

**Table 1. Definitions and experimental values of parameters**

Symbol	Definition	Value Range (Experimental)	Value*
$T_I^\dagger$	Time of the end of residual growth	10 h	10
$T_R^\dagger$	Delay in $R_{\rightarrow L}^{\leftarrow A}$ 's entry into death phase after the onset of starvation	60-80 h	70
$D_R^\ddagger$	Death rate of $R_{\rightarrow L}^{\leftarrow A}$ in the absence of ade after time $T_R$	0.007-0.04/h	0.01
$D_Y^\ddagger$	Death rate of $Y_{\rightarrow A}^{\leftarrow L}$ in the absence of lys averaged from time $T_I$ to $T_R$	0.054/h	0.054
$D_{YLate}^\ddagger$	Death rate of $Y_{\rightarrow A}^{\leftarrow L}$ in the absence of lys after time $T_R$	0.02/h	0.02
$A_s^\S$	Adenine supplied per $Y_{\rightarrow A}^{\leftarrow L}$ cell upon death	3 fmole per cell	3
$L_s^\S$	Lysine supplied per $R_{\rightarrow L}^{\leftarrow A}$ cell upon death	15 fmole per cell	15
$G_{maxY}^\P$	Maximum growth rate of $Y_{\rightarrow A}^{\leftarrow L}$ when lysine is in excess	0.31/h	0.31
$V_{maxL}^\P$	Maximum lysine uptake rate per $Y_{\rightarrow A}^{\leftarrow L}$ cell when lysine is in excess	2.4 fmole per cell/h	2.4
$A_{c-fed}^\parallel$	Ade consumed to produce a fed $R_{\rightarrow L}^{\leftarrow A}$ cell when ade is in excess	1 fmole per cell	
$L_{c-fed}^\parallel$	Lys consumed to produce a fed $Y_{\rightarrow A}^{\leftarrow L}$ cell when lys is in excess	5.4 fmole per cell	
$I_R$	Fold-increase in cell density during residual growth of $R_{\rightarrow L}^{\leftarrow A}$	1-2	1.5
$I_Y$	Fold-increase in cell density during residual growth of $Y_{\rightarrow A}^{\leftarrow L}$	2-4	3
$A_c^{**}$	Ade consumed in order to produce a starving $R_{\rightarrow L}^{\leftarrow A}$ cell	0.5-1 fmole per cell	1
$L_c^{**}$	Lys consumed in order to produce a starving $Y_{\rightarrow A}^{\leftarrow L}$ cell	1.4-2.7 fmole per cell	2
$K_{mL}$	Michaelis-Menten half-saturation constant of lysine transporter	20-80 $\mu$ M (1, 2)	50

\*Values used in calculations.

<sup>†</sup> Data from Fig 2.

<sup>‡</sup>Death rates were measured during the specified time windows and were found to be density-dependent.  $D_R = 0.01$  is the average of 0.007, 0.009, and 0.018 per h, respectively, obtained over a range of initial cell densities varying from 0.05 to  $1.1 \times 10^6$  cells per ml.  $D_Y$  and  $D_{YLate}$  were obtained at initial cell densities ranging from 0.28 to  $1.2 \times 10^6$  cells per ml.

<sup>§</sup>The kinetics of metabolite release approximately coincided with that of cell death (Fig. 2B). Thus, we assume that a starving cell releases a fixed amount of the overproduced metabolite into the medium on

death. Metabolite supplied per dead cell was estimated from Fig. 2B by dividing the final concentration of released metabolite by the final population density of dead cells.

<sup>¶</sup>See SI Fig. 10.

<sup>||</sup>When adenine was present in excess, the maximum uptake rate of adenine  $V_{maxA}$  was 0.5 fmole per cell/h, and the maximum growth rate of  $R_{\rightarrow L}^{\leftarrow A}$  cells was  $G_{maxR} = 0.37/h$  (methods of measurement similar to those in Fig. 10). Thus, it took  $A_{c-fed} = V_{maxA} \times (\ln 2 / G_{maxR}) \sim 1$  fmole adenine to produce a fed  $R_{\rightarrow L}^{\leftarrow A}$  cell, where  $\ln 2 / G_{maxR}$  was the doubling time of  $R_{\rightarrow L}^{\leftarrow A}$ . Similarly, it took  $L_{c-fed} = V_{maxL} \times (\ln 2 / G_{maxY}) = 5.4$  fmole lysine to produce a fed  $Y_{\rightarrow A}^{\leftarrow L}$  cell.

