# Fast and Slow Coupling in the Circadian Clock

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**The mammalian circadian (daily) clock is controlled by the ~20,000 neurons of the suprachiasmatic nucleus (SCN). While the molecular mechanisms for generating rhythms in individual SCN neurons are well characterized, single-cell rhythms are weak and noisy, and it is still unknown how they are integrated to generate robust rhythms at the tissue level. To investigate this, we develop a highly detailed, multicellular, and multi-scale model of the SCN. The model is used to investigate, and make predictions about, the differential roles of fast GABAergic synaptic coupling, and slower paracrine signaling through VIP, which couple neurons in the SCN.**

***Keywords*** **— Circadian clock, coupled oscillators, intercellular signaling**

## I. Introduction

CIRCADIAN rhythms are endogenous oscillations seen in many physiological processes with periods of approximately 24 hours. In mammals, the circadian clock is controlled by the roughly twenty thousand neurons of the suprachiasmatic nucleus (SCN). Within the cells of the SCN, two key processes contribute to timekeeping: a transcription-translation negative feedback loop controlling the production of key clock genes in an approximately 24-hour cycle [1], and electrical activity, which varies throughout the day [2]. While much is known about these intracellular processes, many open questions remain about how coupling between cells creates a robust tissue-level rhythm with consistent spatiotemporal dynamics out of noisy, weak cellular oscillators [3-5].

To explore this, we develop a detailed, multi-scale model of the SCN, able to simulate both the electrical activity [6], at the scale of individual ionic currents and action potentials, and molecular clock rhythms [7], at the level of individual protein and complex concentrations, in every cell of the SCN. We use state-of-the-art methods in scientific computing with graphics processors to fit the model to experimental data, and simulate it at a level of detail not previously attained in SCN simulations. With the model, we focus on the effects of two key coupling mechanisms, fast synaptic signaling through GABA, and slower paracrine signaling through the neuropeptide VIP, and elucidate the importance of both signaling methods in generating robust rhythms in the SCN.

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## II. Results

Fitting the coupling in the model to experimental data yields the interesting prediction that oscillations in isolated SCN neurons can be gained or lost by transient activation of the cAMP/CREB pathway. This has been seen in one experiment [3], but not fully explored. The model predicts that this bistability is due to a reduction in the transcription of the core clock gene Per in the absence of VIP signaling, and that rhythms could be stabilized by increasing its production.

The model also predicts that the spatial distribution of the VIP receptor $VPAC_2R$ can cause the "phase wave," or characteristic spatiotemporal pattern of activation seen experimentally in SCN slices. Previous studies have assumed that this pattern is due to intrinsic differences between cells, but here we show that this is not necessary, and that it may be produced through heterogeneity in signaling instead.

Finally, we explore recent studies showing that subpopulations of SCN neurons have different polarity responses to GABA, some excitatory, and some inhibitory. The model suggests that SCN neurons with excitatory responses to GABA have increased amplitude in their intracellular calcium rhythms, and that this can cause increased synchrony in their molecular rhythms even in the absence of VIP. Furthermore, it predicts that excitatory and inhibitory neurons resynchronize differently after reorganization caused by photoperiod variation as seen in [8].

## III. Conclusion

The model presented here is a unique tool for the circadian community, providing intuition into the role of intercellular signaling in the SCN, and testable predictions that can be used to inform wet lab experiments. These processes are difficult to probe experimentally because of the large separation of timescales between the electrical and molecular activities, but the model demonstrates that both scales are essential in generating the complex behaviors of the SCN.

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