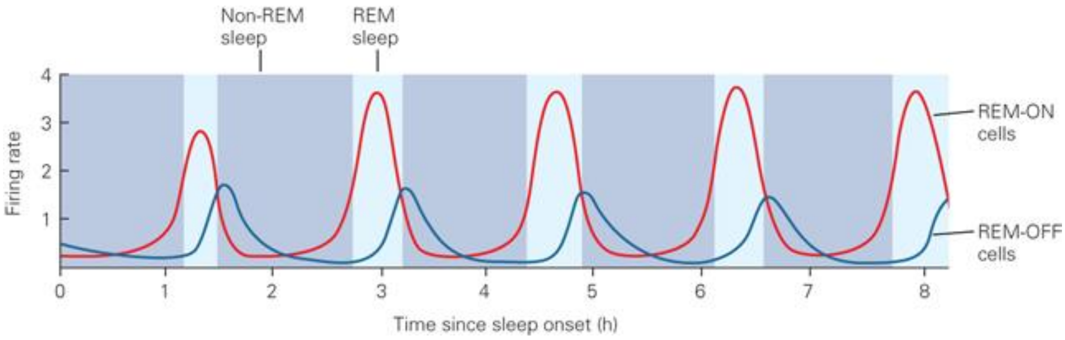
"EMPLOYABILITY OF A MATHEMATICAL MODEL TO STUDY NEURONAL DISCHARGE ACTIVITY DURING REM SLEEP"

Tushita Tandon

1.1 Necessary Terminology

REM	A lot happens when our eyelids shut and our body enters the resting phase. Our sleep wake cycle is divided into three stages viz wakefulness, REM stage and NREM stage. Wakefulness is the first phase when our body mechanism begins to slow down and we begin to come to the REM and N-REM phase.
REM STAGE:	Rapid Eye Movement Stage is a stage in which the heart rate increases, the body temperature rises and the eyes start moving in all directions. It is this stage in which people experience dreams.
NREM Stage:	It is the phase of sleep where the individual does not experience any REM behavior at all.
REM-On and REM-Off:	The REM phase of sleep is experienced in many stages: a long period of REM and subsequent periods. The REM-On phase is the one in which the individual experiences REM while the REM-Off phase is the gap between two REM-On phases.



1.2 The Sleep Cycle

Stage 1: NREM-The individual falls asleep and enters the NREM phase with normal breathing and heart rate. In this phase, the body tissue grows and develops. It is a light –sleep phase, and the individual can be woken up easily. During this phase, the body prepares itself to enter in the REM phase.

Stage 2: REM-An individual enters REM sleep after 90 minutes. The initial REM-On phase lasts for 10 minutes and the subsequent ones gets longer and loner and can reach up to an hour.

Our brain activity changes as we move from NREM to REM phase, with more activity in the brain causing intensive dreaming.

1.3 The Mystery behind Dreaming

REM sleep begins with signals from an area at the base of the brain called the Pons. Signals travel to the brain region called thalamus, then in the cerebral cortex i.e. the outer layer of the brain responsible for learning, thinking and organizing information. This region of the brain along with the frontal lobe i.e. the storehouse of memory forms the dreams. Dreams are the cortex's attempt to find meaning in the random signals that it receives during the REM sleep from the pons in the brainstem. Cortex is that part of the brain that interprets and organizes the information from the environment during consciousness. From these random signals during REM sleep, the cortex tries to interpret these signals and creates a "story" out of the fragmented brain activity.

People who tend to remember the dreams, also called the 'high dream recallers' by researchers, show high activity in the temporo-parietal junction (TPJ). It also vindicates the fact the people experience dreams during their REM sleep phase because during it the brain activity is high just as when the person is fully awake.

1.4 Sleeping Disorders

The pons of the brain, also send signals during the REM phase to shut off neurons in the spinal cord. These signals are then transferred to the connected muscles from the spinal cord, and theses muscles start moving. It causes temporary paralysis of the limb muscles. This interference with paralysis means people will begin to physically act out their dreams. This type of paralysis and related sleeping disorders are called REM Sleep Behavior Disorder. Sleepwalking, sleep-talking, nightmares are all occurrences of the high brain activity during the REM phase.

