

# Individualized and time-variant model for the functional link between thermoregulation and sleep onset

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**SUMMARY** This study makes use of control system model identification techniques to examine the relationship between thermoregulation and sleep regulation. Specifically, data-based mechanistic (DBM) modelling is used to formulate and experimentally test the hypothesis, put forth by Gilbert *et al.* [*Sleep Med. Rev.* 8 (2004) 81], that there exists a connection between distal heat loss and sleepiness. Six healthy sleepers each spent three nights and the following day in the sleep laboratory: an adaptation, a cognitive arousal and a neutral testing day. In the cognitive arousal condition, a visit of a television camera crew took place and subjects were asked to be interviewed. During each of the three 25-min driving simulator tasks per day, the distal-to-proximal gradient and the electroencephalogram are recorded. It is observed from these experimental data that there exists a feedback connection between thermoregulation and sleep. In addition to providing experimental evidence in support of the Gilbert *et al.* (2004) hypothesis, the authors propose that the nature of the feedback connection is determined by the nature of sleep/wake state (i.e. NREM sleep versus unwanted sleepiness in active subjects). Besides this, an individualized and time-variant model for the linkage between thermoregulation and sleep onset is presented. This compact model feeds on real-time data regarding distal heat loss and sleepiness and contains a physically meaningful parameter that delivers an individual- and time-depending quantification of a well known biological features in the field of thermoregulation: the thermoregulatory error signal  $T_{\text{hypo}}(t) - T_{\text{set}}(t)$ . A validation of these physical/biological features emphasizes the reliability and power of DBM in describing individual differences related to the sleep process.

**KEYWORDS** data-based mechanistic model, distal heat loss, distal-to-proximal gradient, individual differences, sleepiness, two-process model of sleep

## INTRODUCTION

Recently, reports are made of systematic individual differences in sleepiness between subjects, the tendency to fall asleep and the sensitivity to sleep deprivation. Recent studies indicate that the magnitude of these individual differences is of substantial

nature (Van Dongen *et al.*, 2004). Handling this Complex Individual Time-variant Dynamic (CITD) character of the human sleep function represents a new challenge within the research domain of sleep, as the existing mathematical models for prediction of sleepiness and performance are valid for a population but for the time being incapable to capture individual and time-varying characteristics of the phenomena.

To gain more insight in the functioning of such CITD systems, purely experimental deduction will not suffice because of the intrinsic complexity of biological systems (Kitano, 2002). However, the combination of engineering system

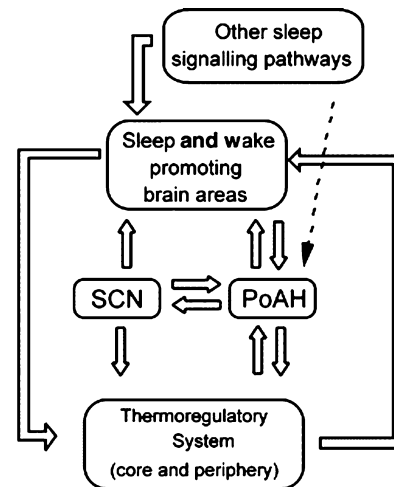
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identification theory and experimental biology – called Systems Biology – offers great perspectives. Systems Biology advocates decompositions of biological systems in several subsystems according to traditional engineering (e.g. Hartwell *et al.*, 1999; McAdams and Sharipo, 1995) and engineering control theory (e.g. Csete and Doyle, 2002). These subsystems are then described by basic mathematical model structures that allow derivation of biological insights in the considered process.

Consider the example of designing an autopilot function for driving a car. First, a mathematical model of the vehicle dynamics is designed, which describes how the driving direction of the car (output) changes when turning the steering wheel (input). By using sensors to measure the output continuously, the operator uses the model to calculate how these measurements should be employed to adjust the inputs in case the desired driving direction is not followed. The car can then be quickly and smoothly guided back to the desired driving track (after Tomlin and Axelrod, 2005).

Classic models for sleepiness, like the two-process model for sleep regulation by Borbely (1982), describe two important components of sleepiness, notably process S – the homeostatic component or the prior amount of sleep and wake – and process C – the circadian component that expresses the fluctuation of sleepiness over a 24-h period. These models allow prediction of the tendency to fall asleep at a certain moment of the day as a function of the prior amount of sleep and wake, but only on a population level. Recently, Van Dongen and Dinges (2003) started with integrating inter-individual characteristics in the two-process model for sleep regulation. Other and more mechanistic models try to describe individual differences in sleepiness in a strictly mathematical way, but are highly complex by the high number of assumptions and parameters. This results in questionable accuracy and applicability (e.g. Nakao *et al.*, 1995). Many equations with a high number of parameters that all have to be known at any moment, are a direct result of the use of such mechanistic models (Young *et al.*, 1987) and confine the usage, reliability and accuracy of such models.

A functional link between thermoregulation and sleep onset has long been recognized and thoroughly reported in both animals and humans (e.g. Brown, 1979; Gilbert *et al.*, 2004; Haskell *et al.*, 1981; Parmeggiani and Rabini, 1970). Distal heat loss [measured through the distal-to-proximal gradient (DPG)] increases and core body temperature (CBT) decreases at attempted sleep onset (Krauchi *et al.*, 1999; Lack and Gradisar, 2002). But it is still unclear whether the relation between thermoregulation and sleep is merely coincidental or causative, and in which direction this possible causality holds. Recently, Gilbert *et al.* (2004), in their comprehensive review, hypothesized a positive feedback integration of thermoregulatory changes and attempted sleep onset when lying down in bed, where changes in CBT and distal heat loss both trigger and reinforce sleep onset (overview: see Fig. 1). According to this model, firstly blood supply to the peripheral vasculature is increased when an individual attempts to sleep. Hence heat



**Figure 1.** Positive feedback connection between thermoregulation and sleep onset (Gilbert *et al.*, 2004) with the internal circadian pacemaker suprachiasmatic nuclei (SCN) and control site for thermoregulation pre-optic anterior hypothalamus (PoAH).

loss at these peripheral regions increases. This increase in skin temperature creates a positive thermal gradient with the environment allowing the conduction, convection and radiation of heat to occur. Secondly, this rapid increase in heat loss stimulates efferent warm sensitive neurones (WSN) in the preoptic anterior hypothalamus (PoAH) which innervate other somnogenic brain structures while thermosensitive neurones innervating wake-promoting brain areas are inhibited. The overall result is the activation of sleep-promoting areas and the inhibition of wake-promoting areas resulting in an increase in sleepiness, which leads to sleep onset. Thirdly, sleep onset itself is associated with a reduction in the set point of thermoregulation resulting in further peripheral heat loss and a sustained reduction in CBT, which again activates the WSN-promoting sleep. In this way, a positive feedback loop is formed between the thermoregulatory system and the sleep/wake-promoting areas of the brain. The promotion of sleep is reinforced resulting in sleep consolidation. Clearly, the thermoregulatory sleep signalling system is not the only mechanism or pathway through which sleep is regulated. But, as Gilbert *et al.* (2004) indicated, experimental evidence supporting this hypothesis is missing. A recent report by the authors investigated thermoregulatory features in relation to sleep initiation in situations where NREM sleep stage 1 is not reached. From this study (Quanten *et al.*, in press), it appeared that the classic thermoregulatory changes also occur under conditions where no actual sleep onset is achieved. This might form additional evidence for the hypotheses that distal heat loss indicates that our body is ready to fall asleep, as stated already by Magnussen (1943).

Therefore, this research is aimed at (1) providing experimental evidence for and testing of the proposed feedback hypothesis by Gilbert *et al.* (2004) between sleep and thermoregulation and (2) quantifying the individual and time-varying differences in the relation between thermoregulation and sleep onset by using modern model identification techniques.

## MATERIALS AND METHODS

### Subjects

Subjects were recruited via the electronic newsletter of the Free University of Brussels. Eight males and six females between 20 and 35 years of age (mean = 27, SD = 5.5) enrolled in the study. Prior to the laboratory study, all subjects were instructed to complete a sleep diary for a period of 1 week. They were informed about the protocol, except for the visit of a television camera crew in the arousal condition, which they were debriefed about, at the end of the last testing day. They gave their informed consent and were paid for their participation. Inclusion criteria were: regular sleep/wake schedule, no sleep complaints, good general health, habitual caffeine usage not exceeding 4 units per day, and having a driving licence. All subjects scored between 0 and 5 on the Pittsburgh Sleep Quality Index (Buysse *et al.*, 1989), indicating that they were moderate to good sleepers. They reported average sleep-onset latencies below 20 min, except for one subject with an average latency of 31.5 min. There were no habitual short or long sleepers in the group (average total sleep time >6 and <9 h) and their sleeping period was at night-time. The study was approved by the Ethics Committee of the Free University of Brussels.

The subjects were asked to maintain a regular sleep/wake schedule and to consume a maximum of 4 units of alcohol and caffeine per day during the course of the study. Compliance was checked by self-report. On the days before testing they were instructed to abstain from caffeine and alcohol from 16:00 hours onward.

### Experimental design

Following an adaptation night (AD) involving 8 h time in bed, there were two sleep deprivation conditions with 3 h time in bed: an arousal (AR) and a neutral (NE) condition, with and without the announced visit of a television camera crew respectively. Each subject participated in the three testing days – respectively adaptation, arousal and neutral testing days – with 4–7 days in between consecutive testing days. On both the adaptation and the sleep deprivation days, the subjects were tested three times, at 2-h intervals (08:45, 10:45 and 12:45 hours). The testing blocks comprised: a 5-min heart rate recording while sitting, completion of subjective sleepiness/arousal scales, a sleep latency test and a 25-min driving simulator test. Table 1 summarizes the experimental design.

The intention of the announced visit of the camera crew was to induce cognitive arousal in some of the sleep-deprived subjects and, hence, a greater variability in the data set. As the objective was to study bio-responses in relation to driver sleepiness, the occurrence of drive sleepiness was the main criterion of interest. The specific effect of this cognitive arousal in relation to sleep onset latency and driver simulator performance was evaluated by De Valck *et al.* (2004).

