

## **Modeling circadian rhythm generation in the SCN with locally coupled self-sustained oscillators.**

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In mammals, circadian rhythms are driven by a pacemaker located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The firing rate of neurons within the SCN exhibits a circadian rhythm. There is evidence that individual neurons within the SCN act as circadian oscillators. Rhythm generation in the SCN was therefore modeled by a system of self-sustained oscillators. The model is composed of up to 10 000 oscillatory elements arranged in a square array. Each oscillator has its own (randomly determined) intrinsic period reflecting the widely dispersed periods observed in the SCN. The model behavior was investigated mainly in the absence of synchronizing zeitgebers. Due to local coupling the oscillators synchronized and an overall rhythm emerged. This indicates that a locally coupled system is capable of integrating the output of individual clock cells with widely dispersed periods. The period of the global output (average of all oscillators) corresponded to the average of the intrinsic periods and was stable even for small amplitudes and during transients. Noise, reflecting biological fluctuations at the cellular level, distorted the global rhythm in small arrays. The period of the rhythm could be stabilized by increasing the array size, which thus increased the robustness against noise. Since different regions of the SCN have separate output pathways, the array of oscillators was subdivided into four quadrants. Sudden deviations of periodicity sometimes appeared in one quadrant, while the periods of the other quadrants were largely unaffected. This result could represent a model for splitting, which has been observed in animal experiments. In summary, the multi-oscillator model of the SCN showed a broad repertoire of dynamic patterns, revealed a stable period (even during transients) with robustness against noise, and was able to account for such a complex physiological behavior as splitting.

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