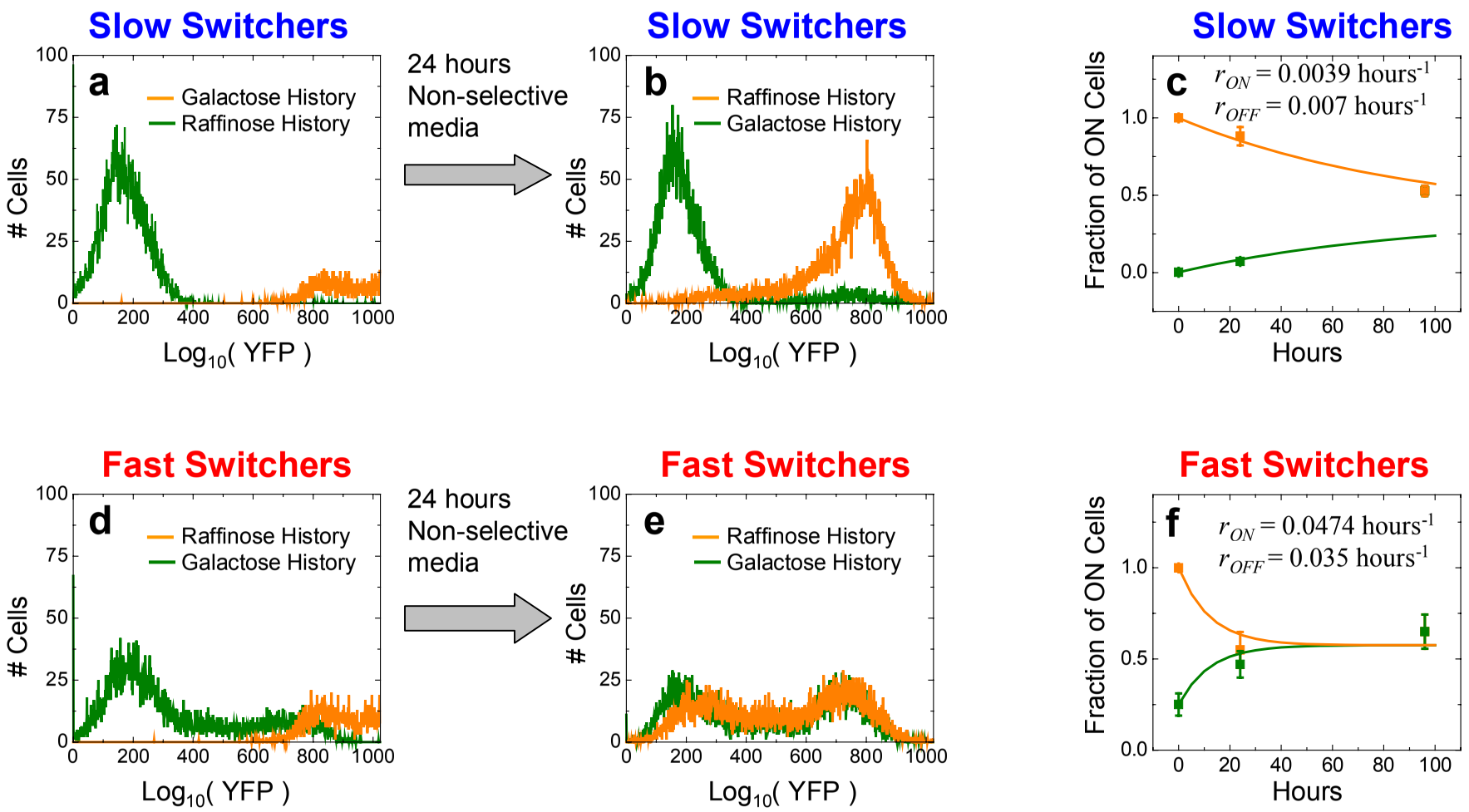

Figure S1. Determination of switching rates for fast and slow switchers. **a**, **d**, YFP fluorescence distribution of cells that have been grown in non-selective media to obtain the t = 0 distributions. **b**, **e**, YFP fluorescence distribution after an additional 24 hours in non-selective media (with galactose and doxycycline concentrations corresponding to fast and slow switchers). **c**, **f**, The fraction of ON cells as a function of time in non-selective media for the galactose (orange) and raffinose (green) history cells. To estimate the fraction at 96 hours the steady state distribution of cells (taken from Fig. 2a-b) were determined. By fitting the data with the function:

