Conservation of Dynamic Modularity in Biological Network Modeling: Modular Boolean Model of Cell Cycle Regulation in *Saccharomyces cerevisiae*

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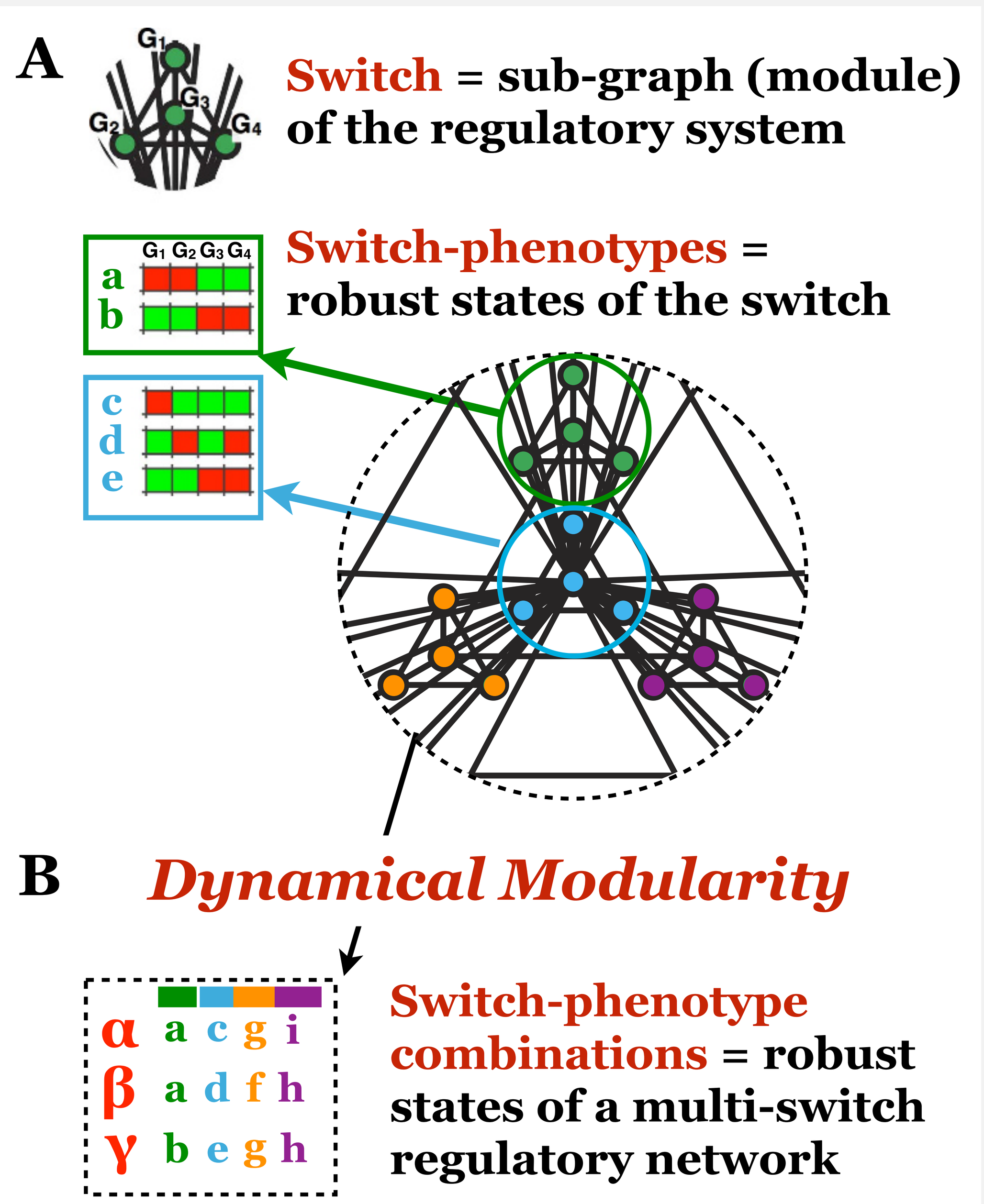
Abstract

Dynamic Modularity is a proposed characteristic of biologically defined Boolean Regulatory Networks. The principle states that when modular networks regulating individual cell behaviors are connected according to biological interactions, the phenotypes of the newly formed network will be discrete combinations of each constituent switch's phenotypes. This hypothesized phenomenon has only yet been studied in the regulatory networks of mammalian cell cycle and apoptosis.

