1 Assumptions and Questions

1. A: All cells initially express RFP
2. A: Oxygen below 10 mmHg turns off expression of RFP, turns on expression of GFP
3. Q: What's a time scale for protein synthesis? (Early on, it's time to transcribe RNA, then synthesize protein. Later, it's time to just synthesize protein from already existent RNA.)
4. Q: What's the time scale for protein degradation?
5. Q: In 10 mmHg, does RFP gene get snipped out immediately and GFP gene enabled, or is there a mean time delay?

2 Model

2.1 Gene - Protein network

We will model a set of genes **G** that encode proteins **P** with the following model:

$$\frac{dP_i}{dt} = \alpha_i G_i - \beta_i P_i, \qquad i = 1, 2, \ldots \tag{1}$$

where α_i is a protein creation rate, and β_i is a protein degradation rate. (Notice that this skips modeling RNA transcription.) We will assume throughout that $0 \leq G_i \leq 1$. Here, we will model the following genes:

index	protein	notes
0	RFP	default fluorescence
1	GFP	activated at $\mathrm{pO}_2 = 10\,\mathrm{mmHg}$

Gene expression can be modeled in any way. Here, we set $G_1 = 1$ if $\mathrm{pO}_2 < 10\,\mathrm{mmHg}$.

2.1.1 Nondimensionalization

Let $\overline{P}$ be the maximum protein level with $G = 1$. Then by equilibrium analysis, $\overline{P} = \frac{\alpha}{\beta}$. If we nondimensionalize the main ODE form, we get

$$\frac{dP_i}{dt} = \beta_i \left(G_i - P_i\right). \tag{2}$$

This functional form sucks, because it doesn't let us set the rate of reaching near $P_i \sim 1$ independently of the decay rate. Blech!

2.1.2 Better model and nondimensionalization

Now, suppose that P^* is a protein value where negative feedback reduces either transcription or synthesis. Then

$$\frac{dP_i}{dt} = \alpha_i G_i \left(P_i^* - P_i\right) - \beta_i P_i. \tag{3}$$

By equilibrium analysis (and noting the maximum gene expression of $G_i = 1$, the maximum equilibrium protein value is

$$\overline{P}_i = \frac{\alpha_i}{\alpha_i + \beta_i} P_i^* = \gamma_i P_i^*, \tag{4}$$

where

$$\gamma_i = \frac{\alpha_i}{\alpha_i + \beta_i}. \tag{5}$$

If we nondimensionalize by this, we get:

$$\frac{dP_i}{dt} = \alpha_i G_i \left(\frac{1}{\gamma_i} - P_i \right) - \beta_i P_i, \tag{6}$$

which has the expected (dimensionless) equilibria $P_i = 1$ if $G_i = 1$, and $P_i = 0$ if $G_i = 0$.

Note that we can write this without γ_i in the form

$$= G_i \alpha_i \left(1 - P_i\right) + \beta_i \left(G_i - P_i\right). \tag{7}$$

In this form, α_i sets the rate of approaching the maximum protein expression (1) when the gene is expressed, and β_i sets the rate of decay when the gene is not expressed.

2.1.3 Parameter estimates

Based upon experimental data, it takes GFP on the order of 1-1.5 days to double its brightness. Let's suppose for now that it takes about 1 day to reach 50% of its maximum value. Then in the absence of degradation, we have

$$\frac{dP_i}{dt} \approx \alpha_i \left(1 - P_i\right). \tag{8}$$

So, if we want to reach $P_i = 0.5$ after 1440 min time, then

$$\alpha_i \sim \frac{\ln 2}{1440\text{min}} \approx 4.8e-4 \text{ min}^{-1}. \tag{9}$$

Similarly, if $G_i = 0$, we can easily fit β_i. More experimental data suggests a half life on the order of 7 days. Thus,

$$\beta_i \sim 6.9e-5 \text{ min}^{-1}. \tag{10}$$

2.1.4 Simple implicit numerical scheme

Suppose that $P_i^n = P_i(t_n) = P_i(t_0 + n\Delta t)$. Then

$$P_i^{n+1} = \frac{P_i^n + \Delta t G_i^n \left(\alpha_i + \beta_i\right)}{1 + \Delta t \left(\alpha_i G_i^n + \beta_i\right)} \tag{11}$$

2.1.5 Optional: Gene switching

Suppose it takes on the order of 1 day in hypoxic conditions to switch from RFP to GFP genes. Then in any time $[t, t + \Delta t]$ we have a probability of setting $G_0 = 0$ and $G_1 = 1$ given by

$$\Delta t 1440. \tag{12}$$

2.2 Motility