

Optimal Schedules of Light Exposure for Multiple Individuals for Quick Circadian Alignment

Anas Mohamed*, Chee Pin Tan**, Andrew J.K Phillips***, Vineetha Kalavally*, Sean W. Cain***

*Electrical and Computer Systems Engineering Department, Monash University Malaysia, Bandar Sunway, Malaysia
(e-mail: anas.mohamed@monash.edu, vineetha@monash.edu).

** Mechatronics Engineering Department, Monash University Malaysia, Bandar Sunway, Malaysia
(e-mail: tan.chee.pin@monash.edu).

*** Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Clayton, Australia
(email: andrew.phillips@monash.edu, sean.cain@monash.edu)

Abstract: The invention of quick transportation modes that allow trans-meridian travel has caused circadian misalignment to be a common problem amongst people today. This leads to lower cognitive alertness in the short term and increases the risks of other maladies in the long term. Light, when applied at correct levels and times, can shift and re-entrain the circadian clock to the local time zone, and minimize the negative impact of any circadian misalignment. In this paper, we developed a new method (algorithm) to calculate common optimal light schedules of light exposure and avoidance, to quickly re-entrain the circadian systems of a group of individuals who have different internal circadian parameters. We used an experimentally validated mathematical model to define a target circadian phase, from which, our optimization algorithm iteratively adjusts the switching times of a bang-bang light input (restricted to two light levels) to minimize the difference between the current phase of all individuals and the target phase, within a set time period. The proposed algorithm generated light schedules that successfully minimizes the re-entrainment time of all the individuals with phase shifts up to 12 hours of delay or advancement.

Keywords: Optimal Control, Bang-bang control, Human Circadian System, Circadian Re-entrainment.

1. INTRODUCTION

The industrial revolution and subsequent rapid development that followed has drastically changed the way humans live. Particularly, with the invention of artificial lighting, more people are active at night. Travel is also more widespread, with people crossing continents and experiencing different time zones within a short timespan of a day. These lifestyle changes subject them to shifts in daily light exposure, in turn causing circadian mistiming and disruptions in the sleep schedule (Nakagawa et al., 1992; Orth et al., 1979). Chronic circadian misalignments have been linked to many health problems (Sephtho and Spiegel, 2003; Stevens, 2005), and therefore it is important for the circadian clock to be properly re-entrained to the shifted schedule at the local time zone, as quickly as possible with minimal time between the entrained states.

Light is the strongest zeitgeber of the human circadian system (Czeisler et al., 1995). Light exposure has been known to shift the phase of the circadian clock (Jewett et al., 1991); these can either be phase advances or delays, depending on the timing of the light exposure (Hébert et al., 2002). Furthermore, the timing and duration of the light can affect the sensitivity of the circadian clock, making it more malleable to further shifts. There exists a large body of work, with suggestions on when and how to administer the light to achieve quick re-entrainment of the circadian clock using intermittent light (Burgess et al., 2002; Gronfier et al., 2004), avoiding morning

light (Daan and Lewy, 1984), and bright light exposure at the morning with restricted light exposure at night (Rosenthal et al., 1990). These techniques and experimental results have been shown to significantly quicken or slow the re-entrainment. However, owing to the fact that a huge number of possible variations of timing and intensity of the light may exist, it is impractical to find the best light schedule that re-entrains the circadian clock in the shortest time via trial and error. This problem is further complicated if individuals with biological differences are considered, and hence it becomes even more challenging to find an optimal light schedule for a group of individuals that re-entrains their circadian clocks as quickly as possible through experimental means alone.

As such, mathematical models that describe of the effects of light on the human circadian system are very useful. The literature for such models is rich and well-established, ranging from complex biochemical models to much simpler abstract models. Most biochemical models do not yet fit well to human Phase Response Curve (PRC) data and hence are far less widely used. On the other hand, abstract models (Forger et al., 1999; Jewett et al., 1999) have been widely used, and their practicality and accuracy have been widely demonstrated (Czeisler et al., 1999; Dean et al., 2007; Van Dongen, 2004). These models consist of two components (or “processes”), namely “Process L” which simulates phototransduction in the retina (Kronauer et al., 1999) and “Process P” which has two variables representing the amplitude and phase of the circadian pacemaker (Winfree, 2001). Previous studies have used these

models to derive optimal light schedules, for example Dean et al (2009) who proposed a method that produces countermeasures to correct circadian misalignments based on endogenous circadian period length, desired sleep-wake schedule, length of intervention, background light level, and countermeasure strength; however, the counter-measure (light) is of fixed duration and intensity. More recently, Serkh and Forger (2014) proposed a method to derive light schedules to rapidly re-entrain the circadian clock in the shortest time, while allowing the amplitude of the circadian pacemaker to be dynamic. However, all afore-mentioned works derived the optimal light schedules only for a single individual. In practice, people rarely live alone, and typical working environments house many individuals, and hence, in most cases, the afore-mentioned works are not practical.

