

Supporting Information

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SI Materials and Methods

Two-Color Data Analysis. GFP and Venus have a significantly overlapped spectrum, and for two-color experiments, we eliminated the cross-talk by using the following linear equation:

$$\begin{cases} S_g = [\text{GFP}] + a[\text{Venus}] \\ S_y = b[\text{GFP}] + [\text{Venus}] \end{cases} \Rightarrow \begin{cases} [\text{GFP}] = (S_g - aS_y)/(1 - ab) \\ [\text{Venus}] = (S_y - bS_g)/(1 - ab) \end{cases},$$

where S_g and S_y are the signals we acquired in the GFP and YFP channels and $[\text{GFP}]$ and $[\text{Venus}]$ represent the GFP and Venus concentrations we are interested in. The cross-talk parameters a and b are obtained using strains containing only GFP or Venus. The two fluorescence proteins have a similar maturation rate and fluorescence intensity; thus, after cross-talk deduction, their signals can be directly compared.

Tests of Independence of GFP and YFP Expression. Observed data D . The observed data D is a 2×2 contingency table for two random binary variables X and Y that each can take on only the value 1 or 0 (Table S1), where n_{xy} is the number of times both $X = x$ and $Y = y$ for x and $y = 1$ or 0, $n_{1\bullet} = n_{11} + n_{10}$, $n_{0\bullet} = n_{01} + n_{00}$, $n_{\bullet 1} = n_{11} + n_{01}$, $n_{\bullet 0} = n_{10} + n_{00}$, and $n = n_{11} + n_{10} + n_{01} + n_{00}$.

Comments about Fisher's exact test. If X and Y are independent, the following would be true. The joint probability mass function $P(X = x, Y = y)$ could be expressed in terms of the probability mass functions $P(X = x)$ and $P(Y = y)$ as follows:

$$P(X = x, Y = y) = P(X = x)P(Y = y),$$

where

$$P(X = x) = n_{x\bullet}/n$$

and

$$P(Y = y) = n_{\bullet y}/n.$$

The expected 2×2 contingency table would be given by:

$$n_{xy} = P(X = x, Y = y)n = P(X = x)P(Y = y)n.$$

Therefore, the expected values (Table S2) would be extremely similar to what is observed.

For every table with the same row and column sums $n_{1\bullet}$, $n_{0\bullet}$, $n_{\bullet 1}$, and $n_{\bullet 0}$ as those observed, Fisher's exact test computes the probability of seeing the table under the null hypothesis that X and Y are independent. The reported two-sided P value is the sum of probabilities over all tables that represent equal or greater deviation from independence than the observed table. Because the observed table is extremely close to what would be expected if X and Y are independent, the P value is virtually unity. This means that the observed table is very consistent with X and Y being independent but says nothing about how unlikely it is that X and Y are positively or negatively correlated. For example, it may be that independence and positive correlation would produce similar data, given the sample size. To distinguish between the possibilities, a Bayesian model comparison is required.

Bayesian model comparison. The computation described herein is a straightforward example of a Bayesian model comparison.

Models m_0 , m_+ , and m_- To Be Compared. By definition, $P(X = x, Y = y)$ can be expressed in terms of the conditional probability mass functions $P(Y = y|X = x)$ and $P(X = x)$:

$$P(X = x, Y = y) = P(Y = y|X = x)P(X = x).$$

Let:

$$\alpha = P(Y = 1|X = 1),$$

$$\beta = P(Y = 1|X = 0),$$

and

$$\gamma = P(X = 1).$$

Because the three sums $P(Y = 1|X = 1) + P(Y = 0|X = 1)$, $P(Y = 1|X = 0) + P(Y = 0|X = 0)$, and $P(X = 1) + P(X = 0)$ must all be unity, it follows that:

$$P(Y = 0|X = 1) = 1 - \alpha,$$

$$P(Y = 0|X = 0) = 1 - \beta,$$

and

$$P(X = 0) = 1 - \gamma.$$

Therefore, $P(X = x, Y = y)$ is completely specified by specifying α , β , and γ . The models to be compared are shown in Table S3.

