sb2cl Lab
Synthetic Biology and Biosystems Control Lab
Valencia UPV

iGEM 2020 Measurement

Modeling: Modeling circuits with ODEs and experimental data

Section 3 Example: Incoherent feed-forward loop (model & data)

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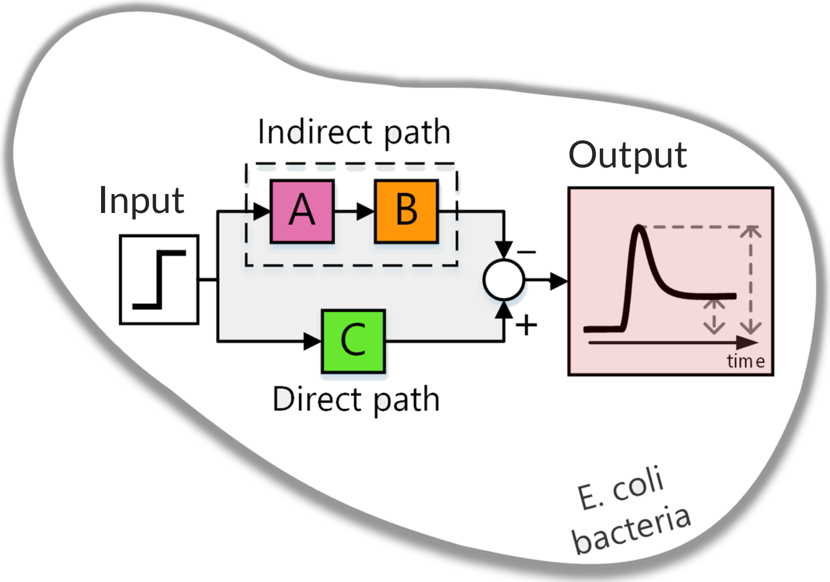
An iGEM Measurement Committee Webinar
Week 3a, June 30th, 2020

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)

Incoherent type1 feedforward circuit (I1-FFL)

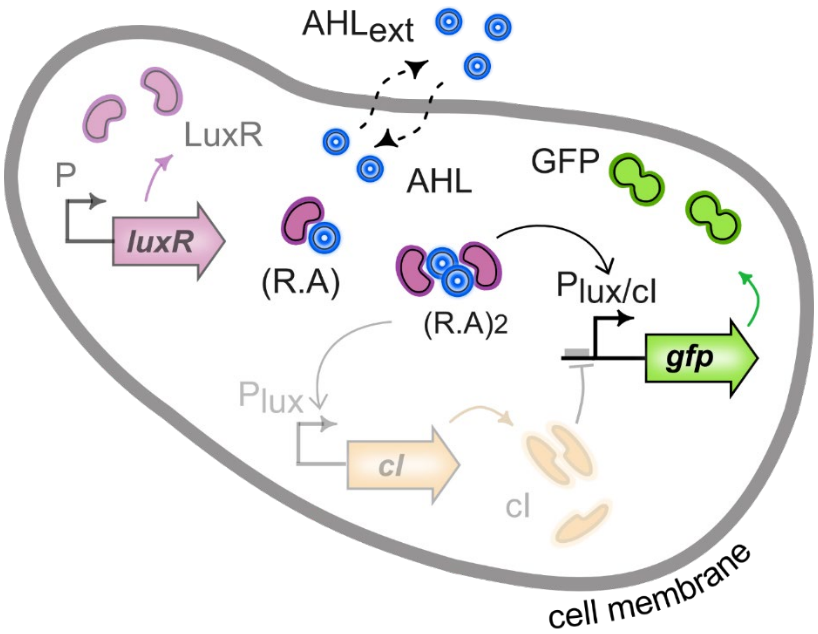


Change-fold detector

Responds to a change in its input and returns to the value it had prior to the stimulus.

