Multiple Feedback loops control asymmetry establishment in the septation initiation network of Fission Yeast Cells

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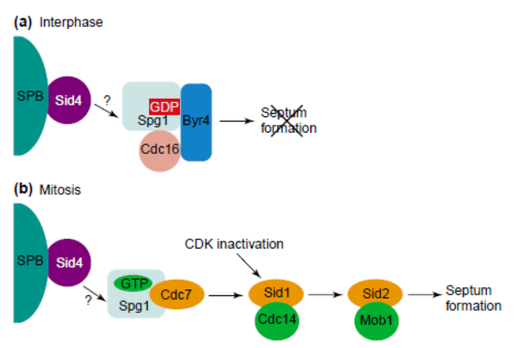
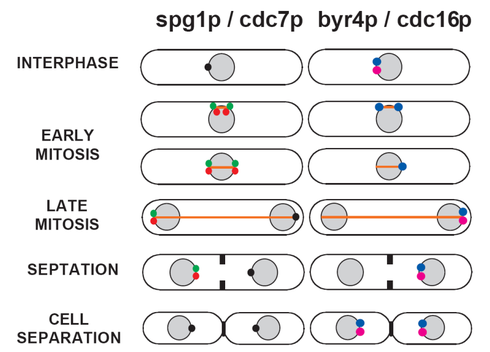
ABSTRACT

The fission yeast, *Schizosaccharomyces pombe* is one of the most extensively studied model organisms in the cell division research field. In this organism the cell division process is regulated by the septation initiation network (SIN). The asymmetric activation of SIN components at the two spindle pole bodies of the cell is required for the appropriate regulation of SIN signaling and cell division. Here we investigate by mathematical modeling how multiple feedback loops control the establishment of asymmetric SIN activation. The predictions of the model are under experimental tests.

INTRODUCTION

Cell division is the most conserved and fundamental process in all eukaryotes. The fission yeast *Schizosaccharomyces pombe* has already proved to be a very simple yet interesting model system to study and analyze the regulation of cell cycle or cell division. In fission yeast, the process of cell division is well regulated by a conserved signaling pathway known as septation initiation network (SIN). SIN is a GTPase mediated signaling network of conserved protein kinase that triggers contraction of the actomyosin ring, what induces cell division and septum formation. The proper segregation of chromosomes into two daughter nuclei (mitosis) and the onset of cell division must be tightly connected to avoid loss of DNA after cell division. Before mitosis, the negative regulator of SIN, the GTPase activating protein (GAP) complex Byr4/Cdc16 is present on both of the spindle pole bodies (SPBs) and facilitate the hydrolysis of Spg1-GTP, which keeps Spg1 inactivate. At the onset of mitosis, the uppermost component of SIN (Cdc7) which positively regulates SIN is present on both of the SPBs symmetrically and the GAP complex Byr4/Cdc16 is absent. As the cells enter into anaphase and chromosomes separate, Cdc7 starts disappearing from one of the SPBs (the 'old' SPB) and it starts increasing on the other SPB that has active Spg1-GTP ('new' SPB). Such asymmetric activation and inactivation of Cdc7 and Byr4/Cdc16 complex is essential for proper completion of SIN. How this asymmetry is established and what are the key biological interactions needed to attain this asymmetry is still an open question. SIN asymmetry.





McCollum & Gould. 2001

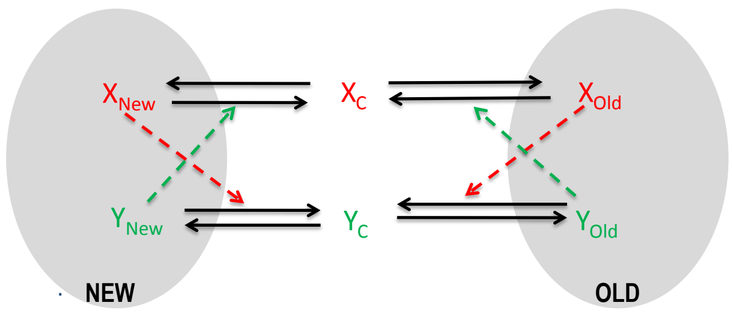
Cerutti et al. 1999

In the present study, with the help of mathematical modeling, we have elucidated the mechanism of asymmetry establishment and revealed the crucial molecular interactions that are needed to establish

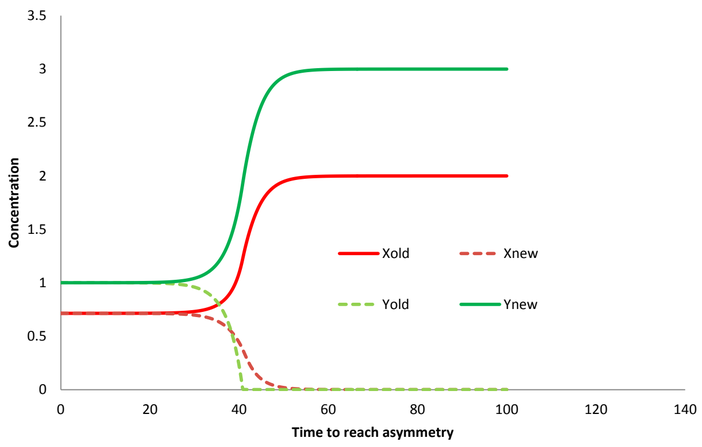
RESULTS

MODEL 1

Hypothetical model to show simple cross antagonism is able to induce asymmetry.