Prior Probability Mass Function $P(m)$ and Density Function $\rho(\alpha, \beta, \gamma|m)$. For the model $m = m_0, m_+,$ or m_- , $P(m)$ will denote the prior probability mass for the model, and $\rho(\alpha, \beta, \gamma|m)$ will denote the prior probability density function for $\alpha, \beta,$ and γ , given the model. Before D , there is no reason to prefer any of the models $m_0, m_+,$ and m_- , and nothing is known about $\alpha, \beta,$ and γ , so the priors are uniform. It follows that:

$$P(m) = \frac{1}{3} \text{ for all values of } m = m_0, m_+, \text{ or } m_-.$$

Also:

$$\int_0^1 d\alpha \int_0^1 d\gamma \rho(\alpha, \beta, \gamma|m_0) = 1,$$

$$\rho(\alpha, \beta, \gamma|m_0) \int_0^1 d\alpha \int_0^1 d\gamma = 1,$$

so

$$\rho(\alpha, \beta, \gamma|m_0) = 1.$$

Also:

$$\int_0^1 d\alpha \int_0^\alpha d\beta \int_0^1 d\gamma \rho(\alpha, \beta, \gamma|m_+) = 1,$$

$$\rho(\alpha, \beta, \gamma|m_+) \int_0^1 d\alpha \int_0^\alpha d\beta \int_0^1 d\gamma = 1,$$

so

$$\rho(\alpha, \beta, \gamma|m_+) = 2.$$

Also:

$$\int_0^1 d\alpha \int_\alpha^1 d\beta \int_0^1 d\gamma \rho(\alpha, \beta, \gamma|m_-) = 1,$$

$$\rho(\alpha, \beta, \gamma|m_-) \int_0^1 d\alpha \int_\alpha^1 d\beta \int_0^1 d\gamma = 1,$$

so

$$\rho(\alpha, \beta, \gamma|m_-) = 2.$$

Likelihood Function $P(D|m)$. The conditional probability $P(D|\alpha, \beta, \gamma)$ can easily be expressed in terms of $P(X = x, Y = y)$:

$$P(D|\alpha, \beta, \gamma) = C(n, n_{11}, n_{10}, n_{01}) [P(X = 1, Y = 1)]^{n_{11}} \\ \times [P(X = 1, Y = 0)]^{n_{10}} [P(X = 0, Y = 1)]^{n_{01}} [P(X = 0, Y = 0)]^{n_{00}},$$

where the coefficient

$$C(n, n_{11}, n_{10}, n_{01}) = \binom{n}{n_{11}} \binom{n - n_{11}}{n_{10}} \binom{n - n_{11} - n_{10}}{n_{01}}$$

is a product of n -choose- k functions and is analogous to the binomial coefficient in that it is the number of permutations of a sequence of realizations of X and Y , such that $X = x$ and $Y = y$ is observed n_{xy} times for all x and $y = 0$ or 1 . The probability $P(D|\alpha, \beta, \gamma)$ can be expanded in terms of α, β , and γ :

$$P(D|\alpha, \beta, \gamma) = C(n, n_{11}, n_{10}, n_{01}) [P(Y = 1|X = 1)P(X = 1)]^{n_{11}} \\ \times [P(Y = 0|X = 1)P(X = 1)]^{n_{10}} [P(Y = 1|X = 0)P(X = 0)]^{n_{01}} \\ \times [P(Y = 0|X = 0)P(X = 0)]^{n_{00}} = C(n, n_{11}, n_{10}, n_{01}) (\alpha\gamma)^{n_{11}} \\ \times [(1 - \alpha)\gamma]^{n_{10}} [\beta(1 - \gamma)]^{n_{01}} [(1 - \beta)(1 - \gamma)]^{n_{00}} \\ = C(n, n_{11}, n_{10}, n_{01}) \alpha^{n_{11}} (1 - \alpha)^{n_{10}} \beta^{n_{01}} (1 - \beta)^{n_{00}} \gamma^{n_{11}} (1 - \gamma)^{n_{00}}.$$