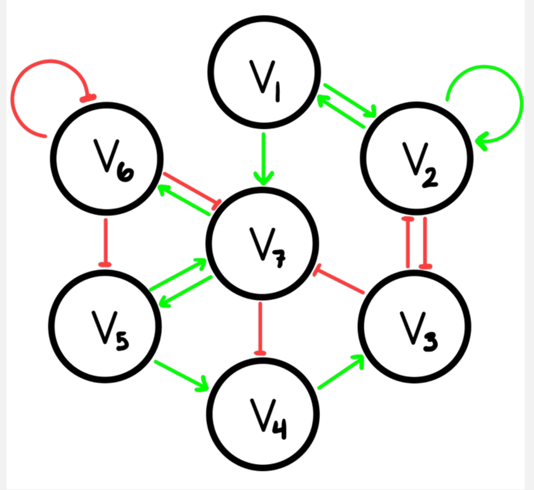
Here we introduce a Boolean regulatory network for cell cycle control in *S. cerevisiae* consisting of two modular networks. The two constituent switches represent the Restriction/START and Spindle Assembly Checkpoints of the cell cycle. This model is shown to reliably replicate the dynamics of the Restriction/START and Spindle Assembly Checkpoints in the cell cycle of *S. cerevisiae*. Notably, the model does not replicate the dynamics of the DNA damage checkpoint biologically observed in phase G2 of the cell cycle. Each constituent switch displays bistable dynamics consistent with their biological regulatory role. The modular nature of this model makes it a promising target for evaluating the presence of Dynamic Modularity in a novel model organism.

Dynamic Modularity

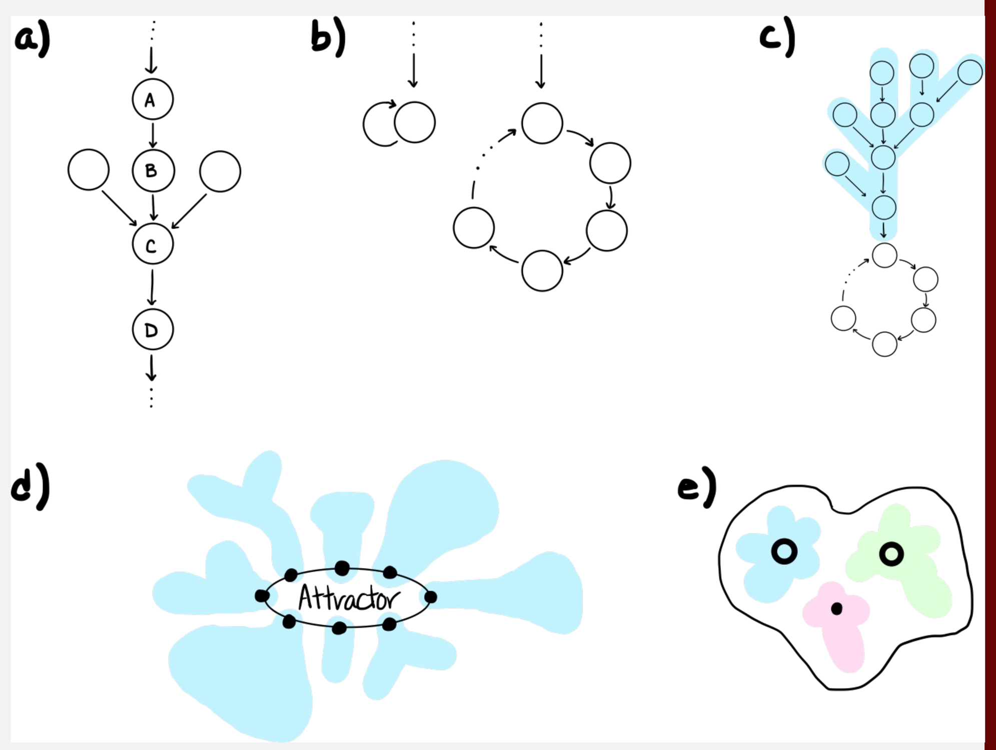
- Distinct Boolean Networks may be linked to form global networks with unique dynamics. In this case each subnetwork is a multistable switch. Dynamic Modularity is a proposed property of biologically defined modular Boolean networks with three principles.
- **Modular Dynamics**: The phenotypes of the global network are constructed of discrete combinations of the constituent switch phenotypes.
- **Phenotypic Conservation**: Every phenotype of a discrete network switch appears at least once in an attractor of the global system.
- **Robust Coordination**: Phenotypes of biological networks are as unique as possible.



