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The *Multiplex Phase Interlocker*: a novel and robust molecular design synchronizing transcription and cell cycle oscillators

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Motivation and Aim: The eukaryotic cell cycle is robustly designed, with molecules interacting and organized within definite network topologies. A transcriptional oscillator interlocks with waves of cyclin-dependent kinases (cyclin/Cdk) to guarantee execution of a timely cell cycle progression. Although details about transcription of cyclins, the regulatory subunits of these kinases, are available, a lack of understanding exists about network motifs responsible for the precise timing of cyclin/Cdk oscillations. Here we investigate the robustness of molecular designs interlocking the transcriptional and cyclin/Cdk oscillators in budding yeast. We have recently identified a transcriptional cascade that regulates the relative timing of waves of mitotic (Clb) cyclin expression, which involves the Forkhead (Fkh) transcription factors (TF) [1]. Here we aim to unravel the network motif(s) responsible for timely cyclin/Cdk oscillations that interlock Clb waves through Fkh-mediated signaling.

Methods and Algorithms: An integrated computational and experimental framework is presented. A kinetic, ODE model of the cyclin/Cdk network is simulated under a quasi-steady state assumption, and fitted to *in vivo* quantitative, time course data of Clb dynamics. Robustness analyses are then performed by testing 1024 possible network motifs for their ability (i) to fit Clb oscillations and (ii) to generate sustained oscillations in the form of limit cycles, on which sensitivity analysis is conducted.

Results: A novel regulatory motif, coined as *Multiplex Phase Interlocker*, is unraveled, that timely synchronize Clb oscillations. This motif uniquely describes a molecular timer (TF) that relies on separate inputs (Clb/Cdk) converging on a common target (TF itself). Within the motif, a progressive TF activation may be realized by multiple Clb/Cdk. Experimental validation supports computational analyses, with the Clb/Cdk-Fkh axis being pivotal for timely transcriptional dynamics.

Conclusion: Altogether, our integrative approach pinpoints how robustness of cell cycle control is realized by revealing a novel and conserved principle of design that ensures a timely interlock of transcriptional and cyclin/Cdk oscillations.

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References

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