In biology, this behavior is called *adaptation*

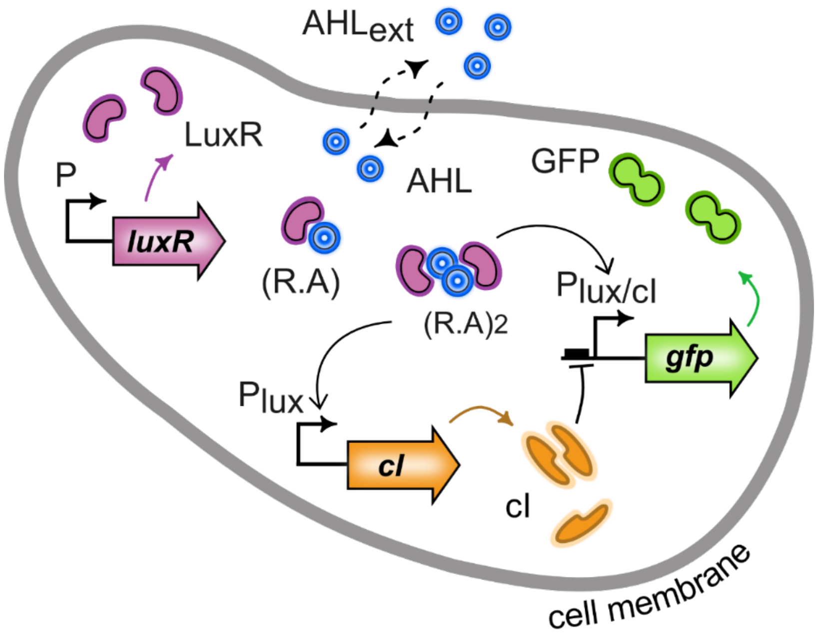
Structure of a design for the I1-FFL gene circuit



Direct path

Input AHL_{ext} diffuses across the cell membrane. AHL together with LuxR protein activates the output protein GFP.

Structure of the I1-FFL gene circuit



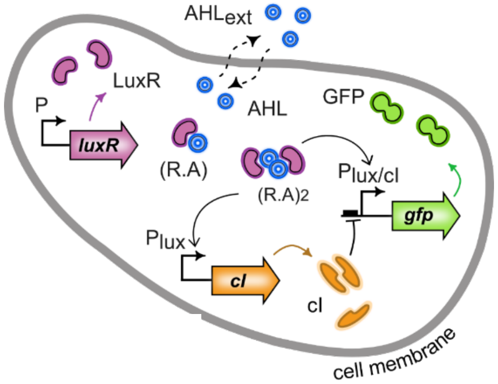
Direct path

Input AHL_{ext} diffuses across the cell membrane. AHL together with LuxR protein activates the output protein GFP.

Indirect path

AHL together with LuxR proteins also activate cI protein. After some time, cI represses the output protein GFP.

Model of the I1-FFL gene circuit



$$\frac{d[R]}{dt} = \frac{\mathrm{p_R C_N k_R}}{\mathrm{dm_R} + \mu} - (\mathrm{d_R} + \mu)[R]$$

$$\frac{d[cI]}{dt} = \frac{\mathrm{p_{cI} C_N k_{cI}}}{\mathrm{dm_{cI}} + \mu}\left(\alpha + (1-\alpha)\,\frac{\frac{1}{\mathrm{k_{dlux}}}\left(\frac{[R][A]}{\mathrm{k_{d2} C_N}}\right)^2}{1 + \frac{1}{\mathrm{k_{dlux}}}\left(\frac{[R][A]}{\mathrm{k_{d2} C_N}}\right)^2}\right) - (\mathrm{d_{cI}} + \mu)[cI]$$

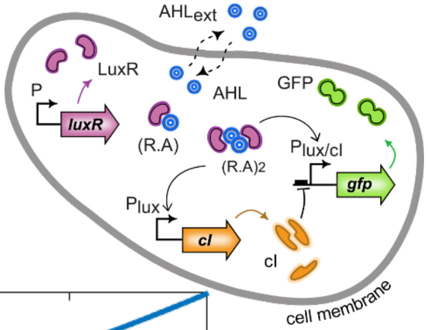
$$\frac{d[GFP]}{dt} = \frac{\mathrm{p_G C_N k_G}}{\mathrm{dm_G} + \mu}\left(\alpha + (1-\alpha)\,\frac{\frac{1}{\mathrm{k_{dlux}}}\left(\frac{[R][A]}{\mathrm{k_{d2} C_N}}\right)^2}{1 + \frac{1}{\mathrm{k_{dlux}}}\left(\frac{[R][A]}{\mathrm{k_{d2} C_N}}\right)^2}\,\frac{1}{1 + \frac{[cI]^2}{\mathrm{k_{dcI} C_N}}}\right) - (\mathrm{d_G} + \mu)[G]$$

