# Effects of Static Oscillatory Network Topology in Suprachiasmatic Nucleus

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## Abstract

The means by which pacemaker cells of the mammalian suprachiasmatic nucleus (SCN) are synchronized is unknown. In the absence of anatomical data on the interneuronal connections among SCN neurons, mathematical models of SCN networks were developed based on possible connection topologies to meet biological restrictions. We employ a mathematical model proposed by Achermann and Kunz [1], to study the problem of interpreting synchronization in the SCN network from a dynamical systems viewpoint. Connection topologies with varying proportions of nearest neighbor neuronal connections and global connections in the SCN were compared against the transitional time to establish synchronization. These connection patterns were tested on two three-dimensional models with 8000 neurons connected as a torus with Kronauer dynamics [2], with weak inhibitory coupling to each other. A theoretical proof is provided for the existence of stable limit cycles using the symmetry of the system of neurons.



## Introduction

Jet-lag is an inconvenient reminder that the body is set to a 24 hour clock, known by scientists as the circadian rhythm. An internal biological clock is fundamental to all living organisms, influencing hormones that play a role in sleep and wakefulness, metabolic rate, and body temperature. In mammals, a master circadian pacemaker driving daily rhythms in behavior and physiology resides in the suprachiasmatic nucleus (SCN), a distinct group of cells found within the hypothalamus. The SCN contains multiple circadian oscillators that synchronize to environmental cycles and to each other in vivo. By synchronization here we mean the phenomenon of cellular bio-chemical oscillations synchronizing their periods as well as phases. The period of the rhythms within the SCN also depends upon intercellular communication.

In 1999, Achermann and Kunz [1] refined the existing Kronauer's model [2] by representing each SCN cell as a Kronauer oscillator, and added coupling terms between oscillators to represent dynamic interactions with other SCN neurons. They did extensive numerical simulations with a variety of nearest neighbor type connections, and numerically showed that the network is indeed is capable of achieving synchrony in two dimensional networks.

A fundamental question at the heart of understanding the dynamics of the SCN is that of the nature and topology of the interconnectivity of neurons.

Theories on these aspects are abound; Lesauter and Silver's [3] core shell model, Miller's [4] completely locally/globally connected network, etc. Computer simulations shows completely globally connected neurons give rise to resynchronizing times which are far smaller than experimentally observed and completely locally connected neurons may either fail to synchronize, or far too slow to resynchronize the network.

In an apparently unrelated context, Strogatz [5] coined the phrase small world models, to describe a class of networks in which each node (or cell) connects, communicates, or interacts mostly with its nearest neighbors, but there is a small fraction of connections (so-called long distance connections) that pan across the network. In connection with the problem of traversing a network he showed that addition of a small percentage of long distance connections lead to a dramatic reduction in the average path length in network traversing.

In view of results on resynchronization times observed in computer simulations reported in [4] and the dramatic effect of few long distance connections have on average distance traversed in a network, it is sensible to investigate the effects of replacing a few nearest neighbor connections by long distance connections in the Achermann and Kunz [1] model of the SCN. We initiate such a study here.

**Stability of symmetric SCN system using Hopf Bifurcation**

The main focus on this section is to study the phase locking phenomena of SCN cells subject to the assumptions of dihedral symmetry and absence of light. Analysis below presets stability of the system and describe how to relate resynchronizing time to an eigenvalue of the linear approximation. System considered here is the Achermann and Knuz model [1] under a three dimensional lattice $N_1 \times N_2 \times N_3$ [4] with coupling constants $c$,

$$\left(\frac{12}{\pi}\right)\dot{x}_{i,j,k} = y_{i,j,k} + ò(x_{i,j,k} - \frac{4}{3}x_{i,j,k}^3) + ck_{i,j,k}^{(k)}(X), \qquad (1)$$

$$\left(\frac{12}{\pi}\right)\dot{y}_{i,j,k} = -\left(\frac{24}{\tau}\right)^2 x_{i,j,k} + ck_{i,j,k}^{(k)}(Y). \qquad (2)$$

Let $D_n$ be the Dihedral group acting on n objects. Thus $D_n$ acts on $\Re^n$ by permuting and reflecting coordinates. Let $G = D_{N_1} \times D_{N_2} \times D_{N_3}$ and let $G$ acts on the state space $M = \Re^{N_1} \times \Re^{N_2} \times \Re^{N_3}$ of SCN dynamics by, $(g_1, g_2, g_3)(x, y)_{g_1 1(l), g_2(m), g_3(n)} = (x, y)_{l,m,n}$. Let us assume the influence functions $k$ in equations (1), (2) are equivariant under the action of $G$ on $M$, i.e., $k_g(l,m,n)(x) = k_{l,m,n}(g(x))$ and $k_g(l,m,n)(y) = k_{l,m,n}(g(y))$.

