4. Exercise list. Thursday Week 1

In this exercise list, you will work with problems on injectivity and its relation to multistationarity. Recall that the main theorem of injectivity says as follows.

Theorem. (Injectivity) Let $N \in \mathbb{R}^{p\times r}$ of rank s, $B \in \mathbb{R}^{n\times r}$, and $S \subseteq \mathbb{R}^n$ a vector subspace. For $\kappa \in \mathbb{R}^r_{>0}$, define the function $f_\kappa(x) = N\operatorname{diag}(\kappa)x^B$. The following are equivalent:

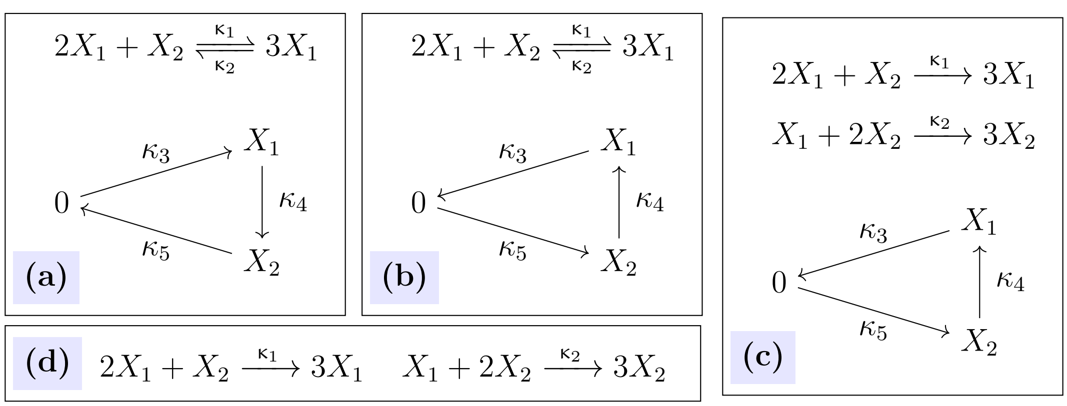
- (inj) f_κ is injective with respect to S for all $\kappa \in \mathbb{R}^r_{>0}$ (that is, $f_\kappa(x) \neq f_\kappa(y)$ for all $x \neq y$ such that $x - y \in S$.
- (lin) The linear map with matrix $N\operatorname{diag}(\mu)B^\top \operatorname{diag}(\lambda)$ is injective on S for all $\mu \in \mathbb{R}^r_{>0}$ and $\lambda \in \mathbb{R}^n_{>0}$.
- (jac) The Jacobian of $f_\kappa(x)$ is injective on S for all $x \in \mathbb{R}^n_{>0}$ and $\kappa \in \mathbb{R}^r_{>0}$.

If S has dimension s, then let $W \in \mathbb{R}^{(n-s)\times n}$ be a matrix whose rows form a basis of $S^\perp$. Consider the matrix $M_{\mu,\lambda}$ whose bottom $n-s$ rows is W and upper s rows is $N'\operatorname{diag}(\mu)B^\top\operatorname{diag}(\lambda)$, with $N' \in \mathbb{R}^{s\times r}$ of full rank such that $\ker(N) = \ker(N')$. Then any of the above is equivalent to

- (det) $\det(M_{\mu,\lambda})$ is a nonzero polynomial in λ, μ with all coefficients of the same sign.

In the application to reaction networks, N is the stoichiometric matrix, so $p = n$, B the reactant matrix, $S = \operatorname{im}(N)$ and W is a matrix of conservation laws. If (inj) holds, then we say that the network is injective. In this case, the network is not multistationary.

Exercise 4.1. Use (det) to determine whether the following networks are injective:



Conclude when possible whether the network admits multistationarity and whether there are positive steady states (by working with the steady state equations). Note that not all networks have conservation laws and that you can reuse computations as the networks share some similarities.

Exercise 4.2. We have discussed in the lecture, that if a network is injective, then it is not multistationary. However, the converse is not true as this exercise shows. Consider the following mass-action network

$$0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_1 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} 2X_1.$$

Show that this network is neither multistationary nor injective.

Exercise 4.3. Decide whether the following networks are injective (the computations probably require the use of software).

- The network of Exercise 1.2:
$$S_1 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} Y_1 \qquad S_2 + Y_1 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} Y_2 \xrightarrow{\kappa_5} P + E, \qquad P \xrightarrow{\kappa_6} S_1,$$
- An extended network of two-substrate catalysis:
$$E + S_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} Y_1 \qquad E + S_2 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} Y_2$$
$$S_2 + Y_1 \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} Y_3 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_1 + Y_2 \qquad Y_3 \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} E + P.$$
- The one-site and two-site phosphorylation cycles from Exercise 3.6. In the latter case, use the monomial parametrization and the injectivity test for monomial maps to show that the two-site phosphorylation cycle admits multistationarity.

Exercise 4.4. In the setting of the injectivity theorem, we saw in class (inj) $\Rightarrow$ (lin), and you will show now the reverse implication. We guide you through it.