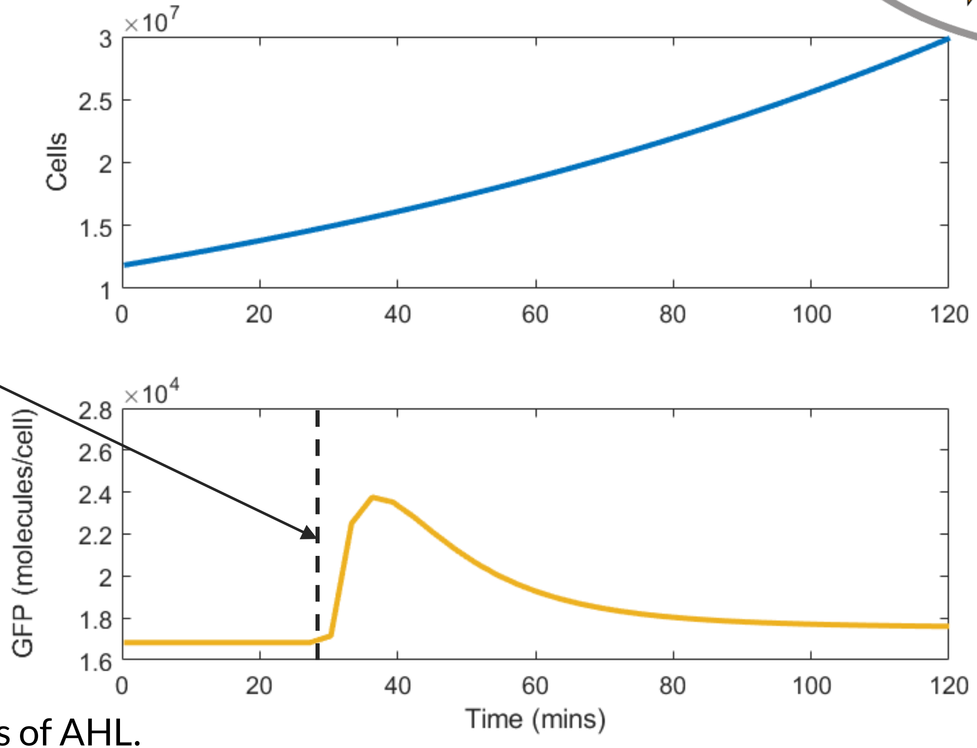
$$\frac{dN}{dt} = \mu N\left(1 - \frac{N}{\mathrm{N_{max}}}\right)$$

Y. Boada, G. Reynoso-Meza, J. Picó, and A. Vignoni. Multi-objective optimization framework to obtain model-based guidelines for tuning biological synthetic devices: an adaptive network case. BMC Syst Biol, 10(1):27, 2016b.

Model of the I1-FFL gene circuit

Simulation of a construct



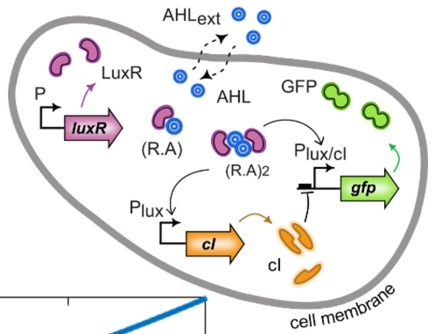


Different induction levels

But only one peak!

The system responds,
but is insensitive to the different levels of AHL.

