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(54) **SYSTEM AND METHOD FOR CONTROL OF A SUBJECT'S CIRCADIAN CYCLE**

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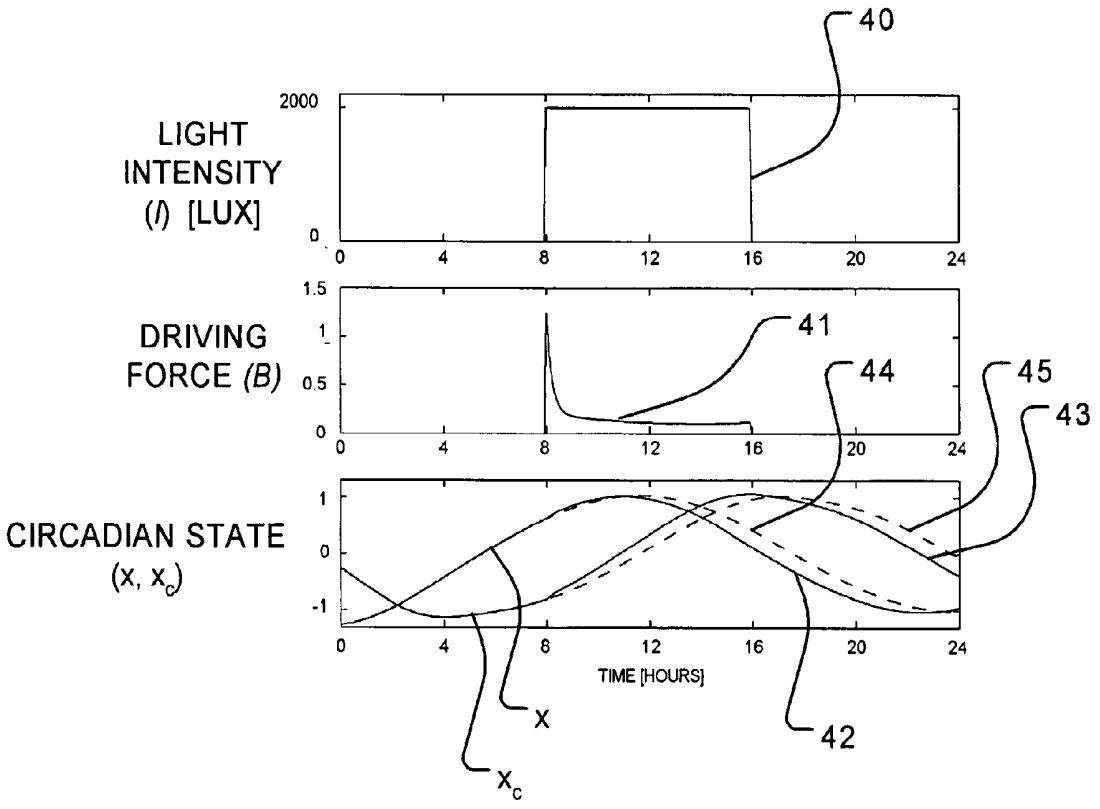
(57) **ABSTRACT**

Aspects of the invention provide systems and methods for controllably adjusting the circadian pacemaker cycle of a subject using light (or other stimulus) through application of model-based predictive control techniques. This approach allows the use of closed-loop feedback to compensate for modeling errors, unknown initial conditions and disturbances. It also allows an optimal level of light (or other stimulus) to be generated based on minimization of a cost function. The cost function may incorporate a term associated with tracking errors and a term associated with the amount of light used. The tracking function may be minimized subject to one or more constraints which may include a minimum and maximum amount of light (or other stimulus).



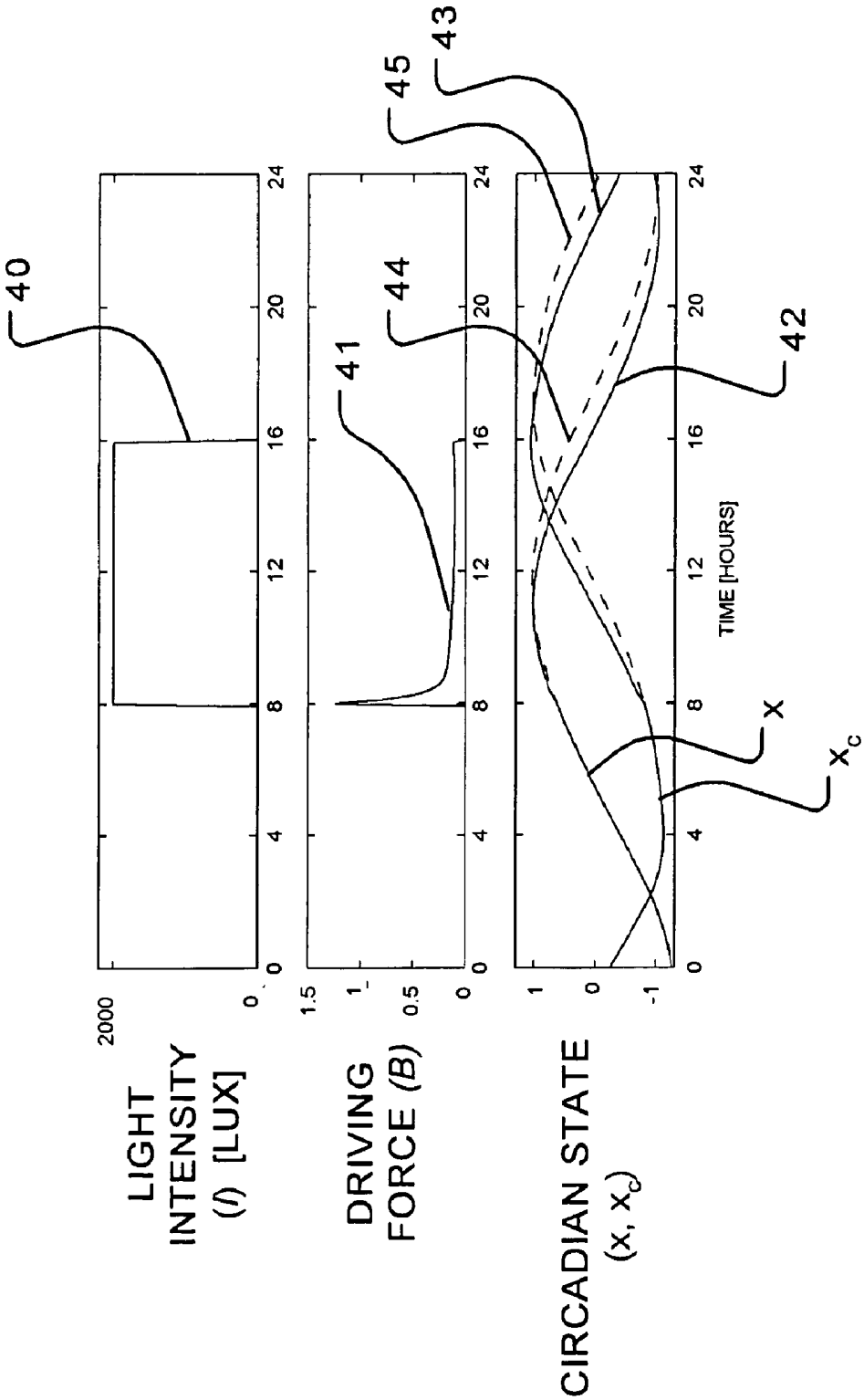

40
41
42
43
44
45
LIGHT INTENSITY (I) [LUX]
DRIVING FORCE (B)
CIRCADIAN STATE (x, x_c)
TIME [HOURS]
x
x_c
2000
0
1.5
1
0.5
-1
4
8
12
16
20
24