The likelihood function $P(D|m)$ is then calculated by integrating over α, β , and γ . This yields:

$$P(D|m_0) = \int_0^1 d\alpha \int_0^1 d\gamma P(D|\alpha, \alpha, \gamma) \rho(\alpha, \beta, \gamma|m_0) \\ = C(n, n_{11}, n_{10}, n_{01}) \left[\int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} \right] \left[\int_0^1 d\gamma \gamma^{n_{11}} (1 - \gamma)^{n_{00}} \right] \\ = C(n, n_{11}, n_{10}, n_{01}) B(n_{1\bullet} + 1, n_{0\bullet} + 1) B(n_{\bullet 1} + 1, n_{\bullet 0} + 1),$$

where

$$B(\mu, \nu) = \int_0^1 dt t^{\mu-1} (1-t)^{\nu-1} \quad [\text{Re } \mu > 0, \text{Re } \nu > 0]$$

is the β -function. Also:

$$P(D|m_+) = \int_0^1 d\alpha \int_0^\alpha d\beta \int_0^1 d\gamma P(D|\alpha, \beta, \gamma) \rho(\alpha, \beta, \gamma|m_+) \\ = 2C(n, n_{11}, n_{10}, n_{01}) \left[\int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} \int_0^\alpha d\beta \beta^{n_{01}} (1 - \beta)^{n_{00}} \right] \\ \times \left[\int_0^1 d\gamma \gamma^{n_{11}} (1 - \gamma)^{n_{00}} \right] \\ = 2C(n, n_{11}, n_{10}, n_{01}) B(n_{1\bullet} + 1, n_{0\bullet} + 1) B(n_{01} + 1, n_{00} + 1) \\ \times \int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} I_\alpha(n_{01} + 1, n_{00} + 1),$$

where

$$I_\eta(\mu, \nu) = \frac{1}{B(\mu, \nu)} \int_0^\eta dt t^{\mu-1} (1-t)^{\nu-1}$$

is the regularized incomplete β -function. Also:

$$P(D|m_-) = \int_0^1 d\alpha \int_\alpha^1 d\beta \int_0^1 d\gamma P(D|\alpha, \beta, \gamma) \rho(\alpha, \beta, \gamma|m_-) \\ = 2C(n, n_{11}, n_{10}, n_{01}) \left[\int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} \int_\alpha^1 d\beta \beta^{n_{01}} (1 - \beta)^{n_{00}} \right] \\ \times \left[\int_0^1 d\gamma \gamma^{n_{11}} (1 - \gamma)^{n_{00}} \right] \\ = 2C(n, n_{11}, n_{10}, n_{01}) B(n_{1\bullet} + 1, n_{0\bullet} + 1) B(n_{01} + 1, n_{00} + 1) \\ \times \int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} [1 - I_\alpha(n_{01} + 1, n_{00} + 1)].$$

Marginal Likelihood $P(D)$. The marginal likelihood $P(D)$ is then:

$$P(D) = \sum_m P(D|m)P(m) = P(D|m_0)P(m_0) + P(D|m_+)P(m_+) \\ + P(D|m_-)P(m_-) = \frac{1}{3} C(n, n_{11}, n_{10}, n_{01}) B(n_{1\bullet} + 1, n_{0\bullet} + 1) \\ \times [B(n_{\bullet 1} + 1, n_{\bullet 0} + 1) + 2B(n_{11} + 1, n_{10} + 1)B(n_{01} + 1, n_{00} + 1)].$$

Posterior Probability Mass Function $P(m|D)$. The posterior probability mass function $P(m|D)$ is then given by Bayes' theorem:

$$P(m|D) = \frac{P(D|m)P(m)}{P(D)}.$$

Therefore:

$$P(m_0|D) = \frac{B(n_{\bullet 1} + 1, n_{\bullet 0} + 1)}{B(n_{\bullet 1} + 1, n_{\bullet 0} + 1) + 2B(n_{11} + 1, n_{10} + 1)B(n_{01} + 1, n_{00} + 1)},$$

$$P(m_+|D) = \frac{2B(n_{01} + 1, n_{00} + 1) \int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} I_\alpha(n_{01} + 1, n_{00} + 1)}{B(n_{\bullet 1} + 1, n_{\bullet 0} + 1) + 2B(n_{11} + 1, n_{10} + 1)B(n_{01} + 1, n_{00} + 1)}$$

and

$$P(m_-|D) = \frac{2B(n_{01} + 1, n_{00} + 1) \int_0^1 d\alpha \alpha^{n_{11}} (1 - \alpha)^{n_{10}} [1 - I_\alpha(n_{01} + 1, n_{00} + 1)]}{B(n_{\bullet 1} + 1, n_{\bullet 0} + 1) + 2B(n_{11} + 1, n_{10} + 1)B(n_{01} + 1, n_{00} + 1)}$$

Most programming languages have routines to compute the functions $B(\mu, \nu)$ and $I_\eta(\mu, \nu)$ quickly. The integrals in the numerators for $P(m_+|D)$ and $P(m_-|D)$ can be readily computed by numeric integration.

