Notes on a genetic network

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If necessary, first review section 3.4.1 Phase-plane analysis: Linear systems.

These notes describe a simple genetic network consisting of two genes. The product of gene 1 has concentration x, and the product of gene 2 has concentration y. We assume that the product of each gene inhibits the transcription of the other gene. In practice, this happens when the gene product of one gene binds to the site of the DNA corresponding to the other gene, thereby inhibiting transcription.

The model is as follows:

$$\dot{x} = -\gamma_1 x + \frac{x}{x+\alpha y+1} = x\left(-\gamma_1 + \frac{1}{x+\alpha y+1}\right) \tag{1}$$

$$\dot{y} = -\gamma_2 y + \frac{y}{y+\beta x+1} = y\left(-\gamma_2 + \frac{1}{y+\beta x+1}\right) \tag{2}$$

where $\gamma_1, \gamma_2 \in (0,1)$ represent the decay rates of the proteins, and the state vector (x,y) has non-negative components.

The production rate of protein 1 is given by the function

$$f(x,y) = \frac{x}{x+\alpha y+1},$$

where $\alpha > 0$. This function is increasing in x ($\partial f/\partial x > 0$) and non-increasing in y ($\partial f/\partial y \leq 0$). Thus, the gene product of gene 1 promotes transcription and translation of gene 1, whereas the gene product of gene 2 inhibits this process. Similarly, the production rate of protein 2 is given by the (non-negative and bounded) function

$$g(x,y) = \frac{y}{y+\beta x+1},$$

where $\beta > 0$, which has similar properties as f, namely it is increasing in y and non-increasing in x.

Throughout the rest of these notes we make the following hypothesis:

$$\mathbf{H}\ \ \frac{1}{\alpha}\left(\frac{1}{\gamma_1}-1\right) < \frac{1}{\gamma_2}-1 \text{ and } \frac{1}{\beta}\left(\frac{1}{\gamma_2}-1\right) < \frac{1}{\gamma_1}-1.$$

H implies in particular that:

$$\alpha\beta > 1, \tag{3}$$

and equality which will turn out to be important later. **Prove** (3).

Nullclines and steady states

The x-nullclines, i.e. the set of points where $\dot{x} = 0$, are given by the straight lines:

$$x = 0 \text{ and } x + \alpha y + 1 - \frac{1}{\gamma_1} = 0,$$

and the y-nullclines by

$$y = 0 \text{ and } y + \beta x + 1 - \frac{1}{\gamma_2} = 0,$$

see the left panel of Figure 1.

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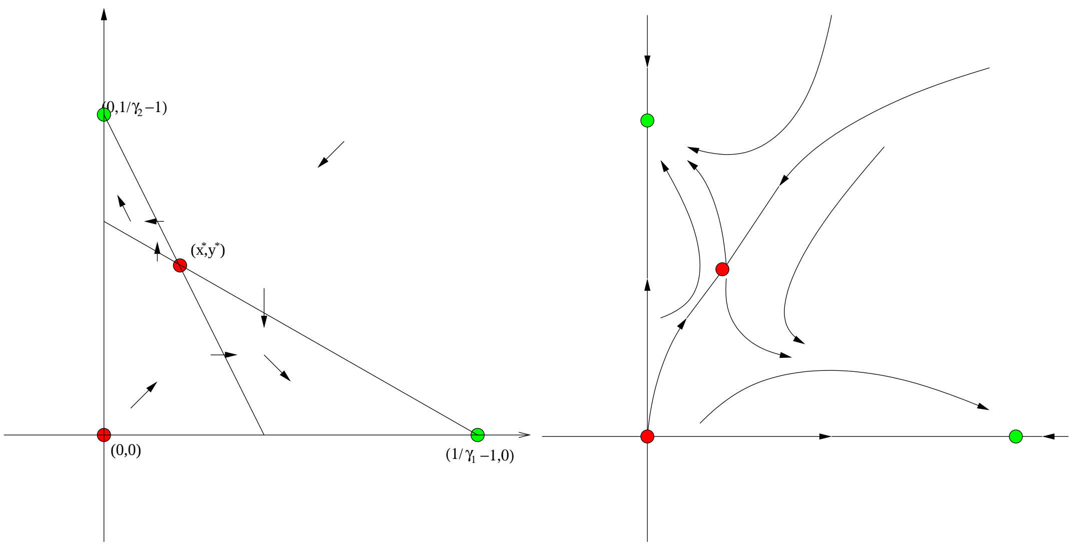

Figure 1: Null-clines, direction of the vector field and steady states for (1) – (2) (left panel), and phase portrait of (1) – (2) (right panel).

Using **H**, we see that there are 4 steady states:

$$(0,0), \quad \left(0, \frac{1}{\gamma_2} - 1\right), \quad \left(\frac{1}{\gamma_1} - 1, 0\right), (x^*, y^*),$$

where (x^*, y^*) is the unique positive solution of the linear equations

$$x^* + \alpha y^* + 1 - \frac{1}{\gamma_1} = 0 \qquad (4)$$

$$y^* + \beta x^* + 1 - \frac{1}{\gamma_2} = 0 \qquad (5)$$

Although we could easily solve these equations, there is no need to find the solution explicitly as we will see later.