$$f_{ON}(t) = \frac{r_{ON}}{r_{OFF} + r_{ON}} + \left(f_{ON}(t=0) - \frac{r_{ON}}{r_{OFF} + r_{ON}} \right) e^{-(r_{ON} + r_{OFF})t}$$

and minimizing the χ^2 cost function, we determine that the inter-phenotype switching rates for the fast switchers are r_{ON} = (0.0474 ± 0.026) hours^{-1} and r_{OFF} = (0.035 ± 0.020) hours^{-1}. The inter-phenotype switching rates for the slow switchers are: r_{ON} = (0.0039 ± 0.0002) hours^{-1} and r_{OFF} = (0.007 ± 0.0007) hours^{-1}.

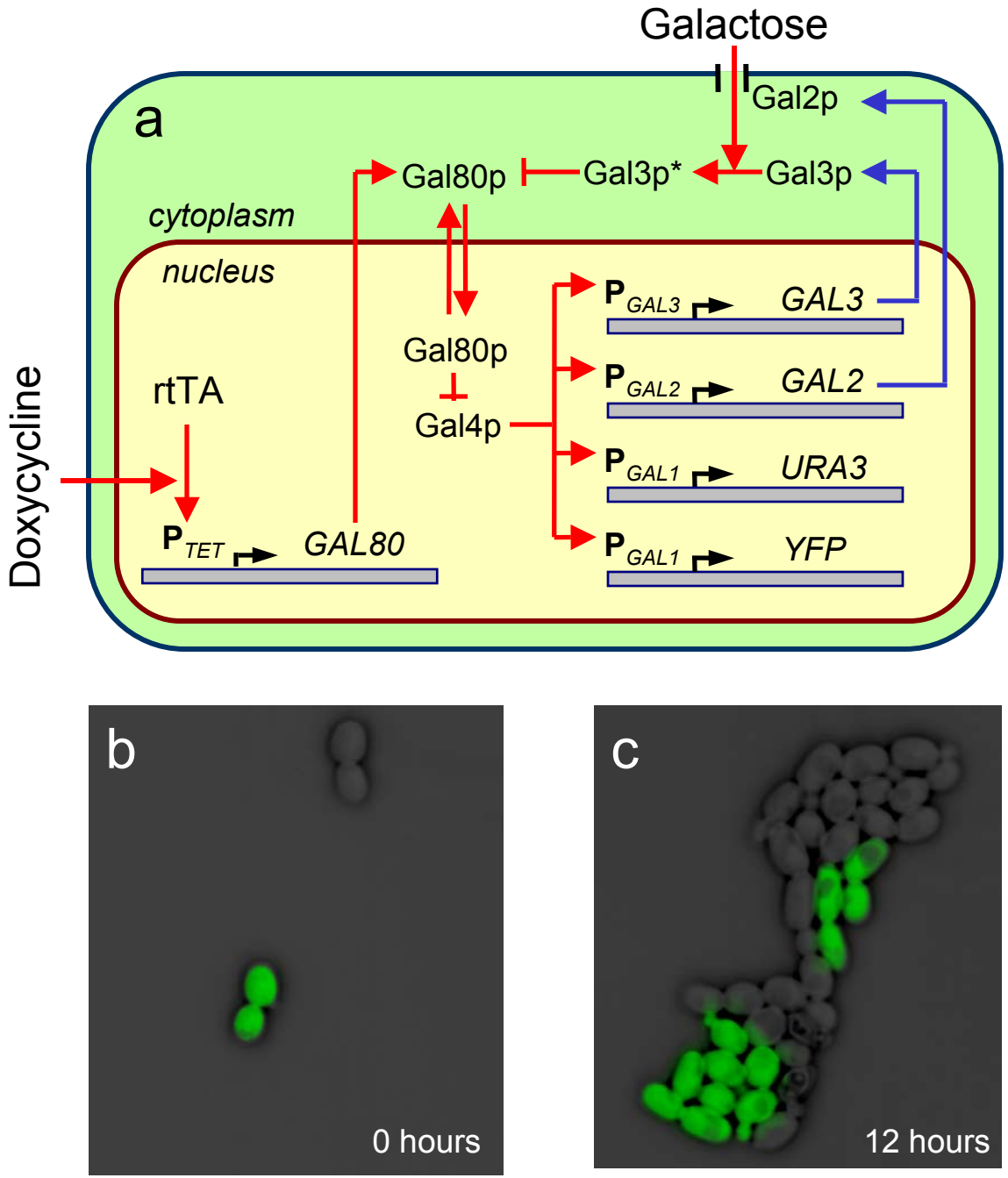

Figure S2. (a) The galactose signaling pathway. The activity of the galactose pathway is read out by using YFP driven by the *GAL1* promoter. Similarly, the endogenous *URA3* expression is also under the control of the *GAL1* promoter, coupling the synthesis of the Ura3 proteins to the activity of the *GAL* pathway. In environment E_1, ON cells will synthesize uracil and thrive, while in environment E_2 the *URA3* gene product converts 5-FOA to a toxic intermediate. Two positive feedback loops expression cause the network to be stable in either an active (ON) or inactive (OFF) state. By changing the extracellular galactose and doxycycline the transition rates between the ON and OFF states can be altered providing us with the fast and slow switchers. Two initially OFF and ON cells (b) that produce a mixed colony of both OFF and ON cells 12 hours later (c).

