Sleep-wake cycles and jet lag

Channa Schramm

University of Michigan REU
chramm@umich.edu

Abstract

The circadian rhythm controls a number of biological processes, such as body temperature, blood pressure, metabolism and alertness, which oscillate over a period of a little more than 24 hours. The sleep-wake cycle is also influenced by this circadian clock, located in the superchiasmatic nucleus (SCN) of the brain. The circadian rhythm in the SCN is affected by light and dark to form a cycle. Sleep-wake cycles are referred to as "entrained" to the circadian rhythm when they oscillate together in a regular pattern. Travel often causes misalignments between the circadian rhythm and the sleep-wake cycle, and therefore a period of re-entrainment is needed, also known as jet lag. Using mathematical models, I am investigating the effects of different light schedules on the circadian rhythm in the SCN, sleep patterns, and rapid eye movement (REM) cycles.

I. Introduction

A circadian rhythm is a cycle of a little more than 24 hours that regulate the physiological processes of living beings, including plants and animals. This includes body temperature, blood pressure, metabolism, and alertness, all processes that oscillate within a period of roughly 24 hours. While the circadian rhythm is internal, it can be effected by external signals such as ambient temperatures, meal times, stress, and exercise. The strongest affecter though is light, and the circadian rhythm tends towards synchronization with cycles of light and dark.

The superchiasmatic nucleus (SCN) functions as the master circadian clock in the brain. Daily sleep-wake cycles are coordinated by interactions between neurotransmitters in the brainstem and hypothalamic neuronal populations that regulate transition between wakefulness, REM sleep, and nREM sleep. The locus coeruleus (LC) is a part of the brain stem that is responsible for the primary processing of the wake promoting neurotransmitter, norepinephrine. The dorsal raphe (DR) produces serotonin. The LC and DR are active during waking hours, partially active during non-REM (nREM) sleep, and almost completely dormant during REM sleep. The ventrolateral preoptic area (VLPO), located in the hypothalamus, is active during sleep, primarily nREM sleep. The VLPO releases the neurotransmitter GABA which inhibit the neurons that are involved in wakefulness and arousal. The REM promoting neurotransmitter acetylcholine is produced by the pedunculopontine and laterodorsal tegmental nucleus (PPT/LDT), with high activation during REM sleep and low activation during nREM sleep.

Most importantly to this paper, a person's sleep-wake cycle is influenced by this internal clock. Sleep-wake cycles are referred to as "entrained" to the circadian rhythm when they oscillate together in a regular pattern. Travel often causes misalignments between the circadian rhythm and the sleep-wake cycle, especially travel between time zones, and therefore a period of re-entrainment is needed also known as jet lag. The symptoms of jet lag, including depressed cognitive alertness, can also arise from work and social schedules misaligned with the timing of the circadian clock.

II. Methods

The models for this research were created implementing a previously developed model of a sleep-wake regulatory network for human sleep [1]. The equations for the firing rates of the LC, VLPO, R, WR, and SCN (equations 1-5) are measured in Hz. They simulate the active neuronal populations using a time scale of minutes. The levels of neurotransmitters are dependent on these firing rates, and the concentrations of norepinephrine (N), GABA (G), REM promoting acetylcholine (AR), wake/REM promoting acetylcholine (AWR), and the GABA produced by the SCN (SCN) are represented in equations 6-10. The sleep drive is directed by a Heaviside function (equation 11), where $Heaviside[Z] = 0$ if $Z < 0$ and $Heaviside[Z] = 1$ if $Z \geq 1$. Thus if the model is in a wake state, H increases toward H_{max}, if the model is in a sleep state, H decreases towards zero. The circadian drive (equations 12-14) is the model developed by Forger, Jewett, and Kronauer [2].

Equations

$$\frac{dF_{LC}}{dt} = \frac{F^{\infty}_{LC}(g_{A,LC} \cdot C_A + g_{SCN,LC} \cdot C_{SCN}) - g_{G,LC} \cdot C_G) - F_{LC}}{\tau_{LC}} \tag{1}$$

$$\frac{dF_{VLPO}}{dt} = \frac{F^{\infty}_{VLPO}(-g_{N,VLPO} \cdot C_N - g_{SCN,VLPO} \cdot C_{SCN} - g_{G,VLPO} \cdot C_G) - F_{VLPO}}{\tau_{VLPO}} \tag{2}$$

