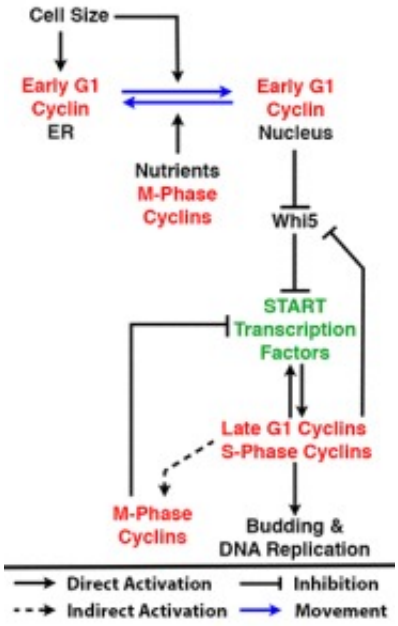
A better understanding of cell division by combining mathematical modeling and experimentation

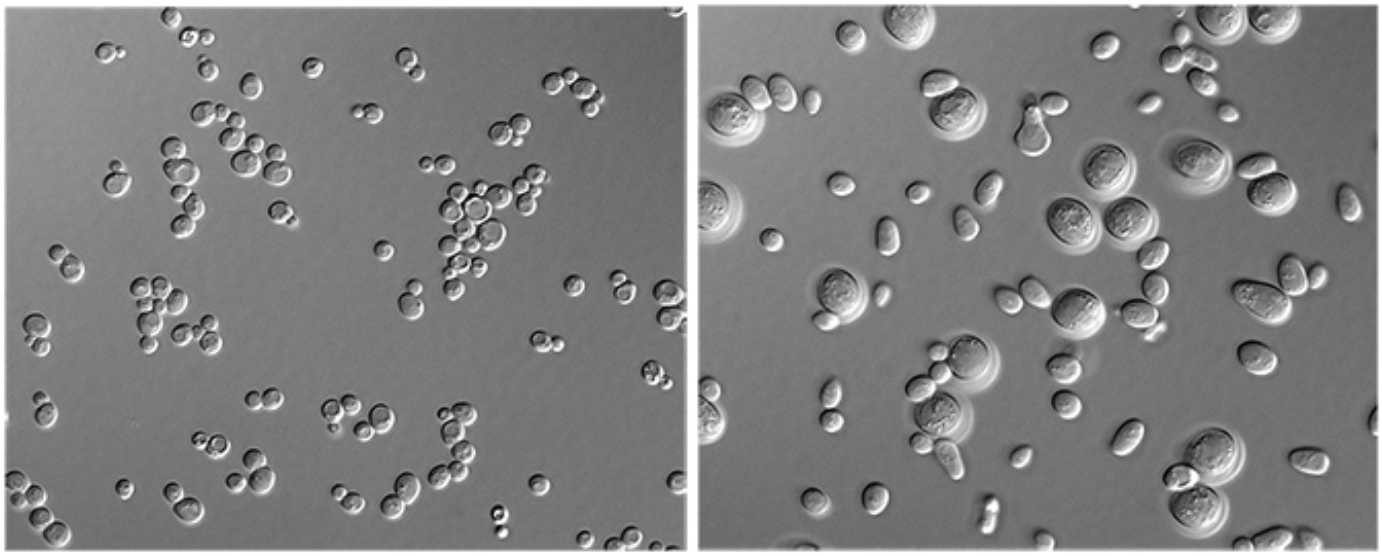
The cell division cycle is the process by which a growing cell replicates its genome and partitions the two copies of each chromosome to two daughter cells at division. It is of utmost importance to the perpetuation of life that these processes of cell growth, chromosome replication (DNA synthesis or S phase) and chromosome partitioning (mitosis or M phase) be carried out with great fidelity. Mistakes in cell growth and division cause serious health problems, especially cancer.



All eukaryotes (cells with nuclei) employ the same fundamental molecular machinery that governs progression through the cell division cycle. However, even in relatively simple unicellular eukaryotes like yeast, the cell division control system is so complex that mathematical and computational methods are needed to reliably track the interactions of dozens of genes, mRNAs, proteins, and multiprotein complexes.

In an article published in the journal Molecular Biology of the Cell, a group of researchers at Virginia Tech combined mathematical modeling with experimental validation of the model's predictions to gain insights into cell division control, especially focusing on how cells monitor their own size. Healthy cells regulate their sizes to efficiently take in nutrients and generate sufficient biomass to support the energy-intensive cell division program. In budding yeast, the decision point to enter the cell cycle is a cell size checkpoint called Start, and is equivalent to the restriction point in mammalian cells.

The key regulators of the cell cycle are proteins called cyclins, which are synthesized and destroyed at different stages of the cell cycle. Activation of Start depends on the cell mass-dependent build-up of an early G1 cyclin in the cell nucleus, activating the synthesis of late G1 and S-phase cyclins. G1 and S-phase cyclins further activate their own synthesis in a positive feedback loop that generates a switch-like entry into S-phase (Fig. 1). Mutations that delay flipping of the Start switch allow cells to grow larger than normal before they divide (Fig. 2), and mutations that cause premature Start result in small cells. Some mutations can prevent the Start switch from flipping at all, resulting in inviable cells.



Wild-Type Yeast

Mutant Yeast That Delay START

The Start model described by Adames, et al. captures the cell size and viability phenotypes of over 200 known yeast cell cycle mutants. To validate this model, simulations of new cell cycle mutants were performed and their phenotypes predicted. The group then constructed dozens of cell cycle mutants, including 15 new mutants, and determined their viability and cell sizes to compare to the model predictions.

When experimental tests confirmed the model, the authors were confident that the model accurately represents something about the underlying molecular mechanism. When experimental tests conflicted with the model's predictions, the authors corrected defects in their understanding of the molecular mechanisms. In some cases, the correction was simply a matter of reevaluating model parameter values. In other cases, the authors' assumptions about the reaction mechanism were faulty. Thirdly, some of the published experimental results were misinterpreted, which the authors addressed by looking more closely at the data that conflicts with the model. Consequently, experimental testing of model predictions allowed the authors to fill in gaps in the existing data and to refine the parameter values and assumptions of the model, demonstrating the advantages of the design-simulate-test-redesign cycle adopted by synthetic and systems biologists.

Publication

Experimental testing of a new integrated model of the budding yeast Start transition.
Adames NR, Schuck PL, Chen KC, Murali TM, Tyson JJ, Peccoud J
Mol Biol Cell. 2015 Nov 5