Boolean Network Modelling

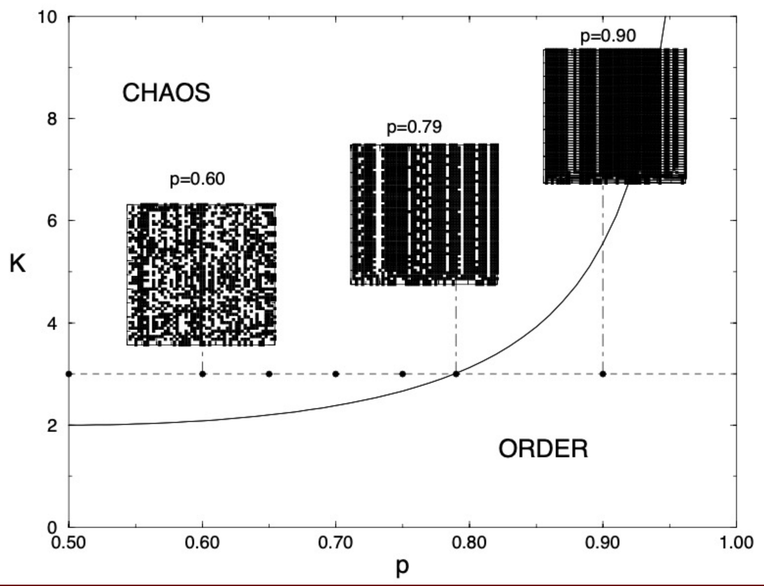


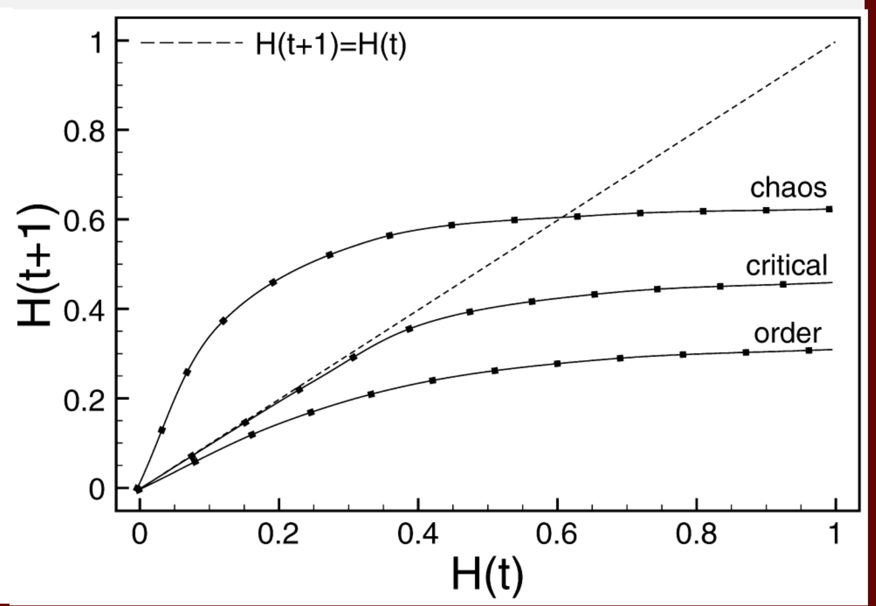
- Boolean Networks are directed multigraphs which transition through states represented by binary strings.



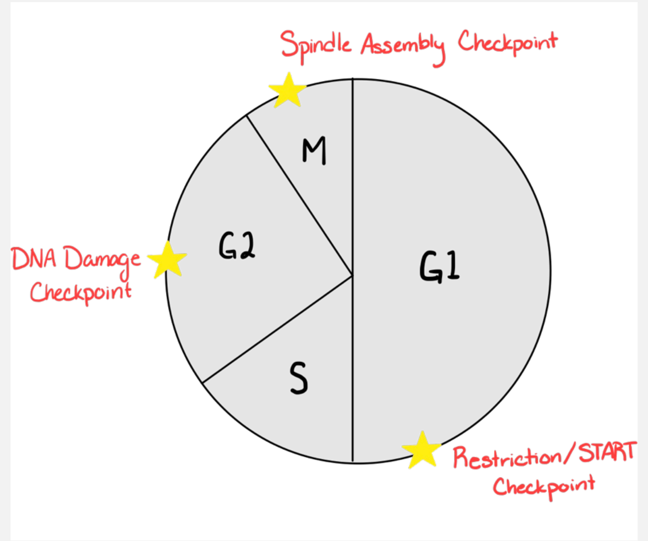
- These transitions are dictated by the regulatory logic and wiring scheme of the network.
- The trajectories of state transitions lead to attractors, creating transition graphs which provide insight into the network's dynamics.