(i) Show that for any $x, y \in \mathbb{R}^n_{>0}$, the sign of $x^B - y^B$ agrees with the sign of $B^\top z$ for some $z \in \mathbb{R}^n$ with the same sign vector as $x - y$. (Hint: use that the logarithm is a strictly increasing function and that $\ln(x^B) = B^\top \ln(x)$. Here ln is taken componentwise.)

(ii) Encode the sign equalities in (i) as multiplication by a diagonal matrix with positive entries, to conclude that if (inj) fails, then (lin) fails as well.

Exercise 4.5. In this exercise you will prove (lin) $\Leftrightarrow$ (jac) from the injectivity theorem. Let $f_\kappa(x) = N\,\mathrm{diag}(\kappa)x^B$ be as in the theorem.

(i) Show that $J_{f_\kappa}(x) = N\,\mathrm{diag}(\mu)B^\top\,\mathrm{diag}(x^{-1})$ with $\mu = \mathrm{diag}(\kappa)x^B$ and where x^{-1} is defined componentwise.

(ii) Show that the following two sets of matrices are equal:
$$\{M_{\mu,\lambda} \colon \mu \in \mathbb{R}^r_{>0}, \lambda \in \mathbb{R}^n_{>0}\} = \{J_{f_\kappa}(x) \colon \kappa \in \mathbb{R}^r_{>0}, x \in \mathbb{R}^n_{>0}\}.$$
Conclude (lin) $\Leftrightarrow$ (jac).

Exercise 4.6. In this exercise you will show that the injectivity theorems specialize to some classical results of algebra.

(i) Consider a linear map $f(x) = Nx$ from $\mathbb{R}^r$ to $\mathbb{R}^p$, with $N \in \mathbb{R}^{p\times r}$. Use the equivalence between (inj) and (lin) to show that if $\ker(N) = \{0\}$, then $f(x) = y$ has at most one solution for all $y \in \mathbb{R}^p$.

(ii) Let $f(x) = a_s x^s + \cdots + a_1 x + a_0$ be a polynomial of degree s in one variable. Use the equivalence between (inj) and (jac) to show that if $a_i \geq 0$ for all $i > 0$, then $f(x)$ has at most one positive root (this result is a special case of the *Descartes rule of signs.*

Exercise 4.7. Show that the polynomial $f = (x-1)^3$ verifies that $f'(1) = 0$ and yet f is injective on $\mathbb{R}_{>0}$. Is this contradicting the injectivity theorem?

Remark for those knowing complex functions: the fact that $f'(1) = 0$ *implies that* f *is not injective in any open neighborhood of* 1 *in* $\mathbb{C}$.

Exercise 4.8. Describe the set of injective mass-action networks with one species and arbitrary (but finite) number of reactions.

Exercise 4.9. Let $C \in \mathbb{R}^{d\times n}$ of rank d, and V be its rowspan. Recall that a *circuit* of V is a nonzero vector $v \in V$ with minimal support. For a subset $I \subseteq \{1,\ldots,n\}$, we let C_I denote the submatrix of C consisting of the columns of C with indices in I.

A non-trivial result on circuits states the following. For a set $J \subseteq \{1,\ldots,n\}$ of cardinality $d-1$ such that the columns of C_J are linearly independent, define the vector $r_J \in \mathbb{R}^n$ as

$$(r_J)_k = \begin{cases} (-1)^{\mu(k,J)} \det\left(C_{\{k\}\cup J}\right) & \text{if } k \notin J \\ 0 & \text{if } k \in J, \end{cases}$$

for $k = 1,\ldots,n$, where $\mu(k,J)$ is the number of indices in J that are strictly less than k. Then the vectors r_J are circuits, and furthermore, any other circuit is a multiple of r_J for some set J.

(i) Use the previous result to find all the circuits of the rowspan V of the following matrix:

$$C = \begin{pmatrix} 1 & 3 & 1 & 2 \\ 0 & 0 & 4 & 3 \end{pmatrix}.$$

Which are the orthants $\mathcal{O}$ of $\mathbb{R}^4$ for which $V \cap \mathcal{O} \neq \emptyset$? Equivalently, which are the possible sign vectors of the elements in V? And which are the sign vectors of the elements in $\ker(C)$?

(ii) How many circuits (up to constant) has the rowspan of a matrix C of size $d \times n$ with $d \leq n$, if all maximal minors of C are nonzero (C is called *uniform* in this case).

Exercise 4.10. Two sign vectors $\sigma, \sigma' \in \{0,+1,-1\}^n$ are said to be *orthogonal* if either for all $i \in \{1,\ldots,n\}$ it holds that $\sigma_i \cdot \sigma'_i = 0$ or there exist i,j such that $\sigma_i \cdot \sigma'_i = 1$ and $\sigma_j \cdot \sigma'_j = -1$. A general theorem in the framework of *oriented matroids* says that a vector $\sigma' \in \{1,0,-1\}^n$ is the sign vector of an element in the kernel of a matrix C if and only if σ' is orthogonal to the sign vectors of all the circuits in the rowspan V of C (and therefore, to the sign vector of any element in V).

Use the previous theorem to prove the following result: There exists a positive vector in the kernel of a matrix C if and only if the sign vectors of all circuits of the rowspan of C have a positive and a negative entry. How can we test this property?