_{k+1}$ is the predicted state vector at the future time step $k+1$. The unmeasured input $\mathbf{v}_k$ is often referred to as process noise and may be modeled as a random variable. To cast the modified Kronauer-Jewett model 112A in the form of equation (16), it may be observed from Figure 4 that model 112A describes a state transition function $\mathbf{x}_{k+1} = \mathbf{f}_k(\mathbf{x}_k, I_k)$ where I is the light input and $\mathbf{x}_k$ is given by equation (14). The Figure 4 model 112A does not contain a process noise term $\mathbf{v}_k$, as a state-space formulation of modified Kronauer-Jewett model 112A has not previously been developed. Particular embodiments of the invention involve the assumption that the process noise $\mathbf{v}_k$ is an additive Gaussian noise. In other embodiments, other forms of PDFs (e.g. uniform probability PDFs) may be used to model the process noise $\mathbf{v}_k$. With the assumption that the process noise $\mathbf{v}_k$ is an additive Gaussian noise, the state-space transition equation for the modified Kronauer-Jewett model 112A may be expressed in the following form:

$$\mathbf{x}_{k+1} = \mathbf{f}(\mathbf{x}_k, \mathbf{I}_k) + \mathbf{v}_k$$

$$\begin{bmatrix} A \\ \phi \\ n \end{bmatrix}_{k+1} = \begin{bmatrix} f_1(\mathbf{x}_k, \mathbf{I}_k) \\ f_2(\mathbf{x}_k, \mathbf{I}_k) \\ f_3(\mathbf{x}_k, \mathbf{I}_k) \end{bmatrix} + \begin{bmatrix} v1 \\ v2 \\ v3 \end{bmatrix} \tag{17}$$

[0058] The general form of the discrete-time state-space output function is:

$$\mathbf{z}_k = \mathbf{h}_k(\mathbf{x}_k, \mathbf{w}_k) \tag{18}$$

where $\mathbf{w}$ is a random variable referred to as the measurement noise. An output function for the modified Kronauer-Jewett model 112A may be chosen based on the states to which measurement information could potentially be correlated. Of the three

states, A, ϕ, and n, the phase ϕ may be observed using physiological markers as described above. Accordingly, in particular embodiments, the phase ϕ may be chosen as the single output of interest. In such embodiments, the phase ϕ may be extracted using the following linear output function:

$$\mathbf{z} = \mathbf{h}_k\left(\mathbf{x}_k, \mathbf{w}_k\right)$$
$$= \mathbf{H}\mathbf{x}_k + \mathbf{w}_k$$
$$= \begin{bmatrix} 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} A \\ \phi \\ n \end{bmatrix} + \mathbf{w}_k \tag{19}$$
$$= \begin{bmatrix} \phi \end{bmatrix} + \mathbf{w}_k$$

In particular embodiments, the measurement noise $\mathbf{w}_k$ may be selected to be an independent random Gaussian variable with variance R. In other embodiments, the measurement noise $\mathbf{w}_k$ may be assumed to have other PDFs. It will be appreciated that the output function (19) could be modified if other quantities (e.g. circadian amplitude A) were of interest.

Incorporating Inputs with Probability Distributions

[0059] Particular embodiments of the invention provide the ability to measure one or more physiological systems of the subject to provide physiological inputs 104 (Figure 3). Such physiological inputs 104 may include CBT, but may additionally or alternatively include other physiological inputs, such as, by way of non-limiting example: hormonal melatonin concentration, hormonal cortisol concentration, rate of cell proliferation, the cardiac regulatory system, chemoreceptive respiratory feedback system and cognitive performance (alertness). Physiological phase estimator 114 (Figure 3) may receive physiological inputs 104 and may use such inputs 104 to provide physiological markers of the circadian phase ϕ as described in more detail below. It is desirable to integrate these physiological inputs 104 into to a common circadian phase domain. In the illustrated embodiment of phase estimating system 100 (Figure 3), physiological phase estimator 14 uses measured physiological inputs 104 to generate corresponding statistical PDFs relating to the phase marker(s) in the circadian phase domain.

[0060] Figure 8 is a schematic depiction of the operation of physiological phase estimator 114 according to a particular embodiment of the invention. In the illustrated embodiment of Figure 8, several sensors 120A, ... 120n (collectively, sensors 120) are configured to sense physiological phenomena of subject 122. Such physiological phenomena may include, by way of non-limiting example, CBT, hormonal melatonin concentration, hormonal cortisol concentration, rate of cell proliferation, the cardiac regulatory system, chemoreceptive respiratory feedback system and cognitive performance (alertness). In the illustrated embodiment, sensor 120A senses the CBT of subject 122 and at least one other sensor 120n is provided to detect another physiological phenomena of subject 122. The outputs of sensors 120 are the physiological inputs 104 (see also Figure 3). In the illustrated embodiment of Figure 8, sensor 120A outputs a physiological input 104A representative of the CBT of subject 122 and sensor 120n outputs a physiological input 104n representative of another physiological phenomena of subject 122.

[0061] Physiological inputs 104 are provided to physiological phase estimator 114. For each of physiological inputs 104, physiological phase estimator 114 comprises a component phase estimator 124A, ... 124n (collectively, component phase estimators 124). Component phase estimators 124 comprise marker components 126A, ... 126n (collectively, marker components 126) and marker-to-phase converter components 128A, ...128n (collectively, marker-to-phase converter components 128). Marker components 126 perform the function of extracting features from their physiological inputs 104. The features extracted by marker components 126 comprise physiological markers indicative of the circadian phase of subject 122. While the features extracted by marker components 126 may generally comprise any discernable features of inputs 104, non-limiting examples of features which may be extracted by marker components comprise: local minima or maxima of inputs 104, the presence of inputs 104 above and/or below a threshold, frequencies of inputs 104, rates of change (i.e. time derivatives) of inputs 104, time integrals of inputs 104 and/or any similar features of the rate of change or time integral of inputs 104. In particular embodiments, marker components 126 may also extract the time associated with any extracted features.

[0062] The features extracted by marker components 126 are preferably associated with PDFs representing the uncertainty present in the accuracy of the feature extraction. In particular embodiments, such physiological feature PDFs may comprise Gaussian PDFs characterized by a mean value and a standard deviation. In other embodiments, the physiological feature PDFs may comprise other distributions

- 23 -

characterized by other parameters. In the case of CBT, the feature extracted by marker component 126A is the CBT minimum (CBT_{min}) and marker component 126A may also extract the corresponding time associated with CBT_{min}. In the above discussion (see Figure 1), the time associated with CBT_{min} is referred to as $\phi_{min}\{CBT\}$. A PDF

5   associated with the time $\phi_{min}\{CBT\}$ at which CBT_{min} occurs may be obtained in accordance with the procedure outlined by E. Brown and C. Czeisler, The statistical analysis of circadian phase and amplitude in constant-routine core-temperature data, Journal of Biological Rhythms, 7:3, 177–202; 1992.

[0063] Marker components 126 may also determine physiological feature PDFs from

10 physiological inputs 104n using Fourier series curve-fitting techniques. A suitable second or third order Fourier series curve fitting technique is shown in Figure 25 in relation to melatonin and cortisol samples taken from an individual during a laboratory study. The phase marker for the melatonin and cortisol examples can be extracted by identifying the time at which the maxima of the fitted curve occurs. A

15 PDF time at which the maxima occurs may be generated and used as the phase PDF. Algorthims such as the procedure outlined by Wang (Y. Wang and M. Brown, A flexible model for human circadian rhythms, Biometrics 52, 588–596; 1996) may be applied.

[0064] In the illustrated embodiment, marker-to-phase converter components 128

20 perform the function of converting the features extracted by marker components 126 and/or their corresponding times into information relating to the circadian phase ϕ of subject 122. For example, in the case of CBT, it has been experimentally determined (as discussed above) that the time $\phi_{min}\{CBT\}$ associated with the feature CBT_{min} can be related to the calibrated circadian phase ϕ (equation (13)) of subject 122 via a 0.8

25 hour time/phase shift (note that when phase is described as phase offset ϕ, its units are units of time and therefore a time shift and a phase shift are equivalent).

[0065] While particular embodiments of marker-to-phase converter components 128 may implement time/phase shifting functions (as is the case for CBT converter component 128A), this is not necessary. In other embodiments, marker-to-phase

30 converter components 128 may involve other conversion functions. For example, in the case where a feature extracted by a marker component 126 is not a time/phase quantity, the corresponding marker-to-phase converter component 128 may use the extracted feature as the basis of a function or a transformation or the like to convert the extracted feature into time/phase information relating to the circadian phase ϕ.

35 [0066] The information relating to circadian phase ϕ that is output by marker-to-phase converter components 128 does not necessarily suggest internal physical

mechanisms in subject 122, but rather this information provides descriptors of observable physiological behavior. The information relating to circadian phase ϕ that is output by marker-to-phase converter components 128 sets the foundation for implementing a recursive state estimation algorithm, which may simultaneously make use of one or more physiological inputs 104 and central state transition updates.

Particle Filter Phase Estimator

[0067] The above-described modeling framework describes the dynamics of circadian physiology in a state-space model and optionally integrates multiple physiological inputs 104. In particular embodiments, phase estimator 100 (Figure 3) uses a particle filter to estimate the circadian state within this modeling framework. In general, it is desired to provide a phase estimation solution that can incorporate statistical process noise (as opposed to an algebraic solution), incremental or on-line processing of information at every time step (as opposed to batch data analysis) and statistical distributions of measurements and parameter estimates (e.g. physiological inputs 104 and the information about circadian phase ϕ extracted from physiological inputs by phase estimator 114). Particular embodiments of phase estimator 100 (Figure 3) involve the use of recursive filtering methods which in turn make use of Bayesian statistics. Such techniques may be referred to Bayesian filtering or Bayesian estimation techniques. A feature of Bayesian estimation is the integration of prediction updates (which may be implemented by prediction updator 116 (Figure 3)) and measurement updates (which may be implemented by measurement updator 118 (Figure 1)) using inferential statistics. In particular embodiments, phase estimator 100 (Figure 3) uses a particle filter as a method for resolving the Bayesian estimation problem.

Overview of Recursive Bayesian Estimation

[0068] Bayesian statistics provides an approach to on-line estimation (i.e. estimation at each time step) in which the probability, or belief, of a system's property is updated based on an initial belief, new measurements, and predictions of the system's internal dynamics. A statistical probability is associated with each operation which allows for natural expression of the uncertainty that is inherent in most real systems and allows for analysis of noisy or otherwise imperfect measurements. Applied to discrete-time state-space models, the values of a state vector are estimated starting from a prior probability distribution and sequentially updated with predictions from a state transition equation and adjustments from a measurement equation.

[0069] Consider a discrete-time state-space model with a state vector x that is evaluated at times $t_i = iT$, where T is the sampling period. Denoting measurements at

time t_i as z_i, the set of all measurements up to time k may be defined as $Z_k \triangleq z_i$, $i=1, ..., k$. The state-space model consists of a state transition equation:

$$\mathbf{x}_k = \mathbf{f}_k\left(\mathbf{x}_{k-1}, \mathbf{u}_{k-1}, \mathbf{v}_{k-1}\right) \tag{20}$$

which describes the evolution of states from a prior state $\mathbf{x}_{k-1}$ to a future state $\mathbf{x}_k$ with measured inputs $\mathbf{u}_{k-1}$ and noise $\mathbf{v}_{k-1}$ and a measurement or output equation:

$$\mathbf{z}_k = \mathbf{h}_k\left(\mathbf{x}_k, \mathbf{w}_k\right) \tag{21}$$

which describes the relationship between an observed measurement $\mathbf{z}_k$ and the system's internal state $\mathbf{x}_k$ and the measurement noise $\mathbf{w}_k$.

[0070] To apply Bayesian statistical logic, both the state transition and measurement equations (20) and (21) are extended to include probability distributions. Assuming a known probability distribution of the states at time t_{k-1} is $p(\mathbf{x}_{k-1}|\mathbf{Z}_{k-1})$, then the probability distribution of states at a future time step $p(\mathbf{x}_k|\mathbf{Z}_{k-1})$ is defined by the Chapman-Kolmogorov equation (also referred to as the prediction update equation):

$$p\left(\mathbf{x}_k|\mathbf{Z}_{k-1}\right) = \int_{-\infty}^{\infty} p\left(\mathbf{x}_k|\mathbf{x}_{k-1}\right) p\left(\mathbf{x}_{k-1}|\mathbf{Z}_{k-1}\right) d\mathbf{x}_{k-1} \tag{22}$$

The term $p(\mathbf{x}_k|\mathbf{x}_{k-1})$ expresses the probability distribution of the state vector $\mathbf{x}$ at time t_k given a state vector x_{k-1} at time t_{k-1} and is related to the state transition equation (20). Prediction update equation (22), which may be implemented by prediction updator 116 (Figure 1), therefore allows the belief in the system state vector to evolve in time based on predictions from state transition equation (20). A probabilistic update of states based on measurements is provided by Bayes theorem which states that:

$$p\left(\mathbf{x}_k|\mathbf{Z}_k\right) = \frac{p\left(\mathbf{z}_k|\mathbf{x}_k\right) \cdot p\left(\mathbf{x}_k|\mathbf{Z}_{k-1}\right)}{p\left(\mathbf{z}_k|\mathbf{Z}_{k-1}\right)} \tag{23}$$

where $p(x_k|\mathbf{Z}_{k-1})$ represents the prior knowledge of the states at time t_k given all measurements up to time t_{k-1}; $p(z_k|x_k)$ is the likelihood from the current observed data point at time t_k; and $p(x_k|\mathbf{Z}_k)$ is the posterior probability of the state variables. The denominator $p(z_k|\mathbf{Z}_{k-1})$ is a normalization constant. Consequently, equation (23) may be expressed as:

$$p\left(\mathbf{x}_k|\mathbf{Z}_k\right) = C p\left(\mathbf{z}_k|\mathbf{x}_k\right) p\left(\mathbf{x}_k|\mathbf{Z}_{k-1}\right) \tag{24}$$

where C is a normalization constant. Equation (24) may be referred to as the measurement update equation. The measurement update equation (24), which may be implemented by measurement updator 118 (Figure 1), allows an update of the system's state vector based on new measurements.

