Assignment 2

A. Negative auto-regulation

a. Calculate the response time of a circuit with negative auto-regulation and compare it to the corresponding simple regulation circuit (that reaches the same steady state). Use the following parameters:

half-saturation constant k = 0.3 μM
maximal production rate beta = 1 μM/h
Hill coefficient n = 2
degradation rate α = 1/h

The following block of code provides you with a starting point for simulating simple regulation (solS) and NAR (solNAR) in Mathematica. It is the same model as you used in excercise 1B, except that the production rate is now a Hill function of Y as we discussed in the lectures.

Hint: Take function that calculates y[t]/yst (e.g., (y[t]/.solNAR)/ystNAR) and ask at what time t this function reaches 0.5 using the Solve[] function, and solving for t.

```
params = {β->1, k->0.3, α->1, n->2}
solNAR = NDSolve[{y'[t] == β 1/(1+(y[t]/k)^n)-α y[t],
y[0]==0.00}/.params,y,{t,0,5}]
solS = NDSolve[{y'[t] == β -α y[t], y[0]==0}/.params,y,{t,0,5}]
ystNAR =y[t]/.NSolve[{0==β 1/(1+(y[t]/k)^n)-α y[t] &&y[t]>0}/.params,y[t]]
ystS = β/α/.params
Plot[{(y[t]/.solNAR)/ystNAR, (y[t]/.solS)/ystS}, {t,0,5}, PlotRange->All,
PlotLegends ->{"NAR", "Simple"}, AxesLabel ->{"time", "y/yst"}]
```

b. Which parameter do you have to change to reach the limit of a step function of inhibition discussed in the lecture? Change the parameter accordingly and simulate the dynamics. What qualitative difference do you observe in the shape of the dynamics?

c. Calculate the response time of NAR and simple regulation by finding the time t where y[t] reaches half of its steady-state. Choose the same parameters as in 1b at the step function limit. Then change the maximal production rate to be 2,20,200 μM/h. You can do this either numerically with the model above, or algebraically using the equation derived in the lecture.

d. Calculate how the response time of NAR and of simple regulation change with respect to the removal rate. To do so, use parameters close to the step-function limit and use the following parameters:

$$\text{maximal production rate } \beta \rightarrow 100\ \mu\text{M}/h$$
$$\text{half} - \text{saturation constant } k \rightarrow 1\ \mu\text{M}$$

e. How does the response time of NAR and simple regulation change with the removal rate α being 1, 2, 10, 20 h^{-1} ? The response time of which regulation is more affected by the removal rate: simple regulation of NAR? You can do this either numerically with the model above, or algebraically using the equation derived in the lecture.

f. Make a summary statement: Which parameter determines the <u>response time</u> of an NAR circuit (at the step-function limit) and which one determines the response time under simple regulation? Which parameter determines the steady-state of the NAR and of the simple regulation circuit?

B. Positive autoregulation

Simulate a circuit with positive auto-regulation with parameters

$\beta \to 24\frac{\mu\mathrm{M}}{\mathrm{h}},\ k \to 10\mu\mathrm{M}, \alpha \to 1/h, n \to 2.$

Using the following code:

```
params = { β->24, k->10, α->1, n->2}

solPAR = NDSolve[{y'[t] == β((y[t]/k)^n)/(1+(y[t]/k)^n) - α y[t],
y[0]==3}/.params,y,{t,0,200}]

Plot[y[t]/.solPAR, {t,0,200}, PlotRange->{All,{0,35}}, AxesLabel->{"time","y[t]"}]

y[200]/.solPAR

ystPAR =y[t]/.NSolve[{0== β((y[t]/k)^n)/(1+(y[t]/k)^n)- α y[t] &&y[t]>=0}/.params,y[t]]
```

a. Determine the steady-state when starting from the OFF state (y[0] = 0 μM). Now simulate the steady state when starting from an ON state (y[0] = 30 μM). How are these different?
b. Change the starting conditions continuously. What is the critical concentration at which the systems switches from the OFF state to the ON state?
c. How many steady-states does the system have? How many are stable?
d. A cell has been in the OFF state for a long time. Now, it gets a pulse of signal such that the production rate of Y increases transiently by $\Delta\beta$ = 50 μM /h. Subsequently the Signal disappears again ($\Delta\beta$ =0). What is the steady-state concentration of Y after the pulse of production is gone? How long (how many hours or minutes) does the pulse have to be for the steady-state to switch?
Hint: Use the same parameters as for exercises a-c and change the equation in the model to accommodate the 50 μM /h increase in production rate, then find time t where the concentration of y passes the switching point.

C. Positive autoregulation without cooperativity

No computer needed for this exercise.

Excercise B models a positive auto-regulation with a Hill coefficient of n=2. Write down the corresponding model with a Hill coefficient of n = 1.

a. How many fixpoints does the circuit have?

b. Is the system mono- or bi-stable? Explain using a graph of production and removal rates as a function of the concentration of y how you reach your conclusion.