2. EXERCISE LIST. TUESDAY WEEK 1

It would be useful/required to implement some of the computations in the following exercises in a computer algebra system. A free alternative easy to use is `Singular`, which can be downloaded from: `https://www.singular.uni-kl.de/` and it can also be used online there. We provide some Brief Notes On Singular to collect the main instructions that you might need. There is also a small introduction in the Lecture Notes of Timo de Wolff. If you feel comfortable with any other software and you have it in your computer, please feel free to use it. We also include a commented example at the end of this list.

Exercise 2.1. Show Corollary 1.19, Part (6) of the lecture: Let $J = \langle f_1, \ldots, f_s \rangle \subseteq \mathbb{C}[z]$ (i.e., we are in the univariate case). Then $I(V(J)) = J$ if and only if $\gcd(f_1, \ldots, f_s)$ is decomposable in linear factors with multiplicity 1.

Exercise 2.2. Show Remark 1.27 of the lecture: Let $f, g \in \mathbb{C}[\boldsymbol{z}]$ and $\succ$ be a monomial ordering. Then it holds:

(1) $\deg(fg; \succ) = \deg(f; \succ) + \deg(g; \succ)$.
(2) If $f + g \neq 0$, then $\deg(f + g; \succ) \leq \max\{\deg(f; \succ), \deg(g; \succ)\}$ with equality if $\deg(f; \succ) \neq \deg(g; \succ)$.

Exercise 2.3. Let $\succ$ be the lexicographic monomial ordering. Consider the *twisted cubic curve*, which is given by $I = \langle z_2 - z_1^2, z_3 - z_1^3 \rangle$ (see Example 1.2, Part (4)). Prove or disprove that the set $\{z_2 - z_1^2, z_3 - z_1^3\}$ is a Gröbner basis for I.

Exercise 2.4. Let $f(x, y) = (x^2 + y^2 - 4)(x^2 + y^2 - 1) + (x - 3/2)^2 + (y - 3/2)^2$. A point $\boldsymbol{s} \in \mathbb{C}^2$ is called *critical*, if all its partial derivatives vanish:

$$\frac{\partial f}{\partial x}(\boldsymbol{s}) \;=\; \frac{\partial f}{\partial y}(\boldsymbol{s}) \;=\; 0.$$

Compute all critical points of f in $\mathbb{C}^2$. Also decide whether they are local minimal or maximal or saddle points.

Exercise 2.5. Consider the following system of polynomials:

$$f_1 \;:=\; x^2 + y + z + 1 \qquad f_2 \;:=\; y^2 + x + z + 1 \qquad f_3 \;:=\; z^2 + x + y + 1.$$

Compute its common zeros. Are there finitely many? If yes: how many zeros are there and how many are distinct? How many of the roots are real?

Exercise 2.6. Let $f \in \mathbb{C}[x, y, z]$ given by:

$$f \;=\; \det \begin{pmatrix} 1 & x & y \\ x & 1 & z \\ y & z & 1 \end{pmatrix} \;=\; 2xyz - x^2 - y^2 - z^2 + 1.$$

The corresponding variety V thus consists of all points (x, y, z) where the matrix does not have full rank. Show: The variety of f has four real singular points – compute them.

FIGURE 1. Picture of the real locus of the variety V from Exercise 2.6 with the two components highlighted in yellow and red. (picture created by Bernd Sturmfels).

Bonus question: If we consider $\mathcal{V}(f)_{\mathbb{R}} \subset \mathbb{R}^3$ without the four singular points $\boldsymbol{s}_1, \boldsymbol{s}_2, \boldsymbol{s}_3, \boldsymbol{s}_4$, then we obtain two connected components in the real locus in $\mathbb{R}^3$. Investigate the defining matrices for the two points

$$\boldsymbol{v} \;:=\; \sum_{i=1}^{4} \frac{1}{4}\boldsymbol{s}_i \quad \text{and} \quad \boldsymbol{w} \;:=\; \boldsymbol{s}_1 + (\boldsymbol{s}_1 - \boldsymbol{v}).$$

There is a specific property of the defining matrix, which distinguishes points in the two (separate) connected components. Try to identify this property via investigating the defining matrices at $\boldsymbol{v}$ and $\boldsymbol{w}$?