Model of the I1-FFL gene circuit



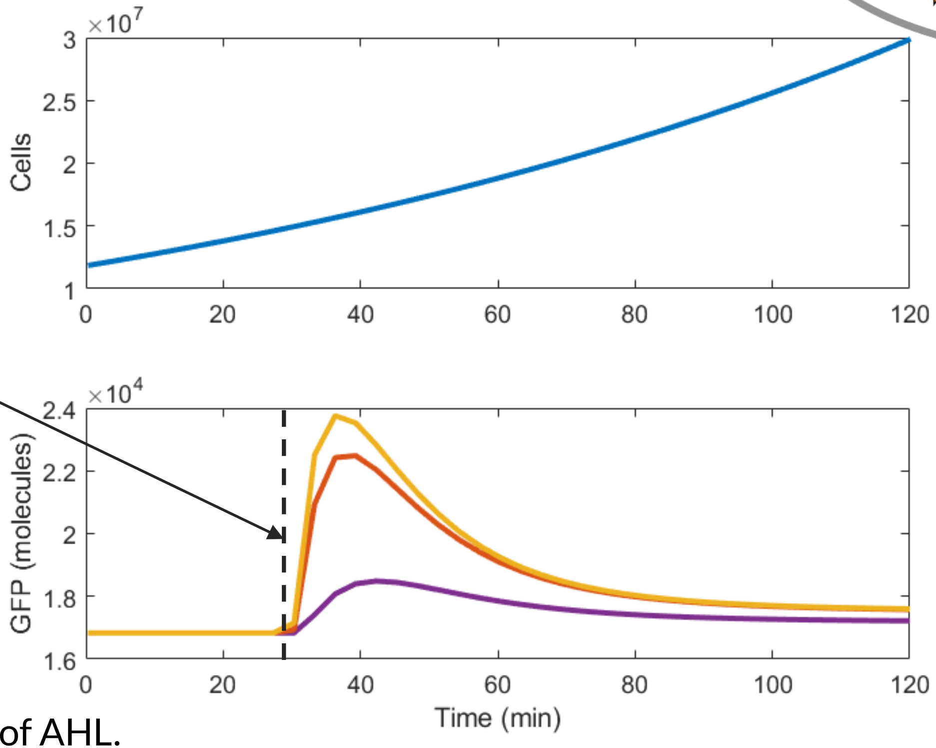
Simulation of another construct

Increasing the C_N of the Hybrid promoter (to increase the Kd)

Different induction levels

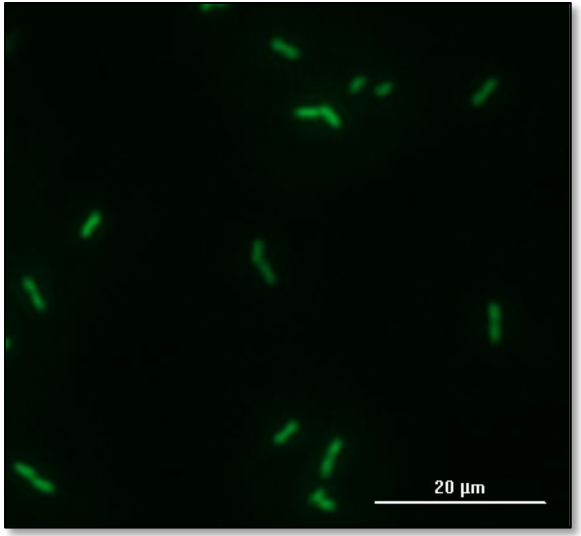
Different peaks maxima!

Now the system responds and changes the peak maximum with different levels of AHL.

