Evolutionary Simulations to Determine the Human Circadian Period Using an Extended Sleep-Wake Model

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***Abstract*—The development of the human sleep-wake cycle and the adaptation to the changing day and night condition on our planet took place over a time frame of 100 000 years. As the result, a representative cross section of today's population sleeps between 4 and 11 hours, with a midsleep point between 1.00 and 9.00 am and a period length of the human circadian pacemaker between 23.5 and 25 hours. Roenneberg et al. published the distribution of midsleep point and sleep duration based on an extensive questionnaire which represents the Middle European society. Czeisler presented a normal distribution of the period length of the human circadian pacemaker as result of a forced desynchrony study. The sleep wake characteristic can be described with the well established two-process model (2PM). The adaptation of the period of our pacemaker to the 24-h day by light is best understood in terms of the phase response curve (PRC). We introduce a combination of these two well established models, called extended two-process model (E2PM). With this model, the sleep-wake behaviour and the circadian period of man under natural day (light) and night (dark) conditions can be simulated simultaneously. With this model, 250 different sleep-wake types were parametrized using evolutionary algorithms. As a breakthrough, the resulting distribution of one important parameter, the sleep-wake cycle duration, matches closely the experimentally acquired distribution of Czeisler.**

***Keywords*-evolutionary algorithms; circadian rhythm; entrainment; light; sleep-wake cycle; chronotype**

I. Introduction

Since decades different models have been proposed to predict the wide range of human sleep-wake behaviour. The following subsections will shed light on the core features of the human sleep-wake rhythm and existing mathematical models. Afterwards, we introduce a combination of two broadly accepted models and use evolutionary algorithms (EA) to optimize the models' parameters to match the widely varying sleep-wake behaviour.

A. Chronotypes

Humans vary in their individual timing of physiological cycles – such as body temperature, hormone release and, most obviously, their sleep and wake times. The distinct timing of the sleep-wake cycle is referred to as *chronotype*. Roenneberg surveyed more than 55 000 Middle Europeans with his Munich Chronotype Questionnaire and published the distributions for sleep duration and midsleep (see black bars in figure 2). Midsleep is the time halfway between sleep onset and wake-up. According to his survey, sleep duration and midsleep are largely normally distributed and uncorrelated [1], [2].

B. Bunker Experiments

Back in the 1970s, Aschoff and Wever [3] pioneered studies of the human sleep-wake rhythm. In the so-called bunker experiments in Andechs, Germany, more than 470 subjects lived self-selected sleep-wake-rhythms in chambers isolated from natural light and any other time cues for weeks [4]. Activity, body temperature and sleep times were recorded. Surprisingly, the period of subsequent sleep-wake cycles of the subjects lengthened during the first few days in isolation, and eventually settled just above the length of the 24-h day . The course of the body temperature – with its peak in the early subjective evening and its nadir in the late night – gives a superior estimation of the *circadian period length* (τ) and its *phase* in the 24-h day. Wever described a normal distribution in human circadian periods ranging from 23 to 26 hours, with an average of 25.2 hours under time isolated and self-selected light-dark conditions [3]. The astonishing results of the bunker experiments underlined the idea of an *endogenous circadian* (i. e. near 24-hour) *pacemaker* that times the sleep-wake pattern in humans. The synchronization process of this body clock with the 24-hour day is called *entrainment* and will be discussed later.

C. Forced Desynchrony Experiments

In the 1990s, Czeisler and his group applied a forced desynchrony protocol to determine the average period length τ of the human endogenous circadian pacemaker. In these experiments, 21 subjects were scheduled to live through artificial 28-hour 'days' for 3.5 weeks, while their body

temperature, melatonin levels and other measures were continuously recorded. By administering such a schedule beyond the range of entrainment of the intrinsic body clock, body temperature, hormone production and other circadian rhythms are decoupled from the sleep-wake rhythm. This allows precise measurement of the *unmasked* human circadian cycle. As a result, a normal distribution of τ was determined to be 24.18 hours $\pm$ 0.04 hours, ranging from 23.53 to 24.59 hours [5]. Czeisler explained the difference to the free-running periods in Aschoff's and Wever's bunker experiments with a probable bias that the subjects induced on themselves due to their self-selected light regime.

