Supplementary Material: Growth Feedback Confers Cooperativity in Resource-Competing Synthetic Gene Circuits

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1. Model Analysis for the Model Without Metabolic Burden

$$\frac{dx_1}{dt} = \frac{v_1\ R_1}{\frac{R_1}{Q_1} + \frac{R_2}{Q_2} + 1} - d_1\ x_1 - kg_0\ x_1 \tag{1a}$$

$$\frac{dx_2}{dt} = \frac{v_2\ R_2}{\frac{R_1}{Q_1} + \frac{R_2}{Q_2} + 1} - d_2\ x_2 - kg_0\ x_2 \tag{1b}$$

Steady States

The steady state for the system 1 is given by:

$$x_{1ss} = \frac{Q_1 Q_2 R_1 v_1}{(d_{01} + kg_0)(Q_1 Q_2 + Q_1 R_2 + Q_2 R_1)} \tag{2}$$

$$x_{2ss} = \frac{Q_1 Q_2 R_2 v_2}{(d_{02} + kg_0)(Q_1 Q_2 + Q_1 R_2 + Q_2 R_1)} \tag{3}$$

Steady States Analysis

Proposition 1: There is no cooperativity between two constitutive gene module competing for resource in an host-circuit system without growth feedback.

Notice that for all values of $R_1 > 0$, $\frac{dx_{2ss}}{dR_1} < 0$ (see 4). Therefore, if the R_1 term of module-1 increase the steady state of module-2 decreases.

$$\frac{dx_{2ss}}{dR_1} = -\frac{Q_1 {Q_2}^2 R_2 v_2}{(d_2 + kg_0)(Q_1(Q_2 + R_2) + Q_2 R_1)^2} \tag{4}$$

2. Model Analysis for the System with Metabolic Burden

The differential equations for the synthetic gene circuit with of two constitute modules is given by:

$$\frac{dx_1}{dt} = \frac{v_1\ R_1}{\frac{R_1}{Q_1}+\frac{R_2}{Q_2}+1} - d_1\ x_1 - \frac{kg_0\ x_1}{\frac{R_1}{Q_1}+\frac{R_2}{Q_2}+1} \tag{5a}$$

$$\frac{dx_2}{dt} = \frac{v_2\ R_2}{\frac{R_1}{Q_1}+\frac{R_2}{Q_2}+1} - d_2\ x_2 - \frac{kg_0\ x_2}{\frac{R_1}{Q_1}+\frac{R_2}{Q_2}+1} \tag{5b}$$

Steady States

In order to find the steady state for system 5, we set the equations equal to zero and solve with respect to x_1 and x_2, respectively. The steady state are given by:

$$x_{1ss} = \frac{Q_1Q_2R_1v_1\left(\left(\frac{R_1}{J_1}+\frac{R_2}{J_2}\right)+1\right)}{(Q_1(Q_2+R_2)+Q_2R_1)\left(d_{01}\left(\frac{R_1}{J_1}+\frac{R_2}{J_2}\right)+d_{01}+kg_0\right)} \tag{6}$$

$$x_{2ss} = \frac{Q_1Q_2R_2v_2\left(\left(\frac{R_1}{J_1}+\frac{R_2}{J_2}\right)^m+1\right)}{(Q_1(Q_2+R_2)+Q_2R_1)\left(d_{02}\left(\frac{R_1}{J_1}+\frac{R_2}{J_2}\right)^m+d_{02}+kg_0\right)} \tag{7}$$

2.1. Cooperative Condition

Proposition 2: Two constitutive gene module competing for resource can cooperate with each order under growth feedback, if the following parameter condition is satisfied.

$$\frac{Q_2}{Q_1(Q_2+R_2)} \leq \frac{J_2}{J_1(J_2+R_2)}\frac{J_2\ kg_0}{J_2kg_0+d_2(J_2+R_2)} \tag{8}$$

For the symmetry case where $J_1 = J_2 = J$,and $Q_1 = Q_2 = Q$, the condition is:

$$\frac{1}{(Q+R_2)} \leq \frac{1}{(J+R_2)}\frac{J\ kg_0}{Jkg_0+d_2(J+R_2)} \tag{9}$$

If the condition above is satisfied, there exist range of $R_1 \in (0, R_{1max})$, where $\frac{dx_2}{dR_1} > 0$. Therefore, if the $R_1 \in (0, R_{1max})$ is increase the module-1 and module-2 steady states increases. R_{1max} is given by:

$$R_{1max} = \frac{\sqrt{d_2J_1{J_2}^3kg_0Q_2(J_2Q_1(Q_2+R_2)-J_1Q_2(J_2+R_2))}-d_2J_1J_2Q_2(J_2+R_2)}{d_2{J_2}^2Q_2} \tag{10}$$

