sb2cl Lab
Synthetic Biology and Biosystems Control Lab
Valencia UPV

2020 Measurement

Modeling: Modeling circuits with ODEs and experimental data

Section 1: Composing circuit models from Hill Functions

by Alejandro Vignoni (alvig2@upv.es)

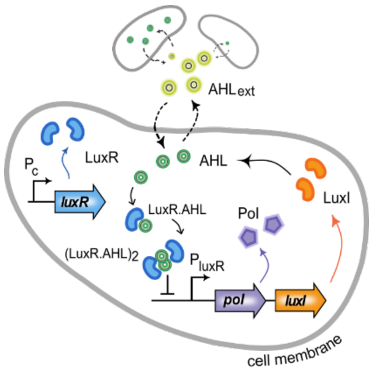
An iGEM Measurement Committee Webinar
Week 3a, June 30th, 2020

Today Webinar's Topics

- Section 1: **Composing circuit models from Hill functions** (15 min)
- Section 2: Relating parameters and data (15 min)
- Section 3: Example: Incoherent feed-forward loop (model & data) (15 min)
- Q&A – (at the end of each 15 minutes block, total 15 min)

Remember our journey: but now going directly to reduced models

Schematic → Biochemical Reactions → Reduced Mathematical Model



$$
\begin{aligned}
&\xrightarrow{\mathrm{C_R}} \mathrm{mR}\\
&\mathrm{gPI} \xrightarrow{\mathrm{k_{e_I}}} \mathrm{gPI} + \mathrm{mPI}\\
&\mathrm{mR} \xrightarrow{\mathrm{p_R}} \mathrm{mR} + \mathrm{R}\\
&\mathrm{mPI} \xrightarrow{\mathrm{p_I}} \mathrm{mPI} + \mathrm{PI}\\
&\mathrm{I} \xrightarrow{\mathrm{k_A}} \mathrm{A} + \mathrm{I}\\
&\mathrm{R} + \mathrm{A} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_{-1}/k_{d1}}}{\rightleftharpoons}} (\mathrm{R}\cdot\mathrm{A})\\
&{}_2(\mathrm{R}\cdot\mathrm{A}) \underset{\mathrm{k_{-2}}}{\overset{\mathrm{k_{-2}/k_{d2}}}{\rightleftharpoons}} (\mathrm{R}\cdot\mathrm{A})_2\\
&\mathrm{gPI} + (\mathrm{R}\cdot\mathrm{A})_2 \underset{\mathrm{k_{lux}}}{\overset{\mathrm{k_{lux}/k_{dlux}}}{\rightleftharpoons}} \mathrm{gPI}\cdot(\mathrm{R}\cdot\mathrm{A})_2\\
&\mathrm{gPI}\cdot(\mathrm{R}\cdot\mathrm{A})_2 \xrightarrow{\alpha \mathrm{k_{e_I}}} \mathrm{gPI}\cdot(\mathrm{R}\cdot\mathrm{A})_2 + \mathrm{mPI}\\
&\mathrm{A} \underset{\mathrm{DV_c}}{\overset{\mathrm{D}}{\rightleftharpoons}} \mathrm{A_{ext}}
\end{aligned}
$$

$$
\begin{aligned}
\dot{n}_1^i &= \frac{\mathrm{C_I p_I}}{\mathrm{d_{m_I}}}\left(\frac{\mathrm{k_{dlux}} + \alpha n_3^i}{\mathrm{k_{dlux}} + n_3^i}\right) - \mathrm{d_I} n_1^i\\
\dot{n}_2^i &= \frac{\mathrm{C_R p_R}}{\mathrm{d_{m_R}}} + \mathrm{k_{-1}} n_6^i - \left(\frac{\mathrm{k_{-1}}}{\mathrm{k_{d1}}} n_4^i + \mathrm{d_R}\right) n_2^i\\
\dot{n}_3^i &= \frac{\mathrm{k_{-2}}}{\mathrm{k_{d2}}}(n_6^i)^2 - (\mathrm{k_{-2}} + \mathrm{d_{RA_2}}) n_3^i\\
\dot{n}_4^i &= \mathrm{k_{-1}} n_6^i + \mathrm{k_A} n_1^i + \mathrm{D}\left(\frac{n_5}{\mathrm{V_c}} - n_4^i\right) - \left(\frac{\mathrm{k_{-1}}}{\mathrm{k_{d1}}} n_2^i + \mathrm{d_A}\right)
\end{aligned}
$$

From
Y. Boada (2018)

Modeling a genetic circuit: What do you want to do?

- Biosensor
- Promoter

- Logic (Inverter)
- Memory
- Level detection

- Reporter
- Enzyme
- SM Signal
- Therapeutic

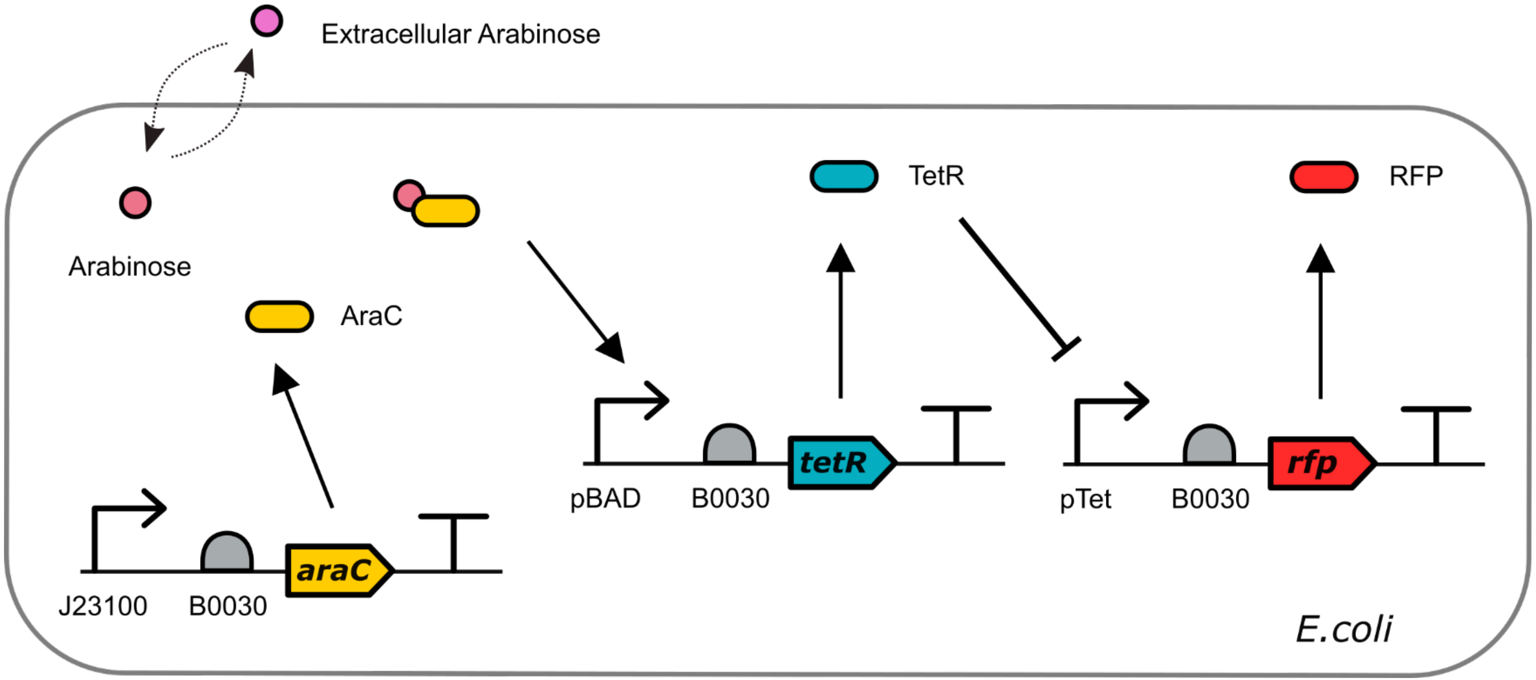
Example: Detect Arabinose

Inverter (TetR)

Fluorescence Protein (RFP)

