Supporting Information

Fange et al. 10.1073/pnas.0811514106

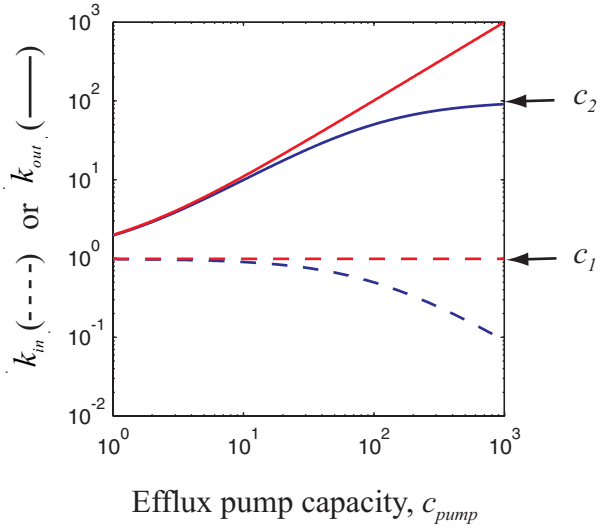

Fig. S1. Influx and efflux rate constants, k_{in} and k_{out}, as functions of drug efflux pump capacity for drug efflux pumping from the periplasm (blue) and cytoplasm (red), respectively. Parameters used: $c_1 = 1$, $c_2 = 100$.

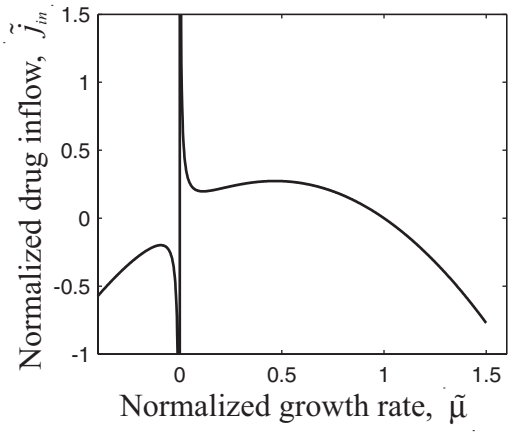

Fig. S2. Visualization of Eq. **S4**. For this particular parameter set, there is one minimum and one maximum for $\tilde{j}_{\text{in}}$ when $\tilde{j}_{\text{in}} > 0$, $\tilde{\mu} > 0$ and one maximum when $\tilde{\mu} < 0$. Plotting $\tilde{j}_{\text{in}}$ on the *x* axis, $\tilde{\mu}$ on the *y* axis, and displaying only the $\tilde{j}_{\text{in}} > 0$, $\tilde{\mu} > 0$ region, give the type of plot shown in Fig. 2*A*. Parameters used: $\tilde{k}_{\text{a}} = 100, \tilde{k}_{\text{d}} = \tilde{k}_{\text{out}} = 1$.

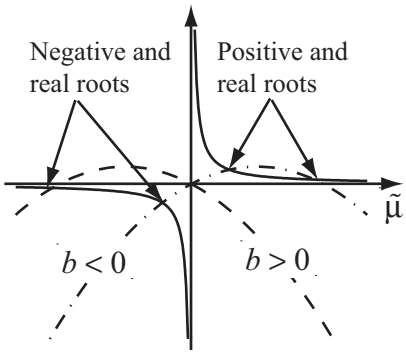

Fig. S3. Visualization of the intersections between $c/\tilde{\mu}$ (solid) and $-a\tilde{\mu}^2 - b\tilde{\mu} = c/\tilde{\mu}$, when $b > 0$ (dashed) and when $b < 0$ (dot-dashed) defined in Eq. **S12**. When $b < 0$ there can be either one or three real roots to Eq. **S5**, which are indicated here as intersection between the solid and dot-dashed lines. When $b > 0$ there can only be one root.