D. Modelling the Entrainment

Researchers determined that light is the major synchronizer for the circadian pacemaker to the 24-hour solar day [6]. The entraining and phase-shifting effects of light to circadian rhythms in general have been studied extensively since 1959 on various species [7], [8].

According to these observations, the *phase-response curve* (PRC) model was introduced by Moore-Ede [9] and others, as illustrated in figure 1. Light shortly *before* the nadir of the body core temperature delays the phase of the circadian processes (and thus the sleep-wake rhythm), light *after* the nadir will advance this phase [10]. The singularity of the PRC corresponds with the nadir of the body temperature.

Changes in the amplitude of the circadian rhythms were reported by Hildebrand [11] and Jewett [10] when inverting the sleep-wake pattern e. g. during night shifts. Achermann [12] and Kronauer [13] proposed a combination of PRC and *amplitude-response curve* (ARC) to model this attenuating impact of light to the circadian amplitudes around the nadir of the body temperature. Recovery occurs when light hits only the outer areas of the ARC.

E. Two-Process Model

The two-process model (TPM) published by Daan et al. [14] simulates sleep-wake cycles for any regular sleep type. As illustrated in the upper part of figure 1, sleep pressure (S) rises and falls between the upper and lower circadian thresholds (C_H and C_L, respectively). When S meets C_H, *sleep* starts and S declines. When S meets C_L, the simulation state changes to *awake* and S rises with logistic growth. The sleep duration can be prolonged by lowering the base levels of C_L and C_H, and the phases of C_L and C_H determine the timing of sleep onset and wake up. The TPM has been tested extensively against real data, and core parameters for S were derived from EEG data [15], [16].

F. Extended Two-Process Model

In the original publication, the TPM does not support the entrainment of its circadian processes to a changing light environment. Combining the TPM with the PRC and

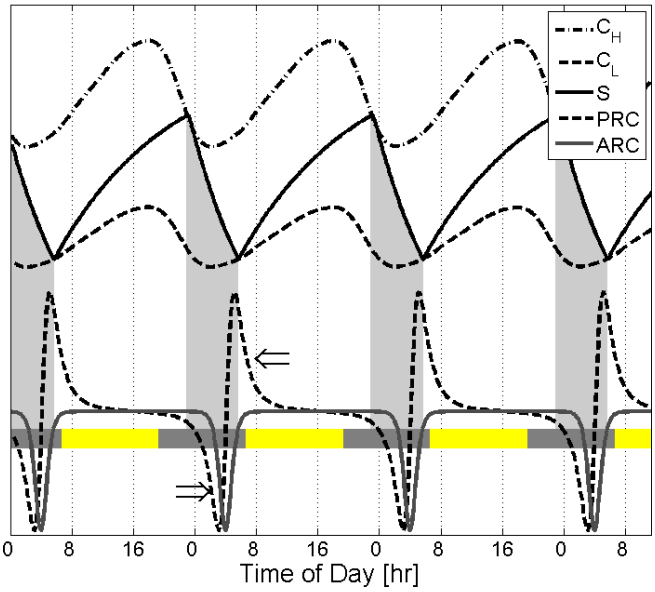
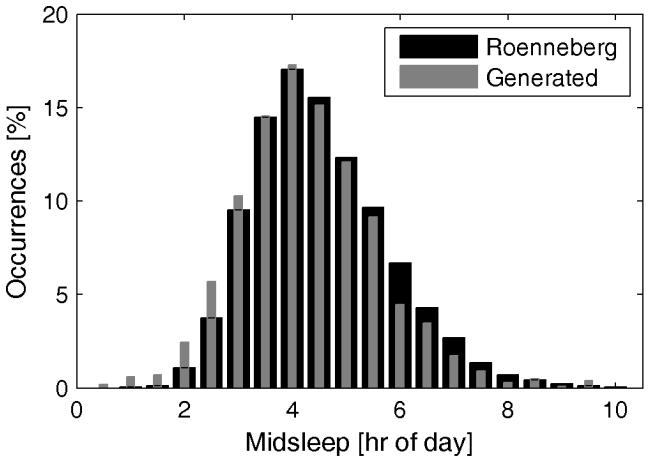