FIGURE 1

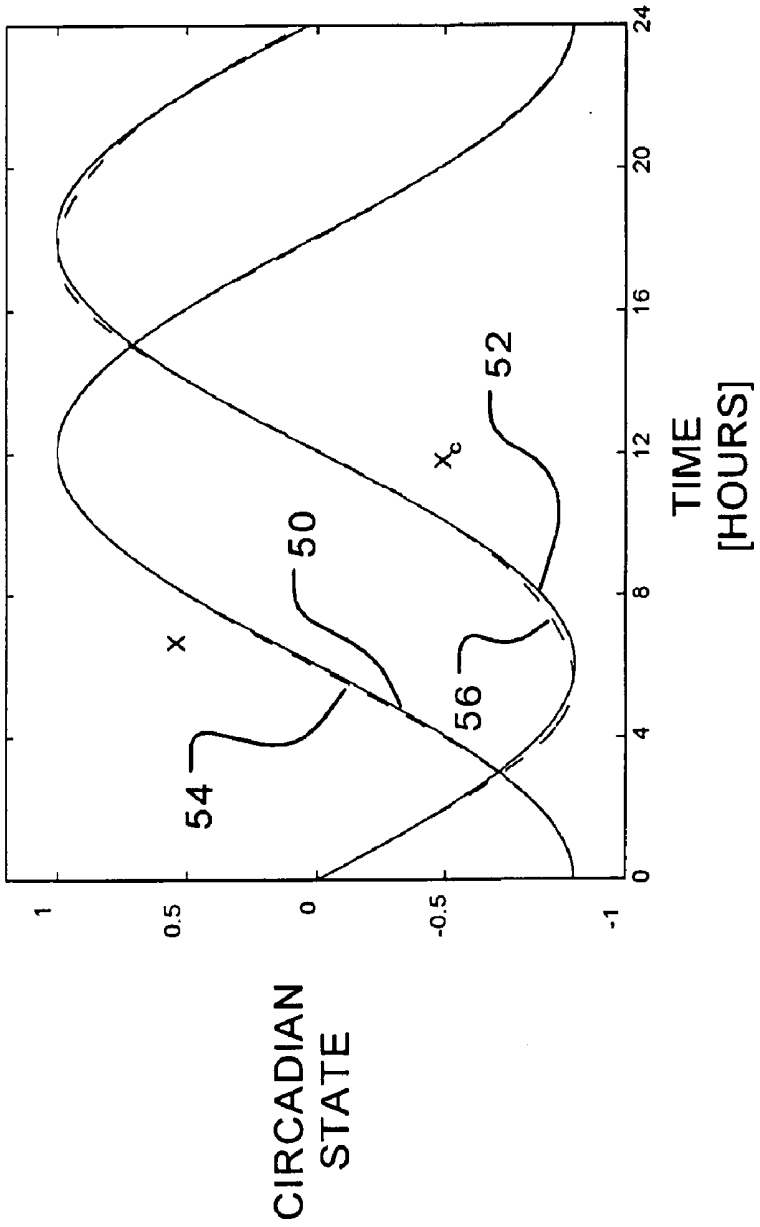

CIRCADIAN STATE
1
0.5
0
-0.5
-1
0
4
8
12
16
20
24
TIME [HOURS]
x
x_c
50
52
54
56

FIGURE 2

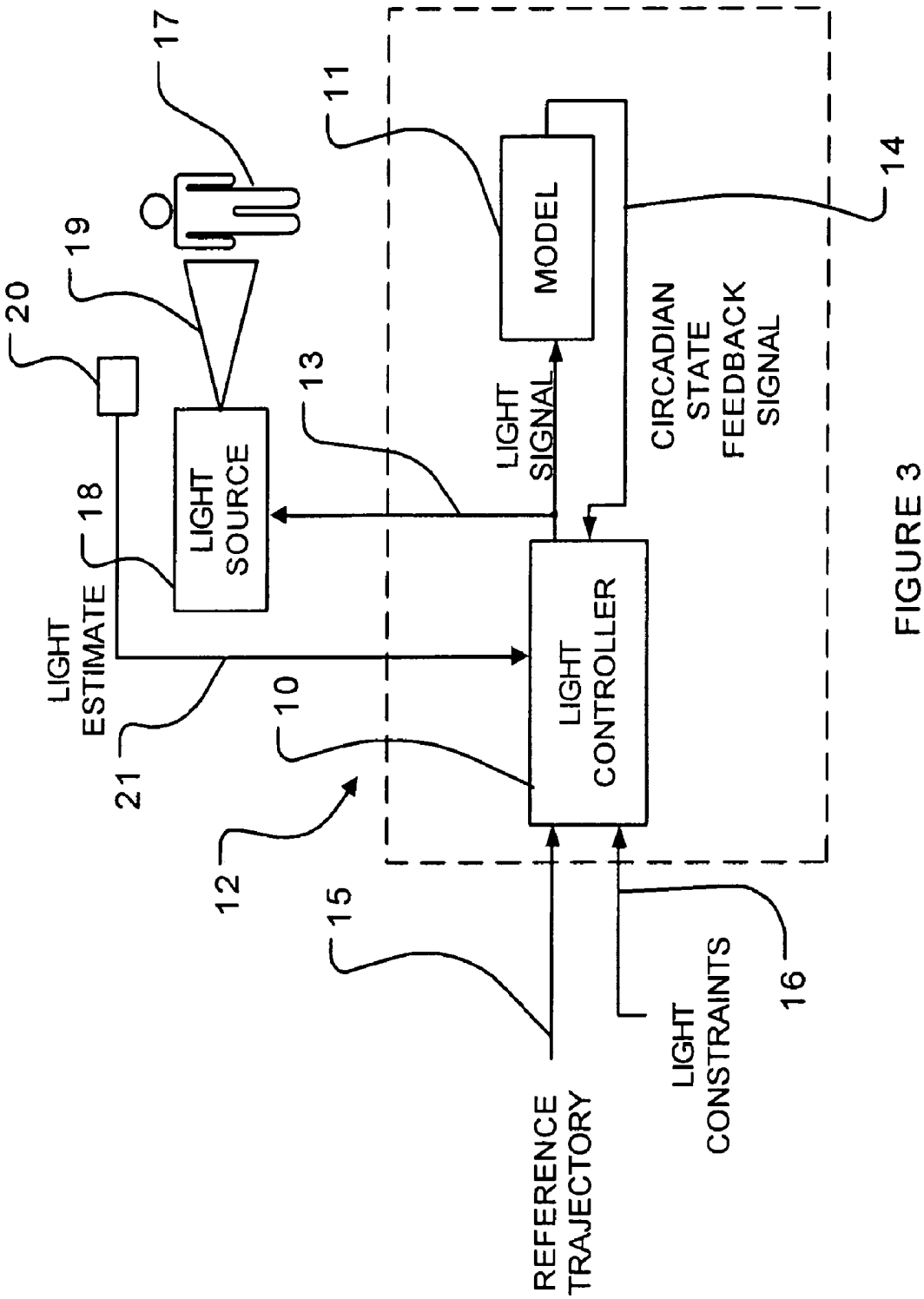

17
11
19
20
MODEL
14
13
LIGHT SIGNAL
CIRCADIAN STATE FEEDBACK SIGNAL
18
LIGHT SOURCE
LIGHT ESTIMATE
21
10
LIGHT CONTROLLER
12
15
16
REFERENCE TRAJECTORY
LIGHT CONSTRAINTS

FIGURE 3

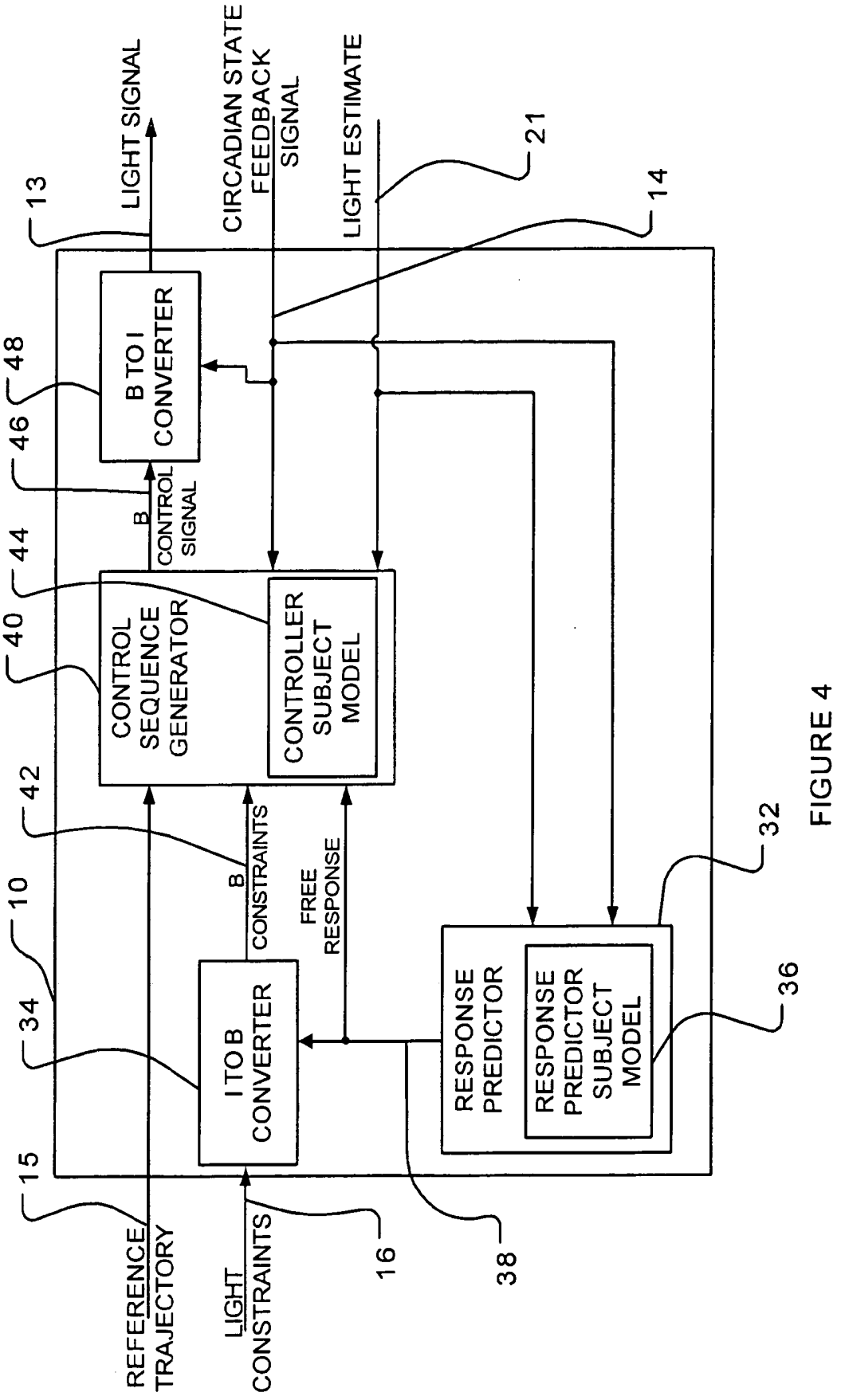

LIGHT SIGNAL
CIRCADIAN STATE FEEDBACK SIGNAL
LIGHT ESTIMATE
13
21
14
B TO I CONVERTER
48
46
B CONTROL SIGNAL
44
CONTROL SEQUENCE GENERATOR
CONTROLLER SUBJECT MODEL
40
42
B CONSTRAINTS
FREE RESPONSE
10
34
I TO B CONVERTER
RESPONSE PREDICTOR
RESPONSE PREDICTOR SUBJECT MODEL
32
36
15
REFERENCE TRAJECTORY
LIGHT CONSTRAINTS
16
38

FIGURE 4

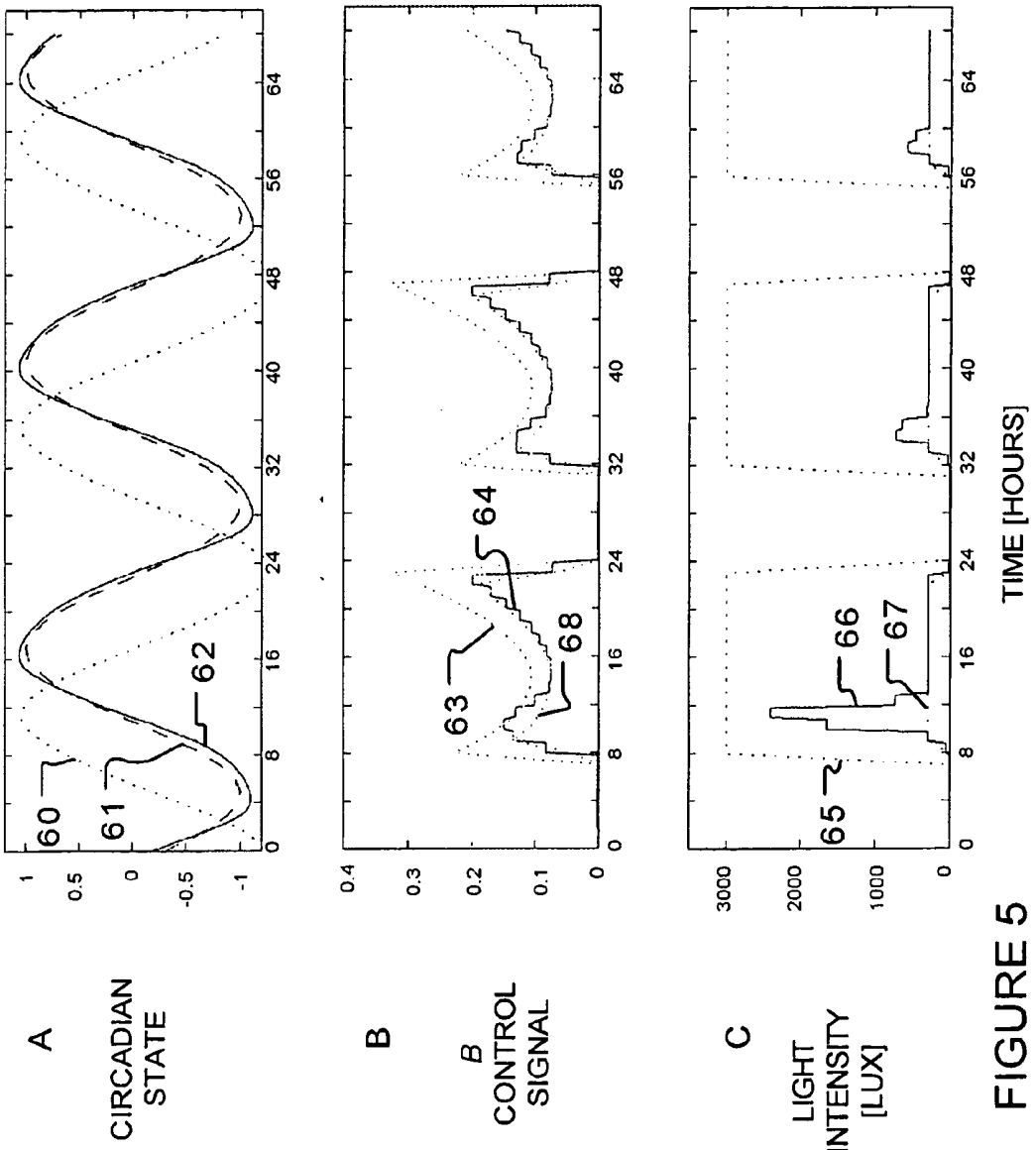

A
CIRCADIAN STATE
60
61
62
B
CONTROL SIGNAL
63
64
68
C
LIGHT INTENSITY [LUX]
65
66
67
TIME [HOURS]