For instance, a person dreaming about a ball game might run headlong into the furniture or blindly strike someone sleeping nearby while trying to catch a ball in the dream. After a lot of research put into the matter, it has been concluded that the brain shows electrical activity, as recorded by the electroencephalogram, is similar to how the brain reacts when a person walks. Therefore, it has been observed that the brain is entirely active during the REM phase of the sleep wake cycle unlike our body that is completely still during sleep.

1.5 Importance of REM sleep

REM sleep stimulates the brain regions that are used in learning. It affects learning of certain mental skills. It has been experimentally proven that people taught a skill and deprived of non-REM sleep could recall what they had learned after sleeping, while those people who were deprived of REM sleep could not. It simply proves the statement stated above that REM sleep helps in learning and enhancing memory.

REM sleeps also help in the development of the brain and makes stronger and efficient neural connections. Professor of Medical Sciences Marcos Frank has proved in his study ho important REM sleep is in the development of brain.

This explains why infants spend much more time sleeping than adults, as this sleep in the REM phase is important for their normal development of not only the brain but also the body.

REM sleep is associated with increased production of proteins in the body that explains the myth about the body growth during sleep.

1.6 What Are Circadian Rhythms?

Etymology…. (*Circadian is* Latin for "around a day")

Like the 24-hour clock, our body also has a 24-hour internal clock that runs simultaneously in the background of the brain and the sleep and wake cycle is called the Circadian rhythm of our body. Also known as the sleep-wake cycle, it is influenced by the regular changes in the mental and physical characteristics that take place during the course of a day.

The circadian rhythm is controlled by the brain's hypothalamus and regulates the timing of periods of sleepiness and wakefulness that oscillate throughout the day. In the hypothalamus the *suprschiasmatic nucleus* or SCN, a pair of pinhead-sized brain structures that contain 20,000 neurons that respond to light and dark signals. Light that reaches photoreceptors in the retina creates signals that travel along the optic nerve to the SCN which functions in synchronization with our sleep/wake cycle. It is also connected with our body temperature, hormone secretion (particularly the hormone melatonin whose secretion increases with darkness), urine production and change in the blood pressure.

Exposure to sunlight can reset the SCN and it's functioning. Hence, for some people the clock works in the 25-hour cycle rather than the 24-hour one.

The changes like these in the functioning of SCN, causes distortion in the sleep-wake cycle. When the sleep-wake cycle is disturbed, the neuronal discharges during the sleeping stages are also affected. By the means of this research, I look forward to solve this issue using mathematically modeling and doing some theoretical research on this field.

2.1 Hypothesis

How does the change in the circadian rhythm affect the neuronal discharge during the REM sleep?

Can we calculate the neuronal discharge activity during the REM sleep cycle versus the N-REM sleep cycle through mathematical modeling of previously established sleep-wake equations?

(IJRST) 2017, Vol. No. 7, Issue No. II, Apr-Jun **e-ISSN: 2249-0604, p-ISSN: 2454-180X**

2.2 Integrating a Mathematical Model to Neuronal Discharge during REM

Using a mathematical model can help us find out the difference in the amount of neuronal discharge during REM and NREM sleep stages.

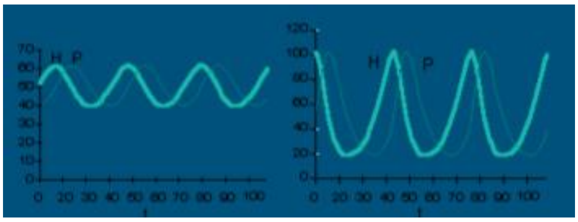
It can also help us understand how the Circadian Rhythms and the amount of sleep we get can affect our neuronal discharge.

Phenomenological model (two process/oscillator) help us understand the interaction of homeostatic and circadian influences on sleep and REM cycles.

2.3 Previous Research

The Writer has looked into the works of many researchers and put down some who have deduced equations that could be used to find the answers.

