The Mathematical Model

Synthetic Genetic Circuits

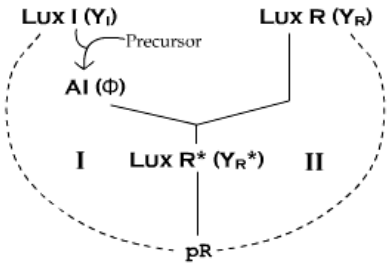
Closed Loop System

Biobrick Parts: J22301
J22291

Mathematical Model

The Differential equations of the dynamics of our system depend on four basic variables:

- Y_R : concentration of LuxR
- Y_I : concentration of LuxI
- ϕi : concentration of AI(internal)
- ϕ_e : concentration of AI(external)



The equations for the Model are as follows:

- **LuxI Feedback Loop:**

i. $$\frac{dY_R}{dt} = \alpha_o \lambda_R - \gamma_R Y_R - \gamma_c Y_R$$

ii. $$\frac{dY_I}{dt} = \alpha_1 \left(\beta_1 + \frac{(1-\beta_1) Y_R^{*n}}{K_R^n + Y_R^{*n}} \right) \lambda_I - \gamma_I Y_I - \gamma_c Y_I$$

Where,

$\alpha_o \rightarrow$ number of luxR transcripts
$\lambda_R \rightarrow$ translational rate of LuxR
$\gamma_R \rightarrow$ degradation rate of LuxR
$\gamma_c \rightarrow$ dilution factor, as cells divide concentration of LuxR decreases
$\gamma_I \rightarrow$ degradation rate of LuxI
$\lambda_I \rightarrow$ translational rate of LuxI

Any gene expression has a sigmoidal form $\alpha_1 \left(\beta_1 + \frac{(1-\beta_1) Y_R^{*n}}{K_R^n + Y_R^{*n}} \right) \lambda_I$

$\beta_1 \rightarrow$ repression coefficient
$\alpha_1 \beta_1 \rightarrow$ basal gene expression
$\alpha_1 \rightarrow$ maximum gene expression
$Y_R^* \rightarrow$ concentration of LuxR* (LuxR* is the complex formed when AI binds to LuxR)
$n \rightarrow$ Hill co-efficient.
$K_R \rightarrow$ half saturation constant.

- **LuxR Feedback Loop:**

i. $$\frac{dY_I}{dt} = \alpha_o \lambda_I - \gamma_I Y_I - \gamma_c Y_I$$

ii. $$\frac{dY_R}{dt} = \alpha_1 \left(\beta_1 + \frac{(1-\beta_1) Y_R^{*n}}{K_R^n + Y_R^{*n}} \right) \lambda_R - \gamma_R Y_R - \gamma_c Y_R$$

Where,

$\alpha_o \rightarrow$ number of luxIR transcripts

$\lambda_R \rightarrow$ translational rate of LuxR

$\gamma_R \rightarrow$ degradation rate of LuxR

$\gamma_c \rightarrow$ dilution factor, as cells divide concentration of LuxR decreases

$\gamma_I \rightarrow$ degradation rate of LuxI

$\lambda_I \rightarrow$ translational rate of LuxI

Any gene expression has a sigmoidal form $\alpha_1\left(\beta_1+\frac{(1-\beta_1)Y_R^{*n}}{K_R^n+Y_R^{*n}}\right)\lambda_I$

$\beta_1 \rightarrow$ repression coefficient

$\alpha_1\beta_1 \rightarrow$ basal gene expression

$\alpha_1 \rightarrow$ maximum gene expression

$Y_R^* \rightarrow$ concentration of LuxR* (LuxR* is the complex formed when AI binds to LuxR)

$n \rightarrow$ Hill co-efficient.

$K_R \rightarrow$ half saturation constant.

- $\frac{d\phi_i}{dt}=\eta(\phi_e-\phi_i)-\gamma_c\phi_i-\gamma_I\phi_i+K_1Y_I$

The above equation can be arrived at using diffusion theory. The derivation for the same is available here.

$K_1 \rightarrow$ rate constant determining the production rate of autoinducer due to LuxI

$\eta \rightarrow$ diffusion rate of autoinducer across the cell

- $\frac{d\phi_e}{dt}=\frac{v_1}{v_2}\left[\eta(\phi_i-\phi_e)+\gamma_c\phi_e\right]-\gamma_c\phi_e$

$v_1 \rightarrow$ volume occupied by cells,

$v_2 \rightarrow$ volume of the medium.