[0071] Figure 9 schematically depicts a method 200 of Bayesian filtering according to a particular embodiment of the invention. Given an initialization of the prior

- 26 -

probability distributions of the states $p(x_0)$ obtained in block 202, prediction update equation (22) may be applied in block 204 to obtain a belief (probability distribution) $p(x_k|Z_{k-1})$ in the system state vector. Method 200 then proceeds to block 206 which involves an inquiry into whether there measurement information is available in the current time step. If no measurement information is available (block 206 NO output), then Bayesian filtering method 200 returns to prediction update block 202 for another iteration. If measurement information is available (block 206 YES output), then method 200 proceeds to block 208 where measurement update equation (24) is used to incorporate the measurement information z_k and to generate an updated belief $p(x_k|Z_k)$ in the system state vector. Method 200 then loops back to prediction update block 204. While method 200 of Figure 9 represents a general sequence of operations for Bayesian filtering, specific implementation of the block 204 prediction update and the block 208 measurement update vary widely however based on the characteristics of the system of interest and on design criteria.

Solving the Circadian State-Spaced Bayesian Filtering Problem

[0072] Particular embodiments of the invention provide methods for solving Bayesian estimation problems applied to the modified Kronauer-Jewett model 112A to generate estimated probabilities/beliefs of the circadian phase ϕ. Figure 10 schematically depicts an estimation system 100 which integrates the modified Kronauer-Jewett model 112A, multiple optional physiological inputs 104, initial conditions 106, physiological phase estimator 114, prediction updator component 116 and measurement updator component 118. In the schematic illustration of Figure 10, modified Kronauer-Jewett model 112A may be incorporated into state transition component 130 ($f(x, I)$) of prediction updator component 116 and possibly into output component 132 ($h(x)$) of measurement updator 118.

[0073] Estimation system 100 may comprise methods for implementing prediction updator 116 and measurement updator 118. Such methods may be based on the properties of the modified Kronauer-Jewett model 112A (e.g. the degree and types of nonlinearities) and the properties of the measurement noise w_k and/or process noise v_k. For clarity, measurement noise w_k and/or process noise v_k are not explicitly shown in the schematic illustration of Figure 10. Observation of the modified Kronauer-Jewett model 112A highlights three features which may be used to implement methods for implementing prediction updator 116 and measurement updator 118:

- the phase state ϕ has a nonlinear parameter space;
- the state transition equation (20) is nonlinear in a way that may lead to bimodal probability densities; and

SUBSTITUTE SHEET (RULE 26)

- the unknown variability of light input I should be treated parametrically rather than as an additive, independent Gaussian random variable.

[0074] A typical assumption for many systems is that the state vector exists in independent linear parameter spaces of continuous real numbers such that $x \in \mathbb{R}^n$. This assumption is not the case for the state vector x of the modified Kronauer-Jewett model 112A (equation (14)). The amplitude state variable A and light response state variable n have typical parameter spaces; however, the phase offset state variable ϕ is an exception. By its definition, ϕ indicates a phase point within a twenty-four hour day, which like the hour hand of a clock is constrained to the range $0 \leq \phi < 24$ and is in a circular parameter space where the time of 0h00 is equivalent to 24h00. The parameter space of the phase state variable ϕ can be thus defined using the modulo operator as $\phi \in (\mathbb{R} \bmod 24)$.

[0075] A second observable feature of modified Kronauer-Jewett model 112A is that the state transition equations (20) are nonlinear. The Van de Pol oscillator equations (1), (2) contain high order terms of x and x_c and the light input equations (3), (5) contain exponential and multiplicative terms. While these equations may be linearized through approximations (C. Mott, M. Huzmezan, D. Mollicone, and M. van Wollen, Modifying the human circadian pacemaker using model-based predictive control, in Proceedings of the 2003 American Control Conference, June 2003, 453–458), such linearizing approximations sacrifice accuracy. One nonlinear property of the circadian system that has been qualitatively established in the prior art is that the timing of light applied around the minima of the CBT (CBT_{min}), or equivalently around the calibrated phase ϕ=4:00h, may lead to a divergence of phase shift directions. More particularly, if light is introduced slightly before CBT_{min}, it will cause a delay shift, and if light is introduced slightly after CBT_{min}, then it will cause an advance shift. It may be inferred that this divergence behavior could lead to bi-modal probability distributions.

[0076] A third observable nonlinearity associated with the modified Kronauer-Jewett model 112A is that variability in light input I may not be accurately modeled by a simple additive Gaussian random variable in the form of $I = I + v$. Two factors relating to the light exposure experienced by a subject are the timing of light exposure changes relative to sleep and wake transitions and light levels which may be related to subject location (e.g. sunlight, dim room, bright room). In particular embodiments, an assumption may be made that light input may be specified as a function of a light timing parameter and light level parameter. It then follows that uncertainty should be introduced as random variability to the light timing and light level parameter values. While not wishing to be bound by any theory or method of operation, it is believed that this assumption (i.e. that light exposure should be characterized by a light timing

parameter and a light level parameter) would be more representative of typical
scenarios than using a simple additive noise, as light timing and light level parameters
would more closely model human behavioral characteristics. According to this
assumption, estimation system 100 (Figure 10) may be provided with the general
capacity to model nonlinear light input variability.

[0077] Implementing a recursive Bayesian filter for a given system requires
developing solutions to prediction update equation (22) and measurement update
equation (24). For linear systems with Gaussian noise, analytical solutions may exist
resulting in the classical Kalman filter. However, approximation methods and
approximate solutions are usually used in cases with nonlinearities. In particular
embodiments, particle-filter-based methods are used to implement prediction updator
116 and measurement updator 118. In general, particle filters represent probability
distributions using a number of point masses (also referred to as particles). A particle
representation is an approximation wherein the approximation accuracy tends to
increase with the number of particles.

Particle Filter Design

[0078] Particular embodiments of the invention involve particle filtering methods
which may be referred to as Sequential Importance Resampling with a Markov chain
Monte Carlo move step.

[0079] Particle filters according to particular embodiments of the invention may
comprise a sequence of operations that propagate a set of particles through a recursive
Bayesian filter operation of the form of Bayesian estimation method 200 (Figure 9).
Particle filters according to particular embodiments of the invention may comprise
one or more additional steps (i.e. in addition to those in the general Bayesian
estimation method 200) to improve stability and/or optimize performance of the
particle filter. These additional steps may be performed within the functional blocks
of Bayesian estimation method 200 (e.g. as a part of prediction update block 204
and/or as part of measurement update block 208) or in additional functional blocks
that may be added to Bayesian estimation method 200. Such additional steps may be
configured to avoid altering the probability distributions promulgated by prediction
update block 204 and measurement update block 208, but may alter various
mathematical properties to improve stability and/or optimize performance of the
particle filter.

[0080] Figure 11 schematically depicts a particle filtering method 220 according to a
particular embodiment of the invention. As discussed above, particle filtering method
220 follows the general procedure of Bayesian estimation method 200 (Figure 9). The
Figure 11 illustration shows prediction update block 204 and measurement update

block 208 in more particular detail and also shows a schematic illustration of a number of particles as they propagate through one iteration of method 220. The Figure 11 illustration begins with a particle distribution **A** which represents the state vector's prior PDF at time step k-1 (i.e. $p(x^i_{k-1}|Z_{k-1})$). Referring to Figure 9, the particle distribution **A** may arise from any of the three paths leading to prediction update block 204. In particle filtering method 220 illustrated in Figure 11, prediction update block 204 serves to propagate the particles of particle distribution **A** based on the state transition model of modified Kronauer-Jewett model 112A. The output of prediction update block 204 is the particle distribution **B** which represents the PDF of the state vector at the time step k (i.e. $p(x^i_k|Z_{k-1})$). Referring to Bayesian estimation method 200 (Figure 9), particle distribution **B** represents the output of prediction update block 204. Figure 12A shows a pseudocode procedure for implementing prediction update block 204 of method 220 according to a particular embodiment of the invention.

[0081] Particle distribution **B** is then received at measurement update block 208. In the illustrated particle filtering method 220 of Figure 11, measurement update block 208 comprises an IMPORTANCE WEIGHT block 222. IMPORTANCE WEIGHT block 222 assigns a weight to each particle in particle distribution **B** based on the likelihood function from the current observed data point at time t_k (i.e. $p(z_k|x^i_k)$). In the illustration of Figure 11, the likelihood function $p(z_k|x^i_k)$ is schematically depicted as a horizontally extending curve. In applying weights to particles based on likelihood function $p(z_k|x^i_k)$, IMPORTANCE WEIGHT block 222 performs the function of measurement update equation (24) and measurement update block 208 of Bayesian estimation method 200 (Figure 9) and the output of IMPORTANCE WEIGHT block 222 is a distribution **C** of weighted particles which represents the posterior probability density $p(x^i_k|Z_k)$. In the schematic illustration of Figure 11, the sizes of the colored particles in particle distribution **C** are representative of their weights. Figure 12B shows a pseudocode procedure for implementing MEASUREMENT WEIGHT block 222 of method 220 according to a particular embodiment of the invention.

[0082] Particle distribution **C** is then provided to RESAMPLE block 224. RESAMPLE block 224 performs a thresholding process to discard particles in areas of low probability (i.e. particles with relatively low weights in distribution **C**). RESAMPLE block 224 also multiplies the particles in area of high probability (i.e. particles with relatively high weights in distribution **C**). The result of RESAMPLE block 224 is particle distribution **D** shown in Figure 11. Preferably, RESAMPLE block 224 does not significantly impact the PDF of the particles – i.e. the PDF of particle distribution **D** is at least approximately equivalent to the PDF of particle distribution **C**. That is, particle distribution **D** still represents the posterior probability density $p(x^i_k|Z_k)$. Figure 12C shows a pseudocode procedure for implementing

RESAMPLE block 224 of method 220 according to a particular embodiment of the invention.

[0083] While particle distribution **D** now represents the desired posterior probability density $p(x_k^i|Z_k)$, a practical issue is that RESAMPLING block 224 reduces the diversity of the particle locations. If left in the form of particle distribution **D**, the particles would eventually (i.e. after a sufficient number of iterations) collapse to a single point. Accordingly, particle filtering method 220 comprises a MOVE block 226 which receives particle distribution **D** and redistributes the particles to output particle distribution **E**. Preferably, MOVE block 226 maintains (at least approximately) the statistical distribution characteristics of particle distribution **D**. In particular embodiments, MOVE block 226 comprises a Markov chain Monte Carlo (MCMC) procedure, which may be implemented using a Metropolis-Hastings technique. Figure 12D shows a pseudocode procedure for implementing MOVE block 226 of method 220 according to a particular embodiment of the invention.

[0084] After MOVE block 226, the particles in distribution **E** are fed back to prediction update block 204 for another iteration.

Probability Density Reconstruction

[0085] While particle distributions represent probability distributions sufficiently well for use in particle filtering Bayesian estimation methods, particle distributions may be difficult to use for drawing conclusions about belief in the state variables (e.g. circadian phase ϕ) that they represent. Continuous PDFs may be better suited for extracting and communicating information. The invention may optionally comprise methods for reconstructing continuous PDFs from particle distributions.

[0086] In one particular embodiment of the invention, a kernel density based method is used to reconstruct continuous PDFs from particle distributions. The kernel density method involves replacing each particle with a continuous "kernel" function. Given a set of particles:

$$\sum_{i=1}^{N} \delta(x_i) \tag{25}$$

and a kernel function $w(x)$, an approximation of the continuous PDF is given by:

$$\hat{p}(x) = \sum_{i=1}^{N} w(x_i) \tag{26}$$

The kernel function $w(x)$ may be selected to be a Gaussian PDF (although other PDFs kernel functions may be used). An example of a Gaussian kernel replacement is

shown in Figures 13A, 13B and 13C, where Figure 13A shows the individual particles ($\delta(x_j)$), Figure 13B shows the individual kernel functions ($w(x_j)$) used to replace the particles ($\delta(x_j)$) and Figure 13C shows the superposition of the kernel functions ($w(x_j)$) according to equation (26).

[0087] Achieving accurate PDF reconstructions using kernel based techniques involves selecting two interrelated parameters: the shape of the kernel function; and the number of particles. The primary shape parameter of a kernel is its bandwidth (also referred to as its width). For Gaussian kernel functions, the standard deviation is considered the corresponding bandwidth parameter. Based on observations from known test case(s), it is known that the accuracy of a kernel based PDF reconstruction technique always increases with the number of particles. Accordingly, more particles are desirable subject to limits on computational resources. However, it may be shown that PDF reconstruction can diverge if the bandwith is selected to be too high or too low.

[0088] To address this challenge a class of optimization solutions referred to as Kernel Density Estimators (KDEs) have been developed for selecting kernel bandwidths based on minimization of the mean integrated squared error (MISE) for a given set of particles. In particular embodiments, a KDE method based on a dual-tree algorithm (A. Gray and Moore, "Very fast multivariate kernel density estimation using via computational geometry," in Proceedings of Joint Stat. Meeting, 2003.) and selected from a Matlab KDE toolbox (A. Ihler, "Kernel density estimation toolbox for MATLAB," http://www.ics.uci.edu/ ihler/code/kde.shtml, 2003) may be used here to implement KDE and to select the standard deviation of the Gaussian kernel functions. This KDE-based bandwidth selection technique is well described in the art and is not reproduced here.

Simulation Examples

[0089] The particle filter approach to circadian phase estimation (e.g. methods 200 and 220) in conjunction with the modified Kronauer-Jewett model 112A provide the capability for real-time tracking of a subject's circadian phase ϕ with Bayesian probability distributions. To explore the theoretical capabilities and limitations of this approach and to determine appropriate tuning parameters for the particle filter, the inventors have performed simulations for a series of scenarios with different particle filter parameter choices, light input assumptions, and noise models.

Simulation Scenario 1

[0090] A preliminary simulation scenario was designed to explore the tuning parameter selection of the number of particles and the level of process noise. A typical

light input scenario was used to test the performance of the particle filter with various combinations of the tuning parameters. As a typical scenario, the light input was set to a pattern representative of an individual consistently following a standard sleep schedule for seven days. Lights were turned off at midnight for an eight hour sleep episode and then turned on at 8:00 AM This simulation scenario also assumes a consistent light intensity of 600 Lux throughout the day.

[0091] Particle filter based Bayesian estimation method 200, 220 was tested by using a uniformly distributed initial particle distribution and observing the convergence after multiple simulation days. This test implies a case in which no *a priori* information is known about the individual's circadian phase ϕ and it is desired to estimate a PDF which indicates a degree of belief in the location of the circadian phase ϕ after a period of time. The time period of the simulation was selected to be one week. The expected result is that an entrainment effect will occur and the PDF representation of the phase ϕ will converge with a mean of $\phi=4$.

[0092] This simulation was run seven times with different numbers of particles and, in a first case, the simulation was run without process noise. The settings for simulation scenario 1 are shown in Table 3.