Comments. The following can easily be shown:

$$\begin{aligned} P(Y = 1|X = 1) &= P(Y = 1|X = 0) \\ \Leftrightarrow P(Y = 1|X = 1) &= P(Y = 1) \\ \Leftrightarrow P(X = 1|Y = 1) &= P(X = 1) \\ \Leftrightarrow P(X = 1|Y = 1) &= P(X = 1|Y = 0) \end{aligned}$$

and

$$\begin{aligned} P(Y = 1|X = 1) &> P(Y = 1|X = 0) \\ \Leftrightarrow P(Y = 1|X = 1) &> P(Y = 1) \\ \Leftrightarrow P(X = 1|Y = 1) &> P(X = 1) \\ \Leftrightarrow P(X = 1|Y = 1) &> P(X = 1|Y = 0) \end{aligned}$$

and

$$\begin{aligned} P(Y = 1|X = 1) &< P(Y = 1|X = 0) \\ \Leftrightarrow P(Y = 1|X = 1) &< P(Y = 1) \\ \Leftrightarrow P(X = 1|Y = 1) &< P(X = 1) \\ \Leftrightarrow P(X = 1|Y = 1) &< P(X = 1|Y = 0). \end{aligned}$$

Therefore, there should be no doubt that the models m_0 , m_+ , and m_- and their different constraints on α , β , and γ correspond to zero, positive, and negative correlation, respectively.

It could be argued that a better approach would be to compute the full posterior $\rho(m, \alpha, \beta, \gamma|D)$ using the full prior $\rho(m, \alpha, \beta, \gamma) = P(m) \rho(\alpha, \beta, \gamma|m)$, and then to compute $P(m|D)$ by marginalizing over α , β , and γ . However, it can be easily seen that this approach is equivalent to the above and would produce the same results.

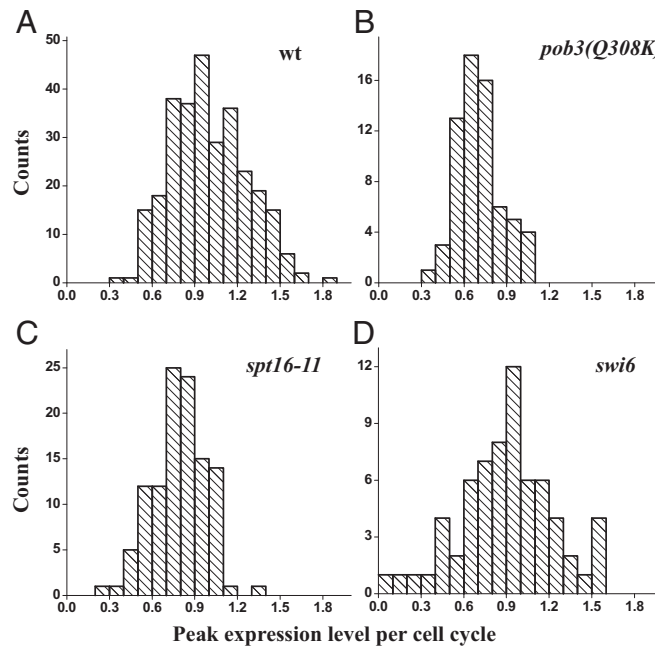
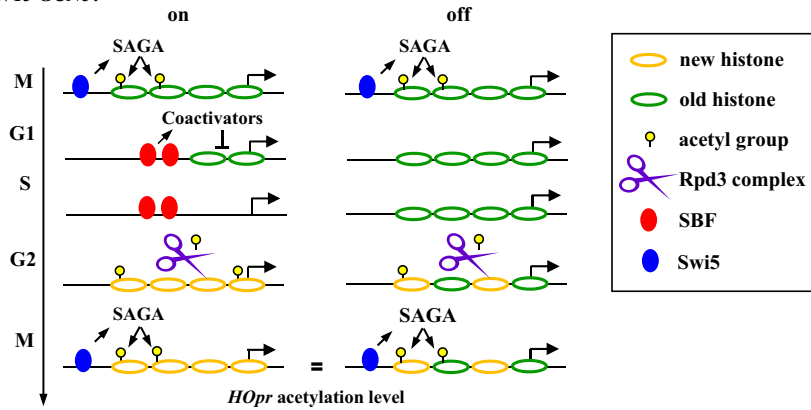


Fig. 51. GFP expression driven by the *CLN2* promoter in WT (wt) (A), *pob3(Q308K)* (B), *spt16-11* (C), and *swi6* (D) strains. The expression level is normalized so that the average expression in wt background is 1. In all the mutant strains, the *CLN2* expression is uniformly reduced without becoming bimodal.