$$\frac{dF_R}{dt} = \frac{F^{\infty}_R(g_{A,R} \cdot C_A - g_{N,R} \cdot C_N + g_{SCN,R} \cdot C_{SCN} - g_{G,R} \cdot c_G) - F_R}{\tau_R} \tag{3}$$

$$\frac{dF_{WR}}{dt} = \frac{F^{\infty}_{WR}(g_{A,WR} \cdot C_A - g_{G,WR} \cdot C_G) - F_{WR}}{\tau_{WR}} \tag{4}$$

$$\frac{dF_{SCN}}{dt} = \frac{F^{\infty}_{SCN}(C + g_{A,SCN} \cdot C_A + g_{N,SCN} \cdot C_N) - F_{SCN}}{\tau_{SCN}} \tag{5}$$

$$\frac{dc_N}{dt} = \frac{c^{\infty}_N(F_{LC}) - c_N}{\tau_N} \tag{6}$$

$$\frac{dc_G}{dt} = \frac{c^{\infty}_G(F_{VLPO}) - c_g}{\tau_g} \tag{7}$$

$$\frac{dc_{AR}}{dt} = \frac{c^{\infty}_{AR}(F_R) - c_{AR}}{\tau_{AR}} \tag{8}$$

$$\frac{dc_{AWR}}{dt} = \frac{c^{\infty}_{AWR}(F_{WR}) - c_{AWR}}{\tau_{AWR}} \tag{9}$$

$$\frac{dc_{SCN}}{dt} = \frac{c^{\infty}_{SCN}(F_{SCN}) - c_{SCN}}{\tau_{SCN}} \tag{10}$$

$$\frac{dH}{dt} = \frac{(H_{max} - H)}{\tau_{hw}}\ Heaviside[F_{LC} - \theta_W] - \frac{H}{\tau_{hs}})\ Heaviside[\theta_W - F_{LC}] \tag{11}$$

$$\frac{dC}{dt} = \frac{\pi}{(12)(60)}\ (x_C + B) \tag{12}$$

$$\frac{dx_c}{dt} = \frac{\pi}{(12)(60)}\ [\mu(x_c - \frac{4x_c^3}{3} - C\frac{24}{0.99669\tau_c}^2 + kB)] \tag{13}$$

$$\frac{dn}{dt} = 60[\alpha(I) \cdot (1 - n) - \beta\ n] \tag{14}$$

Serkh and Forger used the Forger et al model [2] to determine the optimal light schedules to shift the timing of the circadian clock to different time zones. According to Serkh and Forger [3], previous studies have used mathematical simplifications, which does not allow for certain types of schedules to be studied. This restricts the consideration of optimizing the entire schedule as a whole in order to minimize entrainment. The model utilized has no simplifying assumptions, and can be applied to different lengths of schedules and different light levels. Serkh and Forger defined re-etrainment in terms of optimal control theory, allowing for the use of a numerical algorithm based on a method originally used to optimize robotic manipulators in order to compute the optimal solution.

Figure 1: Lux Light Level Chart

LUX	DESCRIPTION
50,000	British summer sunshine
5,000	Overcast sky
500	Well-lit office
300	Minimum for easy reading
50	Passageway/outside working area
15	Good main road lighting
10	Sunset
5	Typical side road lighting
2	Minimum security risk lighting
1	Twilight
0.3	Clear full moon
0.1	Typical moonlight/cloudy sky
0.001	Typical starlight
0.0001	Poor starlight

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Actograms were created using Matlab to graph the output of the equations. The predicted sleep schedules for twenty days is shown in each actogram, with two days plotted next to each other in order to be able to view a full sleep cycle more easily. Sleep onset and offset was measured using a threshold of the firing rate of the LC (4 Hz), while REM onset and offset was measured using a threshold of the firing rates for REM promoting acetylcholine (3 Hz). Light schedules were plotted above each day's predicted sleep, with bars in shades of yellow representing the various light levels and bars of black representing darkness/night. Predicted sleep schedule were plotted in blue for nREM sleep and red for REM sleep. The point of minimum activity within the SCN (turquoise) was also plotted on the actogram, along with the minimum activity of the circadian rhythm (purple). Different levels of light (measured in lux) were used in the models, as indicated in each of the figures. As might be expected, both with slam shifts and optimal light schedules, brighter light allowed for quicker re-entrainment.

