DETERMINISTIC MODELLING

Delivery 4

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Excercise 20

Biochemical switch. **A gene product with concentration g catalyzes its own production and decays linearly according to the following kinetics equation:**

$$\frac{dg}{dt} = k_1 \frac{g^2}{k_3^2 + g^2} - k_2 g, \tag{1}$$

with g and k_i positive constants.

1. Give a physical interpretation of parameters k_2, k_3. Which units has k_1/k_3? How can it be interpreted?

In the equation we can identify two main terms. The first one, $k_1 \frac{g^2}{k_3^2+g^2}$, is the autocatalytic term, which indicates the protein concentration g that is going to be generated depending on the current g in the system. The second one, $-k_2 g$, is a linear decay due to the degradation of the proteins over time. Because of this, we can interpret this second term as the average number of proteins degradated per unit of time. On the other hand, we know from the equation that $[k_1] = [g/t]$, $[k_2] = [1/t]$ and $[k_3] = [g]$. Because of this, we can deduce k_2 is the degradating probability per unit of time of a protein (and $1/k_2$ would be the mean life of a protein before degrading).

We can interpret k_1 as the maximum rythm the system can have in the protein generation, and k_3 as an indicator of the protein concentration needed to reach this maximum rythm. More concretely, it is equivalent to the protein concentration for which the system reaches half of the maximum rythm.

For interpreting k_1/k_3 it is useful to use the interpretations of k_1 and k_3. As we have said $k_1 \equiv r_{\max}$ where $r \equiv \frac{[\_]}{t}$ is rythm of creation and, with this definition, $k_3 \equiv \frac{r_{\max}}{2} t$. Therefore, $k_1/k_3 = \frac{2}{t}$ and this means that we can interpret it as the double of the average number of proteins generated per unit of time.

2. Make the equation non-dimensional and show that it can rewrite as

$$\frac{dg}{dt} = \frac{g^2}{1+g^2} - kg, \tag{2}$$

where g is now a dimensionless concentration and k the dimensionless group.

Using the new non-dimensional variables:

$$g \equiv \frac{G}{k_3} \longrightarrow dG = k_3 dg$$

$$t \equiv \frac{k_1}{k_3} T \longrightarrow dT = \frac{k_3}{k_1} dt$$

Where G and T are the old g and t dimensional variables.

We obtain the non-dimensional equation:

$$\frac{dg}{dt} = \frac{g^2}{1+g^2} - kg$$

where we have defined the dimensionless group $k \equiv \frac{k_2 k_3}{k_1}$.

3. Study the behavior of the system graphically (do not make any calculation): find the equilibria, their stability and the different situations depending on the parameter value.

We can study the system separating the equation:

$$\frac{dg}{dt} = y_1 - y_2 \text{ where } \begin{cases} y_1 \equiv \frac{g^2}{1+g^2} \\ y_2 \equiv kg \end{cases}$$

Now we can represent both functions for different values of k:

$\underline{k >> 1}$

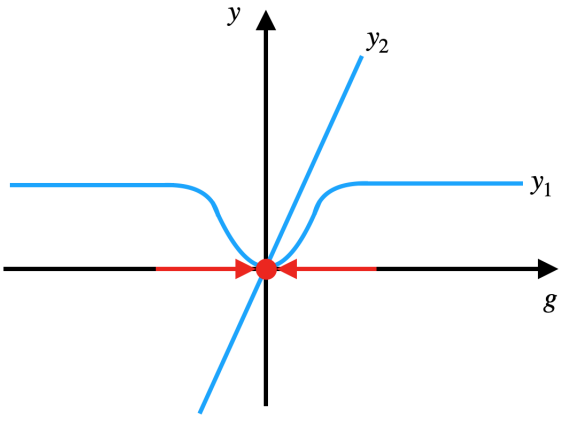

Figure 1: y_1 and y_2 for big values of k.

$\underline{k << 1}$

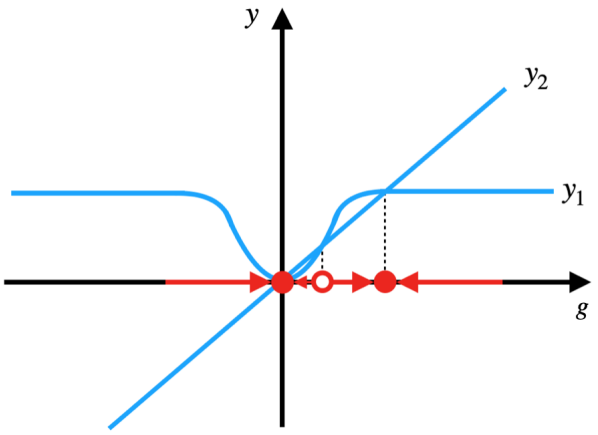

Figure 2: y_1 and y_2 for small values of k.