Notice that if the Condition 8 is satisfied, there is only one positive critical value (a local maximum) for x_{2ss} with respect to R_1, that is $\frac{dx_{2ss}}{dt} = 0$, where $R_1 = R_{1max} \geq 0$. Then, evaluating $\frac{dx_{2ss}}{dR_1}$ for $R_1 = 0$, we get:

$$\left.\frac{dx_{2ss}}{dR_1}\right|_{R_1=0} = -\frac{Q_2 R_2 v_2 \left(d_2 J_1 Q_2 (J_2 + R_2)^2 + J_2 k g_0 (J_1 Q_2 (J_2 + R_2) - J_2 Q_1 (Q_2 + R_2))\right)}{J_1 Q_1 (Q_2 + R_2)^2 (d_2 (J_2 + R_2) + J_2 k g_0)^2} \tag{11}$$

The right hand side of Equation 11 is positive if Condition 8 is satisfied. Therefore, if $R_1 \in (0, R_{1max})$, then $\frac{dx_{2ss}}{dR_1} > 0$.

3. Parameter Values

Module 1		Module 2	
Parameters	Values	Parameters	Values
v_1	0.5	v_2	0.5
Q_1	75	Q_2	75
J_1	1	J_2	1
d_1	0.25	d_2	0.25
R_1	7.5	R_2	7.5

Table S1: Parameter Values for the Synthetic Gene Circuit with Two Constitutive Modules, with $kg_0 = 5$

Module 1	
Parameters	Values
v_1	0.67
Q_1	75
J_1	2
d_1	0.25
R_1	7.5

Module 2	
Parameters	Values
v_2	0.5
Q_2	75
J_2	1
d_2	0.25
k_{02}	0.062
I_{SA}	0.3
N_{cp2}	7.5

Table S2: Parameter Values for the Synthetic Gene Circuit with a Constitutive and Self-activation Modules, with $kg_0 = 4$

Module 1		Module 2	
Parameters	Values	Parameters	Values
v_1	0.67	v_2	0.67
Q_1	3	Q_2	3
J_1	4	J_2	4
d_1	0.25	d_2	0.25
k_{01}	0.025	k_{02}	0.025
I_{SA1}	0.3	I_{SA2}	0.3
N_{cp1}	10	N_{cp2}	10

Table S3: Parameter Values for the Synthetic Gene Circuit with Two Self-activation Modules, with $kg_0 = 2$