**Table 1** Overview of the experimental procedure per experimental conditions

Time (hours)	Experimental condition			Activity
	AD	NE	AR	
22:00	x	x	x	Subjects arrive at laboratory
	x			Adaptation night: 25-min practice session on the driving simulator
	x	x	x	Free time
23:00	x			Bedtime on adaptation night
4:00		x	x	Bedtime on experimental night
7:00	x	x	x	Subjects are awakened
	x	x	x	Shower and breakfast
	x	x	x	Free time
<b>7:50</b>			<b>x</b>	<b>Announcement of the visit of a television camera crew</b>
<b>8:20</b>			<b>x</b>	<b>Arrival of a television camera crew</b>
			<b>x</b>	<b>Subjects are filmed while EEG electrodes are attached and while waiting</b>
8:45	x	x	x	5-min heart rate recordings while sitting
8:50	x	x	x	SSS and POMS
9:00	x	x	x	Sleep latency test
9:30	x	x	x	25-min driving simulator test
<b>10:00</b>			<b>x</b>	<b>Interview with sleep expert</b>
<b>10:35</b>			<b>x</b>	<b>Request for interview with subjects and discussion of interview questions</b>
10:45	x	x	x	5-min heart rate recordings while sitting
10:50	x	x	x	SSS and POMS
11:00	x	x	x	Sleep latency test
11:30	x	x	x	25-min driving simulator test
12:00	x	x	x	Lunch
<b>12:25</b>			<b>x</b>	<b>Interview with subjects</b>
12:45	x	x	x	5-min heart rate recordings while sitting
12:50	x	x	x	SSS and POMS
13:00	x	x	x	Sleep latency test
13:30	x	x	x	25-min driving simulator test
<b>14:00</b>			<b>x</b>	<b>Third testing day: debriefing of subjects on true objective of visit of camera crew</b>
	x	x	x	Subjects are discharged
	x	x	x	In case of extreme sleepiness, a nap is recommended

Activities in bold took place in the arousal condition only. AD, adaptation night; NE, neutral condition; AR, arousal condition; MSLT, multiple sleep latency test; POMS, Profile of Mood Status; SSS, Stanford Sleepiness Scale. From De Valck *et al.* (2004).

### Measurements

#### Multiple sleep latency test

The multiple sleep latency test (MSLT) was conducted according to the standard protocol (Carskadon *et al.*, 1986), except that there were only three, two hourly sessions, instead of the more usual four. EEG recordings were scored in 30 s epochs using the criteria of Rechtschaffen and Kales (1968). The subjects were awakened after three consecutive 30 s epochs of stage 1 sleep or one epoch of any other sleep stage. The Fatigue subscale of the Profile of Mood States (POMS) and the Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973) were used to measure subjective sleepiness. Subjective arousal

was assessed by the Tension subscale of the POMS (MacNair *et al.*, 1971). In both the SSS and the POMS, higher scores are indicative of a higher intensity of the measured construct.

#### Thermoregulation

During simulated driving, CBT (armpit), proximal temperature (midforehead), distal temperature (left hand palmer finger top) and environmental temperature were recorded every 10 s. The DPG is defined as the temperature difference between the distal skin temperature minus the proximal skin temperature. Type-T Comark WFT5M thermocouples were used during the complete experimental procedure (accuracy = 0.1 °C). The thermocouples were coated with plastic spray to prevent potential sweat from interfering with the temperature measurements. The thermocouples were attached to the skin surface with Impega invisible tape, leaving the head of the thermocouple in contact with the surrounding air. CBT was measured under the armpit for practical reasons (minimal disturbance and hence minimized arousal for the test subjects).

In order to determine the best possible position for distal skin temperature measurement in relation to sleep onset, Krauchi has shown that foot skin temperature is affected by postural changes, while finger temperature is not (e.g. Krauchi *et al.*, 1997a,c). The proximal temperature in the presented work is defined in a slightly distinct formulation than the traditional calculation. The traditional determination of the proximal temperature is based on a weighted average of the four skin temperatures (forehead, thigh, infraclavicular area and stomach) as presented by Krauchi *et al.* (1997c).

A problem with using a weighted average of skin temperatures from different body sites is the difference in sensitivity to mental load between those different body sites. Skin temperature at some body sites – like the nose – are sensitive to various kinds of strain, while forehead skin temperature is not (Ishikawa *et al.*, 1998; Vos, 2005). Here, the skin temperature value provides information regarding the status of the sleep function, irrespective of possible additional mental strain. Proximal temperature equals skin forehead temperature, as the unaffected skin forehead temperature solely displays the effect of sleep on the thermoregulation system.

Here, the term 'peripheral heat loss' is used to assess only the dry heat losses (conductive, convective and radiative heat losses) controlled by the peripheral vasomotor changes. As the experiments are performed in a constant and comfortable environment ( $T_{\text{air}} = \pm 23$  °C, RH =  $\pm 50\%$ ), and not in hot or cold environments – no skin evaporative heat loss (latent heat exchanges) is assumed and, hereafter, the term peripheral heat loss only relates to dry heat exchange.

The inclusion of thermoregulatory features in the experimental analysis was done in the last six subjects (54 simulator drivers). Consequently, only data for these last six subjects are at hand for analysing driver sleepiness in relation to biological responses from the drivers, with the additional restriction that one subject had to be excluded as he suffered from insomnia. However, complete and accurate descriptions of the simulator drive in terms of the DPG and EEG, was obtained on only 18

of the 54 occasions. Only one gender is represented in these 18 occasions (all male).

#### Electroencephalogram

The electroencephalogram (EEG) was recorded during driving simulator tests at a sampling rate of 256 Hz using the Procomp+ device and analysed with Biograph V2.1 software (Thoughttechnology Ltd and Mind Media BV, 2000, Roermond-Herten, the Netherlands). Absolute power (mV<sup>2</sup>) in the theta (4–8 Hz), alpha (8–12 Hz), sigma (12–14 Hz), beta-1 (14–20 Hz) and beta-2 (20–35 Hz) bandwidths was computed for both EEG sites (C3-A2 and O2-A1). The raw EEG data were integrated into a single-time signal called 'the relative energy parameter', representing unwanted sleepiness in the drivers (De Waard and Brookhuis, 1991). The relative energy parameter ( $\theta + \alpha/\beta$ ) is calculated from alpha/theta/beta mean values (averaged over 3 min) and these indicators are transformed into a percentage of the initial value in order to standardize the distribution. Sleepy drivers are defined as those subjects experiencing an increase in the relative energy parameter, and non-sleepy drivers are defined as those subjects not experiencing an increase in their relative energy parameter. Additionally, two sleep specialists scored the EEG recordings independently by visual observation of the measured EEG signal. Sleep onset was determined by the starting point of a continuum of three epochs of 30 s of sleep. Their analyses were compared, and in case of disagreement, a mutual agreement had to be reached.

#### Driving simulator

The computer program Drivesim 3.00 of the York driving simulator (York Computer Technologies, Kingston, Ontario, Canada) was used to assess driving performance. The driving simulator consists of a personal computer, a 15" monitor and peripheral steering wheel, accelerator and brake accessories. This type of simulator is validated as an effective and naturalistic research tool to measure psychomotor performance (Arnedt *et al.*, 2000, 2001; Moller *et al.*, 2002). The simulator presents a forward view from the driver's seat on a motorway road scene, with standard lane markings and signs signals appropriate to the road environment. The four-lane route contains no turns, no stop signs or traffic lights, and posted speeds ranging from 70 to 100 km h<sup>-1</sup>. Subjects will be driving for 25 min following the instructions to stay in the right-hand lane to avoid passing cars in the left lane. Corrective steering manoeuvres are a necessity in response to 'virtual wind gusts' not allowing the attention level to slip without crashing.

#### Modelling

Traditionally, three modelling approaches are used worldwide. First, a mechanistic or 'white box' modelling where a model is constructed by moulding all the prior biological knowledge of a process into mathematical formulas. Second, data-based or 'black box' modelling where no assumptions whatsoever are made regarding the biological background of the process, and

a mathematical relation is simply forced through the data based on some identification criterion, like model accuracy ( $R^2$ ) and/or model compactness [Akaike's information criterion (AIC), Akaike, 1973]. The third approach combines the two others: data-based mechanistic (DBM) or 'grey box' modelling. First a simple and compact model is identified in a black box way (hence 'data-based'), but the identified model is only accepted if the identified model can be explained based on existing biological knowledge (hence 'mechanistic'). Recently, it was shown that such an approach delivers new insights in systems biology (Pennisi, 2003).

Although a high amount of variables influence the sleep process, the dynamic response at a certain moment will be determined by a limited number of variables that are dominant at that time. In order to determine the relevance of these dominant variables in describing the process at a certain moment, a DBM modelling technique is used (e.g. Berckmans *et al.*, 1992; Young and Jakeman, 1979; Young and Wallis, 1993). A set of possible compact model structures is estimated based on dynamic experiments on the system (data-based part). The final model structure is chosen based on existing biological knowledge (mechanistic part) resulting in a compact model structure with biological meaningful model structure and parameters. Therefore, DBM assumes a fixed model structure such as:

$$y(t) = \frac{s^n + a_1 s^{n-1} + \dots + a_n}{b_0 s^m + b_1 s^{m-1} + \dots + b_m} u(t - \tau) + \xi(t) \quad (1)$$

where  $s$  is the time derivative operator, i.e.  $s = d/dt$ ;  $y(t)$  is the noisy measured output;  $u(t)$  is the model input;  $\tau$  is the time delay;  $\xi(t)$  is additive noise;  $a_1, a_2, \dots, a_n$  and  $b_0, b_1, \dots, b_m$  are the transfer function denominator and numerator parameters, respectively, and finally the model structure is defined by  $[n \ m \ \tau]$ .

DBM uses specific mathematical identification techniques to determine the best model for such complex processes (Ljung, 1987; Van Huffel and Vandewalle, 1988; Young and Jakeman, 1979). The Simplified Refined Instrumental Variable (SRIV) algorithm developed by Young and Jakeman (1979) uses minimization of the Young identification criterion (YIC; Young and Lees, 1993) for selection of the most appropriate model. Basically, the YIC is an extension of AIC: where AIC is the weighted sum of model accuracy ( $R^2$ ) and model compactness (number of parameters), YIC takes into account the model accuracy, model compactness plus the reliability of the parameter estimation (standard deviation of parameters estimation). The model structure  $[n \ m \ \delta]$  is increased step by step to investigate if an increase in model structure (and hence complexity) leads to a substantial increase in model accuracy, model compactness and/or reliability of the parameter estimation expressed through YIC. As in AIC, the model that minimizes the YIC provides a good compromise between goodness of fit, compactness and parametric efficiency. For more detailed information on the instrumental variable technique, reference is made to Young (1984).

