Design Project: Robust Toggle Switch

Milo Knowles

May 11, 2020

1 IFFL Controller for Temperature Robustness

In the IFFL controller, we introduce two new proteins R_1 and R_2, which serve as negative inducers for X_1 and X_2, respectively. See Figure 1 for a system diagram of the controller.

1.1 Reactions

$X_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X_1^d$	Dimerization reaction	(1)
$X_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X_2^d$	Dimerization reaction	(2)
$X_1^d + D_2 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} C_2$	X_1 represses production of X_2	(3)
$X_2^d + D_1 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} C_1$	X_2 represses production of X_1	(4)
$X_1^d + R_1 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} C_{r1}$	Negative inducer R_1 sequesters X_1	(5)
$X_2^d + R_2 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} C_{r2}$	Negative inducer R_2 sequesters X_2	(6)
$D_1 \xrightarrow{\beta} D_1 + X1$	Translation of X_1, neglecting mRNA dynamics	(7)
$D_2 \xrightarrow{\beta} D_2 + X2$	Translation of X_2, neglecting mRNA dynamics	(8)
$X_1 \xrightarrow{\gamma} \phi$	Degradation or dilution	(9)
$X_2 \xrightarrow{\gamma} \phi$	Degradation or dilution	(10)
		(11)

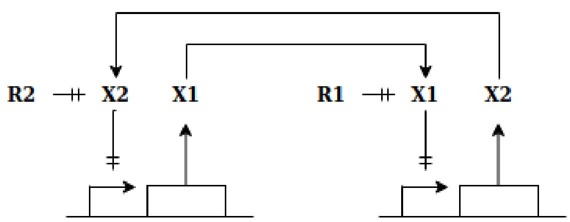

Figure 1: A system diagram for the IFFL controller. On the left, X_2 represses production of X_1, but is also repressed by the negative inducer R_2. Symmetrically on the right, X_1 represses production of X_2, but is also repressed by the negative inducer R_1. When a change in temperature reduces the dissociation constant for X_1 and X_2 it also reduces the dissociation constant for the negative inducers R_1 and R_2. This increases the amount of free X_1 and X_2 (i.e not sequestered by the negative inducers), which compensates for the reduced repressive ability of X_1 and X_2.

1.2 System of ODEs

We can model the system with the following system of ODEs:

$$\frac{dX_1}{dt} = -2k_1X_1^2 + 2k_2X_1^d + \beta D_1 - \gamma X_1 \tag{12}$$
$$\frac{dX_2}{dt} = -2k_1X_2^2 + 2k_2X_2^d + \beta D_2 - \gamma X_2 \tag{13}$$
$$\frac{dX_1^d}{dt} = k_1X_1^2 - k_2X_1^d - k_3X_1^dD_2 + k_4C_2 - k_3R_1X_1^d + k_4C_{1r} \tag{14}$$
$$\frac{dX_2^d}{dt} = k_1X_2^2 - k_2X_2^d - k_3X_2^dD_1 + k_4C_1 - k_3R_2X_2^d + k_4C_{2r} \tag{15}$$
$$\frac{dC_1}{dt} = k_3X_2^dD_1 - k_4C_1 \tag{16}$$
$$\frac{dC_2}{dt} = k_3X_1^dD_2 - k_4C_2 \tag{17}$$
$$\frac{dC_{1r}}{dt} = k_3R_1X_1^d - k_4C_{1r} \tag{18}$$
$$\frac{dC_{2r}}{dt} = k_4R_2X_2^d - k_4C_{2r} \tag{19}$$
$$\tag{20}$$

1.3 Model Assumptions

- The rate constants k_3 and k_4 are the same for all reactions involving complexes C_1, C_2, C_{1r}, and C_{2r}.

1.4 Conservation Laws

In addition, we have the following four conservation laws:

$$D_{1,tot} = D_1 + C_1 \tag{21}$$
$$D_{2,tot} = D_2 + C_2 \tag{22}$$
$$R_{1,tot} = R_1 + C_{1r} \tag{23}$$
$$R_{2,tot} = R_2 + C_{2r} \tag{24}$$

which capture the fact that the DNA can either be free or in a complex, and similarly, that the negative inducers R_1 and R_2 can either be free or in their respective complexes.

1.5 Quasi-Steady-State Approximations