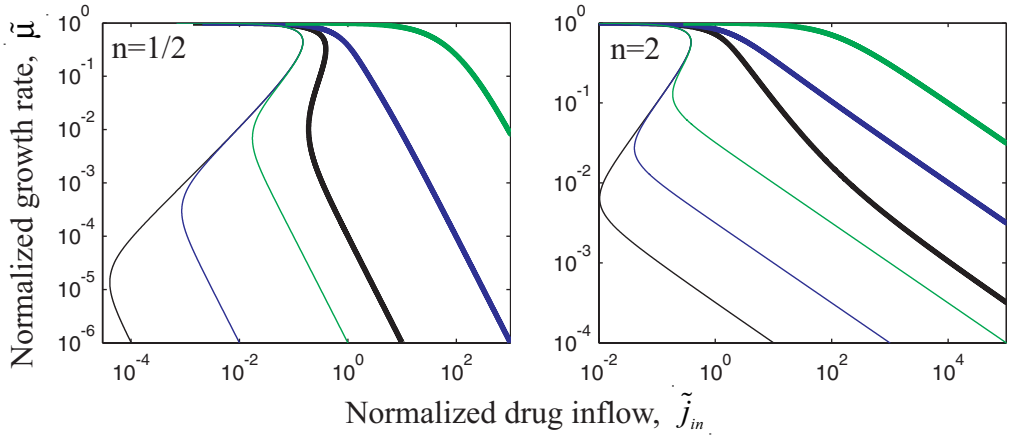

Fig. S4. Normalized growth-rate (*y* axis) as a function of the normalized drug inflow into the cell (*x* axis) for a power-law relation, $\tilde{\mu} = \tilde{r}_f^{1/n}$, between normalized drug free target concentration and normalized growth-rate, where $n = 1/2$ (left) and $n = 2$ (right). $n = 1$ is shown in Fig. 3. Parameters and colors are as in Fig. 3*A*.

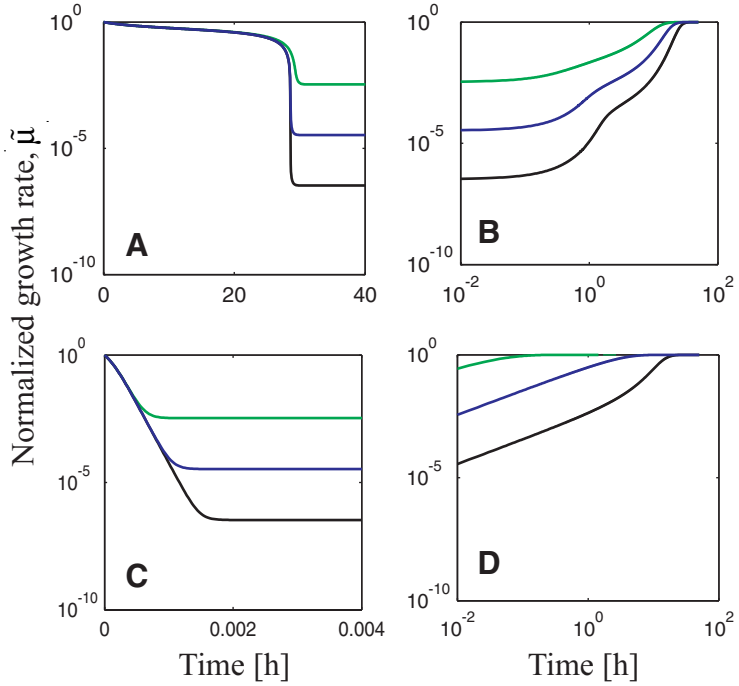

Fig. S5. (*A* and *C*) Growth rate time evolution, starting from normalized growth rate 1 and no internal drug. In *A*, the normalized drug inflow, $\tilde{j}_{\text{in}}$, is set to 0.3, and in *C* it is set to 3×10^4 at time 0, such that the steady-state growth rate is the same in *A* and *C*. (*B* and *D*) show growth rate time evolution starting from the steady states in *A* and *C*, respectively. Here the drug inflow $\tilde{j}_{\text{in}} = 0$ when time $t > 0$. (*A* and *B*) Efflux deficient ($\tilde{k}_{\text{out}} = 10$). (*C* and *D*) Efflux proficient ($\tilde{k}_{\text{out}} = 10^6$). Color-coding is as in Fig. 3.

