

**Table S1: Model parameters**

		Value	Reaction	Propensity	References and Comments
$k_{-a}$	MarA-promoter dissociation rate	$1.8 (\text{min})^{-1}$	$P_{10} \xrightarrow{k_{-a}} P_{00} + A$ $P_{11} \xrightarrow{k_{-a}} P_{01} + A$ $P_{12} \xrightarrow{k_{-a}} P_{02} + A$	$k_{-a} \cdot P_{10}$ $k_{-a} \cdot P_{11}$ $k_{-a} \cdot P_{12}$	<p>Other feedback operons: <math>1.8 \text{ min}^{-1}</math> [1], <math>2.4 \text{ min}^{-1}</math> [2].</p> <p>The stochastic pulsing is not disrupted for a wide range of <math>k_{-a}</math> and <math>k_{-r}</math> values.</p>
$k_a$	MarA-promoter association rate	$\frac{k_{-a}}{1500}$ $(\text{molecules} \cdot \text{min})^{-1}$	$P_{00} + A \xrightarrow{k_a} P_{10}$ $P_{01} + A \xrightarrow{k_a/\beta} P_{11}$ $P_{02} + A \xrightarrow{k_a/\beta'} P_{12}$	$\frac{1}{V} \cdot k_a \cdot P_{00} \cdot A$ $\frac{1}{V} \cdot \frac{k_a}{\beta} \cdot P_{01} \cdot A$ $\frac{1}{V} \cdot \frac{k_a}{\beta'} \cdot P_{02} \cdot A$	<p>Dissociation constant for MarA = <math>25 \text{ nM} = 1500</math> molecules/cell [3].</p> <p>V is the ratio between the volume of the cell at a given time and the average volume of <i>E. coli</i> considered in the paper (<math>1 \mu\text{m}^3</math>).</p>
$k_{-r}$	MarR <sub>2</sub> -promoter dissociation rate	$1.8 (\text{min})^{-1}$	$P_{01} \xrightarrow{k_{-r}} P_{00} + R_2$ $P_{02} \xrightarrow{2 \cdot k_{-r}} P_{01} + R_2$ $P_{11} \xrightarrow{k_{-r}} P_{10} + R_2$ $P_{12} \xrightarrow{2 \cdot k_{-r}} P_{11} + R_2$	$k_{-r} \cdot P_{01}$ $2 \cdot k_{-r} \cdot P_{02}$ $k_{-r} \cdot P_{11}$ $2 \cdot k_{-r} \cdot P_{12}$	<p>Other feedback operons: <math>1.8 \text{ min}^{-1}</math> [1], <math>2.4 \text{ min}^{-1}</math> [2].</p> <p>The stochastic pulsing is not disrupted for a wide range of <math>k_{-a}</math> and <math>k_{-r}</math> values.</p>
$k_r$	MarR <sub>2</sub> -promoter association rate	$\frac{k_{-r}}{150}$ $(\text{molecules} \cdot \text{min})^{-1}$	$P_{00} + R_2 \xrightarrow{2 \cdot k_r} P_{01}$ $P_{01} + R_2 \xrightarrow{k_r} P_{02}$	$\frac{1}{V} \cdot 2 \cdot k_r \cdot P_{00} \cdot R_2$ $\frac{1}{V} \cdot k_r \cdot P_{01} \cdot R_2$	<p>Dissociation constant for MarR<sub>2</sub> = <math>2.5 \text{ nM} = 150</math> molecules/cell [4-6].</p>