Modeling a genetic circuit

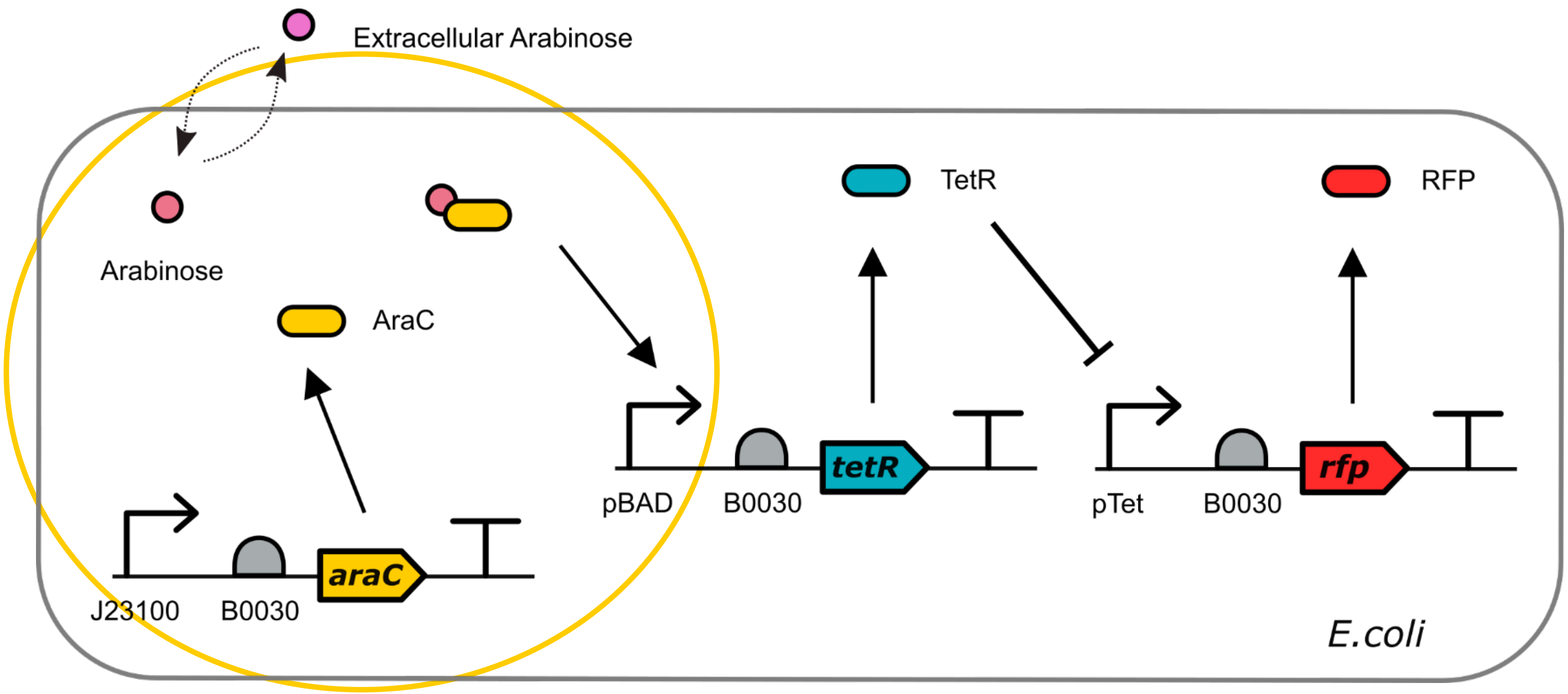
Example Sense-Compute-Act



Modeling a genetic circuit

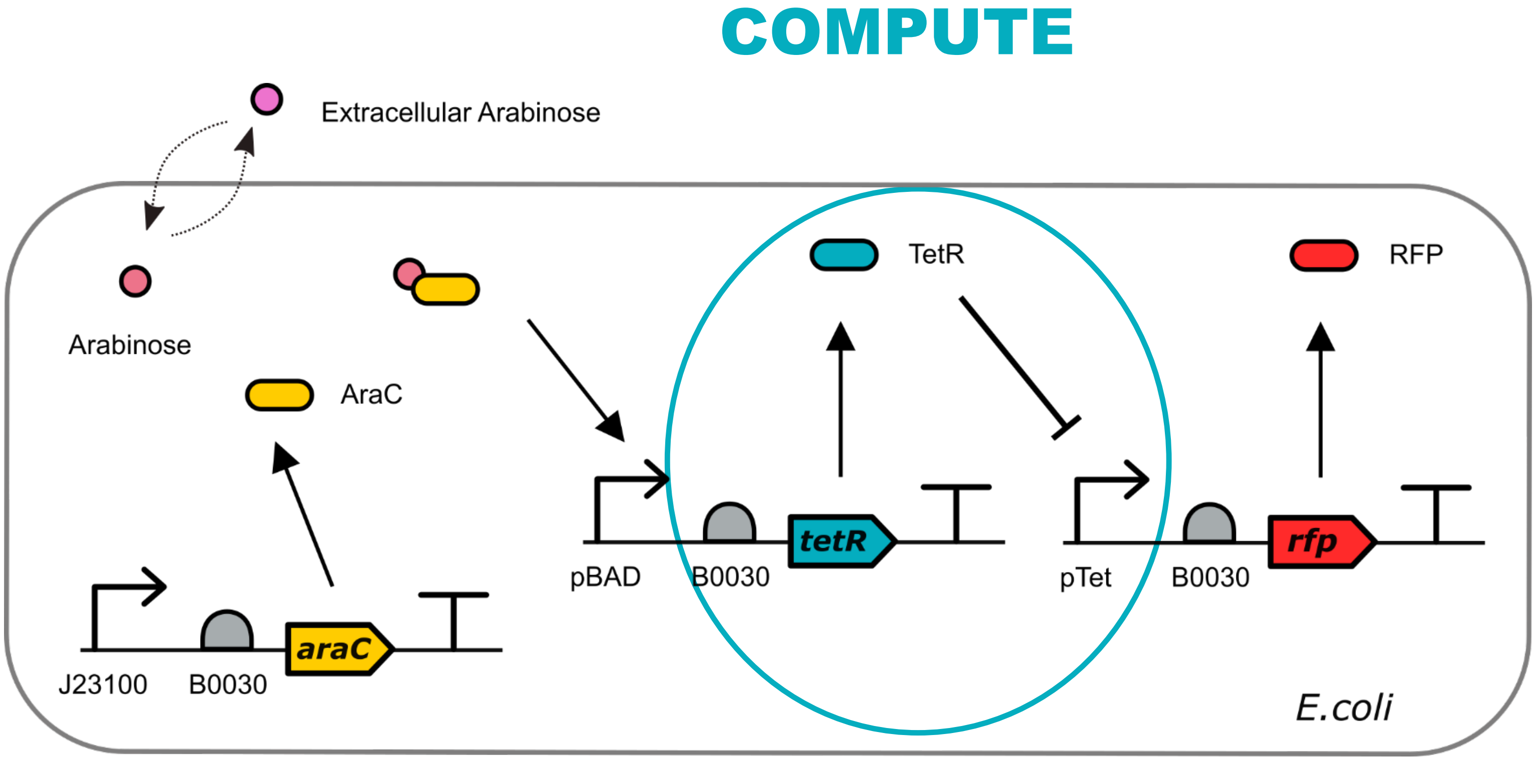
Example Sense-Compute-Act

SENSE



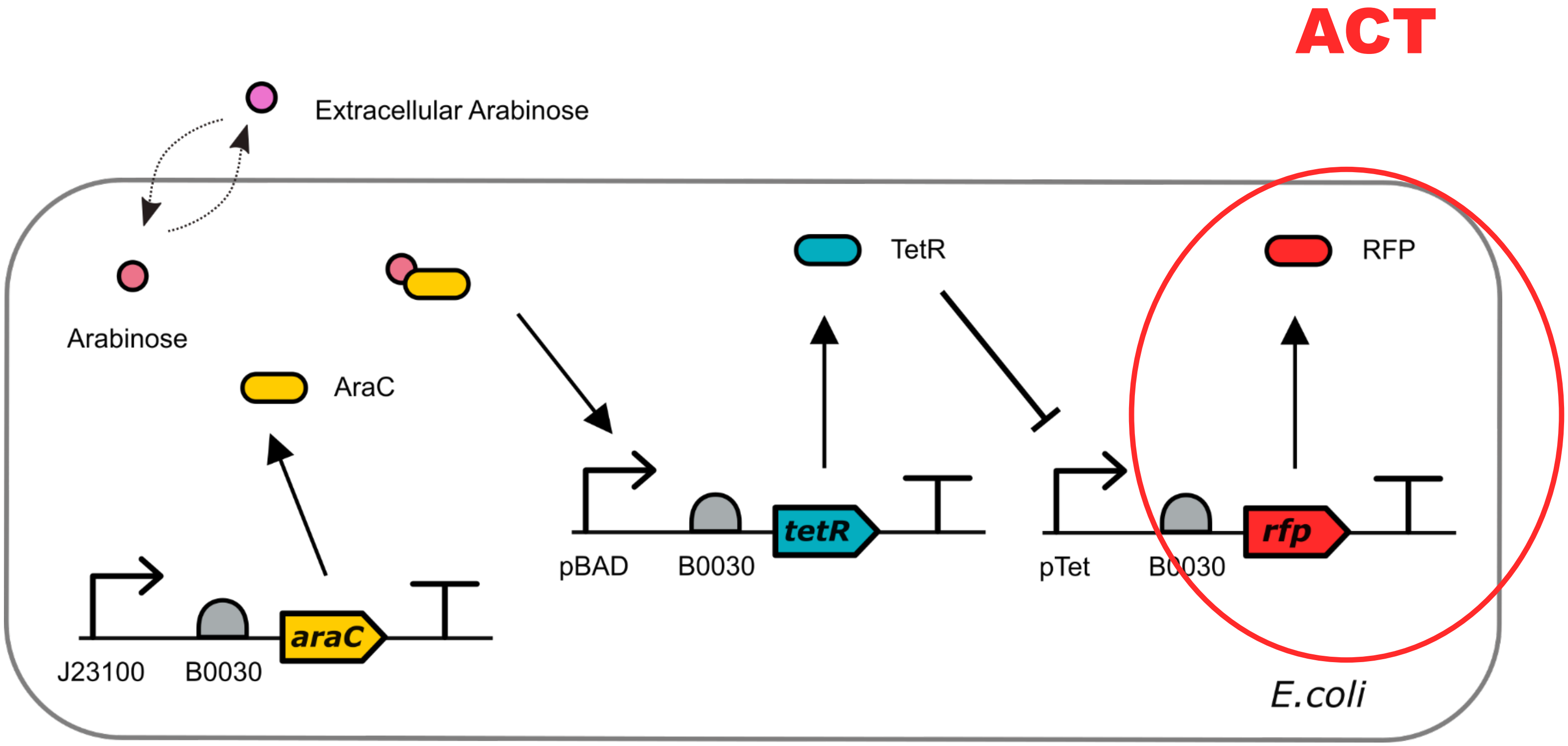
Modeling a genetic circuit

Example Sense-Compute-Act



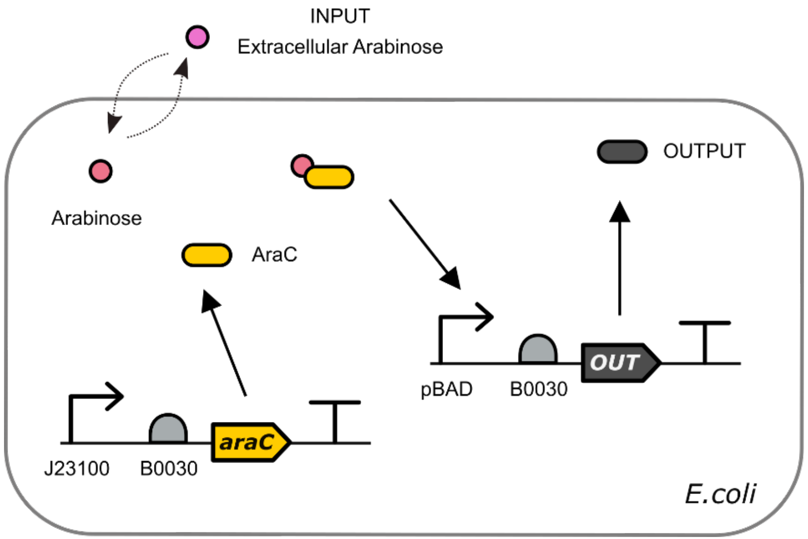
Modeling a genetic circuit

Example Sense-Compute-Act



Modeling a genetic circuit Example Sense-Compute-Act

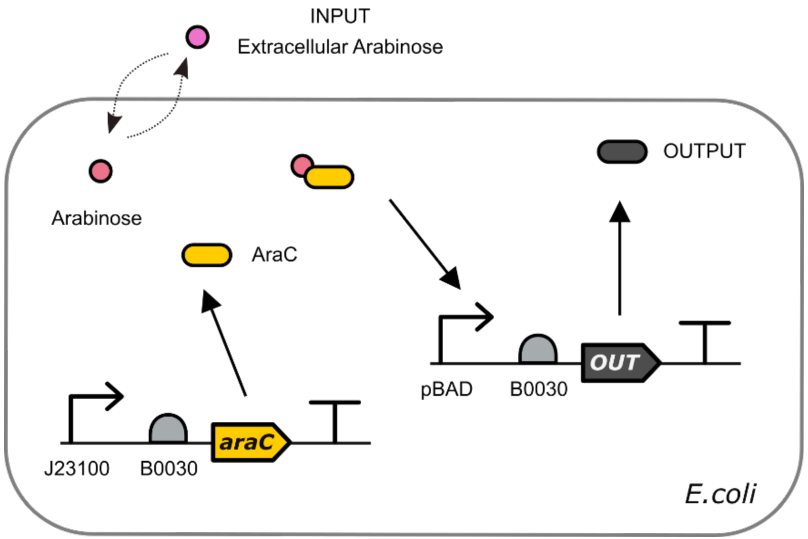
SENSE



$$[\mathrm{OUTPUT}] = \frac{\alpha_{\mathrm{pBAD}}}{d_{\mathrm{OUT}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



$$[\mathrm{OUTPUT}] = \frac{\alpha_{\mathrm{pBAD}}}{d_{\mathrm{OUT}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

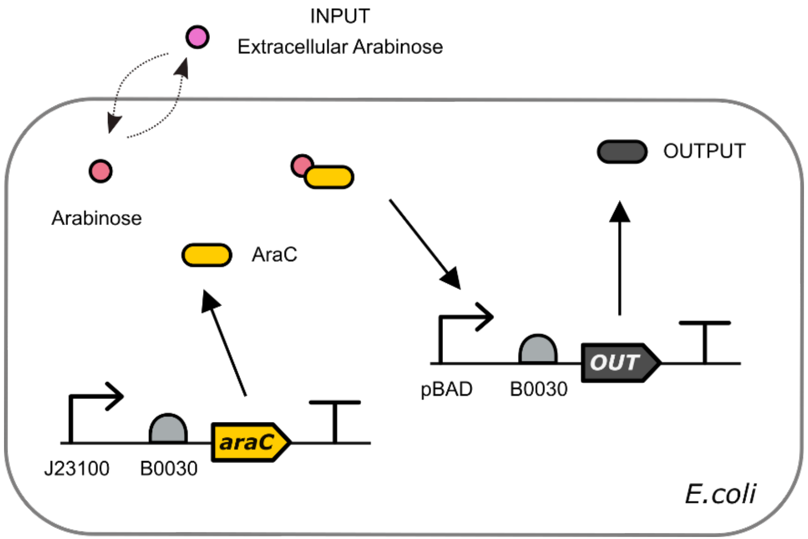
$$\alpha_{\mathrm{pBAD}} = \frac{k_{2_{\mathrm{OUT}}}}{d_{m_{\mathrm{OUT}}}} k_{1_{pBAD}} C_N$$

$$K_{d_{pBAD}} = \frac{K_d K_{dis}\, C_N}{[\mathrm{AraC}]^{n_A}}$$