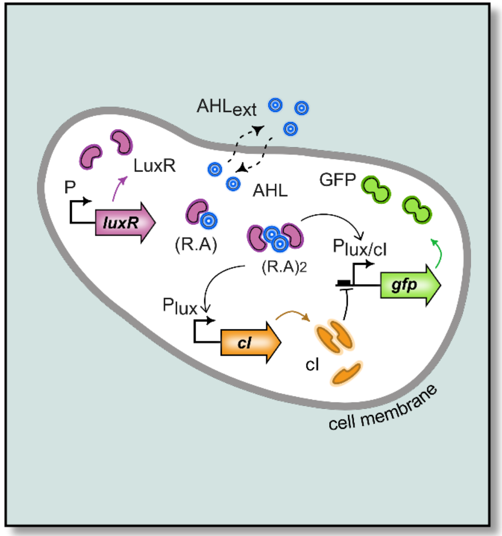


In vivo implementation of one version of I1-FFL circuit

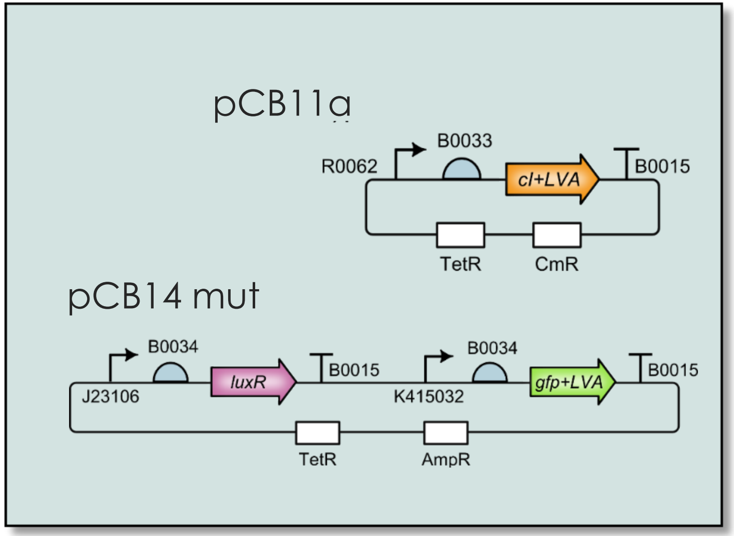
E. coli bacteria



GFP protein after AHL_{ext} induction.



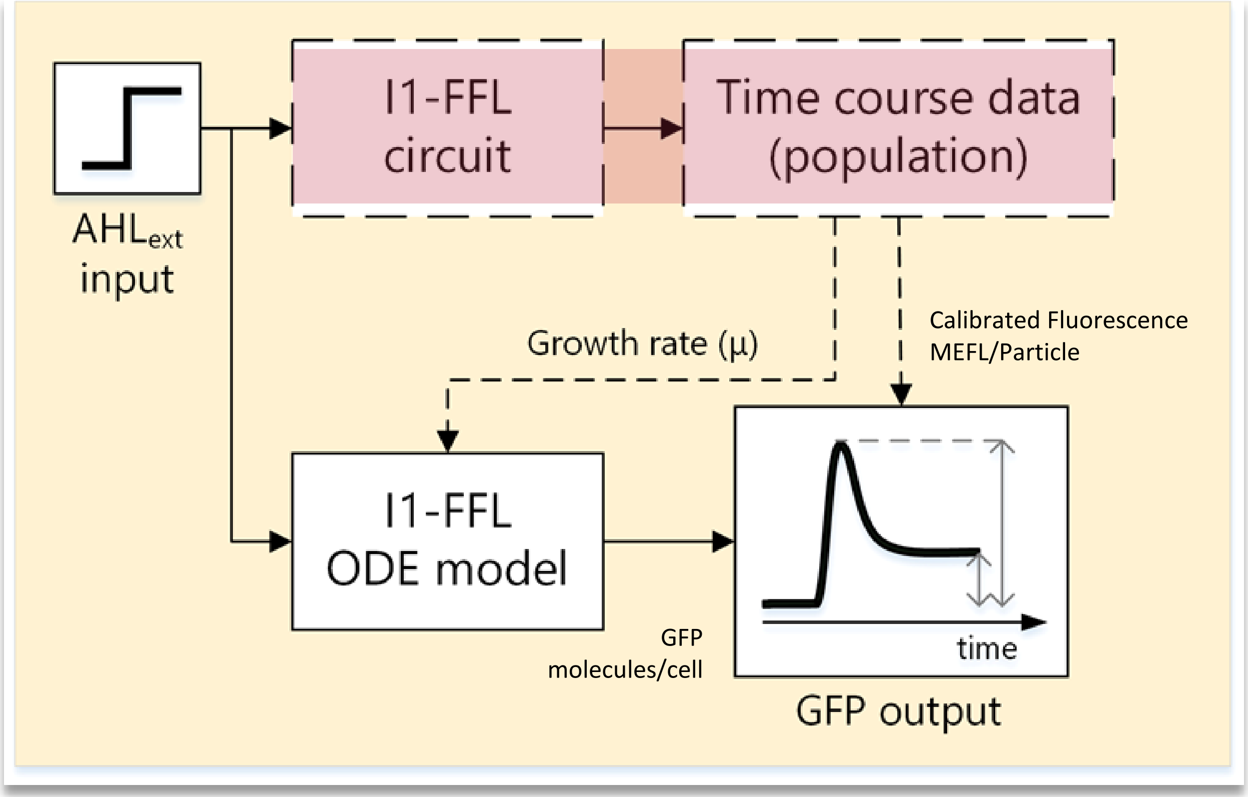
I1-FFL circuit with its biochemical reactions.