<sup>\*\*</sup>Because one fed  $Y_{\rightarrow A}^{\leftarrow L}$  cell gave rise to  $I_Y$  lysine-starved  $Y_{\rightarrow A}^{\leftarrow L}$  cells during residual growth, it took  $L_c = L_{c-fed} / I_Y$  amount of lysine to produce a starving  $Y_{\rightarrow A}^{\leftarrow L}$  cell. Similarly, it took  $A_c = A_{c-fed} / I_R$  amount of adenine to produce an adenine-starved  $R_{\rightarrow L}^{\leftarrow A}$  cell.

1. Sychrova H, Chevallier MR (1993) *Yeast* 9:771-782.
2. Garcia JC, Kotyk A (1988) *Folia Microbiol (Praha)* 33:285-291.

**Fig. 6.** Viability of CoSMO requires both adenine- and lysine-overproduction mutations. Monocultures of two strains with indicated genotypes were washed free of adenine and lysine and mixed at time 0. Plots show the dynamics of live R (red), live Y (green), dead (gray), and total (black) cell densities of the coculture.

**Fig. 7.** Stabilization of CoSMO partner ratio. Duplicate CoSMO cultures, in which partners were mixed at  $R_{\rightarrow L}^{\leftarrow A} : Y_{\rightarrow A}^{\leftarrow L} = 10^3$  (magenta), 1 (cyan), and  $10^{-3}$  (blue) to  $OD_{600}$  of 0.01, were initiated at time 0. Whenever the cultures reached the near-saturation set point of  $OD_{600} = 0.4-1$ , they were diluted to  $OD_{600}$  of [dsim]0.008. At various time points, population densities of DsRed-positive and YFP-positive cells were measured twice by flow cytometry. The average  $R_{\rightarrow L}^{\leftarrow A} : Y_{\rightarrow A}^{\leftarrow L}$  ratio is shown with a vertical bar indicating the range. Triangles mark points of dilution.

**Fig. 8.** A schematic diagram of the experimental protocol for Fig. 5B. A near-saturation Round-0 culture was subjected to 10-fold serial dilutions with three replicate cultures at a fixed volume per dilution so that density requirement of the culture, expressed in the number of cultures (out of 3) that are viable at various dilutions, could be measured. Out of diluted cultures that were able to grow, one near-saturation culture was chosen and subjected to 10-fold serial dilutions. This procedure was repeated 10 times, spanning a total of ~70 generations. The last near-saturation culture chosen was the Round-10 culture, and its density requirement was similarly determined.

**Fig. 9.** Characterization of CoSMO components using flow cytometry. Exponentially growing  $R_{\rightarrow L}^{\leftarrow A}$  (Left) and  $Y_{\rightarrow A}^{\leftarrow L}$  (Right) cells were washed free of supplements at time 0. Percentages of red-fluorescent (R), yellow-fluorescent (Y), and dark (dark) cells were measured at 0 h (Upper) and 97 h (Lower), and their values are indicated.

**Fig. 10.** Measurements of  $G_{maxY}$  and  $V_{maxL}$ .  $Y_{\rightarrow A}^{\leftarrow L}$  cells were grown in SD supplemented with lysine. Time 0 was arbitrarily chosen in early exponential phase. Plots show the

population density of  $Y_{\rightarrow A}^{\leftarrow L}$  (*Left*, green circles) and the concentration of lysine remaining in the medium (*Right*, brown circles) over time. The least-squares-fitting equation for the left panel is  $Y = Y_0 e^{G_{\max Y} t}$  (dotted line) and yields the initial population density  $Y_0$  and the maximum growth rate  $G_{\max Y}$ . The least-squares-fitting equation for the right panel is  $L = L_0 + V_{\max L} Y_0 (1 - e^{G_{\max Y} t}) / G_{\max Y}$  (dotted line), which is the solution to the differential

equation  $\frac{dL}{dt} = -V_{\max L} Y = -V_{\max L} Y_0 e^{G_{\max Y} t}$ , and yields the initial lysine concentration  $L_0$  and the maximum lysine uptake rate per cell  $V_{\max L}$ .