Trabelsi, H., Koch, M., & Faulon, J. L. (2018). Building a minimal and generalizable model of transcription factor–based biosensors: Showcasing flavonoids. Biotechnology and bioengineering, 115(9), 2292-2304.

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



$$[\text{OUTPUT}] = \frac{\alpha_{\text{pBAD}}}{d_{\text{OUT}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\text{Arab}]^{n_a}}{\left(K_{d_{\text{pBAD}}}\right)^{n_a} + [\text{Arab}]^{n_a}}\right)$$

$$\alpha_{\text{pBAD}} = \frac{k_{2_{\text{OUT}}}}{d_{m_{\text{OUT}}}} k_{1_{pBAD}} C_N$$

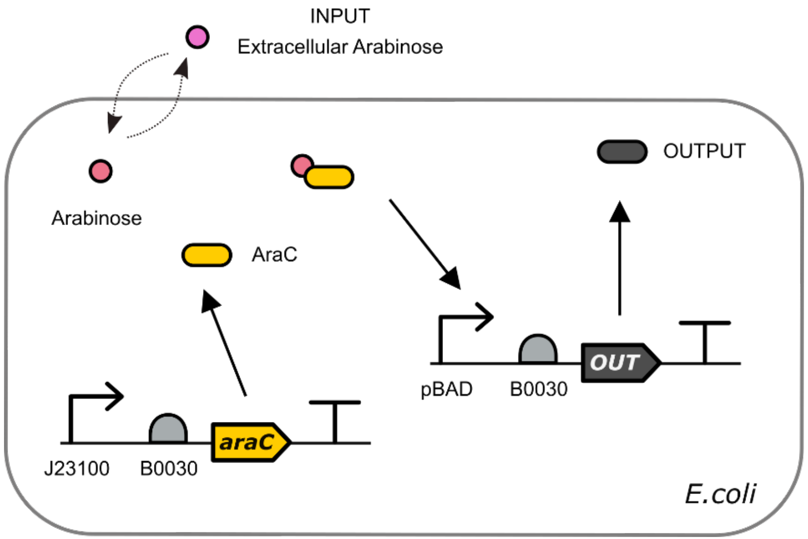
$$K_{d_{pBAD}} = \frac{K_d K_{dis}\, C_N}{[\text{AraC}]^{n_A}}$$

pBAD
AraC

Trabelsi, H., Koch, M., & Faulon, J. L. (2018). Building a minimal and generalizable model of transcription factor–based biosensors: Showcasing flavonoids. Biotechnology and bioengineering, 115(9), 2292-2304.