Notice that there will always be three equilibrium points in this range because when $x \to 0$ the slope of y_2 will be always bigger than y_1.
In the limit between both cases we can see that there will be only two equilibrium points:

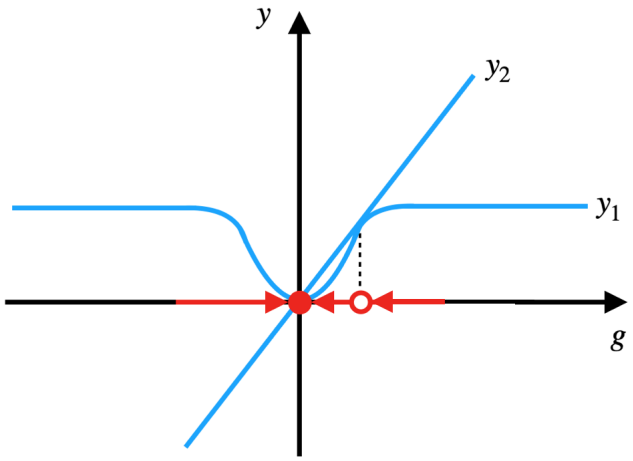

Figure 3: y_1 and y_2 in the limit where they are tangent at $g \neq 0$.

With this information we can draw the bifurcation diagram:

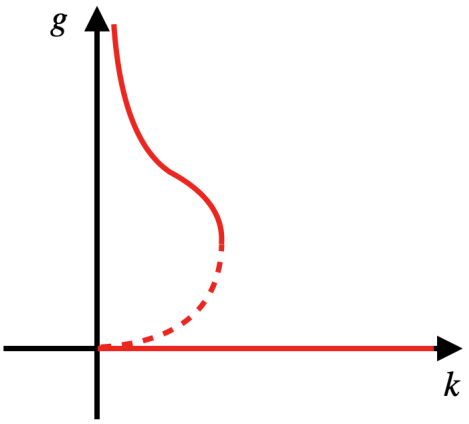

Figure 4: Bifurcation diagram with a saddle-node bifurcation type.

4. In this system there is a region in which a biochemical switch can take place. In this region there is one equilibrium with a low concentration and one with a large concentration of the gene product.

a. How can we switch from the low to high equilibrium without changing parameter k? Discuss it graphically.

As we can see in the bifurcation diagram, we will be able to switch to the high concentration state if we increase the concentration above the unstable equilibrium curve.
Maybe it is better to visualize it in Figure 2 where the arrows help to see the evolution of the system between the equilibrium points. If we start in $g = 0$ and we increase g we will return to $g = 0$ meanwhile we don't exceed the unstable value. From there on, the system will evolve to the high concentration equilibrium.

b. Find the exact conditions and the final value of the concentration.

As we said, the condition to do the switch is:

$$\Delta g > g_*^-$$

where Δg is the increase of concentration that we apply to the system and g_*^- is the unstable equilibrium value of the concentration.
The equilibrium points will satisfy:

$$f(g_*) = 0 \longrightarrow \frac{g_*^2}{1+g_*^2} = kg_* \begin{cases} g_*^{(0)} = 0 \\ g_*^+ = \frac{1+\sqrt{1-4k^2}}{2k} \\ g_*^- = \frac{1-\sqrt{1-4k^2}}{2k} \end{cases}$$

So the condition, given a value of $k < 1/2$, is:

$$\boxed{\Delta g > \frac{1 - \sqrt{1 - 4k^2}}{2k}}$$

the final concentration, if we satisfy the condition, will be the high concentration equilibrium state with

$$\boxed{g_*^+ = \frac{1 + \sqrt{1 - 4k^2}}{2k}}$$

5. Assume now that our system is in the state of large concentration of gene product.

a. Discuss a possibility of switching the system to the low equilibrium by changing the parameter.

As we can see on Figure 1, for high values of k, the only stable state is the low equilibrium one. So, if we increase the values of parameter k enough, the system will evolve to the low equilibrium state.

b. Find the exact conditions for this switch.

We can notice that the $g_*^\pm$ equilibrium solutions exists only if

$$1 - 4k^2 > 0 \longrightarrow k < \frac{1}{2}$$

So the condition in k to have only the low equilibrium state is

$$\boxed{k > \frac{1}{2}}$$

c. How can we get this with k_1, k_2 and k_3 in the original model? Interpret physically this result.