For our analysis linear terms in $k$ provide adequate information, hence, as in Achermann and Kunz [1], we will assume that $k$ is linear. Thus, coupling terms can be written as $k_{l,m,n}(X) = \sum_{p,q,r} k_{l,m,n}^{p,q,r} x_{p,q,r}$. If algebraic sum of coupling terms is equal to zero, i.e., $\sum_{p,q,r} k_{l,m,n}^{p,q,r} = 0$ for all $l,m,n$ then $G$ equvariance of $k$ amounts to the following: $k_{p+\alpha,q+\beta,r+\gamma}^{p,q,r}$ depends on only on $|\alpha|$, $|\beta|$ and $|\gamma|$ where $\alpha$, $\beta$ and $\gamma$ are the position indices relative to the position $p$, $q$ and $r$. Let $\theta_{\alpha,\beta,\gamma} = k_{p+\alpha,q+\beta,r+\gamma}^{p,q,r}$.



The analysis of the bifurcation system is done using the eigenvalues and eigenvectors of the linearized system (1), (2). To avoid having to see through the clutter of three subscripts, consider a simplified version of (1),(2) in which cells are arranged in a one-dimensional array. Results presented in this simplified case can be generalized to the three-dimensional array in an obvious way. The simplified system has the form,

$$\left(\frac{12}{\pi}\right) x_i = y_i + \text{ò}(x_i - \frac{3}{4}x_i^3) - c(x_i - \sum_{\alpha=1}^{N-1} \theta_\alpha x_{i+\alpha}),$$

$$\left(\frac{12}{\pi}\right) y_i = -x_i - c(y_i - \sum_{\alpha=1}^{N-1} \theta_\alpha y_{i+\alpha}); \qquad \sum_{\alpha=1}^{N-1} \theta_\alpha = 1.$$

The linear approximation of it is,

$$A\left(\begin{bmatrix} \upsilon \\ \upsilon \\ \upsilon \\ \vdots \\ \upsilon \end{bmatrix}_{N\times 1}\right) = \begin{bmatrix} \text{ò} & 1 \\ -1 & 0 \end{bmatrix}[\upsilon] - c[\upsilon] + c\sum_{\alpha=1}^{N-1} \theta_\alpha [\upsilon], \qquad (3)$$

where $\upsilon \in \Re^2$. Computation of the eigenvalues and eigenvectors of the linearized system can be done as follows:

$$\mu = \frac{\text{ò}}{2} + i\sqrt{1 - \frac{\text{ò}^2}{4}}.$$

Now the system (3) can be modified as

$$A\left(\begin{bmatrix} \upsilon \\ \xi^{j}\upsilon \\ \xi^{2j}\upsilon \\ \vdots \\ \xi^{kj}\upsilon \end{bmatrix}_{N\times 1}\right)_j = \begin{bmatrix} \grave{o} & 1 \\ -1 & 0 \end{bmatrix}\xi^{kj}\upsilon - c\xi^{kj}\upsilon + c\sum_{\alpha=1}^{N-1}\xi^{k\alpha}\theta_\alpha\xi^{kj}\upsilon.$$



where $\xi = e^{\frac{2\pi i}{N}}$ is the $n^{th}$ primitive root of unity in $\Re$. This provides the eigenvalues of the system as



$$\lambda_k = \frac{\pi}{12}[(\mu - c) + c\sum_{\alpha=1}^{N-1} e^{\frac{i2\pi k\alpha}{N}}\theta_\alpha].$$

where $k = 0,1,2.,N-1$.

$$\lambda_k = \frac{\pi}{12}\{c[\theta_0 + \sum_{(\alpha)\neq 0}\theta_\alpha \cos(2\pi\alpha k / N)] + \grave{o}/2 \pm i\sqrt{1-\grave{o}^2/4}\}$$