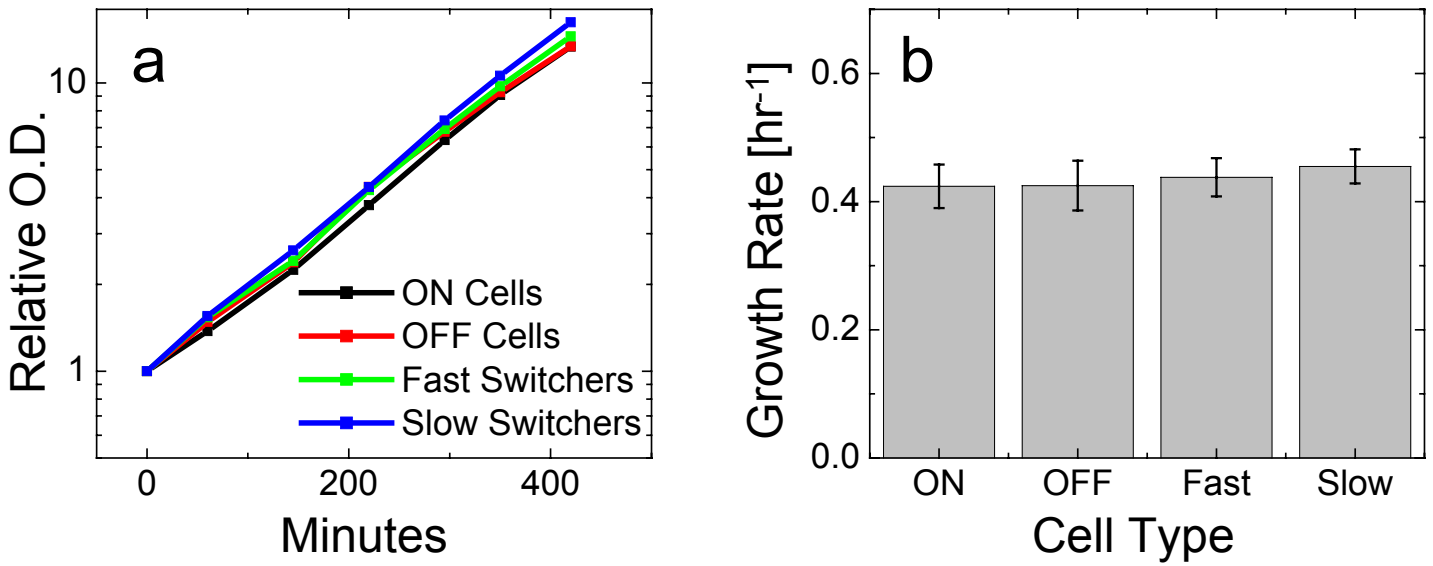

Figure S3. Growth rate in the absence of selection. ON and OFF cells are locked in a high and low *URA3* expression state (no switching). Overnight grown cells were induced with either 0.060% galactose (ON state) or with 0.027 μg/ml doxycycline (OFF state). After 25.5 hours, we started recording the OD_{600} readings. The cells were kept in log-phase throughout the experiment by serial dilution as necessary. Fast and slow refer to the fast and slow switchers respectively. Cells were grown in non-selective media.