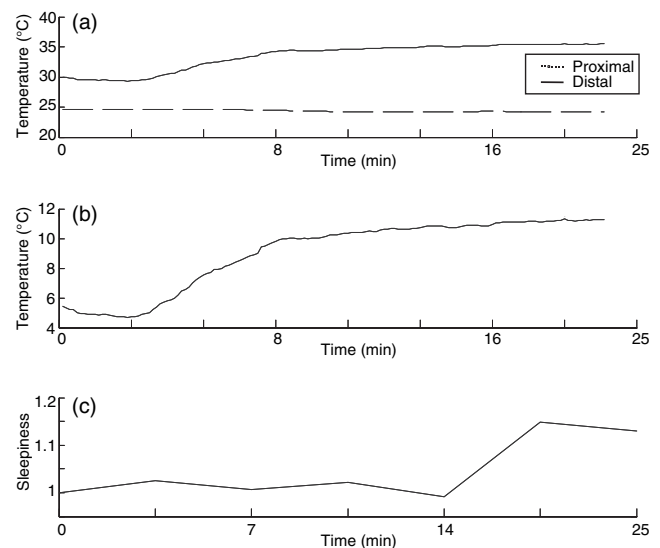
The identified models are so compact that this method becomes applicable to every individual subject. The DBM model structure is completely characterized by the number of model parameters and the time delays between system input(s) and system output(s). As subjects are individually different, their model characteristics will also vary on an individual basis. These individual model characteristics will also vary in time because the subjects' condition itself is a function of time. The hypothesis is that changes in model parameters (increase or decrease in complexity), in parameter values and/or in model time-delays are a quantitative measure for changes in the fundamental biological mechanisms between sleep and thermoregulation of the individual subject.

## RESULTS

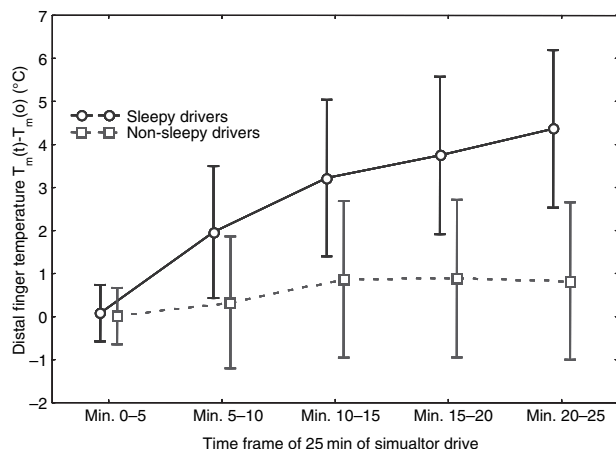
### Thermoregulation and driver sleepiness

Fig. 2 shows a typical example of the mean time course of the both components of and the overall DPG signal, together with the coinciding dynamic course of driver sleepiness, derived from the raw EEG data as described above. In this trial, the test subject was subjected to the following conditions: adaptation night (8 h sleep), starting time 11:30 hours and environmental temperature of 21.1 °C. A distinctive increase in both the DPG and distal finger skin temperature (DFT) of over 4 °C is recorded, coinciding with a clear increase in driver sleepiness towards the end of the simulator drive.

Fig. 3 gives an overview of the interaction between distal heat loss changes and sleep onset over all useful 18 simulator drives in the present study. A statistical package (STATISTICA 5.1)



**Figure 2.** Mean time course of both proximal and distal skin temperatures (a), the associated distal-to-proximal gradient (b) and driver sleepiness derived from the relative energy parameter (De Waard and Brookhuis, 1991) as a percentile distribution of the value at the beginning of the simulator drive at 11:30 hours after an adaptation night (c).



**Figure 3.** Unweighted means and standard error of the means of the levelled distal finger skin temperature  $T_m(t) - T_m(0)$  signal across the 25-min drive for 18 simulator drives performed by six subjects (6 subjects  $\times$  3 simulator drives). The sleepy ( $n = 12$ ) and the non-sleepy simulator drives ( $n = 6$ ) showing a significant interaction effect between the categorical variable sleepiness and time for the distal finger skin temperature values with  $F(4, 64) = 5.6989$  and  $P = 0.00055$  on the 0.05 significance level. Vertical bars denote 0.95 confidence intervals (from Quanten *et al.*, in press).

is used for an ANOVA analysis of the recorded dynamic courses of the DFT. The temperature values for the 25-min simulator drive are processed into five 5-min frame values and defined as the dependent variables. The categorical variable in the ANOVA analysis is the presence or absence of driver sleepiness. Thus a  $2 \times 5$  ANOVA – this means two categorical levels and five dependent levels – can be performed on the thermoregulatory features of 12 sleepy drivers and six non-sleepy drivers. The Greenhouse–Geisser correction is applied on this repeated measures ANOVA on an alpha-correction level of 0.05. As shown in Fig. 3, there is a significant difference between the thermoregulatory response of sleepy drivers and non-sleepy drivers (adjusted Greenhouse–Geisser,  $P = 0.008752$ ). In sleepy drivers, there is a persisting increase in distal finger temperature of over 4 °C during the 25-min simulator drives. Significant differences between the distal finger temperature in the first 5 min of the drive and the last 15 min of the test are found. In contrast to non-sleepy drivers, where no significant increase in distal finger temperature is detected the distal finger temperature level is unaffected. More details are delivered in Quanten *et al.*, in press.

### Model identification and parameter estimation

A DBM model between distal heat loss and driver sleepiness is identified. Distal heat loss, as thermoregulatory response, is in the present work defined as the difference between the distal heat loss at time step  $t$  and the initial heat loss (at time step  $t = 0$ ). In accordance to Nakao *et al.* (1995), we define the change in distal heat loss at time step  $t$  as  $T_m(t) - T_m(0)$  with  $T_m$  as the masking temperature effect coinciding with the heat load

during wake and the heat loss during sleep. Hereby, individual and time-varying differences in basal distal heat loss are accounted for.

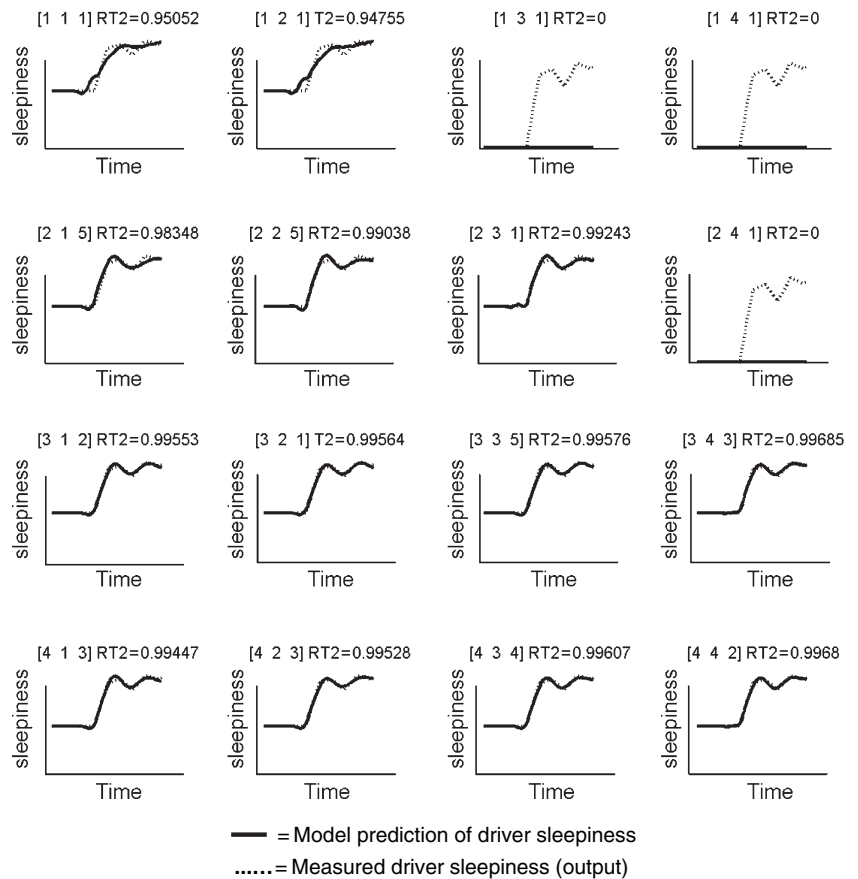
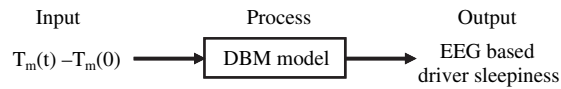
In the present application,  $T_m(t) - T_m(0)$  is defined as the input  $u(t)$  and sleepiness ( $t$ ) derived from EEG is defined as output  $y(t)$  for the DBM model. The modelling results for a typical experiment are shown in Fig. 5 where all possible models from first until fourth order are represented, together with their model structure  $[m \ n \ \tau]$ , model prediction performance in terms of  $R^2$  value, visual fit of the model (prediction) and measured sleepiness signal (output). It is clear that the first-order models on the top row in Fig. 5 fit the data less accurate than the higher-order models. However, no significant improvement in accuracy of the model fit is noticeable between the second-order four-parameter model [2 2 5] and the higher and more complex models. This means that the increase in complexity when choosing a higher-order model results in no relevant or significant increase in model accuracy. Furthermore, Table 2 delivers further evidence in favour of the second-order model. It becomes clear that the parameter estimation of the third-order model is unreliable (high standard deviations on the parameters) with respect to the second-order model. The slightly higher accuracy of the third-order model comes with a high price: higher model complexity and lower reliability of parameter estimates (resulting in a significant higher YIC). Bearing in mind the identification criterion of DBM models (minimize YIC value, Table 2), the second-order four-parameter model is thus accepted as the most accurate description of the dynamics of the system under study (Fig. 4).

