Problem Set 2

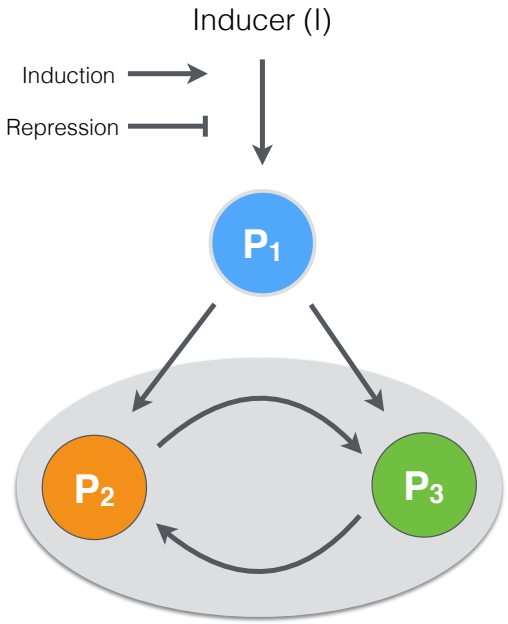

Figure 1: Memory circuit motif. P_1 is induced by external inducer I. Downstream proteins P_2 and P_3 are induced by P_1, and by each other.

1. Use your `PS1` model to classify which model/promoter parameters increase, decrease or does nothing to the steady-state mRNA profile as a function of inducer I (low, medium and high). Create a parameter table with the direction of change for each model parameter for I (low, medium and high).

2. An extracellular initiator I (mM) induces the expression of protein 1, which in turn induces the expression of downstream proteins P_2 and P_3. The downstream proteins also induce each other (Fig. 1). Let's explore the dynamics of this circuit in a well-mixed population of *E. coli* cells with a doubling time of 30 min. Use μmol gDW^{-1} as the concentration basis, where 70% of the mass of a cell is water.

   Assume: (i) the circuit is encoded on a plasmid present at 200 copies per cell (constant); (ii) use characteristic lengths of $\mathcal{L}_X$ = 1000 nt and $\mathcal{L}_T$ = 333 AA; (iii) the promoter control models follow the Moon/Voigt formulation; (iv) translation operates at the kinetic limit; (v) RNAP and Ribosome levels are constant; (vi) $\mathcal{L}_{X,1}$ = 1200 nt, $\mathcal{L}_{X,2}$ = 2400 nt and $\mathcal{L}_{X,3}$ = 600 nt. Let $\mathcal{L}_{L,i} \simeq (1/3)\mathcal{L}_{X,i}$.

a) Write the material balances around mRNA m_1, m_2 and m_3, and p_1, p_2 and p_3 in the form:

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x} + \mathbf{S}\mathbf{r} \tag{1}$$

where $\mathbf{x}$ denotes the 6 $\times$ 1 mRNA/protein vector, $\mathbf{A}$ denote the 6 $\times$ 6 dilution matrix, $\mathbf{S}$ denotes the 6 $\times$ $\mathcal{R}$ stoichiometric matrix, and $\mathbf{r}$ denotes the $\mathcal{R}\times$1 reaction rate vector.

b) Solve (numerically) the system of differential equations for: (i) a functional memory circuit and (ii) a broken circuit in which P_2 does not induce P_3. Use any differential equation solver you wish, assume $\mathbf{x}(t_o) = \mathbf{0}$. Add inducer I = 10 mM at t = 0 min and withdraw inducer t = 60 min. Stop the simulation at t = 360 min. Use the `PS1` promoter parameters for the induction of protein 1, and characteristic values for all other promoter/kinetic parameters. Plot P_j (y-axis) versus time (x-axis, units in min) for both versions of the circuit.

c) The gene circuit balances have a form that allows for a `supercool` mathematical discretization trick. A high-fidelity *discrete* approximation of the solution of Eqn (1) at timesteps k = 0, 1, 2, ..., $\mathcal{T}$ (with step-size τ) is given by:

$$\mathbf{x}_{k+1} = \hat{\mathbf{A}}\mathbf{x}_k + \hat{\mathbf{S}}\mathbf{r}_k \tag{2}$$

where:

$$\hat{\mathbf{A}} = \exp \mathbf{A}\tau \tag{3}$$

and:

$$\hat{\mathbf{S}} = \mathbf{A}^{-1}\left[\hat{\mathbf{A}} - \mathbf{I}\right]\mathbf{S} \tag{4}$$

Compare the discrete solution to the numerical solution from part b) for τ = 0.01 min. Plot P_j (y-axis) versus time (x-axis, units in min) for the numerical and discrete solutions, for the same inducer profile.