FIGURE 5

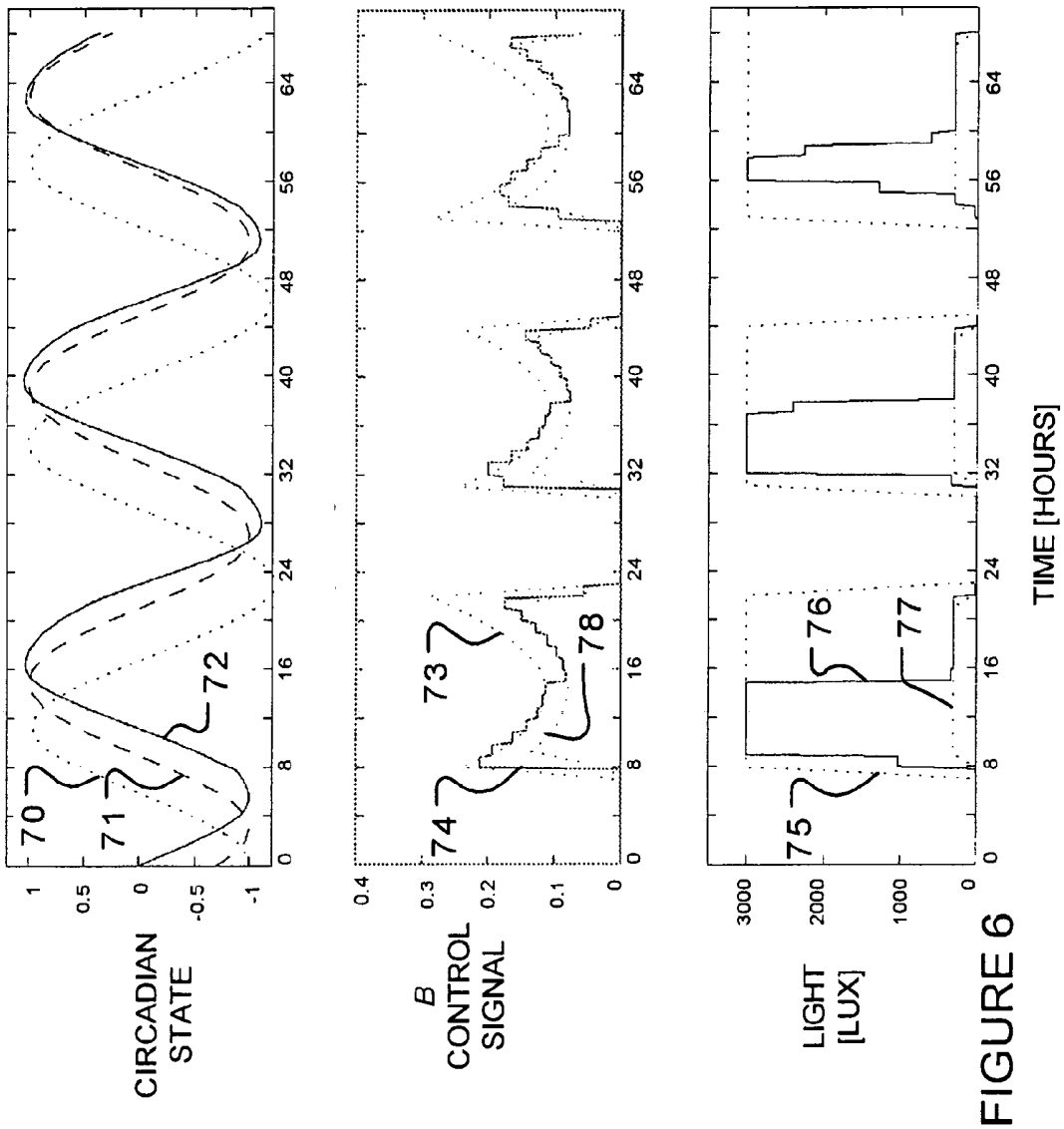

CIRCADIAN STATE
70
71
72
B CONTROL SIGNAL
73
74
78
LIGHT [LUX]
75
76
77
TIME [HOURS]

FIGURE 6

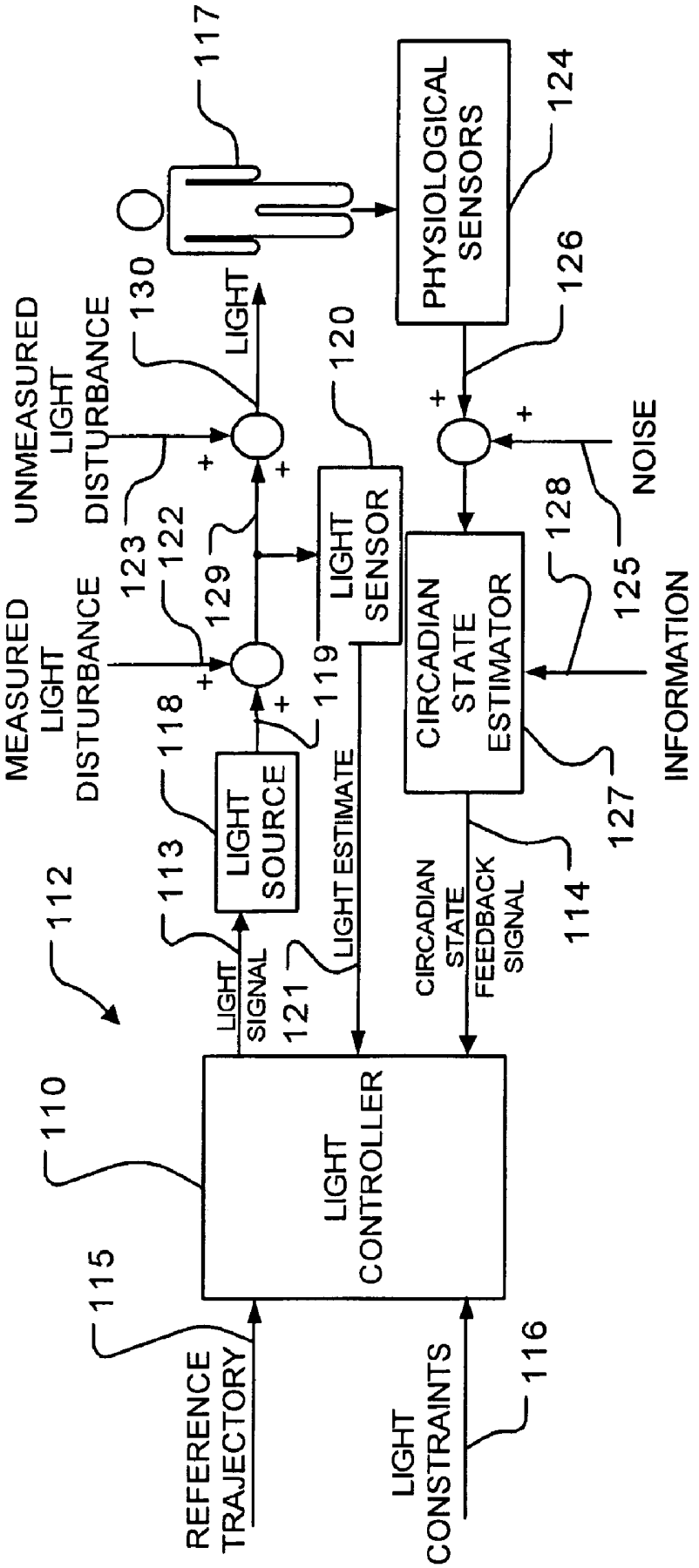

117
PHYSIOLOGICAL SENSORS
124
126
UNMEASURED LIGHT DISTURBANCE
130
LIGHT
120
MEASURED LIGHT DISTURBANCE
123
122
129
LIGHT SENSOR
NOISE
128
125
118
119
CIRCADIAN STATE ESTIMATOR
INFORMATION
112
113
LIGHT SOURCE
LIGHT ESTIMATE
127
LIGHT SIGNAL
121
CIRCADIAN STATE FEEDBACK SIGNAL
114
110
LIGHT CONTROLLER
115
REFERENCE TRAJECTORY
LIGHT CONSTRAINTS
116

FIGURE 7

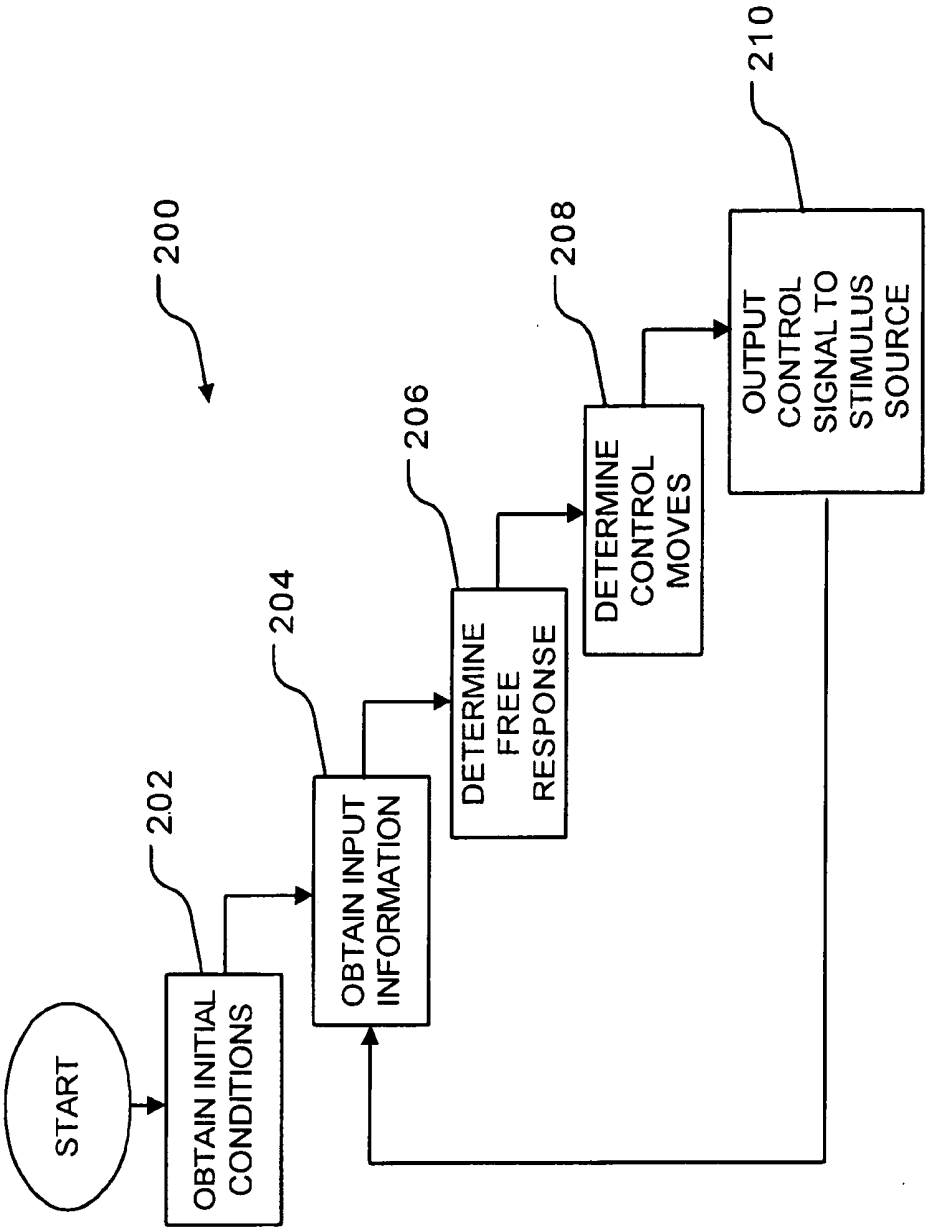

200
START
OBTAIN INITIAL CONDITIONS
202
OBTAIN INPUT INFORMATION
204
DETERMINE FREE RESPONSE
206
DETERMINE CONTROL MOVES
208
OUTPUT CONTROL SIGNAL TO STIMULUS SOURCE
210

FIGURE 8

SYSTEM AND METHOD FOR CONTROL OF A SUBJECT'S CIRCADIAN CYCLE

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 10/859,172 filed 3 Jun. 2004. This application claims the benefit of the priority of U.S. Patent Application No. 60/475,529 filed 3 Jun. 2003.

TECHNICAL FIELD

[0002] The invention relates to a system and method for modifying the circadian cycle of a subject. Particular embodiments of the invention involve providing stimulus to controllably adjust a subject's circadian cycle to track a reference trajectory.

BACKGROUND

[0003] Biological organisms of many kinds exhibit cycles which manifest themselves in a variety of physiological and behavioral characteristics. The cycles may have periods of hours (ultradian), days (circadian), or longer intervals (infradian). Circadian cycles are commonly observed in humans, as is evidenced by fluctuations in core body temperature, hormone levels, alertness and cognitive performance, for example. Of particular interest are alertness and cognitive performance, as these characteristics are correlated to health, safety and productivity.

[0004] There are circumstances where it may be desirable to alter or otherwise control a circadian cycle of a subject. For example, it may be desirable to maximize the alertness or cognitive performance of a subject for particular periods of time during which they are required to perform important or dangerous tasks, such as when they are flying an aircraft or performing an operation.

[0005] The biological basis of circadian cycles in humans is believed to be an endogenous circadian pacemaker: a self-oscillating chemical process in the suprachiasmatic nucleus region of the brain with a period very near to 24 hours (see, for example, C. A. Czeisler, J. F. Duffy, T. L. Shanahan, E. N. Brown, J. F. Mitchell D. W. Rimmer, J. M. Ronda, E. J. Silva, J. S. Allan, J. S. Emens, D. J., Dijk, and R. E. Kronauer., "Stability, precision, and near-24-hour period of the human circadian pacemaker." Science, Vol. 284, No. 5423 (1999), pp. 2177-2181). External stimuli influence the endogenous circadian pacemaker cycle, and in turn, the various circadian cycles that it regulates. Light is a particularly effective stimulus for modifying the circadian pacemaker cycle of a human subject (see, for example, C. A. Czeisler, J. S. Allan, S. H. Strogatz, J. M. Ronda, R. Sanchez, C. D. Rios, W. O. Freitag, G. S. Richardson, and R. E. Kronauer, "Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle." Science, Vol. 233, No. 4764, (August 1986), pp. 667-671).