III. Models - Slam Shifts and Optimal

The first models computed were slam shifts (an abrupt shift in the LD cycle corresponding to instantaneous travel between time zones [3]) for time shifts of 1 to 23 hours. The rate at which a person adjusts to slam shifts is fairly slow and gradual, and even more gradual when the light levels used are lowered (figure 2). Light level also effects the point at which hours shift the sleep schedules are inclined to shift forward or backward from the original cycle (figure 3).

Typically, most shift schedules follow the pattern similar to that in figure 4(a), where the minima of the SCN slightly leads the shifting sleep schedule, but the periods of sleep generally overlap the SCN minima throughout the adjustment. In some cases, like in figure 4(b), the minima of the SCN leads the adjusting sleep schedule by a fair amount. This tends to occur at the one or two hour shifts that precede the schedule similar to figure 4(c), where the minima of the SCN and the sleep schedule shifts in opposite direction. After such a schedule occurs, the hour following returns to the typical schedule as seen in figure 4(d). If the light level is brighter, the opposition between the SCN minima and the sleep schedule occurs at a lower hour shift schedule, and there are more occasions where the SCN minima leads the predicted sleep as well (figure 3).

In most optimal schedules, the minimum of the SCN tended to align very closely with the minimum of the circadian cycle. The exceptions occured when the SCN and ciradian cycle minima lead the predicted sleep in adjusting. When either the SCN or the circadian minima lead, both lead, but they adjust at different rates. One adjusts faster than the other, but there seems to be no pattern to predict which that would be.

IV. Discussion

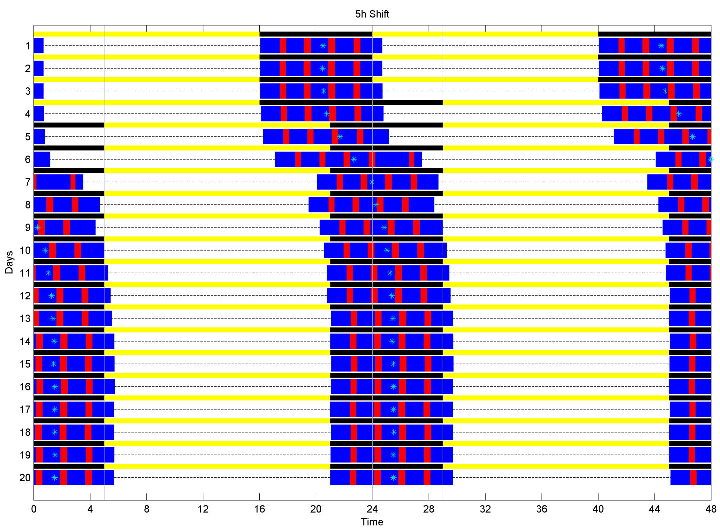
The actograms for the optimized light schedules do not show the expected results. Experimental data predicts re-entrainment in under a week for most time shifts when utilizing bright light, yet in many cases the optimized schedule models actually take longer to re-entrain than the slam-shift models. The models in this paper seem rather to indicate that these models predict when a person would be sleepy, and presumably if left to natural inputs, it would be at these times a person would sleep. Rather, a person would most likely tends toward wakefulness during the light hours of the new time zone. It is also likely that a person would be active during normal waking hours in the new time zone, thus preventing sleep, and altering the model in ways not represented in this research. Thus a model with forced naps or sleep times might adjust more quickly, and give a more realistic application.

References

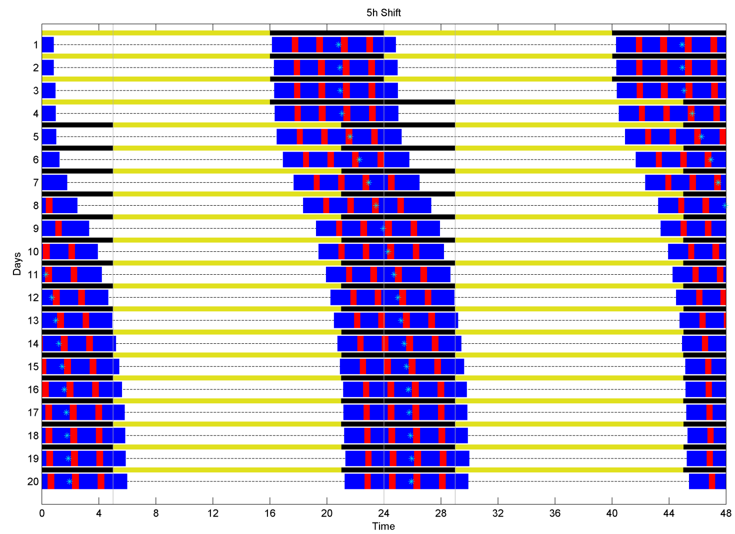
[1] Gleit, Rebecca D., Cecilia G. Diniz Behn, and Victoria Booth. "Modeling Interindividual Differences in Spontaneous Internal Desynchrony Patterns". *Journal of Biological Rhythms* 28.5 (2013): 339-355.

