Computational Biology - Set 2

Sander Broos (11895616)   Nick van Santen (11857846)

April 2022

Question 1:   Perfect adaption

(a)

$$\begin{cases} \frac{dR}{dt} = k_1 S - k_2 X R \\ \frac{dX}{dt} = k_3 S - k_4 X, \end{cases} \tag{1}$$

Given that a steady state solution is used, set $\frac{dX}{dt} = 0$, which yields

$$k_3 S - k_4 X = 0 \tag{2}$$
$$k_4 X = k_3 S \tag{3}$$
$$X = \frac{k_3}{k_4} S. \tag{4}$$

Substituting this in the rate equation of R gives

$$\frac{dR}{dt} = k_1 S - k_2 X R \tag{5}$$
$$= k_1 S - k_2 \frac{k_3}{k_4} S R \tag{6}$$
$$= k_1 S - \frac{k_2 * k_3}{k_4} S R. \tag{7}$$

Entering the values $k_1 = k_2 = 2$, $k_3 = k_4 = 1$ gives

$$\frac{dR}{dt} = 2S - \frac{2*1}{1} S R \tag{8}$$
$$= 2S - 2SR \tag{9}$$
$$= 2S(1 - R). \tag{10}$$

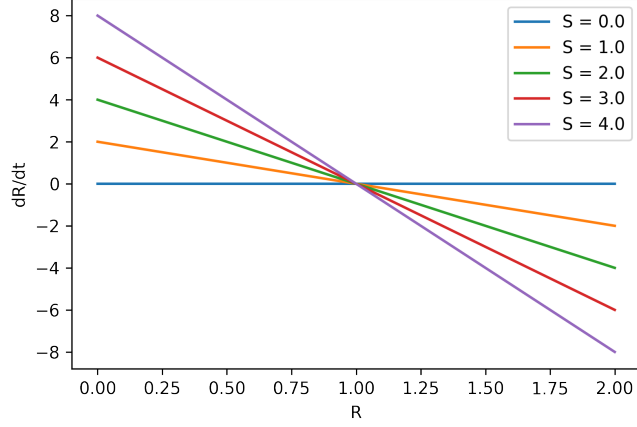For different values of S, the rate equation of R is plotted in the following figure.

Figure 1: The rate-equation of R for different values of S.

(b) $\frac{dR}{dt} = 0$ when $2S(1-R) = 0$, which happens when $S = 0$ or $R = 1$, resulting in the following signal-response curve.
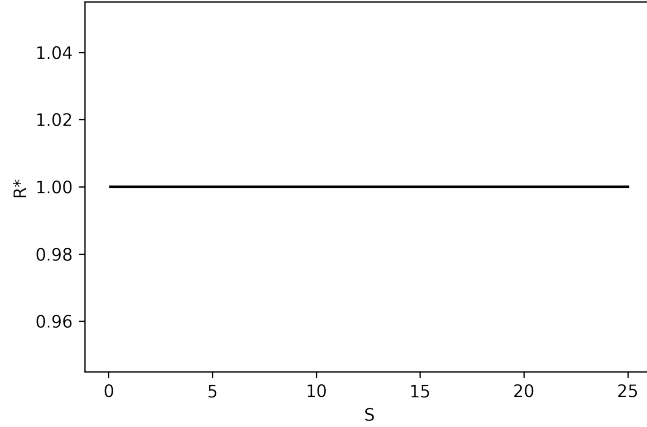

Figure 2: The signal-response curve of this system.

The equilibrium point of R does not depend on S, and is always 1. When $S = 0$, R can be any value and the system will still be in equilibrium. Figure 1 also shows that $\frac{dR}{dt}$ is always 0 when $R = 1$. When $S > 0$, the derivative of the rate equation at $R = 1$ is negative, meaning that these are stable points.

(c) Using the rate equations, the concentrations of R and X can be plotted over time with the `scipy.integrate.odeint` function, which is shown for $\{R_0, X_0\} = \{0, 0\}$. S is increased by 1 every period of 4, starting at zero.
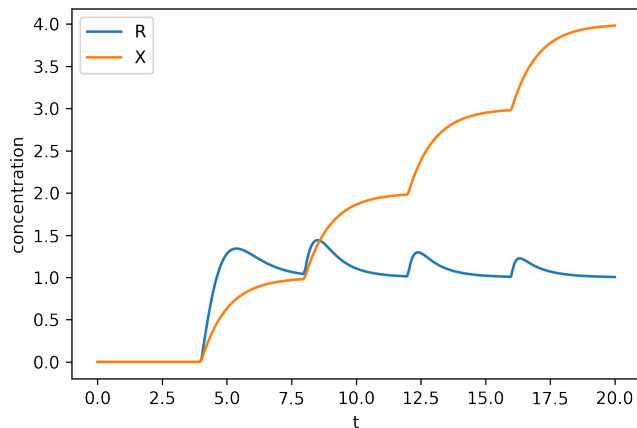

Figure 3: The concentrations of R and X plotted over time while S is increased by 1 every period of 4, starting at zero.

Like the signal-response curve showed, the concentration of R goes to the equilibrium $R^* = 1$ for all $S > 0$. When $S = 0$, the system is already in an equilibrium because X is already at zero, which means $\frac{dR}{dt} = \frac{dX}{dt} = 0$.

