

## Notes on Mathematically Controlled Comparisons

In exercise 3.1. in Alon's book the solution computes response times of a negatively auto-regulated gene using a Hill function and compares that to the response time of simple regulation. In a mathematically controlled comparison, the parameters of the different designs should be chosen so that the resulting steady state levels are the same. The solution does not address this issue. Why is this not necessary?

A similar situation appears in the combination of exercises 3.4 and 4.3. In exercise 3.4. we compute the response time of a positively auto-regulated gene and compare it to a simply regulated gene. Again the solution we had in the exercise session did not consider choosing the parameters of the designs so that the steady state levels are the same. This result was further used in exercise 4.3. where we considered a C1-FFL with OR-gate where the gene Y is positively auto-regulated. In this exercise we further computed the effects that this positive auto-regulation has as compared to a C1-FFL without positive auto-regulation of Y. Again the solution does not consider the (possibly different) steady state levels of the designs. Why is this not necessary?

### Closer look at exercise 3.4.

For a positively auto-regulated gene X we got the following solution for the concentration of X when the basal production rate  $\beta$  suddenly goes up (assuming  $\beta_1 < \alpha$ )

$$X(t) = X_{st}(1 - e^{-(\alpha-\beta_1)t}), \text{ where } X_{st} = \frac{\beta}{\alpha - \beta_1}.$$

If we now consider the concentration of X relative to the concentration of X in steady state (i.e. normalize the above equation by  $X_{st}$ ), we get

$$\frac{X(t)}{X_{st}} = (1 - e^{-(\alpha-\beta_1)t}), \text{ where } X_{st} = \frac{\beta}{\alpha - \beta_1}.$$

This shows that the concentration of X relative to the steady state concentration in fact does not depend on the steady state at all. Therefore the time to reach halfway between the initial state and the steady state (= the response time) does not depend on the steady state. This reasoning applies also to the delay calculations of exercise 4.5. in Alon's book as the threshold values  $K_{yz}$  should be defined relative to the steady state concentration.

How can we then choose the parameters so that the steady states are the same in the case of simple regulation and positively auto-regulated gene? The key observation is that we should keep the degradation/dilution rate  $\alpha$  the same in both designs (as is done in Section 3.4. in Alon's book when analyzing negative auto-regulation). The steady state of the simply regulated gene with production rate  $\beta_{\text{simple}}$  is then

$$\frac{\beta_{\text{simple}}}{\alpha}$$

and the steady state of the positively auto-regulated gene with basal production rate  $\beta_{\text{p.a.r}}$  is

$$\frac{\beta_{\text{p.a.r.}}}{\alpha - \beta_1}.$$

To make these steady state levels equal we thus should choose

$$\beta_{\text{p.a.r}} = \beta_{\text{simple}} \frac{\alpha - \beta_1}{\alpha} < \beta_{\text{simple}}.$$

In the case of positive auto-regulation, it is thus possible to choose a lower basal production rate to reach the same steady state level and thus positive auto-regulation slows down the response time.

### **How about exercise 3.1.?**

The situation is basically the same as above. The concentration of X when normalized by the steady state does not depend on the steady state and thus the response times can be compared. The degradation/dilution rate  $\alpha$  should be the same in both designs and then we should choose the production rates so that the steady state levels are the same. This computation is not performed in the solution as it does not effect the response times.