			$P_{10} + R_2 \xrightarrow{2 \cdot k_r / \alpha} P_{11}$ $P_{11} + R_2 \xrightarrow{k_r / \alpha'} P_{12}$	$\frac{1}{V} \cdot \frac{2 \cdot k_r}{\alpha} \cdot P_{10} \cdot R_2$ $\frac{1}{V} \cdot \frac{k_r}{\alpha'} \cdot P_{11} \cdot R_2$	
$\alpha_{00}$	Transcription rate with no MarR <sub>2</sub> molecules and no MarA molecules bound to the promoter	$0.40 \text{ (min)}^{-1}$	$P_{00} \xrightarrow{\alpha_{00}} P_{00} + M + R_{uf} + A_{uf}$	$\alpha_{00} \cdot P_{00}$	From other systems: $0.36 \text{ min}^{-1}$ [1], $0.1 \text{ min}^{-1}$ [2]. $\alpha_{00}$ , $\beta_{(a/r)}$ and $c_{Act}$ are chosen to match the experimental data (10,000 molecules if MarR <sub>2</sub> binding sites are eliminated, 500 molecules in the basal level – See Supplementary Methods).
$\alpha_{01}$	Transcription rate with one MarR <sub>2</sub> molecule and no MarA molecules bound to the promoter	$\alpha_{00} / c_{Inh1} \text{ (min)}^{-1}$	$P_{01} \xrightarrow{\alpha_{01}} P_{01} + M + R_{uf} + A_{uf}$	$\alpha_{01} \cdot P_{01}$	One molecule of MarR <sub>2</sub> is bound; the transcription rate is modified by $c_{Inh1}$ .
$\alpha_{10}$	Transcription rate with no MarR <sub>2</sub> molecules and one MarA molecule bound to the promoter	$\alpha_{00} \times c_{Act} \text{ (min)}^{-1}$	$P_{10} \xrightarrow{\alpha_{10}} P_{10} + M + R_{uf} + A_{uf}$	$\alpha_{10} \cdot P_{10}$	One molecule of MarA is bound; the transcription rate is modified by $c_{Act}$ .
$\alpha_{11}$	Transcription rate with one MarR <sub>2</sub> molecule and one MarA molecule bound to the promoter	$\alpha_{00} \times c_{Act} / c_{Inh1} \text{ (min)}^{-1}$	$P_{11} \xrightarrow{\alpha_{11}} P_{11} + M + R_{uf} + A_{uf}$	$\alpha_{11} \cdot P_{11}$	One molecule of MarA and one molecule of MarR <sub>2</sub> are bound; the transcription rate is modified by $c_{Act} / c_{Inh1}$ .
$\alpha_{12}$	Transcription rate with two MarR <sub>2</sub> molecules and one MarA molecule bound to the promoter	$\alpha_{00} \times c_{Act} / (c_{Inh1} \times c_{Inh2}) \text{ (min)}^{-1}$	$P_{12} \xrightarrow{\alpha_{12}} P_{12} + M + R_{uf} + A_{uf}$	$\alpha_{12} \cdot P_{12}$	One molecule of MarA and two molecules of MarR <sub>2</sub> are bound; the transcription rate is modified by $c_{Act} / (c_{Inh1} \times c_{Inh2})$ .

$\alpha_{02}$	Transcription rate with two MarR <sub>2</sub> molecules and no MarA molecules bound to the promoter	$\alpha_{00}/(c_{\text{Inh1}} \times c_{\text{Inh2}}) (\text{min})^{-1}$	$P_{02} \xrightarrow{\alpha_{02}} P_{02} + M + R_{uf} + A_{uf}$	$\alpha_{02} \cdot P_{02}$	Two molecules of MarR <sub>2</sub> are bound; the transcription rate is modified by $1 / (c_{\text{Inh1}} \times c_{\text{Inh2}})$ .
$c_{\text{Act}}$	Activation factor	80			From another system: 20 [1].  <i>marRAB</i> is expressed strongly after induction [7]. $\alpha_{00}$ , $\beta_{(a/r)}$ and $c_{\text{Act}}$ are chosen to match experimental data from this study (10,000 molecules if MarR <sub>2</sub> binding sites are eliminated, 500 molecules in the basal level – See Supplementary Methods).
$c_{\text{Inh1}}$	Repression factor for the first MarR <sub>2</sub> binding	800			MarR <sub>2</sub> binding impairs RNA polymerase binding and progression [5,8]. The system is robust to changes in this parameter.
$c_{\text{Inh2}}$	Repression factor for the second MarR <sub>2</sub> binding	10			MarR <sub>2</sub> binding impairs RNA polymerase binding and progression [5,8]. The system is robust to changes in this parameter.
$\lambda_M$	mRNA degradation rate	$\ln(2) / 24 (\text{min})^{-1}$	$M \xrightarrow{\lambda_M} 0$	$\lambda_M \cdot M$	[9], Stochastic pulsing behavior is robust to changes in this parameter.
$\beta_a$	<i>marA</i> translation rate	$0.34 \times 20 (\text{min})^{-1}$	$M \xrightarrow{\beta_a} M + A_{uf}$	$\beta_a \cdot M$	Translation rate = 34% of the <i>lacZ</i> translation rate [7].  <i>lacZ</i> translation rate: 18.8 min <sup>-1</sup> [10], <i>lacZ</i> initialization every 3.2 sec [11].
$\beta_r$	<i>marR</i> translation rate	$0.044 \times 20 (\text{min})^{-1}$	$M \xrightarrow{\beta_r} M + R_{uf}$	$\beta_r \cdot M$	Translation rate = 4.4% of the <i>lacZ</i> translation rate. [7].
$k_{fa}$	MarA folding rate	$5 (\text{min})^{-1}$	$A_{uf} \xrightarrow{k_{fa}} A$	$k_{fa} \cdot A_{uf}$	Fast, due to the small size of the protein and the coupling of this process with translation <i>in vivo</i> [12]. The system is robust to changes in this value.