[0006] The effect of external stimuli (such as light) on the human circadian pacemaker cycle has led to a number of patents, including: U.S. Pat. Nos. 5,163,426; 5,167,228; 5,176,133; 5,304,212; and 5,545,192 (to Czeisler et al.); U.S. Pat. Nos. 5,343,121; and 5,589,741 (to Terman et al.); U.S. Pat. No. 6,350,275 (to Vreman). The techniques proposed by these patents have a variety of limitations which include, inter alia: slow or otherwise non-optimal shifting of the subject's circadian pacemaker cycle; lack of feedback based on measurement of parameter(s) indicative of the state of the subject's circadian pacemaker cycle; lack of mechanisms for incorporating limitations on available stimuli; lack of mechanisms for incorporating differences between individual subjects, modeling errors, unknown initial conditions and/or the introduction of disturbances, and lack of a continuous connection or dependence between assessment of the subject's circadian state and the modification of the subject's circadian pacemaker cycle.

[0007] There is a general desire to provide systems and methods for controllably adjusting a circadian cycle of a subject which overcome or ameliorate some of the aforementioned disadvantages of the prior art.

SUMMARY OF THE INVENTION

[0008] A first aspect of the invention provides a method for controllably adjusting the circadian cycle of a subject using light (or other stimulus) through application of model-based predictive control techniques. This approach allows the use of closed-loop feedback to compensate for modeling errors, unknown initial conditions and disturbances. It also allows an optimal level of light (or other stimulus) to be generated based on minimization of a cost function. The cost function may incorporate a term associated with tracking errors and a term associated with the amount of light used. The tracking function may be minimized subject to one or more constraints which may include a minimum and maximum amount of light (or other stimulus) for example.

[0009] Another aspect of the invention provides a method for controllably adjusting a circadian cycle of a subject to track a reference trajectory. The method involves providing at least one model representative of a response of a circadian state of the subject to a stimulus control signal and generating an optimal stimulus control signal using model predictive control based on the model. Generating the optimal stimulus control signal comprises minimizing a cost function which may comprise a cost term which is a function of a tracking error and a cost term related to an amplitude of the stimulus control signal. Minimizing the cost function is subject to constraints which comprise minimum and maximum stimulus control signal levels.

[0010] Generating the optimal stimulus control signal may be based, at least in part, on a circadian state feedback signal. The circadian state feedback signal may be determined by modeling the response of the circadian state of the subject to the stimulus control signal. Modeling the response of the subject to the stimulus control signal may comprise using a mathematical model based on a Jewett-Kronauer model. The mathematical model may comprise a linearized version of the Jewett-Kronauer model. The circadian state feedback signal may be determined by estimating the circadian state of the subject based, at least in part, on one or more sensed parameters which relate to the physiology of the subject. The sensed parameters may include: heart rate, core body temperature, respiration, endocrine function levels, physical activity levels, blood pressure, blood oxygen concentration and/or skin temperature.

[0011] The stimulus control signal may comprises a light control signal and the method may comprise applying the light control signal to determine an intensity of one or more light sources.

[0012] The at least one model may comprise a response predictor subject model. Generating the optimal stimulus control signal may comprise predicting a free response of the circadian state of the subject starting at a current time and

extending out to a control horizon time using the response predictor subject model. Predicting the free response may comprise assuming that a current value of the circadian state feedback signal represents an initial condition and that the light control signal remains constant between the current time and the control horizon time.

[0013] The at least one model may comprise a controller subject model. Generating the optimal stimulus control signal may comprise determining an optimal series of control moves starting at the current time and extending out to the control horizon time using the controller subject model. Determining the optimal series of control moves may be based, at least in part, on the free response of the circadian state of the subject, the reference trajectory and the circadian state feedback signal.

[0014] The response predictor subject model and/or the controller subject model may comprise a mathematical model defined by a plurality of differential equations. The mathematical model may be based on a Jewett-Kronauer model. The mathematical model may comprise a linearized version of the Jewett-Kronauer model.

[0015] Predicting the free response may be based, at least in part, on a light estimate signal representative of a light intensity experienced by the subject. Determining the optimal series of control moves may be based, at least in part, on the light estimate signal. The method may involve estimating the light intensity experienced by the subject using a model to obtain the light estimate signal. The method may involve sensing the light intensity experienced by the subject using at least one light sensor to obtain the light estimate signal.

[0016] The stimulus control signal may be provided in a domain of a driving input B of the Jewett-Kronauer model. The method may comprise converting the stimulus control signal from the domain of the driving input B to the light control signal in a light intensity domain I. The method may also comprise converting the minimum and maximum stimulus control signal levels from a light intensity domain I to a domain of a driving input B of the Jewett-Kronauer model.

[0017] The cost function may comprise a first weighting factor associated with the tracking error cost term and a second weighting factor associated with the stimulus control signal cost term. The first and second weighting factors may vary over a duration of the circadian cycle of the subject.

[0018] Another aspect of the invention provides a method for controllably adjusting a circadian cycle of a subject to track a reference trajectory. The method involves obtaining input information which comprises a signal representative of the reference trajectory, a feedback signal representative of a circadian state of the subject and one or more stimulus level constraints. The method also involves predicting a free response of the circadian state of the subject starting at a current time and extending out to a first future time using a response predictor subject model representative of a response of the circadian state of the subject to a stimulus. An optimal series of control moves is determined starting at the current time and extending out to second future time using a controller subject model representative of a response of the circadian state of the subject to a stimulus. The optimal series of control moves is based, at least in part, on the free response of the circadian state of the subject, the reference trajectory signal and the current circadian state feedback signal. The method also involves outputting a stimulus control signal comprising a current one of the series of control moves to one or more stimulus sources and applying the stimulus control signal to one or more stimulus sources to determine an intensity thereof.

[0019] Another aspect of the invention comprises a system for controllably adjusting a circadian cycle of a subject to track a reference trajectory. The system comprises one or more inputs for receiving the reference trajectory and for receiving constraints which comprise minimum and maximum stimulus control signal levels. A response predictor is connected to receive a feedback signal representative of a circadian state of the subject and is configured to predict a free response of the circadian state of the subject starting at a current time and extending out to a first future time using a response predictor subject model representative of a response of the circadian state of the subject to a stimulus. A control sequence generator is connected to receive the reference trajectory, the constraints, the feedback signal and the free response of the circadian state of the subject. The control sequence generator is configured to determine an optimal series of control moves starting at the current time and extending out to a second future time using a controller subject model representative of a response of the circadian state of the subject to a stimulus. The control sequence generator is connected to output a stimulus control signal to at least one stimulus source. The stimulus control signal comprises a current control move in the optimal series of control moves and the stimulus control signal determines an intensity of the at least one stimulus source.

[0020] Yet another aspect of the invention provides a system for controllably adjusting a circadian cycle of a subject to track a reference trajectory. The system comprises one or more inputs for receiving the reference trajectory and for receiving constraints which comprise minimum and maximum stimulus control signal levels. The system also comprises means for predicting a free response of a circadian state of the subject starting at a current time and extending out to a first future time based, at least in part, on a feedback signal representative of the circadian state of the subject and means for determining an optimal series of control moves starting at the current time and extending out to a second future time based, at least in part, on the reference trajectory, the constraints, the feedback signal and the free response of the circadian state of the subject. Means for applying a stimulus control signal to at least one stimulus source are also provided. The stimulus control signal comprises at least a portion of the optimal series of control moves and the stimulus control signal determines an intensity of the at least one stimulus source.

[0021] Still another aspect of the invention provides a method for altering a phase of a circadian cycle of a subject. The method comprises providing a controller subject model representing a response of a circadian state of the subject to a stimulus, receiving a reference circadian trajectory, which is phase shifted from a current circadian cycle of the subject, determining a series of stimulus control moves predicted by the controller subject model to result in the circadian cycle of the subject changing to track the reference circadian trajectory and applying at least a portion of the series of stimulus control moves to one or more stimulus sources. The one or more stimulus sources provide stimulus which is received by the subject. Determining the series of stimulus control moves comprises applying an optimization process using the controller subject model.

[0022] Further features and applications of specific embodiments of the invention are described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] In drawings which depict non-limiting embodiments of the invention:

[0024] FIG. **1** is an exemplary graph depicting a response of a subject's circadian state to a pulse of light;

[0025] FIG. **2** is an exemplary graph depicting a comparison of circadian states predicted by a nonlinear model and circadian states predicted using a linear approximation of the nonlinear model;

[0026] FIG. **3** is a block diagram of a system for controllably adjusting a circadian cycle of a subject in accordance with a particular embodiment of the invention;

[0027] FIG. **4** is a schematic diagram of the light controller of the FIG. **3** system in accordance with a particular embodiment of the invention;

[0028] FIG. **5** shows a number of exemplary graphs which demonstrate how the FIG. **3** system may be used to controllably adjust the circadian pacemaker cycle of a subject to track a reference trajectory;

[0029] FIG. **6** shows a number of exemplary graphs which demonstrate how the FIG. **3** system may be used to controllably adjust the circadian pacemaker cycle of a subject to track a reference trajectory;

[0030] FIG. **7** is a block diagram of a system for controllably adjusting a circadian cycle of a subject in accordance with another embodiment of the invention; and

[0031] FIG. **8** shows a method for implementing the FIG. **3** or FIG. **7** system in accordance with a particular embodiment of the invention.

DETAILED DESCRIPTION

[0032] 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 practiced 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.

[0033] Aspects of the present invention provide systems and methods for controlling the circadian pacemaker cycle of a subject to track a reference trajectory. Controlled amounts of light (or other stimulus) are provided to the subject in such a manner that the subject's circadian pacemaker cycle is caused to track the reference trajectory. In some embodiments, the control systems and methods make use of one or more models. Such models may empirically describe the response of a typical subject's circadian state to light or other stimulus. Feedback may be used to compensate for differences between individuals, modeling errors, unknown initial conditions and other disturbances.

[0034] The control systems and methods may incorporate one or more physiological sensors, which sense one or more parameters that are correlated to or otherwise indicate the subject's circadian state. Such parameter(s) may be used as feedback. In some embodiments, the control systems and methods comprise one or more stimulus sensors, which sense the amount light (or other stimulus) applied to the subject and which feed this information back to the controller.

[0035] In some embodiments, the systems and methods determine an "optimum" application of light (or other stimulus) to adjust the subject's circadian cycle to the desired reference trajectory. The "optimum" application of light may be achieved by substantially minimizing a cost function. In some embodiments, the cost function incorporates a term related to the tracking error and a term related to the amount of stimulus required. The optimization cost function may be minimized subject to physical constraints inherent in the system. Such constraints may include a minimum and maximum amount of light (or other stimulus).

[0036] In some embodiments, the models used to predict the subject's circadian state comprise nonlinear models. The systems and methods may comprise a variety of approximation techniques for transforming or otherwise reducing such nonlinear models to linear models.

[0037] In some embodiments, the reference trajectory is selected so that the subject is more alert in certain desired time periods.

[0038] Some embodiments of the invention make use of mathematical models which describe the response of a human circadian pacemaker state to light (or other stimulus). Such models may be empirically determined. In some embodiments, such models comprise a system of differential equations derived from the well known van der Pol equations. Particular embodiments of the invention make use of the model described in M. E. Jewett, D. B. Forger, and R. E. Kronauer, "Revised Limit Cycle Oscillator Model of Human Circadian Pacemaker." Journal of Biological Rhythms, Vol. 14, No. 6 (1999), pp. 493-499, which is hereby incorporated herein by reference.

[0039] The Jewett-Kronauer model comprises a set of differential equations which describe the nonlinear effects of light on the circadian pacemaker cycle. In accordance with the Jewett-Kronauer model, the circadian state of a subject is described by a pair of circadian state variables (x, x_c). The circadian state variables (x, x_c) are mathematical constructs which represent the circadian state of a subject. According to the Jewett-Kronauer model, the response of the circadian state variables (x, x_c) to a driving input B is given by:

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

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

where μ, q and k are constants, which may be empirically determined, and τ_x is the intrinsic period of oscillation of the circadian cycle (in hours). The driving input B is related to light intensity I as will be described further below. In one particular embodiment, μ=0.13, q=⅓, k=0.55 and τ_x=24.2 hours.