Exercise 2.7. Consider the following polynomials

$$f_1 \;:=\; ax + by \qquad f_2 \;:=\; cx + dy.$$

First figure out the answers to the following questions and only then use a CAS to compute the Gröbner bases.

- Which is the output of the computation of a reduced lexicographic Gröbner basis of the ideal generated by f_1 and f_2 in the polynomial ring $K(a,b,c,d)[x,y]$? Here K is a field and (a,b,c,d) are parameters.
- Which is the output of the computation of a reduced lexicographic Gröbner basis of the ideal generated by f_1 and f_2 in the polynomial ring $K[a,b,c,d,x,y]$ in 6 variables?
- Let t be a new variable and consider the polynomial $p = txy - 1$. Which is the output of the computation of a reduced lexicographic Gröbner basis of the ideal generated by f_1, f_2 and p in the polynomial ring $K(a,b,c,d)[t,x,y]$?
- Let s be a new variable and $q = s(ad - bc) - 1$. Which is the output of the computation of a reduced lexicographic Gröbner basis of the ideal generated by f_1, f_2 and q in the polynomial ring $K(a,b,c,d)[s,x,y]$?

Note that you can define a ring with parameters in SINGULAR *for example as follows:* `ring R=(0,a,b,c,d),(x,y),lp;`

Exercise 2.8. Let $a, b > 0$. Consider the following mass-action system $\dot{x} = f(x)$:

$$\dot{x}_1 = x_2 - a\,x_1, \quad \dot{x}_2 = x_2^2 - b\,x_2 x_1.$$

Show that f_1, f_2 are linearly independent (and so there are no linear first integrals). Does the system $f_1 = f_2 = 0$ have finitely many positive solutions for all values of a and b?

Exercise 2.9. Consider a mass-action network involving m complexes $y_1, \dots, y_m$ and with associated mass-action system $\dot{x} = f(x)$ where $x = (x_1, \dots, x_n) \in \mathbb{R}^n$. Denote by x^y the column vector $(x^{y_1}, \dots, x^{y_m})^\top$. Consider the matrix $M \in \mathbb{R}^{n \times m}$ such that $f(x) = Mx^y$.

Fix an integer k with $1 \leq k < m$.

(i) Recall that a level 1 invariant is an element of the real span of $f_1, \dots, f_n$. How could we use Gröbner bases to compute the non-trivial level 1 invariants not involving any of the complexes $y_{k+1}, \dots, y_m$ (or decide that none exists)?
Hint: Given a linear ideal (an ideal generated by polynomials of degree one), a (reduced) Gröbner basis is composed again by linear polynomials obtained from the original ones by Gauss triangulation.

(ii) Let $M[k] \in \mathbb{R}^{n \times m-k}$ be the submatrix of M consisting of its last $m - k$ columns. Prove that it is possible to get a nontrivial level 1 invariant not involving any of the complexes $y_{k+1}, \dots, y_m$ via Gauss triangulation of M if and only if $\operatorname{rank}(M[k]) < \operatorname{rank}(M)$. How many linearly independent invariants only involving $y_1, \dots, y_k$ can be obtained?