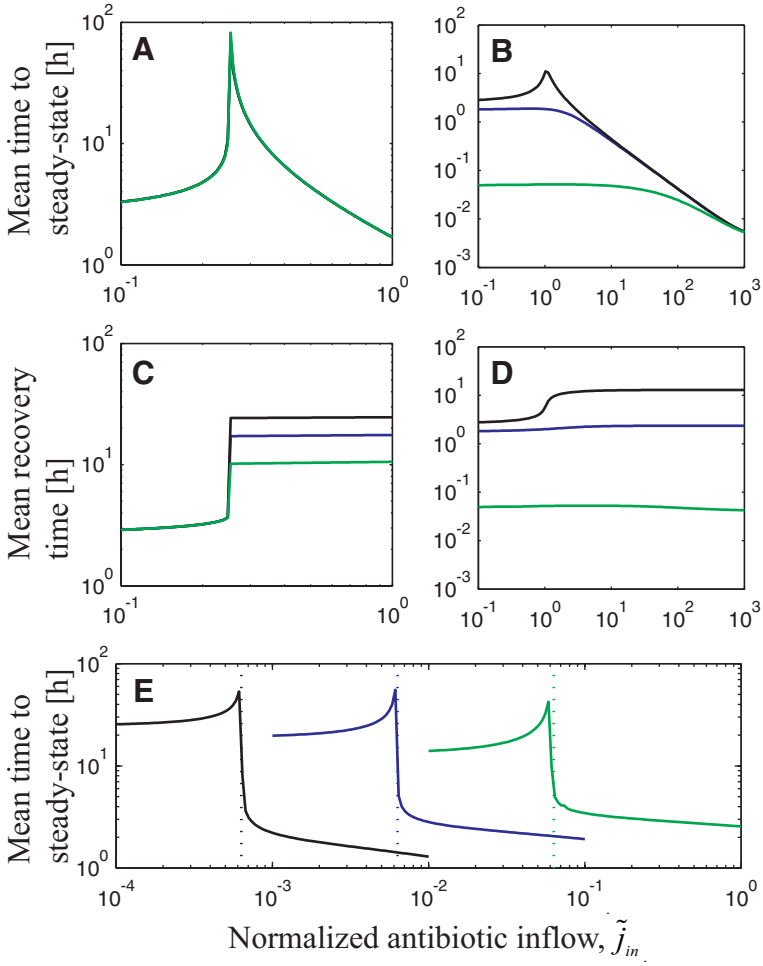

Fig. S6. (*A* and *B*) Mean time to reach steady state (Eq. **S19**) (*y* axis), starting from normalized growth rate $\tilde{\mu}=1$ (no internal drug) when $t=0$, as a function of normalized inflow $\tilde{j}_{\text{in}}$ (*x* axis) when $t>0$. (*C* and *D*) Mean time to reach normalized growth rate $\tilde{\mu}=1$ (Eq. **S19**) when $\tilde{j}_{\text{in}}=0$ for $t>0$, starting from steady state values corresponding to normalized inflow, $\tilde{j}_{\text{in}}$, defined on the *x* axis, when $t=0$. (*A* and *C*) Drug efflux deficiency as in Fig. S5 *A* and *C*. (*B* and *D*) Drug efflux proficiency as in Fig. S5 *B* and *D*. Color-coding as in Fig. 3.