[0040] The parameter B is the driving input for the Jewett-Kronauer model equations (1) and (2). Accordingly, given any value of the driving input B and historical information about the circadian state variables (x, x_c) (i.e. initial conditions), equations (1) and (2) may be used to predict future values of the circadian state variables (x, x_c). As can be seen by examining equations (1) and (2), the circadian state variables (x, x_c) comprise oscillating functions which may be approximately sinusoidal in nature and which are approximately 90° (or ¼ A period) out of phase with each another.

[0041] The Jewett-Kronauer model also comprises another state variable n which is not specifically related to the individual's circadian state, but rather is related to the individual's dynamic response to light. In accordance with the Jewett-Kronauer model, the state variable n is related to a parameter a which is an indication of an individual's perception of a given light intensity I. It will be appreciated that the human eye and brain have a nonlinear response to light intensity. For example, the introduction of a single candle into an otherwise dark room causes a dramatic increase in an individual's ability to perceive his or her environment, whereas the addition of one extra fluorescent tube into a room already lit with five such tubes makes comparatively little difference. The response a of the human eye to light with an intensity I may be modeled by:

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

where I is measured in lux and α_o and p are constants which may be empirically determined. In one particular embodiment, α_o=0.16 and p=0.6.

[0042] The third state variable n of the Jewett-Kronauer model may then be expressed in terms of α, the driving input B and the circadian state variables (x, x_c):

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

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

where β and G are constants which may be empirically determined. In one particular embodiment, β=**0.013** and G=19.875.

[0043] The driving input B is related to light intensity I. It is useful for the purpose of employing the Jewett-Kronauer model in real world applications to provide transformations back and forth between the domain of driving input B and the domain of light intensity I. Such transformations allow systems which make use of the Jewett-Kronauer model to work in either the driving input domain B or in the light intensity domain I. Transformations back and forth between the driving input domain B and the light intensity domain I may involve one or more simplifying approximations.

[0044] Some embodiments of the invention make use of a particular transformation between the driving input domain B of the Jewett-Kronauer model and the light intensity domain I, the derivation of which is presented below. Equation (5) may be rearranged as:

$$\alpha = \frac{B}{G(1-n)(1-mx)(1-mx_c)} \tag{6}$$

As can be appreciated by analyzing equation (4), the state variable n has a nonlinear dependence on the value of α. In some embodiments of the present invention, light pulses are applied to individuals to controllably alter their circadian cycles. In particular applications of the invention, light pulses of interest typically have durations greater than two hours. In these circumstances, it can assumed that the decaying exponential dependence of n on α (as described by equation (4)) will reach a steady state within a period of time significantly less than the duration of the light pulses. Accordingly, in such applications, the time derivative of n can be approximated as zero, such that equation (4) may be solved for an approximate value of n:

$$n_{approx} = \lim_{t\to\infty} n = \frac{\alpha}{\alpha+\beta} \tag{7}$$

Substituting this approximate value of n from equation (7) into equation (6) yields:

$$\alpha \approx \frac{B}{G\left(1-\frac{\alpha}{\alpha+\beta}\right)(1-mx)(1-mx_c)} = \frac{\beta B}{G\beta(1-mx)(1-mx_c)-B} \tag{8}$$

In addition, equation (3) may be rearranged as:

$$I = 9500\left(\frac{\alpha}{\alpha_0}\right)^{\frac{1}{p}} \tag{9}$$

and substituting equation (8) into equation (9) yields:

$$I \approx 9500\left(\frac{\beta B}{\alpha_0[G\beta(1-mx)(1-mx_c)-B]}\right)^{\frac{1}{p}} \tag{10}$$

Equation (10) represents a transformation function of the form I=f(x, x_c, B) which can be used in conjunction with the circadian state variables (x, x_c) to transform a value in the driving input domain B into a corresponding value in the light intensity domain I.

[0045] Using the same approximation for n from equation (7) and substituting it into equation (5) yields:

$$B \approx G\frac{\alpha\beta}{\alpha+\beta}(1-mx)(1-mx_c) \tag{10A}$$

Then, substituting equation (3) into equation (10A) yields:

$$B = \frac{G\alpha_o(I/9500)^p}{\alpha_o(I/9500)^p+\beta}(1-mx)(1-mx_c) \tag{10B}$$

Equation (10B) represents a transformation function of the form B=g(x, x_c, I) which can be used in conjunction with the circadian state variables (x, x_c) to transform a value in the light intensity domain/into a corresponding value in the driving input domain B.

[0046] FIG. **1** depicts the response of the circadian state variables (x, x_c) defined by the Jewett-Kronauer model equations (1)-(10B) to a pulse of light **40**. More particularly, FIG. **1** depicts curves **44**, **45**, which respectively represent the nominal circadian state variables (x, x_c) predicted by model equations (1) and (2) under zero light conditions, and curves **42**, **43**, which respectively represent the circadian state variables (x, x_c) predicted by model equations (1) and (2) in

response to light pulse **40**. As can be seen by comparing curves **42**, **43**, **44**, **45**, light pulse **40** causes a phase shift in circadian state variables (x, x_c).

[0047] The direction of the phase shift caused by light pulse **40** on circadian state variables (x, x_c) depends on the actual phase of these circadian state variables (x, x_c) in relation to the timing of light pulse **40**. In the example graphs of FIG. **1**, after the application of light pulse **40** at t=8 hours, curve **43** leads curve **45**, which indicates that light pulse **40** has caused an advance in the phase of circadian state variable x_c. FIG. **1** also depicts a signal **41** representative of the driving input B associated with light pulse **40**. As shown by curve **41** of FIG. **1**, driving input B exhibits a relatively sharp peak at the outset of light pulse **40** (i.e. around t=8 hours) and then decays over time to a steady state value, until light pulse **40** is terminated, at which point driving signal B returns to zero.

[0048] The Jewett-Kronauer model represented by equations (1)-(10B) is a nonlinear model. In particular, equations (1) and (2), which describe the circadian state variables (x, x_c), comprise a pair of nonlinear equations expressed in terms of the driving variable B and the circadian state variables (x, x_c). Some embodiments of the present invention make use of linearizing transformations or manipulations which allow a nonlinear model to be approximated by a linear model. Such manipulations may involve nonlinear state feedback compensation and/or various linearizing approximations.

[0049] Particular embodiments of the invention employ linearizing approximations to provide linearized versions of equations (1) and (2) of the Jewett-Kronauer model. With respect to equation (1), it may be observed that there are two higher order (i.e. nonlinear) terms of the circadian state variable x, both of which are scaled by the factor μ. It may also be observed that equation (1) is an odd function of x, which has an integral of zero over the range of x ($x \in [-1,1]$). Because these higher order terms introduce relatively small contributions that average to zero over the range of x, one possible approximation for equation (1) involves setting $\mu=0$. With regard to equation (2), there are two higher order terms which are functions of Bx_c and Bx and which are scaled by scaling factors q and k respectively. As with the approximation for equation (1), one possible approximation for equation (2) involves setting the scaling factors q and k to zero. These approximations to equations (1) and (2) (i.e. setting scaling factors μ, q and k equal to zero) result in the following linearized state space equations:

$$\begin{bmatrix} \dot{x} \\ \dot{x}_c \end{bmatrix} = \begin{bmatrix} 0 & \frac{\pi}{12} \\ \left(\frac{24}{r_x(0.99729)}\right)^2 & 0 \end{bmatrix} \begin{bmatrix} x \\ x_c \end{bmatrix} + \begin{bmatrix} \frac{\pi}{12} \\ 0 \end{bmatrix} B \tag{11}$$

$$[x_{out}] = [\,1 \quad 0\,] \begin{bmatrix} x \\ x_c \end{bmatrix} \tag{12}$$

[0050] FIG. **2** depicts a comparison of nonlinear model equations (1) and (2) and linearized model equations (11) under conditions where B=0 (i.e. no driving input). Solid curves **50**, **52** respectively represent the circadian state variables (x, x_c) calculated using equations (1) and (2) and dashed curves **54**, **56** respectively represent the circadian state variables (x, x_c) calculated using linearized approximation equations (11). It can be seen from curves **50**, **52**, **54**, **56**, that the linearized approximation equations (11) produce results which are fairly close to those of model equations (1) and (2), at least for the condition where B=0.

[0051] FIG. **3** is a block diagram of a system **12** for controllably adjusting a circadian cycle of a subject **17** in accordance with a particular embodiment of the invention. System **12** comprises a controller **10** which receives reference trajectory input **15**, light constraint inputs **16**, light estimate input **21** and circadian state feedback signal **14**. In response to these inputs, controller **10** outputs a light control signal **13**. Light control signal **13** may control various characteristics of light **19** output by one or more light sources **18**. In some embodiments, light control signal **13** is representative of the intensity I of light **19** output by light source(s) **18**. The light intensity I may be measured in lux. When light **19** is applied to subject **17**, the circadian pacemaker cycle of subject **17** is altered.

[0052] In the FIG. **3** embodiment, system **12** comprises a circadian state feedback signal **14** that is generated by model **11**. Model **11** preferably comprises a mathematical model of the response of a human circadian state to a given stimulus. In the FIG. **1** embodiment, model **11** receives input information from light control signal **13** which represents the intensity I of light stimulus **19**. Using light control signal **13** and historical circadian state information (which may be stored in a memory (not shown)), model **11** predicts the current circadian state of subject **17** in response to light stimulus **19** and feeds this information back to controller **10** as circadian state feedback signal **14**.

[0053] In one particular embodiment, model **11** comprises the Jewett-Kronauer model described above in equations (1)-(10B). In another particular embodiment, model **11** comprises the Jewett-Kronauer model described above in equations (1)-(10B), except that linearized equation (11) replaces nonlinear equations (1) and (2). In such embodiments, model **11** predicts one or more of the circadian state variables (x, x_c) and feeds this information back to controller **10** as circadian state feedback signal **14**. Those skilled in the art will appreciate that model **11** may make use of transformations between the intensity domain I of light control signal **13** and the driving input domain B of the Jewett-Kronauer model.

[0054] Reference trajectory input **15** is preferably representative of a target time varying circadian pacemaker cycle. System **12** controllably adjusts the circadian pacemaker cycle of subject **17** to track reference trajectory input **15**. In some embodiments, reference trajectory input **15** comprises desired values of one or more of the circadian state variables (x, x_c) of the Jewett-Kronauer model described above. Light constraint inputs **16** may comprise minimum and/or maximum light intensity levels which may be applied to subject **17**. Such minimum and maximum levels may be related to actual physical constraints of light source(s) **18** or to other levels, such as levels designed to promote the comfort of subject **17** for example. Light estimate input **21** is an optional input which comprises an estimate of light **19** experienced by subject **17**. Light estimate input **21** may be in the intensity domain I and may be measured in lux. Light estimate input **21** comes from light estimator **20**. In some embodiments, light estimator **20** comprises one or more sensors for measuring light **19**. In other embodiments, light estimator **20** comprises a model which generates a signal representative of the light experienced by subject **17** and feeds this signal back to controller **10** as light estimate input **21**. Such a model may take into account the current light signal **13**, other sources of light (not shown), such as sunlight, ambient light, background artificial light, and other factors, such as time of day, date,

location, activity patterns, and amount of light that will be incident on the retinas of subject **17**.

[0055] FIG. **4** depicts a particular embodiment of controller **10** of system **12** in more detail. Controller **10** may be implemented using various types of programmable controllers or processors. For example, controller **10** may comprise a programmable computer, an embedded processor or the like. Controller **10** may comprise more than one such processor. Controller **10** may also include memory (not shown) which stores program information and the like. Controller **10** receives: reference trajectory input **15**, light constraint signals **16**, circadian state feedback signal **14** and light estimate input **21**. In response to these inputs, controller **10** generates light control signal **13** which (when applied to light source(s) **18**) causes the circadian pacemaker cycle of subject **17** to track reference trajectory **15**.

[0056] In the FIG. **4** embodiment, controller **10** comprises an I to B converter **34** and a B to I converter **48**. B to I converter **48** transforms drive control signal **46** in the drive signal input domain B into a corresponding light control signal **13** in the intensity domain I. B to I converter **48** may make use of the transformation expressed in equation (10). To perform its transformation, B to I converter **48** has access to circadian state feedback signal **14** which may comprise one or more of the circadian state variables (x, x_c). I to B converter **34** transforms light constraint inputs **16** in the intensity domain I into corresponding drive signal constraint inputs **42** in the drive signal input domain B. I to B converter **34** may make use of a transformation of the form expressed in equation (10B). As shown in FIG. **4**, Ito B converter **34** has access to free response information **38**. As will be explained further below, free response information **38** may comprise information representative of free response values for the Jewett-Kronauer state space variables (x, x_c).