Order, Chaos, and Criticality[1,2]





Modular Boolean Network of *S. cerevisiae* Cell Cycle Dynamics



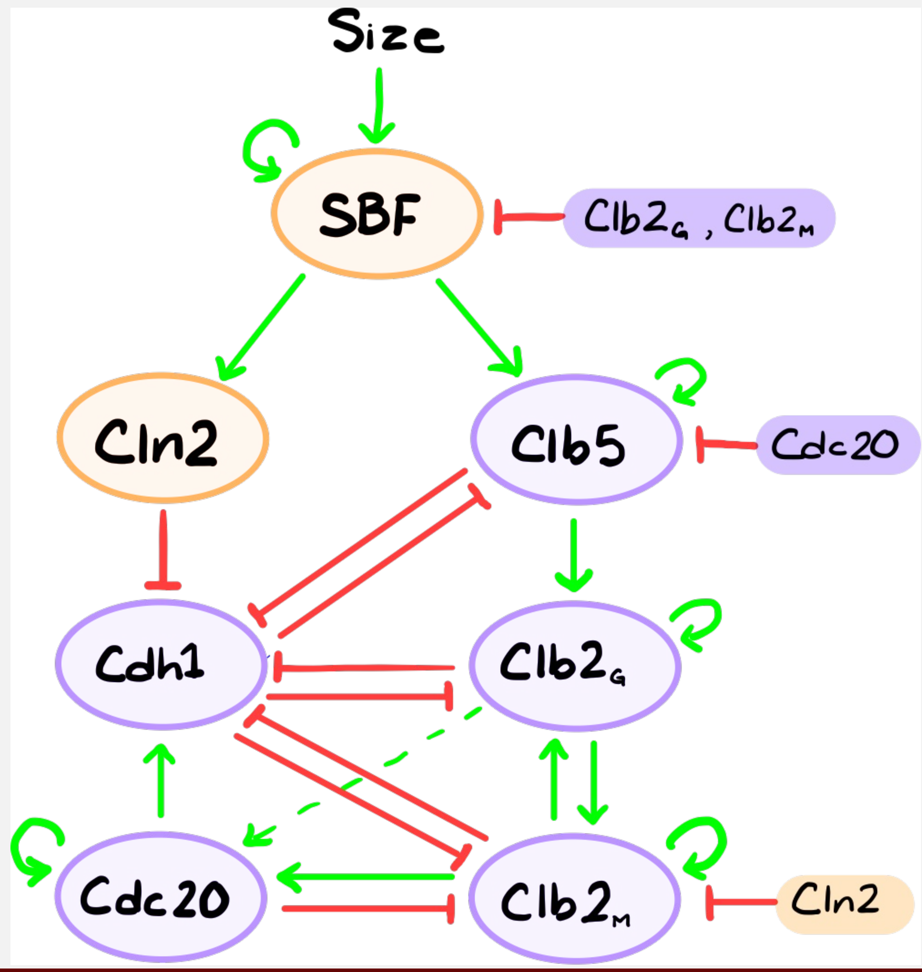
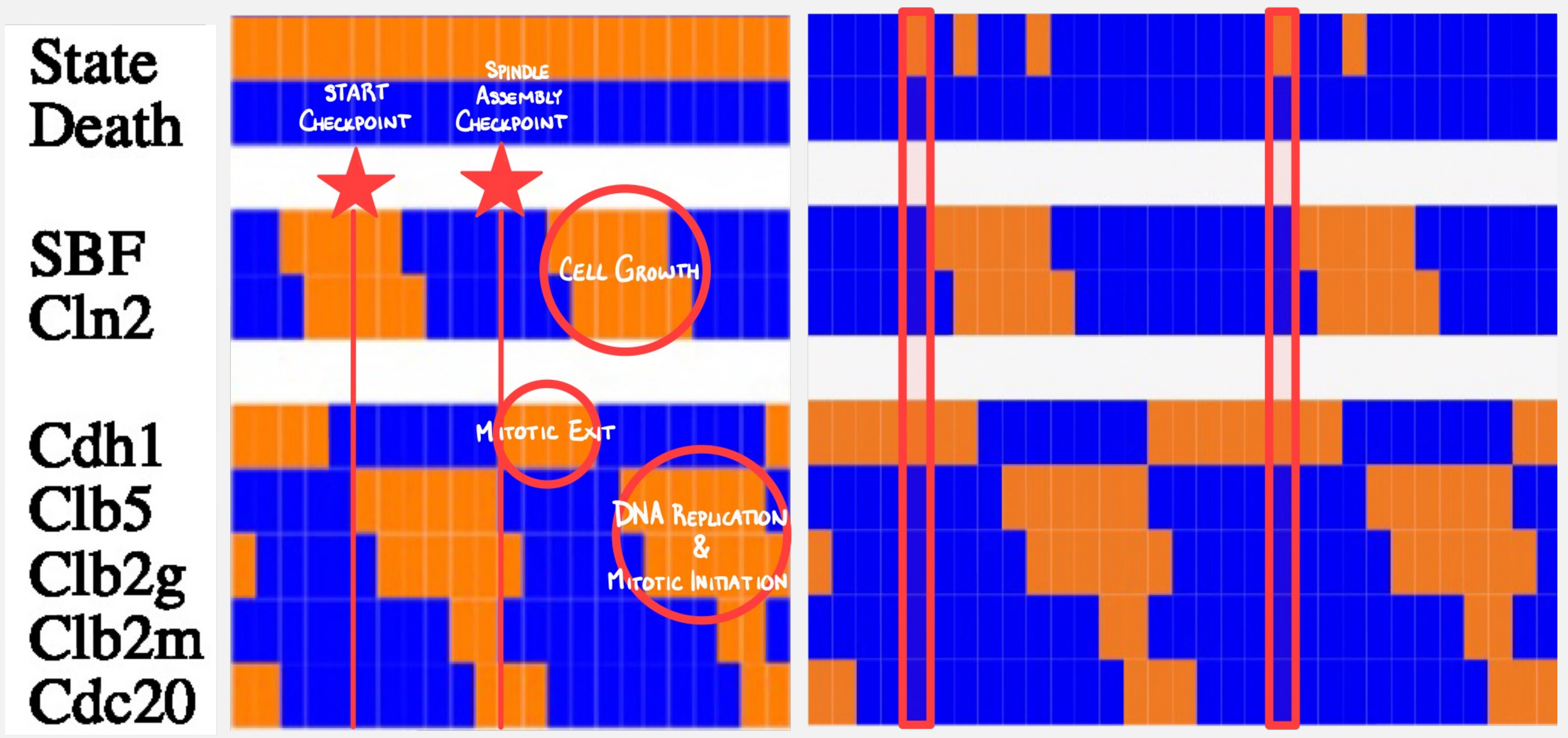