Also, as expected, X goes to the equilibrium point $\frac{k_3}{k_4}S = \frac{1}{1}S = S$ for all increments of S.

Question 2: Feedback loops

(a) For the given parameter values, the rate equations of R are shown for different values of S in the following figures.
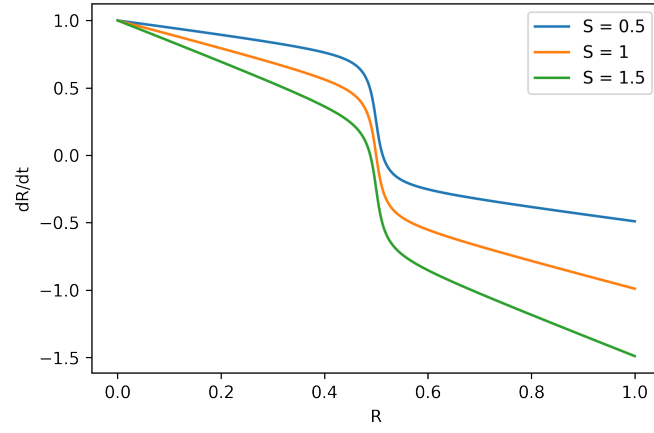
Figure 4: The rate equation of R in the homeostatic system for different values of S.
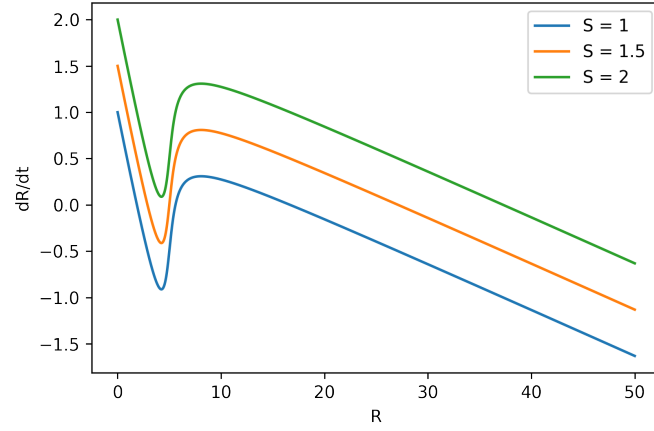

Figure 5: The rate equation of R in the mutual inhibition system for different values of S.
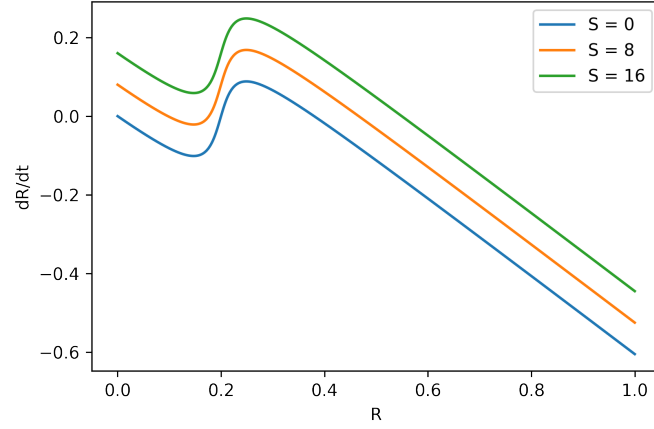
Figure 6: The rate equation of R in the mutual activation system for different values of S.

(b) The signal-response curves of these networks were created by determining the points where $\frac{dR}{dt} = 0$ from the rate equations of R for different values of S. This was done by evaluating the rate equation at different points R (separated by equal interval lengths). If the result switches signs (goes from negative to positive or vice versa) from one evaluation to the next, the value of R in between these two points was taken as the approximation of the equilibrium point. If the derivative of the rate equation was negative (sign went from positive to negative), the point was marked as stable. If the derivative was positive, the point was marked as unstable. The resulting signal-response curves are shown in the following three figures.

