Testing Predictions of a New Model for the Budding Yeast START Transition Using Novel Cell Cycle Mutants

Neil R. Adames[1], Kathy C. Chen[2], P. Logan Schuck[1], John J. Tyson[1,2], Jean Peccoud[1,3]

The cell cycle is the process by which a growing cell replicates its genome and partitions the two copies of each chromosome to two daughter cells. Many of the molecular details of the budding yeast G_1-S transition (START) have recently been elucidated, leading us to expand a previous yeast cell cycle model [1] to include this new information. We tested the accuracy of the new model by performing simulations of various mutants not described in the literature, generating these new mutants, and comparing simulated to observed phenotypes. This approach allowed us to modify the new model to fit nearly all experimental data.

***Keywords* — Cell Cycle, Deterministic Model, Cell Size, Mutant Phenotype, *Saccharomyces cerevisiae*.**

I. Introduction

The eukaryotic cell division cycle is regulated by cyclin-dependent protein kinases (CDKs) that phosphorylate many cellular proteins controlling DNA replication, chromosome segregation, and cell division. In the budding yeast, *Saccharomyces cerevisiae*, the sole CDK is Cdc28. Cdc28 activity and substrate specificity is governed by its obligatory binding partners, cyclins Cln1-3 and Clb1-6 [2]. The transitions between each stage of the cell cycle – G1, S, G2 and M – are controlled by bistable and irreversible biochemical switches involving positive feedback mechanisms [3]. In the case of G1-S transition, the mass of the cell must reach a critical threshold to ensure cell size homeostasis [4].

The molecular mechanisms involved in the G1-S transition – also known as START in yeast – have been well-characterized. In early G1, the only available cyclin is Cln3 and its synthesis is proportional to cell mass [5]. Moreover, *CLN3* mRNA and protein are sequestered at the endoplasmic reticulum (ER) by Whi3 and released into the nucleus to activate two transcription factors, SBF and MBF [6]. Activation of SBF occurs by phosphorylation of Whi5 - a stoichiometric repressor of SBF - by Cln3-Cdc28 [7]. SBF and MBF induce transcription of the partially redundant cyclin pairs, Cln1/Cln2 and Clb5/Clb6, respectively. Cln1/2-Cdc28 induces budding, transcription of S-phase genes and inactivates a stoichiometric inhibitor of Clb5/Clb6-Cdc28 called Sic1 [8]. Clb5/6-Cdc28 then activates numerous DNA replication proteins and the transcription of genes involved in replication.

The switch behavior of G1-S occurs because of the positive feedback from Cln1/2-Cdc28 to fully inhibit Whi5 and activate Swi6 [9].

II. Results and Conclusions

We have formulated a budding yeast START model incorporating most of the new experimental data since Chen et al. (2004). The START model recapitulates the phenotypes of 214/228 yeast cell cycle mutants (among them, 137/145 START mutants and 77/83 FINISH – M-G1 - mutants) described in the literature.

We generated and determined the viability and cell size phenotypes of 15 new cell cycle mutants not described in the literature, and compared the observed phenotypes to the phenotypes predicted by the START model.

The START model correctly predicted the cell size phenotypes of 10 new mutants. The new model also correctly predicted the viability of 2 mutants that were previously described as inviable. For 4 new mutants, the differences in the predicted versus observed cell sizes could be resolved by adjusting model parameters. Changes in model assumptions and architecture were required for the model to correctly predict the viability of other mutants. The current budding yeast START model now simulates the phenotypes of 149/153 START mutants and 80/84 FINISH mutants.

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[1]Virginia Bioinformatics Institute, Virginia Tech, Blacksburg VA 24061
[2]Department of Biological Sciences, Virginia Tech, Blacksburg VA 24061
[3]ICTAS Center for Systems Biology of Engineered Tissues, Virginia Tech, Blacksburg, VA 24061

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