1. Exercise list. Monday Week 1

Exercise 1.1 (A calcium transport network)**.** We consider the reaction network

$$0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_1 \qquad X_1 + X_2 \xrightarrow{\kappa_3} 2X_1 \qquad X_1 + X_3 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} X_4 \xrightarrow{\kappa_6} X_2 + X_3,$$

where X_1 corresponds to calcium in the cytosol, X_2 is calcium in the endoplasmatic reticulum, X_3 is an enzyme catalysing the transfer via a Michaelis-Menten mechanism with complex formation X_4.

(i) Write down the associated mass-action system, the stoichiometric matrix and a basis of the stoichiometric subspace.
(ii) Find equations of the stoichiometric compatibility classes. Is the network conservative?
(iii) Show that the positive steady state variety admits a parametrization in one variable.
(iv) Show that the network is not multistationary.

This network is analysed in the paper [Gatermann, Eiswirth, Sensse, "Toric ideals and graph theory to analyze Hopf bifurcations in mass action systems", Journal of Symbolic Computation 40(6), 2005, Pages 1361-1382]

Exercise 1.2 (An enzymatic network)**.** We consider the reaction network

$$S_1 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} Y_1 \qquad S_2 + Y_1 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} Y_2 \xrightarrow{\kappa_5} P + E, \qquad P \xrightarrow{\kappa_6} S_1,$$

modeling the transformation of two substrates S_1, S_2 to a product P in a two-step catalytic mechanism involving the enzyme E.

(i) Write down the associated mass-action system, the stoichiometric matrix and a basis of the stoichiometric subspace.
(ii) Find equations of the stoichiometric compatibility classes. Is the network conservative?
(iii) Show that at steady state y_1, y_2 are monomials in s_1, s_2, e.
(iv) Is the network consistent?

Exercise 1.3. Consider a mass-action system $\dot{x} = f(x)$ in $\mathbb{R}^n$, with $f = (f_1, \ldots, f_n)$. Show that, for every $\ell = 1, \ldots, n$, there exist polynomials $p_\ell, q_\ell \in \mathbb{R}[x_1, \ldots, x_n]$ with all coefficients nonnegative, such that

$$f_\ell(x) = p_\ell(x) - x_\ell\, q_\ell(x).$$

Exercise 1.4 (Linear first integrals)**.** Consider a mass-action network with n species, stoichiometric subspace S, stoichiometric matrix N and mass-action system $\dot{x} = f(x)$. Recall that a **linear first integral** is a vector λ that satisfies

$$\lambda \cdot x(t) = \sum_{i=1}^{n} \lambda_i\, x_i(t) \text{ is constant for all trajectories } x(t).$$

Let

$$\Lambda = \{\lambda \in \mathbb{R}^n \colon \lambda \text{ is a linear first integral}\}.$$

Show that the following statements are true:

(i) $\lambda \in \Lambda$ if and only if $\lambda \cdot f(x) = \sum_i \lambda_i f_i(x) = 0$ for all $x \in \mathbb{R}^n$.
(ii) $S^\perp \subseteq \Lambda$. (*Hint:* observe that $S^\perp = \ker(N^\top)$).
(iii) Λ is a real vector space.
(iv) Given an initial condition $x_0 \in \mathbb{R}^n_{\geq 0}$, let x^0 be the solution of the mass-action system $\dot{x} = f(x)$ defined in an interval $I \subset \mathbb{R}$ around the origin such that $x^0(0) = x_0$. Then, the points $x^0(t)$ for all $t \in I$ are contained in the translate

$$x_0 + \Lambda^\perp = \{x_0 + v \colon \lambda \cdot v = 0, \ \text{ for all } \lambda \in \Lambda\}.$$

(v) Let x_0, x^0 and I be as in item (iv). Prove that for any $t \in I$, $x^0(t) \in x(0) + S$.

Recall that the linear first integrals arising from $S^\perp$ are called **conservation laws** and define the stoichiometric compatibility classes. These are the linear first integrals that do not depend on the choice of reaction rate constants.

Exercise 1.5. Consider the (linear) mass-action system associated with the mass-action network

$$X_3 \xleftarrow{\kappa_1} X_1 \underset{\kappa_3}{\overset{\kappa_2}{\rightleftarrows}} X_2 \xrightarrow{\kappa_4} X_4.$$

Prove that $\dim \Lambda > \dim S^\perp$ and compute both vector subspaces (where Λ is defined in Exercise 1.4.)