Exercise 2.10. We consider a model of signal transmission widely employed by bacteria and extracted from the paper [G. Shinar and M. Feinberg, Structural sources of robustness in biochemical reaction networks, Science 327(5971), 1389–1391, (2010)]. The building blocks of the two-component system are two proteins X and Y, called *sensor kinase* and *response regulator* respectively. Both proteins exist in activated X_p, Y_p and inactivated form X, Y. The signal is transmitted in a cascade way: first X gets activated, and then X activates Y. In particular, we consider the reaction network with the following reactions and reaction rate constants:

- Activation of X is modeled in two steps

$$\mathrm{X} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{XT} \xrightarrow{\kappa_3} \mathrm{X}_p.$$

- X_p activates the response regulator Y, while inactivating itself:

$$\mathrm{X}_p + \mathrm{Y} \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} \mathrm{X}_p\mathrm{Y} \xrightarrow{\kappa_6} \mathrm{X} + \mathrm{Y}_p.$$

- The species XT has the capacity to dephosphorylate RR, without being itself altered in the process (it is an enzyme). This is represented with the following reactions:

$$\mathrm{XT} + \mathrm{Y}_p \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} \mathrm{XTY}_p \xrightarrow{\kappa_9} \mathrm{XT} + \mathrm{Y}.$$

For simplicity, we denote the concentrations of the species as: $x_1 = [\mathrm{X}], x_2 = [\mathrm{XT}]$, $x_3 = [\mathrm{X}_p]$, $x_4 = [\mathrm{Y}]$, $x_5 = [\mathrm{X}_p\mathrm{Y}]$, $x_6 = [\mathrm{Y}_p]$, $x_7 = [\mathrm{XTY}_p]$.

(i) Check that associated mass-action system is:

$$\begin{aligned}
\dot{x}_1 &= -\kappa_1 x_1 + \kappa_2 x_2 + \kappa_6 x_5 \\
\dot{x}_2 &= \kappa_1 x_1 - \kappa_2 x_2 - \kappa_3 x_2 - \kappa_7 x_2 x_6 + \kappa_8 x_7 + \kappa_9 x_7 \\
\dot{x}_3 &= \kappa_3 x_2 - \kappa_4 x_3 x_4 + \kappa_5 x_5 \\
\dot{x}_4 &= -\kappa_4 x_3 x_4 + \kappa_5 x_5 + \kappa_9 x_7 \\
\dot{x}_5 &= \kappa_4 x_3 x_4 - \kappa_5 x_5 - \kappa_6 x_5 \\
\dot{x}_6 &= \kappa_6 x_5 - \kappa_7 x_2 x_6 + \kappa_8 x_7 \\
\dot{x}_7 &= \kappa_7 x_2 x_6 - \kappa_8 x_7 - \kappa_9 x_7.
\end{aligned}$$

(ii) Prove that this system shows *Absolute Concentration Robustness* in the species Y_p (that is, at all positive steady states, the value of x_6 is the same). You could do this computation by hand or computing a Gröbner basis of the steady state ideal (using a suitable term order) or, in this case, using linear algebra (see Exercise 2.9). Try all these approaches.

(iii) Check that this system has two independent conservation laws (and no more):

$$\mathrm{X}_{\mathrm{tot}} = x_1 + x_2 + x_3 + x_5 + x_7 \qquad\qquad \mathrm{Y}_{\mathrm{tot}} = x_4 + x_5 + x_6 + x_7.$$

How could you check this with a computer?

(iv) Show that the system of steady-state equations and conservation laws admits a positive solution (i.e. there exists a positive steady state given the total amounts) if and only if

$$\frac{(\kappa_8 + \kappa_9)\kappa_3}{\kappa_7 \kappa_9} < Y_{\mathrm{tot}}.$$

Show additionally that if this inequality holds, then there is a unique positive steady state for each choice of positive $\mathrm{X}_{\mathrm{tot}}$. Are there other nonnegative steady states in the same stoichiometric compatibility class?

Note: We will develop tools to avoid making all these computations by hand.