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



$$[\text{OUTPUT}] = \frac{\alpha_{\text{pBAD}}}{d_{\text{OUT}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\text{Arab}]^{n_a}}{\left(K_{d_{\text{pBAD}}}\right)^{n_a} + [\text{Arab}]^{n_a}}\right)$$

$$\alpha_{\text{pBAD}} = \frac{k_{2_{\text{OUT}}}}{d_{m_{\text{OUT}}}} k_{1_{pBAD}} C_N$$

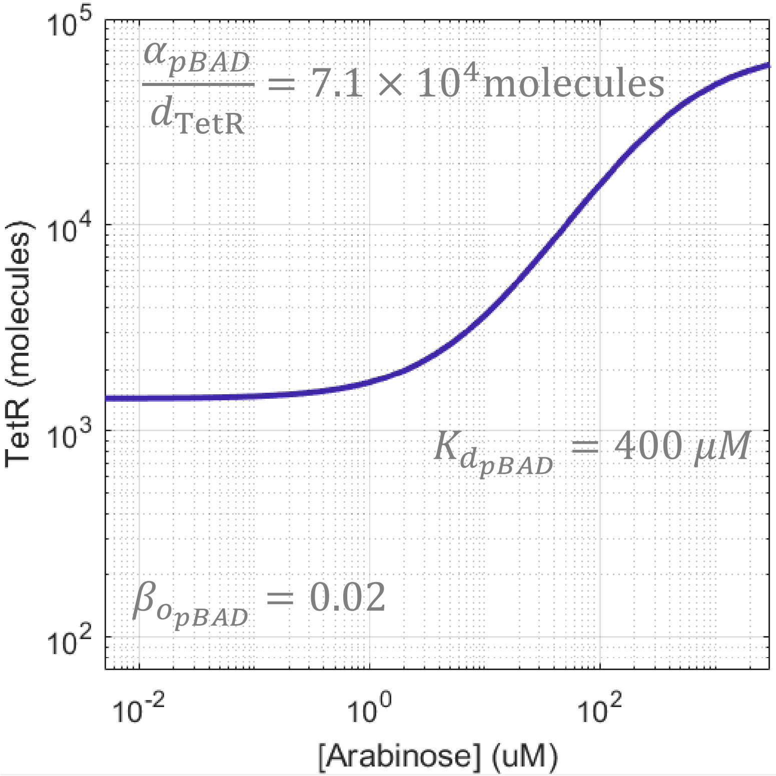
OUTPUT

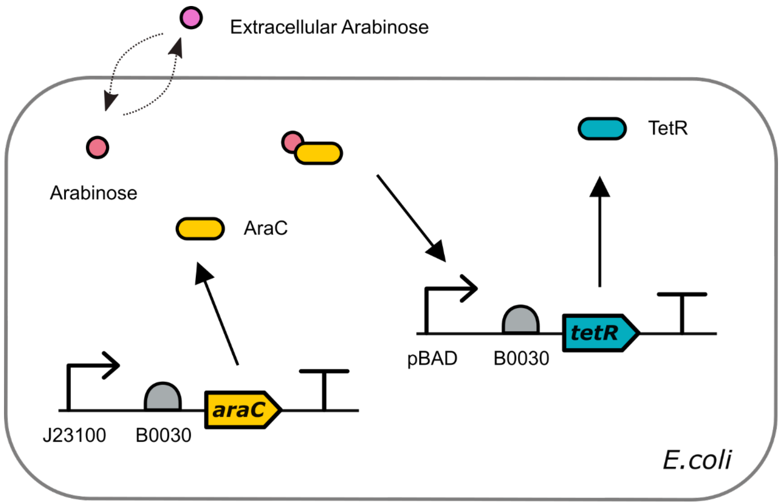
$$K_{d_{pBAD}} = \frac{K_d K_{dis}\, C_N}{[\text{AraC}]^{n_A}}$$

Trabelsi, H., Koch, M., & Faulon, J. L. (2018). Building a minimal and generalizable model of transcription factor–based biosensors: Showcasing flavonoids. Biotechnology and bioengineering, 115(9), 2292-2304.

Modeling a genetic circuit Example Sense-Compute-Act

SENSE

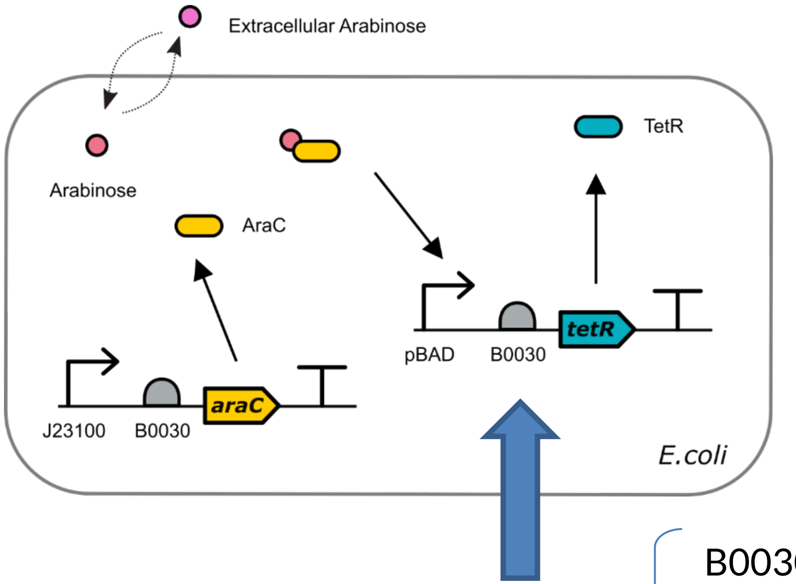




$$[\mathrm{TetR}] = \frac{\alpha_{\mathrm{pBAD}}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



$$[\mathrm{TetR}] = \frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

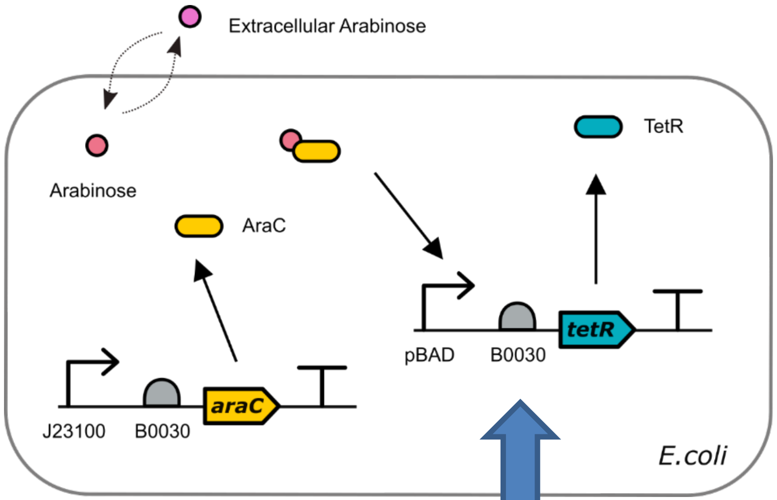
$$\alpha_{pBAD} = k_{2_{\mathrm{TetR}}} \frac{k_{1_{\mathrm{mTetR}}}}{d_{m_{\mathrm{TetR}}}} C_N$$

Let us try with different RBS $\left\{ \begin{array}{l} \text{B0030} \\ \text{B0034} \\ \text{B0032} \end{array} \right.$

What effect does it have in the hill function?

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



$$[\mathrm{TetR}] = \frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

$$\alpha_{pBAD} = k_{2_{\mathrm{TetR}}} \frac{k_{1_{\mathrm{mTetR}}}}{d_{m_{\mathrm{TetR}}}} C_N$$

Let us try with different RBS

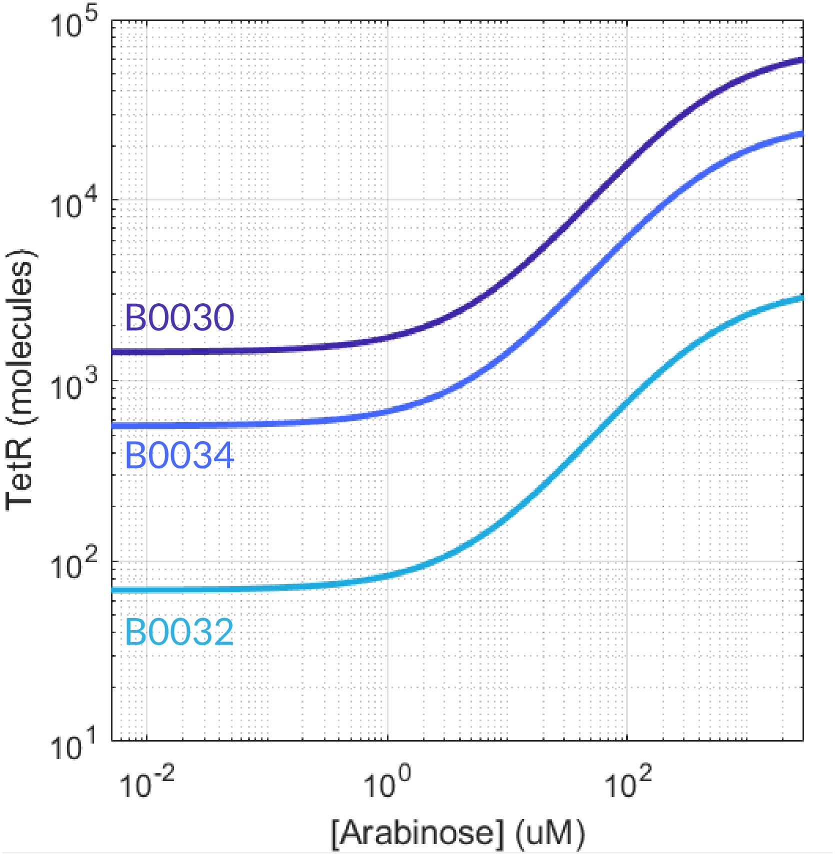
B0030

B0034

B0032

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



$$[\mathrm{TetR}] = \frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

$$\alpha_{pBAD} = k_{2_{\mathrm{TetR}}} \frac{k_{1_{\mathrm{mTetR}}}}{d_{m_{\mathrm{TetR}}}} C_N$$