Figure 7: The signal-response curve of the homeostatic system.
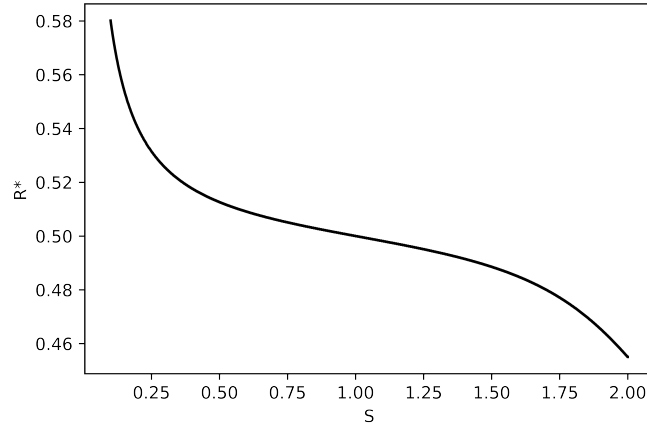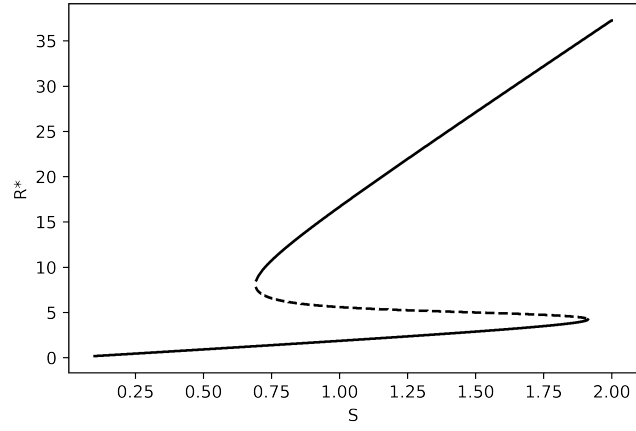
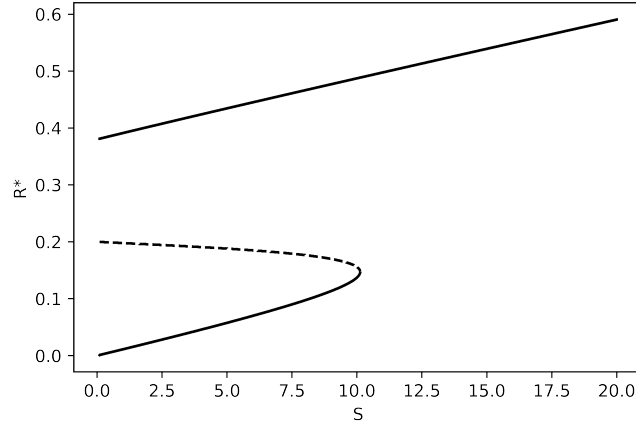Figure 8: The signal-response curve of the mutual inhibition system.

Figure 9: The signal-response curve of the mutual activation system.

Figure 8 shows two bifurcation points in the mutual inhibition system, both of which are saddle-node bifurcations. Figure 9 shows one bifurcation point in the mutual activation system, which is also a saddle-node bifurcation.
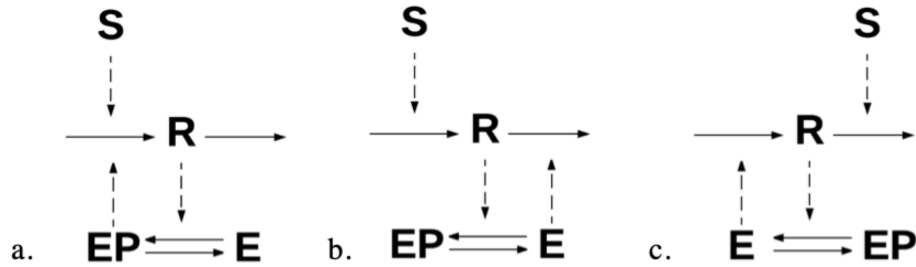
Figure 10: Network graphs of examples of feedback.

(c/d) The above three networks can be identified from the three signal-response curves. In the network in Figure 10a, S increases the synthesis of R. When S is initially increased, R should also increase to remain at equilibrium. When there is enough R, the positive feedback causes the equilibrium point of R to jump because it is increasing its own synthesis through the phosphorylation of E. When S is decreased again, R will also decrease to remain at equilibrium. However, it does not decrease back to its initial concentration anymore because the newly present EP is sustaining the synthesis of R. This corresponds to the signal-response curve in Figure 9, which is mutual activation.

In the network in Figure 10b, S also increases the synthesis of R, but R inhibits E by phosphorylating it. Again, when R is high enough, its equilibrium point will jump because it is reducing its own degradation. However, when S is reduced, R should still return to its initial value. This is because contrary to the network in Figure 10a, there is nothing sustaining the synthesis of R. That corresponds to the signal-response curve in Figure 8, mutual inhibition.

In the network in Figure 10c, S degrades R. S has no effect on the synthesis of R, so there is no discontinuous switch that can be triggered by changing S. This behaviour corresponds to the signal-response curve in Figure 7, homeostasis, where the stable equilibrium point of R also decreases when S increases, contrary to the other two signal-response curves.

(e) R counteracts the effect of S. It does this by inhibiting E, and less E means that the synthesis of R is also slowed down. Thus, when S increases, R decays faster, which means more E, which in turn increases the synthesis of R. In this way, the decay of R is partially offset by its increased synthesis, so R^* changes very little until S gets too high and there is not enough E to counter the decay, which again reduces R^* more quickly.

Question 3:   The LAC-operon

(a) The two differential equations are given by

$$\frac{dM}{dt} = k_1 + k_2 \left(1 - \frac{1}{1 + A^n}\right) - k_3 M \qquad (11)$$

$$\frac{dA}{dt} = k_4 ML - k_5 A - V_{max}\frac{MA}{K_m + A} \qquad (12)$$

These two equations have six terms to be interpreted.

The k_1 term is the natural rate at which mRNA is produced from the regulatory gene.