Exercise 2.11. In the article of Shinar and Feinberg in Science (2010) cited in Exercise 2.10, an additional signaling network is considered (Example (S60) of the Supporting Online Material):

$$\mathrm{XD} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{X} \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} \mathrm{XT} \xrightarrow{\kappa_5} \mathrm{X_p} \qquad \mathrm{XT} + \mathrm{Y_p} \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} \mathrm{XTY_p} \xrightarrow{\kappa_{11}} \mathrm{XT} + \mathrm{Y}$$

$$\mathrm{X_p} + \mathrm{Y} \underset{\kappa_7}{\overset{\kappa_6}{\rightleftharpoons}} \mathrm{X_pY} \xrightarrow{\kappa_8} \mathrm{X} + \mathrm{Y_p} \qquad \mathrm{XD} + \mathrm{Y_p} \underset{\kappa_{13}}{\overset{\kappa_{12}}{\rightleftharpoons}} \mathrm{XDY_p} \xrightarrow{\kappa_{14}} \mathrm{XD} + \mathrm{Y}$$

Compare this network with the network in Exercise 2.10. Is there any form of X acting as an enzyme?

We denote by $x_1, \ldots, x_9$ the concentrations of the species as follows:

$x_1 = [\mathrm{XD}]$ $x_2 = [\mathrm{X}]$ $x_3 = [\mathrm{XT}]$ $x_4 = [\mathrm{X}_p]$

$x_5 = [\mathrm{Y}]$ $x_6 = [\mathrm{X}_p\mathrm{Y}]$ $x_7 = [\mathrm{Y}_p]$ $x_8 = [\mathrm{XTY}_p]$ $x_9 = [\mathrm{XDY}_p]$.

(i) Check that the associated mass-action system is

$$\begin{aligned}
\dot{x}_1 &= -\kappa_1 x_1 + \kappa_2 x_2 - \kappa_{12} x_1 x_7 + (\kappa_{13} + \kappa_{14}) x_9 \\
\dot{x}_2 &= \kappa_1 x_1 - (\kappa_2 + \kappa_3) x_2 + \kappa_4 x_3 + \kappa_8 x_6 \\
\dot{x}_3 &= \kappa_3 x_2 - (\kappa_4 + \kappa_5) x_3 - \kappa_9 x_3 x_7 + (\kappa_{10} + \kappa_{11}) x_8 \\
\dot{x}_4 &= \kappa_5 x_3 - \kappa_6 x_4 x_5 + \kappa_7 x_6 \\
\dot{x}_5 &= -\kappa_6 x_4 x_5 + \kappa_7 x_6 + \kappa_{11} x_8 + \kappa_{14} x_9 \\
\dot{x}_6 &= \kappa_6 x_4 x_5 - (\kappa_7 + \kappa_8) x_6 \\
\dot{x}_7 &= \kappa_8 x_6 - \kappa_9 x_3 x_7 + \kappa_{10} x_8 - \kappa_{12} x_1 x_7 + \kappa_{13} x_9 \\
\dot{x}_8 &= \kappa_9 x_3 x_7 - (\kappa_{10} + \kappa_{11}) x_8 \\
\dot{x}_9 &= \kappa_{12} x_1 x_7 - (\kappa_{13} + \kappa_{14}) x_9.
\end{aligned}$$

(ii) Show that there are non-trivial conservation laws. If possible, find a basis of conservation laws with nonnegative coefficients.

(iii) Compute a reduced Gröbner basis G of the ideal $\langle f_1, \dots, f_9 \rangle$ with respect to the lexicographical order $x_1 > x_2 > x_4 > x_5 > x_6 > x_8 > x_9 > x_3 > x_7$. Check that G contains a polynomial of the form

$$a(\kappa) x_3 x_7 - b(\kappa) x_3,$$

with a, b polynomials in κ of degree 5 with coefficients 0 or 1. Conclude that the value of x_7 at any positive steady state does not depend on the total amounts, i.e., the system shows Absolute Concentration Robustness.

(iv) Prove that there is no level 1 invariant only depending on x_3 and x_7.

Exercise 2.12. Let $f = \sum_{i=0}^{d} c_i x^i$ be a univariate polynomial with real coefficients. Denote by $Z_+(f)$ (resp. $Z_-(f)$) the number of positive (resp. negative) roots of f *counted with multiplicity*, and $\sigma(f)$ the number of sign variations of the sequence $(c_0, c_1, \dots, c_d)$. Descartes' rule of signs says that $Z_+(f) \leq \sigma(f)$ and that the difference $\sigma(f) - Z_+(f)$ is even.