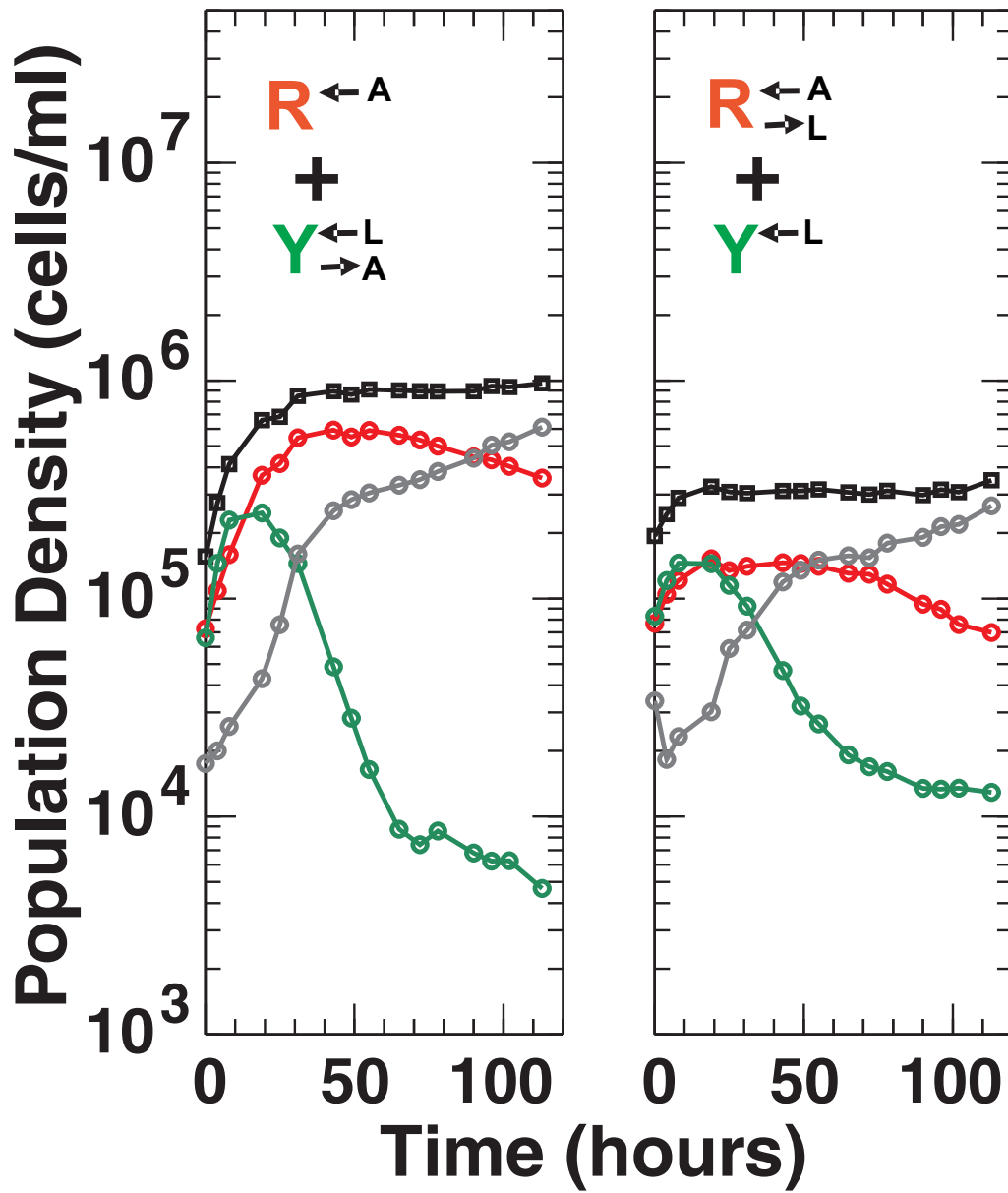


Fig. 6