[2] Jewett, Megan E., Daniel B. Forger, and Richard E. Kronauer. "Revised limit cycle oscillator model of human circadian pacemaker". *Journal of Biological Rhythms* 14.6 (1999): 493-500.

[3] Serkh K, and Forger DB. "Optimal Schedules of Light Exposure for Rapidly Correcting Circadian Misalignment". *PLoS Computational Biology* 10.4 (2014): e1003523.

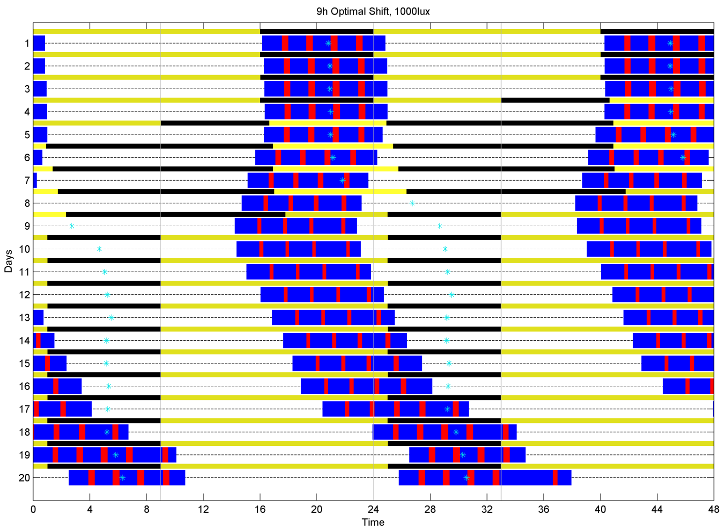


(a) A 5 hour shift utilizing a 10,000 lux light level

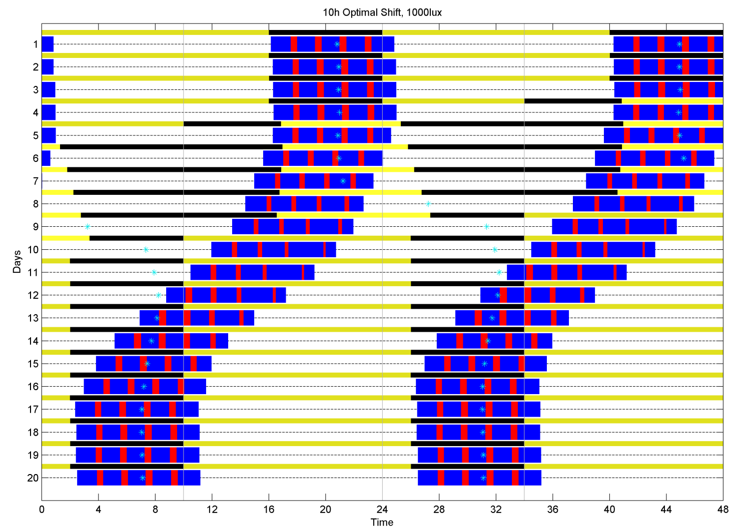


(b) A 5 hour shift utilizing an 100 lux light level

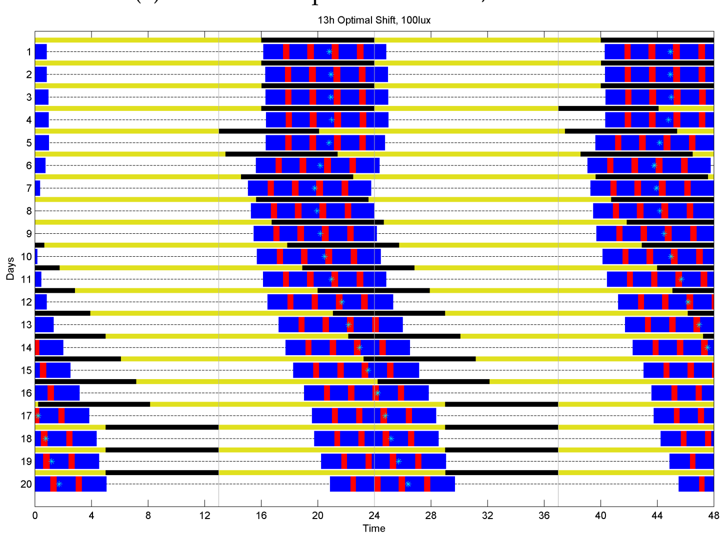
Figure 2: The light schedule for each day is graphed directly above the awake and sleep states. The waking state is shown in white, nREM sleep is shown in blue. REM cycles are marked by red bars and the point of minimum activity within the SCN is shown in turquoise. These two actograms show the re-entrainment of a 5 hour (traveling east) slam shift. The upper figure uses a light level of 10,000 lux (bright yellow) and 0 lux (black), while the lower uses 100 lux (dark yellow) and 0 lux (black). As can be clearly seen with these two actograms, a brighter light allows for quicker re-entrainment.



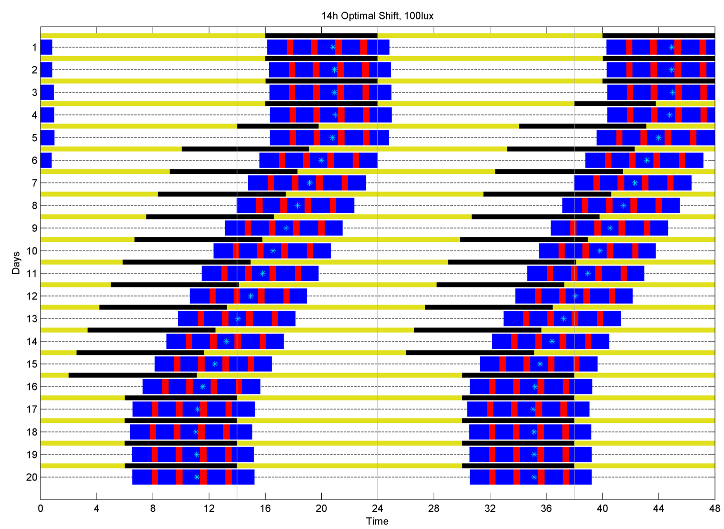
(a) 9 hour shift optimal schedule, 1000 lux