In this paper, we present an optimization algorithm to derive locally optimal light schedules that minimize the difference between the current and target phase, for any number of individuals with various circadian parameters, within a certain time period. We define a cost function, describing the difference between the current phase (for the individuals) and a target phase. A “bang-bang” light schedule is used, where the illumination levels are either darkness or maximum brightness. The switching times are initialized randomly, and the algorithm modifies them iteratively to achieve a local minima for the cost function. Simulation results show that our algorithm entrains the circadian phase of the group at a speed and accuracy that is comparable to the methods in (Serkh and Forger, 2014). However, our algorithm is being applicable to a group of people, as opposed to a single individual.

2. METHODS

There are two main contributions to our developed method for computing the optimal light schedules. Firstly, we formulated the re-entrainment problem in terms of optimal control theory, for a group of individuals, using the same input light schedule. Secondly, we propose a discrete optimization method where each time interval (which corresponds to when the light input is shifted) is progressively optimized.

The model of the human circadian system used in this paper is a 3rd order limit cycle oscillator model (Forger et al., 1999) that can be described in the form:

$$\dot{x}(t) = f(x(t), u(t), t) \quad (1)$$

where $x \in R^3$, $x = [x_1, x_c, n]^T$ are the states and $u(t)$ is the external light input. State x models the component of the circadian pacemaker that reflects the endogenous core body temperature cycle, whilst x_c and n are simply complementary variables. The state equations can be described as follows:

$$\dot{x}_1 = \frac{\pi}{12}(x_c + B) \quad (2)$$

$$\dot{x}_c = -\frac{\pi}{12}\left(\mu\left(x_c - \frac{4}{3}x_c^3\right) - x\left(\frac{24}{0.99669\tau_c}\right)^2 + kB\right) \quad (3)$$

$$\dot{n} = 60(\alpha I)(1 - n) - \beta n \quad (4)$$

where, I is the light input, B is the strength of the light drive, μ is a stiffness constant and k , α and β are constants. For the problem considered in this paper, we define the cost function (to be minimized) as:

$$J(x(t), t) = \sum_{i=1}^N [(x_{ti} - x_{tf_i})^2 + (x_{cti} - x_{ctf_i})^2] \quad (5)$$

where N is the number of individuals, and t_f is the final time, which is user-defined. The cost function is formulated such that any number of individuals can be easily added. In short, we define a target state to be achieved at time t_f , namely x_{tf_i} and x_{ctf_i} , and the optimization algorithm varies the switching times of the input to drive the system states x_{ti}, x_{cti} to the target states x_{tf_i}, x_{ctf_i} at final time t_f ; however this does not guarantee that at time t_f the system states will reach the target states, but will be as close as possible.

We employ a numerical method to solve this optimization problem, which is a modification of the Switch Time Optimization method (Meier and Rysen, 1990) where the control input is “bang-bang”, meaning that it is binary and switches between a lower limit u_0 and upper limit u_1 .

The control $u(t)$ determines the trajectory of the states x_1, x_c and thus determines the cost J . Therefore, to find the optimal increment δu , we determine how small perturbations in the states $\delta x(t)$ will affect J , which we call the “co-state” $\lambda(t)$.

$$\lambda^T(t) = \frac{\delta J}{\delta x(t)} \quad (6)$$

Since the cost J is defined at final time t_f , it follows that:

$$\lambda^T(t_f) = \frac{\delta J}{\delta x(t_f)} = \left[\frac{\partial J}{\partial x} \right]_{t_f} \quad (7)$$

However, since we need to know the sensitivity of the change in state at all times from $[0, t_f]$, we need to scale this co-state backwards from t_f . Expanding δx using Taylor’s expansion, yields the following:

$$\frac{d\lambda^T}{dt} = -\lambda^T(t) \frac{\partial f}{\partial x}(t) \quad (8)$$

Solving $\frac{d\lambda^T}{dt} = -\lambda^T(t) \frac{\partial f}{\partial x}(t)$ backwards from t_f will give the sensitivity of the cost to a change in the states at any time t .