Table 3. Simulation 1 with no process noise Parameter Values

Parameter	Value						
No. Particles	12	24	48	72	240	480	960
Initial distribution	Uniform over [0,24]						
Process Noise, Q_ϕ	(negligible)						
Light levels							
Dark	0 Lux						
Bright	600 Lux						
Measurements	(none)						

A second set of simulations was run, repeating the choice of particle numbers from the first case, but this time with the phase state process noise set to a non-negligible value of $Q=3\times10^{-4}$. Since there was no quantitative data from which a process noise level can be selected, this value was chosen based on qualitative physical assumptions about variability inherent in the circadian pacemaker system. The settings for the second set of simulations are shown in Table 4.

- 33 -

Table 4. Simulation 1 with process noise Parameter Values

Parameter	Value						
No. Particles	12	24	48	72	240	480	960
Initial distribution	Uniform over [0,24]						
Process Noise, Q_ϕ	3×10^{-4}						
Light levels							
Dark	0 Lux						
Bright	600 Lux						
Measurements	(none)						

[0093] These two sets of simulations yield results from 14 different trials. Figure 14 illustrates the state variables A, ϕ, n for a single simulation with 24 particles and no process noise. With only twenty-four particles and negligible process noise, the second plot of Figure 14 illustrates the precise path of each phase particle during the simulation. It may be observed from the second Figure 14 plot, that the phase of the particles becomes further entrained to the timing of the sleep/wake schedule after each light exposure period and have a mean of approximately 4:00 AM as expected.

[0094] The scenario 1 simulation results were used to select a number of particles by examining the phase PDF of each simulation after the seven day period. The selection of an appropriate number of particles may be based on the number of particles above which increasing numbers of particles still converges to substantially the same distribution. Based on the scenario 1 simulations with process noise, it was observed that the phase PDFs using 240, 480 and 960 particles were substantially similar to one another. Accordingly, for a process noise of $Q=3 \times 10^{-4}$, it is desirable to select a number of particles $N>=240$ to achieve convergence to an accurate phase PDF. In the other simulations described herein, a default value of N=240 will was used to minimize computational complexity. The optimal number of particles may vary for different simulation scenarios (e.g. different levels of process noise). Choosing a high number of particles may improve accuracy of the results with no penalty except for computational resources.

Simulation Scenario 2

[0095] This simulation scenario further examines the predictions of entrainment to a fixed schedule and tests different noise models. This scenario simulated the case of an individual following a consistently timed eight hour sleep regimen (between 12:00AM and 8:00AM) for a duration of three weeks. The waking light levels were chosen to be typical of indoor bright light of 380 Lux. In a case in which no *a priori* information is

known about the individual's circadian phase ϕ, the final phase PDF indicates a degree of belief in the location of the circadian phase ϕ after the three weeks on this schedule. This analysis has a significant connection to a clinical scenario since a three-week monitoring period is typically used to ensure that subjects have a well entrained circadian phase prior to entering a laboratory study. The distribution of the final phase PDF will give an indication as to the strength of that assumption.

[0096] To illustrate the effects of noise parameters, three different simulations were conducted using the same baseline schedule. In the first case, no noise sources were included, in the second case, process noise was added to the phase state and in the third case, a further random variability was introduced to the light input. The light variability was introduced as a first Gaussian random variation in the timing of each light to dark transition with variance Q_t, and a second Gaussian random variation in the light level with variance Q_L. The parameters for each of the three simulations are set out in Table 5.

Table 5. Simulation 2 Parameter Values

Parameter	Value Case 2A		
No. Particles	240	240	240
Initial distribution	Uniform over [0,24]		
Process Noise, Q_ϕ	1×10^{-9}	3×10^{-4}	3×10^{-4}
Light levels			
Dark	0 Lux		
Bright	380 Lux		
Light Noise			
Q_t	0	0	2
Q_L	0	0	50
Measurements	(none)		

[0097] Figure 15 shows the phase PDF predicted over the course of the 21 day period for the simulation with no noise. At day 21, the maximum likelihood of the phase ϕ occurs around 4:00AM, which corresponds to the expected result for an individual synchronized to a regular sleep-wake cycle. When process noise is introduced in the second simulation of scenario 2, there is a broadening of the probability distribution which can be seen in Figure 16. Figure 17 shows the phase PDF for the third simulation of scenario 2, with additional variability in the light input. This third case shows a further widening of the phase PDF which represents additional uncertainty in the location of the circadian phase ϕ.

[0098] Another interesting observation can be made by comparing Figures 15, 16 and 17. With the introduction of process noise (i.e. Figure 16), the peak probability was reduced, but the mean was substantially unchanged. However, the introduction of light variability (Figure 17) had the interesting effect of skewing the mean of the phase PDF forward.

Simulation Scenario 3

[0099] A third simulation scenario was conducted to explore phase shifting properties of the circadian pacemaker model in response to a scenario where an individual makes an abrupt eight hour advance in their sleep/wake schedule, as can happen with transmeridian airplane travel for example. As shown experimentally (D. Boivin and F. James, Phase-dependent effect of room light exposure in a 5-h advance of the sleep-wake cycle: Implications for jet lag, Journal of Biological Rhythms, vol. 17:3, 266–267, June 2002.), and predicted by the Kronauer-Jewett model, the introduction of strong light pulses at appropriate circadian phases will increase the rate of adjustment to a shifted schedule. The greatest effect is achieved by introducing light near the nadir of the circadian phase (i.e. around ϕ=4:00h) when the light response is most sensitive, however the phase nadir is also the critical point at which phase shifts may occur in opposite directions on either side of the phase nadir. Therefore, by introducing light near the phase nadir there is a risk of causing a shift in the opposite direction to the one desired. With the Bayesian estimation particle filter methods 200, 220 we can test the probabilistic outcomes of phase shift direction. The light and sleep/wake patterns for the scenario 3 simulations are shown in Figure 18. A bright light pulse was chosen with a duration of five hours, starting at time 3:00 as shown in Figure 18. The simulation parameters for the scenario 3 simulation (shown in Table 6) are identical to those of the second case of simulation scenario 2, except that the initial condition is set to a known prior distribution that represents an individual well entrained to the initial schedule.

Table 6. Simulation 3 Parameter Values

Parameter	Value
No. Particles	240
Initial distribution	Gaussian $N(4.38, 1.3)$
Process Noise, Q_ϕ	3×10^{-4}
Light levels	
Dark	0 Lux
Typical	380 Lux
Bright	10000 Lux
Measurements	(none)

[0100] Figure 19 shows the phase PDFs for simulation scenario 3. It may be observed from Figure 19 that there is a split in the probability distribution after the first introduction of the light pulse. The optimal adjustment to the new schedule occurs on the phase trajectory which decreases to zero and then "wraps around" the 0h/24h boundary to stabilize at 22h by day twelve (ten days after the shift). The other phase trajectory, in which the phase increases from 4h toward 22h doesn't entrain to the new schedule until about day 23 (twenty-one days after the shift), which is twice as long. While the divergent shift behavior has been captured in the prior art Kronauer-Jewett model 112, the capability to analyze probabilistic scenarios in this manner has not been possible previously.

Simulation Scenario 4

[0101] Simulation scenario 4 incorporates physiological measurement feedback. The sleep/wake and light pattern used in simulation scenario 4 were the same as those applied in simulation scenario 3 (Figure 18) where the simulation predicted a bimodal phase PDF resulting from the introduction of bright light stimulus around the circadian phase nadir (i.e. around ϕ=4:00h). It will be appreciated that the bimodal phase PDF of simulation scenario 3 could lead to difficulty making phase prediction decisions, because the two phase PDF trajectories lead to two possible scenarios which are diametrically opposed in their physiological circadian effects. It was expected that incorporating physiological measurements into the simulation in simulation scenario 4 would enhance the phase prediction ability of the system, as a small set of measurements could resolve the ambiguity between two possible trajectories. Simulation scenario 4 involved selecting the phase trajectory in which phase of the individual advances (i.e. on the lower "wrap-around" trajectory of Figure 19). This selection was accomplished by adding two phase measurements at day 6 and

day 8 and using the assumption that the phase measurements have accurate means but relatively low measurement precision $\sigma^2=3$. The parameters of simulation scenario 4 are shown in Table 7.

Table 7. Simulation 4 Parameter Values

Parameter	Value
No. Particles	240
Initial distribution	Gaussian $N(4.38, 1.3)$
Process Noise, Q_ϕ	3×10^{-4}
Light levels	
Dark	0 Lux
Typical	380 Lux
Bright	10000 Lux
Measurements	$\theta(6d) = 1\pm3$
	$\theta(8d) = 22\pm3$

[0102] The phase PDF results of simulation scenario 4 are shown in Figure 20. Comparing the phase PDF trajectories of Figure 20 (simulation scenario 4) to those of Figure 19 (simulation scenario 3), it is apparent that the measurement information incorporated into scenario 4 has provided sufficient information to determine that the individual has a high probability of being on the lower ("wrap around) trajectory. Considering real world applications in ambulatory, non-laboratory settings, sensors will not have the same degree of precision as in controlled, laboratory environments. For such applications, the capability to integrate multiple somewhat noisy measurements in the manner of simulation scenario 4 will be advantageous.

Human Subject Example

[0103] The modified Kronauer-Jewett model 112A of the Bayesian particle filtering methods 200, 220 does not have any customized tuning parameters so it remains a fixed component. However, different types of optional physiological inputs 104 may be provided to the estimation system 100. As discussed above, physiological inputs 104 typically require physiological sensors (e.g. sensors 120 of Figure 8). Such sensors may be invasive or non-invasive and may be ambulatory (i.e. allowing the subject freedom of movement) or non-ambulatory (restricting subject movement). Examples of invasively measurable physiological parameters include, without limitation, CBT (which may be measured rectally), salivary melatonin assays and salivary cortisol assays. Examples of non-invasively measurable physiological parameters include, without limitation, body temperature (which may be measured by

a cerebral temperature sensor) and heart rate (which may be measured by ECG in a Lifeshirt™, for example).

[0104] As discussed above, circadian phase markers for the temperatures and hormone levels may be determined (e.g. in phase estimators 124 of Figure 8) with direct application of a Fourier fit combined with feature detection (e.g. maxima or minima detection) location and suitable marker-to-phase conversion (e.g. time shift). As discussed above, measured temperature markers may be determined with a second-order or third-order Fourier fit using a minimum point feature and may be appropriately converted (e.g. by 0.8h time shift) to correlate to circadian phase ϕ. With melatonin and cortisol, a second and/or third order Fourier fit using a maximum point feature may be selected. However, there are a variety of different phase analysis options which may be selected to convert melatonin and cortisol markers to correlate to circadian phase ϕ (E. Klerman, H. Gershengorn, J. Duffy, and R. Kronauer, Comparisons of the variability of three markers of the human circadian pacemaker, Journal of Biological Rhythms, 17: 2, 181–193, 2002). It has been shown that the melatonin maxima occurs approximately 2.3 hours before CBT minima. Consequently, conversion of melatonin markers (maxima) to circadian phase ϕ may involve a time shift of $\tau_{MEL}=2.3h-0.8h=1.5h$. The cortisol maxima occurs approximately 2.2 hours after CBT minima and may therefore be converted to circadian phase ϕ by a time shift of $\tau_{CORT}=-2.2h-0.8h=-3.0h$.

[0105] These physiological measurements were incorporated into an experimental phase prediction system 300. A schematic illustration of this experimental phase prediction system 300 is shown in Figure 21. A motivating objective involves determination of phase estimates based on non-invasive and ambulatory measurements, so a comparison was made between the invasive and noninvasive physiological measurements. In this experiment, the available information for the subject which can be applied to the phase estimation system includes the sleep history prior to the subject entering the lab, the known light exposure during the experiment and noninvasive physiological data collected when the subject is ambulatory.

[0106] A first data set was generated based only on the light exposure during the experiment – i.e. where the subject's circadian phase prior to the experiment was considered completely unknown. The resulting phase PDFs are shown in Figure 22A. A second data set was generated by adding knowledge of the subject's sleep history which was kept in a log prior to the experiment. A number of assumptions are made in this sleep history analysis since the exact light levels were not known and uncertainty surrounding the accuracy of the sleep log was unknown. Light was assumed to be constant at 380 Lux for the duration of waking. The resulting phase PDFs for the second data set are shown in Figure 23A. As can be seen by comparing Figures 22A

and 23A, the second data set which incorporates sleep history, results in narrower phase PDFs, reflecting the additional information.

[0107] After 59 hours, a constant routine scenario was used in a laboratory setting. Monitoring from all ambulatory sensors was maintained through the constant routine with the addition of the cerebral temperature sensor, melatonin assay and cortisol assay. After the deriving the phase markers of the various physiological inputs, the PDFs of the phase markers were converted to the calibrated phase domain. It was observed that the temperature and melatonin markers predict relatively consistent phase information, but that the cortisol phase prediction was slightly different than that predicted by the other physiological markers. The PDF of the core body temperature phase marker is calculated at the end of the constant routine and corresponds to estimate of circadian phase at a particular point in time as shown in Figure 23B.

[0108] Figure 24 shows the phase PDFs generated using CBT measurement alone (without Bayesian particle filter estimation), the final phase PDF (i.e. at the conclusion of the experiment) generated using model predictions alone (without CBT phase measurement), and the final phase PDF generated using the combination of model predictions and the CBT phase estimate. The combined estimate provides a narrower PDF than either the prediction or measurement alone.

Applications

[0109] The methods and systems described herein find useful applications in a variety of settings. Two general areas include monitoring circadian physiology for alertness and safety in workplace settings and monitoring circadian physiology to assist chronotherapeutic treatments. Circadian rhythms significantly affect human health and safety, and there are a number of applications where knowledge of an individual's circadian phase would prove useful in mitigating risks or delivering therapeutic treatment.

Alertness and Safety

[0110] Individuals required to perform critical tasks when their circadian pacemaker is coordinating the body's metabolic and endocrine systems for sleep experience significant impairments in performance which increases the risk of accidents. Many industrial workplace scenarios involve tasks demanding a high degree of alertness and reliability in addition to requiring workers to operate on irregular or shifting schedules. As a result of schedule variations, individuals experience reduced levels of alertness and cognitive performance due to both sleep loss and circadian rhythm desynchrony. The associated risk of accidents is a concern in operational settings,

such as, by way of non-limiting example, transportation, health care delivery and emergency response. Accidents at the Chernobyl and Three Mile Island nuclear power plants, the NASA Challenger disaster, and the Exxon oil spill in Valdez, Alaska may all be partially attributable to decrements in performance due to the effects of circadian phase and length of time awake.

[0111] Strategies to mitigate the adverse effects of circadian phase desynchrony and sleep loss in shift work environments include education programs, the design of shift work rotation schedules, and the use of light exposure to shift the endogenous circadian pacemaker. Strategies to reduce the effects of jet lag travel also include the specific timing of light exposure to accelerate adaptation to a new time zone. Implementing reliable means to shift an individual's circadian pacemaker however requires accurate knowledge of the individual's circadian phase, which is not currently possible outside of the laboratory.

