# A Dynamical Model of Mitotic Exit in Budding Yeast

Baris Hancioglu[1], Kathy Chen[2], and John J. Tyson[3]

***Short Abstract* — We have developed a nonlinear ordinary differential equations model for the control of Cdc14, an essential phosphatase promoting mitotic exit in yeast. The model captures the dynamics of mitotic exit in wild-type and dozens of mutant cells clarifying the roles of Esp1 and Cdc5 (Polo kinase) in mitotic exit pathways. Understanding how Polo-like kinase fits into the exit pathway is important because it is being actively pursued as a therapeutic target in the treatment of human cancer.**

***Keywords* — Cell Cycle, Exit from Mitosis, Polo kinase (Cdc5), Cdc14, Separase (Esp1), Mitotic Exit Network (MEN).**

## I. BACKGROUND

THE Cell cycle events in eukaryotes are regulated by periodic activation and inactivation of a family of cyclin–dependent kinases (Cdks). Entry into mitosis is initiated by accumulation of Cdk in complexes with B-type cyclins, and exit from mitosis requires inactivation of these Cdk-cyclin complexes and dephosphorylation of Cdk targets. The Cdks are inactivated by Cdc20- and Cdh1-dependent proteolysis, and dephosphorylation is carried out by Cdc14 [1], an essential phosphatase promoting mitotic exit. Understanding how Cdc14 is regulated is crucial to model and explore the dynamics of mitotic exit. How Cdc5 promotes exit from mitosis in mitotic pathways is not clear.

## II. RESULTS

Our model provides a rigorous account of the factors affecting the dual exit pathways, called Cdc14 early anaphase release (FEAR) and mitotic exit network (MEN). The model captures the dynamics of mitotic exit in wild-type and mutant yeast cells, including many details of the physiology, biochemistry and genetics of the process. Our model is inspired by the recent model of Queralt *et al. [2]* , and we have added new components to account for new observations on FEAR and MEN networks reflecting the latest knowledge of biology: (i) Cdc5 phosphorylates Net1 (an inhibitor of Cdc14) directly promoting Cdc14 release in [3] any cell cycle stage [3] [4]. Cdc5 is not only part of MEN, but also part of FEAR, and can induce Cdc14 release even when other FEAR and MEN components are silent (ii) Net1 has multiple phosphorylation sites. The model incorporates multi-phosphorylation of Net1 by protein kinases; Cdk, Cdc5, and the Dbf2/Mob1 kinase in the MEN pathway[5] [6] (iii) Cdc15 acts downstream of Tem1 in MEN network. Even Tem1 is inactive, overexpressed CDC15 can still make MEN active and sustain Cdc14 release. (iv) Net1 phosphorylation at Cdk consensus sites is an important part of FEAR, however it is not an essential requirement for mitotic exit events [7].

## III. CONCLUSION

We propose a novel mechanism for multiphosphorylation of Net1 by several kinases: Cdk, Cdc5 (Polo) and Dbf2/Mob1 (through activation of Cdc15). The model explains factors affecting the activation and inactivation of FEAR and MEN pathways in a rigorous way. Model clarifies and gives more insight into the mitotic exit functions of Polo kinase Cdc5 and regulation of Cdc14.

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[1]Department of Biological Sciences, Virginia Tech, Blacksburg, VA., 24061, USA. E-mail: hbaris@vt.edu

[2]Department of Biological Sciences, Virginia Tech, Blacksburg, VA., 24061, USA. E-mail: kchen@vt.edu

[3]Department of Biological Sciences, Virginia Tech, Blacksburg, VA., 24061, USA. E-mail: tyson@vt.edu