## Gate Cells See the Light

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COMMENT

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## A HETEROGENEOUS SCN

SCN neurons are not all created equal (Antle and Silver, 2005; Silver and Schwartz, 2005). Traditionally, they have been distinguished by expression of neuropeptides, calcium binding proteins, and other molecular markers, or by whether they receive direct retinal input or send axonal projections to other brain areas. It is now clear that they can also be distinguished on the basis of their circadian function: SCN neurons exhibit various periods when dissociated and various phases when synchronized in slice preparations, and a minority may even be nonrhythmic. Moreover, these SCN heterogeneities seem to follow a clear topographic pattern. For example, nonretinorecipient vasopressin cells in the dorsomedial "shell" region generally phase lead retinorecipient vasoactive intestinal polypeptide (VIP) cells in the ventrolateral "core," and some core cells are only weakly rhythmic or nonrhythmic. Mathematical models of integrated SCN function have generally ignored such biological complexities for the sake of mathematical simplicity and have assumed simple global or local coupling of a population of cellular oscillators differing only in intrinsic circadian period (Liu et al., 1997; Kunz and Achermann, 2003; Gonze et al., 2005).

## GENESIS OF THE MODEL

The model described by Antle et al. (2007 [this issue]) is mathematically unconventional but attempts to capture more details of SCN organization than other models. The article is a sequel to an earlier one published by the same authors several years ago (Antle et al., 2003); they now extend their model to accommodate photic input. The model was originally motivated as a way to reconcile 2 seemingly contradictory experimental findings from the authors' own laboratory: calbindin+ cells within the core of the hamster SCN seem to be required for behavioral rhythmicity (LeSauter and Silver, 1999), and yet these cells seem to be nonrhythmic in their clock gene expression (Hamada et al., 2001) and firing rate (Jobst and Allen, 2002). So these core cells might be essential for SCN rhythmic output, but not because they are "pacemaker cells" driving other damped oscillators. Less imaginative investigators might have thrown up their hands at this point or searched for a flaw in their data. (Doubts linger, for instance, about whether the "nonrhythmic" cells are really completely nonrhythmic or whether there might still be weak rhythmicity that is undetectable by the methods used.) Instead, they proposed that the core cells are essential not for rhythmically driving other SCN cellular oscillators but for synchronizing them, which is consistent with recent data from other investigators (Yamaguchi et al., 2003; Aton et al., 2005; Maywood et al., 2006). To explain how nonrhythmic cells could be important for synchronization of other rhythmic cells, they resurrected a coupling scheme originally proposed by Enright (1980).

Rather than having rhythmic cells directly influence one another by local interactions or the global sum of a secreted factor, Enright (1980) proposed a nonrhythmic "discriminator" element to mediate coupling. The function of the discriminator is to sum the outputs of cellular relaxation oscillators and then cause "an explosive triggering and a resetting" of the oscillators to the same phase when the summed output exceeds a threshold. One advantage of this

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scheme emphasized by Enright is that the precision of the coupled system can be much better than that of individual component oscillators, although this is also true for simpler models with direct coupling (Liu et al., 1997). In the Antle model (Antle et al., 2003), the discriminator function is served by certain retinorecipient, nonrhythmic cells of the SCN core (possibly identifiable by expression of calbindin in hamsters or gastrin-releasing peptide [GRP] in mice). These "gate cells" integrate the output of the rhythmic clock cells in the shell region. When this output exceeds some threshold, the gate cells generate a "daily organizing signal," which has the effect of pushing phases of individual clock cells closer to the mean phase of the population. This tends to synchronize the clock cells even in the absence of any direct coupling effects among them.

## WHAT THE MODEL DOES

The crux of the model is the function used by the gate cells to reset the clock cells when the gate is triggered. This takes the form of a phase transition curve (PTC) that specifies a new phase to which an individual clock cell will be reset for any given initial phase at the time the gate is triggered (Fig. 1 in Antle et al., 2007). In this plot, points on the dashed diagonal line represent no phase shift, points above the line represent delays, and points below the line represent advances. The seasoned chronobiologist will notice that this configuration is opposite that of a typical PTC (advances above, delays below) because Antle et al. (2007) have adopted the perplexing convention that circadian phase decreases with time! This makes it difficult to compare the PTC to those derived from biological data, which in any case represent light responses of whole animals rather than single SCN neurons (e.g., Vitaterna et al., 2006). Nevertheless, it is useful to note that the model PTC is somewhat different: It is composed of line segments rather than being a smooth curve, and it has a rather long advance region, a short delay region, and no "dead zone." But it is also similar in 2 important ways: (1) For most of the curve (where the slope is $< 1$), the range of new phases is narrower than the range of initial phases, thus tending to push cells closer together in phase, and (2) there is a phase ($\pi/3$) where stable entrainment can occur because cells that are delayed relative to the gate signal (triggered at an earlier, higher phase) will be advanced, whereas cells that are advanced relative to the gate signal (triggered at a later, lower phase) will be delayed.

