1089-92-8 **Qiong Yang*** (qiongy@stanford.edu) and **James E. Ferrell**. *From molecules to development: revealing simple rules of biological clocks.*

Organisms from cyanobacteria through vertebrates make use of biochemical and genetic oscillators to drive autonomous, repetitive processes like cell cycle progression and vertebrate somitogenesis. Despite the complexity and variety of biological oscillators, their core design invariably includes a negative feedback loop. However, absent crucial elements negative feedback circuits often settle into a stable steady state rather than oscillating. In this talk, I first discuss computationally how several modifications of the basic activator/repressor circuit can promote oscillation. Then I ask which of these strategies are actually utilized in the circuits found in nature by dissecting a mitotic oscillator in the Xenopus laevis early embryos. We found that the core negative feedback system of Cdk1-APC/C operates as a time-delayed, digital switch, with a time lag of 15 min between the activation of Cdk1 and its repressor APC/C and a tremendously high degree of ultrasensitivity. Mathematical modeling indicates that this time delay must be coupled to the ultrasensitivity to ensure robust oscillations and segregation of cell-cycle phases. Principles uncovered here may also apply to other activator-repressor oscillators and help in designing robust synthetic clocks. (Received February 17, 2013)