Now suppose we perturb the states at only specific times t_n where $k = 1, 2, 3 \dots K$ in $[0, t_f]$, we can superimpose the effect of the perturbations $\delta x(t_k)$ on the cost J to find the perturbation in J as follows:

$$\delta J = \sum_{n=1}^N \lambda^T(t_k) \delta x(t_k) \quad (9)$$

The trajectories of the state $x(t)$ can be changed by varying the control $u(t)$. Suppose on the time interval $[t_{k-1}, t_k]$, we

change $u(t)$ by $\delta u(t_{k-1})$, then the resulting perturbation in the states $x(t_n)$ is given by:

$$\delta x(t_k) = \frac{\partial f}{\partial u}(t_{k-1})\delta u(t_{k-1})h_K + \mathcal{O}(h_K^2) \quad (10)$$

Therefore:

$$\delta J = \sum_{k=1}^K \lambda^T(t_k) \frac{\partial f}{\partial u}(t_{k-1})\delta u(t_{k-1})h_K + \mathcal{O}(h_K^2) \quad (11)$$

and taking the limits as $K \rightarrow \infty$ results in:

$$\delta J = \int_0^{t_f} \lambda^T(t) \frac{\partial f}{\partial u}(t)\delta u(t)dt \quad (12)$$

The term $\lambda^T(t) f(x(t), u(t), t)$ is called the Hamiltonian in optimal control theory. Thus (13) can be also written as:

$$\delta J = \int_0^{t_f} \frac{\partial H}{\partial u}(t)\delta u(t)dt \quad (13)$$

Thus, Pontryagin's Minimum Principle can be used to find the optimal control. We see from equation $\delta J = \int_0^{t_f} \frac{\partial H}{\partial u}(t)\delta u(t)dt$ (13) that the cost J is guaranteed to decrease if $u(t)$ is perturbed by:

$$\delta u(t) = -\delta_u \lambda^T(t) \frac{\partial f}{\partial u}(t) \quad (14)$$

where δ_u is a small value. The largest step size of the input u possible that can be taken without breaking the linearity assumption is taken as per the proposal of (Serkh and Forger, 2014). This assumes that the fastest time scale of the human circadian system is known. At each iteration, δ_u is chosen such that the maximum shift in the switching time matches 6 minutes. This value was chosen because the fastest timescale of the Kronauer model of the circadian system used here, is in the order of 10 minutes (Kronauer et al., 1999); this ensures rapid convergence. If the small perturbations are repeatedly applied, a minimum point would eventually be reached.

The control $u(t)$ is limited to the values u_0 and u_1 ; this follows from Pontryagin's Minimum Principle which states that the optimum control at each time t must minimize H . This means that in this problem, an increment in $\delta u(\cdot)$ can therefore be treated as changing the switching times dt_j , $j = 1, 2, \dots, q$ where q is the maximum switching number. Thus the next step is to link δu_j to dt_j ; this is because a change in switching time is effectively a change in the bang-bang input. The conversion can be obtained by re-expressing the integral of $\delta u(\cdot)$ as a sum

$$\int_0^{t_f} \delta u(t)dt = \sum_{j=1}^q \Delta u_j dt_j \quad (15)$$

where $\Delta u_j = u(t_j^-) - u(t_j^+)$. Then we utilize the definition of $\delta J = \int_0^{t_f} \lambda^T(t) \frac{\partial f}{\partial u}(t)\delta u(t)dt$ (12), which includes δu and dt to form a conversion between them. Thus $\delta J = \int_0^{t_f} \lambda^T(t) \frac{\partial f}{\partial u}(t)\delta u(t)dt$ (12) becomes:

$$\delta J = \sum_{j=1}^q \left(\lambda^T \frac{\partial f}{\partial u} \right)_{t_j} \Delta u_j dt_j \quad (16)$$

and:

$$dt_j = -\frac{\delta_u}{\Delta u_j} \left(\lambda^T \frac{\partial f}{\partial u} \right)_{t_j} \quad (17)$$

where δ_u is calculated as:

$$\delta_u = ts / \max_j \left| \frac{1}{\Delta u_j} \left(\lambda^T \frac{\partial f}{\partial u} \right)_{t_j} \right| \quad (18)$$

where, ts is the fastest timescale of the problem.