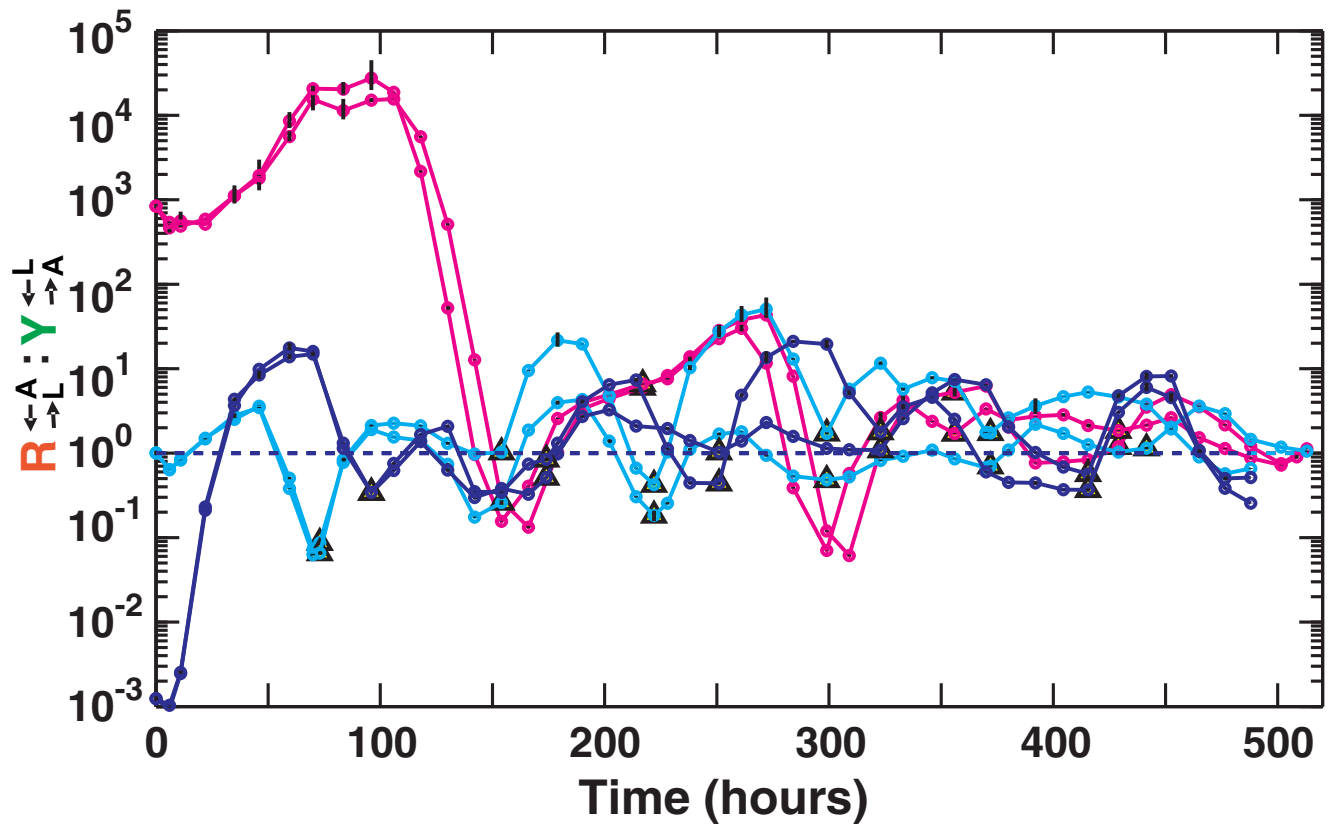


Fig 7

