Assignment 2

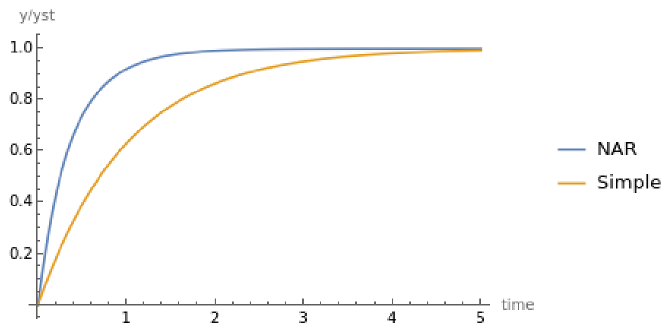
A)

a) Response time for circuit with simple regulation is 0.693147 s.
Response time for circuit with negative autoregulation is 0.248914 s.

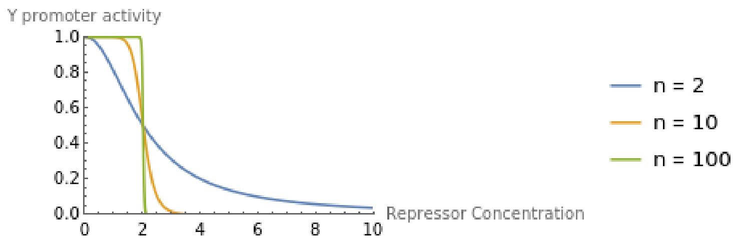
Note: Our goal is to have same steady state concentration for both NAR and simple regulatory circuit.

Code:

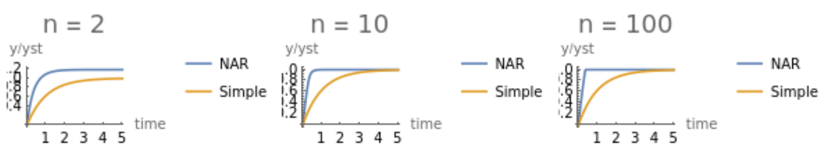
```
params = {β → 1, k → 0.3, α → 1, n → 2}
solNAR = NDSolve [{y '[t] == β / (1 + (y[t] / k)^ n) - α y[t], y[0] == 0.00} /. params , y, {t, 0, 5}]
ystNAR = y[t] /. NSolve[{0 == β / (1 + (y[t] / k)^ n) - α y[t] && y[t] > 0} /. params , y[t]]
params = Insert[params , βsimple → ystNAR ⟦1⟧ , - 1]
solS = DSolve[{y '[t] == βsimple - α y[t], y[0] == 0} /. params , y, {t, 0, 5}] ystSimple = y[t] /.
NSolve[{0 == βsimple - α y[t] && y[t] > 0} /. params , y[t]]
p1 = Plot[{(y[t] /. solNAR) / ystNAR , (y[t] /. solS) / ystSimple }, {t, 0, 5}, PlotRange → All,
PlotLegends → {"NAR", "Simple "}, AxesLabel → {"time", "y/yst"}]
tSimp = t /. NSolve[{y[t] == ystSimple / 2 } /. solS , t] tNAR = t /. NSolve[{y[t] == ystNAR / 2} /.
solNAR , t]
```



b) We will have to increase n (cooperativity) in hill function to reach the limit of step function of inhibition.



With the increase in n, we observe even faster initial growth and lower delay in auto repression to stop production at the desired steady-state.



c) Given, $\beta_{NAR} = 2{,}20{,}200\ \mu M/h$ and $n \to \infty$. Now since $y[t] \ll \beta_{NAR}/\alpha$, we can approximate $T_{1/2}^{NAR} = K/2\beta_{NAR}$. Response time of simple regulatory circuit is $T_{1/2}^{simple} = ln2/\alpha$

$$\Longrightarrow T_{\frac{1}{2}}^{NAR} = 0.3 \frac{\mu M}{2 * 2{,}20{,}200\ \mu M\ h^{-1}} = 6.81 * 10^{-7}\ h$$

And,

$$T_{1/2}^{simple} = \frac{ln2}{1\ h^{-1}} = 0.693\ h$$

d) At the step function limit i.e. $n \to \infty$ and $y[t] \ll \beta_{NAR}/\alpha$, we know $T_{1/2}^{NAR} = K/2\beta_{NAR}$ and $T_{1/2}^{simple} = ln2/\alpha$. This means $T_{1/2}^{NAR}$ is does no depends on α, while $T_{1/2}^{simple}$ is inversely proportional to α.

e) Using the above mentioned formulas, we calculate $T_{1/2}^{NAR}$ and $T_{1/2}^{simple}$.