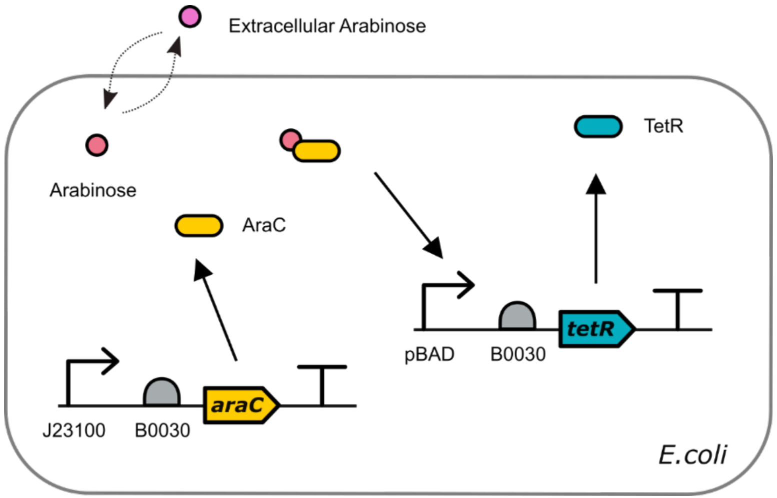
B0030: $\alpha_{pBAD} \approx 7.1 \times 10^4$ molecules

B0034: $\alpha_{pBAD} \approx 2.5 \times 10^4$ molecules

B0032: $\alpha_{pBAD} \approx 3.3 \times 10^3$ molecules

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



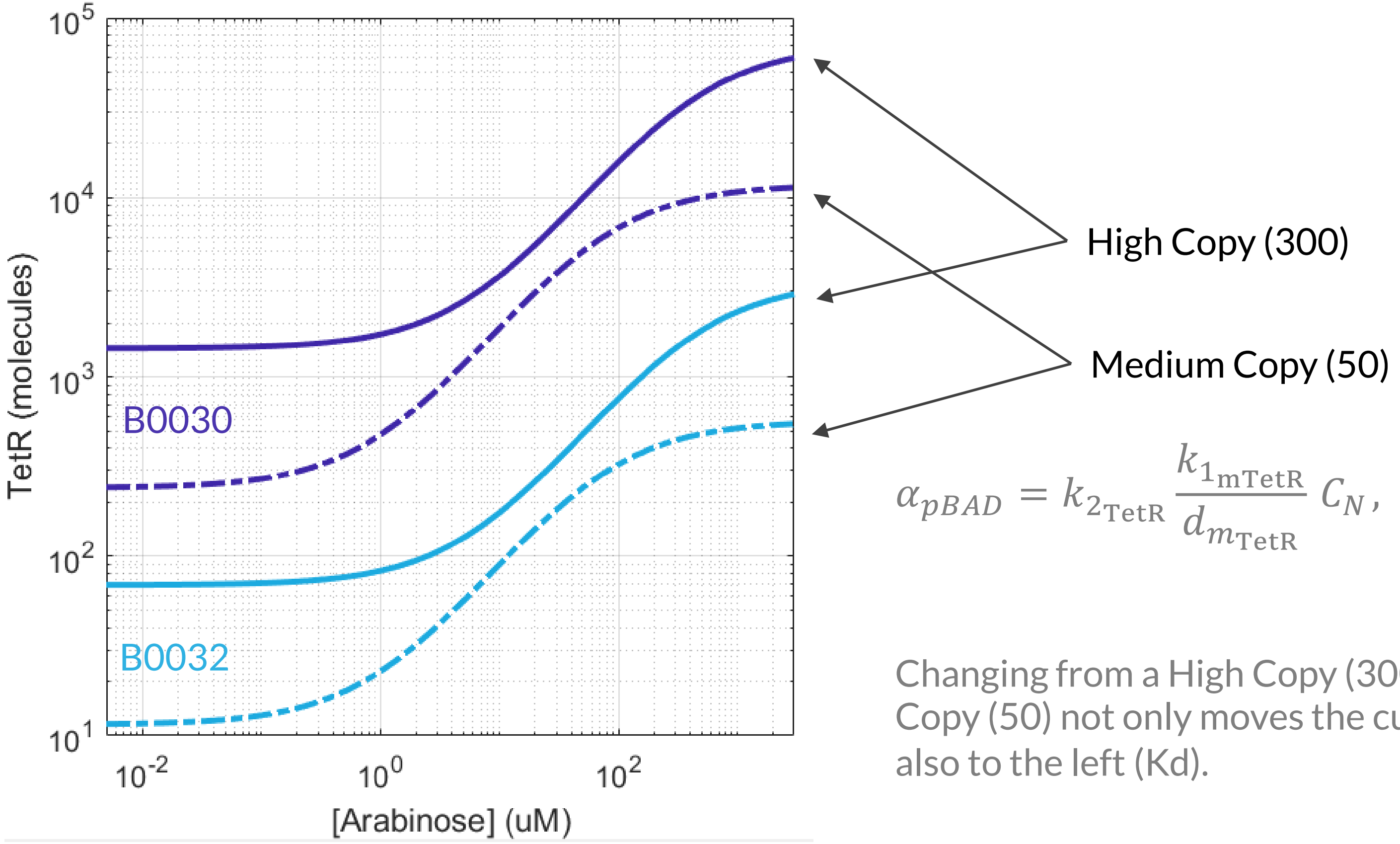
$$[\mathrm{TetR}] = \frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

$$\alpha_{pBAD} = k_{2_{\mathrm{TetR}}}\frac{k_{1_{\mathrm{mTetR}}}}{d_{m_{\mathrm{TetR}}}}C_N$$

Now let us try with different Plasmid Copy Number (High/Medium)

Modeling a genetic circuit Example Sense-Compute-Act

SENSE

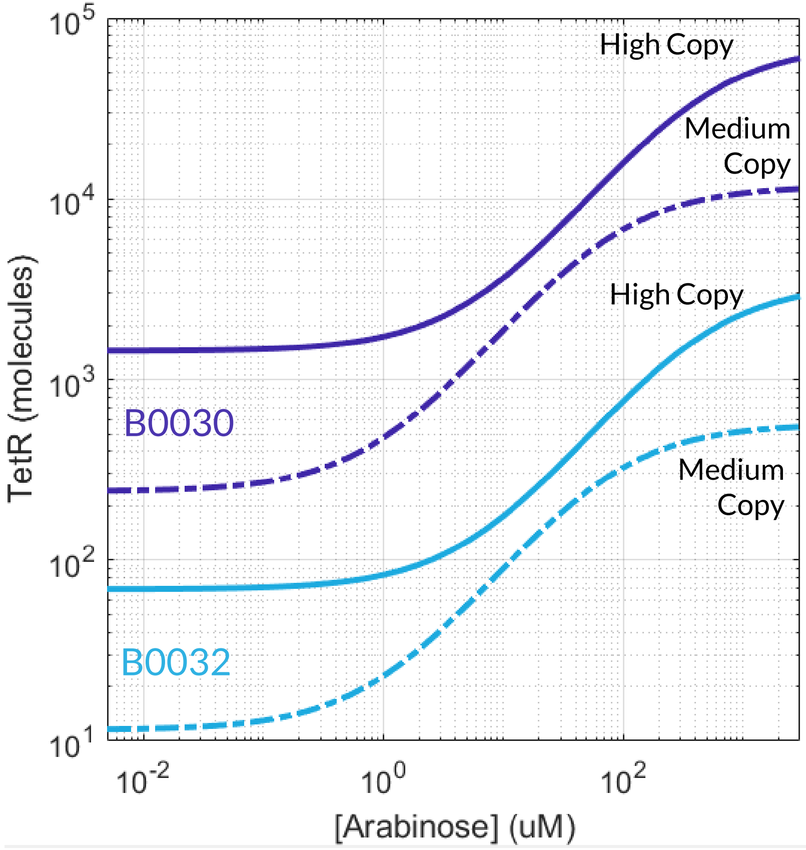


$$\alpha_{pBAD} = k_{2_{\mathrm{TetR}}} \frac{k_{1_{\mathrm{mTetR}}}}{d_{m_{\mathrm{TetR}}}} C_N, \quad K_{d_{pBAD}} = \frac{K_d K_{dis}\, C_N}{[\mathrm{AraC}]^{n_A}}$$

Changing from a High Copy (300) to a Medium Copy (50) not only moves the curve down (α), but also to the left (Kd).