4. Supplementary Figures

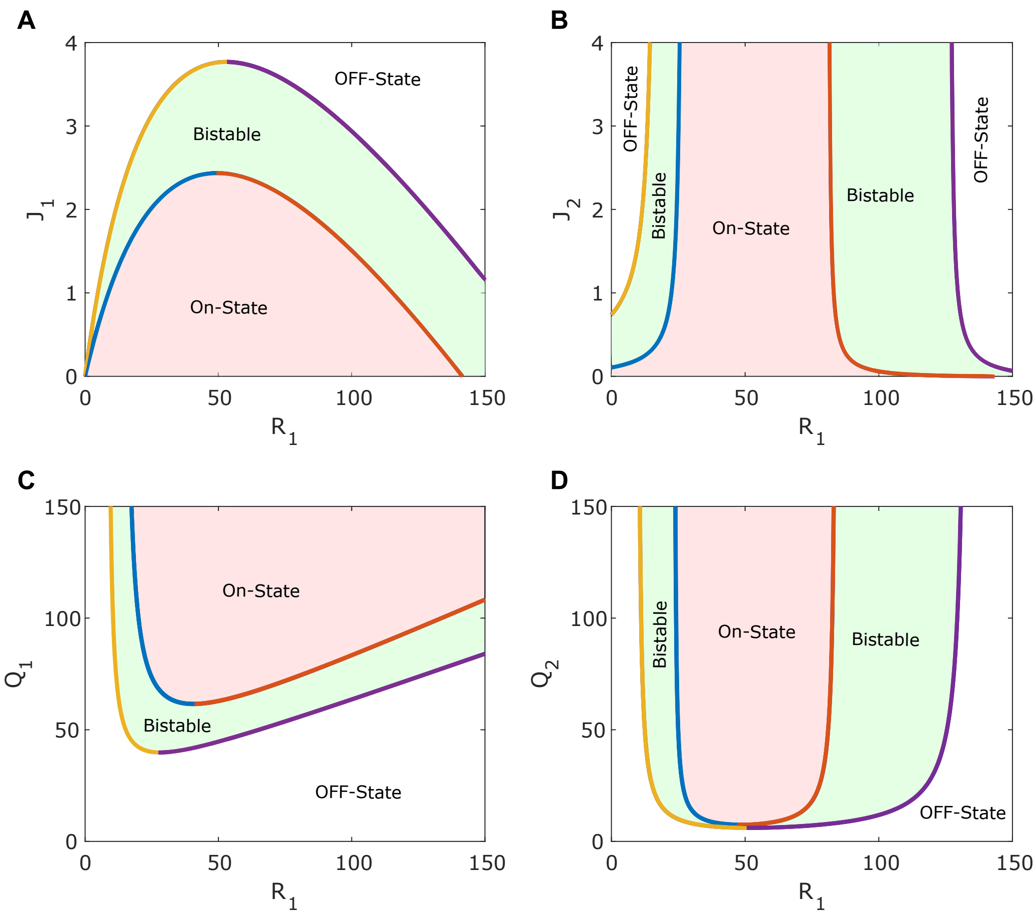

Figure S1: Analysis of the synthetic gene circuit with a constitutive and self-activation modules, for $J_1 \neq J_2$ and $Q_1 \neq Q_2$. (A-B) Two-parameter bifurcation diagram with respect to J_1 (Q_1 in (D)) and R_1 shows the dependence of the saddle-nodes (SN1-4) . SN1 (blue line), SN2 (orange line), SN3 (yellow line), and SN4 (purple line) correspond to the saddle-node bifurcation points. The red region of the represents the ON-state of x_2 Module. The green region corresponds to the system bistability. White region represents the OFF-state of the x_2 module

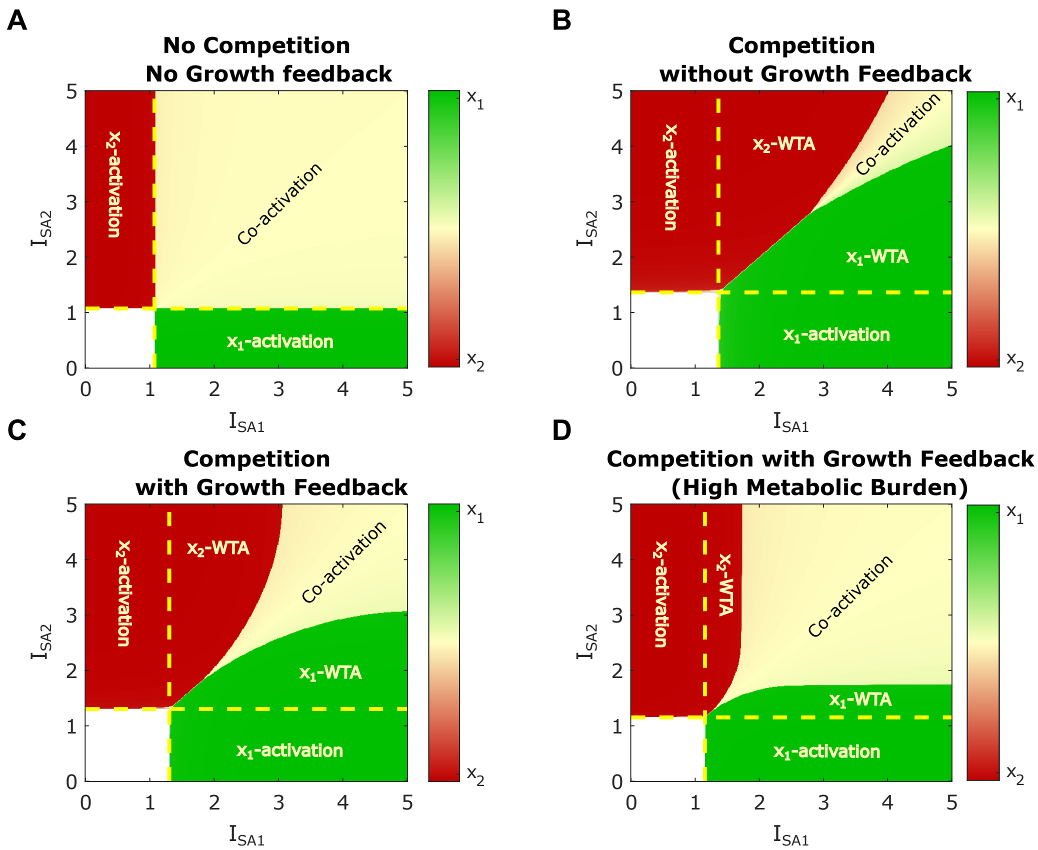

Figure S2: (A-D) Cell fates in the space of inducer I_{SA1} and I_{SA2}, starting from OFF-OFF state, under conditions with neither competition nor growth feedback (A), with resource competition and no growth feedback (B); competition with metabolic burden (C)($J_1 = J_2 = 15$), and high metabolic burden (D) ($J_1 = J_2 = 4$).