Finally, the new switching times are:

$$t_j = t_j + dt_j \text{ for } j = 1, 2, \dots, q \quad (19)$$

2.1 Algorithmic steps

The optimization procedure described in this section can be summarized into the following algorithm.

Step 1: Guess nominal switching times t_1, t_2, \dots, t_q on the range $[t_0, t_f]$. Choose t_f and the binary values of the control $u(t)$, as u_0 and u_1

Step 2: Integrate the system equations ($\dot{x}_1 = \frac{\pi}{12}(x_c + B)$) (2) – ($\dot{n} = \mathbf{60}(\alpha(I)(\mathbf{1} - \mathbf{n}) - \beta\mathbf{n})$) (4) forward from x_0 to determine the state trajectories $x(t)$ using these switching times.

Step 3: Integrate the co-state equation $\frac{d\lambda^T}{dt} = -\lambda^T(t) \frac{\partial f}{\partial x}(t)$ (8) backwards from t_f to determine λ^T

at the switching times.

Step 4: Determine the optimal perturbations for decreasing the cost J , where δ_u is a small perturbation determined according to the following equation.

$$\delta_u = ts / \max_j \left| \frac{1}{\Delta u_j} \left(\lambda^T \frac{\partial f}{\partial u} \right)_{t_j} \right|, \\ dt_j = -\frac{\delta_u}{\Delta u_j} \left(\lambda^T \frac{\partial f}{\partial u} \right)_{t_j}$$

Step 5: Update the solution with

$$t_j = t_j + dt_j \text{ for } j = 1, 2, \dots, q$$

Step 6: If the cost J increases, decrease the active number of switching times from t_q to t_{q-1} where the switching time with the maximum dt is left constant and considered to be optimized. This allows the next switching time with the greatest influence on J to be shifted with dt equal to that of ts .

Step 7: Return to step 1 with the updated switching times and continue the progressive optimization of each switching time until $q = 0$.

The main contribution of this paper is in Step 6, which is the critical modification of the method of (Serkh and Forger, 2014), which ensures that the step size of the maximum dt equals 6 minutes. Due to the way we have formulated the cost $J, t = i-1 N[(xt_i - xt_f)2 + (xct_i - xct_f)2]$ (5), the switching times furthest from the final time (t_f) have the greatest influence on J ; this ensures that the contribution to the reduction in J from the switching time closest to t_0 is the highest. Therefore, while iterating, at some point, the step size from the switching time closest to t_0 will overshoot, causing J to increase, at which point we assume this switching time to be stable and continue to the next switching time with the highest

step size. This progressive optimization ensures that an optimal solution is quickly reached.

3. SIMULATION RESULTS

We tested our algorithm on a numerical-based simulation of 3 individuals using the model in (Forger et al., 1999). The intrinsic circadian period (τ) of each individual were slightly different, at values of 24.2, 24.5, and 23.8 respectively. This represents the range of variation in the human circadian periodicity. All individuals were entrained to a “home” light schedule, after which they were subject to a 12-hour shift in time-zone from the “home”. The simulation was carried out for 30 days after the time-zone shift, during which the individuals were subject to optimized light schedules for the first four days. As such, our optimization algorithm was set to have a set final time (t_f) of 96 hours. The initial switching time was set such that there are two equally spaced (12 hours) switching times every 24 hours ($q = 8$). We then repeated the simulation, without introducing the optimal schedule for the four days after the time-zone shift, where the individuals were only exposed to slam-shift (sudden shift in the light-dark (LD) cycle) light conditions; this serves to differentiate the impact of our optimal light schedule on the circadian system.