For model simulations, the authors begin with a population of 200 SCN neurons (van der Pol oscillators) with periods drawn from a distribution with a 24-h mean, a 1.5-h SD, and phases initially distributed uniformly over 3 h. The gate is triggered when the ensemble output exceeds a threshold value (0.1) that is relatively small relative to the maximum output (1.0) and then is prevented from being triggered again until 20 h later on the next cycle (the "hold-off"). The result of this endogenous triggering mechanism is a fairly coherent population rhythm with the gate triggered on the rising phase. Thus, the model successfully reproduces free-running rhythms of integrated SCN output. This replicates the results of the first study (Antle et al., 2003).

The authors then extend their model to accommodate external resetting stimuli. They propose that the daily organizing signal from the gate cells can be triggered by an external signal such as a light pulse, as well as by the integrated output of clock cells within the SCN. In other words, the same PTC used for endogenous resetting is also used for exogenous light pulses. Simulations demonstrate that the Antle model can produce basic features of a PRC to light and entrainment to daily light pulses within a limited range of periods. Thus, the model accounts parsimoniously for both coupling and photic entrainment of the multioscillator SCN and explains how some SCN cells (gate cells) could be nonrhythmic and yet still be required for rhythmic SCN output. The model also accounts for recovery of rhythmicity from a desynchronized state in response to a series of light pulses, as has been inferred in ground squirrels emerging from hibernation (Hut et al., 2002). This is an impressive set of achievements for a model that may have initially appeared to be a Rube Goldberg contraption to explain seemingly contradictory data!

## FUTURE ENHANCEMENTS

Of course, no model is perfect, and there is certainly room for further refinements and extensions. An obvious long-term goal, for instance, would be substitution of a more molecularly detailed single-cell model for the van der Pol model used here. Another important extension would be to incorporate explicit features of SCN topographical connectivity into the model. Recent identification of putative synchronizing signals (VIP, GRP) (Aton et al., 2005; Brown et al., 2005; Maywood et al., 2006) presents new opportunities to test and extend the model.

One potential area where the model could be improved is in the single-cell resetting function. A more biologically plausible PTC would have smooth,

nonlinear deflections below and above the diagonal line of unchanged phase, a better balance between advances and delays, and a longer dead zone. This should produce a more realistic ensemble PRC to light, with a longer daytime dead zone and without unreasonably large (8-h) delays. It would be interesting to see how introduction of a longer dead zone might affect the degree of phase dispersion among individual neurons. The photic PRC dead zone could also be produced without changing the single-cell PTC, by explicitly gating photic input so that it is effective only during subjective night. Of course, if gate cells are to subserve this function, rhythmically gating light input, they would have to be rhythmic at some level.

Another problem with the model is that the acrophase of the ensemble rhythm occurs at the wrong time. The acrophase falls in the phase delay region of the light PRC (see Fig. 2 in Antle et al., 2007), corresponding to early subjective night, whereas real SCN neuronal firing and neurosecretion (of gate-triggering factors) generally peak in mid-subjective day. This phase mismatch could be corrected by using different resetting functions for endogenous signals versus light. However, the real problem seems to be that endogenous triggering of the gate occurs on the rising phase of the ensemble rhythm, well before the acrophase, whereas exogenous triggering of the gate by light occurs at the time of the light pulse. In other words, the peak of neurosecretion is rendered ineffective for phase resetting due to the hold-off feature of the model. Moreover, it is not clear that the 20-h hold-off time is biologically plausible, especially as it is selectively applied only to endogenous activation of the gate. It would be interesting to try eliminating the hold-off and allowing for a more graded effect of endogenous factors, integrated over time.

Similarly, the all-or-none mechanism proposed for response to light is clearly an oversimplification. The model's accommodation of exogenous resetting stimuli is limited to brief light pulses. It does not address light pulses of varying intensity or duration, full LD cycles, LL, or seasonal variation of photoperiod. Extending the model to produce appropriate responses to such stimuli should be a high priority. One particularly interesting area for further exploration would be the effect of photoperiod on phase dispersion of single-cell oscillators (Rohling et al., 2006).

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