Phase Locking in the Mammalian Circadian Clock

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Abstract

Existence of an internal timing mechanism in mammals has been well established and it is known that the circadian rhythm is generated in a bilateral structure contained in the hypothalamus called the Suprachaismatic Nucleus (SCN) consisting of 16,000 neurons. Individually, each SCN neuron behaves like a clock, and the ensemble of neurons are capable of producing well synchronized and phase locked clock signals with precise timing patterns. In this article, theory of Hopf bifurcations in the presence of symmetries, is used to explain the functionality and phase locking of the SCN from a systems theory viewpoint.

1 Introduction

Circadian rhythms are observed in the physiology of mammals and other higher organisms. In mammals, it is generated in a pacemaker located in the suprachaismatic neucleus (SCN) of the hypothalamus (see e.g. [5]). SCN consists of 16000 neurons arranged in a symmetric bilateral structure, and it is generally believed that each isolated SCN neuron behaves as an oscillator by itself. Experiments conducted using rat embryos, SCN-lesioned rats, and in-vitro preparations have led to following hypotheses (see e.g. [5]).

- Individual SCN neurons behave as oscillators with a period, roughly equal to 24.3 hours, with a standard deviation of 1 hour.
- Natural light (received through retinal photoreceptors) act as periodic input signals to the SCN and force approximately phase locked oscillations in the SCN neurons.
- Even in the absence of light, a large enough ensemble of SCN neurons go into phase locking in about 4 days.

Kronauer [7] proposed an empirical model to describe the oscillations in a single SCN cell in 1990. It uses a Van der Pol oscillator to model stable oscillations in SCN neurons, with an additive term to model response due to light.

$$\begin{aligned} (\frac{12}{\pi})\dot{x} &= y + \epsilon(x - \frac{4}{3}x^3) + B \\ (\frac{12}{\pi})\dot{y} &= -(\frac{24}{\tau})^2 x + By, \end{aligned} \tag{1}$$

where, $B = (1 - mx))CI^{\frac{1}{3}}$, I is the light intensity in lux, and m and C are constants ($m = 1/3, C = 0.018$), and τ is a constant which represents the period of the oscillator (roughly equal to 24) .

Basic idea of Kronauer was to start with experimentally observed clock signals and fit the simplest possible mathematical model that can produce stable oscillations with the same period. Interested reader can find more fine tuned versions of his oscillator model in [8] and [9]. Being primarily interested in clock signals from a single SCN cell, Kronauer paid scant attention to how SCN is organized as a complex structure. Indeed there isn't consensus among neuroscientists regarding the nature and the extent of interconnections between SCN neurons. For example, Lesauter and Silver [19] suggests that there are approximately 300 active neurons feeding into the remaining 8000 neurons, whereas there are others who suggest that all SCN neurons are identical and each neuron may be connected to 1000 or so other neurons [5]. The basic truth of the matter is that no one knows details of the nature of connections within the SCN complex.

As a first attempt at resolving the issue of SCN connections Achermann and Kunz [4] added coupling terms representing nearest neighbor connections (each cell communicates with 4,8 or 20 neighbors) and represented the SCN as a two dimensional 100x100 cell array

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described by,

$$\begin{aligned}(\frac{12}{\pi})\dot{x}_{i,j} &= y_{i,j} + \epsilon(x_{i,j} - \frac{4}{3}x_{i,j}^3) + B + c\kappa_{i,j}^k(x) \\ (\frac{12}{\pi})\dot{y_{i,j}} &= -(\frac{24}{\tau_{i,j}})^2 x_{i,j} + By_{i,j} + c\kappa_{i,j}^k(y),\end{aligned} \tag{2}$$

where, $x_{i,j}$ and $y_{i,j}$ are the state variables associated with the $(i,j)^{\text{th}}$ SCN cell, c is a coupling constant, $\tau_{i,j}$ is the period of the $(i,j)^{\text{th}}$ oscillator, and $\kappa_{i,j}^k(x)$ is equal to the difference between the average of x's of nearest k neighbors and $x_{i,j}$. $\kappa_{i,j}^k(y)$ is defined analogously. Achermann and Kunz fixed the value of c at 0.5 in their simulation experiments.