### Decomposition of the identified model

A second-order transfer function (TF) model can be rewritten into a serial, parallel or feedback connection of two first-order TF models. Fig. 5 shows the total TF for two first-order TF

**Table 2** The model parameter estimates with associated relative standard error, the YIC value and the coefficient of determination  $R^2$  of a first-, second- and third-order continuous-time transfer function model for the experiment as shown in Fig. 2

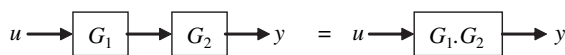
Order of TF	Parameter estimates	Relative standard error (%)	RT2 value	YIC value
[1 1 1]	$a_1 = 0.123$ $b_0 = 0.111$	$E(a_1) = 11.58$ $E(b_0) = 10.74$	0.951	-6.691
[2 2 5]	$a_1 = 0.004$ $a_2 = 0.015$ $b_0 = -0.034$ $b_1 = 0.013$	$E(a_1) = 29.46$ $E(a_2) = 0.94$ $E(b_0) = -9.81$ $E(b_1) = 1.24$	0.99	-6.974
[3 3 5]	$a_1 = 0.091$ $a_2 = 0.015$ $a_3 = 0.001$ $b_0 = 0.001$ $b_1 = 0.007$ $b_2 = 0.001$	$E(a_1) = 26.07$ $E(a_2) = 2.39$ $E(a_3) = 24.03$ $E(b_0) = 1046.50$ $E(b_1) = 14.83$ $E(b_2) = 23.57$	0.996	-0.759



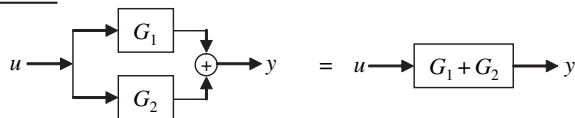
**Figure 4.** Modelling results of DBM model between peripheral skin temperature  $T_m(t) - T_m(0)$  (input) and sleepiness (output) for a typical experiment. Model results for a first-order model (first row), second-order model (second row), third-order model (third row) and fourth-order model (bottom row) are shown, every time with indication of model structure  $[m n \delta]$  and model prediction performance in terms of  $R^2$ -value. The full line represents the model for sleepiness, while the dashed line represents the measured sleepiness (x-axis = time and y-axis is EEG-derived sleepiness).

$$G_1 = \frac{\beta_1}{s + \alpha_1} \quad \text{and} \quad G_2 = \frac{\beta_2}{s + \alpha_2}$$

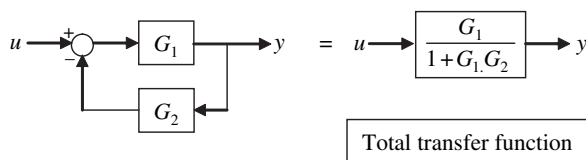
**a. Series**



**b. Parallel**



**c. Feedback**



**Figure 5.** Possibilities for decomposition of a second-order model into two first-order models. Two random first-order processes  $G_1$  and  $G_2$  can be interconnected in three ways: in series, in parallel or in feedback. The total transfer function for the resulting second-order model for each possibility is given to the right.

**Table 3** Parameter values after decomposition of the identified second-order model in series, parallel and feedback connection

	Series	Parallel	Feedback
$\xi_1 = \frac{\beta_1}{s + \alpha_1}$	$\beta_1 = 0$ $\alpha_1 = 0$	$\beta_1 = 0.1140$ $\alpha_1 = -0.0020 + 0.1225.i$	$\beta_1 = -0.0340$ $\alpha_1 = 0.3864$
$\xi_2 = \frac{\beta_2}{s + \alpha_2}$	$\beta_2 = 0$ $\alpha_2 = 0$	$\beta_2 = 0.1140$ $\alpha_2 = -0.0020 + 0.1225.i$	$\beta_2 = -4.7860$ $\alpha_2 = -0.3824$

models in series, parallel and feedback connection, where  $G_1$  and  $G_2$  are defined as first-order TF models.

The results of the decomposition of the identified second-order model [2 2 5] is presented in Table 3, and shows that the decomposition in two first-order TF in series is impossible. The decomposition in two parallel TF functions delivers complex solutions for both the parameters  $\alpha_1$  and  $\alpha_2$  and thus a parallel connection can also be rejected when we assume only real solutions to be possible. The only correct decomposition for the presented second-order TF model is as a combination of two first-order TF models in feedback connection.

For all experiments, independent of the presence of driver sleepiness, similar modelling results are obtained, resulting in a

second-order four parameter model [2 2  $\tau$ ] between  $T_m(t) - T_m(0)$  and sleepiness ( $t$ ) with an overall  $R^2$  of 0.92. In all cases, the identified second-order TF can be decomposed into a (negative) feedback connection between two first-order TF models.

### Physical meaning

Although the functional link between thermoregulation and sleep is a complex integration, and as it is almost impossible to include all the influences and parameters in a manageable model, the identified model consists of only four parameters. DBM is looking for a model that is as compact as possible, but still accurate enough to predict the relation between thermoregulation and sleep when measuring input and output on-line. This excludes the need for complex mechanistic multi-parameter models.

For deriving physical meaning from the DBM model, we start from the suggested (positive) feedback connection, hypothesised by Gilbert *et al.* (2004) and which is summarized in Fig. 1. In this interpretation, any change in the sleep/wake status of a subject can be reduced to the influence of the thermoregulatory system, of circadian features [controlled by the suprachiasmatic nuclei (SCN)], of activation of neurones in the brain (PoAH) and of other sleep signalling pathways (which are not considered here). And in turn, occurring changes in thermoregulatory features are thought to be the result of changing sleep-wake level, circadian clues and functionalities in the brain (PoAH).

All this can be moulded into a mathematical model describing the change in sleep state and thermoregulatory variables as function of the above-mentioned variables. In the Appendix the theoretical derivation of the identified DBM model in physical meaningful terms is presented, based on existing knowledge from literature. This DBM model describing the relation between distal heat loss  $T_m(t) - T_m(0)$  and sleepiness eventually becomes (equations A1–A15):

$$\text{Sleepiness}(t) = \frac{b_0 s + b_1}{s^2 + a_1 s + a_2} (T_m(t) - T_m(0)) \quad (2)$$

with

$$\begin{aligned} b_0 &= \beta_R = \frac{1}{\alpha_R} \\ b_1 &= -\beta_R T_{\text{cir}} \\ a_1 &= -(K_{\text{sig}} + T_{\text{cir}}) \\ a_2 &= K_{\text{sig}} T_{\text{cir}} - A_s S_{\text{cir}} \end{aligned}$$

Notice that equation (2) is of the exact identical form of the model identified from the experimental data (equation 1). The parameter  $b_0 = \beta_R$  in equation (2) represents a physical meaningful and well known parameter from literature.  $\beta_R$  is defined as  $1/\alpha_R$  in equation (A9), with  $\alpha_R$  representing the magnitude of each thermoregulatory response in the relation (from Hammel *et al.*, 1963):

$$R - R_0 = \alpha_R (T_{\text{hypo}} - T_{\text{set}}) \quad (3)$$

where  $R$  is the thermoregulatory response,  $R_0$  the basal thermoregulatory response, and  $\alpha_R$  differs only in magnitude for each thermoregulatory response.

For the present research, thermoregulatory responses are restricted to the ‘masking effects’ of the shift in heat balance at sleep onset, i.e. only distal heat loss is taken into consideration. Equation (3) thus becomes:

$$T_m(t) - T_m(0) = \alpha_R (T_{\text{hypo}}(t) - T_{\text{set}}(t)) \quad [^\circ\text{C}] \quad (4)$$

Through the presented model, values for  $\alpha_R$  can be derived from the measurement of both  $T_m(t) - T_m(0)$  and sleepiness from raw EEG data, and this per individual and per time (equation 2). By doing this, not only the individual and time-varying value of  $\alpha_R$  can be calculated, but as  $T_m(t) - T_m(0)$  is a measurable variable, also the thermoregulatory error signal  $T_{\text{hypo}}(t) - T_{\text{set}}(t)$  at a certain time  $t$  can be derived for each individual by simple measuring distal heat loss and raw EEG (equation 4).

## DISCUSSION

This study investigates the relation between thermoregulatory features and sleep onset in experimental conditions where no actual sleep onset is achieved. Apparently, ‘traditional’ thermoregulatory changes (in the present study increased distal heat loss) also occur under driver sleepiness conditions, although driver sleepiness is not associated with an actual sleep period or NREM sleep stage. These results might fund the hypothesis that thermoregulatory changes are not merely coincidental associated with sleep, but could be considered as a sign of preparedness for sleep onset (Gilbert *et al.*, 2004; Magnussen, 1943).

Using modern model identification techniques from control theory, a feedback connection between distal heat loss and sleepiness is identified with a high accuracy (overall  $R^2$  of 0.92) revealing experimental evidence for the hypothesis of Gilbert *et al.* (2004) of a feedback integration between thermoregulatory features and sleep onset. But the negative feedback model identified in the previous section seems somewhat contradictory to the conceptual positive feedback model presented by Gilbert *et al.* (2004). However, this discrepancy can be explained from the distinct nature of the processes in both studies: the positive feedback model intended to explain how thermoregulatory changes can initiate and consolidate NREM sleep, while the present study investigates the interaction between thermoregulation and sleep in conditions of unwanted sleepiness in active subjects (NREM sleep is not allowed).

### Feedback integration of thermoregulation and sleep

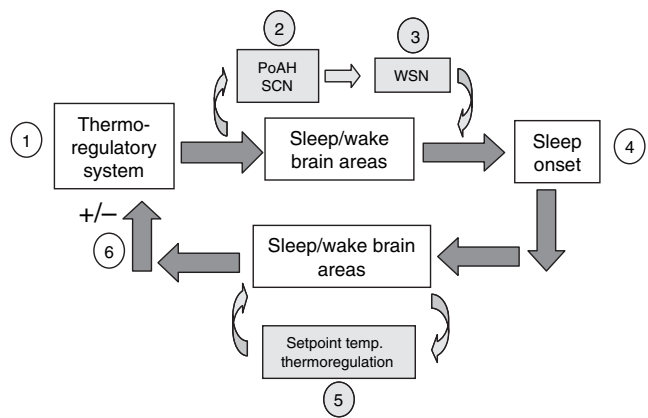
The hypothesis of the positive feedback connection (Gilbert *et al.*, 2004; McGinty and Szymusiak, 2001; McGinty *et al.*, 1996; Nakao *et al.*, 1995; Sakaguchi *et al.*, 1979) is deduced

from results of numerous previous studies that investigated the relation between thermoregulatory changes and natural sleep onset. The most important notices in this context are shortly described hereafter. Firstly, the central concept in thermoregulation is the thermoregulatory set point  $T_{set}$ . This is a critical threshold value to activate the thermoregulatory responses. Several studies however, have attributed also sleep enhancing effect to this set point: total sleep time proved to be proportional to the difference between  $T_{hypo} - T_{set}$  (e.g. Saka-guchi *et al.*, 1979). This difference between hypothalamic temperature and the set point for thermoregulation  $T_{hypo} - T_{set}$  is the central 'error signal' that triggers thermoeffector processes in the human body, and is referred to as the proportional control of thermoregulation. Secondly, the PoAH site is considered to be the predominant site for the integration of thermal information (Boulant, 2000). The PoAH receives thermoafferent information from thermoreceptors in the skin and the spinal cord, and it is also affected by thermosensitive neurones in the POAH itself (Carlisle, 1969; Refinetti and Carlisle, 1986). Moreover, several studies confirm that PoAH, next to its thermoregulatory features, plays a role in sleep initiation. PoAH contains populations of both WSN and cold sensitive neurones (CSN). WSN are sleep-promoting neurones in the PoAH that are sleep-active: they experience an increase in activation during sleep with respect to wake. Contrarily, CSN are wake- or arousal-promoting areas in the POAH and their discharge rate is higher under wake conditions (Alam *et al.*, 1995). These neurones are differentiated by changes in neural discharge rate in response to the local hypothalamic temperature level. Both groups work as a balance: for instance mild cooling of the PoAH ( $-1.0$  to  $-1.8$  °C) suppresses NREM and REM sleep for 3 h, because this local cooling selectively activates wake-promoting CSN while at the same time inhibits activation of sleep enhancing WSN (McGinty *et al.*, 1996).