A *SWI5 GCN5*:



B *SWI5 gcn5*:

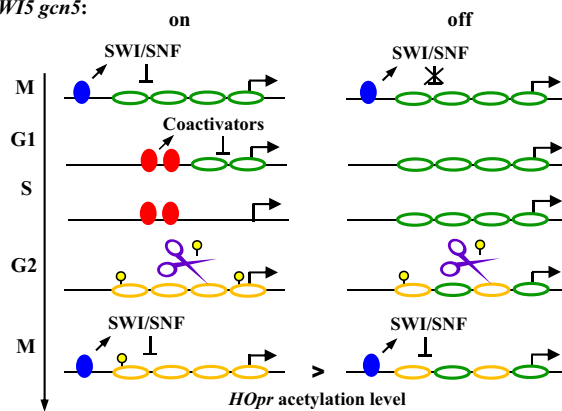


Fig. S2. Model for the memory of *HO* expression in *SWI5* background. (A) Similar to the *swi5* case, the histones on the *HO* promoter (*HOpr*) are more acetylated after the “on” cycle than after the “off” cycle. However, in the presence of both *Swi5* and *Gcn5*, *Gcn5* will be recruited to the *HOpr* and acetylates the nearby histones, therefore “resetting” the histone acetylation marks. In the end, there is no difference in histone acetylation after the on- or off-cycle; therefore, there is no memory effect. SAGA, Spt-Ada-Gcn5-acetyltransferase. (B) In *gcn5* cells, the histone acetylation pattern cannot be reset. The higher acetylation level on the *HOpr* following an on-cycle likely facilitates SWI/SNF remodeling and SBF binding, leading to a higher on-cycle probability.

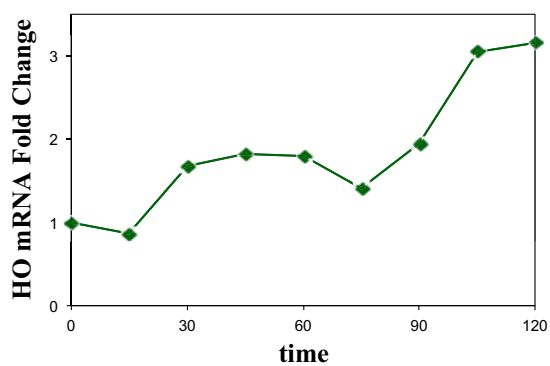
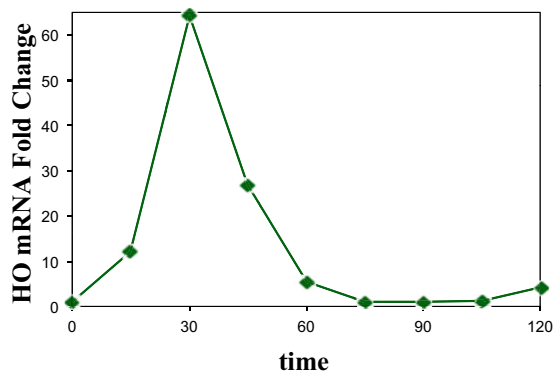
A. Stationary Phase Arrest and Release**B. *cdc28*-ts Arrest and Release**

Fig. S3. Comparison of two cell cycle synchronization methods. *HO* mRNA was quantified by RT-PCR using synchronized cells released from G1 arrest by nutrient starvation (A) or by inactivation of a temperature-sensitive cyclin-dependent kinase (*Cdc28*) (B). Note that in B, the fold change of the *HO* mRNA is far greater than that in A, indicating that the *cdc28* temperature-sensitive method gives much better cell cycle synchrony during the release from arrest.

