Topics in Applied Algebraic Geometry

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Homework # 1, due Tuesday February 21

Exercise 1. The following chemical reaction network is the 1-site phosphorylation system:

$$
\begin{aligned}
S_0 + E \underset{k_2}{\overset{k_1}{\rightleftarrows}} ES_0 \overset{k_3}{\to} S_1 + E \qquad (1)\\
S_1 + F \underset{\ell_2}{\overset{\ell_1}{\rightleftarrows}} FS_1 \overset{\ell_3}{\to} S_0 + F \ .
\end{aligned}
$$

The players in this network are a kinase enzyme (E), a phosphatase enzyme (F), and two substrates (S_0 and S_1). The substrate S_1 is obtained from the unphosphorylated protein S_0 by attaching a phosphate group to it via an enzymatic reaction involving E. Conversely, a reaction involving F removes the phosphate group from S_1 to obtain S_0. The intermediate complexes ES_0 and ES_1 are the bound enzyme-substrate complexes. Under the ordering of the 6 species as $(S_0, S_1, ES_0, FS_1, E, F)$ and the 6 complexes as $(S_0 + E, S_1 + E, ES_0, S_0 + F, S_1 + F, FS_1)$, call

$$\Psi(x) \ = \ (x_1x_5,\ x_2x_5,\ x_3,\ x_1x_6,\ x_2x_6,\ x_4)\,.$$

(i) Write the matrices A_κ, Y of the corresponding dynamical system:

$$\frac{dx}{dt} \ = \ \Psi(x) \cdot A_\kappa \cdot Y = (f_1(x), \ldots, f_6(x)) \ .$$

(ii) Find the conservation relations and prove that $\langle f_1, \ldots, f_6\rangle$ is a binomial ideal.

(iii) Find a positive steady state $c \in \mathbb{R}^6_{>0}$ and parametrize all positive steady states.

Exercise 2. Consider the following dynamical system:

$$\frac{dx}{dt} = \left(-2\alpha x_1^2x_4 + 2\gamma x_3^4, 3\alpha x_1^2x_4 - 3\beta x_2^3x_4^2, 4\beta x_2^3x_4^2 - 4\gamma x_3^4, \alpha x_1^2x_4 - 2\beta x_2^3x_4^2 + \gamma x_3^4\right),$$

where $x = (x_1, \ldots, x_4), \alpha, \beta, \gamma \in \mathbb{R}_{>0}$. Check that this system represents the mass-action kinetics dynamical system associated to the network

$$
\begin{tikzcd}
 & 2X_1 + X_4 \arrow[dr, "\alpha"] & \\
4X_3 \arrow[ur, "\gamma"] & & 3X_2 + 2X_4 \arrow[ll, "\beta"']
\end{tikzcd}
$$

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

$$
\begin{tikzcd}[column sep=small]
 & & X_1+4X_3 \\
3X_3 & 4X_3 \arrow[l, "4\gamma"'] \arrow[ur, "2\gamma"] \arrow[dr, "\gamma"] & \\
 & & 4X_3+X_4
\end{tikzcd}
\qquad
\begin{tikzcd}[column sep=small]
 & & 2X_1+X_2+X_4 \\
X_1+X_4 & 2X_1+X_4 \arrow[l, "2\alpha"'] \arrow[ur, "3\alpha"] \arrow[dr, "\alpha"] & \\
 & & 2X_1+2X_4
\end{tikzcd}
\qquad
\begin{tikzcd}[column sep=small]
 & & 3X_2+X_3+2X_4 \\
2X_2+2X_4 & 3X_2+2X_4 \arrow[l, "3\beta"'] \arrow[ur, "4\beta"] \arrow[dr, "2\beta"] & \\
 & & 3X_2+X_4
\end{tikzcd}
$$

(previously:)

$$x_1^2x_4 \overset{2\alpha}{\to} x_1x_4\,,\ x_1^2x_4 \overset{3\alpha}{\to} x_1^2x_2x_4\,,\ x_1^2x_4 \overset{\alpha}{\to} x_1^2x_4^2,$$

$$x_2^3x_4^2 \overset{3\beta}{\to} x_2^2x_4^2\,,\ x_2^3x_4^2 \overset{4\beta}{\to} x_2^3x_3x_4^2\,,\ x_2^3x_4^2 \overset{2\beta}{\to} x_2^3x_4$$

$$x_3^4 \overset{2\gamma}{\to} x_1x_3^4\,,\ x_3^4 \overset{4\gamma}{\to} x_3^3\,,\ x_3^4 \overset{\gamma}{\to} x_3^4x_4.$$

What can you conclude?

Exercise 3. Consider the reaction network

$$A_2 \xleftarrow{k'} A_1 \xleftarrow{k} 2A_2 \xrightarrow{k} 3A_1.$$

Compute the stoichiometric subspace. Find the smaller subspace containing $(\frac{dc_1}{dt}, \frac{dc_2}{dt})$ for every trajectory $c(t)$ (where $c_i(t)$ denotes the concentration of species A_i in time t). How many steady states are there in each stoichiometric compatibility class?