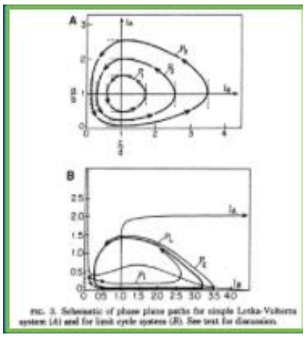
1. Lotka – Volterra model



X’(t) = aX – bXY

Y’(t) = -cY + dXY

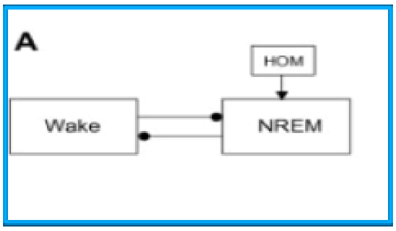
The simple Lotka-Volterra equations are, with X representing REM –on (mPRF) and Y REM-off (LC/DR) activity, and where t is time



Model originally made for prey and predator population in isolated ecosystems. It was thus a logical starting point for descriptions of interaction between inhibitory (“predator”) and excitatory (“prey”) neuronal population.

Plotting a phase plane to find oval shapes of the interaction between X and Y.

The ovals in the graph represent the activity of neurons observed during the REM-on and REM-off phase with respect to time.



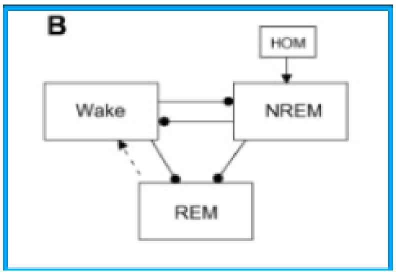
2. Phillips and Robinson model:

Sleep–wake flip-flop switch with other external inputs, but it does not include REM sleep generating mechanisms.

3. The Tamakawa et al., Diniz Behn et al. and Diniz Behn and booth models

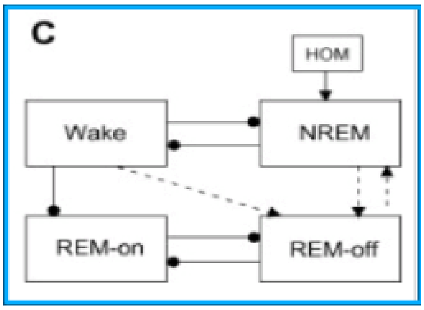
(IJRST) 2017, Vol. No. 7, Issue No. II, Apr-Jun **e-ISSN: 2249-0604, p-ISSN: 2454-180X**

- They all incorporate the reciprocal interaction hypothesis for REM sleep generation in their network structures.
- A basic network structure extracted from these models includes the sleep-wake switch with homeostatic sleep drive coupled to a REM sleep-promoting population.



4. The Rempe et al. and Kumar et al. models are based on mutual inhibition hypotheses for REM sleep generation.

   In a basic network structure for these models, the sleep-wake switch with homeostatic sleep drive is coupled to REM-off populations with mutual inhibitory projections between them



5. Both models include an inhibitory projection from the wake-promoting population to the REM-on population

   The Kumar et al. model also includes a direct excitatory projection from the wake-promoting population to the REM-off population.

3.1 The Mathematical Model

In all models, the output variables of interest are the average firing rates of the state-promoting neuronal populations, as shown in the Figure. Behavioral state is then interpreted according to the state-promoting populations that are firing at rates exceeding defined thresholds. Firing rate models typically follow the form developed by Diniz Behn and Booth in which the average firing rate of population X, f_X (in Hz), depends nonlinearly on the firing rates of presynaptic- the transmitting neuron populations f_Y (in Hz), and other external inputs to the population, l; X and Y can be W = wake, S = NREM, R = REM-on and NR = REM-off