The fact that Gilbert *et al.* (2004) suggested a positive feedback connection between thermoregulatory processes and the sleep process while the authors in this work experimentally derived a negative feedback connection, can be explained when looking at the very nature of the relation between both processes.

When an individual is attempting to fall asleep in his bed, blood flow to the peripheral body sites is increased (Lack and Gradisar, 2002) through specialized thermoregulatory systems called the arteriovenous anastomoses. The exact physiological reason for this increased peripheral blood flow is yet unknown. This results in shunting of blood in these regions (Hales, 1985). Fig. 6 schematically shows the steps initiated by this increase in peripheral blood flow at natural sleep onset:

1. This increased blood flow in peripheral regions results in an increased heat transfer per unit time in these regions. The resulting rise in peripheral skin temperature in term creates a positive thermal gradient with the surrounding micro-environment, enabling further peripheral heat loss.
2. This increase in peripheral skin temperature is capable to activate WSN (McGinty *et al.*, 1998; Raymann *et al.*, 2005; Van Someren, 2000), that are known to be sensitive to



**Figure 6.** Control theory representation of integration of thermoregulatory processes and the sleep-wake process as hypothesised by Gilbert *et al.* (2004). See Discussion section for details on the specific biological processes 1 to 6 under different sleep conditions. The nature of the feedback connection ( $\pm$ ) is determined by the nature of the sleepiness process.

changes in peripheral temperatures and to changes in hypothalamic PoAH temperature (e.g. Bruck and Hinckel, 1982; Dickenson, 1977; Wit and Wang, 1968).

3. One possible pathway for WSN activation is an increase in the hypothalamic temperature  $T_{hypo}$  in the PoAH. As these peripheral temperature changes are of a significant magnitude, they might override the changes in local brain temperature at sleep onset, driving the WSN to increase their firing rate according to the relation delivered by McGinty and Szymusiak (2001):

$$WSN_{discharge} = \alpha T_{hypo} + \beta(T_{hypo} - T_{set-sleep}) + C \quad (5)$$

where  $WSN_{discharge}$  is the discharge rate or the activity of WSN,  $T_{hypo}$  is the baseline hypothalamic temperature,  $T_{set-sleep}$  is defined as setpoint or the 'inflection point' of activity of WSN,  $\alpha$  and  $\beta$  are the slopes or proportionality of the sleep inducing or hypnogenic drive above and below the inflection point  $T_{set-sleep}$  and  $C$  is a fixed basal discharge rate (De Lecea *et al.*, 1996; McGinty and Szymusiak, 2001). The inflection point  $T_{set-sleep}$  can change the activity of WSN independent of the hypothalamic temperature  $T_{hypo}$ .

4. The overall effect of the increase in blood flow in peripheral skin regions, when a subject attempts to fall asleep, is thus the activation of sleep-promoting WSN neurones and an inhibition of wake-promoting neurones through the increase in peripheral heat loss, resulting in an increase of sleepiness and even sleep initiation.
5. Once NREM sleep initiation is attained, the thermoregulatory system reacts to this change by lowering the thermoregulatory set point  $T_{set}$  (Rosenthal, 1998).
6. Hence heat loss mechanisms are activated as the error signal for thermoregulation  $T_{hypo} - T_{set}$  becomes positive by the decrease in  $T_{set}$ . This results in excess heat that needs to be transported away from the body and thus reinforces the cycle by a further increase in (peripheral) heat loss (positive feedback).

This cycle at attempted sleep onset is indeed a positive feedback between thermoregulation and sleep where thermoregulatory changes are thought to both initiate and reinforce sleep onset. However, the experimentally derived feedback model in this work proved to be a negative feedback connection between thermoregulation and sleep. Can this discrepancy with the positive feedback between thermoregulation and sleep as hypothesized by Gilbert *et al.* (2004) be explained by the difference between attempted sleep onset and excessive sleepiness in active subjects? In other words, can the fact that NREM sleep is not reached in the experiments of this study explain the negative feedback between thermoregulation and sleep?

Anyway, in this work the presence of a clear and detectable increase in peripheral heat loss at driver sleepiness is shown. Again, the schematic overview in Fig. 6 is used to run over the consecutive steps initiated by this peripheral heat loss.

1. In the present study, the sleepy drivers did experience a significant increase in distal heat loss when compared with non-sleepy drivers.
2. Similar to the mechanisms at attempted sleep onset, this increase in distal heat loss leads to an increase WSN activity in the PoAH.
3. Under the assumption that hypothalamic temperature  $T_{\text{hypo}}$  increases due to increased peripheral skin temperature, how can the inhibition of WSN be explained in sleepy drivers? This is possible as the inflection point of WSN discharge rate  $T_{\text{set-sleep}}$  (equation 5) is capable of changing the discharge rate of WSN irrespective of hypothalamic temperature  $T_{\text{hypo}}$  (McGinty and Szymusiak, 2001). A strong increase in inflection point  $T_{\text{set-sleep}}$  can eliminate the hypothetical increase in hypothalamic temperature  $T_{\text{hypo}}$  in terms of activation rate of WSN. This increase in the inflection point  $T_{\text{set-sleep}}$  is hypothesized as the 'struggle against sleep' of the sleep/wake switch in the human brain.
4. As WSN activation is inhibited (and possibly even lowers) through an increase in  $T_{\text{set-sleep}}$ , the inhibition of CSN is removed resulting in a possible increased arousal for the drivers.
5. This results in no change (or a slight decrease) in the thermoregulatory set point  $T_{\text{set}}$  and in the error signal for thermoregulatory control  $T_{\text{hypo}} - T_{\text{set}}$ .
6. All this leads to a cease in the peak peripheral heat loss and thus in a negative feedback connection.

The negative feedback integration between thermoregulation and sleep identified in this work is derived from a series of driver simulator studies where no actual NREM sleep onset is achieved. This fundamental difference between actual attaining sleep onset or not explains the difference in type of feedback connection (positive or negative) between thermoregulation and sleep.

Both feedback models – the negative and the positive feedback connection – however are more complementary than contradictory. Any positive feedback integration in nature is – from the systems analysis point of view – per definition unstable. A positive feedback relation keeps on reinforcing and

amplifying itself until its values reach infinity. At one point, every positive feedback connection in nature has to be broken to avoid this state of instability. In the considered sleep-thermoregulation process, this is the moment of waking up. Every time it sets in (going to sleep), the positive feedback connection between thermoregulatory features and sleep has to be broken at a certain point (waking up), and thus evolves into a negative feedback connection where several mechanisms inhibit further sleep prolongation and stimulate arousal. And again, even the thermoregulatory system is thought to play a role in waking up. A recent study reported a decrease in distal heat loss at the point of waking in contrast to the increase in distal heat loss at sleep initiation. This indicates a remarkable similarity between the thermoregulatory processes initiating sleep and those dissipating sleep (Krauchi *et al.*, 2004). Thermoregulation seems to play an active and more profound role in the human sleep/wake switch presented by Saper *et al.* (2001, 2005). Thermoregulation can be thought to play an initiation and consolidating (positive feedback) or terminating (negative feedback) role in switch between sleep and wake states.

From the results shown in this study however, it can only be concluded that the nature of the feedback connection – positive or negative – between thermoregulation and sleep is determined by the very nature of the (sleep) process, in this case NREM sleep onset versus unwanted sleepiness in active subjects.

### Individual and time-varying model features

The identified second-order relation between distal heat loss and sleepiness in this study is not merely a statistical relation. This second-order DBM model is suitable for and capable of handling the CITED features of the interaction between sleep and thermoregulation. Furthermore, both model order and model parameters content biological meaning regarding the integration between thermoregulation and sleep on an individual and time-varying basis.

As indicated in the introduction to this chapter, sleep research is more and more fascinated by individual and time-varying differences in sleep characteristics. Recently, as one of the first Van Dongen and Dinges (2003) integrated individual components in the two-process model of sleep regulation. Quantifying these individual differences between subjects that themselves are time-varying systems is an extremely complex challenge and needs a specific approach.

The DBM approach is in this work successfully applied to the functional link between thermoregulation and sleep. Based on the measurement of the dominant processes – peripheral heat loss  $T_m(t) - T_m(0)$  and sleepiness ( $t$ ) as a function of time – it is possible to accurately ( $R^2 = 0.92$ ) describe the relation between both processes by a low-order four-parameter DBM model. This model enables, through its physical meaningful parameter, quantification of individual and time-varying properties of the considered processes merely based on a short measurement of the dominant signals, peripheral heat loss and the EEG (sleepiness).

The theoretically derived physical meaning of the model parameter  $b_0$  enables calculation of the error signal for human thermoregulation  $T_{\text{hypo}}-T_{\text{set}}$ . The theoretically derived physical meaning of the model parameter  $b_0$  is validated by calculating its physical value  $T_{\text{hypo}}-T_{\text{set}}$  for different individuals and different time steps, and comparing the obtained numerical values with existing reports in literature quantitatively describing such temperature changes. To our knowledge, no report quantitatively describes the value of the human thermoregulatory error signal  $T_{\text{hypo}}-T_{\text{set}}$ , as a measurement technique for the thermoregulatory error signal  $T_{\text{hypo}}-T_{\text{set}}$  – a difference between two brain temperature in the hypothalamus – on living subjects is not known. The magnitude of the thermoregulatory error signal  $T_{\text{hypo}}-T_{\text{set}}$  is usually derived from indirect measurements of thermoregulatory responses. However, by using anaesthetized animals or manipulations of the hypothalamic temperature  $T_{\text{hypo}}$  by using implanted thermodes, some researchers succeeded in quantifying the dynamic behaviour of the hypothalamic temperature  $T_{\text{hypo}}$  in relation to the sleep function.

One of the earliest reports in this kind using kangaroo rats where  $T_{\text{hypo}}$  is manipulated by means of implanted water-perfused stainless steel thermodes, reported a substantial increase in metabolic heat production when reducing  $T_{\text{hypo}}$  over 2 °C, and similarly a significant fall in metabolic heat

production when increasing  $T_{\text{hypo}}$  to almost 3 °C (Glotzbach and Heller, 1976). Perhaps one of the most accurate descriptions of the effect of the level of  $T_{\text{hypo}}$  on thermoregulatory responses and the sleep process is the study by Berner *et al.* (1999). By inhibition of sleep inhibiting neurones (5HT) by injection of lidocaine in non-anaesthetized rats, they recorded a decrease in  $T_{\text{hypo}}$  of  $1.30 \pm 0.06$  °C over a group of 25 male animals, resulting in a heat loss increase of 2 °C indirectly measured by a small water-perfused environmental chamber housing the animals. Finally, several studies relate increases in firing rate of sleep-promoting WSN to an increase in  $T_{\text{hypo}}$ . A typical increase of  $T_{\text{hypo}}$  around an inflection point between 1 and 2 °C results in a multiplication of neurone activity with a factor 3–5 (e.g. Hays *et al.*, 1999).