DNA sequences of the three gene circuits *cI, luxR* and *gfp*.

Source: Image x20, SB2CL Lab UPV 2019.

Model parameter estimation of the I1-FFL circuit



Cost function of the I1-FFL circuit

5 experimental scenarios

Mean squared error (MSE)

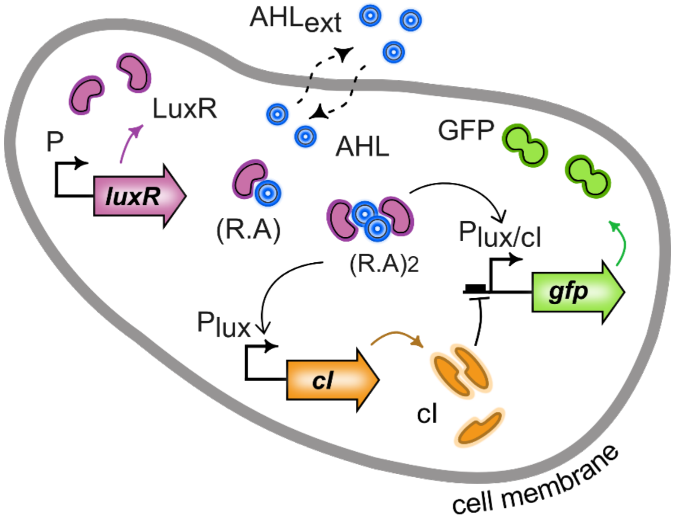
$$J_{[i=1,\ldots,5]}(\theta) = \frac{1}{n}\sum_{q=1}^{n}\frac{1}{m}\sum_{k=1}^{m}\left(x^{m}_{10_{iq}}(k) - x_{10_{iq}}(kT)\right)^2$$

$$\min_{\theta\in\Re^{17}} J(\theta) = [J_1(\theta), \ldots, J_5(\theta)] \in \Re^5$$