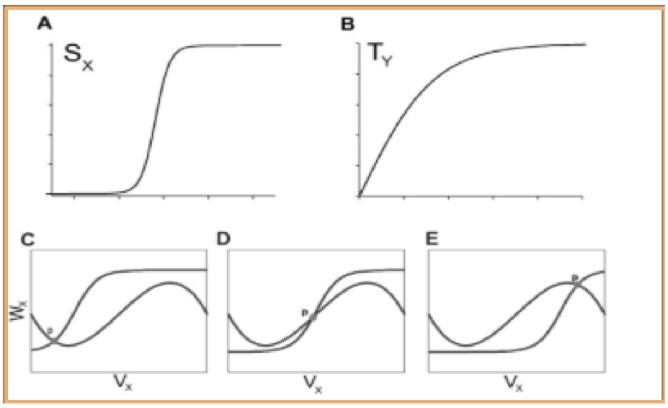
$$\tau_W \frac{df_W}{dt} + f_W = S_W(g_{SW} c_S), \quad c_W = T_W(f_W),$$

$$S_W(c) = \frac{W_{max}}{2}\left(1 + \tanh\left(\frac{c - \beta_W}{\alpha_W}\right)\right),$$

$$\tau_S \frac{df_S}{dt} + f_S = S_S(g_{WS} c_W, H), \quad c_S = T_S(f_S),$$

$$S_S(c, H) = \frac{S_{max}}{2}\left(1 + \tanh\left(\frac{c - \beta_S(H)}{\alpha_S}\right)\right),$$

Parameters g_{YX} weight the effect of presynaptic firing rate f_Y on population X with the sign (positive or negative) indicating whether synaptic input is excitatory or inhibitory. The firing rate response function S_X is monotonically increasing and usually sigmoidal in shape. The time constant T_X

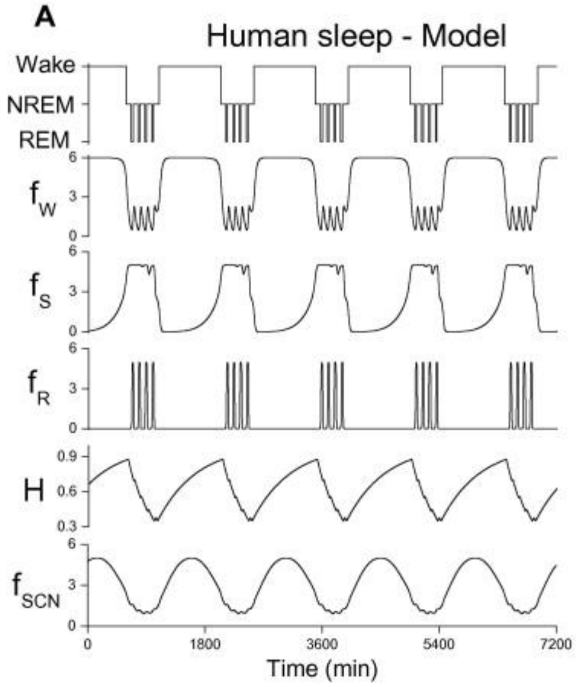


dictates firing rate changes on the population level.

3.2 Theoretical Results

Network model simulates stereotypical human sleep

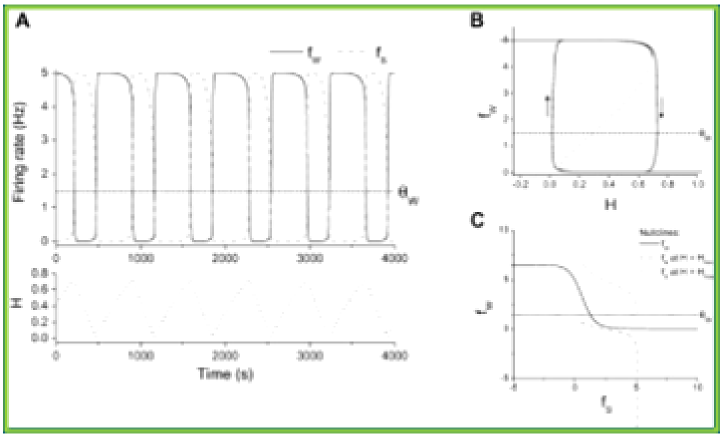
- Hypnogram in the top trace summarized transitions in simulated behavioral state (wake, NREM or REM sleep)
- Transitions in activity of associated state-promoting neuronal populations shown in lower traces