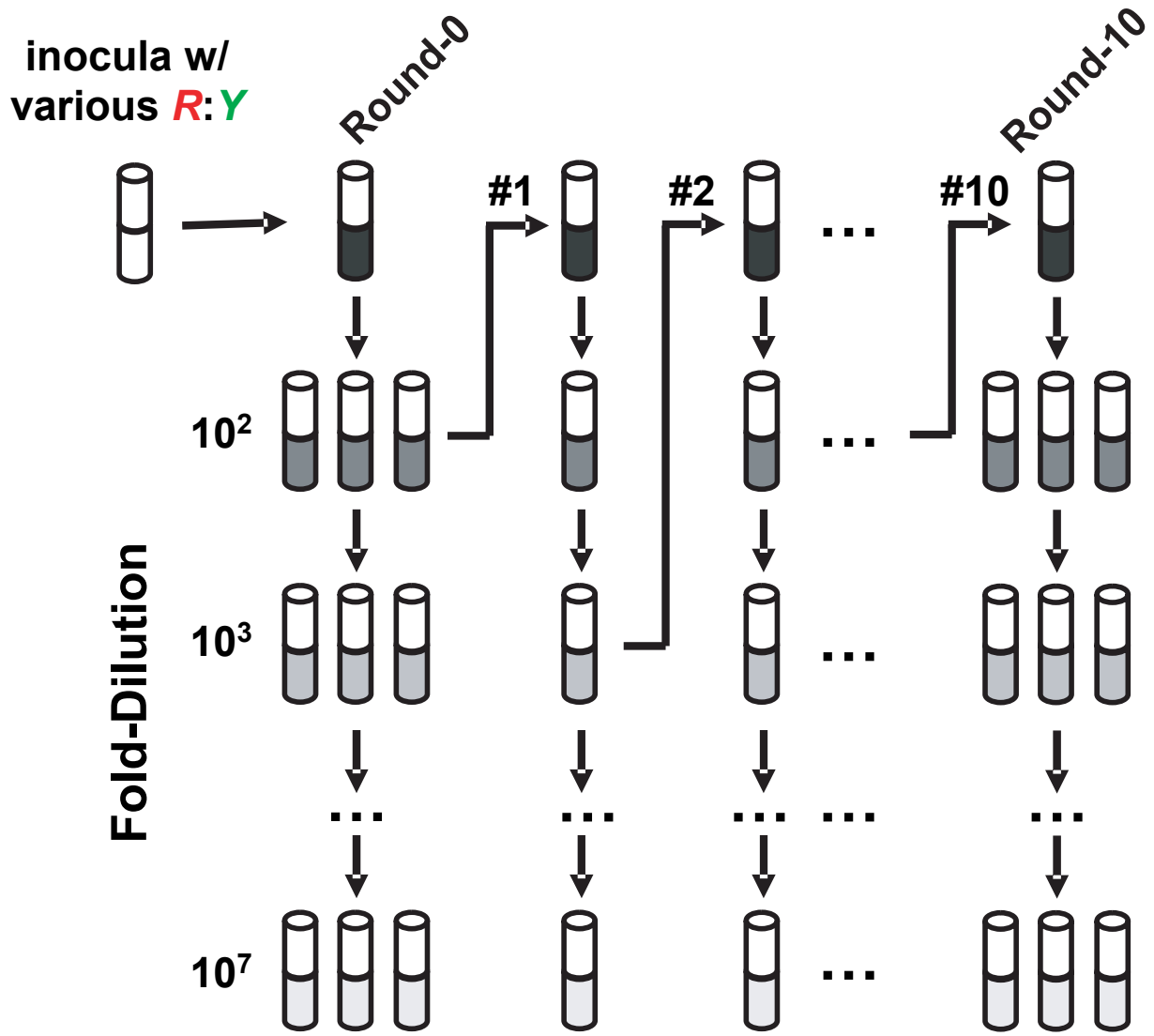


Fig. 8

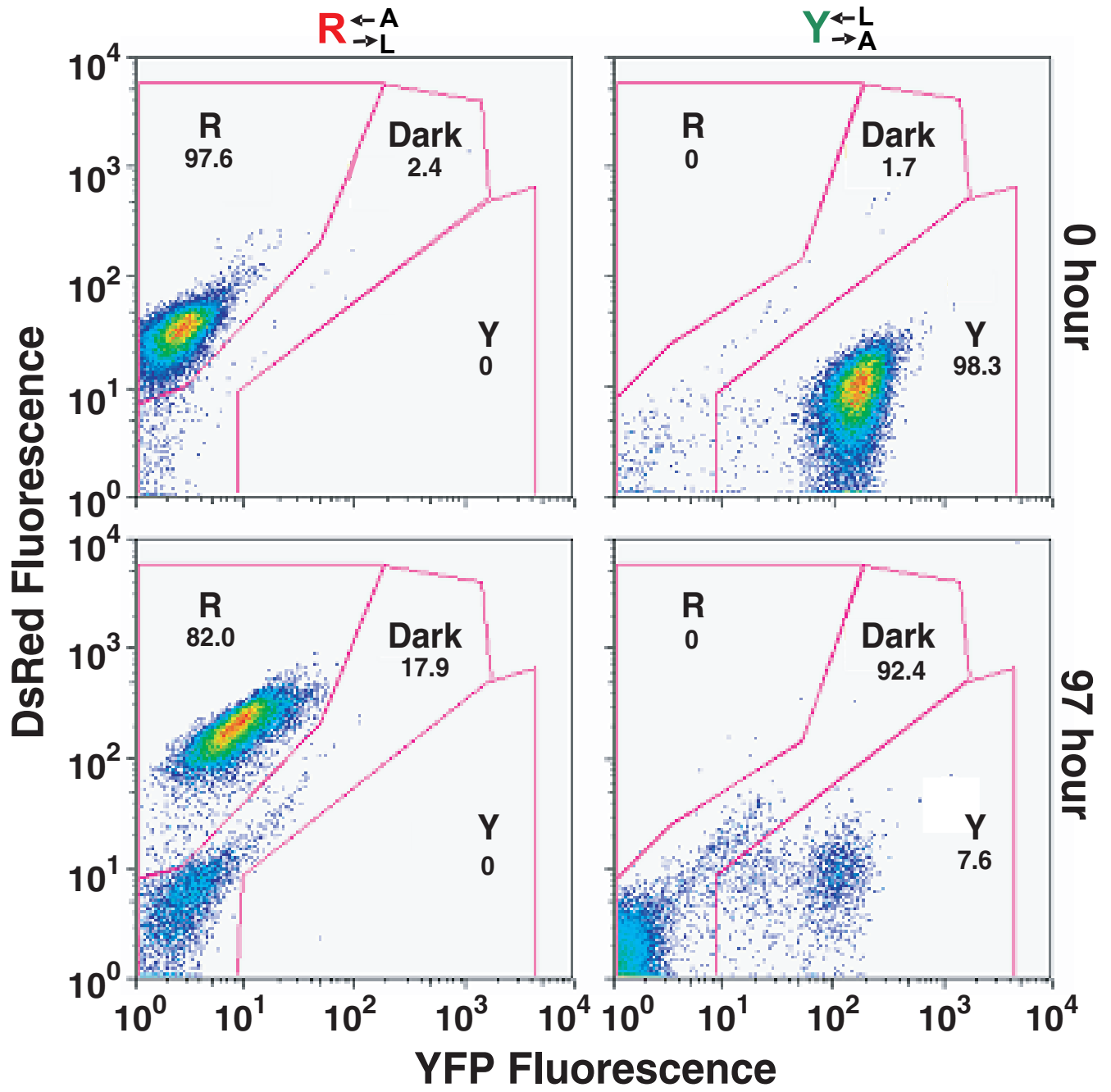