Medical Treatment

[0112] The traditional medical concept of "homeostasis", that the human body maintains a constant internal state, is giving way to the recognition of continuous time-varying fluctuations. Applying this information, medical treatments are being developed to deliver treatment at not only the right location but at the right time. For instance, the cycles present in human circadian physiological systems bring about predictable changes in the body's tolerance to anticancer agents and a tumor's responsiveness to them. Indeed, it has been shown that the tolerability and the efficacy of chemotherapeutic drugs can vary by 50% or more as a function of dosing time in mice or rats. Circadian-modulation of continuous drug delivery systems for chemotherapy patients has been demonstrated in randomized, multi-centre trials to have enhanced tumor response and increased survival rates.

[0113] When administering chronomodulated therapy, it is desirable to synchronize treatment timing to the endogenous circadian phase of the individual being treated. In recent trials, physical activity patterns measured with wrist worn accelerometers, have been used to infer sleep/wake schedules and thus circadian phase. While the activity measures can lead to a general estimate of circadian phase if an individual has maintained a consistent schedule, there are known variabilities between individuals and considerable uncertainty in the method. Enhanced methods of accurately monitoring circadian phase translate to increased efficacy of chronotherapies.

[0114] Certain implementations of the invention comprise computer processors which execute software instructions which cause the processors to perform methods of the invention. For example, one or more processors in a phase estimation system may implement data processing steps in the methods described herein by executing

software instructions retrieved from a program memory accessible to the processors. The invention may also be provided in the form of a program product. The program product may comprise any medium which carries a set of computer-readable instructions which, when executed by a data processor, cause the data processor to execute a method of the invention. Program products according to the invention may be in any of a wide variety of forms. The program product may comprise, for example, physical media such as magnetic data storage media including floppy diskettes, hard disk drives, optical data storage media including CD ROMs and DVDs, electronic data storage media including ROMs, flash RAM, or the like. The instructions may be present on the program product in encrypted and/or compressed formats.

[0115] Where a component (e.g. a software module, processor, assembly, device, circuit, etc.) is referred to above, unless otherwise indicated, reference to that component (including a reference to a "means") should be interpreted as including as equivalents of that component any component which performs the function of the described component (i.e. that is functionally equivalent), including components which are not structurally equivalent to the disclosed structure which performs the function in the illustrated exemplary embodiments of the invention.

[0116] As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. For example:

- One or more measured circadian phase estimate inputs ϕ may be received from external systems, rather than being calculated from a physiological input 104.

- Phase estimate outputs of the circadian state estimation system may be made in real-time, may be predicted into the future, or may be calculated for historical periods.

- Light input 102 may be measured directly from light sensor, or may be estimated based on other known or assumed environmental conditions. As a non limiting example light input could be estimated from actigraphy sensors from which sleep (dark) and wake (bright) periods are inferred.

- Multiple methods for implementing Bayesian equations in the prediction updator 116 and the measurement updator 118 may be used, and may include alternate particle filter operations, or other non particle filter methods.

- Sensors 102, physiological phase estimators 114, and the prediction updator 116 and measurement updator 118 may be physically separate. As a nonlimiting example, remote sensors may be distributed on individuals and

sensor information transmitted to a physiological phase estimators, and prediction and measurement updators on a computational system.

- 43 -

CLAIMS

WHAT IS CLAIMED IS:

1.   A method for predicting a circadian state of an individual, the method
comprising:

        providing a state-space model representative of the response of the
circadian state to light stimulus, the model comprising at least one state
variable representative of a probability distribution function (PDF) of a phase
offset of the circadian state of the individual; and

        using the model to estimate an updated PDF of the phase offset,
wherein using the model to estimate the updated PDF of the phase offset
comprises performing a Bayesian estimation process commencing with an
initial PDF of the phase offset and iterating toward the updated PDF of the
phase offset.

2.   A method according to claim 1 wherein performing the Bayesian estimation
processing comprises:

        converting the initial PDF into an initial set of discrete particles
representative of the initial PDF, each of the initial particles comprising a
point;

        iteratively propagating the initial set of discrete particles through the
Bayesian estimation process to obtain an updated set of discrete particles; and

        converting the updated set of discrete particles into the updated PDF of
the phase offset.

3.   A method according to claim 2 wherein iteratively propagating the initial set
of discrete particles through the Bayesian estimation process comprises, for
each iteration:

        obtaining a first set of discrete particles, the first set of discrete particle
comprising one of: the initial set of discrete particles or an output set of
discrete particles from a previous iteration;

        performing a prediction update operation on the first set of discrete
particles, the prediction update operation based on application of a state
transition equation of the state-space model to the first set of discrete particles
and the prediction update operation outputting a second set of discrete
particles.

- 44 -

4.   A method according to claim 3 wherein interatively propagating the initial set
of discrete particles through the Bayesian estimation process comprises, for
each iteration in which there is a new measurement: performing measurement
update operation on the second set of discrete particles, the measurement
update operation based on application of a measurement PDF that expresses
the likelihood of the new measurement to the second set of discrete particles to
obtain a third set of discrete particles; and outputting the third set of discrete
particles.

5.   A method according to claim 3 wherein iteratively propagating the initial set
of discrete particles through the Bayesian estimation process comprises, for
each iteration in which there is a new measurement:
        performing an importance weight operation on the second set of
discrete particles, the importance weight operation based on application of a
measurement PDF that expresses the likelihood of the new measurement to the
second set of discrete particles to obtain a third set of discrete particles,
wherein the third set of discrete particles are each assigned a weight based at
least in part on the measurement PDF;
        performing a resampling operation on the third set of discrete particles
to obtain a fourth set of particles, the resampling operation comprising:
                removing individual ones of the third set of discrete particles if
                the weights of the individual ones of the third set of discrete particles
                are below a first threshold; and
                dividing individual ones of the third set of discrete particles
                into multiple particles if the individual ones of the third set of discrete
                particles are above a second threshold;
        performing a move operation on the fourth set of particles to obtain a
fifth set of discrete particles, the move operation redistributing the fourth set of
particles; and
                outputting the fifth set of discrete particles.

6.   A method according to claim 5 wherein performing the resampling operation
comprises ensuring that the fourth set of particles incorporates at least
approximately the same statistical information as the third set of discrete
particles.

7.   A method according to any one of claims 5 to 6 wherein performing the move
operation comprises ensuring that the fifth set of discrete particles incorporates

SUBSTITUTE SHEET (RULE 26)

- 45 -

at least approximately the same statistical information as the fourth set of particles.

8. A method according to any one of claims 5 to 7 wherein performing the move operation comprises Markov chain Monte Carlo (MCMC) procedure.

9. A method according to claim 8 wherein the Markov chain Monte Carlo (MCMC) procedure comprises using a Metropolis-Hastings technique.

10. A method according to any one of claims 1 to 9 comprising obtaining one or more physiological inputs related to the phase offset of the circadian state of the individual and using the one or more physiological inputs in the Bayesian estimation process to refine the updated PDF of the phase offset.

11. A method according to claim 10 wherein obtaining the one or more physiological inputs comprises measuring the physiological inputs using one or more corresponding sensors.

12. A method according to any one of claims 10 to 11 wherein the one or more physiological inputs comprise core body temperature (CBT).

13. A method according to any one of claims 10 to 12 wherein the one or more physiological inputs comprise one or more of: cortisol level and melatonin level.

14. A method according to any one of claims 10 to 13 wherein the one or more physiological inputs comprise one or more of: a rate of cell proliferation, an input related to a cardiac regulatory system of the individual, an input related to the chemoreceptive respiratory feedback system of the individual and an input related to the cognitive performance of the individual.

15. A method according to any one of claims 10 to 14 wherein using the one or more physiological inputs in the Bayesian estimation process to refine the updated PDF of the phase offset comprises, for each physiological input:
        identifying a feature within the physiological input, the identified feature related to the phase offset;
        obtaining a physiological feature PDF representing the likelihood of the identified feature; and

SUBSTITUTE SHEET (RULE 26)

converting the physiological feature PDF into a phase offset domain.

16. A method according to claim 15 wherein, for each physiological input, identifying the feature within the physiological input comprises fitting a curve to measured input data and identifying the feature in the fitted curve.

17. A method according to claim 16 wherein the fitted curve comprises a Fourier series.

18. A method according to any one of claims 16 and 17 wherein the identified feature comprises one or more of: a minimum of the fitted curve; a maximum of the fitted curve; a point where the curve crosses a threshold; and a region where the curve is located on one side of a threshold.

19. A method according to any one of claims 16 to 18 wherein, for each physiological input, the physiological feature PDF reflects a degree of certainty in the fitted curve.

20. A method according to any one of claims 16 to 19 wherein, for each physiological input, the physiological feature PDF reflects a degree of certainty in the identified feature.

21. A method according to any one of claims 15 to 20 wherein converting the physiological feature PDF into the phase offset domain comprises:
         identifying a feature time at which the identified feature occurs; and
         shifting the feature time within the time domain.

22. A method according to any one of claims 15 to 21 wherein converting the physiological feature PDF into the phase offset domain comprises:
         identifying a feature-time PDF which reflects a degree of confidence as to the time at which the identified feature occurs; and
         shifting the feature-time PDF within the time domain.

23. A method according to any one of claims 1 to 22 wherein performing the Bayesian estimation process comprises incorporating process noise into the state-space model.

- 47 -

24.   A method according to claim 23 wherein the process noise is additive, such that it may be added to a state transition equation of the state-space model.

25.   A method according to any one of claims 23 and 24 wherein the process noise comprises at least one of: a Gaussian PDF and a uniform PDF.

26.   A method according to any one of claims 1 to 25 wherein performing the Bayesian estimation process comprises incorporating measurement noise into the state-space model.

27.   A method according to claim 26 wherein the measurement noise is additive, such that it may be added to a measurement equation of the state-space model.

28.   A method according to any one of claims 26 and 27 wherein the measurement noise comprises at least one of: a Gaussian PDF and a uniform PDF.

29.   A method according to any one of claims 1 to 28 wherein the providing the state-space model representative of the response of the circadian state to light stimulus comprises providing a model which accommodates statistical uncertainty in the light stimulus.

30.   A method according to claim 29 wherein providing the model which accommodates statistical uncertainty in the light stimulus comprises modeling one or more times corresponding to changes in light stimulus using one or more corresponding light-time PDFs representative of the one or more times.

31.   A method according to claim 30 wherein the one or more corresponding light-time PDFs comprise at least one of: a Gaussian PDF and a uniform PDF.

32.   A method according to any one of claims 29 to 31 wherein providing the model which accommodates statistical uncertainty in the light stimulus comprises modeling one or more levels of light stimulus intensity using one or more corresponding light-level PDFs representative of the one or more levels.

33.   A method according to claim 32 wherein the one or more corresponding light-level PDFs comprise at least one of: a Gaussian PDF and a uniform PDF.

- 48 -

34.   A system for predicting a circadian state of an individual, the system
        comprising a processor configured to: provide a state-space model
        representative of the response of the circadian state to light stimulus, the
        model comprising at least one state variable representative of a probability
        distribution function (PDF) of a phase offset of the circadian state of the
        individual; and use the model to estimate an updated PDF of the phase offset,
        wherein using the model to estimate the updated PDF of the phase offset
        comprises performing a Bayesian estimation process commencing with an
        initial PDF of the phase offset and iterating toward the updated PDF of the
        phase offset.

35.   A system according to claim 34 comprising any of the features of claims 1 to
        33.

36.   A system according to claim 34 comprising components configured to perform
        operations incorporating any of the features of claims 1 to 33.

37.   A system according to claim 34 wherein the processor is configured to
        perform operations incorporating any of the features of claims 1 to 33.

38.   A computer program product comprising computer-readable instructions,
        which when executed by a suitably configured processor, cause the processor
        to perform any of the methods of claims 1 to 33.

39.   Methods incorporating any one or more features, combinations of feature or
        subcombinations of feature described herein.

40.   Systems incorporating any one or more features, combinations of features or
        subcombinations of features described herein.

41.   Computer program products comprising computer-readable instructions,
        which when executed by a suitably configured processor, cause the processor
        to perform a method incorporating any one or more features, combinations of
        feature or subcombinations of feature described herein.
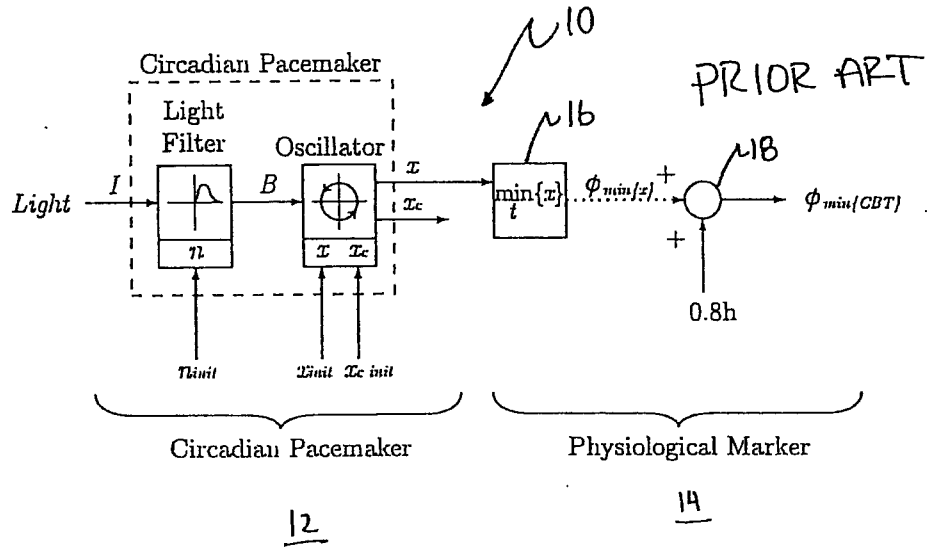
FIGURE 1
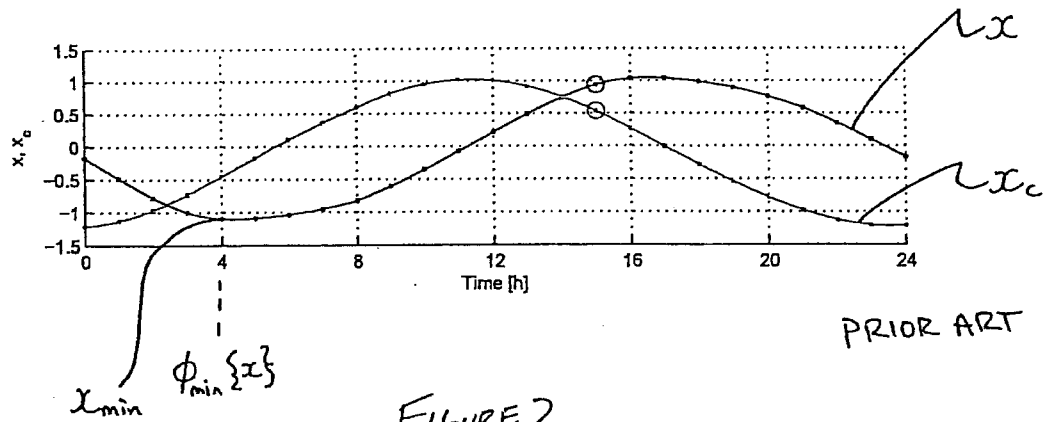
FIGURE 2

