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Molecular synchronization, the Kai system, and biological oscillators

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In most textbook examples, oscillations in cell biology are driven by the periodic creation and destruction of one or more chemical species. The past few years, however, have seen growing interest in a different sort of oscillator. In these systems, the total concentrations of the major protein components are constant, but the molecules move sequentially through a cycle of different states (e.g. covalent modifications). Macroscopic oscillations appear when the progress of the many individual molecules becomes *synchronized*. The recently-characterized cyanobacterial circadian clock provides a particularly elegant example of such molecular synchronization. Remarkably, with only the 3 proteins KaiA, KaiB, and KaiC, a $\sim$24 hour oscillation in KaiC phosphorylation can be reconstituted *in vitro*. We can thus dissect this biochemical circuit in almost unprecedented detail. Here, we give an overview of the Kai system and its relationship to other oscillators. We begin with a review of the major experimental facts about the Kai system, emphasizing possible mechanisms to synchronize KaiC phosphorylation. We then examine in more detail models in which this synchronization occurs through sequestration of KaiA via *differential affinity*: KaiA, which stimulates KaiC phosphorylation, has a higher affinity for KaiC during certain stages of the phosphorylation cycle; as long as some KaiC molecules at these stages are present in the reaction mixture, they bind all the available KaiA, thereby preventing the other KaiC's from being phosphorylated and proceeding through the cycle. We also discuss the implications of this mechanism for phenomena such as temperature compensation. Finally, we suggest that, in light of lessons learned from the Kai system, a number of other biological oscillators can fruitfully be viewed as examples of molecular synchronization.