Metabolic control analysis in a simple model

1. **Calculating elasticities and control coefficients.**

   We will be exploring MCA properties and relations for a simple branched pathway, illustrated below:

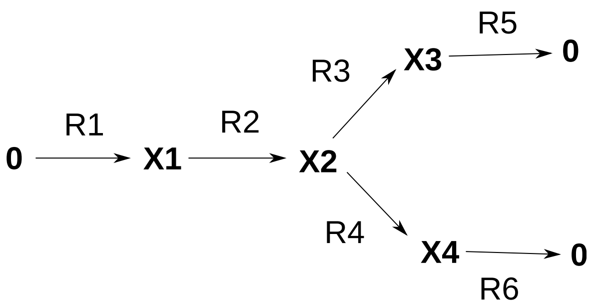

Figure 1: A simple branched model metabolic network. X_i are metabolites; R_j are reactions.

   (a) The files `dYdT2015.m` and `ComputeNu2015.m` contain ODEs describing the system. The MATLAB command `[t,y] = ode45(@dYdT, [0 1e3], x0, [], k)` will solve these ODEs for initial condition x_0 and parameters k. Set all kinetic constants to 0.1. Given an initial condition at $t = 0$ where all concentrations are unity, use MATLAB to find the steady state of the system (we will assume that $t = 1000$ is long enough for the system to equilibrate). Record both the concentrations and the fluxes in this state.

   (b) Recall that an elasticity ϵ^{ν}_{X} describes the instantaneous relative change in a reaction rate ν induced by a relative change in a concentration X (for example, how enzymatic rate depends on substrate concentration). `elasticity.m` perturbs the steady-state concentration values by a small amount, and uses an ODE solver to compute the changes in flux provoked over a short time interval ($t = 10^{-6}$). These changes in flux are then used to write down the elasticities of the system, using $\epsilon^{\nu_j}_{X_i} = \frac{\delta \nu_j}{\delta X_i}\frac{X_i}{\nu_j}$. Obtain these elasticities, pick a couple and confirm that they match your expectation.

   (c) Flux control coefficients $C^{J_j}_{k_i}$ measure the relative change in *steady state* flux J_j through reaction (or pathway) j provoked by a change in the rate parameter k_i of the same, or a different reaction i. Use your steady-state concentration result to compute the steady-state fluxes of the unperturbed system. Then, perhaps following the approach of `elasticity.m`, perturb the rate parameters associated with each reaction by a small amount (say 10^{-5}) and find the new steady-state fluxes.

   (d) Use these changes in flux to write down the flux control coefficients of the system, using

$$C^{J_j}_{k_i} = \frac{\delta J_j}{\delta k_i}\frac{k_i}{J_j}. \tag{1}$$

   (e) If there's time, do the same for concentration control coefficients

$$C^{X_j}_{k_i} = \frac{\delta X_j}{\delta k_i}\frac{k_i}{X_j} \tag{2}$$

2. **Summation and connectivity theorems.**

   We have now obtained the flux and concentration control coefficients describing the influence of rate parameter perturbations on a metabolic system. We also have elasticities for this system, describing how reaction rates change with concentrations. We will now verify and interpret the fundamental theorems of metabolic control analysis.

   (a) The flux control summation theorem states that $\sum_i C^{J_j}_{k_i} = 1$ foor any j. Verify that this is the case (within numerical error). Which reactions are 'rate-limiting'? Verify that reactions with several nonzero control coefficients exhibit control in the directions you would expect.

   (b) How can a situation arise in which $C^{J_i}_{k_i} = 0$ (the rate parameter of a reaction plays no role in controlling flux through that reaction)?

   (c) The flux connectivity theorem suggests that $\sum_i C^{J_j}_{k_i}\epsilon^{\nu_i}_{X} = 0$ for J_j that responds to chemical X. Observe that reactions 3 and 4, by mass action, depend on the concentration of X_2. Show that the connectivity theorem is obeyed for the link between J_3 (and J_4) and X_2.