CS441

Circadian Rhythm, You Gotta Be With 'em

-- The Effect of Weak Oscillators on Entrainment in the SCN

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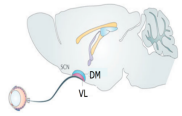
Colby

Background

The SCN

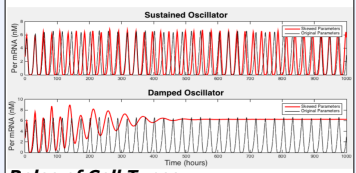
Most mammalian cells contain internal clocks -- sets of genes whose cyclical expression regulates a wide variety of cellular functions. The Suprachiasmatic Nucleus (SCN) "entrains" (or matches) these disparate cellular oscillations to external, environmental oscillations, such as to light-dark cycles.



SCN Regions and Cell Types

The SCN is made up of two regions: the light-sensitive, ventro-lateral (VL) region (comprising about 25% of the SCN) and the light-insensitive dorso-medial (DM) region (comprising about 75% of the SCN).

Within both regions, self-sustained neurons (neurons that oscillate without cell-to-cell signaling) comprise a minority of the cells and non-self-sustained neurons (neurons that require cell-to-cell signaling to oscillate) comprise a majority.



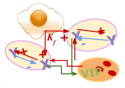
Roles of Cell Types

Self-sustained cells generate the endogenous rhythm of the SCN via a negative feedback loop. Non-self-sustained cells allow the SCN to entrain to à wide variety of external rhythms.

Our Study

In 2016, Gu et al. suggested that non-self sustained SCN neurons in mice limited the entrainment range of the SCN when they comprised a large proportion of the VL and increased the entrainment range of the SCN when they comprised a large proportion of the DM.

To test this hypothesis, we replicated Gu et al.'s experiments with four different models of the SCN. Using these models, we tested to see if the results in Gu et al. are generalizable to the whole mammalian circadian clock. In all four models tested, we were able to reproduce the results of Gu et al., suggesting that non-self sustained oscillators increase entrainment flexibility in the VL and limit entrainment flexibility in the DM. The results of all the models are given in the table below.



A schematic of the Poincare Model.

Conclusions

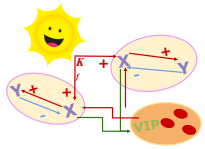
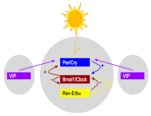
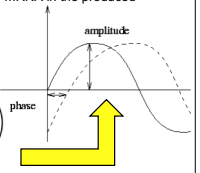
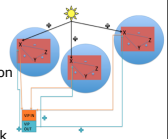
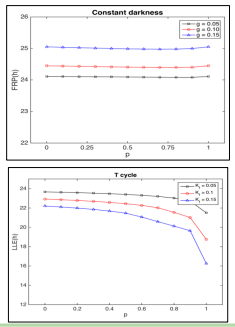
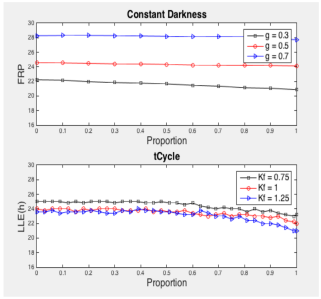
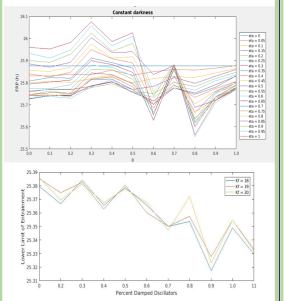
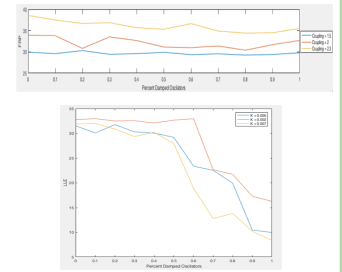
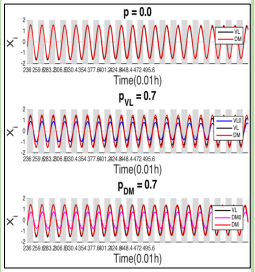
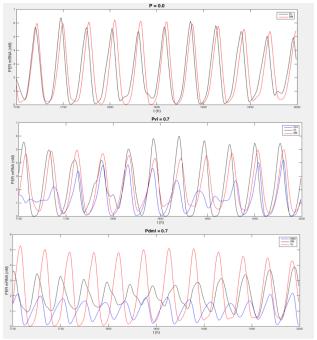
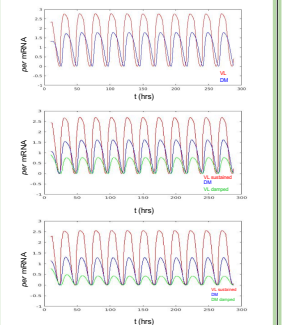
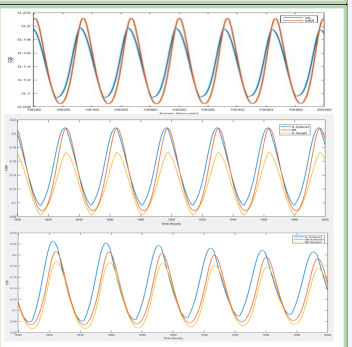
- Reproduced and Confirmed Results from Gu et al. using the Poincare Model.
- Reproduced results from Gu et al. using 3 different models, demonstrating that results of Gu et al. are not model dependent, and are more generalizable.

References:

"The effects of non-self-sustained oscillators on the entrainment ability of the suprachiasmatic nucleus"; Gu, Tang, Rohling & Yang; Nature Scientific Reports; 2016.

"Spontaneous Synchronization of Coupled Circadian Oscillators"; Gonze, Bernard, Waltermann, Kramer, Herzel; BioPhysics J; 2005.

https://www.nature.com/articles/nrn3086

	Gu et al.	Goldbeter et al.	Taylor et al.	Gonze et al.
Model	 Each cell has 2 state variables, X and Y. External light signal and internal VIP both affect X.	 Each cell contains a 17-state signaling network containing three distinct feedback loops. Per transcription is upregulated by VIP signaling from other cells and light signaling from the sun.	 Light **speeds up** and **increases** the amount of *per* mRNA in the produced 	Cells (blue circles) receive light input, transmit time signals (VIP IN), and receive time synchronization signals (VIP OUT).  Cells generate VIP IN via a 3 state negative feedback loop involving: a clock gene (X), creates clock protein (Y), which activates a clock inhibitor (Z). Simulations are produced using 100 cells and mean field coupling.
Figure 1 All the cells are light-sensitive. Under complete darkness, the change in non-self-sustained cell proportion doesn't affect entrainment. Under an external light-dark cycle, however, a larger proportion and a stronger light-sensitivity both bring a wider entrainment range.				
Figure 2 The SCN cells have 25% VL cells and 75% DM cells, and are under an external 23.6h cycle. Result: VL cells always leads the DM cells in their periods. Whether there are non-self-sustained cells, and where those cells are located, does not change this pattern. Damped cells show a lower amplitude.				
Figure 3 In both experiments, a higher light intensity brings a wider entrainment range. Assuming DM is all self-sustained: The higher the proportion of non-self-sustained cells in VL, the narrower the entrainment range, and the larger the lowest limit of entrainment. Assuming VL is all self-sustained: The higher the proportion of non-self-sustained cells in DM, the wider the entrainment range, and the smaller the lowest limit of entrainment.