Fig. 9



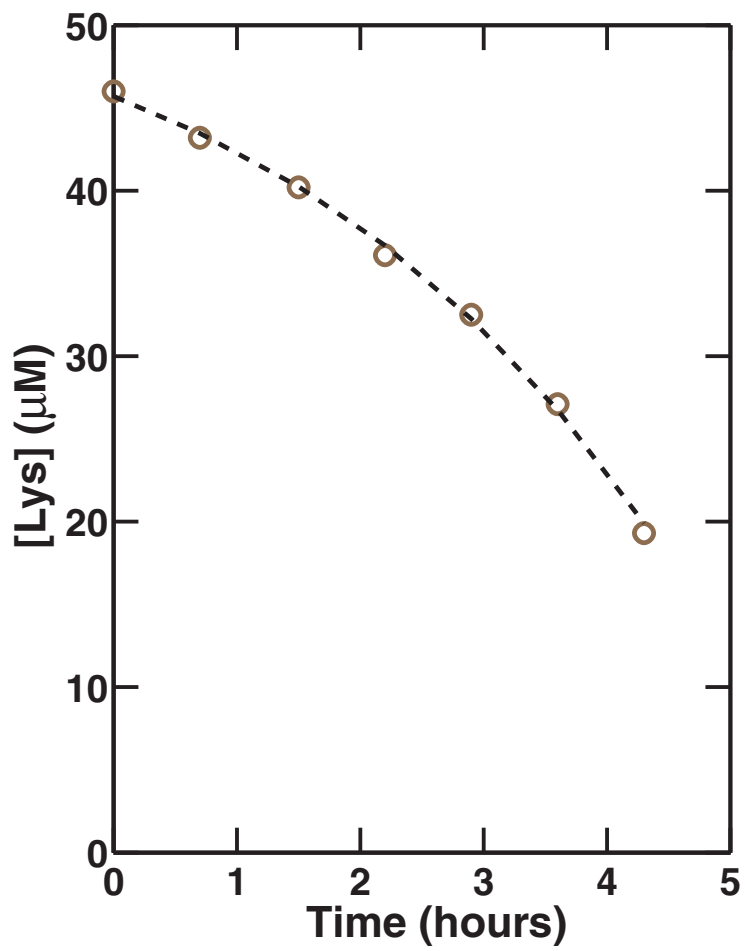
