INTRODUCTION

Negative autoregulation (NAR) occurs when the product of a gene represses its own production.

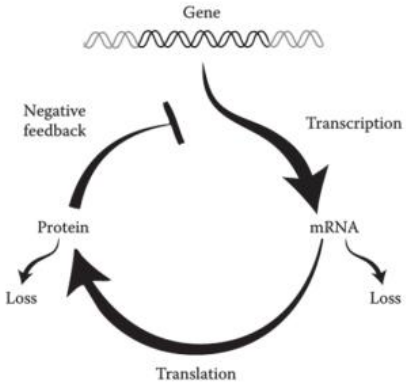

Figure 3: NAR scheme for the mRNA-protein model.

In the NAR module the equations for protein concentration $p(t)$ and mRNA concentration $r(t)$ (assuming the gene and the protein activator always present) are:

$$\frac{dp(t)}{dt} = k_{trl} \cdot r(t) - k_{pl} \cdot p(t) \tag{19}$$

$$\frac{dr(t)}{dt} = k_{trs}^{max} \frac{1}{1 + \frac{p(t)}{K}} - k_{rl} \cdot r(t) \tag{20}$$

In the NAR module the equations for protein concentration $p(t)$ and mRNA concentration $r(t)$ (assuming the gene and the protein activator always present) are:

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$$\frac{dr(t)}{dt} = k_{trs}^{max} \frac{1}{1 + \frac{p(t)}{K}} - k_{rl} \cdot r(t) \tag{20}$$

where k_{trs}^{max} is the absolute maximum amount of transcription that can occur from the gene, k_{pl} and k_{rl} are kinetic constants that governs the decay of protein and mRNA respectively, and k_{trl}, k_{trs} are constants that control gene transcription and translation. K is the ratio of the rate of protein dissociation from the operator to the rate of protein association with the operator.
These equations can be rewritten in an adimensional way such that we end with 2 parameters instead of the original 5:

$$\frac{dp'(t')}{dt'} = \alpha \cdot r'(t') - \beta \cdot p'(t') \tag{21}$$

$$\frac{dr'(t')}{dt'} = \frac{1}{1 + p'(t')} - r'(t') \tag{22}$$

where $\alpha = k_{trl} \frac{k_{trs}^{max}}{k_{rl}^2 K}$, $\beta = \frac{k_{pl}}{k_{rl}}$ and $t' = k_{rl} \cdot t$. Moreover, the relationship between $p(t)$, $r(t)$ and their adimensional homologous is:

$$p(t) = K p' \left(\frac{t'}{k_{rl}} \right) \tag{23}$$

$$r(t) = \frac{k_{trs}^{max}}{k_{rl}} r' \left(\frac{t'}{k_{rl}} \right) \tag{24}$$

ODE RESOLUTION AND CONCLUSIONS

Analitical calculation of the value of r'(t') and p'(t') at the steady state as a function of α, β.

$$\frac{dp'(t')}{dt'} = \alpha * r'(t') - \beta * p'(t') = 0$$

$$\frac{dr'(t')}{dt'} = \frac{1}{1 + p'(t')} - r'(t') = 0$$

$$r'(t') = \frac{\beta}{\alpha} * p'(t') \rightarrow \frac{1}{1 + p'(t')} - r'(t') = 0 \rightarrow \frac{1}{1 + p'(t')} - \frac{\beta}{\alpha} * p'(t') = 0$$

$$\rightarrow 1 + p'(t') - \frac{\alpha}{\beta * p'(t')} = 0 \rightarrow * p'(t') \rightarrow p'(t') + (p'(t'))^2 - \frac{\alpha}{\beta} = 0$$

$$\rightarrow p'(t') = -\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\alpha}{\beta}}$$

$$p'(t') = \frac{\alpha}{\beta} * r'(t') \rightarrow \frac{1}{1 + p'(t')} - r'(t') = 0 \rightarrow \frac{1}{1 + \frac{\alpha * r'(t')}{\beta}} - r'(t') = 0$$

$$\rightarrow 1 + \frac{\alpha * r'(t')}{\beta} - \frac{1}{r'(t')} = 0 \rightarrow * r'(t') \rightarrow r'(t') + \frac{\alpha * \left(r'(t')\right)^2}{\beta} - 1 = 0$$

$$\rightarrow r'(t') = -\frac{\beta}{2 * \alpha} + \sqrt{\frac{\beta^2}{4 * \alpha^2} + \frac{\beta}{\alpha}}$$

With $\Delta t=0.1$, $p_0=m_0=0$, results by using $\alpha=\beta=1$, $\alpha=\beta=3$, $\alpha=\beta=1/4$. Final (asyntotic) values of the concentrations for all the integrators.

