Stability of steady states for a general autoregulatory loop

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6 October 2006

This is a handout for SB200, *"A systems approach to biology"*, for the autumn semester of 2006-7. It provides details of the theorem which I proved on the blackboard in Lecture 4, which gives a graphical method for determining the stability of a steady state for a general autoregulatory loop. If you have any comments or questions, and especially if you notice any misprints or errors, please send me a message at `jeremy@hms.harvard.edu`.

The autoregulatory loop is shown schematically in Figure 1, where x_1 and x_2 are the concentrations of protein and mRNA, respectively. This scheme allows for first-order degradation of mRNA and protein, with (positive) rate constants b and a, respectively, but the rate of mRNA translation can be an arbitrarily function, $f(x_2)$, of mRNA concentration and the rate of gene expression can be an arbitrary function, $g(x_1)$, of protein concentration. This translates into the following system of differential equations

$$\begin{aligned} dx_1/dt &= f(x_2) - ax_1 \\ dx_2/dt &= g(x_1) - bx_2 \ , \end{aligned} \tag{1}$$

which defines a two-dimensional dynamical system. We assume throughout that $a, b > 0$.

We want to work out the stability of a steady state of this system. As we discussed in Lectures 2 and 3, the stability a steady state depends on the eigenvalues of the Jacobian matrix at that steady state. Since this is a two-dimensional system, we can work out the stability more quickly by calculating the determinant and the trace of the Jacobian (recall the Determinant/Trace diagram for two-dimensional dynamical systems that we discussed in Lecture 3). It is easy to work out the Jacobian matrix at any state $x = (x_1, x_2)$. Let us call this $J(x)$. Calculating the partial derivatives, we find that

$$J(x) = \begin{pmatrix} -a & \dfrac{df}{dx_2} \\ \dfrac{dg}{dx_1} & -b \end{pmatrix} \ . \tag{2}$$

Note that the partial derivatives in the Jacobian can be replaced by ordinary derivatives because f and g are each functions of only a single state variable. We see from (2) that $\mathrm{Tr}J(x) = -(a+b) < 0$,

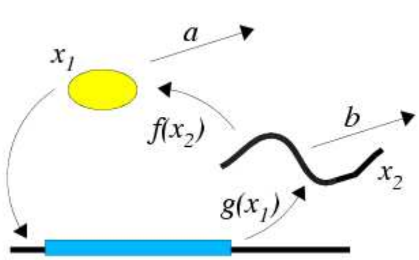

Figure 1: The general autoregulatory loop. A single gene is transcribed into mRNA which is translated into protein which feeds back on its own expression. Both mRNA and protein are degraded.

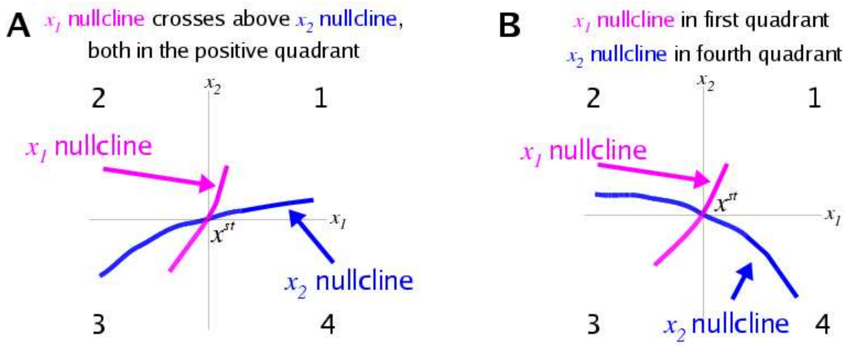

Figure 2: Two situations in which the x_1 nullcline crosses over the x_2 nullcline as x_1 increases, resulting in a stable steady state at the crossing point, $x = x^{st}$. In both panels, x_1 is on the horizontal axis and x_2 on the vertical axis.