Average firing rate (in Hz) of wake-promoting (fW), NREM sleep-promoting (fS) and REM sleep-promoting (FR) neuronal populations. Homeostatic sleep drive variable (H), (similar to Process S of the two-process model,) that increases during wake and decreases during sleep. Network accounts for the influence of the circadian rhythm on sleep-wake behavior by including input from the SCN (f_{SCN}) that varies on a 24 h time scale.

3.3 Numerical Results

Graph A.



- fw = firing rates of wake-promoting populations
- fs = firing rates of sleep-promoting populations
- Wake = when fw is above θw
- H = homeostatic sleep drive
- Increase = wake
- Decrease = sleep

Graph B.

- Hysteresis loop with Z-shaped bifurcation curve (no stable pt.)
  - H increases for fw ≥ θw

(IJRST) 2017, Vol. No. 7, Issue No. II, Apr-Jun **e-ISSN: 2249-0604, p-ISSN: 2454-180X**

- H decreases for $fw < \theta$

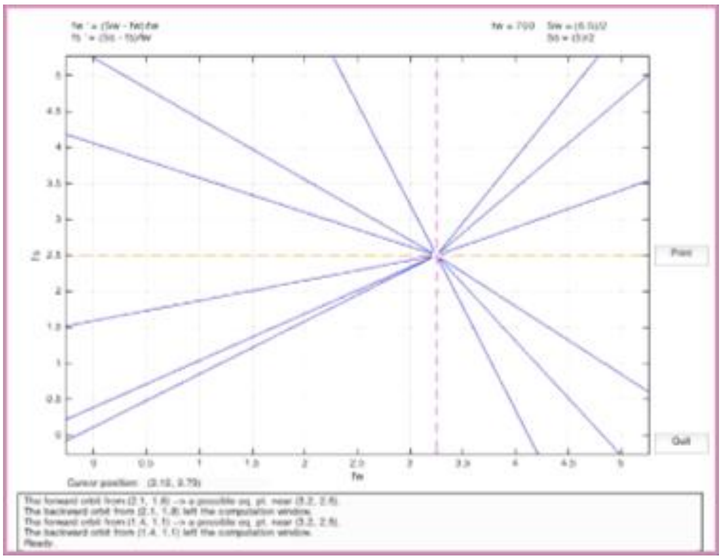
Graph C.

- Fs-fw phase plane with different nullclines
- fs nullcline is discontinuous.

3.4 Graphical Explanation

Diniz Behn and Booth Model.

Using pplane15 in MATLAB, we were able to create graphs of the models and identify the stable points.