α	$T_{1/2}^{NAR}$ (hr)	$T_{1/2}^{simple}$ (hr)
1	0.005	0.693
2	0.005	0.346
10	0.005	0.069
20	0.005	0.034

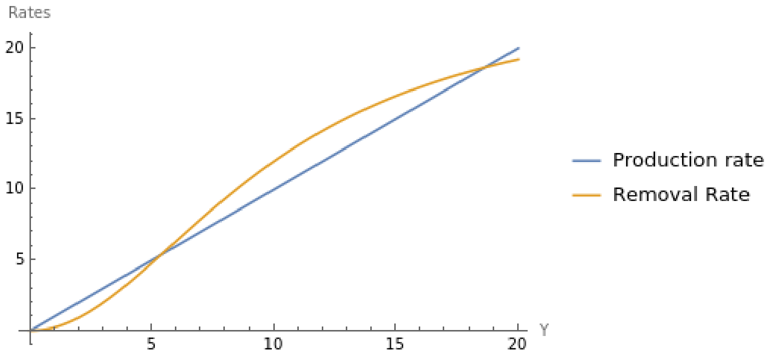
f) Summary statement:

- Response time of NAR circuit depends on half − saturation constant k and maximal production rate β.
- Response time of simple regulatory circuit depends on removal rate α.
- Steady state concentration of NAR circuit depends on half − saturation constant k.
- Steady state concentration of simple regulatory circuit depends on maximal production rate β_{simple} and removal rate α.

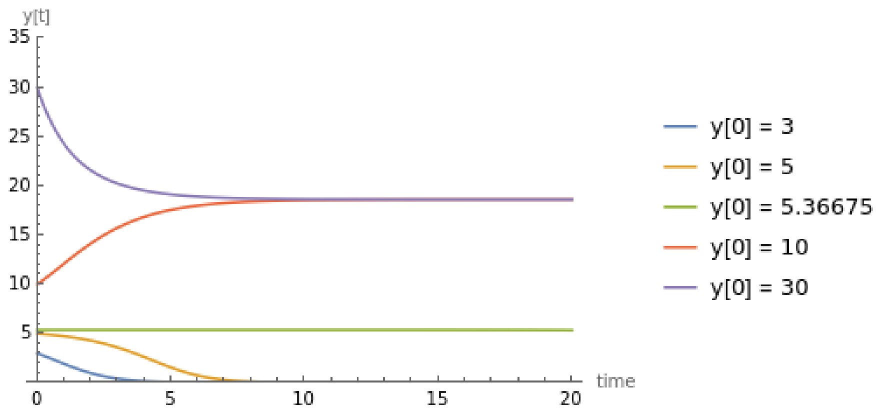
B)

a) Steady state concentration of y given $y[0] = 0\ \mu M$ is $0\ \mu M$.
Steady state concentration of y given $y[0] = 30\ \mu M$ is $18.6332\ \mu M$.

The given PAR circuit has three fixed points $(y = 0\ \mu M\ , y = 5.36675\ \mu M\ and\ y = 18.6332\ \mu M)$. The fixed point $y = 5.36675\ \mu M$ is unstable, thus steady state concentration of y is either $0\ \mu M$ or $18.6332\ \mu M$ which depends on initial conditions.



b) Critical concentration at which the systems switches from the OFF state to the ON state is $y = 5.37775\ \mu M$.