					Other examples: $60 \text{ min}^{-1}$ for Cytochrome C [13], $0.9 \text{ min}^{-1}$ for the synthetic oscillator [1].
$k_{fr}$	MarR folding rate	$5 (\text{min})^{-1}$	$R_{uf} \xrightarrow{k_{fr}} R$	$k_{fr} \cdot R_{uf}$	Fast, due to the small size of the protein and the coupling of this process with translation <i>in vivo</i> [12]. The system is robust to variations in this value.  Other examples: $60 \text{ min}^{-1}$ for Cytochrome C [13], $0.9 \text{ min}^{-1}$ for the synthetic oscillator [1].
$k_{dr}$	MarR dimerization rate	$0.01 (\text{molecules} \cdot \text{min})^{-1}$	$2 \times R \xrightarrow{k_{dr}} R_2$	$\frac{1}{V} \cdot k_{dr} \cdot \frac{R \cdot (R-1)}{2}$	Assumed to be consistent with the cI protein in <i>E. coli</i> , $0.01 \text{ mol}^{-1} \text{ min}^{-1}$ [14]. The system is robust to variations in this value.  Another example: $0.18 \text{ min}^{-1}$ for the synthetic oscillator [1].
$k_{-dr}$	MarR <sub>2</sub> dimer disruption rate	$k_{dr}/50 (\text{min})^{-1}$	$R_2 \xrightarrow{k_{-dr}} 2 \times R$	$k_{-dr} \cdot R_2$	Assumed to be consistent with the cI protein in <i>E. coli</i> , $k_{dr}/50 \text{ min}^{-1}$ . The system is robust to variations in this value.  Other example: $k_{dr}/100 \text{ min}^{-1}$ for the synthetic oscillator [1].
$\lambda_{auf}$	Unfolded MarA degradation rate	$\lambda_r (\text{min})^{-1}$	$A_{uf} \xrightarrow{\lambda_{auf}} 0$	$\lambda_{auf} \cdot A_{uf}$	We assumed only folded MarA to be actively degraded by Lon protease [15], setting the degradation rate for unfolded MarA at a reduced level, comparable to what we used for degradation of the folded MarR <sub>2</sub> protein. There is only a small amount of unfolded protein; as a result, the system is robust to variations in this parameter.
$\lambda_a$	MarA degradation	$\ln(2) (\text{min})^{-1}$	$A \xrightarrow{\lambda_a} 0$	$\lambda_a \cdot A$	[15]
$\lambda_{ruf}$	Unfolded MarR degradation rate	$\lambda_r (\text{min})^{-1}$	$R_{uf} \xrightarrow{\lambda_{ruf}} 0$	$\lambda_{ruf} \cdot R_{uf}$	We assumed the same degradation rate as the folded MarR <sub>2</sub> protein. There is only a small amount of unfolded protein; as a result, the system is robust to variations in this parameter.

$\lambda_r$	MarR and MarR <sub>2</sub> degradation	$\ln(2) / 24 \text{ (min)}^{-1}$	$R \xrightarrow{\lambda_r} 0$ $R_2 \xrightarrow{\lambda_r} 0$	$\lambda_r \cdot R$ $\lambda_r \cdot R_2$	We assumed the protein to be stable, using a degradation time that matches the dilution rate due to cell division in rich medium [16]. Changes in the parameter do not disrupt stochastic pulsing.
$k_{sal}$	MarR <sub>2</sub> allosteric inhibition rate	20 $\text{(molecules} \cdot \text{min)}^{-1}$	$Sal + MarR_2 \xrightarrow{k_{Sal}} MarR_2 - Sal$	$\frac{1}{V} \cdot k_{Sal} \cdot MarR_2 \cdot Sal$	Selected to fit experimental data from [17] and [18]. The system is robust to changes in this parameter.
$k_{-sal}$	MarR <sub>2</sub> -Salicylate complex disruption rate	0.5 $\text{(min)}^{-1}$	$MarR_2 - Sal \xrightarrow{k_{-Sal}} Sal + MarR_2$	$k_{-Sal} \cdot MarR_2 - Sal$	Selected to fit experimental data from [17] and [18]. The system is robust to changes in this parameter.
		As detailed in Supplementary Methods, the parameters given below are used to fit the model to the following experimental data: 3.3-fold repression with only one MarR <sub>2</sub> site active and a 20-fold repression with both sites active [7,19]; competition in the binding between MarA and MarR <sub>2</sub> [5], either by sliding block [20] or alignment of the marbox with the -35 box [8]; approximately 9,000 molecules with 5mM of salicylate induction [4] and maximum expression with salicylate of 10,000 molecules ([17] with the data from [4]); basal expression of 500 molecules (Maximum level / Repression fold with both sites active).			
$\alpha$	Inhibition in the binding of the first molecule of MarR <sub>2</sub> when MarA and no MarR <sub>2</sub> are bound	1000	$P_{10} + R_2 \xrightarrow{2 \cdot k_r / \alpha} P_{11}$		
$\alpha'$	Inhibition in the binding of the second molecule of MarR <sub>2</sub> when MarA and MarR <sub>2</sub> are bound	1.5	$P_{11} + R_2 \xrightarrow{k_r / \alpha'} P_{12}$		
$\beta$	Inhibition in the binding of MarA when one MarR <sub>2</sub> molecule is bound	1.5	$P_{01} + A \xrightarrow{k_a / \beta} P_{11}$		

$\beta'$	Inhibition in the binding of MarA when two MarR <sub>2</sub> molecules are bound	1.5	$P_{02} + A \xrightarrow{k_a/\beta'} P_{12}$		
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