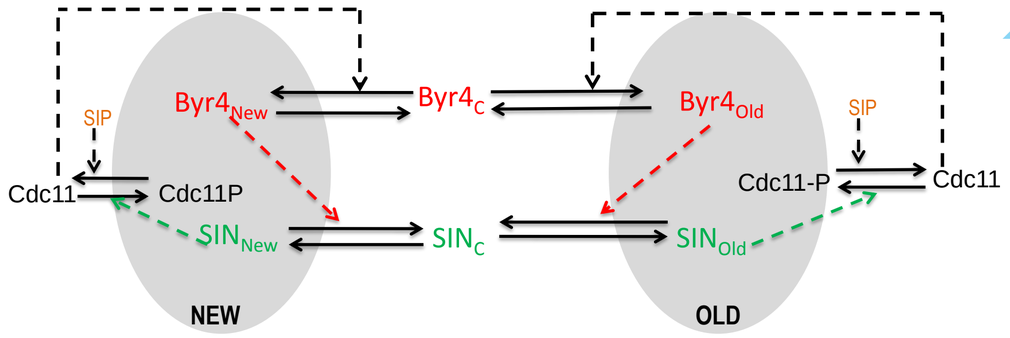


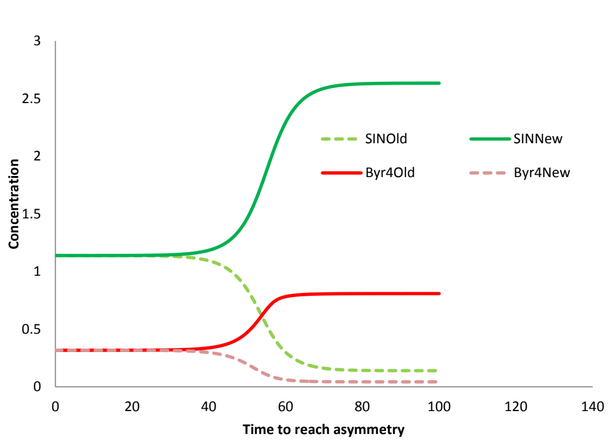
Solid arrows-Transition
Dashed arrows-activation



MODEL 2

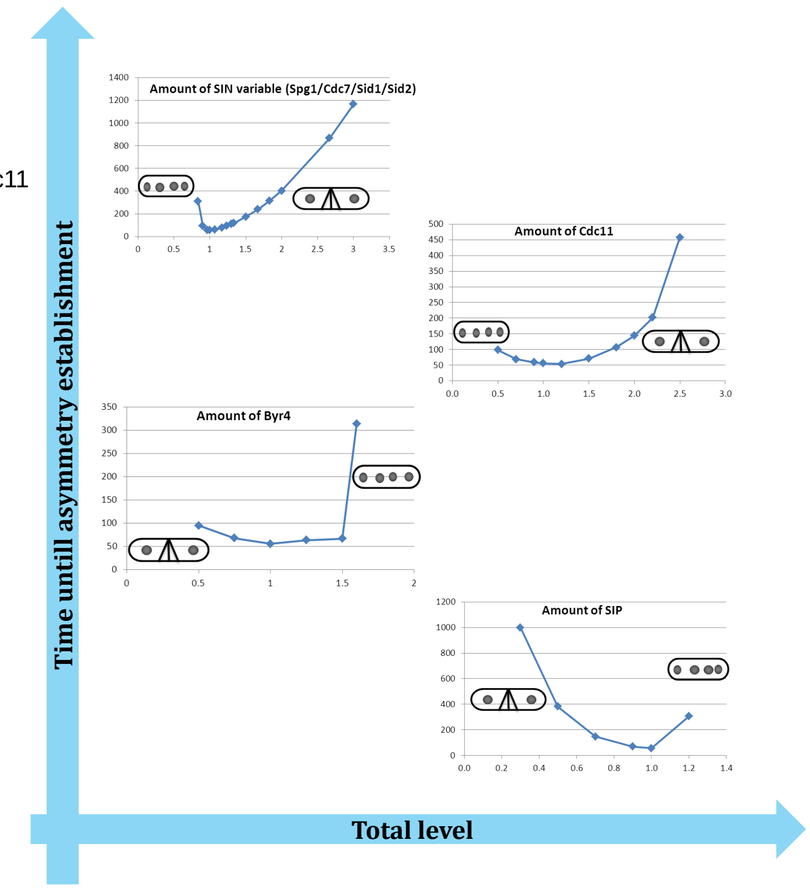
Biological interactions that are responsible to attain asymmetry?