[0057] Control system **10** comprises response predictor **32** which comprises a response predictor subject model **36**. Response predictor **32** receives light estimate input **21** and circadian state feedback signal **14** and generates free response information **38**. In preferred embodiments, free response information **38** comprises a prediction of the future circadian state of individual **17** under the assumptions that the initial circadian state of individual **17** is indicated by circadian state feedback signal **14** and the current light level I indicated by light estimate input **21** remains constant. Response predictor **32** calculates the free response future circadian state of individual **17** (i.e. free response information **38**) out to a control horizon H.

[0058] In particular embodiments, response predictor **32** calculates a plurality of future free response values of the circadian state of individual **17** after each of a number p of discrete sampling intervals between the current time and the control horizon H. In general, the control horizon H and the sampling interval may be of any duration depending on the application, processor resources, etc. In some preferred embodiments, the sampling interval is in a range of 1 minute to 1 hour. In particularly preferred embodiments, each sampling interval is in a range of 10-30 minutes. In some preferred embodiments, the length of the control horizon H is in a range of 12-72 hours. In particularly preferred embodiments, the length of the control horizon H is in a range of 24-36 hours.

[0059] In the FIG. **4** embodiment, response predictor **32** comprises a response predictor subject model **36** which may be used to generate free response information **38**. In one particular embodiment, response predictor subject model **36** comprises the Jewett-Kronauer model described above in equations (1)-(10B). In another particular embodiment, response predictor subject model **36** comprises the Jewett-Kronauer model described above in equations (1)-(10B), except that linearized equation (11) replaces nonlinear equations (1) and (2). In such embodiments, response predictor subject model **36** uses light estimate input **21** and circadian feedback signal **14** to predict the free response of one or more of the circadian state variables (x, x_c) out to the control horizon H under the assumptions described above. In some embodiments, free response information **38** takes the form of a matrix comprising free response values of one or more of the circadian state variables (x, x_c) at p discrete sampling intervals. Those skilled in the art will appreciate that response predictor subject model **36** may make use of transformations between the intensity domain I of light estimate input **21** and the driving input domain B of the Jewett-Kronauer model.

[0060] Controller **10** also comprises a control sequence generator **40** which comprises a controller subject model **44**. In one particular embodiment, controller subject model **44** comprises the Jewett-Kronauer model described above in equations (1)-(10B). In a preferred embodiment, controller subject model **44** comprises the Jewett-Kronauer model described above in equations (1)-(10B), except that linearized equation (11) replaces nonlinear equations (1) and (2).

[0061] Control sequence generator **40** receives B domain constraints **42** (i.e. light constraints **16** converted from the intensity domain I to the B domain by Ito B converter **34**), free response information **38**, light estimate input **21** and circadian state feedback signal **14** and uses these inputs to generate a series of control moves in the B domain (not shown). In preferred embodiments, control sequence generator **40** determines a series of "optimal" control moves in the B domain (not shown) which extend over a time period beginning at the current time and extending out to the control horizon H. As explained further below, this series of control moves is "optimized" by minimizing a cost function over the time period between the current time and the control horizon H. At each sampling interval, control sequence generator **40** outputs the first control move of this series as B domain control signal **46**. B domain control signal **46** is converted by B to I converter **48** into light control signal **13** in the intensity domain I. As discussed above, light control signal **13** controls the operation of light source(s) **18** and the amount of light **19** experienced by subject **17**.

[0062] In some embodiments, the cost function used by control sequence generator **40** is a least squares cost function. In one particular embodiment, the cost function used by control sequence generator **40** is expressed as:

$$J = \sum_{k=1}^{P} \|\delta(k)[\hat{x}(t+k\,|\,t) - r(t+k)]\|^2 + \sum_{k=1}^{P} \|\lambda(k)B(t+k-1)\|^2 \quad (13)$$

where p is the number of samples between the current time t and the control horizon H, $\delta(k)$ is a weighting factor associated with the tracking error (i.e. the difference between the circadian state $\hat{x}$ predicted by controller subject model **44** and the reference circadian state r described by reference trajectory **15**), $\lambda(k)$ is a weighting factor associated with the cost of the driving input B and k is an index variable that indexes a particular sampling interval within the control horizon H. In

some embodiments, weighting factors $\delta(k)$ and $\lambda(k)$ are constant. In other embodiments, however, weighting factors $\delta(k)$ and $\lambda(k)$ are functions of k, such that additional weight may be applied to tracking particular points on the reference trajectory **15**, such as the maxima and minima of reference trajectory **15** or the zero crossing points of reference trajectory **15** for example.

[0063] Control sequence generator **40** may make use of controller subject model **44** and the inputs described above to determine the "optimal" control moves (in the B domain) which will minimize the cost function of equation (13) over the control horizon H. Such control moves may comprise a series of B values (i.e. at each sampling time) from the current time and extended out to the control horizon H. After each sample interval, the control horizon H is extended by the time of one sampling interval and the control sequence generator **40** recalculates the "optimal" moves.

[0064] In practical situations, there will be light constraints **16** on the light intensity I. Such light constraints **16** may comprise minimum and maximum light intensity levels which may be related to actual physical constraints of light source(s) **18** or to other levels, such as levels designed to promote the comfort of subject **17** or the sleep/wake schedule of subject **17** for example. Light constraints **16** in the intensity domain I are converted to B domain constraints **42** by I to B converter **34** and are provided to control sequence generator **40**. Preferably, light constraints **16** (and corresponding B domain constraints **42**) comprise light constraint values for times extending out to the control horizon H. In some embodiments, light constraints **16** (and corresponding B domain constraints **42**) may be constant.

[0065] As discussed above, I to B converter **34** may make use of a transformation of the form of equation (10B) to transform light constraints **16** in the intensity domain into corresponding B domain constraints **42**. However, calculation of future B domain constraints **42** from future I domain constraints **16** in accordance with equation (10B) requires information about the future values of circadian state variables (x, x_c). This creates an iterative problem, because future values of the circadian state variables (x, x_c) depend in turn on the future B domain constraints **42**.

[0066] In the FIG. **4** embodiment, I to B converter **34** overcomes this iterative problem by making use of the free response information **38** as an approximation of the future values of circadian state variables (x, x_c). As discussed above, the free response information **38** preferably comprises a prediction of the future circadian state of individual **17** under the assumptions that the initial circadian state of individual **17** is indicated by circadian state feedback signal **14** and the current light intensity I indicated by light estimate input **21** will remain constant. In some embodiments, free response information **38** takes the form of a matrix comprising free response values of one or more of the circadian state variables (x, x_c) at p discrete sampling intervals.

[0067] As discussed above, intensity domain light constraints **16** preferably comprise maximum and minimum light intensity levels. These maximum and minimum light intensity levels correspond with maximum and minimum B domain levels, B_{max} and B_{min}. Once the current and future B domain constraints **42** are determined by I to B converter **34**, control sequence generator **40** determines the "optimal" control moves by minimizing a cost function in subject to the constraints:

$$B_{min}(k) \leqq B(k) \leqq B_{max}(k) \text{ for } k=1 \ldots p \quad (14)$$

In embodiments where the cost function is given by equation (13), control sequence generator **40** selects B values for each sampling interval between the current time and extending out to the control horizon H (i.e. where k=p) which minimize the cost function of equation (13) within the constraints given by equation (14). Those skilled in the art of control systems and model-based predictive control are familiar with various techniques and algorithms for numerically or otherwise solving this minimization problem. Typically, such techniques involve constrained quadratic programming methods.

[0068] FIGS. **5** and **6** depict a number of examples of the operation of system **12** to controllably adjust the circadian pacemaker cycle of subject **17** to track a reference trajectory **15** in the presence of lighting constraints **16**. In the examples of FIGS. **5** and **6**, it is assumed that subject **17** is an astronaut in orbit. Astronauts in orbit may experience cycles of sunlight and darkness with greatly reduced periods. It may be desirable to artificially maintain an approximately 24 hour circadian pacemaker cycle to ensure optimal alertness and increased quality of sleep during missions.

[0069] For the purposes of the examples illustrated in FIGS. **5** and **6**, it is assumed that the intensity of light **19** (FIG. **1**) is constrained in the following manner:

[0070] (i) the range of light extends from darkness (I=0 lux) to a maximum light intensity (I=10,000 lux);

[0071] (ii) subject **17** sleeps between time t=0 and time t=8 hours (and every 24 hours thereafter) and no light can be applied during sleep (I=0 lux);

[0072] (iii) a minimum amount of light ($I \geqq 300$ lux) is necessary to perform daily activities while awake (i.e. not sleeping); and

[0073] (iv) the minimum amount of light is reduced ($I \geqq 100$ lux) for the first hour after rising and the last hour before sleeping.

These constraints are represented in FIG. **5** by the dashed curves **65** and **67**, where curve **65** represents the maximum light intensity I_{max} and curve **67** represents the minimum light intensity I_{min}. It is also assumed that the sunlight experienced by the astronaut is insignificant in comparison to applied light **19**.

[0074] In the example depicted in FIG. **5**, subject **17** is maintaining a regular 24 hour schedule of 8 hours asleep and 16 hours awake and the subject's circadian pacemaker cycle (represented by circadian state variable x and curve **62**) is initially closely synchronized to the desired reference trajectory **61**. Curve **60** represents the circadian state variable x_c as a function of time. In the example of FIG. **5**, circadian state variable x_c is not controlled. During operation, Ito B converter **34** converts the intensity domain light constraints I_{max} (curve **65**) and I_{min} (curve **67**) into B domain constraints B_{max} (curve **63**) and B_{min} (curve **68**). As discussed above, control sequence generator **40** generates an optimal set of control moves in the B domain which will allow circadian state variable x (curve **62**) to track reference trajectory **61** by minimizing a cost function subject to the B domain constraints. B domain control signal **46** is represented in FIG. **5** by curve **64**. As discussed above, B to I converter **48** converts B domain control signal **46** (curve **64**) into light control signal **13** (represented in FIG. **5** by curve **66**). As expected from the regular sleep pattern of subject **17**, the subject's circadian pacemaker cycle (as represented by circadian state variable x and curve **62**) continues naturally on its 24 hour rhythm, and little additional light **66** is required to maintain it.

[0075] In the example illustrated in FIG. **6**, subject **17** receives a mission requirement that involves shifting the waking hours ahead by 3 hours. The shift must occur within 2 days. Accordingly, it is desirable to shift the circadian pacemaker cycle of subject **17** such that within two days, the subject's circadian pacemaker cycle (as represented by state variable x and curve **72**) tracks the reference trajectory **71**. It can be seen that initially (i.e. at time t=0), reference trajectory **71** has a three hour phase lead with respect to the subject's circadian pacemaker cycle as represented by circadian state variable x (curve **72**).

[0076] Curve **70** represents the circadian state variable x_c as a function of time. In the example of FIG. **6**, circadian state variable x_c is not controlled. The light constraints in the FIG. **6** example are substantially similar to those in the example of FIG. **5**, with I_{max} represented by curve **75**, I_{min} represented by curve **77**, B_{max} represented by curve **73** and B_{min} represented by curve **78**. Control sequence generator **40** determines the optimum control moves in the B domain which will controllably adjust circadian state variable x (curve **72**) towards reference trajectory **71** by minimizing a cost function subject to the B domain constraints. B domain control signal **46** is represented in FIG. **6** by curve **74**. As discussed above, B to I converter **48** converts B domain control signal **46** (curve **74**) into light control signal **13** (represented in FIG. **6** by curve **76**). As shown in FIG. **6**, by the third day, light control signal **13** (curve **76**) causes an application of light **19** to subject **17** which controllably adjusts the subject's circadian pacemaker cycle (as represented by circadian state variable x and curve **72**) to successfully track reference trajectory **71** by the third day. Comparing curve **76** of FIG. **6** with curve **66** of FIG. **5**, it can be seen that considerably more light is required to substantially shift a subject's circadian pacemaker cycle.

[0077] FIG. **7** depicts a system **112** according to another embodiment of the invention. System **112** is similar in many respects to system **12** of FIGS. **3** and **4**. Features and components of system **112** that are similar to features and components of system **12** are given similar reference numerals preceded by a "1". System **112** differs from system **12** in that system **112** comprises one or more physiological sensors **124** and a circadian state estimator **127** in the place of model **11** (FIG. **3**). Together, physiological sensors **124** and circadian state estimator **127** obtain a circadian state feedback signal **114** that is based, at least in part, on the physiological parameters sensed by sensors **124**.