In compiling the existing knowledge, the following validation criterion for the present study is applied: is the obtained individual and time-varying value of thermoregulatory error signal  $T_{\text{hypo}}-T_{\text{set}}$  realistic, when calculated from model parameter  $b_0$  and distal heat loss  $T_m(t)-T_m(0)$ ? And are individual and time-varying differences expressed through the calculated DBM parameters?

Table 4 presents an overview of the typical individual and time-varying character of the presented second-order feedback models between distal heat loss and sleepiness with indication of experiment number, subject number, increase (+) or

**Table 4** Overview of the results for the repeated simulator drives for three subjects under different experimental conditions, with indication of experiment number, subject number, presence of sleepiness, experimental conditions, measured change in distal heat loss ( $T_m(t)-T_m(0)$ ), estimated model parameter values, derived biological meaningful parameter  $\alpha_R$  and the calculated thermoregulatory error signal  $T_{\text{hypo}}-T_{\text{set}}$

Subject	Experimental condition	Sleepiness	$T_m(t)-T_m(0)$	Model parameters	$\alpha_R$	$T_{\text{hypo}}-T_{\text{set}}$
Subject 1	Sleep deprivation (time in bed = 3 h)	Yes	4.993	$a_1 = 0.004$ $a_2 = 0.015$ $b_0 = -0.034$ $b_1 = 0.013$	-29.4	0.170
Subject 2	Adaption night (time in bed = 8 h)	Yes	5.491	$a_1 = -0.017$ $a_2 = 0.015$ $b_0 = 0.08$ $b_1 = 0.005$	12.5	0.440
Subject 2	Adaption night (time in bed = 8 h)	Yes	5.401	$a_1 = -0.059$ $a_2 = 0.01$ $b_0 = 0.004$ $b_1 = 0.004$	250	0.022
Subject 1	Sleep deprivation (time in bed = 3 h)	No	2.204	$a_1 = 0.114$ $a_2 = 0.007$ $b_0 = -0.21$ $b_1 = -0.006$	-4.76	0.463
Subject 1	Sleep deprivation (time in bed = 3 h)	No	-4.114	$a_1 = 0.013$ $a_2 = 0.012$ $b_0 = 0.023$ $b_1 = 0.004$	43	-0.096
Subject 3	Arousal (time in bed = 3 h)	No	-1.162	$a_1 = 0.312$ $a_2 = -0.005$ $b_0 = 0.521$ $b_1 = -0.01$	1.9	-0.611
Subject 3	Arousal (time in bed = 3 h)	No	-2.416	$a_1 = 0.022$ $a_2 = 0.004$ $b_0 = 0.034$ $b_1 = -0.0001$	29.4	-0.082

decrease (-) in sleepiness, measured change is distal heat loss ( $T_m(t) - T_m(0)$ ), estimated model parameter values from the SRIV algorithm, quantified physical meaningful parameter  $\alpha_R$  from the DBM model and the calculated thermoregulatory error signal  $T_{\text{hypo}} - T_{\text{set}}$ . First of all, all calculated values for the thermoregulatory error signal  $T_{\text{hypo}} - T_{\text{set}}$  in Table 4 are in a realistic and reliable interval between 0.002 and 0.9 °C when considering existing reports. This enhances credibility of the derived physical meaningful parameter. When taking a closer look at Table 4, it shows that there exist not only inter-individual differences in both  $\alpha_R$  and thermoregulatory error signal  $T_{\text{hypo}} - T_{\text{set}}$ , but also time-varying discrepancies for the same subject (intra-individual). For instance, in the situation where both sleepiness and distal heat loss increase, there is an inter-individual difference in both  $\alpha_R$  and  $T_{\text{hypo}} - T_{\text{set}}$  for subject 1 compared with subject 2. When looking at subject 1 throughout the three different conditions in Table 4 [increase in sleepiness and  $T_m(t) - T_m(0)$ , decrease in sleepiness and increase in  $T_m(t) - T_m(0)$ , decrease in sleepiness and  $T_m(t) - T_m(0)$ ], it is clear that the model is capable of handling the time- and condition-varying changes in both parameters  $\alpha_R$  and  $T_{\text{hypo}} - T_{\text{set}}$ . Furthermore, even under similar conditions (e.g. subject 2) the model handles the time-varying characteristics of the thermoregulation/sleep process, expressed through different values of both parameters. It must be mentioned that the derived individual and time-varying physiological meaningful parameter  $T_{\text{hypo}} - T_{\text{set}}$  at the moment does not hold any information regarding the sleepiness state of the subject. This model only enables derivation of the individual and time-varying error signal of thermoregulation in the hypothalamus from real-time measurements of EEG and peripheral heat loss.

## REFERENCES

- Akaike, H. Information theory and the extension of the maximum likelihood criterion principle. In: V. N. Petrov and F. Csaki (Eds). *Proceedings of the Second International Symposium on Information Theory*. Akademiai Kiado, Budapest, 1973: 267–281.
- Alam, A. A., McGinty, D. and Szymusiak, R. Neuronal discharge of preoptic/anterior hypothalamic thermosensitive neurons: relation to NREM sleep. *Am. J. Physiol.*, 1995, 269: R1240–R1249.
- Arnedt, J. T., Wilde, G. J., Munt, P. W. and MacLean, A. W. Simulated driving performance following prolonged wakefulness and alcohol consumption: separate and contributions to impairment. *J. Sleep Res.*, 2000, 9: 233–241.
- Arnedt, J. T., Acebo, C., Seifer, R. and Carskadon, M. A. Assessment of a simulated driving task for sleep research. *Sleep*, 2001, 24S: A413.
- Berckmans, D., De Moor, M. and De Moor, B. New model concept to control the energy and mass transfer in a three-dimensional imperfectly mixed ventilated space. *ROOMVENT1992 3rd International Conference on Air Distribution in Rooms: Air Movement in Large Spaces*, Aalborg, Denmark, Vol. 2, 1992: 151–168.
- Berner, N. J., Grahn, D. A. and Heller, H. C. 8-OH-Dpat-sensitive neurons in the nucleus raphe magnus modulate thermoregulatory output in rats. *Brain Res.*, 1999, 831: 155–164.
- Bligh, J. *Temperature Regulation in Mammals and Other Vertebrates*. North Holland Publishing Company, Amsterdam, The Netherlands, 1973: 435.
- Borbely, A. A. A two-process model of sleep regulation. *Hum. Neurobiol.*, 1982, 13: 417–425.
- Boulant, J. A. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. *Clin. Infect. Dis.*, 2000, 31: S157–S161.
- Brown, C. C. Toe temperature change: a measure of sleep onset? *Waking Sleeping*, 1979, 3: 353–359.
- Bruck, K. and Hinckel, P. Thermoafferent systems and their adaptive modifications. *Pharmacol. Ther.*, 1982, 17: 357–381.
- Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. and Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.*, 1989, 28: 193–213.
- Carlisle, H. J. Effect of preoptic and anterior hypothalamic lesions on behavioural thermoregulation in the cold. *J. Comp. Physiol. Psychol.*, 1969, 69: 391–402.
- Carskadon, M., Dement, W., Mitler, M., Roth, T., Westbrook, P. and Keenan, S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep*, 1986, 9: 518–524.
- Csete, M. and Doyle, J. C. Reverse engineering of biological complexity. *Science*, 2002, 295: 1664–1668.
- De Lecea, L., Criado, J. R., Prospero-Garcia, O., Gautvik, K. M., Schweitzer, P., Danielson, K. M., Dunlop, C. L. M., Siggins, G. R., Henriksen, S. J. and Sutcliffe, J. A cortical neuropeptide with neuronal depressant and sleep-modulating properties. *Nature*, 1996, 381: 242–245.
- De Valck, E., Cluydts, R. and Pirrera, S. Effect of cognitive arousal on sleep latency, somatic and cortical arousal following partial sleep deprivation. *J. Sleep Res.*, 2004, 13: 295–304.
- De Waard, D. and Brookhuis, K. A. Assessing driver status: a demonstration experiment on the road. *Accid. Anal. Prev.*, 1991, 23: 297–307.
- Dickenson, A. H. Specific responses of rat raphe neurones to skin temperature. *J. Physiol. (Lond.)*, 1977, 273: 277–293.
- Gilbert, S. S., Van den Heuvel, C. J., Ferguson, S. A. and Dawson, D. Thermoregulation as a sleep signalling system. *Sleep Med. Rev.*, 2004, 8: 81–93.
- Glotzbach, S. F. and Heller, H. G. Central nervous regulations of body temperature during sleep. *Science*, 1976, 194: 537–538.
- Hales, J. R. Skin arteriovenous anastomoses, their control and role in thermoregulation. In: K. Johansen and W. W. Burggren (Eds) *Cardiovascular Shunts*. Alfred Benzon Symposium 21, Copenhagen, Munksgaard, 1985: 233–245.
- Hammel, H. T., Jackson, D. C., Stolwijk, J. A., Hardy, J. D. and Stromme, S. B. Temperature regulation by hypothalamic proportional control with adjustable set point. *J. Appl. Physiol.*, 1963, 18: 1146–1154.
- Hartwell, L. H., Hopfield, J. J., Leibler, S. and Murray, A. W. From molecular to modular cell biology. *Nature*, 1999, 402: C47–C52.
- Haskell, E. H., Palca, J. W., Walker, J. M., Berger, R. J. and Heller, H. C. Metabolism and thermoregulation during stages of sleep in humans exposed to heat and cold. *J. Appl. Physiol.*, 1981, 51: 948–954.
- Hays, T., Szymusiak, R. and McGinty, D. Intrinsic nonlinear firing rate responses to temperature found in rat diagonal band neurons in vitro. *Sleep Res. Online*, 1999, 2S: 43.
- Heller, H. C. and Glotzbach, S. F., 1977. Thermoregulation during sleep and hibernation. In: Robertshaw D (ed) *International review of physiology and environmental physiology II*, p. 147–188.
- Hoddes, E., Zarcone, V., Smythe, H., Phillips, R. and Dement, W. C. Quantification of sleepiness: a new approach. *Psychophysiology*, 1973, 10: 431–436.
- Ishikawa, K., Genno, H., Kanbara, O., Yasuda, M. and Osuli, M. Evaluation of stress using facial skin temperature. *The Proceedings of PIE*, 1998: 158–159.
- Kitano, H. Computational systems biology. *Nature*, 2002, 420: 206–210.
- Krauchi, K., Cajochen, C., Hoffman, M. and Wirz-Justice, A. Melatonin and orthostasis: interactions of posture with subjective sleepiness, heart rate, and skin and core temperature. *J. Sleep Res.*, 1997a, 26: 79.

