**Master-Slave Clock Networks: Modeling, Analysis and Neurobiology**
(0422886-FY04)

Hava Siegelmann
University of Massachusetts, Amherst

Mary Harrington
Smith College

Christopher V. Hollot
University of Massachusetts, Amherst

Yossi Chait
University of Massachusetts, Amherst

Eric L. Bittman
University of Massachusetts, Amherst

We use a combination of computational and neurobiological methods to explore the mechanisms which generate endogenous daily (circadian) rhythms in a mammal. The master circadian pacemaker, which resides within the suprachiasmatic nucleus of the hypothalamus (SCN), is comprised of thousands of cell-autonomous oscillators. A luciferase reporter allows us to track oscillations in the expression of critical clock genes in real time in brain slices containing the SCN. We propose that the SCN can be understood at the cellular level as a resonant-curcuit oscillator, defined by the feedback interaction of three functions: resonator, amplitude-stabilizer and phase-shifter. The inhibitory effect of PER-CRY on BMAL exhibits resonance, the positive effect of BMAL on PER-CRY produces the necessary phase shift, and the mass kinetic dynamic of *Per* expression provides amplitude stabilization. We provide a biologically based computational model which explicates how SCN neurons which have different periods couple in synchrony and produce a 24 h period by linking mRNA expression and neuronal firing rate.

We also compare different connectivity architectures and demonstrate how small world networks are necessary for coherence if the number of connections is constrained. Circadian oscillations can also be measured in peripheral organs of transgenic rodents. To date we have observed circadian oscillations of biolumninesence in tissues obtained from transgenic (*Per2::luc*) mice (generously provided by Dr. J.S. Takahashi, Northwestern University), including liver, lung, cornea, spleen, pituitary, kidney, adrenal gland, esophagus, seminal vesicles, thymus, bladder, and skin. We developed a computational model of coupling of three oscillators, representing the ventral SCN, dorsal SCN and a peripheral tissue.

Our model correctly predicts results of phase response curve experiments, simulates the greater ease of east-west than west-east travel jet lag, and predicts the temporary phase difference between SCN and peripheral organs, as in Vansteensel et al. (2003). Using a restricted feeding experimental protocol, we will determine the role of feedback from body to the SCN, using laboratory experiments to test the model predictions.

**Publications**

Bittman, E, Chait, Y, Hollot C, Harrington M, Siegelmann H. Is the mammalian circadian clock a resonant-circuit oscillator? Soc. Res. Biol. Rhythms, 2004.

Bush W, Siegelmann H, Harrington M. Oscillatory neural network for modeling the SCN, Computational and Systems Neuroscience, 2005.