Modeling a genetic circuit Example Sense-Compute-Act

SENSE



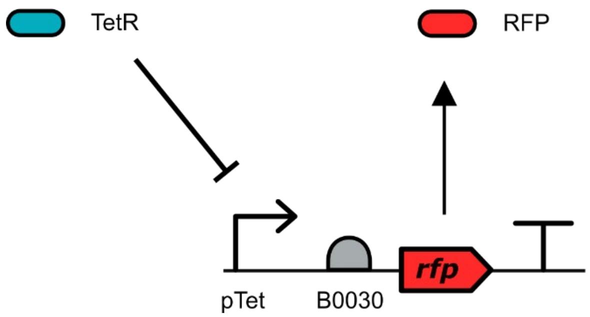
α_{pBAD}	High Copy	Medium Copy
B0030	7.1×10^4 molecules	1.2×10^4 molecules
B0032	3300 molecules	560 molecules

	High Copy	Medium Copy
$K_{d_{pBAD}}$	440 μM	14 μM

Changing from a High Copy (300) to a Medium Copy (50) not only moves the curve down (α), but also to the left (Kd).

Modeling a genetic circuit Example Sense-Compute-Act

COMPUTE - ACT



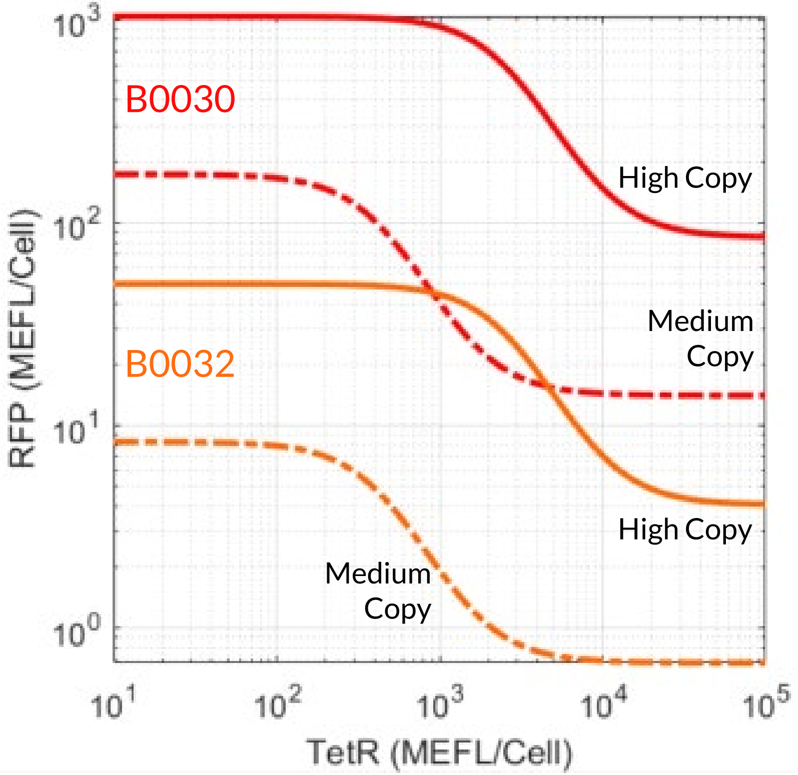
$$[\mathrm{RFP}] = \frac{\alpha_{\mathrm{pTet}}}{d_{\mathrm{RFP}}}\left(\beta_{o_{\mathrm{pTet}}} + \frac{\left(1-\beta_{o_{\mathrm{pTet}}}\right)\left(K_{d_{\mathrm{pTet}}}\right)^{n_t}}{\left(K_{d_{\mathrm{pTet}}}\right)^{n_t} + [\mathrm{TetR}]^{n_t}}\right)$$

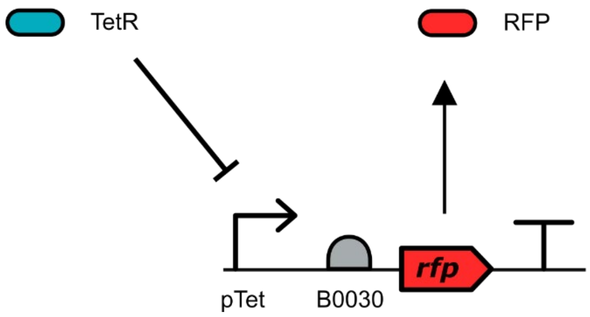
$$\alpha_{\mathrm{pTet}} = k_{2_{\mathrm{RFP}}} \frac{k_{1_{\mathrm{m_{RFP}}}}}{d_{\mathrm{m_{RFP}}}} C_N$$

$$K_{d_{\mathrm{pTet}}} = K_d \, C_N$$

Modeling a genetic circuit Example Sense-Compute-Act

COMPUTE - ACT



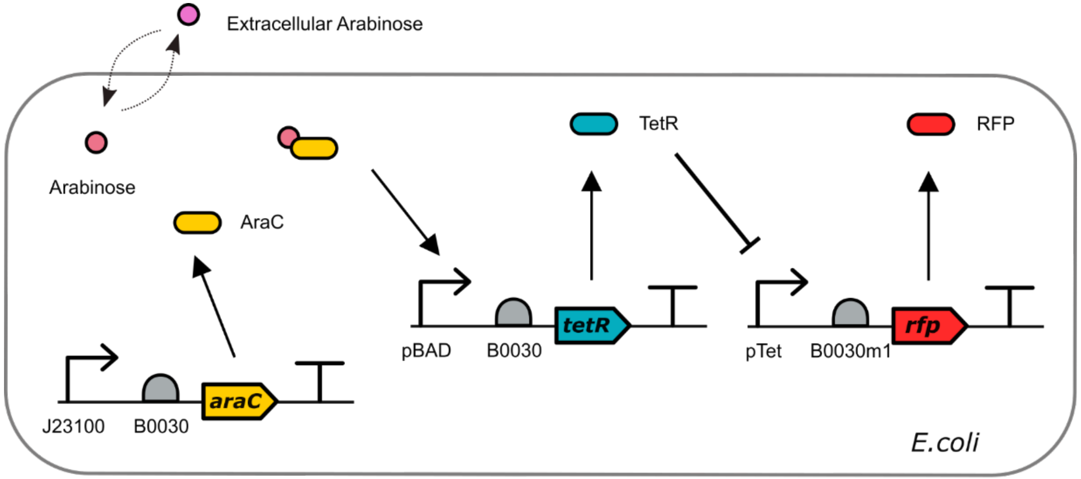


$$[\mathrm{RFP}] = \frac{\alpha_{\mathrm{pTet}}}{d_{\mathrm{RFP}}}\left(\beta_{o_{\mathrm{pTet}}} + \frac{\left(1-\beta_{o_{\mathrm{pTet}}}\right)[\mathrm{TetR}]^{n_t}}{\left(K_{d_{\mathrm{pTet}}}\right)^{n_t} + [\mathrm{TetR}]^{n_t}}\right)$$

Let us try with different RBS and Plasmid Copy Numbers

Modeling a genetic circuit Example Sense-Compute-Act

SENSE - COMPUTE - ACT

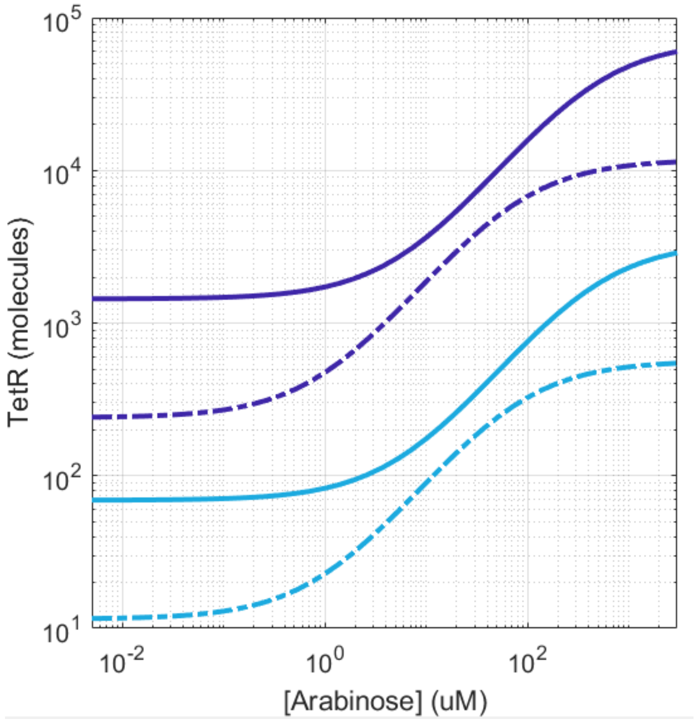


$$[\mathrm{TetR}] = \frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

$$[\mathrm{RFP}] = \frac{\alpha_{\mathrm{pTet}}}{d_{\mathrm{RFP}}}\left(\beta_{o_{\mathrm{pTet}}} + \frac{\left(1-\beta_{o_{\mathrm{pTet}}}\right)[\mathrm{TetR}]^{n_t}}{\left(K_{d_{\mathrm{pTet}}}\right)^{n_t} + [\mathrm{TetR}]^{n_t}}\right)$$