$\frac{v_1}{v_2} \rightarrow \rho v_c$

Where, $\rho \rightarrow$ cell number density

$v_c \rightarrow$ volume of individual cell

- LuxR* is a complex that is obtained by the binding of autoinducer molecules to LuxR. The formation of LuxR* is very fast and for all practical purposes, we can assume the levels of LuxR* to be in quasi-equilibrium. Hence, the concentration of LuxR* is given as,

$$Y_R^*=Y_R\left(\frac{\phi_i^n}{K_\phi^n+\phi_i^n}\right)$$

This equation is derived using elementary rate kinetics. The derivation can be found here.

- Due to growth of cells in the medium, the volume fraction occupied by the cells increases with time. Hence,

$$\frac{d(\rho v_c)}{dt} = \gamma_c(\rho v_c)$$

In order to facilitate computation, we rescale our set of differential equations in order to make them dimensionless. We define the following quantities:

$$t = \tilde{t} * \bar{t}$$
$$\phi_e = \widetilde{\phi_e} * \overline{\phi_e}$$
$$\phi_i = \widetilde{\phi_i} * \overline{\phi_i}$$
$$Y_I = \widetilde{Y_I} * \overline{Y_I}$$

All barred quantities have dimensions similar to their corresponding unbarred variables and all tilde quantities are dimensionless scaling factors.

In order to draw effective parameters, we set some of the parameters as follows,

$$(i)\bar{t} = \frac{1}{\gamma_c}$$
$$(ii)\overline{\phi_i} = \overline{\phi_e} = \bar{\phi}$$
$$(iii)\bar{\phi} = K_\phi$$
$$(iv)\frac{\alpha_1 \lambda_R}{\gamma_c \overline{Y_R}} = 1 \Rightarrow \overline{Y_R} = \left(\frac{\alpha_1 \lambda_R}{\gamma_c}\right)$$
$$(v)\frac{\alpha_1 \lambda_I}{\gamma_c \overline{Y_I}} = 1 \Rightarrow \overline{Y_I} = \left(\frac{\alpha_1 \lambda_I}{\gamma_c}\right)$$
$$(vi)\frac{\alpha_o}{\alpha_1} = \alpha$$
$$(vii)\gamma_c = 1$$
$$(viii)K_\phi = \frac{K_1 \alpha_1 \lambda_I}{K_\phi}$$

Our final equations in the rescaled dimensionless form are as follows,

Loop 1: LuxI in feedback

$$\frac{dY_R}{dt} = \alpha - (1+\gamma_R)Y_R$$

$$\frac{dY_I}{dt} = \left(\beta + (1-\beta)\frac{(\alpha_1\lambda_R)^{n1} Y_R{}^{n1} \left(\frac{\phi_i{}^n}{1+\phi_i{}^n} \right)^{n1}}{K_R{}^{n1} + (\alpha_1\lambda_R)^{n1} Y_R{}^{n1} \left(\frac{\phi_i{}^n}{1+\phi_i{}^n} \right)^{n1}} \right) - (1+\gamma_I)Y_I$$

Loop 2: LuxR in feedback

$$\frac{dY_I}{dt} = \alpha - (1+\gamma_I)Y_I$$

$$\frac{dY_R}{dt} = \left(\beta + (1-\beta)\frac{(\alpha_1\lambda_R)^{n1} Y_R{}^{n1} \left(\frac{\phi_i{}^n}{1+\phi_i{}^n} \right)^{n1}}{K_R{}^{n1} + (\alpha_1\lambda_R)^{n1} Y_R{}^{n1} \left(\frac{\phi_i{}^n}{1+\phi_i{}^n} \right)^{n1}} \right) - (1+\gamma_R)Y_R$$

$$\frac{d\phi_i}{dt} = K_\phi Y_I + \eta(\phi_e - \phi_i) - (1+\gamma_i)\phi_i$$

$$\frac{d\phi_e}{dt} = \rho v_c \left[\eta(\phi_i - \phi_e) + \phi_e \right] - \gamma_e \phi_e$$

$$\frac{d(\rho v_c)}{dt} = \rho v_c$$

Effective parameters were drawn at random from certain ranges based on biological considerations and the model was simulated.

Parameter ranges:

$n1$ =2

n =2

K_ϕ =antilog (3, 5) [Based on our analysis that K_ϕ >10^3]

β =antilog (-2,-1) [Basal expression is 1/100th-1/10th]

γ_R =antilog (-1, 0) [degradation rate is 1/10th-1th of the rate of dilution (γ_c) which is set to 1]

γ_I =antilog (-1, 0) [same reason]

γ_i =antilog (-1, 0) [same reason]

γ_e =antilog (-1, 0) [same reason]

η =antilog (1, 2)* K_ϕ [based on our analysis that η >10* K_ϕ; so 10 times to 100 times K_ϕ]

K_R =antilog (-1, 1) [to span full range of curve characteristics)

α =antilog (-1, 0) [we consider max protein expression rate to be 1 and basal to be 0.1]