The k_2 term is the maximum rate at which mRNA can be produced from the LAC-operon. It can be seen that $1 - 1/(1 + A^n)$ can be rewritten to obtain the hill function $A^n/(1 + A^n)$. Thus when very little allolactose is present the repressor is active and blocks the RNA polymerase from binding and thus stops the production of mRNA. At high concentrations of allolactose, all proteins are deactivated and RNA polymerase freely traverses the DNA and produces mRNA.

The k_3 term is the natural decay of the mRNA into proteins. As more mRNA is present, more mRNA decays into proteins, which then block the RNA polymerase from forming mRNA. This is the negative feedback loop.

The k_4 term is the production rate of allolactose. Allolactose is formed from lactose by permease. Since it is assumed that permease is proportional to mRNA, the production is written as a product between M and L. This creates a positive feedback loop. As more mRNA is present, more allolactose will be produced. The allolactose will then deactivate more repressor, which will cause more mRNA to be produced from the RNA polymerase. Which in turn will produce more allolactose again.

The k_5 term is the natural decay rate of allolactose. This is a negative feedback loop, since more allolactose would mean more decay.

The V_{max} term describes the hydrolyzation of the allolactose caused by β-galactosidase. The mRNA concentration is used instead of the β-galactosidase concentration since they are proportional to each other.

(b) The streamplots can be found in figures 11, 12, and 13 with $L = 1$, 2, and 3, respectively. Each plot also shows the nullclines of the system.

The nullclines are derived by setting equations 12 and 11 to zero, which are then rewritten such that we gather a function that is only dependent on A. First, the nullcline of A is derived. We see that

$$\frac{dA}{dt} = k_4 ML - k_5 A - V_{max}\frac{MA}{K_m + A} = 0 \qquad (13)$$

$$M\left(k_4 L - \frac{V_{max}A}{K_m + A}\right) = k_5 A \qquad (14)$$

$$M = \frac{k_5 A}{\left(k_4 L - \frac{V_{max}A}{K_m + A}\right)} \qquad (15)$$

8

Next, the nullcline of M is derived.

$$\frac{dM}{dt} = k_1 + k_2 \left(1 - \frac{1}{1 + A^n}\right) - k_3 M = 0 \tag{16}$$

$$k_3 M = k_1 + k_2 \left(1 - \frac{1}{1 + A^n}\right) \tag{17}$$

$$M = \frac{k_1 + k_2 \left(1 - \frac{1}{1+A^n}\right)}{k_3} \tag{18}$$

Figure 11: A streamplot of the lac-operon system. The system had parameters $L = 1$, $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$
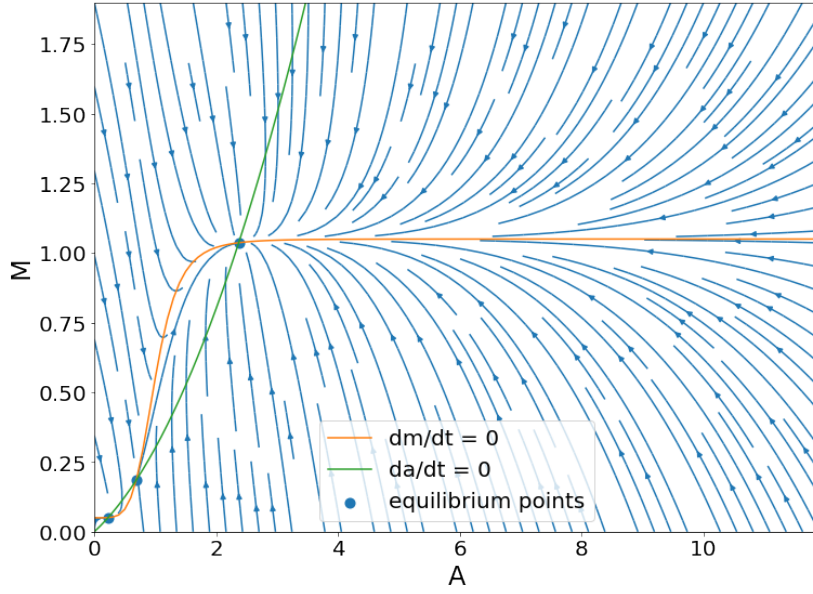
9

Figure 12: A streamplot of the lac-operon system. The system had parameters $L = 2$, $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$