$$\text{subject to:} \quad \text{I1-FFL model} \;\; (5.1)$$

17 decision variables $\boldsymbol{\theta} \in \mathbb{R}^{17}$

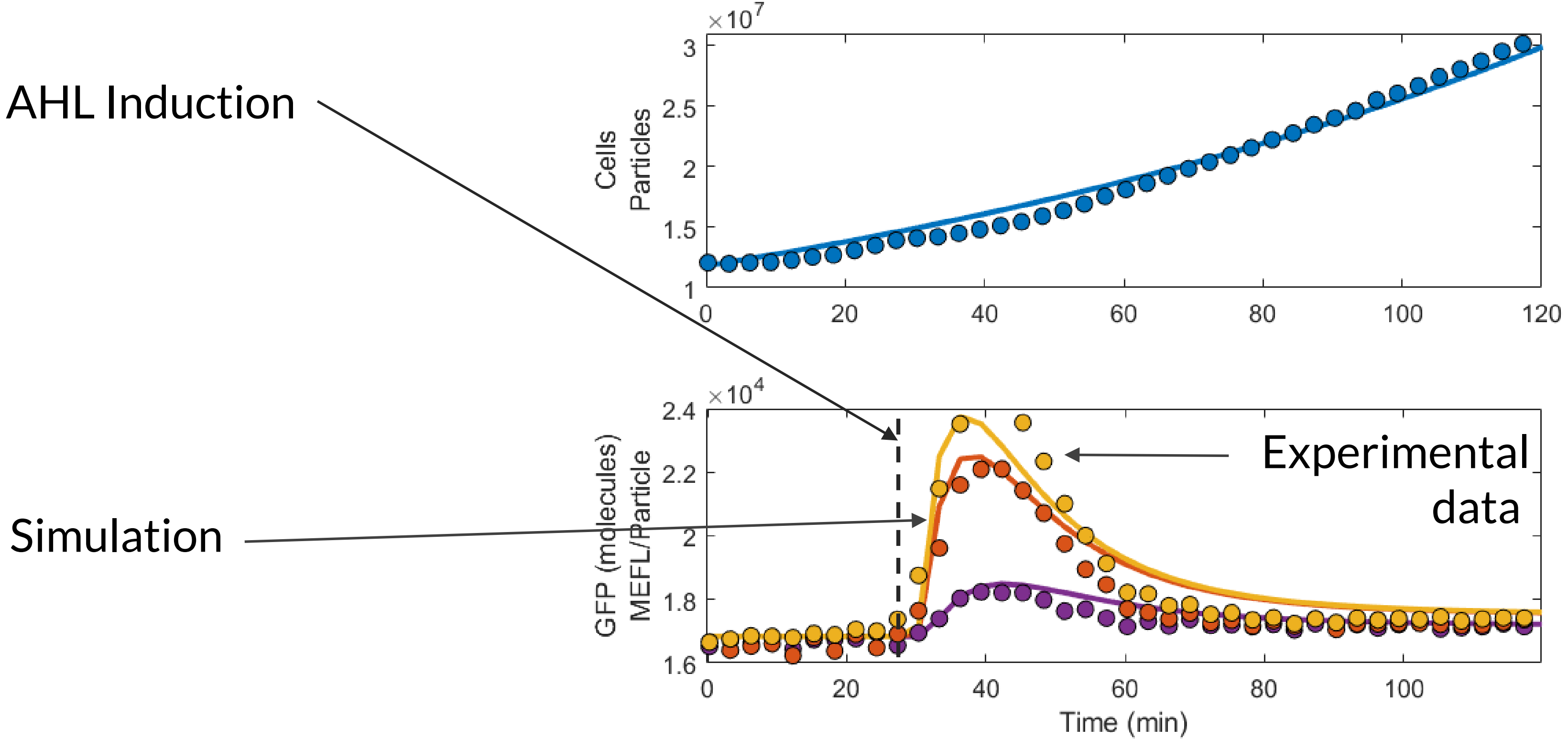
Unknown Parameter	Description	Range of values
$d_{\mathrm{cI}}, d_{\mathrm{GFP}}$	cI, GFP degradation rate	[0.01 0.3] min^{-1}
γ_1	pLux Promoter Hill constant	[50 100] nM
γ_3	Hybrid pLuxR/cI promoter coefficient	[0.0001 0.5]
γ_4	Hybrid pLuxR/cI promoter coefficient	[0.0005 5]
γ_5	Hybrid pLuxR/cI promoter coefficient	[1 100]
$k_{p_{\mathrm{cI}}}, k_{p_{\mathrm{gfp}}}$	cI, GFP translation rate	[1 60], [1 100] min^{-1}
β_1	Hybrid promoter basal expression	[0 0.01]
β_2	Hybrid promoter leakiness	[0 0.01]
$k_{m_{\mathrm{cI}}}, k_{m_{\mathrm{gfp}}}$	cI, gfp transcription rate	[0.1 75], [0.1 25] min^{-1}
k_{-2}, k_{-3}	Monomer and dimer dissociation rate	[0.05 0.3], [0.1 1] min^{-1}
k_2, k_3	Monomer and dimer association rate	[0.0006 0.06] min^{-1}
k_{mat}	GFP maturation time	[20 120] min



Parameter estimation based on MOOD

spMODE algorithm (http://matlabcentral/fileexchange/39215)

Comparison between model and data for the I1-FFL circuit
Parameter estimation



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

Scripts and files in the Git Repository

https://github.com/iGEM-Measurement-Tools/Modeling-Tutorials