[0078] Physiological sensors **124** sense one or more physiological parameters from subject **117**. Preferably, the physiological parameters sensed by sensors **124** are correlated to or otherwise related to the circadian state of subject **117**. Preferably, the physiological parameters sensed by sensors **124** vary periodically in a manner that is related to the periodic variation of the circadian cycle of subject **17**. Examples of physiological parameters include, without limitation: heart rate, core body temperature, respiration, endocrine function levels, physical activity levels, blood pressure, blood oxygen concentration and/or skin temperature.

[0079] The sensed values **126** of the physiological sensors **124** are provided to circadian state estimator **127**. In some embodiments, the sensed values **126** of the physiological sensors **124** are communicated to circadian state estimator **127** via a wireless communication means (not shown). This allows subject **117** to be mobile. In other embodiments, the sensed values **126** of the physiological sensors **124** are communicated to circadian state estimator **127** via one or more corresponding wires. Noise **125** may appear parasitically in the sensed values **126** of the physiological sensors **124** prior to their reaching circadian state estimator **127**. Noise **125** may be modeled as part of circadian state estimator **127** and/or in the model(s) associated with light controller **110**. In some embodiments, noise **125** is modeled stochastically.

[0080] Circadian state estimator **127** receives the sensed values **126** of the physiological sensors **124** and uses this information to determine an estimate of the circadian pacemaker state of subject **117**. This estimate of the circadian pacemaker state of subject **117** is provided to controller **110** as circadian state feedback signal **114**. Preferably, circadian state feedback signal **114** generated by circadian state estimator **127** comprises one or more of the circadian state variables (x, x_c) of the Jewett-Kronauer model. In some embodiments, circadian state estimator **127** comprises a model (not shown) which relates the values of one or more physiological parameters to the circadian state of subject **117**. Such a model may be empirically determined and may use the sensed values **126** from physiological sensors **124**.

[0081] Circadian state estimator **127** may receive other information **128** which it uses to help determine an estimate of the circadian state of subject **117**. Information **128** may include one or more parameters that may be entered by subject **117**, such as the sleep/wake schedule of subject **117** for example. Information **128** may include one or more parameters that are particular to subject **117**, such as an indicator of the responsiveness of subject **117** to light (or other stimulus) for example. Information **128** may include one or more parameters associated with the environment in which subject **117** spends his or her time, such as temperature, time of day, time zone and background stimulus level for example.

[0082] As with system **12** of FIGS. **3** and **4**, system **112** comprises one or more light sources **118** that output light **119** in response to light control signal **113** from controller **110**. In the illustrated embodiment, system **112** comprises one or more light sensors **120** which measure light intensity **129** present in the environment of subject **117**. Light intensity **129** measured by light sensor(s) **120** represents an estimate of the light intensity experienced by subject **117**. Light **129** differs from the light output **119** from light source(s) **118**, as measured light disturbances **122** (for example, from other light sources) may be measured as a part of light **129**. In addition, light **129** differs from the light **130** actually experienced by subject **117**, as unmeasured light disturbances **123** may not be measured by light sensor **120**. Light **129** measured by light sensor **120** is fed back to controller **110** as light estimate signal **121**. Controller **110** uses light estimate signal **121** as discussed above in relation to controller **10**. In some embodiments, controller **110** uses light estimate signal **121** to adjust light control signal **113** to compensate for the addition of light disturbances **122** and/or **123**.

[0083] In other respects, system **112** is substantially similar to system **12** of FIGS. **3** and **4**. In particular, the components and operation of light controller **110** are substantially similar to the components and operation of light controller **10** shown in FIG. **4** and described in detail above.

[0084] FIG. **8** schematically depicts a method **200** for controlling a circadian cycle of a subject in accordance with a particular embodiment of the invention. Method **200** may be executed by controller **10**, **110** of systems **12**, **112**. After commencing, method **200** proceeds to block **202**, which involves determining the initial conditions. The initial conditions may include the initial circadian state of the subject. In

one particular embodiment, the initial conditions comprise values of one or more of the state variables (x, x_c, n) of the Jewett-Kronauer model. In other embodiments, the initial conditions determined in block **202** comprise values of state variables associated with other models. The initial conditions determined in block **202** may be used by controller **10**, **110** of systems **12**, **112**. In particular, the initial conditions may be used by response predictor **32** as the initial conditions for response predictor subject model **36** and/or by control sequence generator **40** as the initial conditions for controller subject model **44**. The initial conditions determined in block **202** may also be used as the initial conditions for model **11** of system **12**.

[0085] In some embodiments, determining the initial conditions in block **202** involves arbitrarily assigning initial conditions. In other embodiments, determining the initial conditions in block **202** involves estimating the circadian state of the subject based on measurement of one or more physiological parameters. Such estimation may be substantially similar to the estimation performed by circadian state estimator **127** described above and may incorporate other information similar to information **128** described above. In still other embodiments, determining the initial conditions in block **202** may comprise determining an initial time and using a population average circadian state for the initial time.

[0086] Method **200** then proceeds to block **204** where input information is obtained. As shown best in FIG. **4**, the input information includes the desired reference trajectory **15**, light constraints **16**, light estimate **21** and circadian state feedback signal **14**. In particular embodiments which employ the Jewett-Kronauer model, reference trajectory **15** and circadian state feedback signal **14** may comprise one or more of the Jewett-Kronauer circadian state variables (x, x_c). In other embodiments, reference trajectory **15** and circadian state feedback signal **14** comprise values of state variables associated with other models. In some embodiments (such as system **12** of FIG. **3**), circadian state feedback signal **14** is derived from a model **11**. In other embodiments, (such as system **112** of FIG. **7**), circadian state feedback signal **14** is derived from sensed physiological parameters **126** and a corresponding estimate of the subject's circadian state. Light constraints **16** may comprise minimum and maximum light levels. In some embodiments, minimum light levels are determined with reference to varying expected ambient light levels. As discussed above, light estimate **21** may comprise a sensed value of the light experienced by the subject and/or an estimated value of the light experienced by the subject.

[0087] Block **206** of method **200** involves determining the free response of the subject out to a control horizon H. As discussed above in the description of FIG. **4**, determining the free response in block **206** may be performed by response predictor **32**. Response predictor **32** may use a response predictor subject model **36**. Determining the free response in block **206** may involve the assumptions that the current circadian state of the subject (as determined by circadian state feedback signal **14**) represents the initial conditions and that current light control signal **13** remains constant.

[0088] In block **208**, method **200** involves determining the optimal control moves out to the control horizon H. As discussed above in the description of FIG. **4**, determining the optimal control moves in block **208** may be performed by control sequence generator **40**. Control sequence generator **40** may make use of a controller subject model **44**, which may be linearized. Determining the optimal control moves in block **208** may comprise minimizing a cost function which has a term associated with tracking error and a term associated with the amount of control signal required. The cost function may comprise weighting factors which may be constant or time dependent. The cost function incorporates each control move (i.e. one for each sampling interval) as independent variables. Minimization of the cost function is accomplished by finding the set of control moves that produces a minimum. This minimization operation may be performed by expressing the equations for the cost function and the constraints as a linear matrix inequality and then solving the linear matrix inequality in accordance with one of many well known numerical techniques.

[0089] Model based predictive control techniques of the type employed in blocks **206** and **208** of method **200** are well known to those skilled in the art and are described comprehensively in "Predictive Control with Constraints", Jan Maciejowski, 2002 (Pearson Education POD), which is hereby incorporated herein by reference.

[0090] Once the optimal control moves are determined in block **208**, method **200** proceeds to block **210** which involves outputting a control stimulus signal. As discussed above, the control stimulus signal may comprise a light control signal **13**. Preferably, the control stimulus signal comprises the first control move of the optimal series of control moves determined in block **208**.

[0091] After outputting a control stimulus signal in block **210**, method **200** loops back to block **204** and then repeats itself. Preferably, the loop which comprises blocks **204**, **206**, **208** and **210** is performed at least once every sampling interval.

[0092] The systems and methods of the current invention have useful application in a variety of fields including, without limitation: controlling workplace lighting to maintain maximum employee performance; synchronizing multiple subjects to a common circadian cycle to improve operational efficiency; modifying circadian cycles of individuals undergoing medical therapy to improve their response to pharmaceutical drugs; modifying circadian cycles of athletes to allow peak performance at certain times; controlling lighting in the home to help make the daily processes of waking and falling asleep more comfortable, and providing individualized light recommendations or control for personal advisory systems.

[0093] Controlling workplace lighting by providing additional light or restricting the level of light as appropriate can create benefits for various types of employees. Example applications include workers in windowless or underground rooms, submarine personnel and miners who receive no natural light; hospital employees, utility employees and other types of shift workers who may receive some natural light at times that may be inappropriate to the workers' circadian pacemaker cycle; and workers (or other travelers) aboard aircraft or spacecraft, who experience abnormal natural light levels due to the speed of their travel in relation to the sun. The systems and methods of the invention could be applied to control the levels of light stimulus to help advantageously regulate the circadian cycles of these types of subjects.

[0094] Another application of the systems and methods of the invention comprises synchronization of the circadian cycles of multiple subjects. Scientific research often requires the performance of experiments such as controlled tests of a new technology, drug, method or product on a given sample group of animals. The sample group may consist of rats, mice, primates and other animals, or human subjects. In many

instances, the response of each test subject in the sample group will vary depending on the state of the test subject's circadian cycle. It would be advantageous, therefore, to normalize the initial conditions of each test subject in a sample group by providing a means for synchronizing the circadian pacemaker cycle of each member of the sample group before conducting the experiment. The particular pattern of light exposure could be customized for each member of the sample group in order to most efficiently entrain their circadian pacemaker cycle to a desired common cycle.

[0095] In addition to improving the accuracy of scientific experimentation, synchronization of the circadian cycles of multiple human subjects may be beneficial in certain kinds of military operations. In particular, when a given military operation requires the simultaneous action of many individuals, the probability of success of the operation may be higher if the individual members of the force are all operating at maximum alertness and cognitive performance.

[0096] Another application of the systems and methods of the present invention relates to adjusting the circadian pacemaker cycle of individuals who compete in athletic events. In some circumstances, such athletes have to travel relatively long distances to compete and after traveling such a distance, it may be advantageous to control the circadian pacemaker cycle of such athletes to achieve maximum performance during the athletic event.

[0097] Another application of the systems and methods of the present invention is in the area of medical therapy. It is well understood by medical professionals that a patient undergoing pharmaceutical drug treatment responds differently to prescribed drugs at different states of her endogenous circadian pacemaker cycle. The methods and systems of the present invention could be used to control the patient's circadian pacemaker cycle such that the drugs could be administered at optimum times to have a desired effect.

[0098] Yet another area in which the systems and methods of the present invention may be useful is generally known as home automation. Basic lighting and sound systems used in homes require manual control to adjust the levels of intensity. Before during, and immediately after waking, and also in the evening immediately before and after falling asleep, such manual control may be inconvenient and uncomfortable. The systems and methods of the invention may be employed to control lighting and/or sound systems to turn them on or off at specific times or to increase/decrease their intensity at specific rates of change. Such systems could function as part of a waking alarm, generating a gradually increasing level of light (and/or other stimulus) at a specific time over a given interval of time, so as to beneficially modify the subject's circadian pacemaker cycle towards a cycle consistent with experiencing wakefulness at desired times.

[0099] Still another field of application of the systems and methods of the present invention relates to a personal ambient light advisory system, to assist with adjusting an individual's circadian pacemaker cycle. The invention could be applied as an off-line system that uses models to generate recommended light levels for a given set of constraints and objectives. The advisory system could optionally also incorporate real-time sensor input regarding light levels, activity patterns, or physiological parameters. The controller could then update its advice on light levels in real-time. Systems of these types could be implemented on personal digital assistants (PDA's), cellular telephones, personal computers or other portable devices with computational capability for example. Such an advisory system could comprise or otherwise be coupled with a light delivery apparatus such as a portable high-intensity light source, where it could provide recommendations for use or directly control the light output. Potential users of such systems include transmeridian airline travelers and shift work professionals.

[0100] Certain implementations of the invention comprise computer processors which execute software instructions which cause the processors to perform a method of the invention. 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 signals comprising instructions which, when executed by a data processor, cause the data processor to execute a method of the invention. The program product 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, DVDs, electronic data storage media including ROMs, flash RAM, or the like or transmission-type media such as digital or analog communication links. The program product may also comprise data, databases or other information which may be accessible to, but not necessarily executed by, a processor.