These results are presented as actograms in Fig. 1 - Fig. 3, where each horizontal bar represents a day. The switching times are represented by the intersection of the yellow and black bars. The black and yellow bars themselves represent the light and dark (LD) periods respectively. The minimum core body temperature (CBTmin) is represented by the red squares. CBTmin is a key circadian marker that reflects the entrainment of the individual to a certain time-zone. When properly entrained, the CBTmin occurs slightly after the midpoint of the dark region of the LD cycle. In addition to the actograms, the process of re-entrainment was also plotted in polar form, where both the phase and amplitude of the circadian pacemaker is shown as in Fig. 4. These are plotted for the same individuals as in Fig. 1 - Fig. 3 for the same light schedules from A-G. The results show that compared to a slam-shift (in which the individuals are all exposed to a shifted LD cycle), our optimized light schedule (in which the individuals are exposed to optimal schedules for four days) performed better in terms of the time it takes for the circadian clock to re-entrain. The optimal schedule is optimized for the three individuals, and they achieved re-entrainment much more quickly (on an average of 10 days) than the slam shift (which took an average of 23 days). This is also observed in Fig. 4 where CBTmin moved much faster through the polar phase-amplitude space. Furthermore, in the case of all individuals, it can be seen that the optimal schedule predicted takes a straighter path from the state of the circadian clock before the shift and the state after the shift when the schedules were optimized. However when it is just a slam-shift schedule, the shift took place with minimal shift in the amplitude of the circadian pacemaker for all the individuals. The inter-individual differences in the “straightness” through the polar plot is most likely due to the difference in the intrinsic circadian pacemaker of the three individuals. We note that the in the example above, the optimal

schedules were calculated for 4 days. We did not observe any improvement in re-entrainment time after extending the period of optimal schedules beyond four days for three individuals as shown in Table I. However, the optimized schedule we achieved was for an arbitrary input. This is a local minima that was achieved and it may be possible to reach a better local minima with different initial conditions. This particular number of switching time is chosen because it follows the natural LD cycle, but it is not necessary to do so. In general, higher switching times produce better results. Although, this is an aspect of this work that could be further explored.

Table 1. Trend of variation of the average time for re-entrainment of the circadian clock of three individuals with increase in the period of optimization

Period of optimal schedule (days)	Average time for re-entrainment of three individuals (days)
0	23
1	20
2	17
3	15
4	10
5	10
6	10

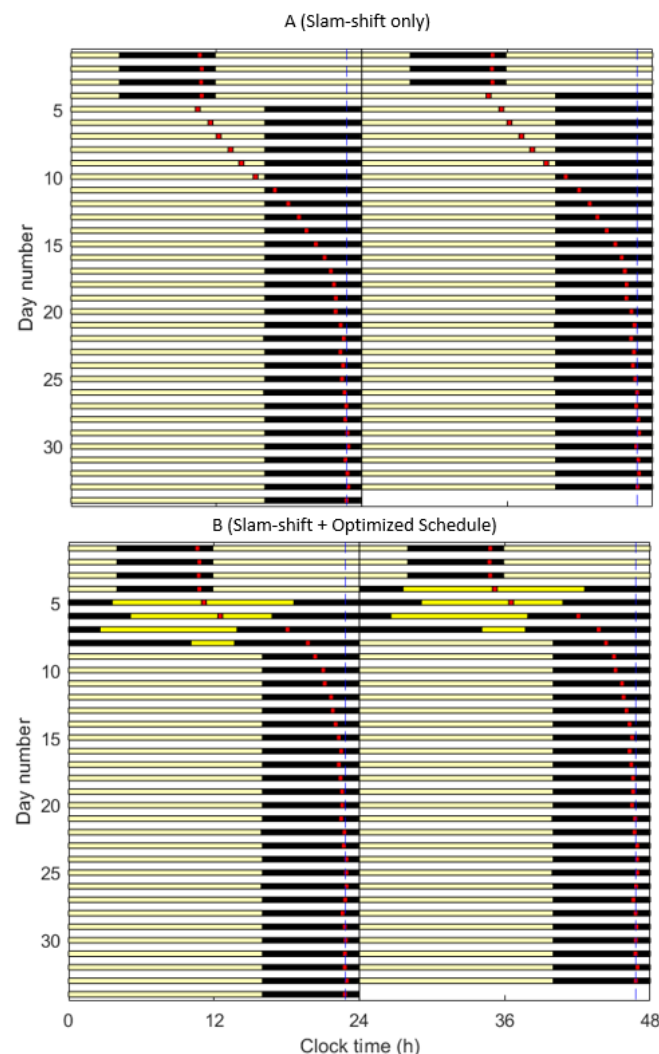


Fig. 1. Comparison of light schedules for a 12 hour shift of the light dark cycle for one individual. The light yellow bars represent periods of moderate light (100 lux) and the dark bars represent darkness (0 lux). The predicted circadian phase is indicated by the red squares, which are simulated core body temperature minima (CBT_{min}). It is plotted against a pattern of bright light and darkness. A illustrates the schedules of the individual subjected to slam shift. B illustrates the same individual subjected to the optimal light schedule for four days after the time-zone shift, in which the individual was subjected to periods of bright light of 1000 lux and periods of darkness. The timing of the entrained core body temperature minimum in the new time zone is represented by the dotted line.