(i) Find a polynomial f of degree 2 with $Z_+(f) = 0$ but such that $\sigma(f) = 2$. Find a polynomial g of degree 3 with $Z_+(f) = 1$ but such that $\sigma(f) = 3$.

(ii) Prove the following statements:
- $Z_-(f) \leq \sigma(f(-x))$.
- $\sigma(f) + \sigma(f(-x)) \leq n$.
- If all roots of f are real, then $Z_+(f) = \sigma(f)$. This is the case if f is the characteristic polynomial of a symmetric matrix.
- If all roots of f in $\mathbb{C}$ have *negative* real part, then $\sigma(f) = 0$.
- The number of non-zero real roots of f is bounded above by $2m - 2$, if m is the number of monomials of f.

Exercise 2.13. Consider the following reaction network corresponding to a *two-component system with a hybrid histidine kinase* from [Kothamachu, Feliu, Cardelli, Soyer, Unlimited multistability and Boolean logic in microbial signaling, J. R. S. Interface, 12

(2015)]:

$$\begin{array}{cc} \mathrm{HK_{00}} \xrightarrow{\kappa_1} \mathrm{HK_{p0}} \xrightarrow{\kappa_2} \mathrm{HK_{0p}} \xrightarrow{\kappa_3} \mathrm{HK_{pp}} & \mathrm{HK_{0p}} + \mathrm{Htp} \xrightarrow{\kappa_4} \mathrm{HK_{00}} + \mathrm{Htp_p} \\ \mathrm{Htp_p} \xrightarrow{\kappa_6} \mathrm{Htp} & \mathrm{HK_{pp}} + \mathrm{Htp} \xrightarrow{\kappa_5} \mathrm{HK_{p0}} + \mathrm{Htp_p} \end{array}$$

Call $x_1 = [\mathrm{HK}_{00}]$, $x_2 = [\mathrm{HK}_{p0}]$, $x_3 = [\mathrm{HK}_{0p}]$, $x_4 = [\mathrm{HK}_{pp}]$, $x_5 = [\mathrm{Htp}]$ and $x_6 = [\mathrm{Htp}_p]$, and consider the following conservation laws:

$$x_1 + x_2 + x_3 + x_4 = c_1, \qquad\qquad x_5 + x_6 = c_2.$$

Let $\dot{x} = f(x)$ be the associated mass-action system.

(i) Compute a reduced Gröbner basis of the ideal generated by f_1, f_2, f_3, f_5, $x_1 + x_2 + x_3 + x_4 - c_1$ and $x_5 + x_6 - c_2$ with respect to the lexicographic term order with $x_1 > x_2 > x_3 > x_4 > x_6 > x_5$. Does it have the form predicted in the Shape Lemma?

(ii) Is is true that there are at most 3 complex solutions for any choice of complex constants $\kappa_1, \dots, \kappa_6, c_1, c_2$?. Is the mixed volume associated to the supports of the six polynomials in (i) equal to 3?

(iii) Is it true that there are at most 3 positive steady states for any choice of reaction rate constants $\kappa = (\kappa_1, \dots, \kappa_6) \in \mathbb{R}^6_{>0}$ and $c = (c_1, c_2) \in \mathbb{R}^2_{>0}$?

(iv) Let $g_1 = g_1(x_5)$ be the first element in the Gröbner basis computed in item (i) depending only on x_5. Using Descartes' rule of signs, find necessary inequalities in the coefficients of g_1 (that is, on (κ, c)) for the system to have 3 positive steady states.

(v) How can you choose values of (κ, c) so that g_1 has 3 positive solutions? Is this sufficient to ensure that there are three positive steady states for these values?

Exercise 2.14. Consider the following reaction network

$$X_2 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_1 + X_4 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} X_3.$$

(i) Show that $x_1 + x_2 + x_3 = T_1$, $x_2 + x_3 + x_4 = T_2$ are conservation laws, and that the dimension of the stoichiometric subspace is 2.