[0101] Where a component (e.g. a controller, model, assembly, device, 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.

[0102] 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:

[0103] Systems **12**, **112** may be implemented using various types of programmable controllers or processors. For example, systems **12**, **112** may comprise a programmable computer, an embedded processor or the like. Systems **12**, **112** may comprise more than one such processor. Systems **12**, **112** may also include memory (not shown) which stores program information and the like.

[0104] In physical embodiments, various features of systems **12**, **112** may reside in the same physical component. For example, in system **12** of FIG. **3**, model **11** and light controller **10** are shown as being distinct features. However, those skilled in the art will appreciate that system **12** may comprise a single processor and that both model **11** and light controller **10** may be implemented on such a processor.

[0105] The systems and methods described above make use of the Jewett-Kronauer model equations (1)-(10B) which represent one particular model of the response of the human circadian cycle to light stimulus. Those skilled in the art will appreciate that other models may exist in the art or may become known in the future. The invention should be understood to include such alternative models. Such models may be used as a basis for any of the models of systems **12**, **112**. Those skilled in the art

will also appreciate that such models are not limited to light stimulus, nor are they limited to a single type of stimulus.

[0106] Systems **12**, **112** described above make use of light stimulus. Those skilled in the art will appreciate that the models used in systems **12**, **112** may model the response of the human circadian cycle to different stimulus, such as melatonin stimulus, heat stimulus and audio stimulus for example. The light source(s) of systems **12**, **112** may be replaced by one or more additional and/or alternative sources of stimuli.

[0107] Systems **12**, **112** described above make use of light stimulus to modify a subject's circadian cycle. Those skilled in the art will appreciate that different wavelengths of light stimulus will have different effects on the circadian cycle. Those skilled in the art will also appreciate that this information may be incorporated into systems **12**, **112** and/or into the models associated therewith. For example, the models used in systems **12**, **122** may include light wavelength as a parameter, light sensors used in systems **12**, **112** may sense a specific wavelength spectrum of light, and the light stimulus used in systems **12**, **112** may be provided by one or more variable wavelength light sources.

[0108] The systems and methods of the invention are not limited to application on human subjects and may be used on animals given the appropriate model. For example, the circadian cycles of animals, such as racehorses, could also be modified to ensure peak performance at certain times.

[0109] Although light is a preferred stimulus, the invention may incorporate one or more other types of stimulus, including without limitation, sound, introduction of melatonin, introduction of food and the timing of physical activity.

[0110] Those skilled in the art will appreciate that there may be more than one circadian cycle in a subject, that there may be more than one circadian pacemaker, and that the invention may be applied to any combination of them.

Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

What is claimed is:

1. An automated method for controllably adjusting a circadian state of a subject to a desired circadian phase over a time period between a first time and a future time, the method comprising, in an automated system:

(a) providing a stimulus source for applying a stimulus output to the subject;

(b) receiving a reference trajectory, the reference trajectory specifying a desired circadian state of the subject for each of a plurality of time steps between the first time and the future time;

(c) receiving constraints comprising minimum and maximum levels of the stimulus output at each of the plurality of time steps between the first time and the future time;

(d) receiving a circadian state feedback signal comprising an estimate of the subject's circadian state at a current time step;

(e) receiving a stimulus estimate of a stimulus intensity experienced by the subject at the current time step;

(f) using a computer-implemented response predictor model to predict a free response estimate of the subject's circadian state at each of the time steps between the current time step and the future time, wherein using the computer-implemented response predictor model to predict the free response estimate of the subject's circadian state comprises assuming that: (i) the subject's circadian state at the current time step is given by the circadian state feedback signal; and (ii) the stimulus estimate will be constant at each of the time steps between the current time step and the future time;

(g) using a computer-implemented control sequence generator to:

generate an optimized series of inputs to the stimulus source comprising one input to the stimulus source for each of the time steps between the current time step and the future time; and

predict a controller subject model response estimate of the subject's circadian state at each of the time steps between the current time step and the future time, wherein predicting the controller subject model response estimate comprises assuming that: (i) the subject's circadian state at the current time step is given by the free response estimate at the current time step; and (ii) the optimized series of inputs will be applied to the stimulus source at each of the time steps between the current time step and the future time;

wherein using the computer-implemented control sequence generator to generate the optimized series of inputs comprises performing a computer-implemented numerical optimization process to minimize a cost function subject to the constraints, the cost function based in at least a computationally significant part on a difference between: (i) the reference trajectory at each of the time steps between the current time step and the future time; and (ii) the controller subject model response estimate at each of the time steps between the current time step and the future time;

(h) applying the optimized input corresponding to the current time step to the stimulus source to thereby effect a constant stimulus output intensity level between the current time step and an immediately subsequent time step; and

(i) incrementing the current time step to be the immediately subsequent time step and repeating steps (d) though (i);

wherein application of the optimized input to the stimulus source in each repetition of step (h) causes the subject's circadian state to track the reference trajectory between the first time and the future time subject to the constraints.

2. A method according to claim **1** wherein each iteration of steps (d) through (i) comprises, before incrementing the current time step:

using the circadian state feedback signal, the optimized input corresponding to the current time step and a computer-implemented third model to estimate the subject's circadian state at the immediately subsequent time step, wherein estimating the subject's circadian state at the immediately subsequent time step comprises assuming: (i) the subject's circadian state at the current time step is given by the circadian state feedback signal; and (ii) the optimized input corresponding to the current time step will be applied to the stimulus source between the current time and the immediately subsequent time;

setting the estimate of the subject's circadian state at the immediately subsequent time step to be the circadian state feedback signal received during the next iteration of step (d).

3. A method according to claim **1** wherein receiving the circadian state feedback signal in step (d) comprises estimating the subject's circadian state at the current time step based at least in part on a physiological measurement indicative of the subject's circadian state.

4. A method according to claim **1** wherein the plurality of time steps between the first time and the future time comprise equal time steps, each having a duration in a range of 1 minute to 1 hour.

5. A method according to claim **1** wherein a difference between the first time and the future time is in a range of 12 hours to 72 hours.

6. A method according to claim **1** wherein repeating steps (d) through (i) comprises repeating steps (d) through (i) until the current time step reaches the future time.

7. A method according to claim **1** wherein repeating steps (d) through (i) comprises continuing to repeat steps (d) through (i) after the current time reaches the future time until a control horizon, to thereby maintain the subject's circadian state at the desired circadian phase after the future time and until the control horizon.

8. A method according to claim **7** comprising extending the control horizon to be one time step further into the future as part of each iteration of steps (d) through (i).

9. A method according to claim **1** wherein response predictor model comprises a mathematical model defined by a plurality of differential equations.

10. A method according to claim **9** wherein the mathematical model is based on a linearized version of a van der Pol oscillator equation.

11. A method according to claim **1** wherein using a control sequence generator to predict a controller subject model response estimate of the subject's circadian state comprises using a controller subject model, the controller subject model comprising a mathematical model defined by a plurality of differential equations.

12. A method according to claim **11** wherein the mathematical model is based on a linearized version of a van der Pol oscillator equation.

13. A method according to claim **2** wherein the third model comprises a mathematical model defined by a plurality of differential equations.

14. A method according to claim **13** wherein the mathematical model is based on a linearized version of a van der Pol oscillator equation.

15. A method according to claim **3** wherein the physiological measurement indicative of the subject's circadian state comprises one or more of: heart rate, core body temperature, respiration, endocrine function levels, physical activity levels, blood pressure, blood oxygen concentration and skin temperature.

16. A method according to claim **1** wherein receiving the stimulus estimate comprises sensing the stimulus received by the subject.

17. A method according to claim **1** wherein receiving the stimulus estimate comprises receiving information correlated with the stimulus experienced by the subject and estimating the stimulus estimate based at least in part on the information.

18. A method according to claim **17** wherein the information correlated with the stimulus experienced by the subject comprises one or more of: the optimized input applied to the stimulus source; estimates of sunlight; estimates of one or more artificial light sources; time of day; date; location of subject; activity patterns of the subject; and estimates of an amount of light incident on the retinas of the subject.

19. A method according to claim **1** wherein the cost function is also based in at least a computationally significant part on a cost term associated with amplitudes of the optimized series of inputs to the stimulus source at each of the time steps between the current time step and the future time.

20. A method according to claim **19** wherein the cost function comprises:

a first weighting factor associated with the difference between: (i) the reference trajectory at each of the time steps between the current time step and the future time; and (ii) the controller subject model response estimate at each of the time steps between the current time step and the future time; and

a second weighting factor associated with the amplitudes of the optimized series of inputs to the stimulus source at each of the time steps between the current time step and the future time.

21. A method according to claim **20** wherein the first and second weighting factors vary over a duration of the circadian cycle of the subject.

22. A method according to claim **1** wherein the constraints comprise a maximum stimulus output level of zero for at least a sleep portion of each twenty-four hour day between the first time and the future time.

23. A method according to claim **22** wherein the sleep portion occurs at a constant time within each twenty-four hour day between the first time and the future time.

24. A method according to claim **1** wherein the constraints are determined based at least in part on one or more of: physical constraints of the stimulus source; stimulus levels selected to promote comfort of the subject; and scheduled sleep behavior of the subject.

25. A method according to claim **1** comprising:

at an intermediate time between the first time and the future time, receiving one or more of: a new desired circadian phase, a new reference trajectory, a new future time and new constraints; and

for repetitions of steps (d) through (i) taking place after the intermediate time, respectively substituting one or more of: the new desired circadian phase for the desired circadian phase, the new reference trajectory for the reference trajectory, the new future time for the future time and the new constraints for the constraints.

26. An automated system for controllably adjusting a circadian state of a subject to a desired circadian phase over a time period between a first time and a future time, the automated system comprising:

(a) a stimulus source for applying a stimulus output to the subject;

(b) one or more inputs for receiving:

a reference trajectory specifying a desired circadian state of the subject for each of a plurality of time steps between the first time and the future time; and

constraints comprising minimum and maximum levels of the stimulus output at each of the plurality of time steps between the first time and the future time;

(c) a circadian state estimator configured to estimate a circadian state feedback signal comprising an estimate of the subject's circadian state at a current time step;

(d) a stimulus estimator configured to estimate a stimulus intensity experienced by the subject at the current time step;

(e) a computer-implemented response predictor configured with a response predictor model for predicting a free response estimate of the subject's circadian state at each of the time steps between the current time step and the future time under assumptions that: (i) the subject's circadian state at the current time step is given by the circadian state feedback signal; and (ii) the stimulus estimate will be constant at each of the time steps between the current time step and the future time;

(f) a computer-implemented control sequence generator configured:

to generate an optimized series of inputs to the stimulus source comprising one input to the stimulus source for each of the time steps between the current time step and the future time; and

with a controller subject model for predicting a controller subject model response estimate of the subject's circadian state at each of the time steps between the current time step and the future time under assumptions that: (i) the subject's circadian state at the current time step is given by the free response estimate at the current time step; and (ii) the optimized series of inputs will be applied to the stimulus source at each of the time steps between the current time step and the future time;

wherein the control sequence generator is configured to generate the optimized series of inputs by performing a computer-implemented numerical optimization process to minimize a cost function subject to the constraints, the cost function based in at least a computationally significant part on a difference between: (i) the reference trajectory at each of the time steps between the current time step and the future time; and (ii) the controller subject model response estimate at each of the time steps between the current time step and the future time; and

(g) one or more outputs for applying the optimized input corresponding to the current time step to the stimulus source to thereby effect a constant stimulus output intensity level between the current time step and an immediately subsequent time step;

wherein the system is configured to incrementing the current time step over each of the plurality of time steps between the first time and the future time and wherein application of the optimized input to the stimulus source in each time step causes the subject's circadian state to track the reference trajectory between the first time and the future time subject to the constraints.

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摘要(译)

本发明的各方面提供了用于通过应用基于模型的预测控制技术使用光（或其他刺激）可控地调节受试者的昼夜节律起搏器周期的系统和方法。这种方法允许使用闭环反馈来补偿建模误差，未知的初始条件和干扰。它还允许基于成本函数的最小化来生成最佳水平的光（或其他刺激）。成本函数可以包括与跟踪误差相关联的术语和与所使用的光量相关联的术语。可以根据一个或多个约束来最小化跟踪功能，所述约束可以包括最小和最大量的光（或其他刺激）。