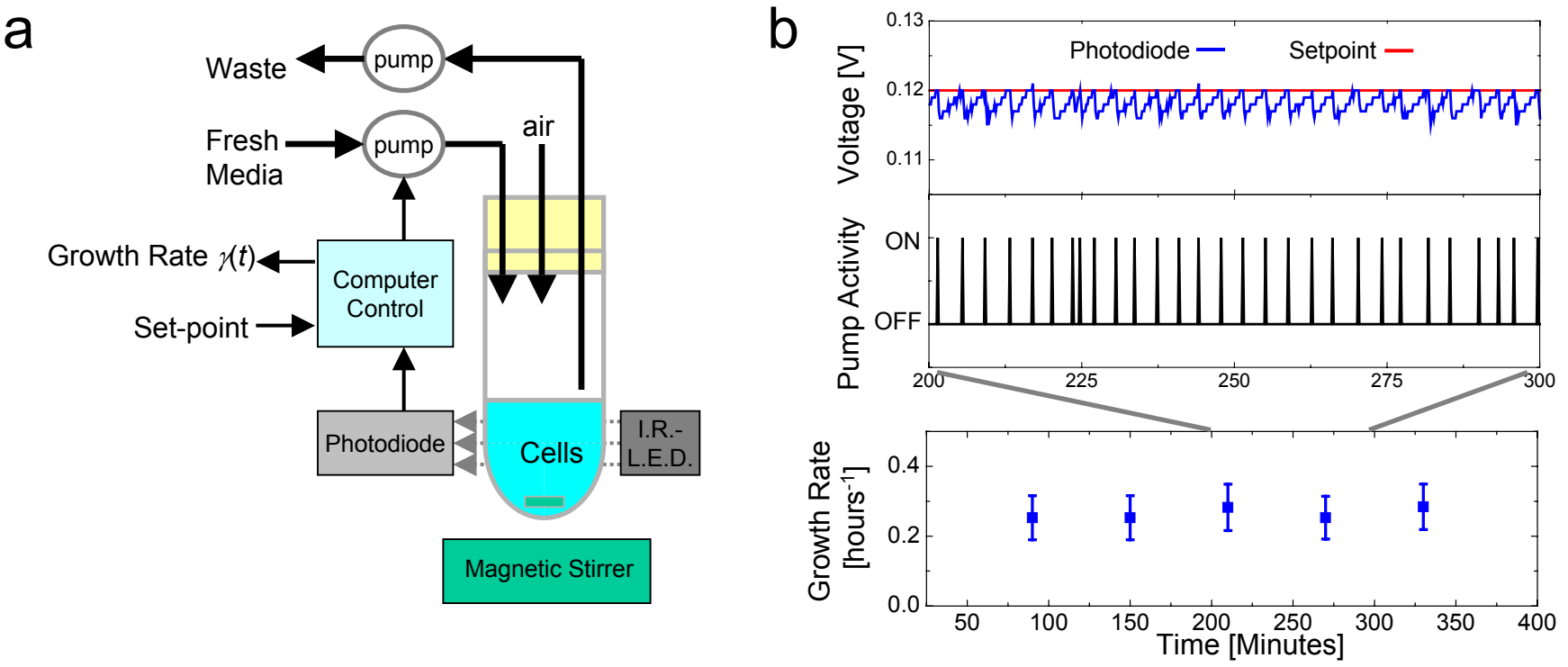

Figure S4. (a) Schematic of the custom made turbidostat setup used for all growth rate measurements. Cells were maintained at 10-15 ml volumes in test tubes while magnetic stir bars (green) kept the cultures well mixed. An infrared LED (gray) and photodiode (orange) pair (operating around 940 nm) were used to measure the relative OD using a D/A converter and custom Labview software. A peristaltic pump provided fresh media to dilute the population whenever the OD went above a critical threshold value. A second continuously operating peristaltic pump coupled to a pickup tube kept the culture volume fixed. (b) The pumping rate was then used to calculate the dynamic population growth rate.