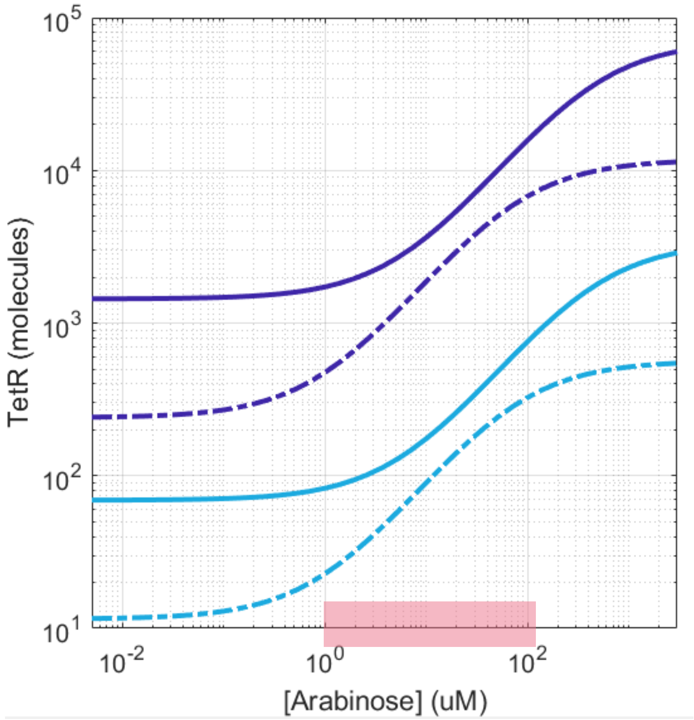
Modeling a genetic circuit Example Sense-Compute-Act

SENSE - COMPUTE



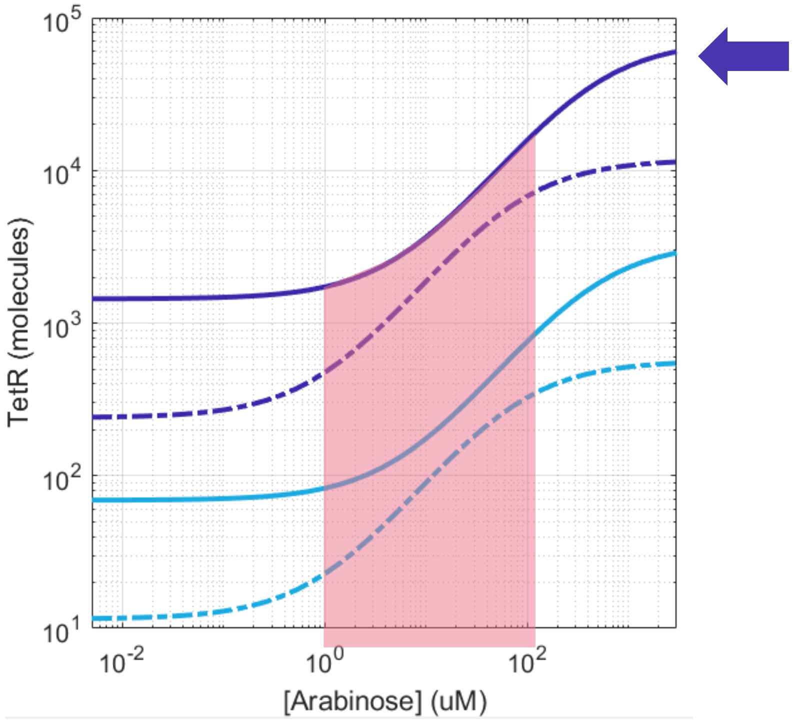
Modeling a genetic circuit Example Sense-Compute-Act

SENSE - COMPUTE



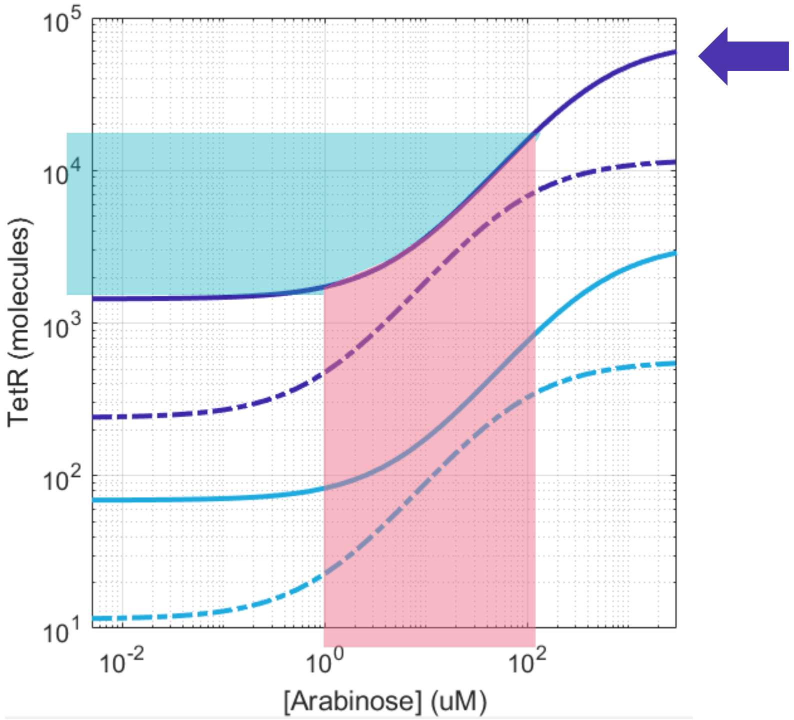
Modeling a genetic circuit Example Sense-Compute-Act

SENSE - COMPUTE



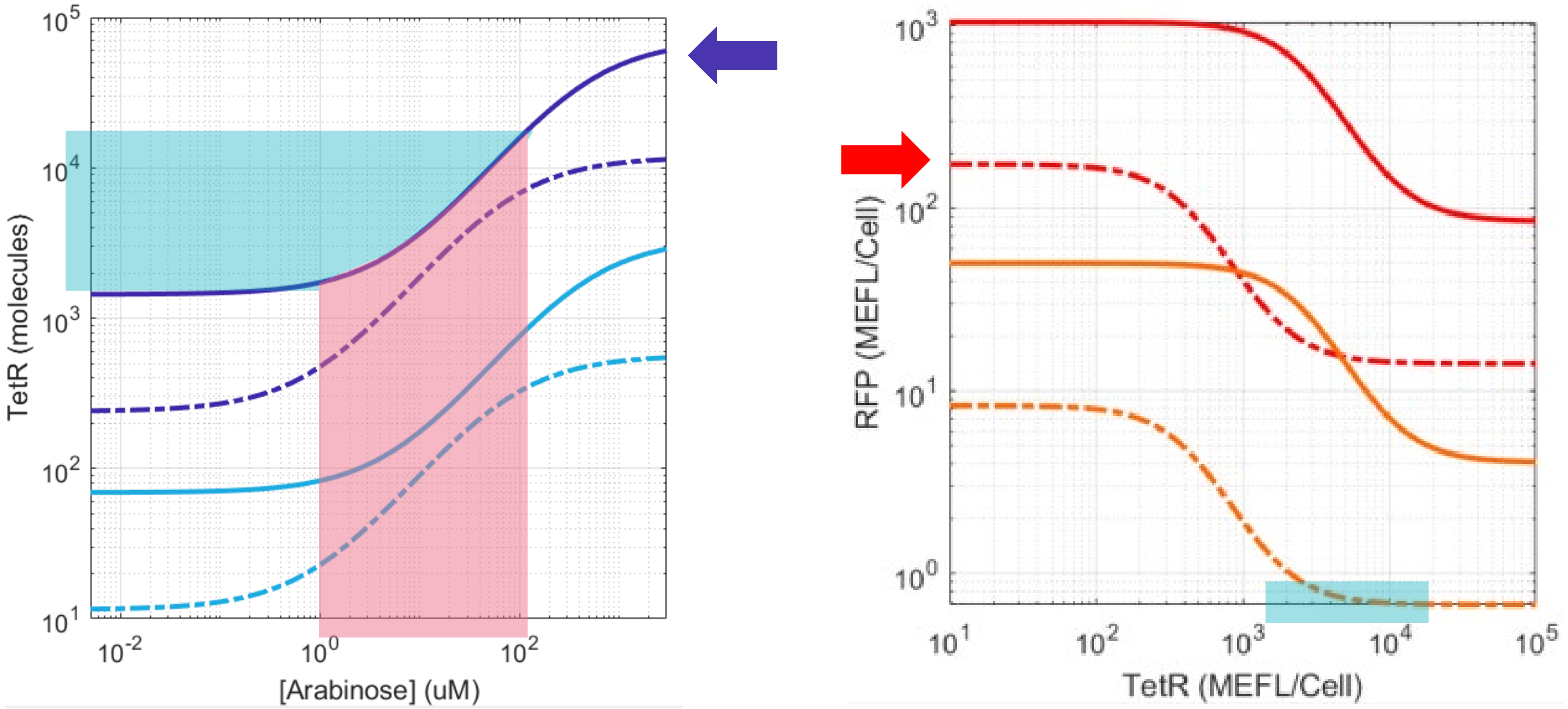
Modeling a genetic circuit Example Sense-Compute-Act