Figure 1. Illustration of the *extended two-process-model* (E2PM) for several days. Upper part: process S (sleep pressure, solid) oscillates between the upper and lower circadian thresholds C_H and C_L, respectively (dashed, stitched curves). Gray areas indicate the sleep state. Lower part: yellow bars indicate daylight illumination, black bars night light. Light that hits the phase-response curve (PRC, dashed line) during wakefulness induces *phase advances* in the *subjective morning* and *phase delays* in the *subjective evening*, respectively. The amplitude response curve (ARC, solid grey) reflects the *attenuation of the circadian processes* if light meets wakefulness during the subjective midnight.

ARC thus enables synchronization to the 24-hour day under real-world light conditions as illustrated in figure 1: the oscillators PRC, ARC, C_H and C_L run *at the same period length* τ. Light that hits the PRC during wake times shifts the phase of all of those oscillators, and light on the ARC affects the amplitudes of the circadian thresholds C_H and C_L. The homoeostatic sleep-wake behaviour will then adapt to the *altered phase relationships* between the oscillators. This in return changes the timing at which the simulation is influenced by light. In this way, a *feedback loop* is established, and entrainment of the sleep-wake rhythm to light can be simulated.

G. Evolutionary Algorithms

Over hundreds of millions of years, evolution has created an incredible range of life forms perfectly adapted to its respective habitats on earth. Survival of the fittest, cross combination and random mutation led to this great optimization result. *Evolutionary algorithms* (EA) were developed in the 1980s to mimic this process in order to solve high-dimensional optimization problems [17]. First, a random population of feasible solutions is generated and the *fitness* for each solution is determined with a *cost function*. Then, the best solutions are *selected* for the next *generation* and produce offspring by *recombining* their variables. An addi-



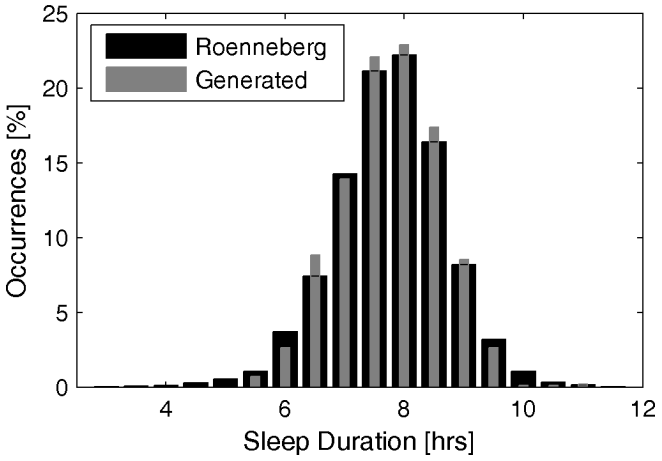


Figure 2. Distribution of habitual midsleep point (upper half) and sleep duration (lower half) of Middle Europeans according to Roenneberg's survey [2] (black bars) and for all successfully parametrized sleep-wake types during seven EA parameter optimization iterations (grey bars). The initial set of sleep-wake types was randomly generated within Roenneberg's range of midsleep and sleep duration.

tional amount of *mutation* provides good exploration of the search space and prevents convergence on potentially local minima. This process is iterated for a predefined number of generations or until the optimization target is reached.