Achermann and Kunz [4] carried out extensive supercomputer simulations to demonstrate phase locking phenomena and the influence of the light-dark cycle. This work showed that the Kronauer model is essentially correct in the sense that, once coupling terms between SCN cells have been added, it is possible to reproduce reasonably realistic responses in computer simulations.

Our work is built upon the work on Achermann and Kunz and aimed at furthering the theoretical understanding of phase locking in the SCN oscillators. Our analysis relies heavily on the Hopf bifurcation theory of systems with symmetries (see e.g. [18]). In essence we will show that phase locking in the SCN is closely related to the way SCN neurons are interconnected, and indeed it is possible to make educated guesses on the nature of connections from a purely mathematical/engineering angle. We are in the process of verifying some of our theoretical predictions via supercomputer simulations and experimental work involving rat SCN sections.

We will also address the issue of entrainment by light. In particular we point out that feedback signals due to light play a major role in entrainment.

2 Phase Locking and Hopf Bifurcation in the SCN

Thus far there doesn't seem to be any theoretical analysis carried out on what mathematical mechanisms could be behind the phase locking phenomenon in the SCN. Let us first consider the unforced case (i.e. set light intensity to zero), and ask,

- Why does phase locking occur in the SCN?
- Is it possible to relate the speed for phase locking to the nature of coupling between SCN cells?

As a first approximation let us assume that all SCN cells are identical, and arrange SCN neurons in a three dimensional array containing N_1, N_2 and N_3 cells in each side. The neuron at location (i,j,k) will have associated with it state variables $x_{i,j,k}, y_{i,j,k}$. We use Achermann, Kunz model to describe the coupled dynamics, and will not consider the influence of light. Thus, our model is described by,

$$\begin{aligned}(\frac{12}{\pi})\dot{x}_{i,j,k} &= y_{i,j,k} + \epsilon(x_{i,j,k} - \frac{4}{3}x_{i,j,k}^3) + c\kappa_{i,j,k}(x) \\ (\frac{12}{\pi})\dot{y_{i,j,k}} &= -(\frac{24}{\tau})^2 x_{i,j,k} + c\kappa_{i,j,k}(y),\end{aligned} \tag{3}$$

where, $\kappa_{i,j,k}(.)$ are functions that describe the influence on the (i,j,k) neuron by the other neurons. One of our aims is to relate the structure of κ to known SCN phenomena; in this case the time to phase locking. For the sake of convenience we will fix $\tau = 24$ in this section.

2.1 Analysis

To begin with, our aim is to start with a system that has enough geometric structure to carry out analysis to some extent. Eventually we plan to extend the results to systems within a reasonably small neighborhood of this nominal system, which hopefully will include realistic SCN dynamics.

Let us denote by D_n the dihedral group acting on n objects. Recall that D_n is generated by Z_n, the group of cyclic permutations, and μ, which preserves the first element and maps j to $n-j+2$. D_n acts on $\Re^n$ by permuting coordinates. Let us define $G = D_{N_1} \times D_{N_2} \times D_{N_3}$. Then, G acts on the state space $M = \Re^{2N_1} \times \Re^{2N_2} \times \Re^{2N_3}$ of SCN dynamics by, $(g_1, g_2, g_3)(x,y)_{g_1(i),g_2(j),g_3(k)} = (x,y)_{i,j,k}$. In what follows we will write $g(i,j,k)$ in place of $(g_1(i), g_2(j), g_3(k))$.

The key assumption made regarding the structure of SCN dynamics is the following:

Assumption: Influence functions κ are equivariant under the action of G on M, i.e. $\kappa_g(i,j,k)(x) = \kappa_{i,j,k}(g(x))$ and $\kappa_g(i,j,k)(y) = \kappa_{i,j,k}(g(y))$

Remark 1. In Achermann and Kunz [4] the cell array is folded into the shape of a cylinder. Here, the cell array is folded in the remaining directions as well, thus shaping it to form a cartesean product of three rings. Groups D_{N_i} act on these rings by rotating them and reflecting the rings around each cell.