For α=β=1

Euler:

```
> print(p_r_matrix[100,1:3])
[1]  0.6179948  0.6180295 10.0000000
```

Midpoint:

```
> print(p_r_matrix[100,1:3])
[1]  0.6180023  0.6180081 10.0000000
```

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  0.6180008  0.6180086 10.0000000
```

For α=β=3

Euler:

```
> print(p_r_matrix[100,1:3])
[1]  0.618034  0.618034 10.000000
```

Midpoint:

```
> print(p_r_matrix[100,1:3])
[1]  0.618034  0.618034 10.000000
```

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  0.618034  0.618034 10.000000
```

For $\alpha=\beta=1/4$

Euler:

```
> print(p_r_matrix[100,1:3])
[1]  0.6041466  0.6273729 10.0000000
```

Midpoint:

```
> print(p_r_matrix[100,1:3])
[1]  0.6026121  0.6283956 10.0000000
```

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  0.6026366  0.6283804 10.0000000
```

For greater alfa and beta, we obtain similar concentrations between methods. Concentrations also converge when these parameters are high and when we higher order methods such as midpoint or fourth order Runge-Kutta. The concentrations should be the same because the concentration gets constant in the steady state, so all the methods should reach the same point requiring different number of iterations. What happens here is that the number of iterations needed for reaching the steady state is larger for lower parameters and larger for less accurate methods.

Increasing the number of iterations from 10 to 50 for $\alpha=\beta=1/4$ the less accurate method gives the same result than every method with the higher parameter value ($\alpha=\beta=3$).

```
for(time in seq(time_increment*2, 50, by=time_increment)){
p0=p_r_matrix[x-1,1]
r0=p_r_matrix[x-1,2]

pn=p0 + time_increment*(alpha*r0 - beta*p0)
rn=r0 + time_increment*(1/(1+p0)-r0)