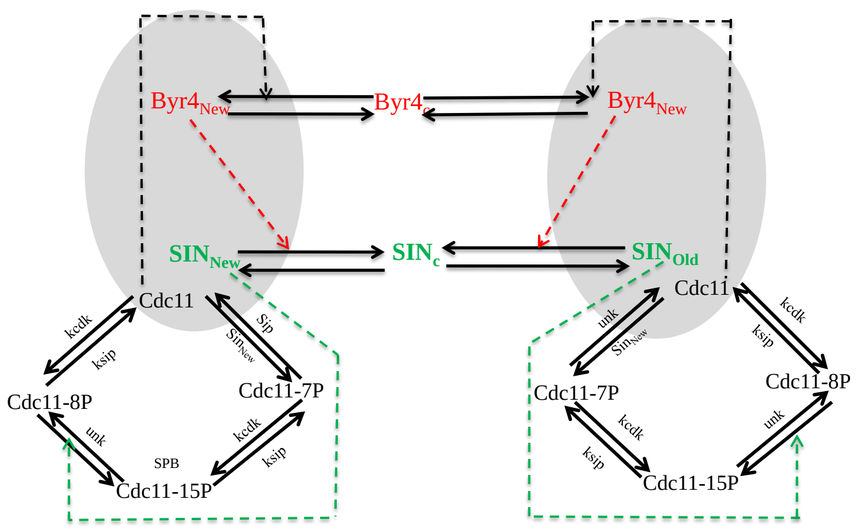
MUTANTS ANALYSIS

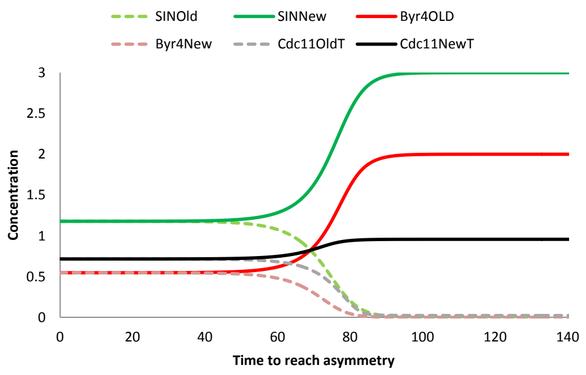
Analysis of the dependence of asymmetry timing on parameters



MODEL 3

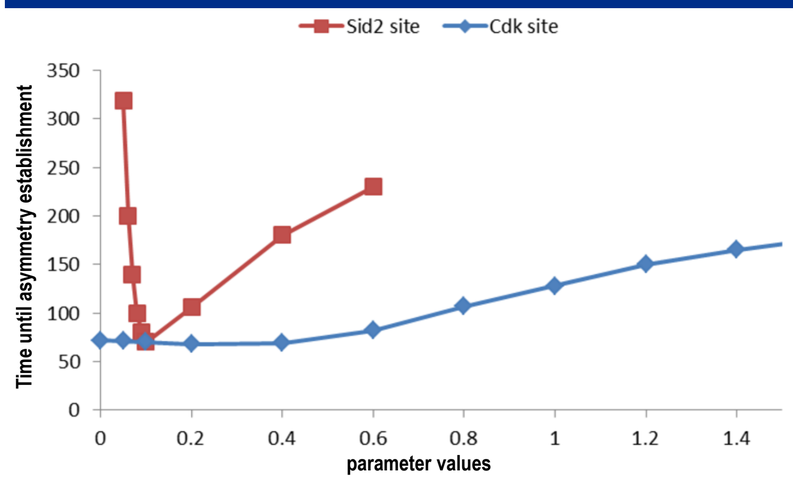
The four forms of cdc11





Time courses of a simulation of the above proposed model. At time 0 the Byr4 at the old SPB got a little advance (0.01%) in autophosphorylation rate. This small bias induced the feedback loops to collect all Byr4 to the old SPB and all SIN to the new SPB – also affecting the phosphorylation states of Cdc11 by the cell cycle regulatory Cdk at the two SPBs.

PREDICTIONS



Increase or decrease in the efficiency of the SIN component Sid2 in phosphorylating Cdc11 both have delaying effects (from the basal rate of 0.1), while perturbation of the Cdk phosphorylation sites have minimal effects on asymmetry establishment timing.

SUMMARY

Our result revealed that for asymmetry establishment, the minimum requirement is to have antagonistic relationship (inhibiting each other) between the negative regulators (Byr4/Cdc16) and positive regulators of SIN (Spg1, Cdc7/Sid1/Sid2). We established what molecular interactions might be responsible for such antagonism. We proposed that Cdc11 exists is four forms, hypo phosphorylated, phosphorylated by Cdk, by SIN and phosphorylated by Cdk and SIN components both. SIP helps in dephosphorylation of Cdc11 which further promote the recruitment of Byr4/Cdc16 to the old SPB, explaining the important role of SIP in asymmetry establishment. The model is under experimental test in the collaborating laboratories.

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