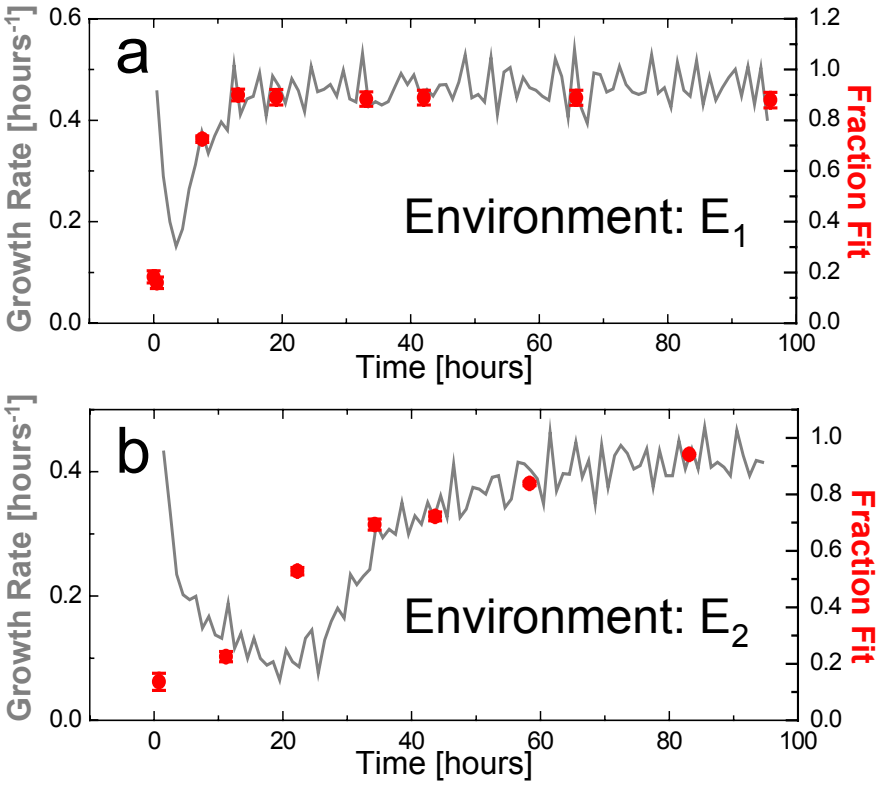

Figure S5. Dynamic measurement of cellular expression levels in the two environments. **a**, Fast switching cells growing in E_2 were transferred to E_1 at t = 0 and the fraction of ON and OFF cells were measured at several points in time (red symbols). The increase in the dynamic growth rate (gray line) coincides with the increase in the fraction of fit cells (ON). **b**, Fast switching cells growing in E_1 were transferred to E_2 at t = 0. The increase in growth rate coincides with a significant increase in the fraction of fit cells.