Linearization at steady states

The Jacobian matrix of (1) – (2) is:

$$Jac(x,y) = \begin{pmatrix} -\gamma_1 + \frac{\alpha y + 1}{(x+\alpha y+1)^2} & -\frac{\alpha x}{(x+\alpha y+1)^2} \\ -\frac{\beta y}{(y+\beta x+1)^2} & -\gamma_2 + \frac{\beta x+1}{(y+\beta x+1)^2} \end{pmatrix}$$

Verify this.

Evaluating this at the 4 steady states:

$$Jac(0,0) = \begin{pmatrix} -\gamma_1 + 1 & 0 \\ 0 & -\gamma_2 + 1 \end{pmatrix}$$

implies that $Jac(0,0)$ has two positive eigenvalues and thus the steady state $(0,0)$ is a source (sometimes called an unstable node).

$$Jac\left(0, \frac{1}{\gamma_2} - 1\right) = \begin{pmatrix} -\gamma_1 + \frac{1}{\alpha\left(\frac{1}{\gamma_2}-1\right)+1} & 0 \\ * & -\gamma_2 + \gamma_2^2 \end{pmatrix},$$

where the value of $*$ is irrelevant. The upper left entry is negative. This follows from the first inequality in **H**:

$$\frac{1}{\alpha}\left(\frac{1}{\gamma_1} - 1 < \frac{1}{\gamma_2} - 1\right) \;\Rightarrow\; \frac{1}{\left(\frac{1}{\gamma_1} - 1\right) + 1} > \frac{1}{\alpha\left(\frac{1}{\gamma_2} - 1\right) + 1} \;\Rightarrow\; \gamma_1 > \frac{1}{\alpha\left(\frac{1}{\gamma_2} - 1\right) + 1}.$$

The lower right entry is negative as well since $\gamma_2 \in (0,1)$. These two entries are the eigenvalues of the Jacobian matrix, and as they are negative, the steady state $\left(0, \frac{1}{\gamma_2} - 1\right)$ is a sink (sometimes called a stable node). A similar calculation shows that the steady state $\left(\frac{1}{\gamma_1} - 1, 0\right)$ is also a sink. **Verify this**.

Finally, we consider

$$Jac(x^*, y^*) = \begin{pmatrix} -\gamma_1 + \frac{1}{x^*+\alpha y^*+1} - \frac{x^*}{(x^*+\alpha y^*+1)^2} & -\frac{\alpha x^*}{(x^*+\alpha y^*+1)^2} \\ -\frac{\beta y^*}{(y^*+\beta x^*+1)^2} & -\gamma_2 + \frac{1}{(y^*+\beta x^*+1)^2} - \frac{y^*}{(y^*+\beta x^*+1)^2} \end{pmatrix}$$

Notice that we have broken up each of the fractions appearing in the upper left and lower right entries, in a sum of two fractions. The reason will be clear in a minute. Using (4) – (5), this Jacobian matrix can be simplified to:

$$Jac(x^*, y^*) = \begin{pmatrix} -\frac{x^*}{(x^*+\alpha y^*+1)^2} & -\frac{\alpha x^*}{(x^*+\alpha y^*+1)^2} \\ -\frac{\beta y^*}{(y^*+\beta x^*+1)^2} & -\frac{y^*}{(y^*+\beta x^*+1)^2} \end{pmatrix}$$

Notice that the trace is negative. The determinant is given by:

$$\det\left(Jac(x^*, y^*)\right) = (1-\alpha\beta)\frac{x^* y^*}{(x^*+\alpha y^*+1)^2(y^*+\beta x^*+1)^2},$$

which is negative by (3). Since the determinant of a matrix equals the product of its eigenvalues, it follows that $Jac(x^*, y^*)$ has one positive and one negative eigenvalue, and therefore the steady state (x^*, y^*) is a saddle.

Phase portrait We illustrate the phase portrait of (1) – (2) in the right panel of Figure 1. The orthant is divided into 4 regions, and the vector field in each region has a direction indicated by the arrow. Notice that the positive x and y-axis are invariant sets: solutions starting there, remain there for all times. We can perform a phase line analysis for equation (1) with $y = 0$: Using the fact that $\gamma_1 \in (0,1)$, we see that all solutions (except for the steady state at $x = 0$) converge to $\frac{1}{\gamma_1} - 1$. Similarly, all solutions of (2) with $x = 0$ (except for the steady state at $y = 0$) converge to $\frac{1}{\gamma_2} - 1$.

A more detailed analysis shows the existence of a so-called *separatrix*. This is a curve which connects $(0,0)$ to (x^*, y^*), and goes from there off to infinity. All initial conditions starting on this curve give rise to solutions converging to (x^*, y^*). Solutions starting on "the left" of the separatrix and in the interior of the orthant converge to steady state $\left(0, \frac{1}{\gamma_2} - 1\right)$. Solutions starting on the right converge to $\left(\frac{1}{\gamma_1} - 1, 0\right)$. This phenomenon of having two asymptotically stable steady states, is often referred to as *bistability*.

Clearly, the location of the vector containing the initial concentrations of both proteins, is crucial to their long-term fate. In general, exactly one of the proteins will vanish. Which one, is completely determined at the start of the experiment.

Homework: Redo the analysis if we replace hypothesis **H** by

$$\mathbf{H_r}\ \ \frac{1}{\alpha}\left(\frac{1}{\gamma_1} - 1\right) > \frac{1}{\gamma_2} - 1 \text{ and } \frac{1}{\beta}\left(\frac{1}{\gamma_2} - 1\right) > \frac{1}{\gamma_1} - 1.$$

Notice that the only difference with **H** is that the inequalities are reversed.