Diagram of the Eukaryotic Cell Cycle (Above)

Wiring Scheme of Modular 2-Switch Network (Right)

Phase and Restriction Switch Dynamics are Robustly Replicated

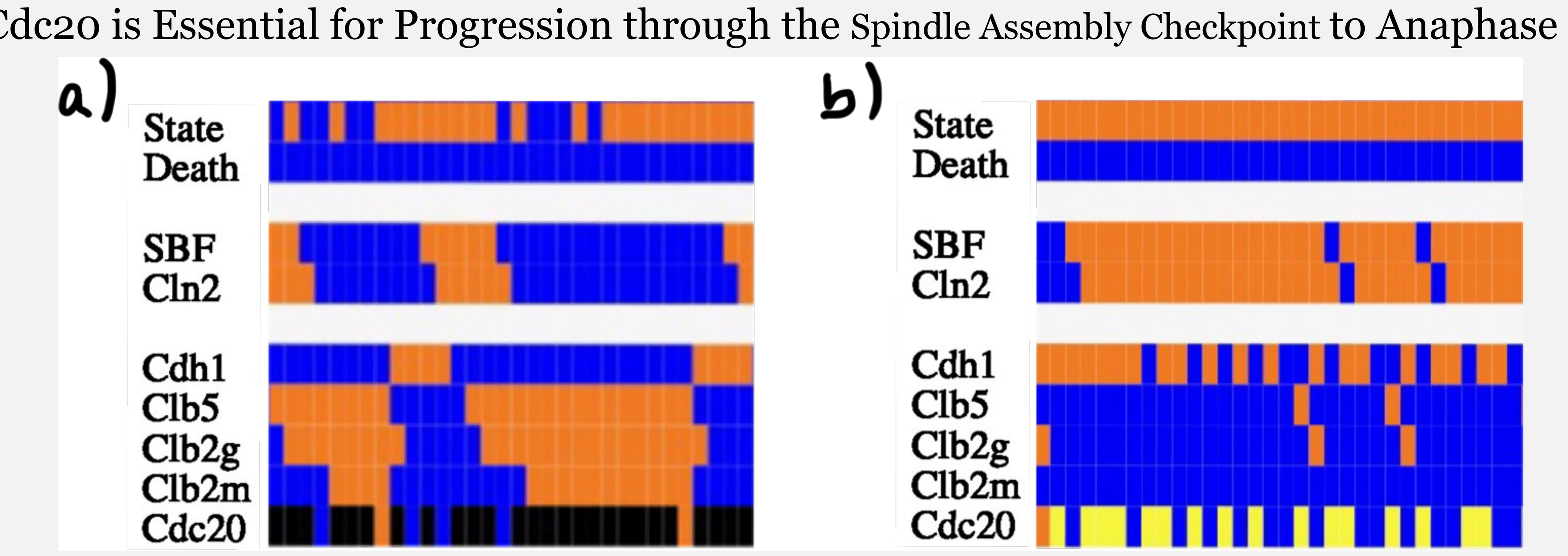
Regulatory Factor	Biological Role
SBF	Protein complex responsible for activating transcription during the G1 to S transition.
Cln2	G1 cyclin responsible for promoting Restriction/START checkpoint passage. Expression is dependent on SBF.
Clb5	B-type cyclin involved in DNA replication during S phase. Promotes DNA synthesis initiation. Aids formation of mitotic spindles. Most active during late G1 phase.
Clb2g Clb2m	Clb2 is a B-type cyclin involved in response to DNA damage. Promotes transition from G2 to M. In this model Clb2g and Clb2m are separate nodes to replicate the longer time scale in which Clb2 is active, with Clb2g being the initial phase of activity in G2 and Clb2m the secondary phase of activity during mitosis.
Cdh1	Activates anaphase-promoting complex/cyclosome (APC/C). Drives progression through spindle assembly checkpoint by directing ubiquitination of cyclins like Cdc20 causing mitotic exit.



Wild Type Dynamics of the Modular 2-Switch Network. (Orange=ON, Blue=OFF)

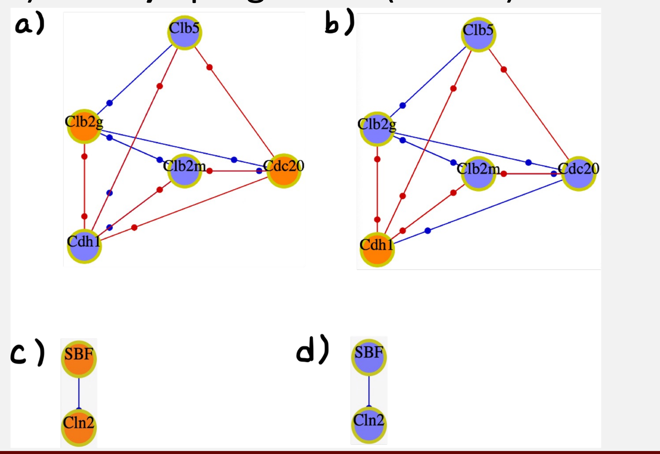
Model Characterization

Cdc20 is Essential for Progression through the Spindle Assembly Checkpoint to Anaphase



Network Dynamics with **A)** downregulated (Black) and **B)** upregulated (Yellow) Cdc20.

Modular Switch Networks Display Checkpoint Dynamics
Each Switch displays two point-attractors as expected for checkpoint regulatory dynamics.



References

1. Mendenhall, M. D.; Hodge, A. E. Regulation of Cdc28 Cyclin-Dependent Protein Kinase Activity during the Cell Cycle of the Yeast Saccharomyces Cerevisiae. Microbiol. Mol. Biol. Rev. 1998, 62 (4), 1191–1243. https://doi.org/10.1128/MMBR.62.4.1191-1243.1998.
2. Jungck, J. R.; Viswanathan, R. Chapter 1 - Graph Theory for Systems Biology: Interval Graphs, Motifs, and Pattern Recognition. In Algebraic and Discrete Mathematical Methods for Modern Biology; Robeva, R. S., Ed.; Academic Press: Boston, 2015; pp 1–27. https://doi.org/10.1016/B978-0-12-801213-0.00001-0.