Using the definition of k

$$\frac{k_2 k_3}{k1} > \frac{1}{2} \longrightarrow \boxed{k_2 > \frac{k1}{2k_3}}$$

As we have said before, we can intepret k_1/k_3 as the double of the average number of proteins created per unit of time, and k_2 as the average number of proteins degradated over time. So this result makes sense, because it says that when the average number of degradation proteins (per unit of time) is higher than the average number of proteins generated (per unit of time) the gen will be switched off.

6. Now, let's assume that there exists a chemical substance S that is able to activate the gen at a rate proportional to its concentration, s. This contributes with an additional term $k_4 s_0$ (let's assume $s = s_0$ constant) in the dynamical equation for g given above.

a. Write the new equation and make it dimensionless.

$$\frac{dG}{dT} = k_1 \frac{G^2}{k_3^2 + G^2} - k_2 G + k_4 s_0$$

Now we can do the same adimensionalization as before but adding a new non-dimensional parameter

$$s \equiv \frac{k_4}{k_1} s_0$$

so the dimensionless equation is

$$\frac{dg}{dt} = \frac{g^2}{1 + g^2} - kg + s.$$

b. Consider the bistability region. Assume that initially there is no gene product, i.e. g(0)=0, and suppose s is slowly increased from zero (the activating signal is turned on); what happens to g(t)? What happens if s then goes back to zero? Does the gene turn off again? Discuss it graphically.

When $s = 0$ we have the situation shown in Figure 2 where the $g = 0$ is a stable equilibrium point, therefore, if we start at $g(0) = 0$ it will remain at this point.

If we increase s, we can study it graphically again with the plot

$$\frac{dg}{dt} = y_1 - y_2$$

with now $y_2 \equiv kg - s$.

For very small s we will have the lower concentration equilibrium displaced a little bit to the right as we can see here:

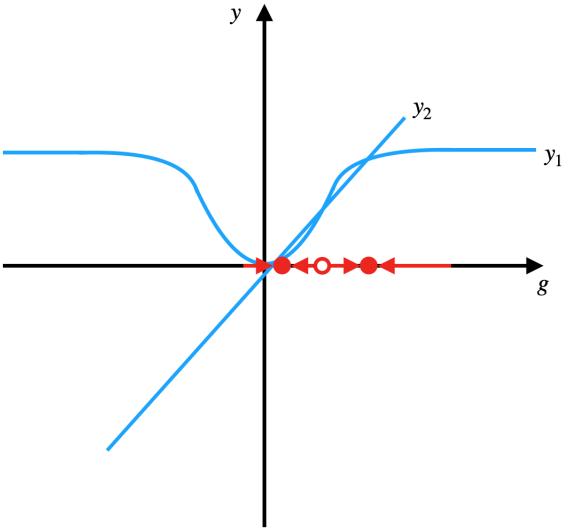

Figure 5: y_1 and y_2 for very small values of s.

So the concentration will increase from 0 to this new displaced equilibrium point.

As s increases more, at some point we will have a new situation:

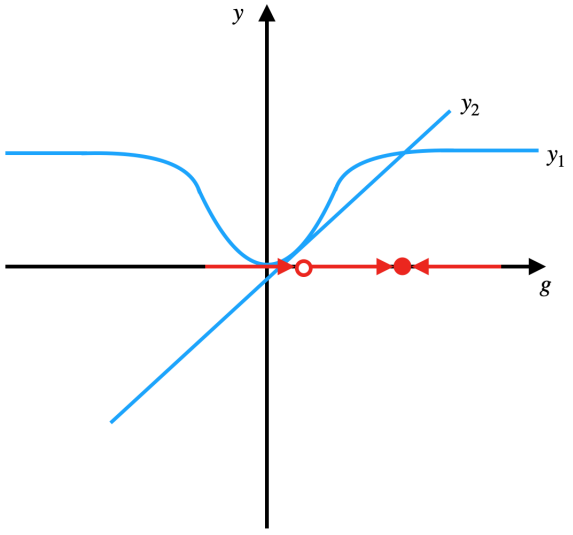

Figure 6: y_1 and y_2 for small values of s

where the previous stable point becomes unstable without going back to $g = 0$.

At this point, a little perturbation that increasses the concentration will cause the system to go to the high concentration equilibrium state (that is stable).