II. Model Parameter Optimization with Evolutionary Algorithms

To prove the capabilities of the E2PM, it must be able to simulate the whole range of human sleep-wake habits. 250 *sleep-wake types* were randomly selected as target set according to the sleep-wake distribution presented by Roenneberg [2] (see figure 2). Fitting the model parameters (τ and phase angles, amplitudes, level and shape parameters for C_L, C_H, ARC and PRC) to these sleep-wake habits is a complex optimization task for which EA were used. Parametrization of a single sleep-wake type with EA works as follows: First, a target sleep-wake pattern is generated for a simulation length of 40 days, based on the desired

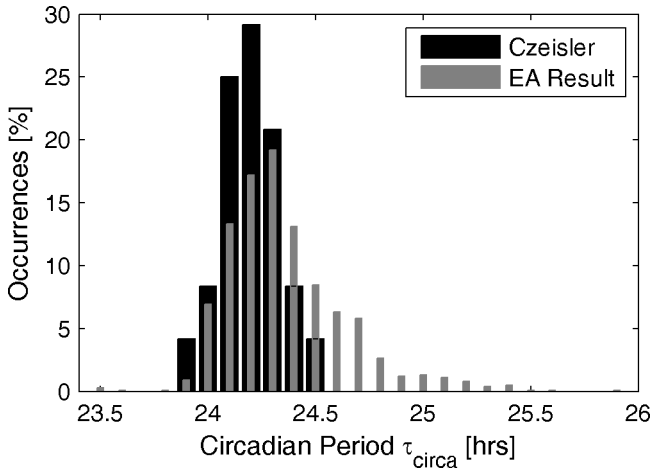


Figure 3. Distributions of endogenous circadian period τ, experimentally measured by Czeisler et al. [5] (black bars) and as a result of EA parameter optimization (grey bars) display a close match.

habitual midsleep point and sleep duration. Next, a set of 100 random solutions are generated within a feasible range (e.g. $22 \leq \tau \leq 27h$).

Solutions (i. e. parameter sets) are commonly called *individuals*, and the amount of individuals is called *population*. Each individual is now simulated for 60 days with the E2PM under a fixed illumination pattern of 12 hours daylight and 12 hours without light, according to the Middle European equinox. The simulation time slot interval is set to 10 minutes. For each time slot of the simulation, the simulation output, i. e. state of *sleep* or state of *wake*, is stored in a result pattern. The fitness of the individual is calculated as the absolute difference between the target and result sleep-wake pattern. That is, for each time slot, the error is increased if the targeted and simulated states differ.

Based on the calculated fitness of the entire population, merely the best individuals are selected for the subsequent generation; the remaining 50 % are discarded. Random pairs of selected individuals are recombined, i. e. variables from both parents are propagated to their offspring by arithmetic, heuristic and simple cross-combination [17], [18], until the initial population size is reached. Then, simple and non-uniform mutations are applied to a random subset of the new population, whereby the best solutions are spared (elitist model). The impact of the non-uniform mutations decreases with higher generation numbers [19]. Next, the fitness for new or mutated parameter sets is calculated, before the process of selection, recombination and mutation starts again. This procedure is repeated for 80 generations.

The described combination of different recombination and mutation operators ensures fine-tuning during higher generations and reduces the likelihood to get stuck in local minima, which is a core challenge in traditional optimization.

III. Results

The resulting parameter sets were simulated with the E2PM and tested for stability. Solutions that did not match the self-selected target of less than 10 minutes difference per day between desired and simulated sleep-wake behaviour were recalculated. A high mutation rate of 15 % actually led to better results and less recalculation demand. Being a heuristic approach, EA might not always find the best solution, but usually will provide good results.

The described parametrization procedure was executed seven times on all generated sleep-wake types, and the resulting successful parameter sets were consolidated. Examination of the solutions displayed normal distribution for most of the parameters at the centre of their range.

Outstanding is the distribution of τ (figure 3). Within the limits of 22 hours to 27 hours during the EA parametrization, τ was normally distributed with an average of 24.41 h $\pm$ 0.28. This result lies in between the experimentally measured τ = 24.18 h $\pm$ 0.04 h by Czeisler [5] and τ = 25.2 h measured by Wever [3]. As far as our investigations go, such result can only be achieved with the described combination of ARC, PRC and TPM to one single model.

IV. Conclusion

To our knowledge, it is the first time that these two experimental data sets were matched by simulations with EA based parameter optimization. The combination of TPM, PRC and ARC to model sleep homoeostasis and circadian entrainment by ambient light may be considered a usable approach for a realistic simulation of the human sleep-wake behaviour. Further publications of simulation results on phase shifting responses to various light conditions and sleep homoeostasis are in work.

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