Remark 2. G equivariance is best understood by considering a single ring containing just three cells. For the element g that rotates cells (1,2,3) to cells (2,3,4), g equivariance amounts to, $\kappa_2(x_1,x_2,x_3) = \kappa_1(x_2,x_3,x_1)$, and $\kappa_3(x_1,x_2,x_3) = \kappa_1(x_3,x_1,x_2)$. Similarly, for g which reflects around cell 2, i.e. $g(1,2,3) = (3,2,1)$, g equivariance amounts to $\kappa_3(x_1,x_2,x_3) = \kappa_1(x_3,x_2,x_1)$, and $\kappa_2(x_1,x_2,x_3) = \kappa_2(x_3,x_2,x_1)$. An example of such a κ is, $\kappa_i(x_1, x_2, x_3) = (x_i - (1/2)\sum_{j \neq i} x_j)$.

Remark 3. In the Achermann, Kunz model [4] functions κ fail to be G equivariant for the reason that elements in the first row are not treated as neighbors of elements in the last row and vice-versa. However, if the ring is closed in the vertical direction by making a seemingly small modification in the model (and thereby declaring first and last rows as adjacent) then the resulting κ turn out to be $G = D_{100} \times D_{100}$ equivariant.

Our analysis borrows heavily from the ideas in [18], where Hopf bifurcation of systems with symmetries is considered at length. Reader may wish to refer to pages 388-399 of [18] for a very readable account on the analysis of systems with D_n symmetry.

Following Acermann and Kunz [4] we will assume that κ is linear, and write $\kappa_{i,j,k}(x) = \sum_{p,q,r} \kappa_{i,j,k}^{p,q,r} x_{p,q,r}$, and assume that $\sum_{p,q,r} \kappa_{i,j,k}^{p,q,r} = 0$ for all i, j, k. Then, the G equivariance of κ amounts to the following:

$\kappa_{p+\alpha,q+\beta,r+\gamma}^{p,q,r}$ depends only on $|\alpha|, |\beta|$ and $|\gamma|$.

In view of this we define $\theta_{\alpha,\beta,\gamma} = \kappa_{p+\alpha,q+\beta,r+\gamma}^{p,q,r}$.

For brevity let us write the system (7) in the form

$$\dot{z} = F(z). \tag{4}$$

To analyze bifurcation of the system we need to understand the eigenvalues and eigenvectors of the linear approximation of (4) around the origin. Due to limitation in length we will summarize results here. Details will be published shortly elsewhere. Interested reader can construct the missing details (which are somewhat tedious, but rather straightforward) by following the discussion in [18] pages 388-399.

Let us define $\xi = e^{i2\pi/N_1}, \eta = e^{i2\pi/N_2}$ and $\omega = e^{i2\pi/N_3}$

Lemma 1 *: Eigenvalues of DF_0 are,*

$$\begin{aligned} \lambda_{l,m,n} \quad = \quad & \frac{\pi}{12}\{c[\theta_{0,0,0} + \sum_{(\alpha,\beta,\gamma)\neq 0} \theta_{\alpha,\beta,\gamma} \cos(2\pi\alpha l/N_1) \\ & \cos(2\pi\beta mm/N_2) \cos(2\pi\gamma n/N_3)] \\ & + \epsilon/2 \quad \pm \quad i\sqrt{1-\epsilon^2/4}\}, \end{aligned} \tag{5}$$

and the corresponding eigenvectors are of the form,

$$V_{l,m,n} = \sum_{(p,q,r)=(1,1,1)}^{(N_1,N_2,N_3)} \xi^{lp} \eta^{mq} \omega^{nr} \mathbf{v} \otimes \mathbf{a}_p \otimes \mathbf{b}_q \otimes \mathbf{c}_r, \tag{6}$$

where, $\mathbf{v}$ is a fixed vector in $\Re^2$.

Observe that eigenvector $V_{0,0,0}$ has the same vector $\mathbf{v}$ in all components. Also, since $\sum_{\alpha,\beta,\gamma} \theta_{\alpha,\beta,\gamma} = 0$, it follows that $\lambda_{0,0,0} = (\pi/12)[\epsilon/2 + i\sqrt{1-\epsilon^2/4}]$. Since ϵ is very small and positive, dynamics of this mode correspond to Hopf bifurcation (there is more to verify to apply Hopf bifurcation theorem, but that turn out to be trivial), and the fact that all components of the eigenvector are equal imply that the resulting periodic solution (up to a first approximation) is given by,

$$\begin{aligned} x_{p,q,r} &= \delta\|v\| \cos(\frac{12}{\pi}(t-\phi)) \\ y_{p,q,r} &= \delta\|v\| \sin(\frac{12}{\pi}(t-\phi)), \end{aligned}$$

where, ϕ is a phase angle which is common to all p, q, r. In other words Hopf bifurcation of the $(0, 0, 0)$ mode give rise to phase locked oscillations. It is also easy to see that no other eigenvector has the property that all components are equal. Therefore, we conclude that Hopf bifurcation of any other mode will destroy phase locking property. Thus we have reached the following ansatz.

