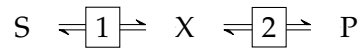


Systems Biology Tutorial 5: Metabolic Control Analysis

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



The rate equations for the reactions are given by:

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

$$v_2 = \frac{\frac{V_{f2}}{K_x} \left(x - \frac{p}{K_{eq2}} \right)}{1 + \frac{x}{K_x} + \frac{p}{K_p}} \quad (2)$$

A PySCeS model for this pathway is available as `lin2.psc`. Inspect this file; it has values for the kinetic parameters and initial values for the variable concentrations, species S and P are fixed/clamped.

1. Load the model into PySCeS and perform a time simulation for $0 \leq t \leq 10$. Plot the concentration of X *vs.* time. Plot the rates of both reactions *vs.* time. What are the values of the steady-state concentration \bar{x} and the flux J ?
2. Calculate the steady state directly with PySCeS. Do the values of J and \bar{x} agree with the graphs?
3. Calculate $C_{v_1}^J$ and $C_{v_2}^J$ using perturbation control analysis. To do this, increase k_{1f} (or V_{f2} respectively) by 1% from its original value and note the new flux. Calculate the flux-control coefficient using the perturbation formula you learnt in the MCA lecture. Pointers for doing this are given in the skeleton notebook.
4. Do the flux control coefficients for the model sum to 1? If not, explain the difference.
5. By how many percent would v_2 change upon a 1% increase in K_x ? Answer this in three ways:
 - (a) Define a Python function for v_2 . Using `numdifftools.Derivative()` as you did in Tutorial 3, obtain the parameter elasticity $\varepsilon_{K_x}^{v_2}$. Evaluate this at the steady-state \bar{x} .
 - (b) Calculate the elasticity of the enzyme ($\varepsilon_{K_x}^{v_2}$) using the analytical (symbolic) derivative of the function. We use the `SymPy` package for symbolic Python to do this; code is given in the skeleton notebook. Evaluate the function by substituting the numerical values for the parameters (for X, use the steady-state concentration \bar{x}).
 - (c) Calculate the elasticity with PySCeS directly.
6. Increase K_x in the model by 1% and obtain a new model simulation. Determine the %-change in v_2 at the new steady state ($R_{K_x}^J$). (You can change the value of the parameter directly in the Jupyter notebook, no need to change and re-load the PSC file). Did the local behaviour of the reaction match that of the pathway as a whole? If v_2 had complete control of the pathway, what change would you have expected?
7. Give expressions for the flux-control coefficients in terms of elasticity coefficients using the connectivity and flux summation theorems. `SymPy` code is in the skeleton notebook.
8. Determine the elasticities of $\varepsilon_x^{v_1}$ and $\varepsilon_x^{v_2}$ at steady state using PySCeS. 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 3, and to those calculated by PySCeS directly?
9. Use the partitioned response $R_x^J = C_{v_1}^J \varepsilon_x^{v_1} + C_{v_2}^J \varepsilon_x^{v_2}$ to show that a 1% change in the concentration of X will not affect the flux (i.e. test the flux connectivity theorem).