Above simplified result can be generalized to the three-dimensional torus structure of size $N_1 \times N_2 \times N_3$

$$\lambda_{l,m,n} = \frac{\pi}{12}(c[\theta_{(0,0,0)} + \sum_{(\alpha,\beta,\gamma)\neq 0}\theta_{(\alpha,\beta,\gamma)}\cos(2\pi\alpha l / N_1)\cos(2\pi\beta m / N_2)\cos(2\pi\gamma n / N_3)] + \grave{o}/2 \pm i\sqrt{1-\grave{o}^2/4},$$

where $\xi = e^{(i2\pi)/N_1}, \mu = e^{(i2\pi)/N_2}$, $\omega = e^{(i2\pi)/N_3}$ and $\upsilon$ is a vector in $\Re^2$ Let us concentrate on the $V_{0,0,0}$. The small positive $\grave{o}$ and the equal components $\upsilon$ will enable the Hopf Bifurcation on dynamics of this mode. The equal components of $V_{0,0,0}$ leads to a periodic solution:

$$x_{l,m,n} = \delta|v|\cos(\frac{12}{\pi}(t-\phi)),$$

$$y_{l,m,n} = \delta|v|\sin(\frac{12}{\pi}(t-\phi)),$$

where $\phi$ is the phase angle for any $(l,m,n)$. So it is deduced that the mode $(0,0,0)$ give rise to phase locked oscillations in the system. Consideration of any other mode will end up with eigenvectors which have oscillatory components which are not in phase, i.e., those modes will destroy the phase locking property of the system. Observe that the resynchronization time is equal to the time that other (hence non phase locked) modes to die out. Time constant which determine the decay rate of any mode is the reciprocal of the real part of the eigenvalue of that mode. Since the slowest mode is the one with the eigenvalue with the smallest real part, it follows that the resynchronization time is governed by the $\lambda_1$ which is the dominant stable eigenvalue.

## Network connection topology

The complex functional behavior of various areas of animal cortex can be understood from the dynamical properties of relevant neurobiology networks. However, these networks are very hard to understand using standard dynamical systems analysis since they are complex in structure, network connections are time dependent, networks grow and shrink in size, connectivity has directional features, etc. By suppressing some of the complexities, one may obtain a simpler model where we can focus on aiming for a partial understanding of some key features from a mathematical view point.

Strogatz [5] did much work on network patterns and came up with the concept of a Small world network [5]. In Strogatz' analysis, attempts to randomize the regular networks with a measure of probability parameter $p$ . In regular networks, each node (or cell) connects to a few local cells only, while a random pattern mix neighborhood and long distance connections [5].

The small values of $p$ has a highly nonlinear effect on $L(p)$, contracting the distance not just between the pairs of cell that it connects, but between their immediate neighborhoods. This dramatic decrease in path length with increase of $p$ proposes the methodology called Small world which used as the connection topology of our research. One of the main aspect of research is to find out the effect of the small world networks on SCN system synchronization.

## Simulation Results

Simulations were carried out to study the behavior SCN neurons under different connection patterns and various light conditions. The model considered consists of 16000 neurons in the SCN under the assumption of 8000 neurons/unilateral with a standard deviation of one hour period. Also we assumed all the neurons are GABAergic [6] and behaves as Achermann and Kunz oscillators.

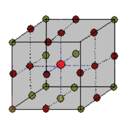

**Figure 1: Local type: Single neuron communicates with 27 nearest neighbors.**

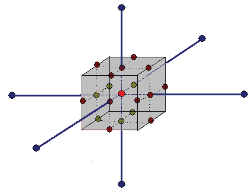

**Figure 2: Small-World type: Single neuron communicates with 19 nearest neighbors and 6 long distance neurons.**



To illustrate the effects of pure local connections, the neurons were coupled to the nearest 26 neurons (Local Type) as in figure 1. The figure 2 exemplifies the connection pattern of small world network by connecting to most of nearest neurons and 6 long distance connections (Small-World Type).