FIGURE 3

FIGURE 8

Circadian Pacemaker

∠ 112, 112A

Light Filter

Oscillator

Light ⟶ I ⟶ [n] ⟶ B ⟶ [x xc] ⟶ x / xc ⟶ T ⟶ φ / A

x xc

xinit   xc init

T⁻¹

ninit   φinit Ainit
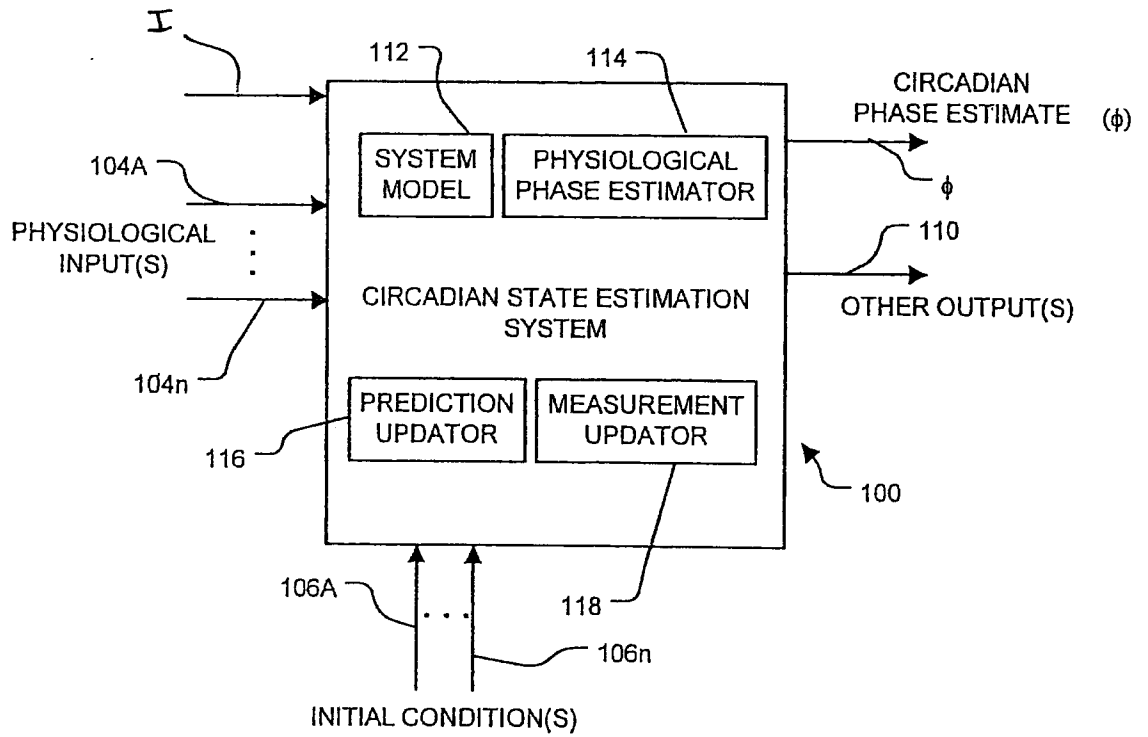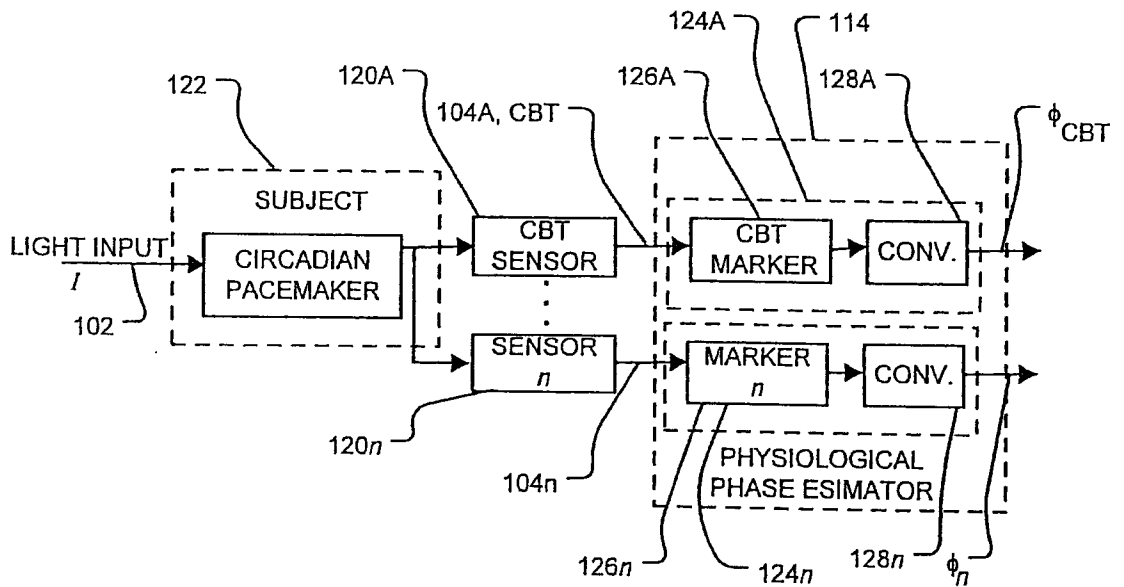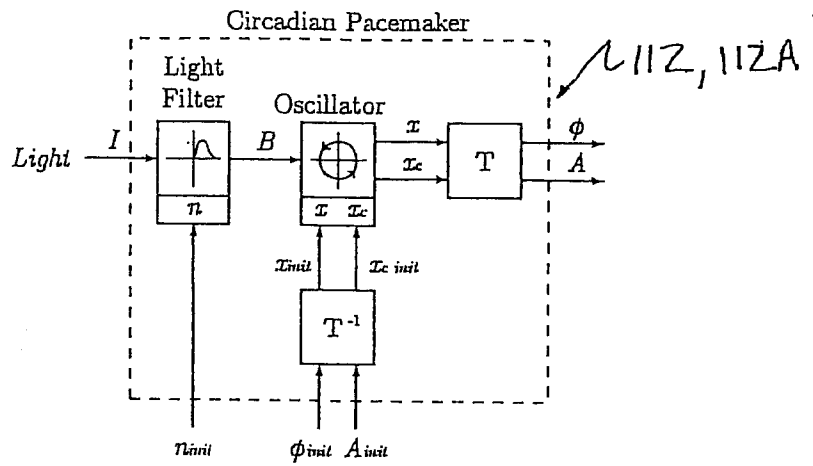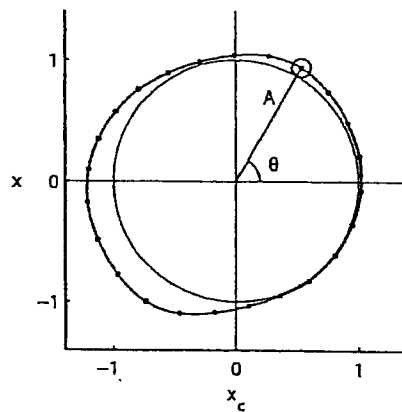
FIGURE 4

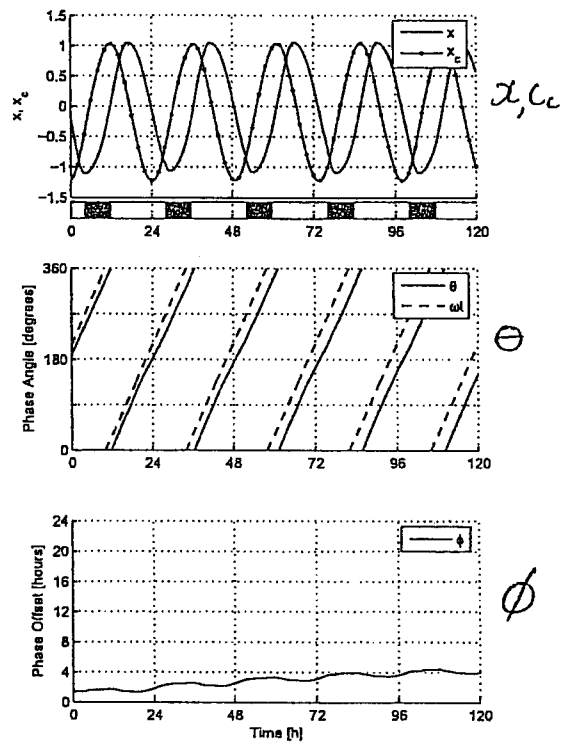FIGURE 5

CONSTANT PHASE OFFSET
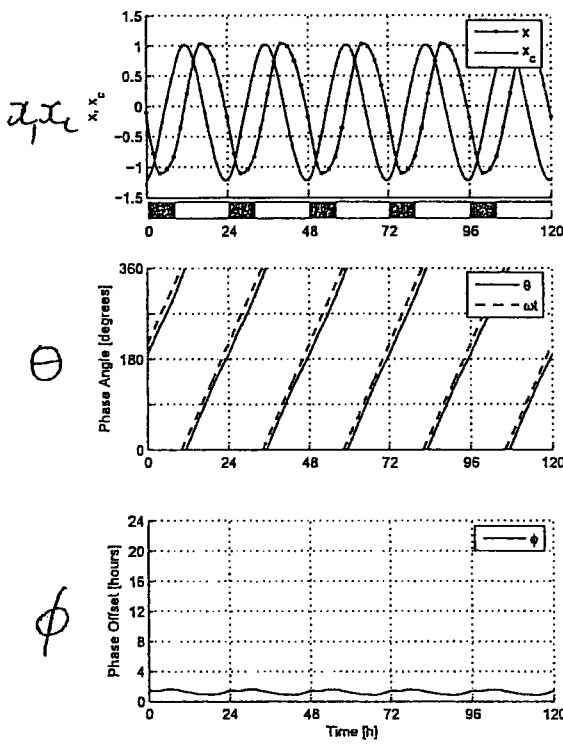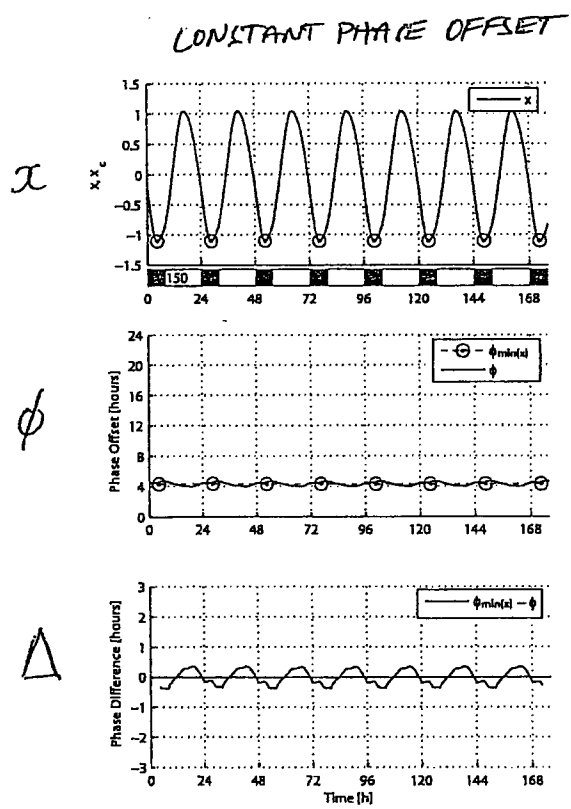
CHANGE IN PHASE OFFSET