independently of x. It follows that the stability of any steady state will depend soley on the sign of the derivative of the Jacobian at that steady state. The Determinant/Trace diagram tells us that if x^{st} is a steady state and $\det J(x^{st}) < 0$, then x^{st} is an unstable steady state, while if $\det J(x^{st}) > 0$, then x^{st} is a stable steady state. In the latter case x^{st} could be either a stable node or a stable spiral but to tell which, we would have to work out the discriminant of the characteristic equation (given by $\mathrm{Tr}^2 - 4\det$). We will not bother with that here, since all we want to do is to work out the stability. For that we need just the determinant of the Jacobian, which is given by

$$\det J(x^{st}) = ab - \left[\left(\frac{df}{dx_2} \right) \Big|_{x=x^{st}} \right] \times \left[\left(\frac{dg}{dx_1} \right) \Big|_{x=x^{st}} \right] ,$$

where we have been careful to indicate that the derivatives need to be evaluated at $x = x^{st}$.

It will be helpful for what follows to rewrite this slightly in the form

$$\det J(x^{st}) = ab(1-\alpha) \tag{3}$$

where α is given by

$$\alpha = \left[\left(\frac{1}{a} \right) \left(\frac{df}{dx_2} \right) \Big|_{x=x^{st}} \right] \times \left[\left(\frac{1}{b} \right) \left(\frac{dg}{dx_1} \right) \Big|_{x=x^{st}} \right] .$$

There is an easy way to calculate α that only depends on knowing how the nullclines cross at the steady state. Recall that the nullclines of the dynamical system are given by setting each differential equation in (1) separately to 0. The x_1 nullcline corresponds to the set of points x in state space which satisfy $dx_1/dt = 0$, or, in other words, to the graph of $x_1 = f(x_2)/a$. Similarly, the x_2 nullcline corresponds to the graph of $x_2 = g(x_1)/b$. The steady states occur where the nullclines intersect.

Let us consider the simplest case first and suppose that the nullclines intersect as shown in Figure 2B. In this case, as x_1 increases from left to right, the x_2 nullcline goes through the steady state into the fourth quadrant. It follows that the tangent to the x_2 nullcline at the steady state points into the fourth quadrant. (By "tangent" we mean here the vector which just grazes the curve at the steady state.) The slope of the tangent to the graph of a function is simply the derivative of the function. Here, the function is $x_2 = g(x_1)/b$, whose derivative, evaluated at the steady state $x = x^{st}$, is

$$\left(\frac{1}{b} \right) \left(\frac{dg}{dx_1} \right) \Big|_{x=x^{st}} \tag{4}$$

Because the x_2 nullcline goes from left to right into the fourth quadrant, the slope of the tangent is negative. Hence, the quantity in (4) is negative.

Figure 2B has the x_1 nullcline going into the first quadrant. We can make a similar argument here but we have to be careful because in this case the x_1 nullcline is the graph of $x_1 = f(x_2)/a$ and the roles of x_1 and x_2 are reversed: the independent variable, x_2, is on the vertical axis while the dependent variable, x_1, is on the horizontal axis. We can still calculate the derivative of the function at the steady state,

$$\left(\frac{1}{a}\right)\left(\frac{df}{dx_2}\right)\bigg|_{x=x^{st}} \tag{5}$$

and this quantity is still equal to the slope of the tangent to the x_1 nullcine but the slope has to be measured with respect to x_2 which is on the vertical, not the horizontal, axis, and increases from bottom to top. It should be easy to see that **the slope measured against the vertical axis going from bottom to top is the reciprocal of the slope measured against the horizontal axis going from left to right**. Because the tangent to the x_1 nullcline points into the first quadrant, the quantity in (5) is the reciprocal of a positive number and is hence also positive.

If (4) is negative and (5) is positive, then, clearly,

$$\alpha = \left[\left(\frac{1}{a}\right)\left(\frac{df}{dx_2}\right)\bigg|_{x=x^{st}}\right] \times \left[\left(\frac{1}{b}\right)\left(\frac{dg}{dx_1}\right)\bigg|_{x=x^{st}}\right] < 0$$

and so it follows from (3) that

$$\det J(x^{st}) = ab(1-\alpha) > 0 \,.$$

Hence, x^{st} is a stable steady state.