Exercise 4. Consider the reaction network $2A+B \rightleftharpoons 3A, A \rightleftharpoons 0, B \rightleftharpoons 0$ (i.e, there are two species A and B, and each one of them can flow in and out of the system). Write down the corresponding dynamical system.Is there any conservation relation? Show that there exists a choice of rate constants for the 6 reactions for which the system has 3 positive steady states.

Exercise 5. In this exercise you will prove that the general model for T-cell specificity has precisely one positive steady state in each linear invariant subspace. The general model is described by the following reaction network:

$$
\begin{tikzcd}
T+M \arrow[r, "a_0"] & X_0 \arrow[r, "a_1"] \arrow[l, bend left, "b_0"] & X_1 \arrow[r, "a_2"] \arrow[ll, bend left, "b_1"] & \dots \arrow[r, "a_i"] & X_i \arrow[r, "a_{i+1}"] \arrow[llll, bend left, "b_i"] & \dots \arrow[r, "a_n"] & X_n \arrow[llllll, bend left, "b_n"]
\end{tikzcd}
$$

For each species shown in the diagram, that is, $T, M, X_0, \dots, X_n$, we denote their concentration by: $x_T, x_M, x_0, \dots, x_n$.

(i) Find the ODE system associated to the reactions using the mass-action assumption.

(ii) Check that there are conservation laws $x_M+x_0+\cdots+x_N = M_{\text{tot}}$ and $x_T+x_0+\cdots+x_N = T_{\text{tot}}$.

(iii) Use the steady-state equations to show that at steady state, $x_i = \mu_i x_T x_M$ for all $i = 0, \dots, N$, and where μ_i is a constant that depends on the rate constants.

(iv) Use the conservation law for T_{tot} to find an expression for x_T in terms of x_M at steady state, under the assumption $x_M \geq 0$.

(v) Use the conservation law for M_{tot} to conclude that there is one positive steady state for each choice of $T_{\text{tot}}, M_{\text{tot}} > 0$.

You can start by studying the system for $N = 2$.

We will give two different results that will prove this last statement immediately!

Exercise 6. We consider the model of signal transmission widely employed by bacteria discussed in class. The buildings blocks of this two-component systems are two proteins X and Y, called *sensor kinase* and *response regulator* respectively.

We consider the reaction network with the following reactions:

- Activation of X is modeled in two steps

$$\mathrm{X} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{XT} \xrightarrow{\kappa_3} \mathrm{X}_p. \tag{2}$$

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

$$\mathrm{X}_p + \mathrm{Y} \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} \mathrm{X}_p\mathrm{Y} \xrightarrow{\kappa_6} \mathrm{X} + \mathrm{Y}_p. \tag{3}$$

- 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:

$$\mathrm{XT} + \mathrm{Y}_p \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} \mathrm{XTY}_p \xrightarrow{\kappa_9} \mathrm{XT} + \mathrm{Y}. \tag{4}$$

For simplicity, we denote the concentrations of the species as:

$$\begin{array}{llll} x_1 = [\mathrm{X}] & x_2 = [\mathrm{XT}] & x_3 = [\mathrm{X}_p] & \\ x_4 = [\mathrm{Y}] & x_5 = [\mathrm{X}_p\mathrm{Y}] & x_6 = [\mathrm{Y}_p] & x_7 = [\mathrm{XTY}_p]. \end{array}$$

Under the mass-action kinetics assumption the evolution of the concentration of each species in time is described by the following system of ODEs:

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

This system has two independent conservation laws:

$$\begin{aligned}
\mathrm{X}_{\text{tot}} &= x_1 + x_2 + x_3 + x_5 + x_7 \\
\mathrm{Y}_{\text{tot}} &= x_4 + x_5 + x_6 + x_7.
\end{aligned}$$

- Prove that this system shows *Absolute Concentration Robustness* in the species Y_p (that is, for positive steady states, the value of x_6 does not depend on the total amounts $\mathrm{X}_{\mathrm{tot}}, \mathrm{Y}_{\mathrm{tot}}$).
- Show that the steady-state equations and the conservation equations admit a positive solution (i.e. there exists a positive steady state given the total amounts) if and only if

$$\frac{(k_8 + k_9)k_3}{k_7 k_9} < Y_{\mathrm{tot}}.$$

- Show that if the 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 compatibility class?

  Again, we will develop tools to avoid making all these computations by hand.

Exercise 7. Consider the reactions

$$A + B \xrightarrow{k_1} C \qquad B \xrightarrow{k_2} A + C \qquad C \xrightarrow{k_3} B.$$

Let x_A, x_B, x_C denote the concentration of species A, B, C respectively.

(i) Find the ODE system associated to the reactions using the mass-action assumption.

(ii) Show that $x_B + x_C$ is conserved.

(iii) Show that a positive steady state always exist and is unique.

(iv) Show that the value of x_A at a positive steady state is independent of the system's initial conditions (i.e., absolute concentration robustness exists for x_A).

(v) In the two-component example in the previous exercise we have shown that absolute concentration robustness exists and, as a consequence, positive steady states do not always exist. Why does the system in this exercise have absolute concentration robustness and, at the same time, positive steady states always exist?