Figure 13: A streamplot of the lac-operon system. The system had parameters $L = 3$, $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$
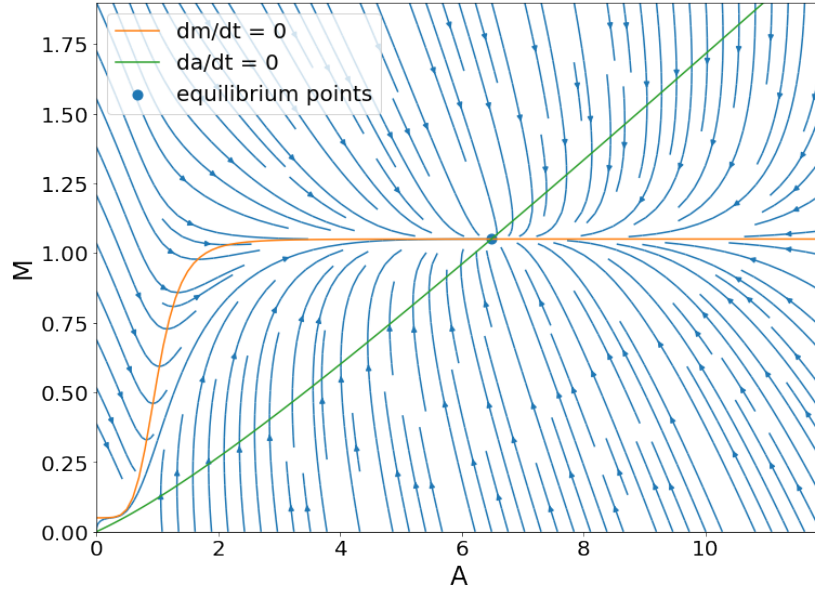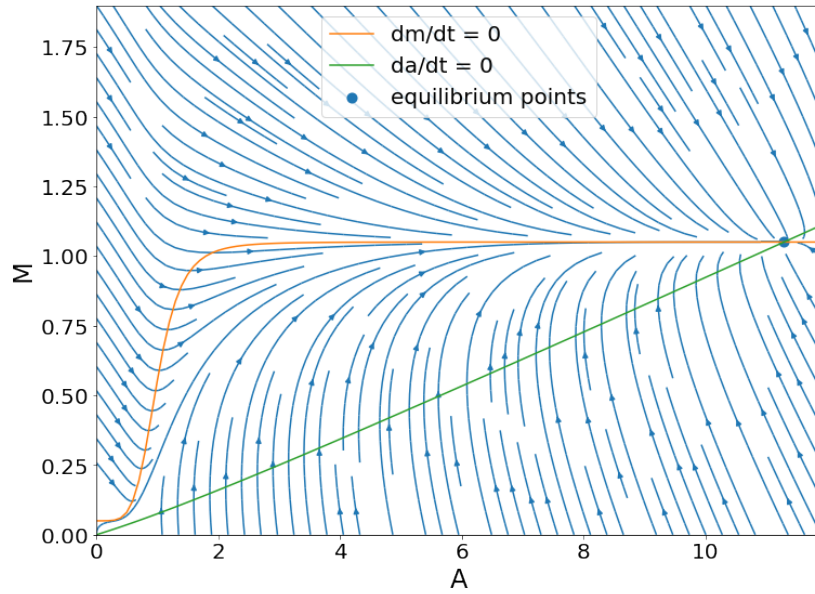
(c) The equilibrium points are obtained by numerically calculating the intersection between the two nullclines given by equations 15 and 18. This is performed by subtracting Equation 18 from Equation 15. Then at intervals, this equation is sampled. An intersect is present when the values flip signs between sample points. `scipy.optimize.root` is then used to obtain a better estimation of the intersection. An initial guess of the middle point between the sample points is used for `scipy.optimize.root`.

These equilibrium points are then identified by calculating the eigenvalues of the Jacobian matrix equated at the equilibrium points. The Jacobian matrix is given by

$$J(A, M) = \begin{pmatrix} \frac{dA/dt}{\partial A} & \frac{dA/dt}{\partial M} \\ \frac{dM/dt}{\partial A} & \frac{dM/dt}{\partial M} \end{pmatrix} \tag{19}$$

All four derivatives in the jacobi matrix are derived to be:

$$\frac{dA/dt}{\partial A} = -k_5 - V_{max} M \frac{(K_m + A) - A}{(K_m + A)^2} = -k_5 - V_{max} M \frac{K_m}{(K_m + A)^2} \tag{20}$$

$$\frac{dA/dt}{\partial M} = k_4 L - V_{max} \frac{A}{K_m + A} \tag{21}$$

$$\frac{dM/dt}{\partial A} = \frac{\partial}{\partial A} \left(-\frac{k_2}{1 + A^n} \right) = \frac{k_2 n A^{n-1}}{(1 + A^n)^2} \tag{22}$$

$$\frac{dM/dt}{\partial M} = -k_3 \tag{23}$$

The eigenvalues are then computed with `numpy.linalg.eigvals`.

The equilibrium points, eigenvalues of the Jacobian matrix, and type of equilibrium point in the case of $L = 1$, 2, and 3 is shown in tables 1, 2, and 3. These equilibrium points are dynamic equilibrium points since they reach a non-zero equilibrium point.

Equilibrium point (A, M)	Eigenvalues jacobi (λ_1, λ_2)	Equilibrium type
(0.22721, 0.05061)	(-0.20536, -1.01504)	Stable
(0.69071, 0.18585)	(0.25284, -1.50418)	Saddle
(2.37172, 1.03685)	(-0.29085, -1.01765)	Stable

Table 1: The equilibrium points and their respective characteristics. The system had parameters $L = 1$, $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$

Equilibrium point (A, M)	Eigenvalues jacobi (λ_1, λ_2)	Equilibrium type
(6.48669, 1.04991)	(-0.22905, -1.00011)	Stable

Table 2: The equilibrium points and their respective characteristics. The system had parameters $L = 2$, $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$

Equilibrium point (A, M)	Eigenvalues jacobi (λ_1, λ_2)	Equilibrium type
(11.29001, 1.04999)	(-0.21188, -1.00001)	Stable

Table 3: The equilibrium points and their respective characteristics. The system had parameters $L = 3$, $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$

(d) Figure 14 shows the time evolution of A and M over time. Initially the system starts with $A = 0.05$, $M = 0$ and $L = 1$. L is increased by 1 every period of 30. The streamplot in Figure 11 shows that the starting values are close to a stable equilibrium point (the most left point). Thus the system transitions towards this equilibrium point.