Table S1. Number of cell cycles showing on/on, on/off, off/on, or off/off GFP/YFP expression

	Y = 1	Y = 0	Total
X = 1	$n_{11} = 0$	$n_{10} = 12$	$n_{1\bullet} = 12$
X = 0	$n_{01} = 20$	$n_{00} = 726$	$n_{0\bullet} = 746$
Total	$n_{\bullet 1} = 20$	$n_{\bullet 0} = 738$	$n = 758$

Table S2. Expected values of cell cycle counts given uncorrelated GFP/YFP expression

	Y = 1	Y = 0
X = 1	$n_{11} = 0.3166$	$n_{10} = 11.6834$
X = 0	$n_{01} = 19.6834$	$n_{00} = 726.3166$

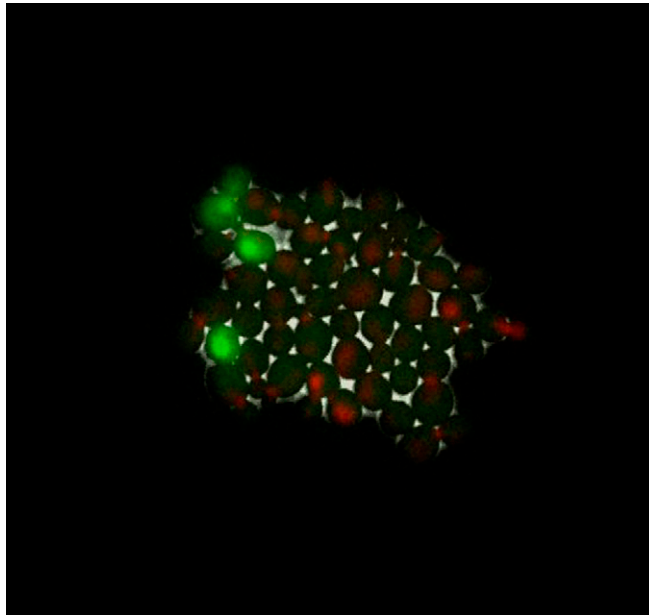
Table S3. Description of three models of GFP/YFP correlation

Model	Model's constraints on α , β , and γ	Meaning
m_0	$0 \leq \beta = \alpha \leq 1, 0 \leq \gamma \leq 1$	X and Y are not correlated because $\alpha = \beta$
m_+	$0 \leq \beta < \alpha \leq 1, 0 \leq \gamma \leq 1$	X and Y are positively correlated because $\alpha > \beta$
m_-	$0 \leq \alpha < \beta \leq 1, 0 \leq \gamma \leq 1$	X and Y are negatively correlated because $\alpha < \beta$