p_r_matrix[x,1]=pn
p_r_matrix[x,2]=rn
p_r_matrix[x,3]=time
x=x+1
}
print(p_r_matrix[500,1:3])
1]  0.618034  0.618034 50.000000
```

The concentrations are:

$$p'(t') = r'(t') = \frac{1}{2} + \sqrt{\frac{1}{4} + 1} = 0{,}618034$$

Which coincide for all the integrators

With $\Delta t=0.1$, $p_0=m_0=0$, results with $\alpha=\beta=1$, $\alpha=\beta=3$, $\alpha=\beta=1/4$. Final (asyntotic) values of the concentrations for protein and mRNA.

Knowing that the concentrations have the following values:

$$p'(t') = -\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\alpha}{\beta}}$$

$$r'(t') = -\frac{\beta}{2 * \alpha} + \sqrt{\frac{\beta^2}{4 * \alpha^2} + \frac{\beta}{\alpha}}$$

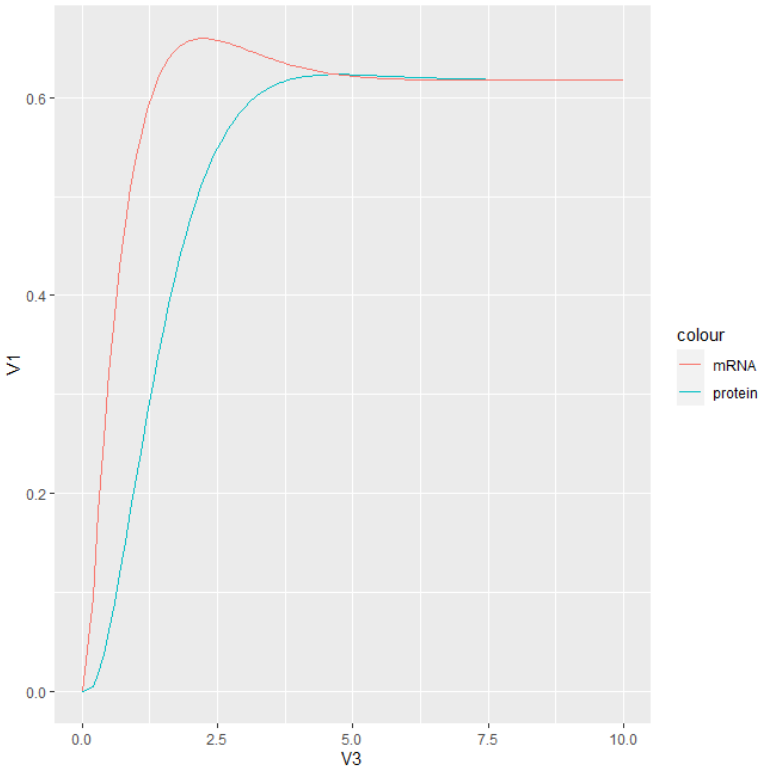
If α, β have the same values $p'(t') = r'(t') = \frac{1}{2} + \sqrt{\frac{1}{4} + 1} = 0{,}618034$

1. With Δt=0.1, p0=m0=0, compare the results with α=β=1, α=1 β=1/4, α=1/4 β=1 What changes do you see? How can you explain this behaviour?

For α=β=1

RK4:

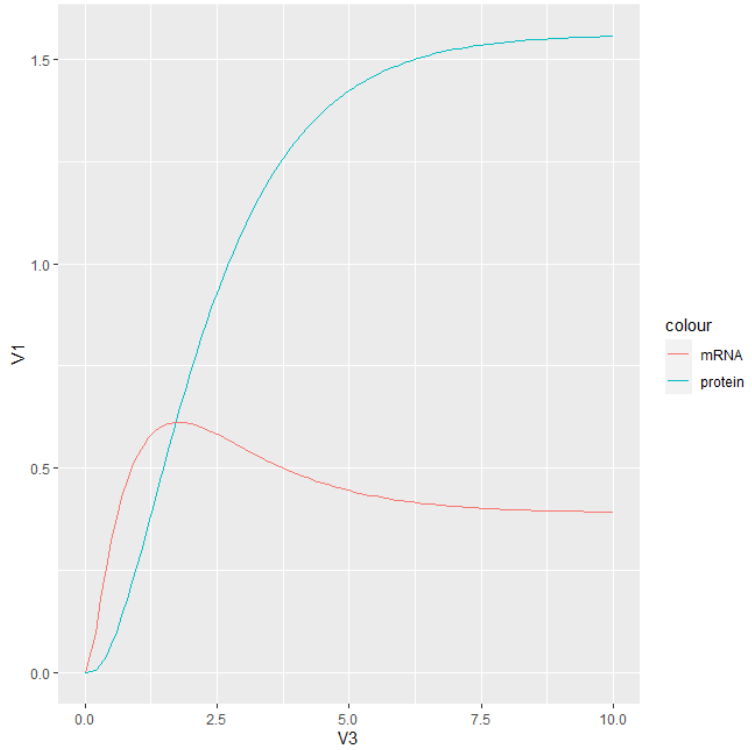
```
> print(p_r_matrix[100,1:3])
[1]  0.6180008  0.6180086 10.0000000
```



For α=1 β=1/4

RK4:

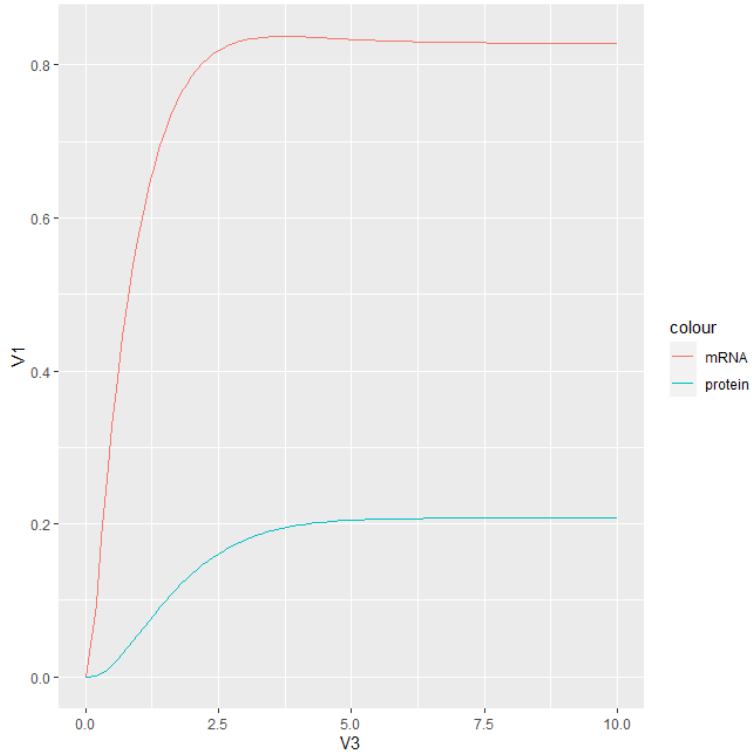
```
> print(p_r_matrix[100,1:3])
[1]  1.5571603  0.3925402 10.0000000
```



For $\alpha=1/4$ $\beta=1$

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  0.2071324  0.8284334 10.0000000
```



$$p'(t') = -\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\alpha}{\beta}}$$

$$r'(t') = -\frac{\beta}{2 * \alpha} + \sqrt{\frac{\beta^2}{4 * \alpha^2} + \frac{\beta}{\alpha}}$$

Asymptotic values for p and r change differently with each variable when p value rises with higher values of alfa, r value rises with higher values of beta and viceversa.

With Δt=0.1, p0=m0=0, results with α=β=1, α=1 β=1/4, α=1/4 β=1. Value of r'(t') and p'(t') at the steady state for each pair of α,β numerical solution comparison to the analytical one.

For α=β=1

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  0.6180008  0.6180086 10.0000000
```

$$p'(t') = -\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\alpha}{\beta}}$$

$$r'(t') = -\frac{\beta}{2 * \alpha} + \sqrt{\frac{\beta^2}{4 * \alpha^2} + \frac{\beta}{\alpha}}$$

r'(t')= p'(t') 0,618034

For α=1 β=1/4

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  1.5571603  0.3925402 10.0000000
```

p'(t') = 1,56155
r'(t') = 0,434017

For α=1/4 β=1

RK4:

```
> print(p_r_matrix[100,1:3])
[1]  0.2071324  0.8284334 10.0000000
```

p'(t') = 0,2071
r'(t') = 0,82843