- Krauchi, K., Cajochen, C. and Wirz-Justice, A. A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. *J. Am. Physiol.*, 1997c, 83: 134–139.
- Krauchi, K., Cajochen, C., Werth, E. and Wirz-Justice, A. Warm feet promote the rapid onset of sleep. *Nature*, 1999, 401: 36–37.
- Krauchi, K., Cajochen, C. and Wirz-Justice, A. Waking up properly: is there a role of thermoregulation in sleep inertia? *J. Sleep Res.*, 2004, 13: 121–127.
- Lack, L. and Gradisar, M. Acute finger temperature changes predict sleep onset over a 45-h period. *J. Sleep Res.*, 2002, 11: 275–282.
- Ljung, L. *System Identification: Theory for the User*. Prentice Hall, Englewood Cliffs, NJ, USA, 1987.
- MacNair, D. M., Lorr, M. and Droppelman, L. F. *EDITS Manual for the Profile of Mood States*. Educational and Industrial Testing Service, San Diego, CA, 1971.
- Magnussen, G. On narcolepsy II. Studies on diurnal variations in the skin temperatures in narcoleptics. *Acta Psychiatr. Neurol.*, 1943, 18: 457–485.
- McAdams, H. H. and Sharipo, L. Circuit simulation of genetic networks. *Science*, 1995, 269: 650–656.
- McGinty, D. and Szymusiak, R. Brain structures and mechanisms involved in the generation of NREM sleep: focus on the preoptic hypothalamus. *Sleep Med. Rev.*, 2001, 5: 323–342.
- McGinty, D., Thomson, D., Szymusiak, R. and Morairty, S. Suppression of sleep by local preoptic/anterior hypothalamic cooling. *J. Sleep Res.*, 1996, 25: 18.
- McGinty, D., Szymusiak, R. and Alam, N. Preoptic/basal forebrain thermoregulatory control of NREM sleep. *J. Sleep Res.*, 1998, 7: 174.
- Moller, H., Lowe, A., Kayumov, L., Hossain, N. and Shapiro, C. Can impaired alertness be detected more sensitively using a computerized driving simulator? *Sleep*, 2002, 25(sup): 252–253.
- Nakao, M., McGinty, D., Szymusiak, R. and Yamamoto, M. A thermoregulatory model of sleep control. *Jpn. J. Physiol.*, 1995, 45: 291–309.
- Nakao, M., Nishiyama, H., McGinty, D., Szymusiak, R. and Yamamoto, M. A model-based interpretation of the biphasic daily pattern of sleepiness. *Biol. Cybern.*, 1999, 81: 403–414.
- Parmeggiani, P. L. and Rabini, C. Sleep and environmental temperature. *Arch. Ital. Biol.*, 1970, 108: 369–387.
- Pennisi, E. Systems biology: tracing life's circuitry. *Science*, 2003, 302: 1646.
- Quanten, S., De Valck, E., Cluydts, R., Aerts, J.-M. and Berckmans, D. Thermoregulatory changes at driver sleepiness. *International Journal of Vehicle Design Special Issue on "Driver Comfort & Safety: measurements on vehicle drivers"*, (in press).
- Raymann, R. J. E. M., Swaab, D. F. and Van Someren, E. J. W. Cutaneous warming promotes sleep onset. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 2005, 288: 1589–1597.
- Rechtschaffen, A. and Kales, A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Government Printing Office, Washington, DC, USA, 1968.
- Refinetti, R. and Carlisle, H. J. Effects of lateral hypothalamic-lesions on thermoregulation in the rat. *Physiol. Behav.*, 1986, 38: 219–228.
- Rosenthal, M. S. Physiology and neurochemistry of sleep. *Am. J. Pharm. Educ.*, 1998, 62: 204–208.
- Sakaguchi, S., Glotzbach, S. F. and Heller, H. C. Influence of hypothalamic and ambient-temperatures on sleep in kangaroo rats. *Am. J. Physiol.*, 1979, 237: R80–R88.
- Saper, C. B., Chou, T. C. and Scamel, T. E. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci.*, 2001, 24: 726–731.
- Saper, C. B., Scammell, T. E. and Lu, J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*, 2005, 437: 1257–1263.
- Stephenson, L. A., Wenger, C. B., O'Donovan, B. H. and Nadel, E. R. Circadian rhythms in sweating and cutaneous blood flow. *Am. J. Physiol.*, 1984, 246: R321–R324.
- Tomlin, C. J. and Axelrod, J. D. Understanding biology by reverse engineering the control. *Proc. Natl. Acad. Sci. USA*, 2005, 102: 4219–4220.
- Van Dongen, H. P. A. and Dinges, D. F. Investigating the interaction between the homeostatic and circadian processes of sleep-wake regulation for the prediction of waking neurobehavioural performance. *J. Sleep Res.*, 2003, 12: 181–187.
- Van Dongen, H. P. A., Baynard, M. D., Maislin, G. and Dinges, D. F. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep*, 2004, 27: 423–433.
- Van Huffel, S. and Vandewalle, J. Iterative speed improvement for solving slowly varying total least squares problems. *Mech. Syst. Signal Process.*, 1988, 2: 327–348.
- Van Someren, E. J. W. More than a marker: interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol. Int.*, 2000, 17: 313–354.
- Vos, W. Infrared camera meet mentale werkbelasting. *TNO Magazine September*, 2005, 9: 11–12.
- Wit, A. and Wang, S. Temperature-sensitive neurons in the preoptic/anterior hypothalamic region: effects of increasing ambient temperature. *Am. J. Physiol.*, 1968, 125: 1151–1159.
- Young, P. C. *Recursive Estimation and Time-series Analysis*. Springer-Verlag, Berlin, Germany, 1984.
- Young, P. C. and Jakeman, A. J. Refined instrumental variable methods of recursive time-series analysis: part II, single input output systems. *Int. J. Control*, 1979, 30: 1–30.
- Young, P. C. and Lees, M. J. The active mixing volume: a new concept in modelling environmental systems. In: V. Barnett and K. J. Feridun Turkman (Eds) *Statistics for the Environment*. Wiley, Chichester, UK, 1993: 3–39.
- Young, P. C. and Wallis, S. G. Solute transport and dispersion in channels. In: K. J. Beven and M. J. Kirkby (Eds) *Channel Networks*. J. Wiley, Chichester, UK, 1993: 129–173.
- Young, P. C., Behzali, M. A., Wang, C. L. and Chotai, A. Direct digital and adaptive control by input-output, state variable feedback pole assignment. *Int. J. Control*, 1987, 46: 867–1881.

## APPENDIX

The derivation of physical meaning from this DBM model is started from the suggested feedback connection between sleep and thermoregulation as hypothesised by Gilbert *et al.* (2004). In this interpretation, a change in the sleep/wake status of a subject can be due to the influence of the thermoregulatory system, due to circadian features, due to activation of neurones in the brain and/or due to other sleep signalling pathways (Fig. 1). Other sleep signalling pathways or mechanisms surely are important in sleep regulation. However, regardless of the mechanisms initiating sleep, such a mechanism will interact with other sleep signalling pathways like thermoregulation. This means that even if sleep is regulated by other mechanisms, sleep itself will evoke thermoregulatory effects. And these temperature changes will always reinforce the sleep process (Gilbert *et al.*, 2004).

The other way round, changes in thermoregulatory features are in this hypothetical model thought to be the result of changing sleep-wake level, circadian clues and functionalities in the brain for instance influenced by the microenvironment.

All the information summarized in Fig. 1 can be moulded into mathematical formulas describing the change in both sleep state and thermoregulatory variables as

function of the above-mentioned variables (after Gilbert *et al.*, 2004):

$$\frac{d(\text{SLEEP})}{dt} = \text{TR}_S + \text{PoAH}_S + \text{SCN} \quad (\text{A1})$$

$$\frac{d(\text{TR})}{dt} = \text{SLEEP} + \text{SCN} + \text{PoAH}_{\text{TR}} \quad (\text{A2})$$

where TR indicates thermoregulatory changes; PoAH indicates changes in neural activity, with PoAH<sub>S</sub> relating to changes in neural activity affecting sleep and PoAH<sub>TR</sub> relating to changes in neural activity affecting sleep; SCN indicates circadian rhythms; SLEEP indicates sleep level.

In order to work with these equation, all variables from (A1) and (A2) need to be expressed in the same dimensions. The choice is made to describe all variables in °C.

### Thermoregulatory variables

Describing the thermoregulatory changes (TR) in °C is trivial, as the error signal for thermoregulatory features  $T_{\text{hypo}}(t) - T_{\text{set}}(t)$  is a temperature difference (°C) (e.g. Bligh, 1973; Heller and Glotzbach, 1977; Sakaguchi *et al.*, 1979).  $T_{\text{hypo}}(t)$  is the hypothalamic temperature and  $T_{\text{set}}$  is the critical threshold temperature for triggering thermoeffector responses such as shivering (heat production) or panting (heat loss).

### Sleep/wake inducing neurones in the PoAH

The influence of neural activity (in the PoAH) on sleep is effected through activation/deactivation of sleep- or wake-promoting neurones. The sleep/wake level here is approached as a sigmoid function for sleepiness, where low values indicate low sleepiness (and hence high wake level and arousal), and high values indicate high sleepiness (drowsiness and sleep onset). Hence the variable PoAH<sub>S</sub> indicating changes in neural activity affecting sleep is expressed as the dynamic course of the discharge rate of sleep-promoting WSN as defined by McGinty and Szymusiak (2001):

$$\text{WSN}_{\text{discharge}} = \alpha T_{\text{hypo}} + \beta (T_{\text{hypo}} - T_{\text{set-sleep}}) + C \quad (\text{A3})$$

where  $\text{WSN}_{\text{discharge}}$  is the discharge rate or activity of WSN,  $T_{\text{set-sleep}}$  in the setpoint of the 'inflection point' of activity of WSN,  $\alpha$  and  $\beta$  are the slopes of the proportionality of the hypnogenic above and below the setpoint  $T_{\text{set-sleep}}$  (inflection point of WSN), and  $C$  is a fixed basal discharge rate. The WSN basal discharge rate  $C$  is then converted to a temperature term by introduction of parameter  $D_t$  ( $s^{-1} \text{ } ^\circ\text{C}^{-1}$ ) as follows:

$$\text{WSN}_{\text{temp}} = \alpha T_{\text{hypo}} + \beta (T_{\text{hypo}} - T_{\text{set-sleep}}) + \frac{C}{D_t} \quad (\text{A4})$$

$$\text{WSN}_{\text{temp}} = \alpha_T T_{\text{hypo}} + \beta_T (T_{\text{hypo}} - T_{\text{set-sleep}}) + C_T$$

where  $\alpha_T$  and  $\beta_T$  are the slopes of the proportionality of the hypnogenic above and below the setpoint  $T_{\text{set-sleep}}$  (inflection

point of WSN) and  $C_T$  is a fixed constant indication (°C) of basal discharge rate.