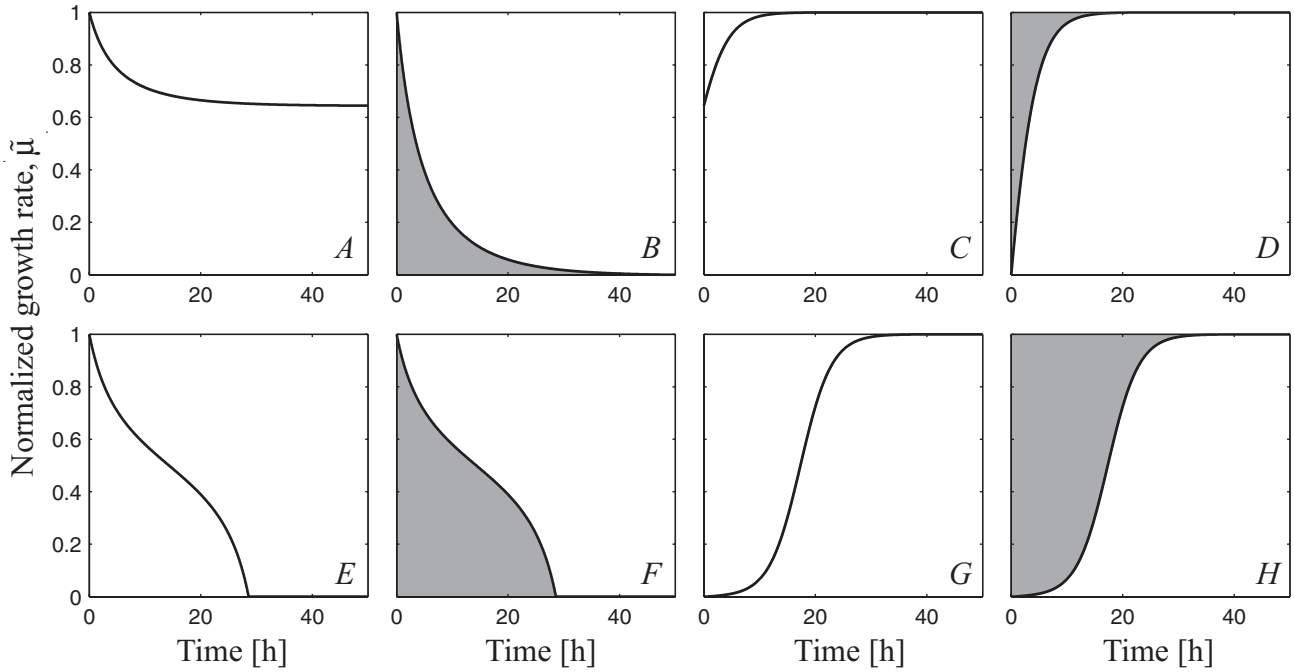

Fig. S7. Growth rate dynamics (*A*, *C*, *E*, and *G*) with corresponding mean times (shaded areas in *B*, *D*, *F* and *H*). (*A* and *E*) illustrate the time evolution of the growth rate toward the new steady-state after drug addition. (*C* and *G*) Growth rate recovery after drug removal. In *A* and *C*, the inflow is above, and in *E* and *G*, the inflow is below its critical value, at which the steady-state growth rate bifurcates.

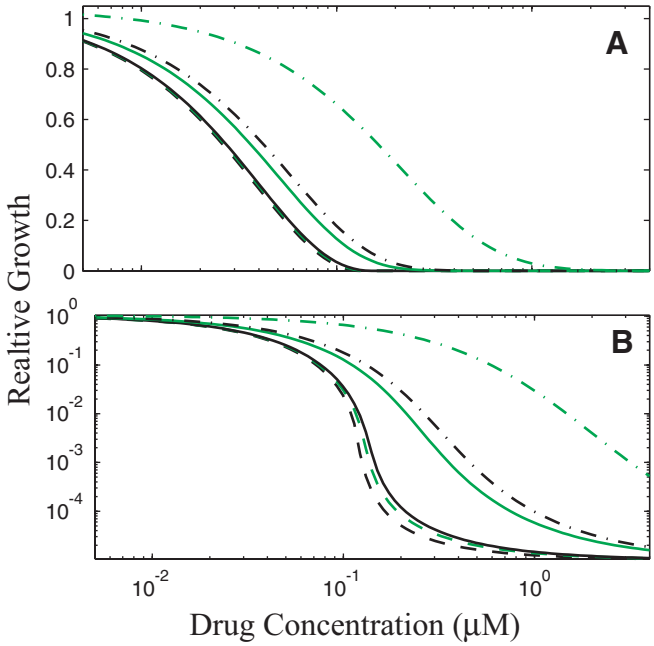

Fig. S8. Ratios between the extent of steady state cell growth during 16 h in the presence (growth rate, μ) and absence (growth rate, $\mu_0 = 2 \times 10^{-4}\cdot s^{-1}$) of drug in the medium as functions of the external drug concentration for wild type (black) and target resistance mutant (green) strains in drug efflux pump proficient (dot-dashed, $k_{out} = 2s^{-1}$), intermediate (solid, $k_{out} = 0.15s^{-1}$) and deficient (dashed, $k_{out} = 0.01\,s^{-1}$) backgrounds. The K_D values for wild type and target mutant are 1 nM ($k_a = 10^6\,M^{-1}\cdot s^{-1}$, $k_d = 10^{-3}\,s^{-1}$) and 10 nM ($k_a = 10^6\,M^{-1}\cdot s^{-1}$, $k_d = 10^{-2}\,s^{-1}$), respectively. The target concentration is 20 μM and the rate constant, k_{in}, for drug inflow is 0.01 s^{-1}, corresponding to a membrane permeability of 1.7×10^{-7} cm/s (when $A/V = 6\ \mu m^{-1}$). (*A*) Growth ratios in linear scale. (*B*) Growth ratios in logarithmic scale.

Other Supporting Information Files

SI Appendix