Code:

```
params = { β → 24, k → 10, α → 1, n → 2}
solPAR1 = NDSolve [{y '[t] == β ((y[t] / k)^ n) / (1 + (y[t] / k)^ n) - α y[t], y[0] == 3} /. params ,
y, {t, 0, 20}]
solPAR2 = NDSolve [{y '[t] == β ((y[t] / k)^ n) / (1 + (y[t] / k)^ n) - α y[t], y[0] == 5} /. params ,
y, {t, 0, 20}]
solPAR3 = NDSolve [{y '[t] == β ((y[t] / k)^ n) / (1 + (y[t] / k)^ n) - α y[t], y[0] == 10} /. params
, y, {t, 0, 20}]
solPAR4 = NDSolve [{y '[t] == β ((y[t] / k)^ n) / (1 + (y[t] / k)^ n) - α y[t], y[0] == 30} /. params
, y, {t, 0, 20}]
solPAR5 = NDSolve [ {y '[t] == β ((y[t] / k)^ n) / (1 + (y[t] / k)^ n) - α y[t], y[0] == 5.36675 } /.
params , y, {t, 0, 20}]
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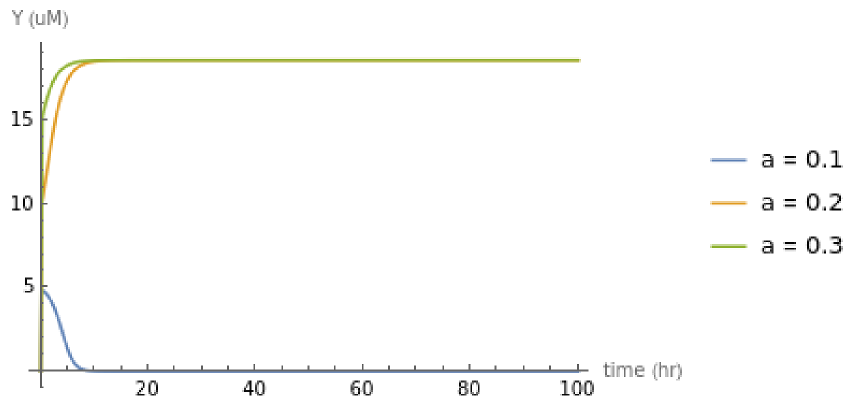
```
Plot[{y[t] /. solPAR1 , y[t] /. solPAR2 , y[t] /. solPAR5 , y[t] /. solPAR3 , y[t] /. solPAR4 }, {t, 0, 20}, PlotRange → {All, {0, 35}}, AxesLabel → {"time", "y[t]"} , PlotLegends → {"y[0] = 3" , "y[0] = 5" , "y[0] = 5.36675 " , "y[0] = 10" , "y[0] = 30"}]
```

c) System has three steady-states and only two of them are stable.
   - $y = 0\ \mu M, stable\ steady\ state.$
   - $y = 5.36675\ \mu M, unstable\ steady\ state.$
   - $y = 18.6332\ \mu M, stable\ steady\ state.$

d) The steady-state concentration of Y after the pulse of production is gone depends on the duration of the pulse. If the pulse duration ≤ 0.10 hr then the steady state concentration is 0 and if pulse duration ≥ 0.20 hr then steady state concentration of Y is 18.6332 μM.



Note: a is the duration of the pulse in hr.
Pulse duration to switch the steady state from 0 μM to 18.6332 μM has to be approximately greater than or equal to 0.2 hrs, which is evident from the above graph.

Code:

```
params = { β → 24, k → 10, α → 1, n → 2 }
p[t] = UnitStep [t] - UnitStep [t - r]

sol = solPAR = ParametricNDSolve [ {y '[t] == 50 * p[t] + β ((y[t] / k)^ n) / (1 + (y[t] / k)^ n) - α y[t], y[0] == 0} /. params , y, {t, 0, 200} , {r}]
Plot[Evaluate [Table[y[a][t] /. sol, {a, 0.1, 0.3, .1}]], {t, 0, 100}, PlotRange → All , PlotRange → {All, {0, 50}} , AxesLabel → {"time (hr)" , "Y (uM)"} , PlotLegends → {"a = 0.1" , "a = 0.2" , "a = 0.3"} ]
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C)

$$\frac{dy}{dt} = \beta \frac{y}{k + y} - \alpha * y$$

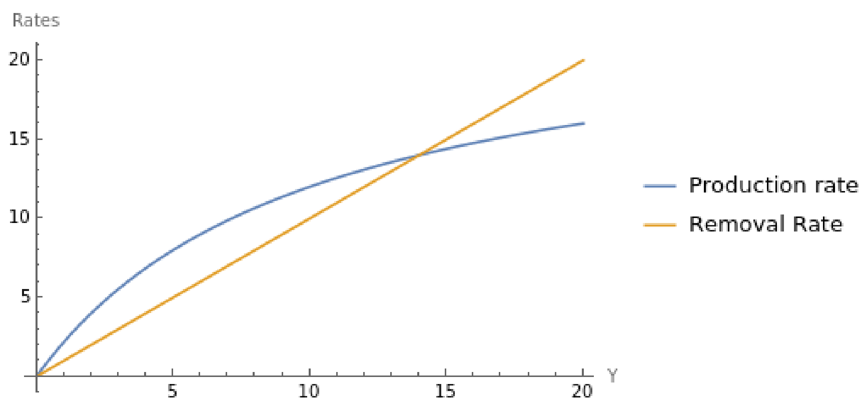
a) On fixed points $\frac{dy}{dt} = 0$.

$$\frac{dy}{dt} = \beta \frac{y}{k + y} - \alpha * y = 0$$

$$\Rightarrow y = 0 \, , y = \frac{\beta}{\alpha} - k$$

Systems has two fixed points $y = 0 \; and \; y = \frac{\beta}{\alpha} - k$.

b) System is monostable as fixed point $y = \frac{\beta}{\alpha} - k$ is stable while fixed point $y = 0$ is unstable. Fixed point $y = \frac{\beta}{\alpha} - k$ is stable, because shifting y to either side $(of \; \frac{\beta}{\alpha} - k)$ causes a return to the fixed point.



Code:

```
Plot[{24*y/(y+10) , y} , {y, 0 , 20} , PlotLegends->{"Production rate" , "Removal Rate"} ,
AxesLabel -> {"Y" , "Rates"}]
```