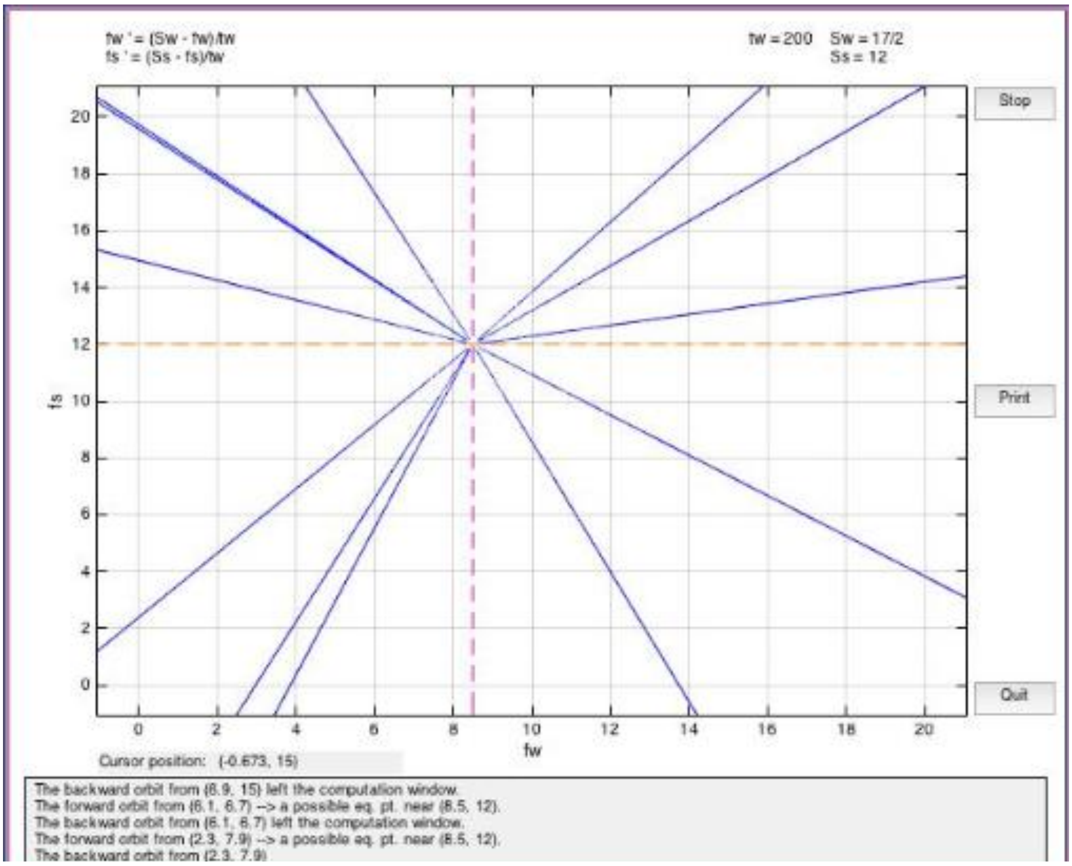
$$t_w \frac{df_w}{dt} + f_w = s_w(g_{sw}c_s), \quad c_w = T_w(f_w),$$

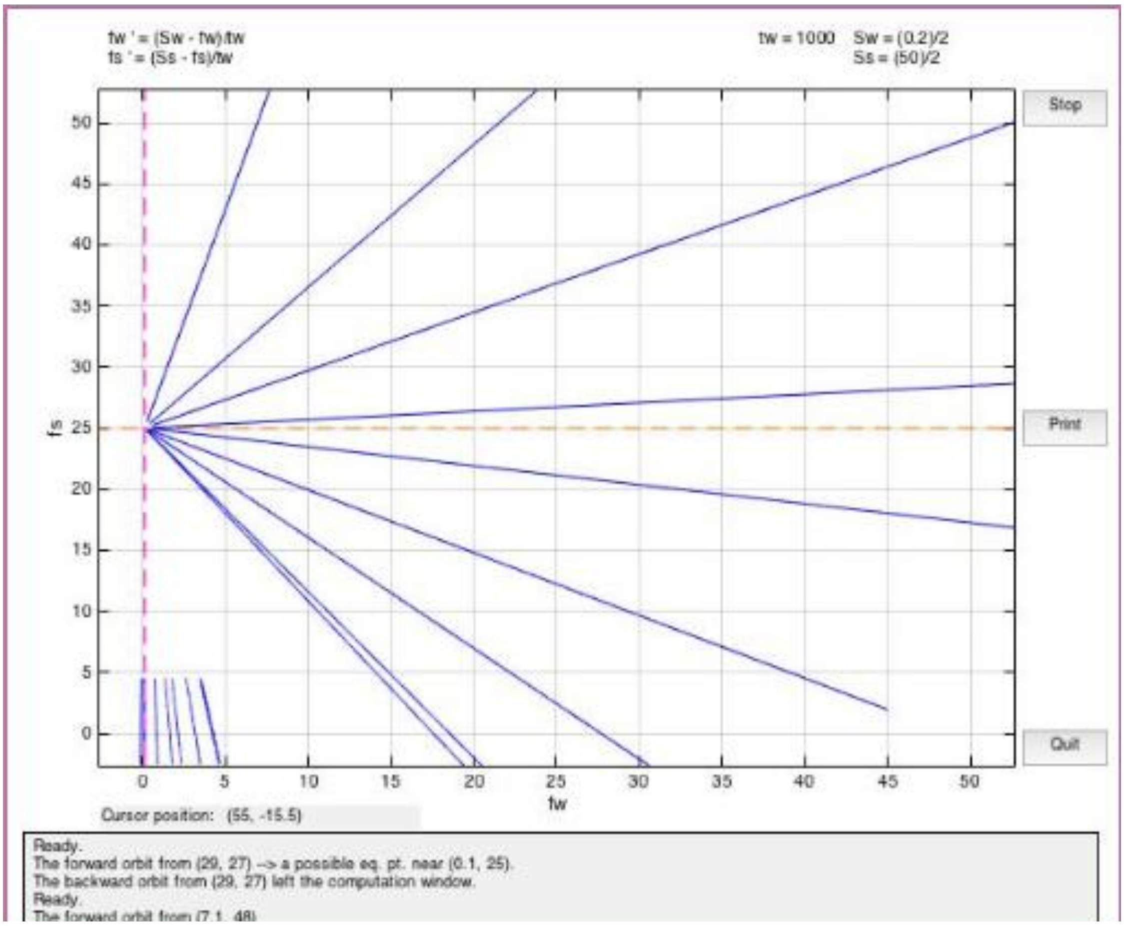
$$s_w(c) = \frac{w_{max}}{2}\left(1+\tanh\left(\frac{c-\beta_w}{\alpha_w}\right)\right),$$