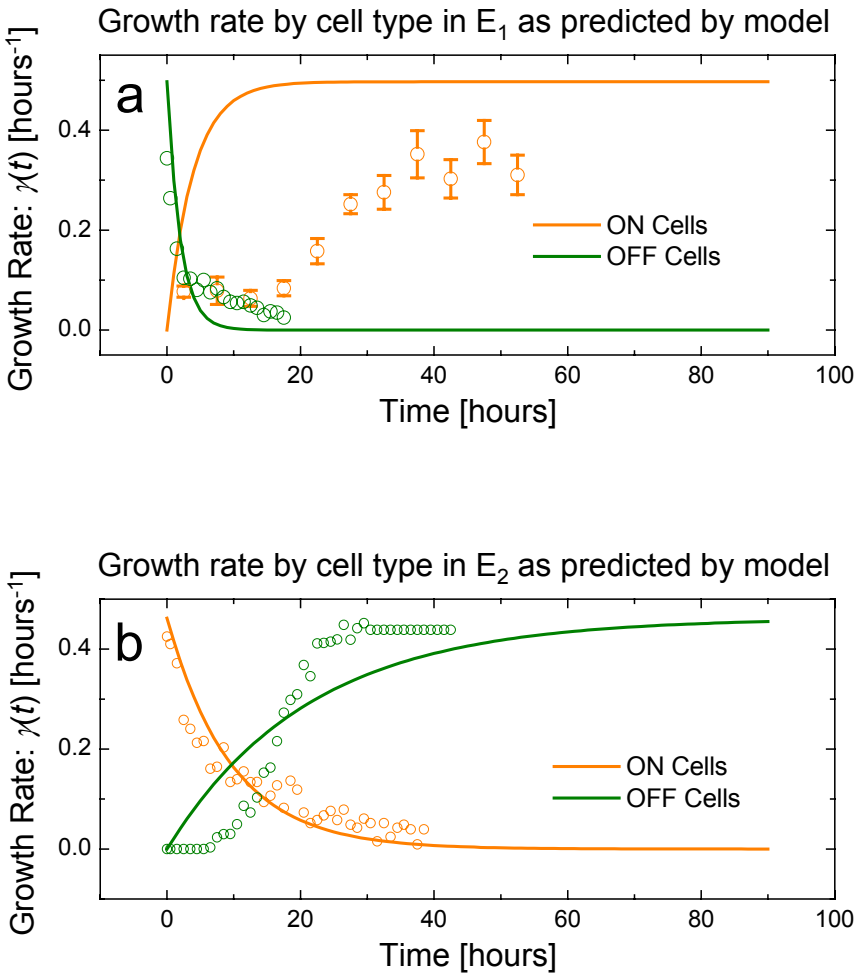

Figure S6. Modeling cellular growth in fluctuating environments. **a**, In environment E_1, OFF cells (green) exponentially cease their growth rate due to the lack of intracellular uracil. Similarly, ON cells (orange) are assumed to need some time to recover from the previous environment (E_2 with 5-FOA) and begin growing at their maximal rate. **b**, In E_2, the opposite scenario occurs where ON cells (orange) decrease their growth rate with time as the effects of 5-FOA build up in the cell, and OFF cells (green) recover their maximal growth rate on a slightly longer timescale. Circles indicate experimentally measured growth rates for cells locked into the ON (orange) and OFF (green) states through addition of galactose and doxycyline respectively (see Supplementary Methods for details).

SUPPLEMENTARY TABLE

Table S1. Model parameters

Parameter	Environment	Value	Source
r_{ON} (slow)	1 & 2	0.0039 ± 0.0002 hours^{-1}	Fig. S1
r_{OFF} (slow)	1 & 2	0.007 ± 0.0007 hours^{-1}	Fig. S1
r_{ON} (fast)	1 & 2	0.0474 ± 0.026 hours^{-1}	Fig. S1
r_{OFF} (fast)	1 & 2	0.035 ± 0.02 hours^{-1}	Fig. S1
γ_1	1	0.50 ± 0.01 hours^{-1}	Fig. 2c
γ_2	2	0.46 ± 0.01 hours^{-1}	Fig. 2d
d_1	1	0.62 hours^{-1}	Fit to Fig. 2c
d_2	2	0.17 hours^{-1}	Fit to Fig. 2d
r_1	1	0.12 hours^{-1}	Fit to Fig. 2c
r_2	2	0.042 hours^{-1}	Fit to Fig. 2d

SUPPLEMENTARY METHODS

Supplementary Experimental Methods for Figure S6

In order to lock the cells into their ON state, cells were grown overnight in selective minimal media missing uracil and containing 0.230% Galactose in 10 ml volume. After about 32 hours, cells were spun down, washed, and put into a turbidostat containing the same selective minimal media in addition to 5-FOA (at a final concentration of 0.19 μg/ml). The decrease in the growth rates of the cells was then measured for about 40 hours.