(ii) For the associated mass-action system $\dot{x} = f(x)$, find a Gröbner basis of the ideal $\langle f_2, f_3, x_1 + x_2 + x_3 - T_1, x_2 + x_3 + x_4 - T_2 \rangle$ with respect to the lexicographic order with $x_1 > x_2 > x_3 > x_4$. What is the number of complex solutions for generic choices of the parameters? Are these solutions in the complex torus generically? (Note that the positive steady states in stoichiometric compatibility classes are among these solutions).

(iii) Consider now the family of all polynomial systems with the same support as $f_2, f_3, x_1 + x_2 + x_3 - T_1, x_2 + x_3 + x_4 - T_2$. What is the generic number of solutions in the complex torus $(\mathbb{C}^*)^4$? (You can either compute a Gröbner basis again by letting all the coefficients be parameters, or you can compute the mixed volume associated with this sparse system – if you have software to compute mixed volumes, try both!).

Let's analyze the following code in Singular:

```
ring r = (0,k1,k2,k3,k4,k5,k6,C1,C2,C3),(x6,x5,x1,x3,x4,x2),dp;
poly f1 = -k1*x1*x3+k2*x5+k6*x6;
poly f2 = -k4*x2*x4+k5*x6+k3*x5;
poly f3 = -k1*x1*x3+(k2+k3)*x5;
poly f4 = -k4*x2*x4+(k5+k6)*x6;
poly f5 = -f3;
poly f6 = -f4;
poly g1 = x3+x5-C1;
poly g2 = x4+x6-C2;
poly g3 = x1+x2+x5+x6-C3;
ideal i1 = f1,f3,f4;
i1;
ideal i2=std(i1);
ideal i3 =eliminate(i2,x5*x6);
i3;
```

We define the polynomials $f_1, f_2, \dots, f_6$

We declare a polynomial ring over $\mathbb{Q}(\kappa)$, with $\kappa = (k_1, \dots, k_6, C_1, C_2, C_3)$, variables $x_6 > x_5 > x_1 > x_3 > x_4 > x_2$ and lexicographic term order

We define the conservation laws

We define the ideal generated by f_1, f_3, f_4

We ask to display the ideal obtained by elimination of x_5 and x_6

The output will display `i1` but not `i2`. The last output shows `i3`:

```
                     SINGULAR                                 /
A Computer Algebra System for Polynomial Computations       /   version 4.1.1
                                                         0<
by: W. Decker, G.-M. Greuel, G. Pfister, H. Schoenemann     \   Feb 2018
FB Mathematik der Universitaet, D-67653 Kaiserslautern        \

i3_[1]=(k1*k3*k5+k1*k3*k6)*x1*x3+(-k2*k4*k6-k3*k4*k6)*x4*x2

 Auf Wiedersehen.
```

Polynomial which generates i3 $\cap \mathbb{Q}(k, C)[x1, x2, x3, x4]$

All commands end with ;. Usual term orders in Singular are: `dp (graded reverse lexicographic) and lp (lexicographic)`. An ideal is an ordered sequence of polynomials (understood as generators).

Note that we always need to start defining a ring, for instance, with two variables, characteristic 0, and two different term orders (these are different rings):

`ring R = 0, [x,y], dp;` or `ring S =0, [x,y], lp;`

The command `ideal i2 = std(i1);` computes a Gröbner basis of the ideal `i1`. To force Singular to compute a *reduced* GB, use the command: `option(redSB);`.

To substitute values of parameters or variables, use for instance

`ideal s =subst(i2,k1,1,k2,2,k3,3,k4,4,k5,5,C1,10,C2,20,C3,15);`

If an ideal i (as we said, an ordered set of polynomials) has been defined over the ring R, we can consider the ideal is generated by the same polynomials in S by typing `ideal is = imap(S,i);` .

At some moment you might want to use the command `solve` of the library `solve.lib`.