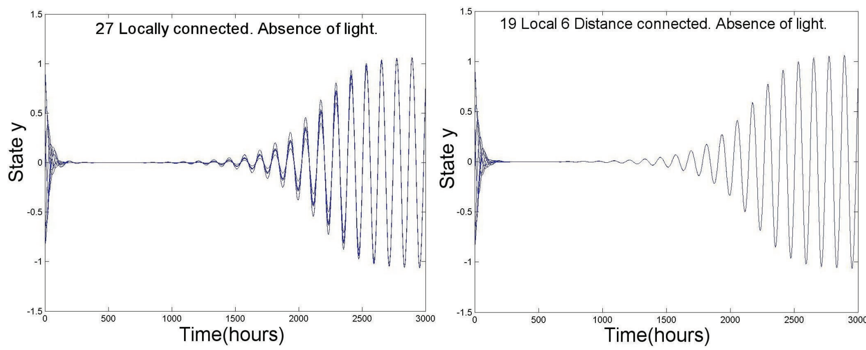


**Figure 3: Graph of state variables in two connection topologies with absence of light**

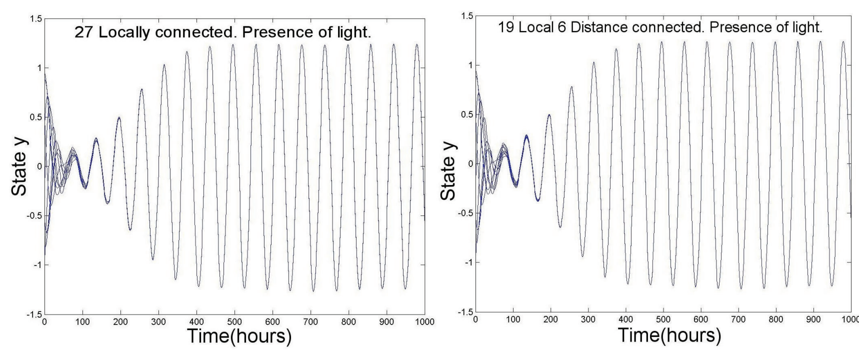


**Figure 4: Graph of state variables in two connection topologies with presence of light.**

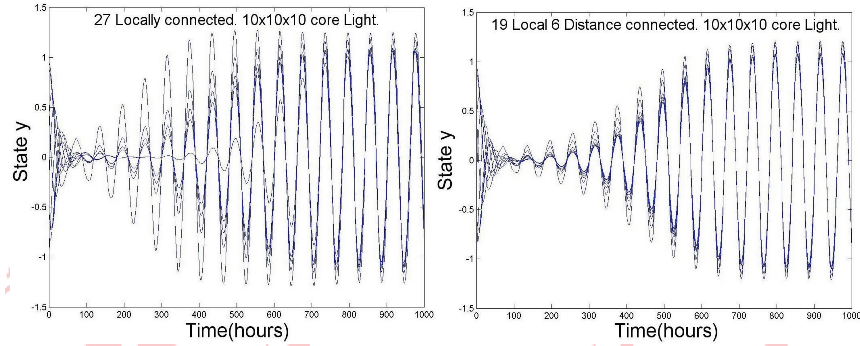


**Figure 5: Graph of state variables in two connection topologies under the presence of core light**



Figures 3, 4 and 5 display synchronization of neurons to produce a stable circadian rhythm. Pure locally connected (27 locally connected) networks indicate a dramatic difference in synchronization of phase and amplitude, while small world networks (19 Local and 6 long distance) rapidly synchronize with each other.

**Table 1**
**Synchronization and phase locking times for different light conditions.**

| Light condition | Connection pattern | Phase locking (days) | Synchronization (days) |
|---|---|---|---|
| Absence of Light | *Local Type* | 2.5 | 21 |
| Absence of Light | *Small-World Type* | 2 | 2 |
| 10x10x10 core light | *Local Type* | 3 | 17 (more) |
| 10x10x10 core light | *Small-World Type* | 2.5 | 11 |
| Presence of light | *Local Type* | 2.5 | 4 |
| Presence of light | *Small-World Type* | 2.5 | 3 |

Table 1 indicates a significance change of phase locking time under different connection patterns; *Local Type* and *Small-World Type*. The phase locking time dramatically reduces with few long distance connections that represent the small world networks (regardless of the light condition on the system). The synchronization occurs much faster in systems with few long distance connections when compared with locally connected networks. The presence of light will also make a difference in phase locking and synchronization times. It can be clearly seen more exposure to ambient light tends to phase lock and synchronize faster.

## Concluding Remarks

The key result we obtained out of these simulations can be divided in to two categories. The impact of ambient light and effect of long distance connections. It was observed, with increased exposure of ambient light on SCN systems tends reduce the phase locking time as well as it dramatically reduce the synchronization time. That is increased exposure of ambient light make stronger phase locks and stronger synchronizations.

It was clearly observed that existence of few long distance connections tends to reduce the synchronization and phase locking times under all different light conditions. This interesting result of time reduction strengthens Strogatz's [1] hypothesis of small world network where few long distance connections enables stronger communications in networks. The above results also show that to obtain the optimal connection pattern it is necessary to make educated long distance connections rather than increasing the number of communication paths.

In theory of Hopf Bifurcation, it was proved the existence of limit cycle under the symmetry of systems which produces the stable state periods. This result guarantees the existence of stable periodic oscillations for systems which has only one positive real eigenvalue.

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