All higher modes of SCN dynamics are asymptotically stable.

Indeed, we can say more. Suppose SCN neurons are set in motion in arbitrary phases and the time until phase locking occur is measured. This time is equal to the time it takes for all other modes to decay down to zero, and as a rule of thumb this is taken to be equal to three times the time constant of the dominant stable eigenvalue. Thus we conclude that time until phase locking is roughly equal to $3/Re(\hat{\lambda})$ where, $\hat{\lambda}$ is the dominant stable eigenvalue.

Let us consider three special cases of connection topologies and attempt to compute the time to phase locking. We assume in all cases that the connection strength, i.e. c is equal to 0.5, and that the cell array has sides of 20 cells each, i.e. $N_j = 20, \ j = 1, 2, 3$.

2.2 Two special cases

Case 1: *Each neuron is connected to all other cells and connection strengths are equal.*

Here, κ is such that $\theta_{0,0,0} = -1$ and $\theta_{\alpha,\beta,\gamma} = \frac{1}{(N_1 N_2 N_3 - 1)}$. It is straightforward to show that $\lambda_{l,m,n} = (\frac{\pi}{12})[-2c + \epsilon/2 \pm i\sqrt{1-\epsilon^2/4}]$. Since $c = 0.5$ and $\epsilon = 0.018$ this correspond to a transient time of roughly 12 hours, a far shorter time than the observed time of about 100 hours. Indeed it is well known that SCN connections are more sparce than what is assumed here.

Case 2: *Each neuron is connected only to its nearest neighbors on each side.*

This is at the other extreme from case 1. Here, $\theta_{0,0,0} = -1$ and $\theta_{\alpha,\beta,\gamma} = 1/6$ if exactly one of α, β or γ is equal to 1 or -1 and zero otherwise. An easy calculation shows that the real part of the dominant stable eigenvalue is approximately equal to $-1/120$. Hence phase locking will take approximately 400 hours; far longer than what has been observed.

3 Entrainment

Ambient light is known to entrain the circadian rhythm to follow a cycle of the same period as the light cycle (see e.g. [5]). In the presence of normal daily light the natural phase locked oscillations of roughly 24.3 hour period change to phase locked oscillations of 24 hour period. Here we begin to study the entrainment phenomena.

Let $I(t)$ denote the intensity of light at time t. $I(t)$ is a positive and periodic signal of period equal to 24 hours. In the Kronauer-Achermann-Kunz model (2) $I(t)$ enters the equations as an input term. It is easy to embed $I(t)$ in a two dimensional unforced system undergoing Hopf bifurcation, and hence treat $I(t)$ as the output of an autonomous system. This then allows us to consider the Kronauer-Achermann-Kunz model as an autonomous system undergoing Hopf bifurcation with symmetry. We take the symmetry group to be $D_{N_1} \times D_{N_2} \times D_{N_3}$ as before, and an analysis analogous to the one in the previous section shows that the system will settle down into phase locked oscillations. Oscillations in each SCN cell is described by Kronauer equation (1). For the sake of simplicity let us scale time to get rid of the factor $12/\pi$ to get,

$$\begin{aligned} \dot{x} &= y + \epsilon(x - \frac{4}{3}x^3) + B(x,t) \\ \dot{y} &= -(\frac{24}{\tau})^2 x + B(x,t)y, \end{aligned} \tag{7}$$

where, $B = (1 - mx))CI^{\frac{1}{3}(t)}$, $I(t)$ is the light intensity in lux, $\epsilon = 0.13$, $m = 1/3$, $C = 0.018$ and $\tau = 24.3$. The time scaling converts a signal $\sin(2\pi t/24)$ in the original time scale into $\sin(t)$ in the new time scale.