And from now on, if we continue increasing s there will only be one stable equilibrium point that increasses with s:

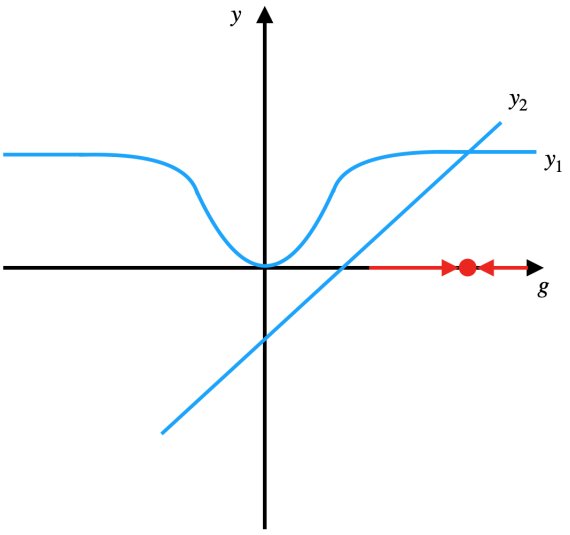

Figure 7: y_1 and y_2 for big values of s

If now s goes back to 0, the concentration will remain in the high concentration equilibrium point because its stability doesn't change. Therefore the gene doesn't turn off again and remains active.

c. Find parametric equations for the bifurcation curves in terms of the two non-dimensional parameters in the equation, classify the bifurcations that occur and plot the stability diagram.

In Figure 6 we can see that a saddle-node bifurcation occurs and therfore the curves are tangent to each other while intersect.

This gives us two conditions:

$$y_1 = y_2 \longrightarrow \frac{g^2}{1+g^2} = kg - s$$

$$y_1' = y_2' \longrightarrow \frac{2g}{(1+g^2)^2} = k$$

So we obtain the parametric equations:

$$\boxed{k = \frac{2g}{(1+g^2)^2}}$$

$$\boxed{s = \frac{g^2}{1+g^2}\left[\frac{2}{1+g^2} - 1\right]}$$

And therefore the stability diagram for these equations:

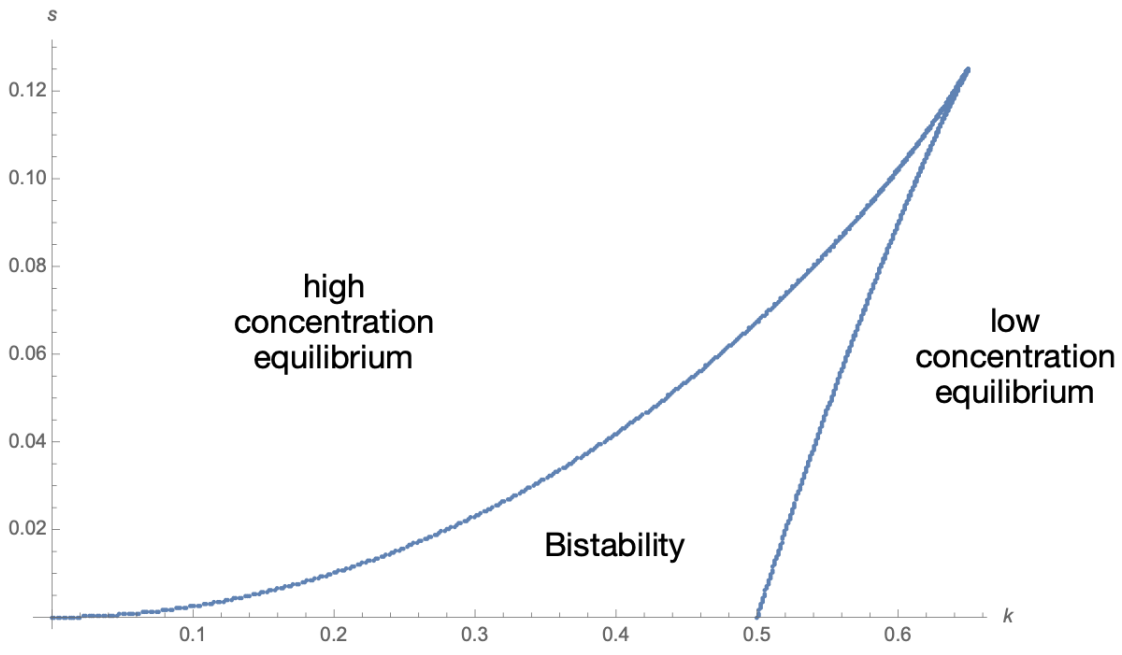

Figure 8: Stability diagram.

d. Give a biological interpretation of the dynamics found.

As we have seen, the equilibrium state of the gen will depend on k and s. The k represents the degradation of the protein and s the amount of catalyst.

When the amount of catalyst is high (compared to the degradation), as we would expect, the gen will be activated and will produce protein (gen ON). On the other hand, when the degradation is high compared to the amount of catalyst, the production of protein due to the catalyst won't compensate the amount of protein lost in the degradation and the gen won't produce the protein (gen OFF).

Finally, when the catalyst and the degradation effects are comparable, we see that there is a bistability zone where the protein will have two possible ON states with different concentration values (one higher than the other).