This equilibrium point vanishes once L becomes 2. Since the system is still close to the nullclines the system transitions slowly at the start. The system settles in the new equilibrium point.

When L becomes 3 the system is already on the nullcline for M. Therefore there is no change in M. The system does however need to adjust A to reach its new equilibrium point.

This system reminds of the mutual inhibition network from question 2. The system has a discontinuous switch where the equilibrium point lies much higher once a value of L is crossed. But it does not look like mutual activation, since the system can be returned to its original equilibrium state by lowering L again, as the nullclines will only have one intersection when L is low enough.
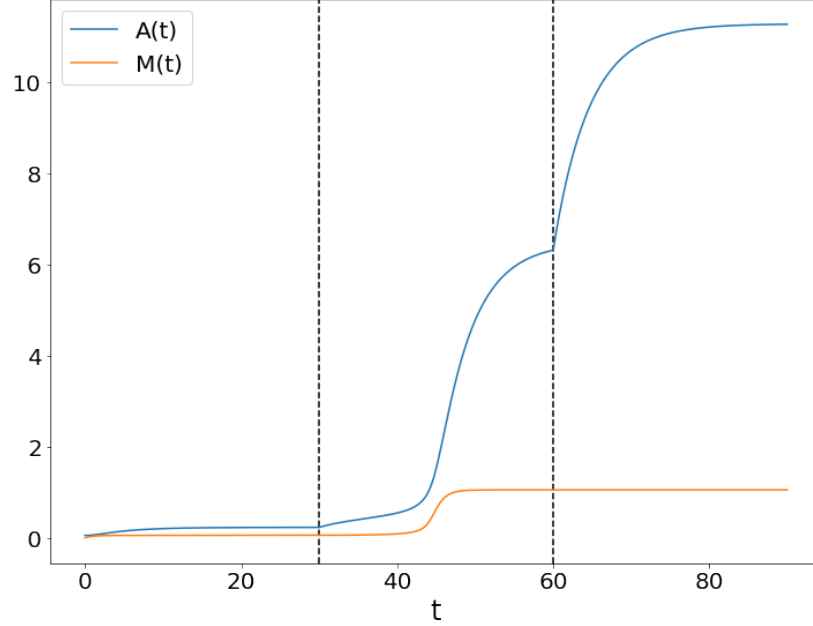
Figure 14: The time evolution of a lac-operon system. The system had parameters $V_{max} = 1$, $n = 5$, $K_m = 2$, $k_1 = 0.05$, $k_2 = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.2$ Initial parameters were $A = 0.05$, $M = 0$ and $L = 1$. L was increased by 1 every period. The vertical dashed lines show these moments.

(e) Initially, when $L = 1$, the allolactose concentrations are sufficiently low such that are able to deactivate very few proteins. Therefore mRNA can not be produced due to the RNA polymerase. mRNA, therefore, creates an equilibrium at which the production rate from the regulatory gene is balanced against the decay into the proteins.

When $L = 2$ more lactose is in the system. The production of allolactose increases. When the allolactose concentration becomes 1 it starts to overcome the hill function and is thus actively deactivating the repressor. At this moment the RNA polymerase is able to transcribe the lac genes into mRNA. This causes a rapid rise in mRNA concentration, which then causes more allolactose to be formed. This eventually reaches an equilibrium where the decay rates balance the production.

Adding even more lactose in the system, $L = 3$, causes more allolactose to be formed since there is more lactose present which can be transformed. This does however not have any significant effect on the mRNA concentrations. This is because the repressors are already de-activated. The increase in allolactose, therefore, does not cause a higher production of mRNA. That is why the mRNA concentrations remain the same when L is increased to 3.

13

Question 4:   Ionic Channels

(a) This system reaches a thermodynamic equilibrium where x and y are zero, while z equals 1. This is because of the positive constant rates. S_1 will transition to S_2. S_2 is able to transition to S_1 and S_3. S_3, however, does not have any transition. Thus once the ion channel is in S_3 it has no possibility to transition to one of the other states. Thus over time all states will transition towards S_3 and the system reaches equilibrium.

This can also be seen from the ODEs

$$\frac{dx}{dt} = k_2 y - k_1 x \tag{24}$$

$$\frac{dy}{dt} = k_1 x - (k_2 + k_3)y \tag{25}$$

$$\frac{dz}{dt} = k_3 y \tag{26}$$

z reaches an equilibrium when $dz/dt = 0$. Since $k_3 > 0$ this is only possible when $y = 0$. y can only remain zero when x is also zero. Otherwise a transition from S_1 to S_2 would happen. Therefore the ODEs also show a thermodynamic equilibrium.