In the simulations reported by Achermann and Kunz, amplitude of the light intensity is limited at $10,000 lux$. In our simulations we allow $I(t)$ to be of the form $10,000(1 + 0.5\sin t)$, $15,000(1 + \sin t)$ in the original Kronauer model, and $20,000(1 + \sin t)$ and $20,000(1 + .5\sin t)$ in the stabilized model considered later on. Since this is a first attempt at gaining a theoretical understanding, we take $I^{1/3}(t) = 10(1 + sin(t))$ in a sample stability analysis carried out.

The main question we ask in this section is whether or not (7) has a stable limit cycle of the same period as that of light. Our simplifying assumptions (validity of the original Kronauer model, and the sinusoidal light intensity) will not have an impact on the general nature of our conclusions.

It has been reported that the light intensity in Southern parts of USA peaks at 80,000 lux or more during summer months. We have carried out extensive simulations with peak amplitudes of light ranging from 20,000 lux to 80,000 lux, and they have failed to produce phase responses of the same frequency as the light input. We argue that there is an inherent deficiency in the Kronauer model that is responsible for this behaviour, and below point out a possible remedy.

Analysis of forced Van der Pol oscillators has been a hot topic of research starting in forties and lasting until late eighties [10, 11, 14, 16]. It was shown in [10, 16] that $\ddot{x} + k(y^2 - 1)\dot{x} + cx = kb\cos(t)$ has a unique stable periodic solution when $b > 3/2$ and when k is larger than a constant which depends on b, and shown in [14] that for $0 < b < 3/2$ the resulting small amplitude oscillations are unstable.

Even thought these results are not directly applicable in our case they shed much light into our situation. The extra term $B(x,t)y$ in (7) plays the role of a time varying feedback control law. Results in the literature and our simulations show that the amplitude of oscillations is below 2.0, hence the term $(1 - mx)$ is, for the most part, a positive constant. Therefore, heuristically, $B(x,t)y$ term has a destabilizing effect on the Van der Pol oscillator (to see this replace $B(x,t)$ by a positive constant and compute eigenvalues of the linear approximation) making entrainment more difficult. Figures 1,2 shows several representative simulations using (7).

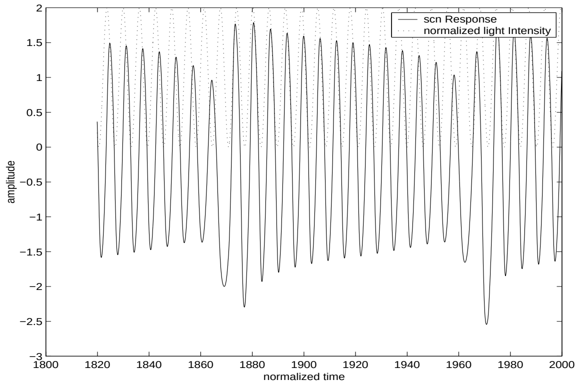

Figure 1: Output of (7) when $I(t) = 15000(1 + \sin t)$, $B = c(1 - mx)I^{1/3}$

A simple remedy is to change the sign of the feedback term. We hasten to add that this isn't motivated by physiology, and the needed correction may turn out to be quite different. Our purpose here is to show that it is indeed possible to make small changes in the model to demonstrate entrainment behaviour.

Let us now consider the linear approximation of (7) without the B term in the first equation,

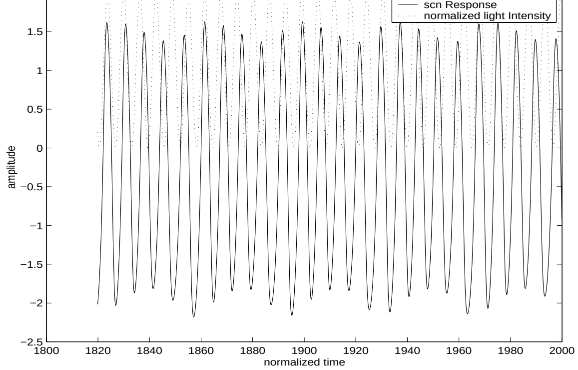

Figure 2: Output of (7) when $I(t) = 10000(1 + .5\sin t)$, $B = c(1 - mx)I^{1/3}$

$$\begin{aligned} \dot{x} &= y + \epsilon x \\ \dot{y} &= -(\frac{24}{\tau})^2 x + C * 10(1 + sin(t))y, \end{aligned} \qquad (8)$$

where, $\epsilon = 1/3$, and $C = 0.018$.