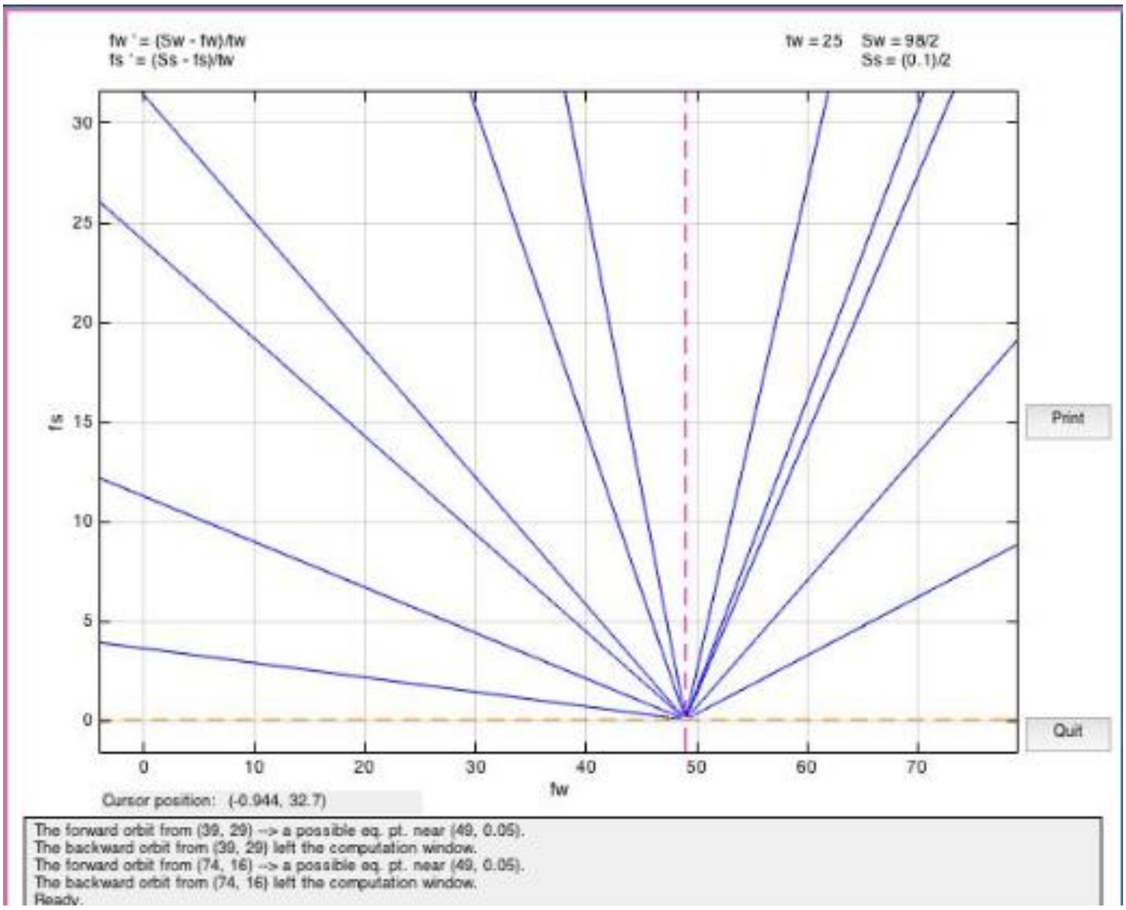
$$t_s \frac{dfs}{dt} + fs = s_s(g_{ws}c_w, H), \quad c_s = T_s(f_s),$$

