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**Analysis of Cell Cycle Phase Response Captures the Synchronization Phenomena and Reveals a Novel Cell Cycle Network Topology**  
YING LI, YIHAN LIN, NORBERT SCHERER, AARON DINNER, University of Chicago — Cell cycle progression requires a succession of temporally-regulated sub-processes, including chromosome replication and cell division, which are each controlled by their own regulatory modules. The modular design of cell cycle regulatory network allows robust environmental responses and evolutionary adaptations. It is emerging that some of the cell cycle modules involve their own autonomous periodic dynamics. As a consequence, the realization of robust coordination among these modules becomes challenging since each module could potentially run out of sync. We believe that an insight into this puzzle resides in the coupling between the contributing regulatory modules. Here, we measured the phase response curve (PRC) of the cell cycle oscillator by driving the expression of a master regulator of the cell cycle in a pulsatile manner and measuring the single cell phase response. We constructed a return map that quantitatively explains the synchronization phenomena that were caused by periodic chemical perturbation. To capture the measured phase response, we derived a minimalist coupled oscillator model that generalizes the basic topology of the cell cycle network. This diode-like coupling suggests that the cell is engineered to ensure complete coordination of constituent events with the cell cycle.

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