Table S4. Strain List

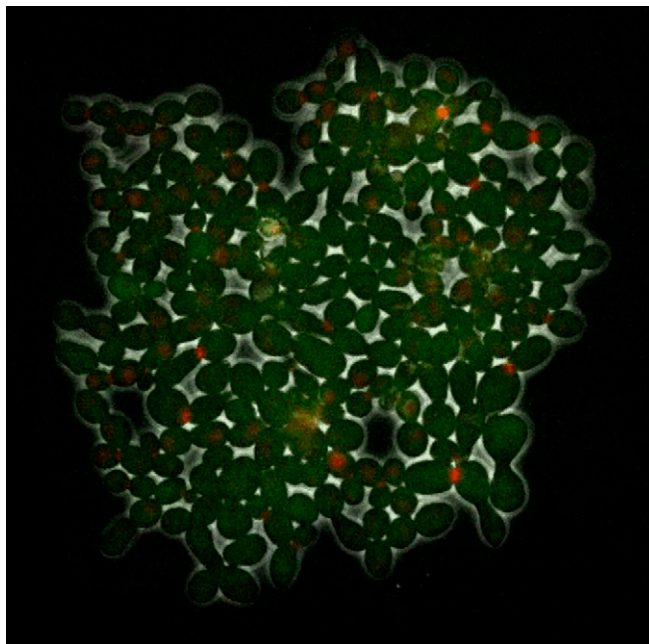
Name	Genotype
yLB73	<i>MATa HO-GFP-NLS-PEST::HIS3 MYO1-MYO1-mCherry::SpHis3 ADE2</i>
DY14800	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 swi5::URA3-hisG-URA3 ADE2</i>
902-23B	<i>MATa HO-GFP-NLS-PEST::HIS3 MYO1-MYO1-mCherry::SpHis3 spt16-11 ADE2</i>
903-7D	<i>MATa HO-GFP-NLS-PEST::HIS3 MYO1-MYO1-mCherry::SpHis3 pob3(Q308K):KanMX ADE2</i>
DY14482	<i>MATa CLN2::GFP-NLS-PEST::URA3 MYO1-MYO1-mCherry::SpHis3 pob3(Q308K):KanMX ADE2</i>
DY14484	<i>MATa CLN2::GFP-NLS-PEST::URA3 MYO1-MYO1-mCherry::SpHis3 spt16-11 ADE2</i>
DY14488	<i>MATa HO-GFP-NLS-PEST::HIS3 MYO1-MYO1-mCherry::SpHis3 gcn5::TRP1 ADE2 lys2</i>
DY14559	<i>MATa HO-GFP-NLS-PEST::HIS3 MYO1-MYO1-mCherry::SpHis3 swi2(E834K) ADE2 lys2</i>
DY14739	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 gal11::LEU2 ADE2</i>
DY14797	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 rpd3::LEU2 ADE2</i>
DY14799	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 swi5::URA3-hisG-URA3 rpd3::LEU2 ADE2</i>
DY15394	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 swi5::URA3-hisG-URA3 ace2::TRP1 ADE2</i>
DY15436	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 ace2::TRP1 ADE2</i>
DY15391	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 ash1::LEU2 ADE2</i>
DY15397	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 swi5::URA3-hisG-URA3 ash1::LEU2 ADE2</i>
DY15404	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 swi5::URA3-hisG-URA3 ash1::LEU2 ace2::TRP1 ADE2</i>
DY15910	<i>MATa/MATa diploid HO-GFP-NLS-PEST::NatMX4 HOpr-Venus-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3/MYO1 swi5::KanMX/swi5::hisG ADE2/ade2 lys2/lys2</i>
DY16632	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 swi6::TRP1 ADE2</i>
yLB79	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 cln1, cln2, cln3::LEU2 TRP1::MET-CLN2 swi5::URA3-hisG-URA3 ADE2</i>
yLB80	<i>MATa HO-GFP-NLS-PEST::NatMX4 MYO1-MYO1-mCherry::SpHis3 cdc20::MET-CDC20:TRP1 swi5::URA3-hisG-URA3 ADE2</i>
DY13565	<i>MATa cdc28-13</i>
DY12843	<i>MATa cdc28-13 SWI5-Myc::KanMX</i>
DY8844	<i>MATa cdc28-13 SWI2-Myc::TRP1</i>
DY13561	<i>MATa cdc28-13 GCN5-Myc::KanMX lys2</i>
DY13563	<i>MATa cdc28-13 GAL11-Myc::HIS3MX</i>
DY13576	<i>MATa cdc28-13 SWI4-Myc::TRP1 lys2 met15</i>

All strains are derived from congenic W303 (*leu2-3,112 his3-11,15 ura3-1 trp1-1 can1-100 ade2-1*).



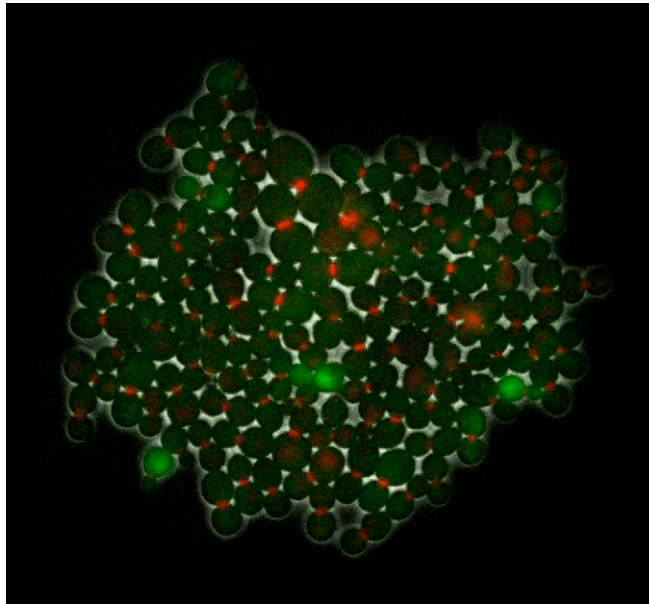
Movie S1. Stochastic *HO* expression in *swi5* background.

[Movie S1](#)



Movie S2. *HO* expression in *cln123* strain that goes through G1 arrest-release.

[Movie S2](#)



Movie S3. *HO* expression in *cdc20* strain that goes through G2/M arrest-release.

[Movie S3](#)