Lemma 2 *Origin is a locally exponential stable equilibrium point of (8).*

Idea of the proof is quite simple. It turns out that $W(x,y,t) = (x^2 + 2y^2)(30 - cos(t))$ is a local Lyapunov function with better than quadratic decay rate. The tedious details will be reported in [17]. Essential idea is to show that the derivative of $x^2 + 2y^2$ ensures negative definiteness of $\dot{W}$ when $0 < t < \pi$ and the term $(x^2 + 2y^2)sin(t)$ dominates when $5\pi/4 < t < 7\pi/4$

This then shows that for small positive values of γ, the system,

$$\begin{aligned} \dot{x} &= y + \epsilon(x - \frac{4}{3}x^3) + \gamma B(x,t) \\ \dot{y} &= -(\frac{24}{\tau})^2 x - B(x,t)y, \end{aligned} \qquad (9)$$

has a small stable periodic solution of the same period as the light signal. To prove entrainment we need to show that this conclusion holds even when $\gamma = 1$. We haven't succeeded in proving this as of yet. Figures 3-5 show several representative simulations using (9) with $\gamma = 1$.

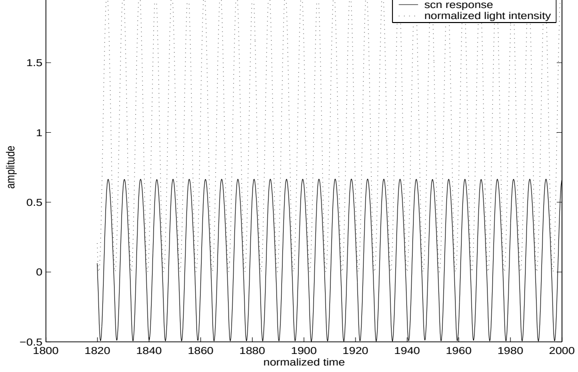

Figure 3: Output of (9) when $I(t) = 20000(1 + \sin t)$, $B = c(1 - mx)I^{1/3}$

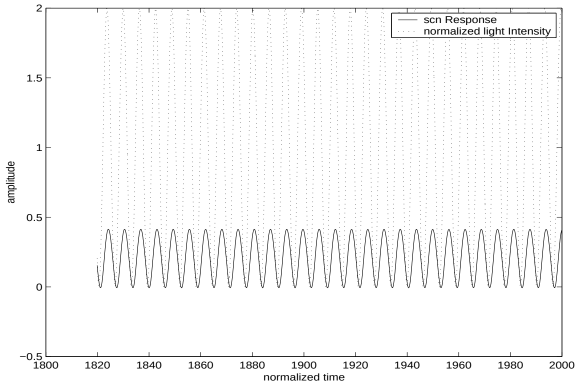

Figure 4: Output of (9) when $I(t) = 20000(1 + .5\sin t)$, $B = c(1 - mx)I^{1/3}$

4 Concluding Remarks:

SCN models provide an interesting biological control system with a rich structure. We are at a very early stage of exploiting this structure in order to enable making educated guesses on the interconnection topologies and reasonable mathematical models. Here we have shown that certain symmetries of the system have a strong impact on the transient period for phase locking, and nature of feedback control terms due to light signals may have an impact upon whether or not entrainment is possible. Repurcussions of this on the circadian rhythm of mammals living in extreme northern latitudes during winter months will be an interesting problem to study.

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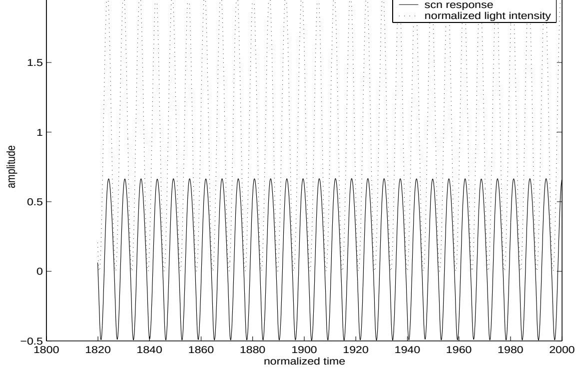

Figure 5: Output of (9) when $I(t) = 10(1 + \sin t)$, $B = c(1 - mx)I$

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