$$s_s(c,H) = \frac{s_{max}}{2}\left(1+\tanh\left(\frac{c-\beta_s(H)}{\alpha_s}\right)\right),$$

$$fw' = (Sw = fw)/tw$$
$$fs' = (Ss = ts)/tw$$


fw ' = (Sw - fw)/tw
fs ' = (Ss - fs)/tw
tw = 200
Sw = 17/2
Ss = 12
Stop
Print
Quit
fs
fw
Cursor position: (-0.673, 15)
The backward orbit from (6.9, 15) left the computation window.
The forward orbit from (6.1, 6.7) --> a possible eq. pt. near (8.5, 12).
The backward orbit from (6.1, 6.7) left the computation window.
The forward orbit from (2.3, 7.9) --> a possible eq. pt. near (8.5, 12).
The backward orbit from (2.3, 7.9)


fw ' = (Sw - fw)/tw
fs ' = (Ss - fs)/tw
tw = 1000 Sw = (0.2)/2
Ss = (50)/2
Stop
Print
Quit
fs
fw
Cursor position: (55, -15.5)
Ready.
The forward orbit from (29, 27) --> a possible eq. pt. near (0.1, 25).
The backward orbit from (29, 27) left the computation window.
Ready.



3.5 Summary

Computational neuroscience is, "sufficiently broad and mature to provide appropriate mathematical formalisms to model brain activity at many temporal and spatial scales". However, more detailed simulation requires multi-scale models. This can be attempted by taking further focused studies based on empirical data collection and analysis. Incorporation of brainstem/hypothalamic populations, neuropeptides, and the effects of non-photic and photic inputs are challenging. The obtaining of experimental data from subjects who can exhibit dynamic sleep patterns, since using dead animals/humans only helps with anatomy..

3.6 Opinion and Suggestions

Research and modelling of the biological rhythms of our body that concerns sleep and its processes is essential. This will, in turn, facilitate the understanding of how human body works and provide vital clues to curing sleeping disorders. Cumulatively, it will improve our understanding of our natural bodily clocks and the reason for the way we live from a day to day basis.

Bibliography

- http://www.webmd.com/sleep-disorders/guide/sleep-101
- https://www.sciencedaily.com/terms/circadian_rhythm.htm

(IJRST) 2017, Vol. No. 7, Issue No. II, Apr-Jun **e-ISSN: 2249-0604, p-ISSN: 2454-180X**

- http://ajpregu.physiology.org/content/ajpregu/251/6/R1011.full.pdf
- http://dl2af5jf3e.search.serialssolutions.com/?sid=Entrez:PubMed&id=pmid:24530893
- https://healthunits.com/news/rem-sleep-is-essential-for-your-childs-brain-development/
- https://sleepfoundation.org/sleep-topics/sleep-drive-and-your-body-clock/page/0/2
- http://www.life.illinois.edu/clockworks/pdfs/1999suprachiasmatic.pdf