Now let us consider Figure 2A. In this case both nullclines go from left to right into the first quadrant but the x_1 nullcline goes above the x_2 nullcline. If we measure the slopes of the tangents at the steady state **against the x_1 axis**, then this is equivalent to saying that the slope of the tangent to the x_1 nullcline is greater than the slope of the tangent to the x_2 nullcline. Furthermore, both slopes are positive because the nullclines go into the first quadrant. Hence,

$$\left[\left(\frac{1}{a}\right)\left(\frac{df}{dx_2}\right)\bigg|_{x=x^{st}}\right]^{-1} > \left[\left(\frac{1}{b}\right)\left(\frac{dg}{dx_1}\right)\bigg|_{x=x^{st}}\right] > 0 \,. \tag{6}$$

The reciprocal on the first term arises because, as explained above, the derivative in (5) equals the slope of the tangent to the x_1 nullcline measured **against the x_2 axis**. Because both sides of (6) are positive (this is a point on which you have to be really careful) we can multiply across the inequality to get

$$1 - \left[\left(\frac{1}{a}\right)\left(\frac{df}{dx_2}\right)\bigg|_{x=x^{st}}\right] \times \left[\left(\frac{1}{b}\right)\left(\frac{dg}{dx_1}\right)\bigg|_{x=x^{st}}\right] > 0 \,.$$

The quantity on the left is $1-\alpha$, so that

$$\det J(x^{st}) = ab(1-\alpha) > 0 \,.$$

Hence, in this case too, x^{st} is a stable steady state.

Finally, let us consider the situation in Figure 3. This looks similar to Figure 2A but now the x_1 nullcline goes under the x_2 nullcline. It follows by a similar argument to the one we just did that

$$\left[\left(\frac{1}{b}\right)\left(\frac{dg}{dx_1}\right)\bigg|_{x=x^{st}}\right] > \left[\left(\frac{1}{a}\right)\left(\frac{df}{dx_2}\right)\bigg|_{x=x^{st}}\right]^{-1} > 0 \,.$$

Since both terms in the inequality are positive, we can multiply across to get

$$\left[\left(\frac{1}{b}\right)\left(\frac{dg}{dx_1}\right)\bigg|_{x=x^{st}}\right] \times \left[\left(\frac{1}{a}\right)\left(\frac{df}{dx_2}\right)\bigg|_{x=x^{st}}\right] - 1 > 0 \,,$$

so that $1-\alpha < 0$. Hence, in this case,

$$\det J(x^{st}) = ab(1-\alpha) < 0 \,,$$

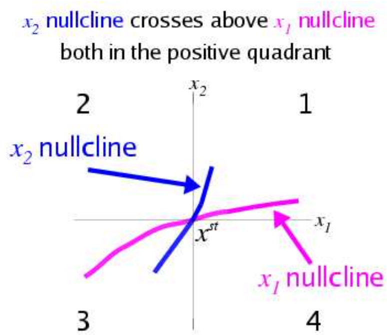

Figure 3: The x_1 nullcline crosses below the x_2 nullcline as x_1 increases, resulting in an unstable steady state at the crossing point, $x = x^{st}$.

so that x^{st} is an unstable steady state.

We can sum up what we have learned in the following result.

Theorem: *Let x^{st} by a steady state of the autoregulatory loop in Figure 1, as modelled by the equations in (1) with $a, b > 0$. If the x_1 nullcline crosses above the x_2 nullcline at x^{st}, as x_1 increases, as shown in Figure 2A and B, then x^{st} is a stable steady state. If the x_1 nullcline crosses below the x_2 nullcline at x^{st}, as shown in Figure 3, then x^{st} is unstable.*

This result is very useful for systems like the λ-repressor autoregulatory loop, as we saw in the Lectures. It means that you do not have to calculate eigenvalues numerically, just plot the nullclines and look at the geometry of their intersections. Unhappily, we do not have anything as nice as this for more complex situations.