Note that in this case there are linear first integrals whose coefficients vary with the reaction rate constants, that is, are not conservation laws

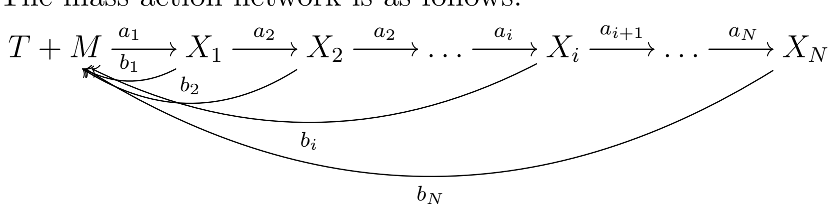
Remark. The equality $\Lambda = S^\perp$ is tacitly assumed in the literature, but it might not be true as you proved in this exercise. There is a a combinatorial condition on the reaction network G due to Feinberg and Horn [*Chemical mechanism structure and the coincidence of the stoichiometric and kinetic subspaces*, Arch. Ration. Mech. Anal. 66(1) (1977), 83–97] to ensure that $\Lambda = S^\perp$: *There is a single terminal strongly connected component in each connected component of G.*

Exercise 1.6. Provide a reaction network for which the mass-action kinetics system associated to it is the Lotka-Volterra predator-prey system:

$$\dot{x} = \alpha\, x - \beta\, xy, \quad \dot{y} = \delta\, xy - \gamma\, y,$$

where $\alpha, \beta, \gamma, \delta \in \mathbb{R}_{>0}$. In most biological networks, the reaction network gives insight about the mechanism. Do you see an interpretation of the reactions here?

Exercise 1.7. In this exercise, you will prove that a model for the specificity of a T-cell in the immune system, according to McKeithan's formulation, has a single positive steady state in each stoichiometric compatibility class (hence is not multistationary). The mass-action network is as follows:



For each species $T, M, X_1, \dots, X_N$, we denote its concentration by $x_T, x_M, x_1, \dots, x_N$, respectively.

(i) Describe the associated mass-action system.

(ii) Check that the following are two linearly independent conservation laws: $x_M + x_1 + \cdots + x_N = M_{\text{tot}}$ and $x_T + x_1 + \cdots + x_N = T_{\text{tot}}$. Are there any other linearly independent conservation laws?

(iii) Prove that any steady state x verifies that $x_i = \mu_i \, x_T x_M$ for any $i = 1, \ldots, N$, where μ_i can be written in terms of the given reaction rate constants.

(iv) Use the conservation law for T_{tot} to find an expression of x_T in terms of x_M at steady state.

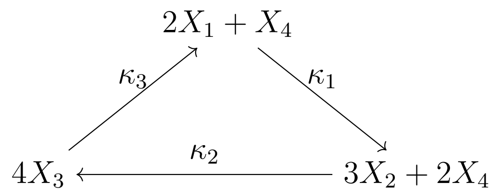
(v) Use the conservation law for M_{tot} to conclude that for each choice of $T_{\text{tot}}, M_{\text{tot}} > 0$ there exists a unique positive steady state x with $x_M + x_1 + \cdots + x_N = M_{\text{tot}}$ and $x_T + x_1 + \cdots + x_N = T_{\text{tot}}$.

Hint: Start with the case $N = 2$. We will give in the course results that will provide a straightforward proof of this last statement.

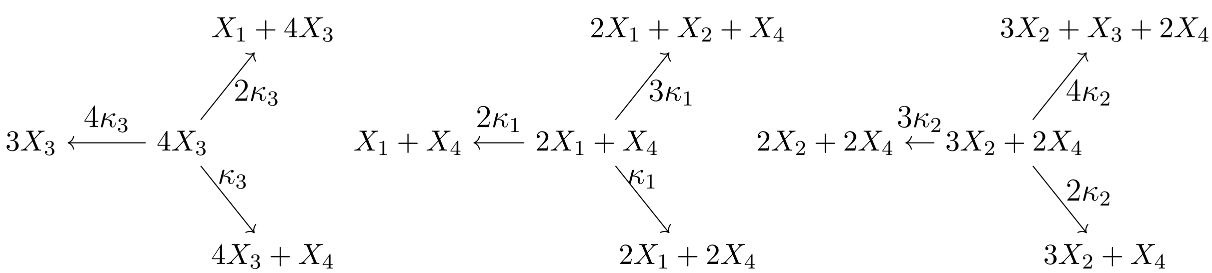
Exercise 1.8. Consider the following ODE system:

$$\begin{aligned}
\dot{x}_1 &= -2\kappa_1 x_1^2 x_4 + 2\kappa_3 x_3^4 \\
\dot{x}_2 &= 3\kappa_1 x_1^2 x_4 - 3\kappa_2 x_2^3 x_4^2 \\
\dot{x}_3 &= 4\kappa_2 x_2^3 x_4^2 - 4\kappa_3 x_3^4 \\
\dot{x}_4 &= \kappa_1 x_1^2 x_4 - 2\kappa_2 x_2^3 x_4^2 + \kappa_3 x_3^4.
\end{aligned}$$

where $x = (x_1, \ldots, x_4) \in \mathbb{R}^4$ and $\kappa_1, \kappa_2, \kappa_3 \in \mathbb{R}_{>0}$. Check that this system is the mass-action system associated with the network



Now, consider the mass-action system associated with the following 9 reactions and compare it with the one previously obtained.



What can you conclude?