(b) The streamplot of this system with $k_1 = 2$, $k_2 = 2$, and $k_3 = 1$ is shown in Figure 15. The streamplot shows that all initial configurations for x and y will evolve towards the origin. This is in line with the prediction of a), which showed that a thermodynamic equilibrium will be reached with $x = 0$ and $y = 0$.

The nullclines for x and y are derived from setting Equations 24 and 25 to 0. Thus the nullcline for dx/dt is

$$\frac{dx}{dt} = k_2 y - k_1 x = 0 \tag{27}$$

$$k_2 y = k_1 x \tag{28}$$

$$y = \frac{k_1}{k_2} x \tag{29}$$

The nullcline for dy/dt on the other hand is

$$\frac{dy}{dt} = k_1 x - (k_2 + k_3)y \tag{30}$$

$$(k_2 + k_3)y = k_1 x \tag{31}$$

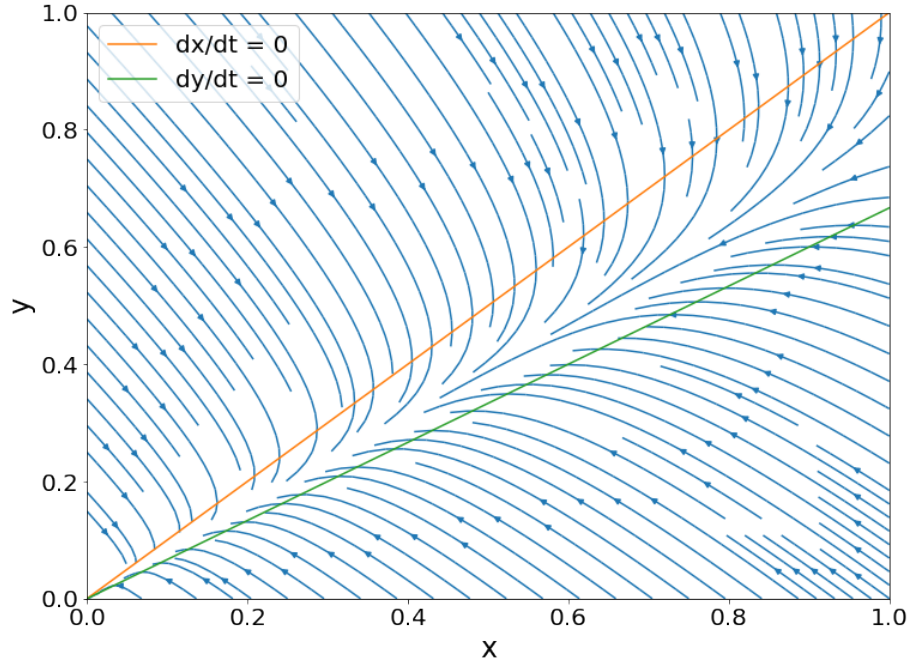$$y = \frac{k_1}{k_2 + k_3} x \tag{32}$$

14

Figure 15: A streamplot of the ionic channel system with $k_1 = 2$, $k_2 = 2$ and $k_3 = 1$. The nullclines are given by equations 29 and 32.

(c) The fractions x, y and z are plotted for the initial values $\{x_0, y_0, z_0\} = \{1, 0, 0\}$ and $\{x_0, y_0, z_0\} = \{0, 1, 0\}$ over time in the figure below.
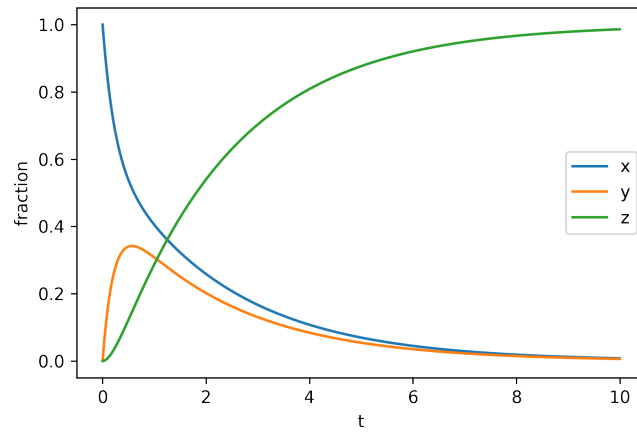

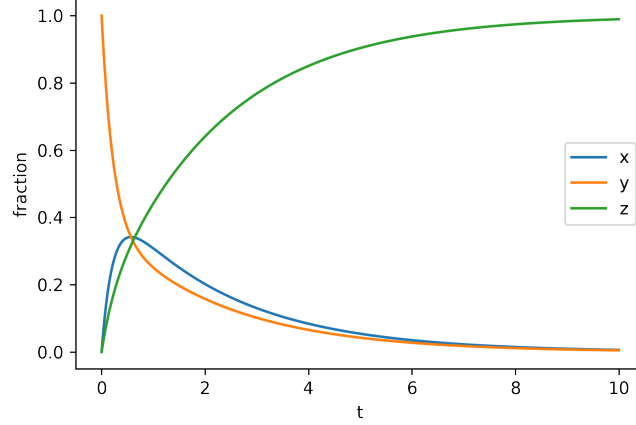Figure 16: Initial values $\{x_0, y_0, z_0\} = \{1, 0, 0\}$.