SENSE - COMPUTE



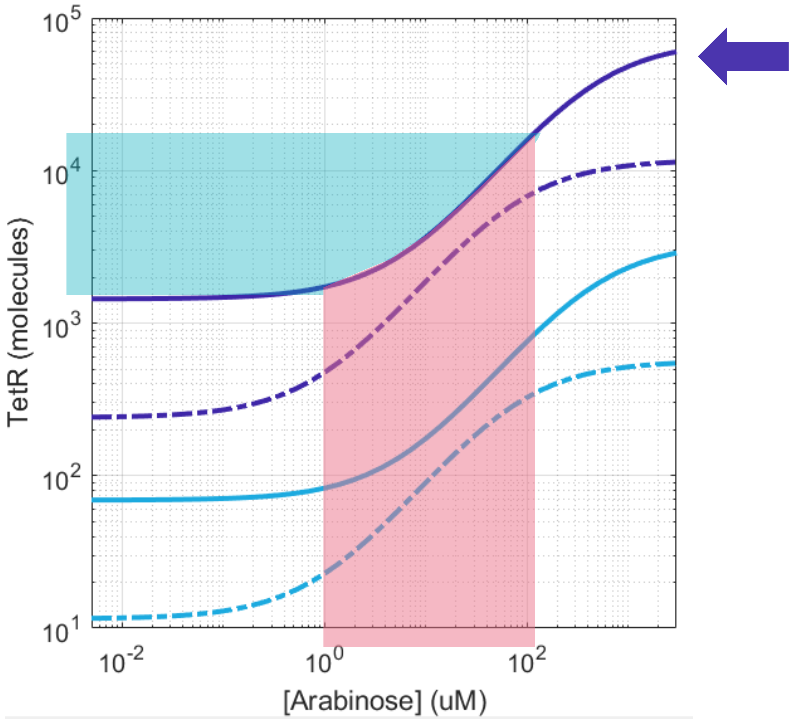
Modeling a genetic circuit Example Sense-Compute-Act

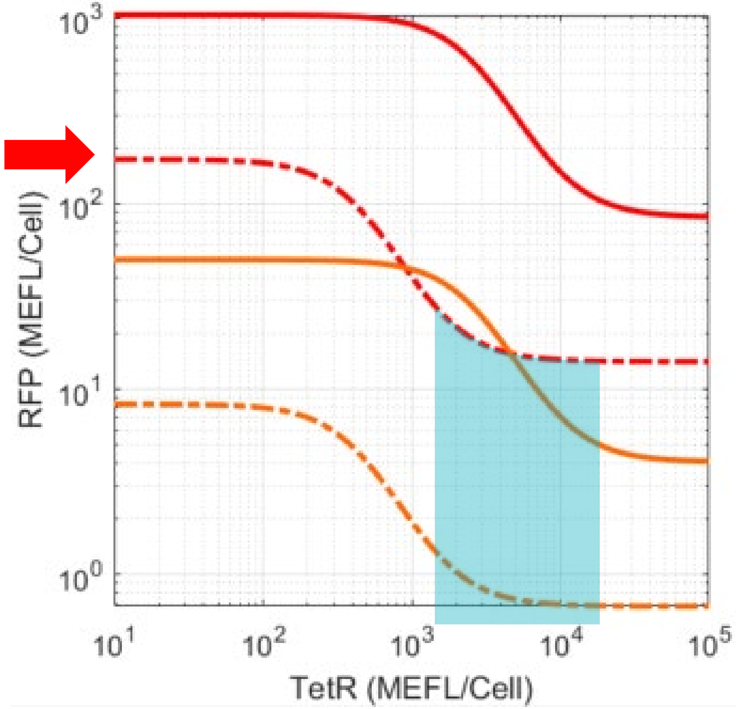
SENSE - COMPUTE - ACT



Modeling a genetic circuit Example Sense-Compute-Act

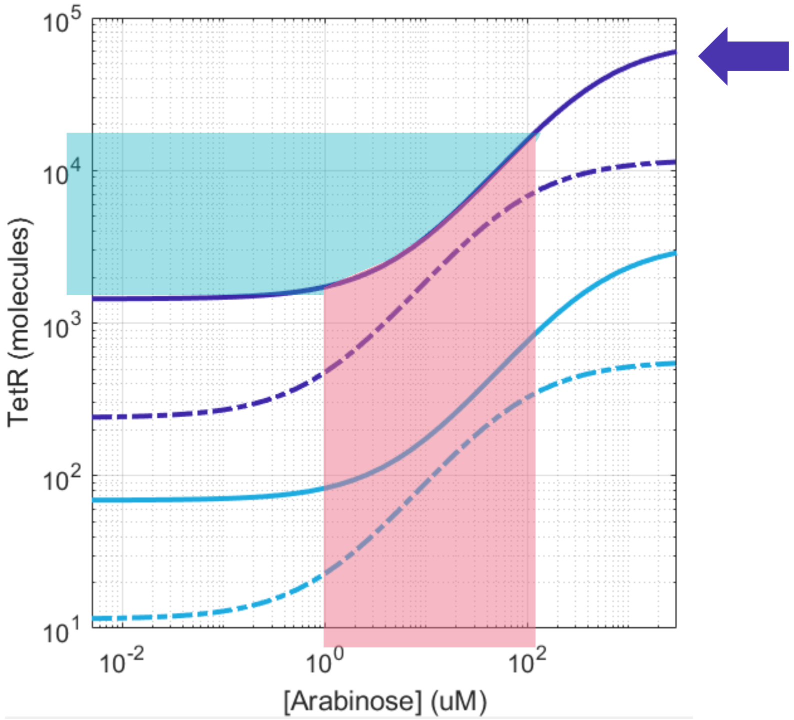
SENSE - COMPUTE - ACT

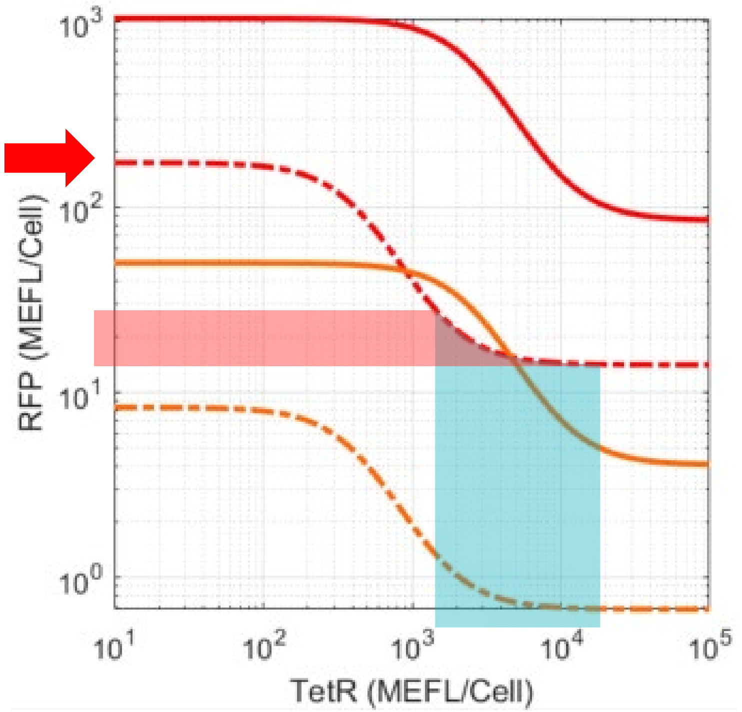




Modeling a genetic circuit Example Sense-Compute-Act

SENSE - COMPUTE - ACT





Questions?

Ask writing in the chat or contact me by email (alvig2 [at] upv [dot] es)

Stay tuned, next Section 2:

Relating parameters and data

Modeling a genetic circuit Example Sense-Compute-Act

SENSE

Basal Expression

$$[\mathrm{TetR}] = \frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\left(\beta_{o_{pBAD}} + \frac{\left(1-\beta_{o_{pBAD}}\right)[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}\right)$$

$$[\mathrm{TetR}] = \beta_{o_{pBAD}}\frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}} + \left(1-\beta_{o_{pBAD}}\right)\frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}\frac{[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}$$

$$[\mathrm{TetR}] = \beta^{*}_{o_{pBAD}} + \frac{\alpha^{*}_{pBAD}}{d_{\mathrm{TetR}}}\frac{[\mathrm{Arab}]^{n_a}}{\left(K_{d_{\mathrm{pBAD}}}\right)^{n_a} + [\mathrm{Arab}]^{n_a}}$$

$$\beta^{*}_{o_{pBAD}} = \beta_{o_{pBAD}}\frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}} \qquad \frac{\alpha^{*}_{pBAD}}{d_{\mathrm{TetR}}} = \left(1-\beta_{o_{pBAD}}\right)\frac{\alpha_{pBAD}}{d_{\mathrm{TetR}}}$$