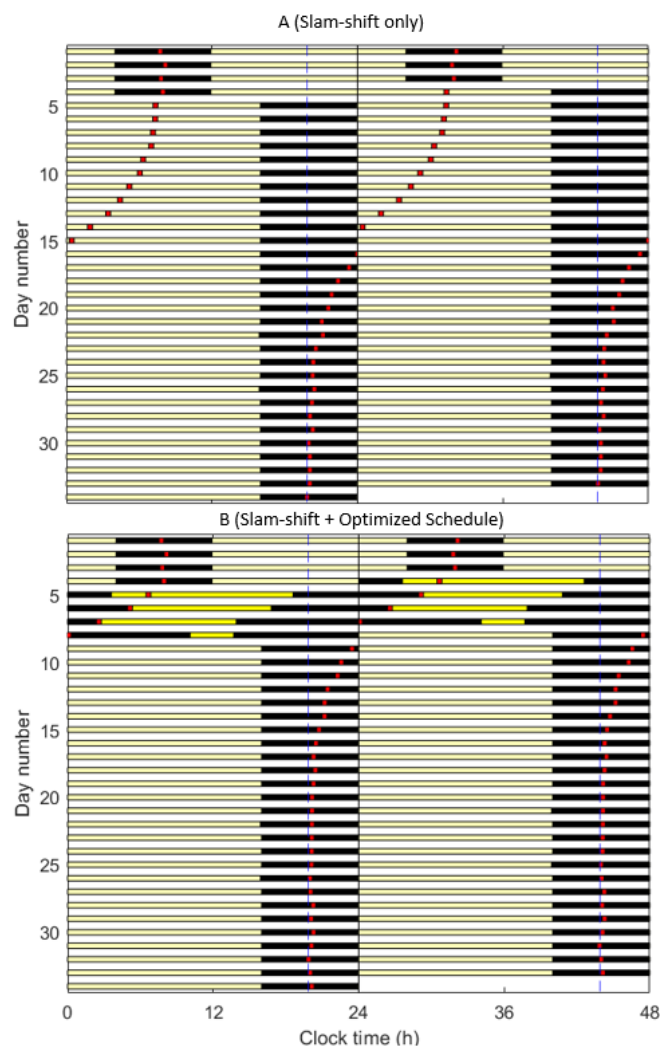


Fig. 2. Individual two.

4. CONCLUSION

This paper has developed a method (algorithm) for calculating optimal light schedules of light exposure and restriction to quickly re-entrain the circadian system of multiple individuals as quickly as possible. It is a modified switch time optimization method in which the number of active switching times are reduced as the optimization progresses. This allows for one switching time to have the largest step size possible for the human circadian system at one time. The modification takes advantage of the cost function that was defined for this problem wherein the switching time furthest from the final time has the largest impact on the cost. The number of

switching times are dynamic as the iterations progress to improve the speed and the optimality of the result. Our results demonstrate the efficacy of the developed method. While the mathematical model of the circadian we used is experimentally validated, it is simple in its representation. Future works can benefit from using more advanced models of the circadian system where more individual parameters can be adjusted. Moreover, the results from this optimization scheme produces a light schedule that only cycles between two levels.

