Simulation outline for the publication

"Cell size regulation in budding yeast does not depend on linear accumulation of Whi5"

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Outline

"*growth_simulations.py*" contains the library of functions for import into any given script. Simulations were implemented using a discretized time format, with normally distributed noise in cell cycle variables included where noted in the main text. To mimic experimental conditions, we seeded populations with 400 cells with normally distributed parameter sets and exponentially distributed cell ages using the "*starting_popn"* function in the "*growth_simulations.py"* script. We simulated growth and proliferation of these populations until they reached a critical carrying capacity using the "*discr_time_dilution*" function in the "*growth_simulations.py"* script. Once the population reached this carrying capacity of 10000 cells, each new cell birth event led to the random selection of a cell to be removed from the population, keeping the total population size constant while allowing us to simulate growth of the population over many cell cycles.

Each cell cycle is stored as a "Cell" object instance, allowing flexible definition of new cell characteristics. Different cell growth models were implemented using the input parameter "modeltype", with modeltypes 15 and 16 corresponding to the noisy rate model with a constant Whi5 production rate per cell cycle, and a synthesis rate proportional to cell volume respectively.

Model description

The simulations in Figure S1 from the paper were performed using a model in which cells pass through Start stochastically at a rate that depends inversely on the Whi5 concentration, i.e.

$$\mu([W]) = \frac{k}{[W]^n},$$

where *k* is a rate constant, *[W]* is the concentration of Whi5, and *n* is an exponent (taken for the simulations in Figure S1 to be *n=2*). Here μ represents the rate of passage through Start per unit time for a cell with a given concentration of Whi5, with division occurring after a constant time interval post-Start. For simplicity we took the division asymmetry between mother and daughter cells to be constant, with a constant ratio *r* between daughter cell volume and mother cell volume at division. This model was constructed to represent one realization of the general stochastic rate model described in (1). We tested a model with this rate of passage through Start for two different synthesis profiles of Whi5. The first is described further in (2) and corresponds to one in which a constant amount Δ of Whi5 is produced between Start and division, which is then diluted during the subsequent G1 phase. This represents the "WT" case

in Figure S1 due to its consistency with previous studies of the production rate of Whi5 (1). We note that this first model is capable of generating size control, with the average cell size, standard deviation in cell size and CV remaining robustly regulated throughout our simulations (see Figure S1).

The second model for Whi5 synthesis is one in which Whi5 is produced at a rate proportional to volume:

$$\frac{dW}{dt} = k_w V(t)$$

Where k_w is the production rate of Whi5 for a given cell volume *V*, and W is the abundance of Whi5. This leads to a steady state concentration of Whi5 $[W]^* = \frac{k_w}{\lambda}$, where λ is the exponential volume growth rate. Within the second model, the attainment of a steady state Whi5 concentration leads cells to proceed through Start with a constant rate $\mu = \frac{k\lambda^n}{k_w^n}$, independent of their cell volume. Passage times through Start will then follow an exponential distribution with rate parameter μ. The average relative growth acquired during the G1 phase is then $E\left(\frac{V_s}{V_b}\right) = E\left(e^{\lambda t}\right) = \frac{\mu}{\mu-\lambda}$. We therefore simulated cell growth, varying the synthesis rate k_w to test different regimes of this model. We tested three cases: high $k_w = 3.0$ to generate excess growth in G1 with a high concentration of Whi5, small $k_w = 0.1$ to generate only small amounts of growth in G1, with a low concentration of Whi5, and an intermediate synthesis rate $k_w = 0.7$. This third case was selected to generate an average cell size which matched that of "WT" cells simulated with a volume independent production of Whi5 each cell cycle (see Figure S1). For concreteness, we performed our simulations for the case *n=2, λ=1, k=2, r=0.5*, but our conclusions about the inability of the second model to produce size control do not rely on a specific choice of these parameters. Over the range of parameters we tested, this second model is incapable of generating size control, with the average cell size and standard deviation in cell size either arbitrarily increasing or decreasing depending on the rate of Whi5 production. In either case, this second model gives rise to an unconstrained increase in the CV over successive generations (Figure S1). This result is to be expected, since any model in which the rate of passage through Start μ is determined by the Whi5 concentration will display a constant rate μ if the Whi5 concentration reaches a steady state value. A constant rate of passage through Start will not provide feedback towards a mean cell size, and errors in interdivision times are therefore expected to accumulate over successive cell cycles, similar to the geometric random walk predicted for symmetrically dividing cells (3).

Our simulations were performed using a discretized time approach, in which the probability for cells passing through Start in a given time interval *dt* was taken to be μdt. To simulate population growth for many generations we implemented a Moran process; for populations that exceeded a size of 10,000 cells, each cell division event was accompanied by the selection

and removal of a cell at random. The code for our simulations is available online at https://github.com/felixbarber/growth_rate_simulations.

References

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