(b) 10 hour shift optimal schedule, 1000 lux

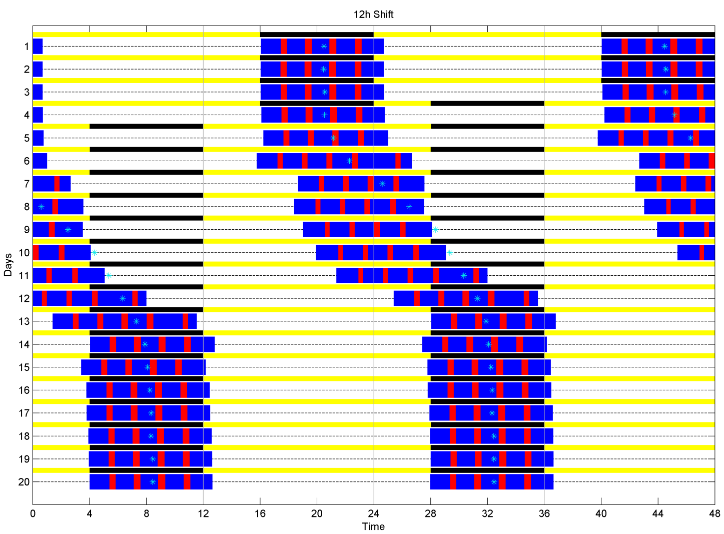


(c) 13 hour shift optimal schedule, 100 lux

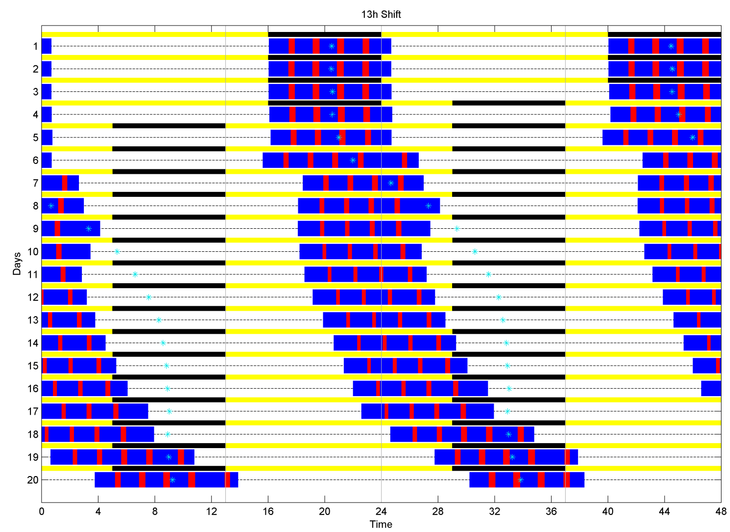


(d) 14 hour shift optimal schedule, 100 lux

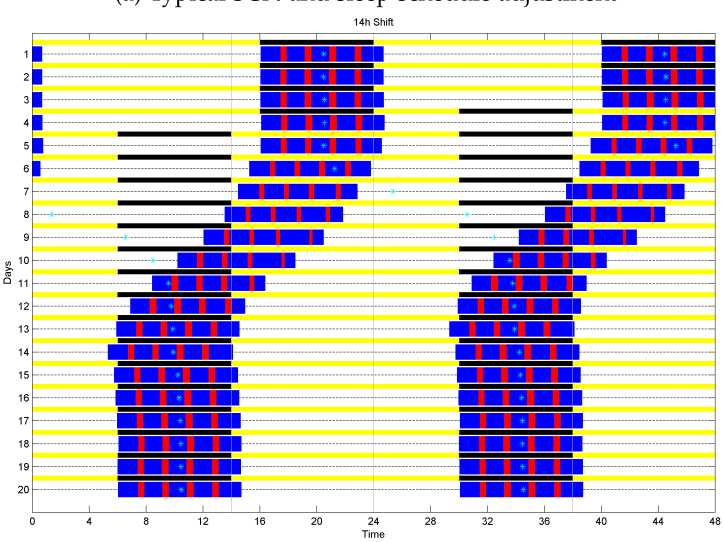
Figure 3: Light leve effects the point at which hours shift the sleep schedules are inclined to shift forward or backward from the original cycle. For the optimal adjustment schedule using 1000 lux light levels, the change occurs between a 9 hour shift and a 10 hour shift. At 100 lux light levels, that change occurs between a 13 hour shift and a 14 hour shift. It is also seen in figures (a) and (b), that in brighter light, the SCN and circadian minima adjust more quickly than the sleep cycle does.