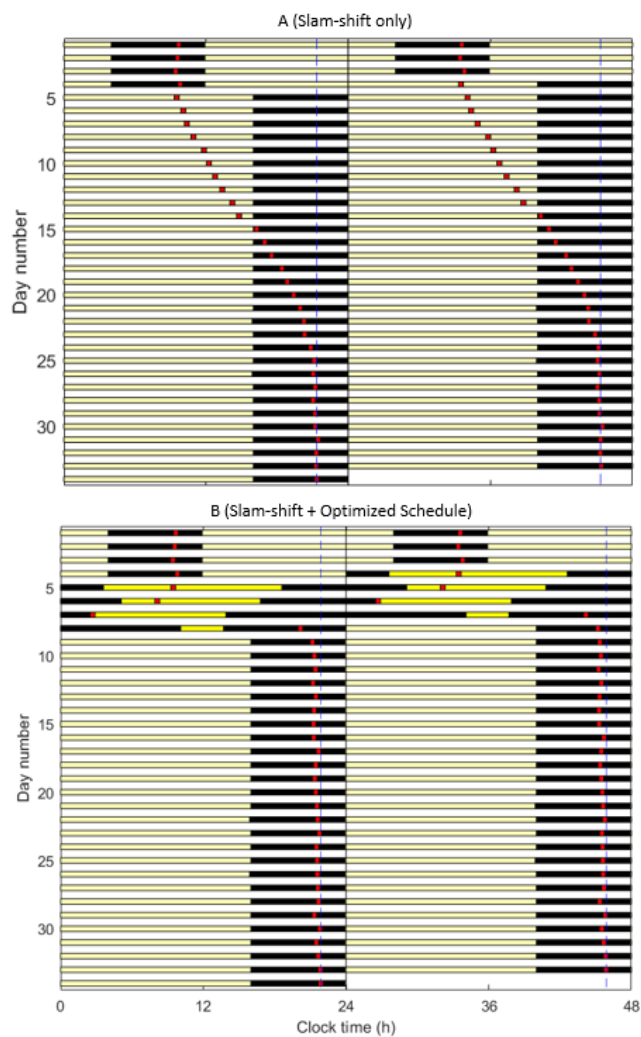


Fig. 3. Individual three.

Thus future work may be needed to make the light schedules more dynamic. Practical validation of this method is also an avenue of work, where the applicability of a bang-bang system in a real world environment can be explored by applying the predicted light schedules on a tuneable luminaire which can then be exposed to individuals, followed by investigations on the state of their circadian pacemakers.

REFERENCES

Burgess, H.J., Sharkey, K.M., Eastman, C.I., 2002. *Bright light, dark and melatonin can promote circadian adaptation in night shift workers*. Sleep Med. Rev. 6, 407–420.

Czeisler, C.A., Duffy, J.F., Shanahan, T.L., Brown, E.N., Mitchell, J.F., Rimmer, D.W., Ronda, J.M., Silva, E.J., Allan, J.S., Emens, J.S., Dijk, D.-J., Kronauer, R.E., 1999. *Stability, Precision, and Near-24-Hour Period of the Human Circadian Pacemaker*. Science 284, 2177–2181.

Czeisler, C.A., Shanahan, T.L., Klerman, E.B., Martens, H., Brotman, D.J., Emens, J.S., Klein, T., Rizzo, J.F., 1995. Suppression of melatonin secretion in some blind patients by exposure to bright light. *N. Engl. J. Med.* 332, 6–11.