### Sleep/wake level

Sleep is previously defined in control theory terms as (Nakao *et al.*, 1995):

$$\text{SLEEP} = [\text{sensitivity}] \times [\text{sigmoidal function}] \quad (\text{A5})$$

$$\text{SLEEP} = [y(t) + C_w h(t) + c_g] \times \frac{1}{1 + \exp(-(T_{\text{hypo}}(t) - T_{\text{set}}(t))/c_i)} \quad (\text{A6})$$

with  $c_g$  the response magnitude of WSN,  $y(t)$  is a circadian oscillator defined as  $y(t) = a \sin(\omega t)$ ,  $c_w$  denotes the sensitivity of warm sensitive neurones,  $h(t)$  is the heat memory and  $c_i$  determines the curvature of the sigmoid function ( $c_i = 0.5$ ) (for more details, see Nakao *et al.*, 1995, 1999). The second term in equation (A6) indicates that the error signal of temperature regulation is transformed into a sigmoid sleep signal. The sensitivity function defined by Nakao *et al.* (1995, 1999) is a combination of the response magnitude and the sensitivity of WSN. This coincides very well with the properties of WSN in the PoAH as presented in equation (A3) and posted by (McGinty and Szymusiak, 2001). As DBM modelling is based on real-time measurement and hence excludes the necessity for an oscillatory function, relation (A6) can be written more specifically for DBM use as follows:

$$\text{Sleepiness}(t) = [\text{sensitivity WSNtemp}] \times [\text{sigmoidal function}]$$

$$\text{Sleepiness}(t) = \frac{\alpha_T T_{\text{hypo}} + \beta_T (T_{\text{hypo}} - T_{\text{set-sleep}}) + C_T}{1 + \exp(-(T_{\text{hypo}}(t) - T_{\text{set}}(t))/c_i)} \quad (\text{A7})$$

### Circadian variations controlled by the SCN

The effect of the SCN on changes in sleep or thermoregulatory functions comes down to the circadian rhythms of sleep and thermoregulatory functions. As DBM models are intended and used for on-line purposes, there is no need to include oscillatory functions in the equations (A1) or (A2). Including the instantaneous value of the circadian clocks suffices. As  $T_{\text{set}}$  is subject to a circadian rhythm (Stephenson *et al.*, 1984) and as all circadian thermoregulatory changes (CBT, heat loss, heat production, etc.) originate from these circadian changes in  $T_{\text{set}}(t)$ ,  $T_{\text{set}}(t)$  is here considered as the most premature and the most robust indication of our circadian clock.

### Thermoregulatory setpoint $T_{\text{set}}$ changes driven by PoAH

The error signal for the thermoregulatory is situated in the PoAH and is defined as the difference between hypothalamic temperature and the temperature setpoint for thermoregulation  $T_{\text{hypo}}(t) - T_{\text{set}}(t)$ . But as  $T_{\text{hypo}}$  has no direct influence on a change in  $T_{\text{set}}$ , the momentum and past values of  $T_{\text{set}}(t)$  are

here considered as an indicator for  $T_{\text{set}}$  changes driven by PoAH.

Compiling all this information, equations (A1) and (A2) can be rewritten as follows:

$$\frac{d(\text{Sleepiness})(t)}{dt} = \{ (T_{\text{hypo}}(t) - T_{\text{set}}(t)) \} + \{ \alpha_T T_{\text{hypo}}(t) + \beta_T (T_{\text{hypo}}(t) - T_{\text{set-sleep}}(t)) + C_T \} - S_{\text{cir}} \{ T_{\text{set}}(t) \}$$

$$\text{with Sleepiness} = \frac{\alpha_T T_{\text{hypo}}(t) + \beta_T (T_{\text{hypo}}(t) - T_{\text{set-sleep}}(t)) + C_T}{1 + \exp(-(T_{\text{hypo}}(t) - T_{\text{set}}(t))/c_i)} \quad (\text{A8a})$$

$$\frac{dT_{\text{set}}}{dt} = -A_s \cdot \text{Sleepiness} + T_{\text{cir}} T_{\text{set}} \quad (\text{A8b})$$

where the negative signs indicate an inverse proportional influence of the considered variable on the change in sleepiness ( $t$ ) or  $T_{\text{set}}(t)$ . This is the case for the influence of circadian variations in CBT on changes in sleepiness (when CBT rhythm is increasing, wakefulness is increasing and hence sleepiness decreases) and for the influence of sleepiness on changes in  $T_{\text{set}}$  (at sleep onset,  $T_{\text{set}}$  decreases. If the exact quantitative effect of a variable on the change in sleepiness or  $T_{\text{set}}$  is not known, an extra parameter expressing this effect is introduced. Therefore, we define the following parameters:

$S_{\text{cir}}$  = parameter representing contribution of the circadian rhythm to changes in sleepiness.

$A_s$  = parameter representing contribution of sleep level to changes in thermoregulatory set-point.

$T_{\text{cir}}$  = parameter representing contribution of circadian rhythm to changes in thermoregulatory set-point.

$B_P$  = parameter representing contribution of changes in sleep/wake-promoting neurones to changes in thermoregulatory setpoint.

The major function of the error signal of the proportional control of thermoregulation  $T_{\text{hypo}}(t) - T_{\text{set}}(t)$  is to provoke thermoregulatory responses (shivering, sweating, skin blood flow, heat loss, etc.) to the human body's heat balance. The relation between the error signal and the evoked thermoregulatory responses is proposed as follows (e.g. Hammel *et al.*, 1963):

$$R - R_0 = \alpha_R (T_{\text{hypo}} - T_{\text{set}}) \quad (\text{A9})$$

where  $R$  is the thermoregulatory response at time  $t$ ,  $R_0$  the basal thermoregulatory response at time  $t = 0$ , and  $\alpha_R$  differs only in magnitude (absolute value) for each thermoregulatory response.

For the present project, thermoregulatory responses are restricted to distal heat loss. Equation (A9), where  $\alpha_{\text{DHL}}$  indicates distal heat loss as considered thermoregulatory response and  $\delta$  represent the adjective time delay of the distal heat loss to the error signal, thus becomes:

$$T_m(t - \delta) - T_m(0) = \alpha_{\text{DHL}} (T_{\text{hypo}}(t) - T_{\text{set}}(t)) \quad (\text{A10})$$

$$(T_{\text{hypo}}(t) - T_{\text{set}}(t)) = \frac{T_m(t - \delta) - T_m(0)}{\alpha_{\text{DHL}}} \quad (\text{A11})$$

Including equation (A11) into (A8a) delivers:

$$\frac{d(\text{Sleepiness})(t)}{dt} = \left\{ \frac{(T_m(t - \delta) - T_m(0))}{\alpha_{\text{DHL}}} \right\} + \{ \alpha_T T_{\text{hypo}}(t) + \beta_T (T_{\text{hypo}}(t) - T_{\text{set-sleep}}(t)) + C_T \} - S_{\text{Cir}} \{ T_{\text{set}}(t) \} \quad (\text{A12a})$$

$$\frac{dT_{\text{set}}}{dt} = -A_s \cdot \text{Sleepiness} + T_{\text{cir}} T_{\text{set}} \quad (\text{A12b})$$

With sleepiness defined as in (A8a), this becomes:

$$\frac{d(\text{Sleepiness})(t)}{dt} = \beta_R (T_m(t - \delta) - T_m(0)) + K_{\text{sig}} \cdot \text{Sleepiness}(t) - S_{\text{Cir}} \{ T_{\text{set}}(t) \} \quad (\text{A13a})$$

$$\frac{dT_{\text{set}}}{dt} = -A_s \cdot \text{Sleepiness} + T_{\text{cir}} T_{\text{set}} \quad (\text{A13b})$$

with  $\beta_R = 1/\alpha_{\text{DHL}}$

$$K_{\text{sig}} = 1 + \exp\left(-\frac{(T_{\text{hypo}}(t) - T_{\text{set}}(t))}{c_i}\right)$$

The first-order differential equations (A13a) and (A13b) may be converted to the required TF form using the Laplace operator ( $s = d/dt$ ). This gives:

$$\text{Sleepiness}(t) = \frac{\beta_R}{s - K_{\text{sig}}} (T_m(t - \delta) - T_m(0)) - \frac{S_{\text{cir}}}{s - K_{\text{sig}}} T_{\text{set}}(t) \quad (\text{A14a})$$

$$T_{\text{set}} = -\frac{A_s}{s - T_{\text{cir}}} \text{Sleepiness}(t) \quad (\text{A14b})$$

Combining equations (A14a) and (A14b) delivers:

$$\text{Sleepiness} = \frac{b_0 s + b_1}{s^2 + a_1 s + a_2} (T_m(t - \delta) - T_m(0)) \quad (\text{A15})$$

with

$$\begin{aligned} b_0 &= \beta_R \\ b_1 &= -\beta_R T_{\text{cir}} \\ a_1 &= -(K_{\text{sig}} + T_{\text{cir}}) \\ a_2 &= K_{\text{sig}} T_{\text{cir}} - A_s S_{\text{cir}} \end{aligned}$$

Notice that equation (A15) is of the exact identical form of the model identified from the experimental data. The parameter  $b_0 = \beta_R$  in equation (A15) represents a physical meaningful and well-known parameter from literature.  $\beta_R$  is defined as  $1/\alpha_{\text{DHL}}$  in equation (A10), with  $\alpha_{\text{DHL}}$  representing the magnitude the thermoregulatory response distal heat loss (after Hammel *et al.*, 1963):

$$T_m(t - \delta) - T_m(0) = \alpha_{\text{DHL}} (T_{\text{hypo}}(t) - T_{\text{set}}(t)) \quad [\text{C}] \quad (\text{A10})$$

From the presented model, values for  $\alpha_{\text{DHL}}$  can be derived from the measurement of both  $T_m(t) - T_m(0)$  and sleepiness from raw EEG data, and this per individual and per time. By

doing this, not only the individual and time-varying value of  $\alpha_{\text{DHL}}$  can be calculated, but as  $T_{\text{m}}(t) - T_{\text{m}}(0)$  is a measurable variable, the thermoregulatory error signal  $T_{\text{hypo}}(t) - T_{\text{set}}(t)$  at

a certain time  $t$  can also be derived for each individual by simple measuring distal heat loss and raw EEG (equation A10).