FIGURE 6A

FIGURE 6B

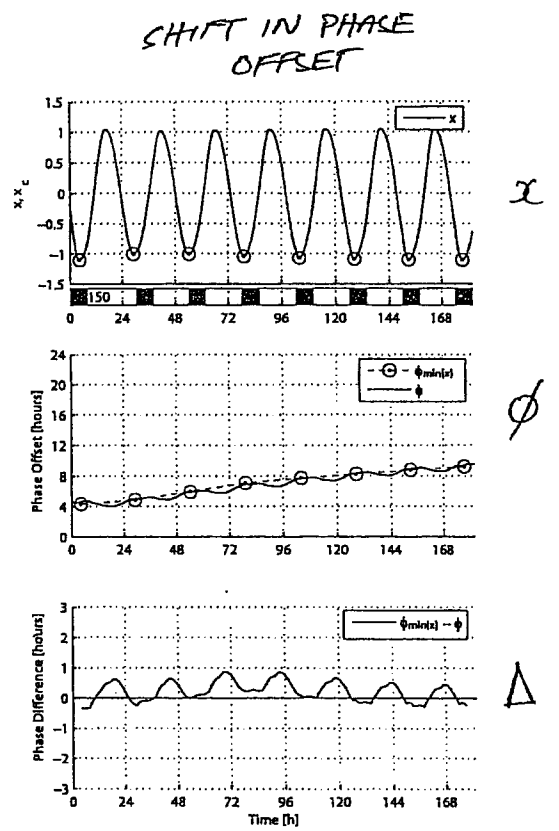FIGURE 7A   FIGURE 7B
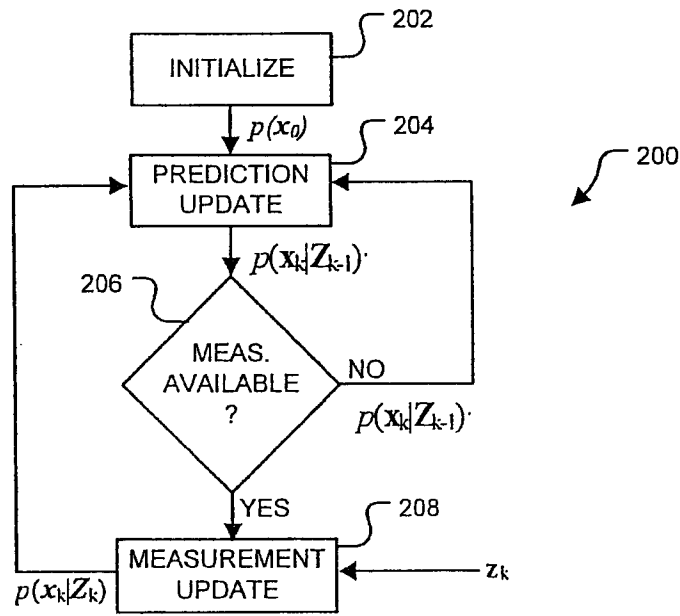
FIGURE 9
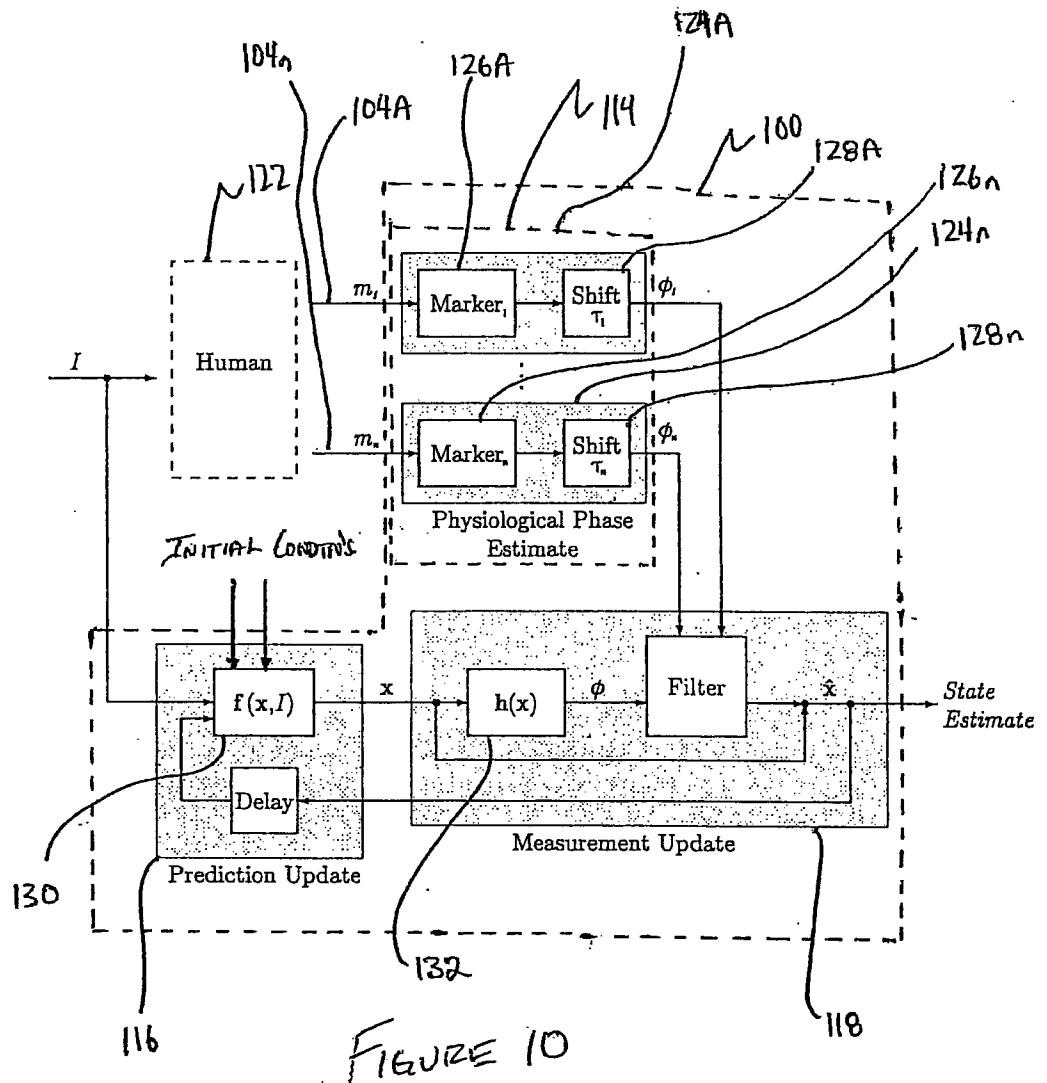
FIGURE 10
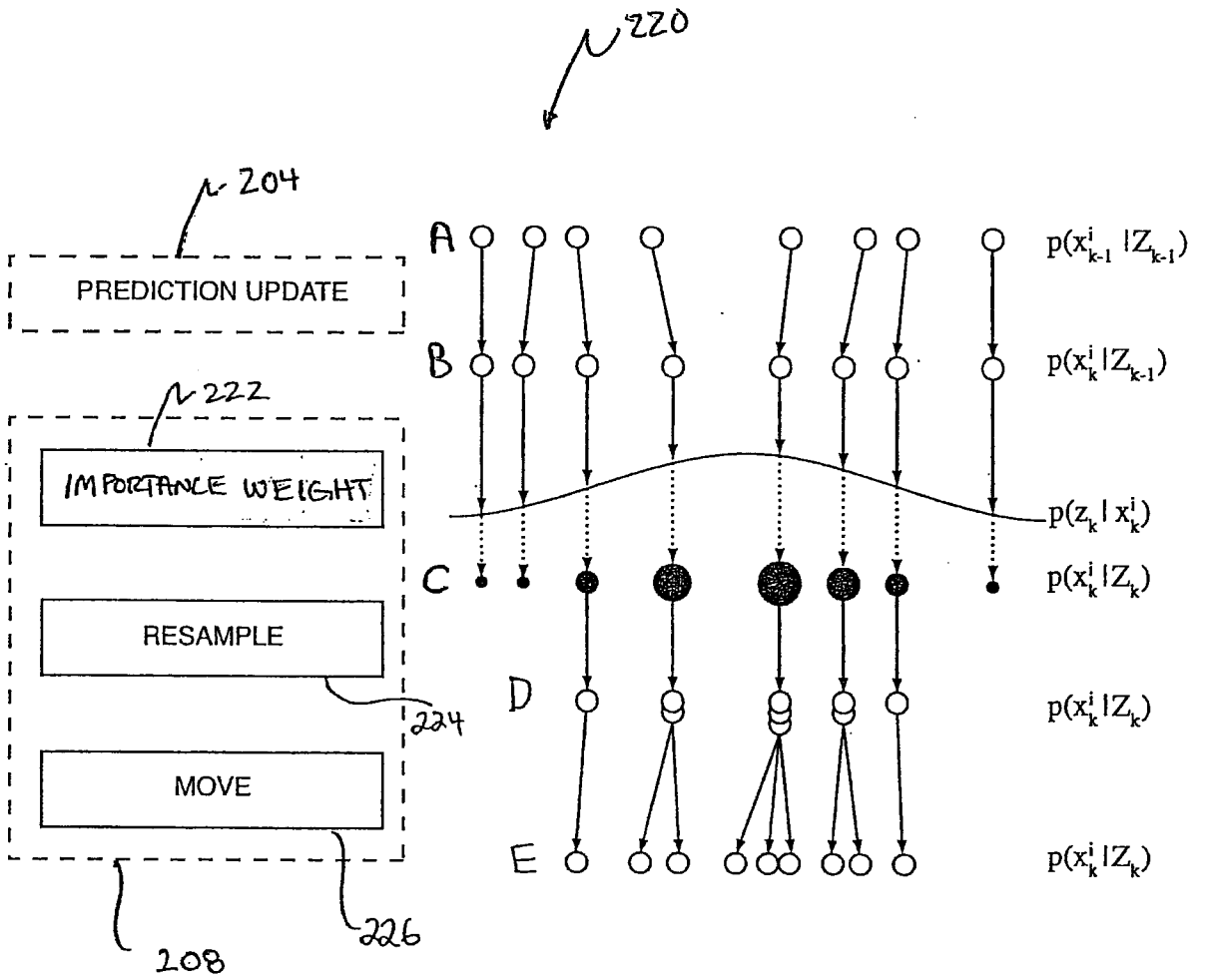
FIGURE 11

PREDICTION UPDATE PROCEDURE (BLOCK 204)

Algorithm 2 Prediction Update

1: **procedure** $[x_k^i]$ = INCREMENT($x_{k-1}^i, u_{k-1}, z_k, Q_k, R_k$)
2:     $H = \nabla h(x_{k_1})$
3:     $S = HQ_kH' + R_k$
4:     $\Sigma = Q_k - Q_kH'S^{-1}HQ_k$
5:     **for** $i = 1 : N$ **do**
6:         $\bar{x}_k^i = f(x_{k-1}^i, u_{k-1})$ ▷ prediction update
7:         $\bar{z}_{k-1}^i = h(\bar{x}_k^i, u_{k-1})$
8:         $\hat{x}_k^i = \bar{x}_k^i + \Sigma H'R_k^{-1}\text{MODMINUS}(z_k, \bar{z}_{k-1}^i, 24)$ ▷ measurement update
9:         Draw $x_k^i \sim \mathcal{U}(\hat{x}_k^i, \text{diag}\Sigma)$ ▷ draw x_k^i from $p(x_k|x_{k-1}^i, z_k)$
10:       $x_k^i(2) = \text{mod}(x_k^i(2), 24)$ ▷ keep phase within [0, 24)
11:     **end for**
12: **end procedure**

FIGURE 12A

IMPORTANCE WEIGHT PROCEDURE (BLOCK 222)

Algorithm 3 Measurement Update

1: **procedure** $[w_k^i]$ = IMPORTANCEWEIGHT(x_k^i, z_k, Q_k, R_k)
2:     $S = HQ_kH' + R_k$
3:     **for** $i = 1 : N$ **do**
4:         $\hat{z}_k^i = h(x_k^i, u_k)$
5:         $d_\phi = \text{MODMINUS}(z_k, \hat{z}_k^i, 24)$ ▷ phase difference using modulo
6:         $w_k^i = \mathcal{N}(d_\phi; 0, S(2,2))$ ▷ set particle weight to $p(z_k|x_k^i)$
7:     **end for**
8:     **for** $i = 1 : N$ **do**
9:         $w_k^i = w_k^i/\Sigma_{i=1}^N w_k^i$ ▷ normalize the weights
10:     **end for**
11: **end procedure**

FIGURE 12B

RESAMPLE PROCEDURE (BLOCK 224)

Algorithm 4 Systematic Resampling

1: **procedure** $[x_k^i, w_k^i] = \text{RESAMPLE}(x_k^i, w_k^i)$
2:    $j = 1$
3:    $C = N^{-1}$
4:    $CSW = 0$
5:    **while** $C < 1$ **do**
6:        **if** $CSW > C$ **then**
7:            $C = C + N^{-1}$
8:        **else**
9:            select i randomly from $[j, N]$
10:            $CSW = CSW + w_k^i$ ▷ increment cumulative sum of weights
11:            $x_k^i = x_k^j$ ▷ swap new particle
12:            $j = j + 1$
13:        **end if**
14:    **end while**
15:    **for** $i = 1 : N$ **do**
16:        $w_k^i = N^{-1}$ ▷ set weights to uniform values
17:    **end for**
18: **end procedure**

FIGURE 12C

MARKOV CHAIN MONTE CARLO MOVE (BLOCK 226)

Algorithm 5 Markov chain Monte Carlo Move

1: **procedure** $[x_k^i] = \text{MCMC-MOVE}(x_k^i, u_k, Q_k, R_k)$
2:    $S = HQ_k H' + R_k$
3:    **for** $i = 1 : N$ **do**
4:        $\hat{z} = h(x_k^i, u_k)$
5:        $d_\phi = \text{MODMINUS}(z_k, \hat{z}_k^i, 24)$
6:        $L^i = \mathcal{N}(d_\phi; 0, S)$ ▷ likelihood of current particle $p(z_k | x_k^i)$

7:        draw $\tilde{x}_k^i \sim \mathcal{U}(f(x_{k-1}^i, u_k), Q_k)$ ▷ generate a new random proposal
8:        $\hat{z} = h(\tilde{x}_k^i, u_k)$
9:        $d_{\tilde{\phi}} = \text{MODMINUS}(z_k, \hat{z}_k^i, 24)$
10:        $\tilde{L}^i = \mathcal{N}(d_{\tilde{\phi}}; 0, S)$ ▷ likelihood of proposed particle $p(z_k | \tilde{x}_k^i)$

11:        $P_a = \min(1, L^i / \tilde{L}^i)$ ▷ probability of acceptance of new particle
12:        draw $r \sim [0, 1]$ ▷ random number from 0 to 1
13:        **if** $P_a \geq r$ **then**
14:            $x_k^i = \tilde{x}_k^i$ ▷ replace x with new proposal
15:        **end if**

16:    **end for**
17: **end procedure**

FIGURE 12D

$\delta(x_i)$

$\omega(x_i)$

$\sum \omega(x_i)$

FIGURE 13A   FIGURE 13B   FIGURE 13C
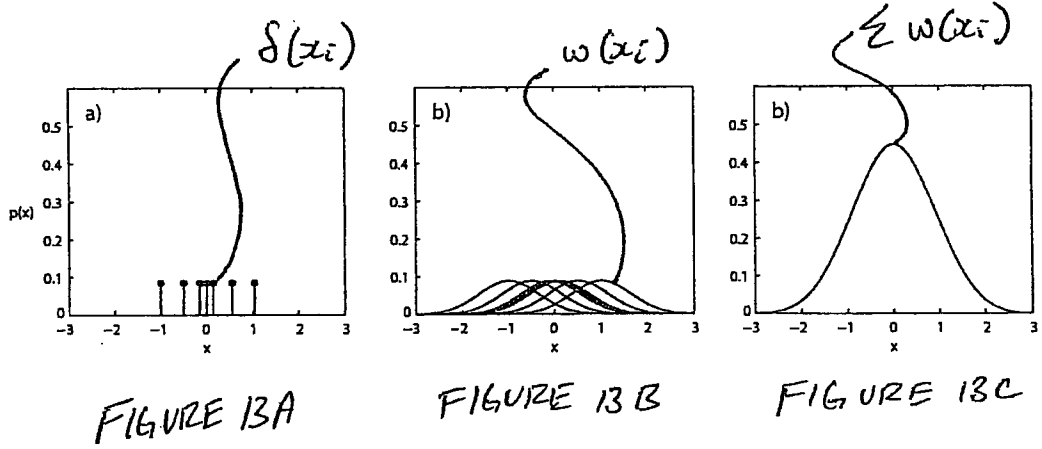
SIMULATION SCENARIO 1 - 24 FILTER PARTICLES