Afterwards, the cells were spun and washed to remove the 5-FOA, before being put back into the turbidostat (now containing media witout 5-FOA). The increase in the growth rates of the cells (recovery dynamics) was then measured for about 54 hours.

In order to lock the cells into the OFF state, cells were grown overnight in selective minimal media containing uracil (at a final concentration of 0.02 μg/ml) and 5-FOA (at a final concentration of 0.19 μg/ml), and doxycycline (at a final concentration of 0.0135 μg/ml). After about 32 hours, cells were spun down, washed, and put into the turbidostat containing the same selective minimal media without uracil and containing 5-FOA (at a final concentration of 0.19 μg/ml) as well as Doxycycline (at a final concentration of 0.0135 μg/ml). The decrease in the growth rates of the cells was then measured for about 18.5 hours.

Afterwards, the turbidostat culture media was supplemented with uracil (at a final concentration of 0.02 μg/ml) in order to recover the cellular growth. The increase in the growth rates of the cells (recovery dynamics) was followed for about 32 hours.

Supplementary Note for Figure S6

We estimate the death and recovery rates directly by locking the cells into the ON and OFF states and then measuring the resulting changes in growth rates when cells are transitioned from the fit-to-unfit (resulting in estimates for d_1 and d_2) and unfit-to-fit environments (resulting in estimates for r_1 and r_2).

We find that the death curves are nicely predicted by our assumption for exponential decay in growth rates along with the decay rates, d_1 and d_2 obtained from our fits. While the exact functional form for the recovery curve measured for OFF cells in +FOA media is different from that we had originally assumed, the timing of the adaptation (r_2) is nevertheless nicely captured. On the other hand, for ON cells in –URA media, we find a large discrepancy between the predicted recovery rate and the measured

recovery curve. It is important to note that the measured curve is probably not an accurate reflection of the recovery time in our switching phenotype experiments. This data suggests that it takes 30-40 hours for the cells to 'fully recover'; on the other hand, we find that the data in Figs 2c-d indicates recovery takes 10-20 hours. We expect that this difference is due to the reason that the locked-ON cells have a high expression state of Ura3 compared to the switching cells. This might mean that these cells enter E_1 with a higher amount of toxin and require a longer time to recover.

One potential issue we encounter when performing this experiment is the level of gene expression present in the ON and OFF cells. We lock cells into the ON or OFF states by inducing the cells with galactose or doxycycline, respectively. This makes the expression levels of the ON or OFF states higher or lower than the respective levels we observe for the switching cells.

For cells locked into the ON state, this causes the level of Yfp and Ura3 expression to be much higher than the level of gene expression in ON cells which are allowed to transition between the phenotypic states. It is difficult to say with certainty, therefore, that the results we obtain under these conditions will closely mirror the values we are attempting to measure.

While for most of these parameters we find a good agreement between the predicted recovery and death rates, we did not use these estimates in order to predict the response seen in Figs. 2c-d. Because of gene expression differences between this experiment and our previous results, we do not know whether these measurements are more accurate than the assumed functional forms for the death and recovery curves (e.g. recovery curve for ON locked cells in Env. 1 cannot reflect the actual situation for switching cells).

Growth in non-selective media

Cells were induced overnight with the following additions to non-selective media: 0.060% Galactose for the ON cells, 0.027 μg/ml doxycycline for the OFF cells, 0.004% galactose and 0.00282 μg/ml doxycycline for the fast switchers, and 0.03% galactose and 0.0135 μg/ml doxycycline for the slow switchers.

After 25.5 hours of growth at 30^o in a shaker, we started recording the OD_{600} readings. The cells were kept at the log-phase throughout the experiment by serial dilution as necessary.