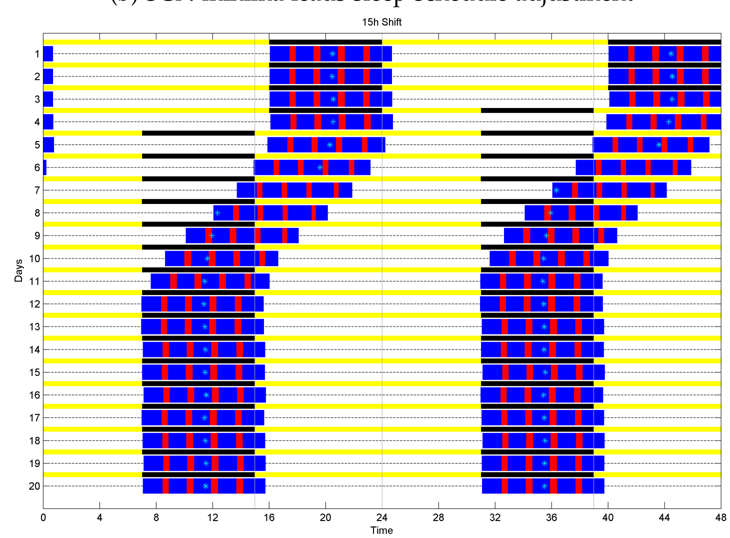
(a) Typical SCN and sleep schedule adjustment



(b) SCN minima leads sleep schedule adjustment



(c) SCN minima and sleep schedule adjust oppositely



(d) Typical SCN and sleep schedule adjustment

Figure 4: Typically, most shift schedules follow the pattern similar to that in (a), the minima of the SCN slightly leads the shifting sleep schedule. In (b), the minima of the SCN leads the adjusting sleep schedule by a fair amount. The minima of the SCN and the sleep schedule shifts in opposite directions in (c) and then returns to a typical shifting pattern in (d).