A

ϕ

n
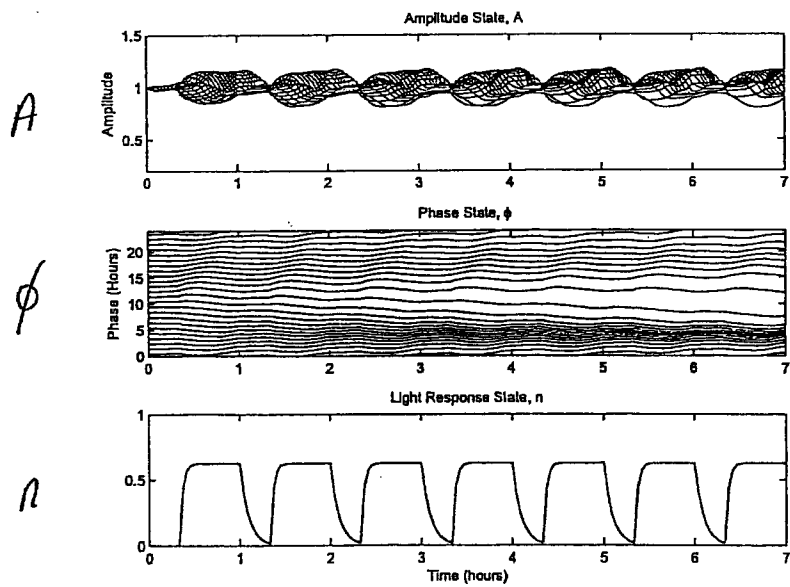
FIGURE 14

FIGURE 15

FIGURE 16

SIMULATION SCENARIO 2
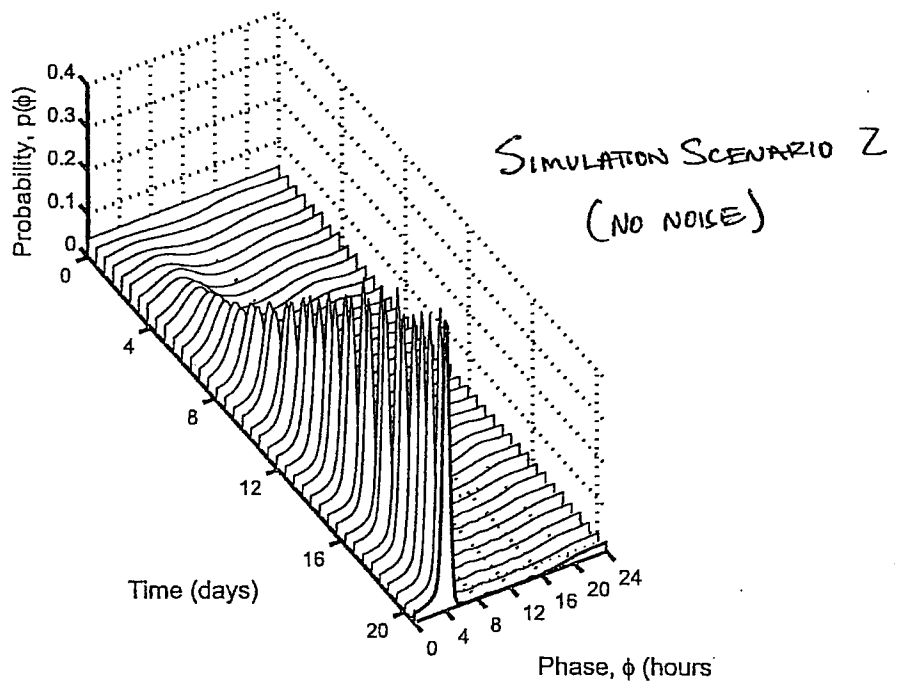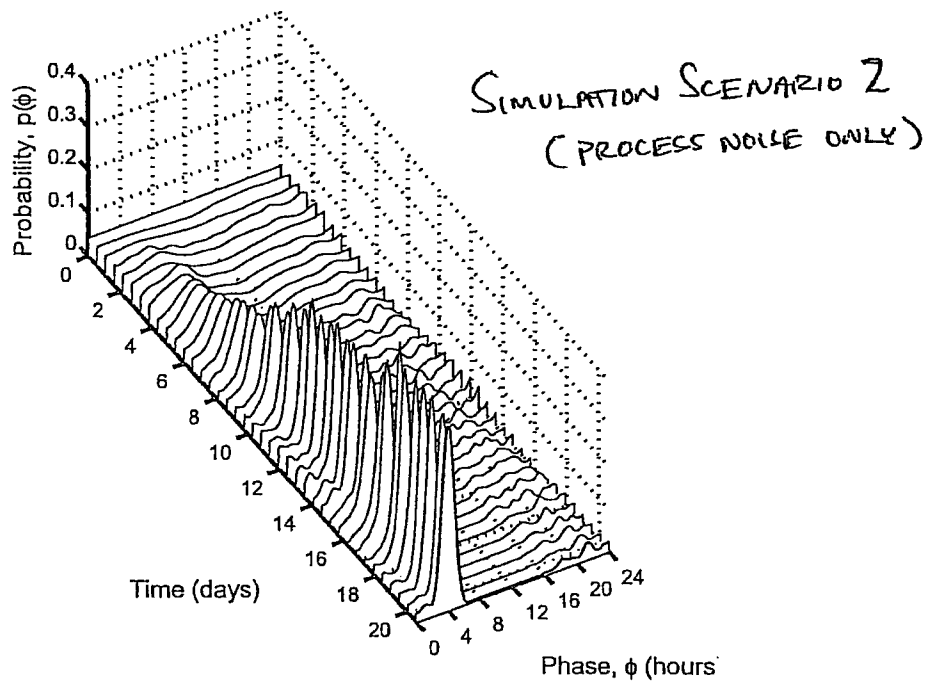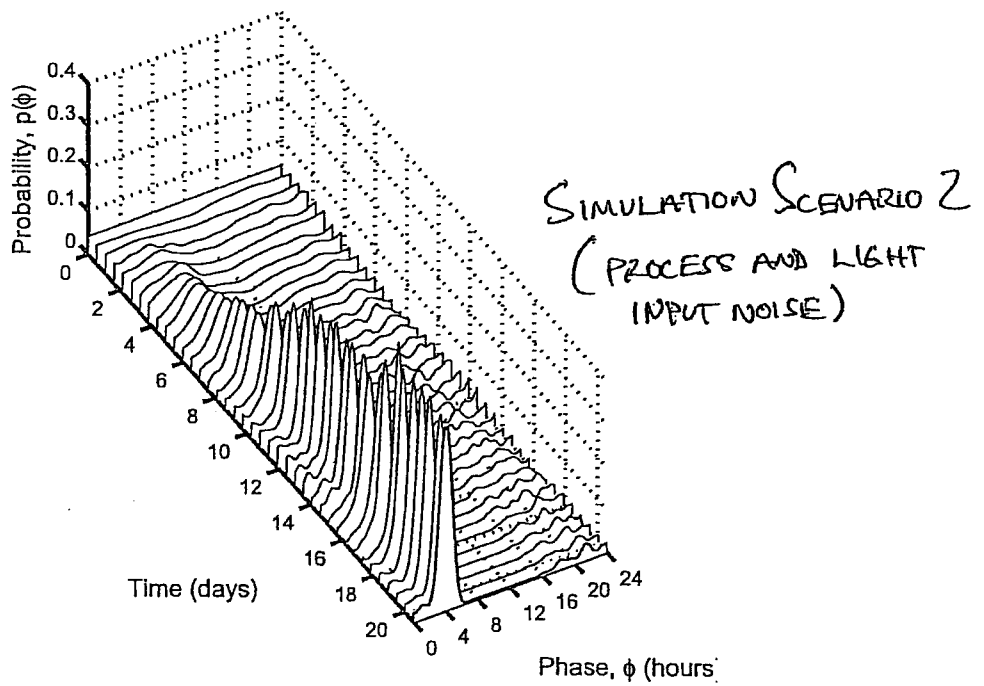(PROCESS AND LIGHT
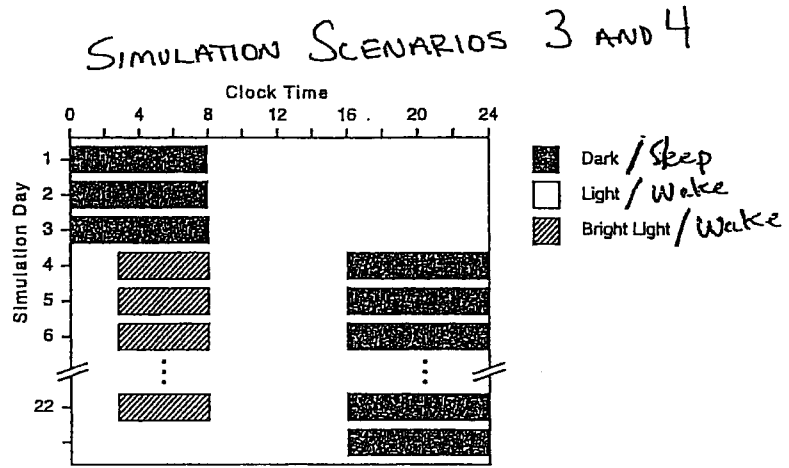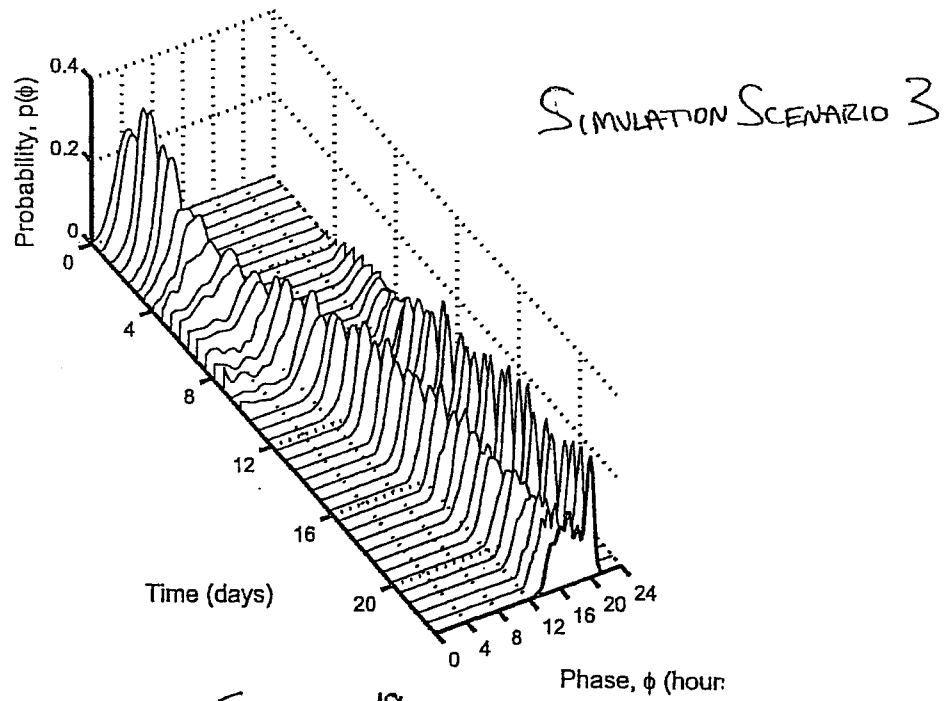INPUT NOISE)

FIGURE 17

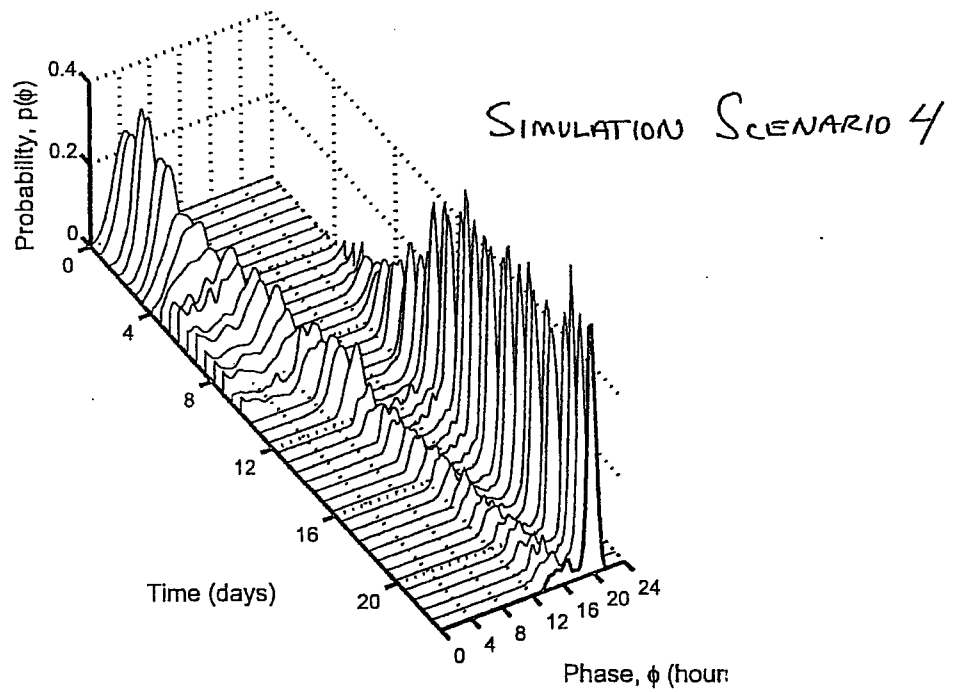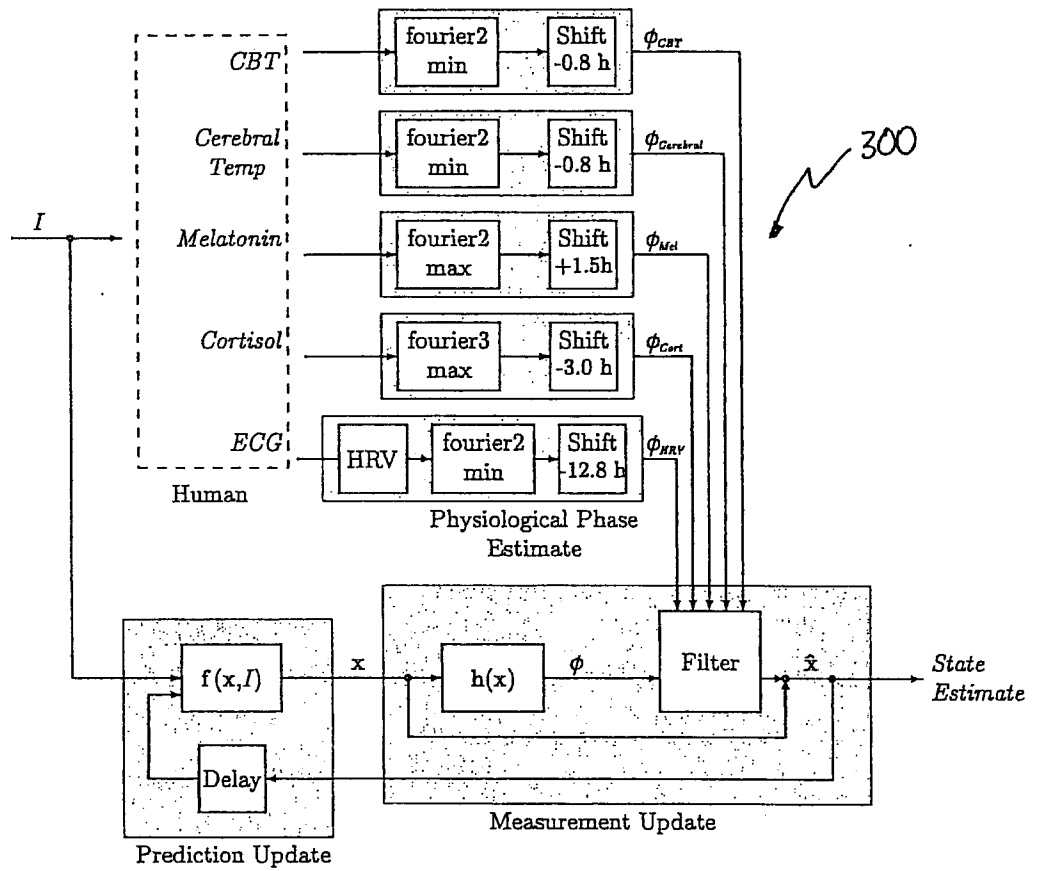SIMULATION SCENARIOS 3 AND 4

