A Parallactic View

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RESPONSE

A Parallactic View

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The commentary by Dr. Michael Hastings (2001 [this issue]) on our conjecture is a very insightful and expert contribution to the debate. Indeed, sparking a discussion on the connection between molecular and physiological analysis has been a goal of our article as much as generating testable predictions on this connection. That discussion will undoubtedly continue, in this journal as well as elsewhere, and there is little point in trying to settle all the issues right here. The points raised by Dr. Hastings highlight a few facts our model does not easily cope with. These facts can be studied from different angles, giving different parallactic views (*sensu* Enright, 1989) from each side. I restrict myself to one example in Hastings's comment and one from a fascinating recent publication (Toh et al., 2001) that illustrates the importance of generating proper models.

Hastings's Figure 1 combines the photoperiodic effects on *per1* expression as mRNA and as protein in the SCN of Siberian hamsters, plotting both on a ZT scale with ZT 0 defined as lights-on. Since Pittendrigh, it has been customary to define the *circadian time* (CT) scale by setting that phase of an oscillation that coincides with lights-on in an LD 12:12 cycle to CT 0 or the phase coinciding with lights-off to CT 12. Obviously, this definition breaks down with entrainment to different photoperiods. This renders also the definition of *zeitgeber time* (ZT) in different photoperiods on the basis of lights-on = ZT 0, an arbitrary choice but one with parallactic consequences. For the sake of symmetry, I prefer to define zeitgeber time by setting ZT = 0 at midnight, just as local time is defined. As winter turns to spring and summer, dawn shifts forward to earlier ZT rather than staying in place and dusk shifts to later ZT. One can estimate the phase of the cycle of *Per1* expression, for example, by computing the circular mean vector direction (or acrophase). For *Per1* mRNA, the data in the upper panel of Hastings's Figure 1 yield ZT 10.3 in LD 8:16 and ZT 9.7 in LD 16:8. The protein data in the lower panel have mean vectors at ZT 18.6 and ZT 16.7, respectively. In both cases, the *Per1* cycle shifts forward with dawn rather than backward with dusk—even more so when the rise time or the modal value of the expression would be used as a phase reference. Hastings emphasizes the increase in duration of the expression—indeed, not readily explained by our model—and proposes a mechanism for it. We focused on the change in phase, which is readily predicted by our hypothesis but remains unaddressed by Hastings's proposition.

Similar parallaxis remains with us in viewing other data. Toh et al. (2001) recently reported on an *hPer2* mutation causing human familial advanced sleep phase syndrome (FASPS). FASPS is interpreted by the authors as due to a putative massive reduction in endogenous cycle length. In terms of the E/M model, the affliction can be attributed to malfunctioning of the E oscillator (*Per2*!) responsible for the afternoon peak in SCN activity that keeps a diurnal animal awake in the late afternoon. For future progress—in animals as well as in humans—it should be valuable to have at least two sets of predictions to experimentally discriminate between. Indeed, it would be most welcome to have a specific set of predictions, alternative to those in our Figure 3, to be derived from Hastings's own conjecture of a circadian system characterized by "morning-related . . . *Per1/Per2* expression and evening-related expression of *Cry1/Cry2*" (p. 122).

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