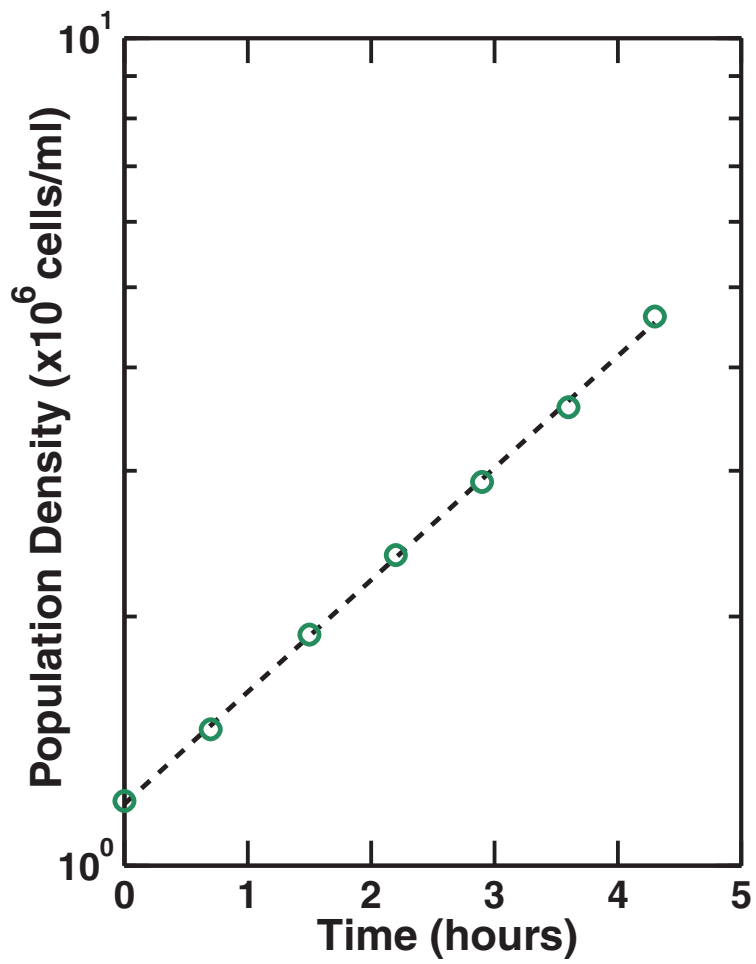


Fig. 10