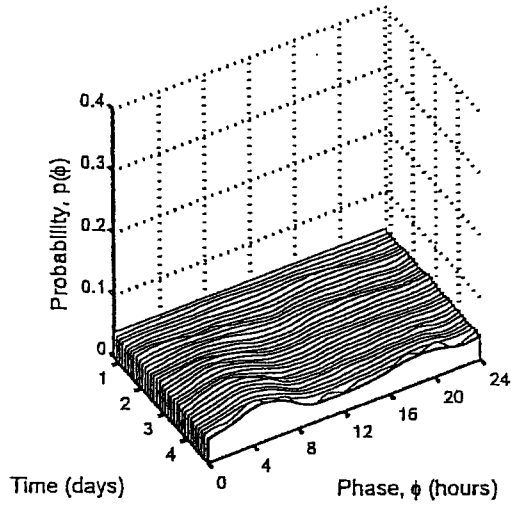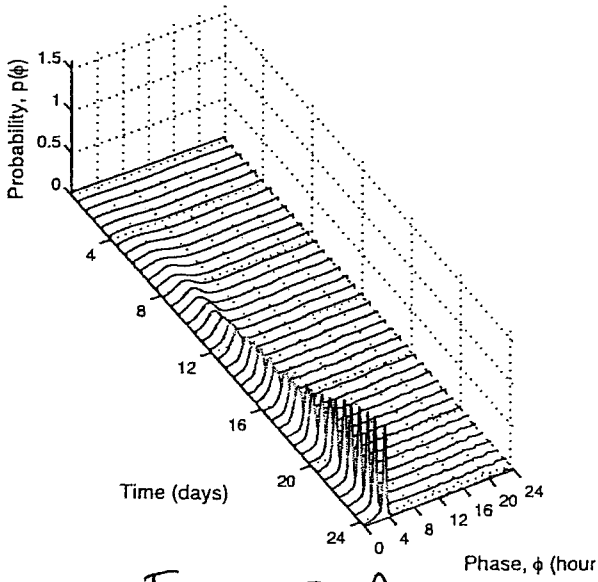FIGURE 1B

FIGURE 19
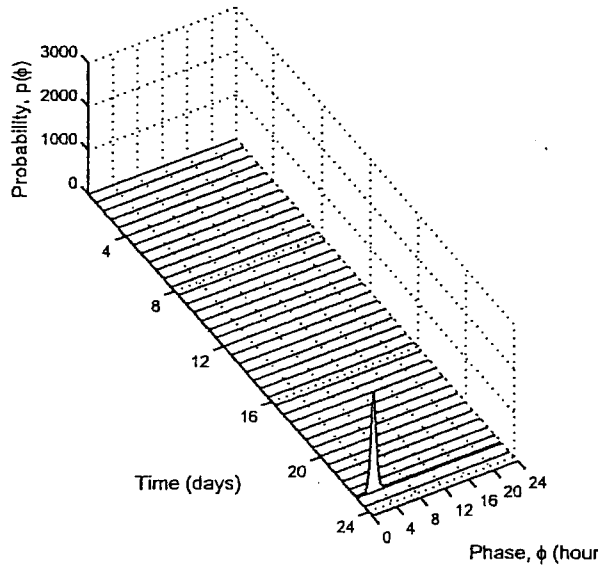
FIGURE 20

FIGURE 21

NO SLEEP HISTORY INFO:

FIGURE 22A

FIGURE 23A

FIGURE 23B

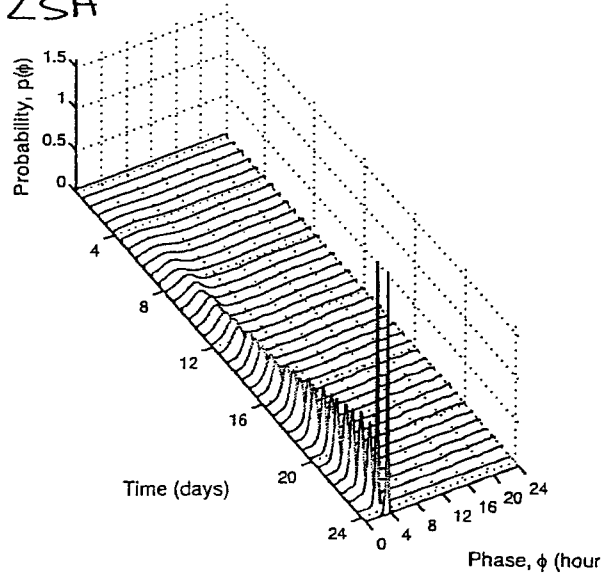

FIGURE 23C
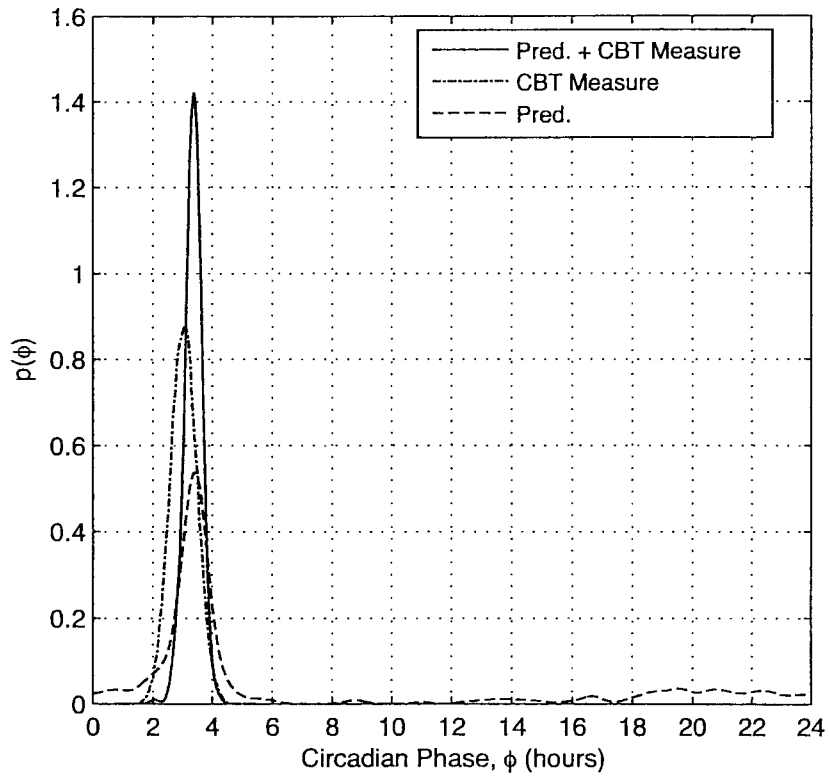
FIGURE 24
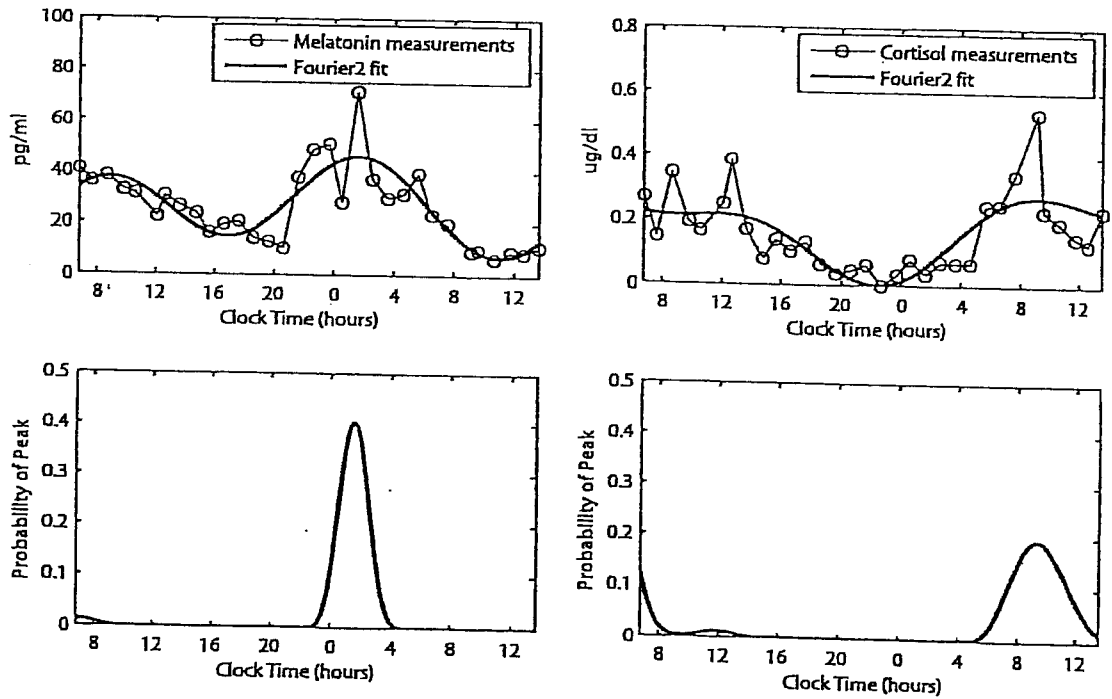
FIGURE 25

A.   CLASSIFICATION OF SUBJECT MATTER
      IPC: *A61B 5/00* (2006.01) , *A61B 5/01* (2006.01) , *A61B 5/16* (2006.01)
      According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
      IPC (7): A61B-5/00, A61B-5/01, A61B-5/16

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases: Intellect, Delphion, Pluspat, Questel Orbit, IEEE Xplore, Google
Keywords: circadian, prediction, bayesian, estimation, model, PDF (probability distribution function)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0015122 20 Jan. 2005 (20-01-2005) by Mott et al. ** see entire document**	1-38
A	US 2005/0105682 19 May 2005 (19-05-2005) by Heumann et al. ** see entire document**	1-38
A	JP 2007/044203 22 Feb. 2007 (22-02-2007) by Kanayama ** see entire document**	1-38
A	US 5 176 133 5 Jan. 1993 (05-01-1993) by Czeisler et al. ** see entire document**	1-38
A	US 5 167 228 1 Dec. 1992 (01-12-1922) by Czeisler et al. ** see entire document**	1-38

[ ]   Further documents are listed in the continuation of Box C.   [X]   See patent family annex.

*	Special categories of cited documents :	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent but published on or after the international filing date	"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
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
30 September. 2008 (30-09-2008)	2 October 2008 (02-10-2008)

| Name and mailing address of the ISA/CA
 Canadian Intellectual Property Office
 Place du Portage I, C114 - 1st Floor, Box PCT
 50 Victoria Street
 Gatineau, Quebec K1A 0C9
 Facsimile No.: 001-819-953-2476 | Authorized officer

 Karen Oprea   819- 934-2668 |

Box No. II	Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. :   39-41

    because they relate to subject matter not required to be searched by this Authority, namely :

    claims 39-41 are directed to appaatus and methods having any new useful and inventive features, combination of features or sub-combination of features as described herein. Such claims are considered to be omnibus claims and thereby no opinion is required by this Authority.

2. [ ] Claim Nos. :

    because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

    because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III	Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest   [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2005015122	20-01-2005	NONE	
US2005105682	19-05-2005	NONE	
JP2007044203	22-02-2007	NONE	
US5716133	10-02-1998	AT217707T T	15-06-2002
		DE69526718D D1	20-06-2002
		DE69526718T T2	02-01-2003
		EP0723141 A1	24-07-1996
		JP8271346 A	18-10-1996
US5167228	01-12-1992	AT152921T T	15-05-1997
		AT152923T T	15-05-1997
		AU612182B B2	04-07-1991
		AU698567B B2	05-11-1998
		AU2309688 A	19-01-1989
		AU5453194 A	24-05-1994
		AU5845290 A	08-01-1991
		AU6474994 A	25-08-1994
		CA1327630 C	08-03-1994
		CA2062718 A1	16-12-1990
		CA2148130 A1	11-05-1994
		CA2206209 A1	06-06-1996
		DE3855909D D1	19-06-1997
		DE3855909T T2	18-12-1997
		DE69030729D D1	19-06-1997
		DE69030729T T2	02-01-1998
		DK477282T T3	15-12-1997
		EP0363440 A1	18-04-1990
		EP0477282 A1	01-04-1992
		EP0688234 A1	27-12-1995
		EP0800415 A1	15-10-1997
		ES2103743T T3	01-10-1997
		FI952035 A	22-06-1995
		JP2503875T T	15-11-1990
		JP2928636B2 B2	03-08-1999
		JP8504622T T	21-05-1996
		JP10510449T T	13-10-1998
		US5163426 A	17-11-1992
		US5176133 A	05-01-1993
		US5304212 A	19-04-1994
		US5503637 A	02-04-1996
		US5545192 A	13-08-1996
		WO8810091 A1	29-12-1988
		WO9015639 A1	27-12-1990
		WO9409851 A1	11-05-1994
		WO9616697 A1	06-06-1996