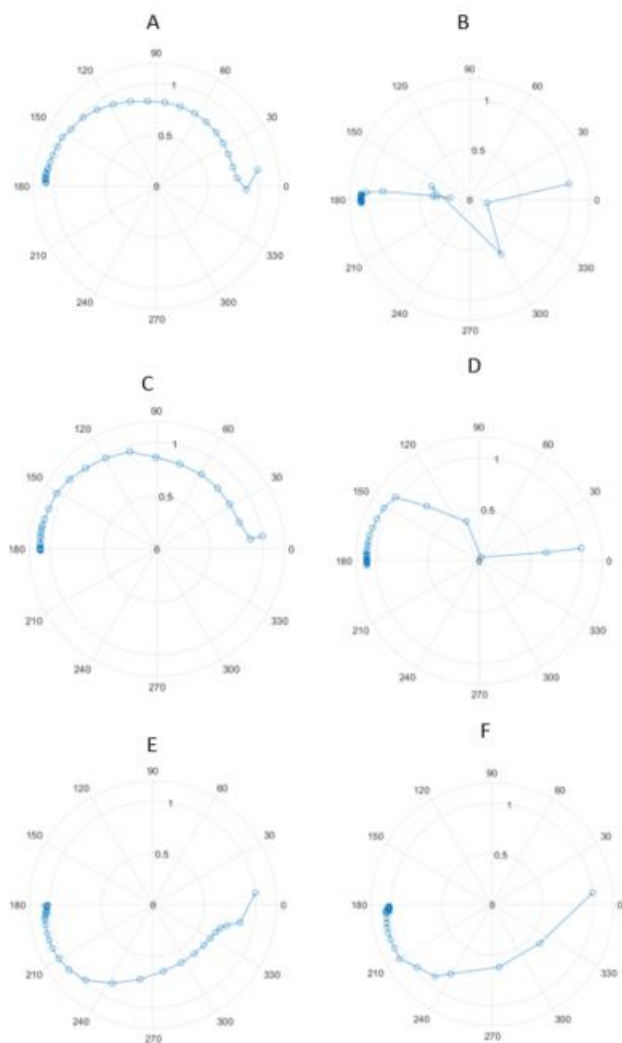


Fig. 4. Polar phase-amplitude plots showing the entrainment process corresponding to the schedules shown in figure 1. The phase of the circadian pacemaker is shown in degrees, with 00 corresponding to the pre-entrained CBTmin (prior to the 12 hour time shift). A 12 hour shift would result in a shift of 1800. The radius of the plot corresponds to the amplitude of the circadian pacemaker. (A,C and E) plots of individuals subjected to slam-shift. (B, D and F) plots of individuals subjected to optimized schedule.

Daan, S., Lewy, A., 1984. *Scheduled exposure to daylight: A potential strategy to reduced 'jet-lag' following transmeridian flight*. Psychopharmacol. Bull. 20, 566–568.

Dean, D.A., Fletcher, A., Hursh, S.R., Klerman, E.B., 2007. *Developing mathematical models of neurobehavioral performance for the "Real World."* J. Biol. Rhythms 22, 246–258.

Forger, D.B., Jewett, M.E., Kronauer, R.E., 1999. *A simpler model of the human circadian pacemaker*. J. Biol. Rhythms 14, 533–538.

Gronfier, C., Wright Jr, K.P., Kronauer, R.E., Jewett, M.E., Czeisler, C.A., 2004. *Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans*. Am. J. Physiol.-Endocrinol. Metab. 287, E174–E181.

Hébert, M., Martin, S.K., Lee, C., Eastman, C.I., 2002. *The effects of prior light history on the suppression of melatonin by light in humans*. J. Pineal Res. 33, 198–203.

Jewett, M.E., Forger, D.B., Kronauer, R.E., 1999. *Revised limit cycle oscillator model of human circadian pacemaker*. J. Biol. Rhythms 14, 493–500.

Jewett, M.E., Kronauer, R.E., Czeisler, C.A., 1991. *Light-induced suppression of endogenous circadian amplitude in humans*. Nature 350, 59.

Kronauer, R.E., Forger, D.B., Jewett, M.E., 1999. *Quantifying Human Circadian Pacemaker Response to Brief, Extended, and Repeated Light Stimuli over the Photopic Range*. J. Biol. Rhythms 14, 501–516.

Meier, E.-B., Ryson, A.E., 1990. *Efficient algorithm for time-optimal control of a two-link manipulator*. J. Guid. Control Dyn. 13, 859–866.

Nakagawa, H., Sack, R.L., Lewy, A.J., 1992. *Sleep propensity free-runs with the temperature, melatonin and cortisol rhythms in a totally blind person*. Sleep 15, 330–336.

Orth, D.N., Besser, G.M., King, P.H., Nicholson, W.E., 1979. *Free-running circadian plasma cortisol rhythm in a blind human subject*. Clin. Endocrinol. (Oxf.) 10, 603–617.

Rosenthal, N.E., Joseph-Vanderpool, J.R., Levendosky, A.A., Johnston, S.H., Allen, R., Kelly, K.A., Souetre, E., Schultz, P.M., Starz, K.E., 1990. *Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome*. Sleep 13, 354–361.

Sephton, S., Spiegel, D., 2003. *Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease?* Brain. Behav. Immun. 17, 321–328.

Serkh, K., Forger, D.B., 2014. *Optimal Schedules of Light Exposure for Rapidly Correcting Circadian Misalignment*. PLoS Comput. Biol. 10, e1003523.

Stevens, R.G., 2005. *Circadian disruption and breast cancer: from melatonin to clock genes*. Epidemiology 16, 254–258.

Van Dongen, H., 2004. *Comparison of mathematical model predictions to experimental data of fatigue and performance*. Aviat. Space Environ. Med. 75, A15–A36.

Winfrey, A.T., 2001. *The geometry of biological time*. Springer Science & Business Media.