Systems Biology Tutorial 6: MCA

In this tutorial, we will explore MCA with a simple 2-step pathway:

$$\mathrm{S} \;\overset{\boxed{1}}{\rightleftharpoons}\; \mathrm{X} \;\overset{\boxed{2}}{\rightleftharpoons}\; \mathrm{P}$$

The rate equations for the reactions are given by:

$$v_1 = k_{1f}\left(s - \frac{x}{K_{eq1}}\right) \tag{1}$$

$$v_2 = \frac{V_{2f}\,\frac{x}{K_x}\left(1 - \frac{p/x}{K_{eq2}}\right)}{1 + \frac{x}{K_x} + \frac{p}{K_p}} \tag{2}$$

A Mathematica notebook for this pathway is available as Tut6.nb. Inspect this file and note the following:

- species S and P are fixed/clamped;
- values for the kinetic parameters and the initial value of x are provided.

1. Use `NDSolve` to obtain a solution for x as a function of time for $0 \leq \mathrm{t} \leq 10$. Plot x vs time. Plot the rates of both reactions vs time. What are the values of the steady-state concentration of X and the flux J?

2. Calculate $C^J_{v_1}$ and $C^J_{v_2}$ using perturbation control analysis. To do this, increase k_{f1} and V_{f2} respectively by 1% from their original values and note the new fluxes. Calculate the flux-control coefficient using the perturbation MCA formula you learnt in the MCA lecture.

3. Do the flux control coefficients for the model sum to 1? If not, explain the difference. Refer to the approximation that is made when using perturbation control analysis.

4. By how many percent would v_2 change upon a 1% increase in K_x? Calculate the parameter elasticity $\varepsilon^{v_2}_{K_x}$ of the enzyme using the analytical derivative method that you used for the sensitivity determination in Tut 3.

5. Increase the K_x by 1% and obtain a new model simulation. Determine the %-change in the flux at the new steady state ($R^J_{K_x}$). Does the change in the flux agree with the change in the activity of enzyme 2?

6. Determine the elasticities of $\varepsilon^{v_1}_x$ and $\varepsilon^{v_2}_x$ at steady state using the analytical method of Tut 3. Calculate the flux control coefficients using your answers. Do the flux control coefficients sum to 1? How do they compare to the flux control coefficients that we determined in Question 2?

7. Use the partitioned response $C^J_{v_1}\varepsilon^{v_1}_x + C^J_{v_2}\varepsilon^{v_2}_x$ to show that a change in the concentration of x will not affect the flux, $R^J_x = 0$. (i.e. test the flux connectivity theorem).