Figure 17: Initial values $\{x_0, y_0, z_0\} = \{0, 1, 0\}$.

As predicted, for both sets of initial values the system goes to the equilibrium $x = 0, y = 0, z = 1$. Also, the peaks of $\frac{dy}{dt}$ and $\frac{dx}{dt}$, as shown in Figure 16 and 17 respectively, match the positions on the nullclines in the streamplot and thus happen when $y = \frac{k_1}{k_2+k_3}x = \frac{2}{3}x$ and $y = \frac{k_1}{k_2}x = x$.

(d) $k_1 = 0$ prevents the state transition from S_1 to S_2. Therefore the only transitions which are possible are from S_2 to the other two. On a molecular level this means that only open channels are able to transition to a closed channel. Once a channel is closed it will remain closed. This would eventually lead to the stoppage of ion transportation over a membrane.

(e) Setting $k_1 = 0$ yields the equations

$$\frac{dx}{dt} = k_2y - 0 * x = k_2y \tag{33}$$

$$\frac{dy}{dt} = 0 * x - (k_2 + k_3)y = -(k_2 + k_3)y \tag{34}$$

$$\frac{dz}{dt} = k_3y \tag{35}$$

All three rates now only depend on y. When $y = 0$, the system is in equilibrium, regardless of x and z.

The expected behaviour is that x and z increase while y is not zero, and y will always eventually go to zero - which will in turn stop x and z from increasing.

(f) The fractions x, y and z are plotted for the initial values $\{x_0, y_0, z_0\} = \{0, 1, 0\}$ and $\{k_2, k_3\} = \{2, 1\}$ over time in the figure below.

16
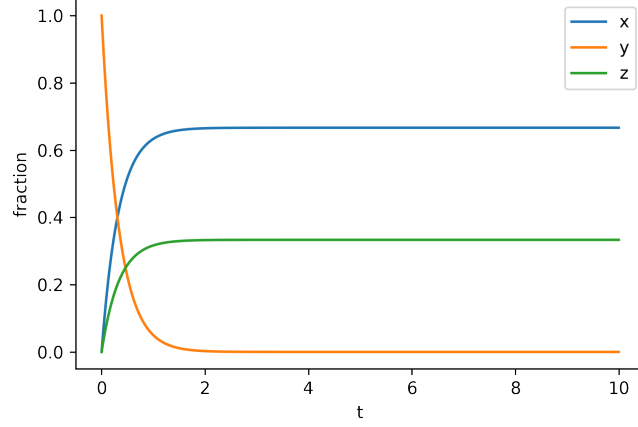
As expected, y goes to zero while x and z increase before also staying constant.

(g) When $t \to \infty$, y goes to zero. Thus, as can be seen from the ODEs, x and z then remain constant and the system reaches equilibrium and the fractions are then not time dependent. Thus, the equilibrium points can be written as constants defined by

$$\lim_{t \to \infty} \{x(t), y(t), z(t)\} = \{x^*, y^*, z^*\}. \tag{36}$$

(h)

$$y(t) = e^{-(k_2 + k_3)t} \tag{37}$$

The equilibrium point for y is reached in the case where t approaches ∞. Thus we take the limit of $y(t)$ as t approaches ∞.

$$y^* = \lim_{t \to \infty} y(t) = \lim_{t \to \infty} e^{-(k_2 + k_3)t} = e^{-\infty} = 0 \tag{38}$$

(i) The equilibrium point x^* can be derived as follows.

$$\frac{dx}{dt} = k_2 y$$

$$dx = k_2 y(t) dt$$

$$\int_{x(0)=0}^{x^*} dx = k_2 \int_0^\infty y(t) dt$$

$$x^* - 0 = k_2 * -\frac{1}{k_2 + k_3} [y(t)]_0^\infty$$

$$x^* = -\frac{k_2}{k_2 + k_3} * (y(\infty) - y(0))$$ (39)

$$= -\frac{k_2}{k_2 + k_3} * (y^* - e^0)$$

$$= -\frac{k_2}{k_2 + k_3} * (0 - 1)$$

$$= \frac{k_2}{k_2 + k_3}.$$

The equilibrium point z^* can be derived as follows.

$$\frac{dz}{dt} = k_3 y$$

$$dz = k_3 y(t) dt$$

$$\int_{z(0)=0}^{z^*} dz = k_3 \int_0^\infty y(t) dt$$

$$z^* - 0 = k_3 * -\frac{1}{k_2 + k_3} [y(t)]_0^\infty$$

$$z^* = -\frac{k_3}{k_2 + k_3} * (y(\infty) - y(0))$$ (40)

$$= -\frac{k_3}{k_2 + k_3} * (y^* - e^0)$$

$$= -\frac{k_3}{k_2 + k_3} * (0 - 1)$$

$$= \frac{k_3}{k_2 + k_3}.$$

(j) Filling in $\{k_2, k_3\} = \{2, 1\}$ yields $x^* = \frac{2}{3}$ and $z^* = \frac{1}{3}$. In the graph from (f), the final value of x is 0.6666666667337748 while the final value of z is 0.3333333333668874. This indeed matches the theoretical prediction.