1. 1. In a biological system with feedback control, $u_1, u_2, , u_n$ are the n population sizes which are governed by

$$\frac{du_1}{dt} = f(u_n) - k_1 u_1, \tag{1}$$

$$\frac{du_j}{dt} = u_{j-1} - k_j u_j, j = 2, 3, \ldots, n; \tag{2}$$

in which the functional form for the feedback regulation of the nth species on the 1st species is given as

$$(i) f(u) = \frac{a + u^m}{1 + u^m}, \quad (ii) f(u) = \frac{1}{1 + u^m}, \tag{3}$$

where constants $a, m > 0$.

(a) Determine which of these represents a positive feedback control and which a negative feedback control.

Positive feedback is when $f'(u) > 0$ Negative feedback is when $f'(u) < 0$
Quotient rule: $\frac{d}{dt}\frac{u}{v} = \frac{vu' - uv'}{v^2}$
(i)
$\frac{d}{du}f(u) = \frac{(mu^{m-1})(1+u^m)-(a+u^m)(mu^{m-1})}{(1+u^m)^2} \longrightarrow \frac{df(u)}{du} = \frac{mu^{m-1}(1+u^m-a-u^m)}{(1+u^m)^2} \longrightarrow \frac{df(u)}{du} = \frac{mu^{m-1}(1-a)}{(1+u^m)^2}$
For (i) :
$\frac{df(u)}{du} < 0$ (i) is negative feedback when $a > 1$
$\frac{df(u)}{du} > 0$ (i) is positive feedback when $a < 1$
(ii)
$\frac{d}{du}f(u) = \frac{(0)(1+u^m)-(1)(mu^{m-1})}{(1+u^m)^2} \longrightarrow \frac{df(u)}{du} = \frac{-mu^{m-1}}{(1+u^m)^2}$ Always negative $\frac{df(u)}{dt} = \frac{-mu^{m-1}}{(1+u^m)^2} < 0$
For (ii) it is always negative feedback as the derivative is always negative.

(b) Determine the steady states and show that with positive feedback multi-stability is possible while if $f(u)$ represents negative feedback there is only a unique steady state.

Steady state occurs at equilibrium when both derivatives are equal to zero.

In the case of negative feedback, $f(u_n)$ is a strictly decreasing u function. The function starts at 1 at $t = 0$ and approaches 0 at $t \to \infty$, This means that the function crosses the linear function $k_n u_n$ only once, at that intersection there is the only one steady state point. The function $f(u) - k_1 u$ will only equal zero once, since this is a monotonic decreasing function subtracting a positive linear function. Therfore for a negative feedback there is only one possible equilibrium. This means there is only one unique steady state possible for negative feedback $f(u)$.

In the case of positive feedback, $f(u_n)$ is a strictly increasing u function. The Function starts at a at t_0 and approaches 1 as $t \to \infty$, This means that the function crosses $k_n u_n$ only once and thus only one fixed point in the above scenario.

However, Multistablity is possible for positive feedback if the $f(u)$ has a sigmoidal form, cubic, or higher order polynomial form. There would be regions where the slope is greater or less than k_1. This allows the function to cross the line k_1 u at multiple points, creating multiple steady states. For example if there are three steady states there would be two stable and one unstable steady states.

Trying to solve for exact solutions for Equilibrium leads to expressions with no available solutions

$\frac{du_j}{dt} = u_{j-1} - k_j u_j = 0 \to u_{j-1} = k_j u_j \to u_j = \frac{u_{j-1}}{k_j} \to u_j = \frac{u_{j-2}}{k_j k_{j-1}} \to u_j = \frac{u_{j-2}}{k_j k_{j-1}} = \frac{u_{j-3}}{k_j k_{j-1} k_{j-2}} = \cdots = \frac{u_1}{k_j k_{j-1} \ldots k_3 k_2}$ $A = k_j k_{j-1} \ldots k_3 k_2 \to u_j = \frac{u_1}{A}$

$u_j = \frac{u_1}{A}$

(ii)

$\frac{du_1}{dt} = f(u_n) - k_1 u_1 \to \frac{du_1}{dt} = \frac{1}{1+u_n^m} - k_1 A u_n = 0$

$K = k_1 A$

$\frac{1}{1+u_n^m} - K u_n = 0 \to \frac{1}{1+u_n^m} = K u_n \to 1 = K u_n (1 + u_n^m) \to 0 = K u_n (1 + u_n^m) - 1 \to$

$0 = u_n + u_n u_n^m - \frac{1}{K} \to$

$0 = u_n^{m+1} + u_n - \frac{1}{K}, \quad K > 0, m > 0.$

m+1 polynomial with no exact solution available.

(i)

$\frac{du_1}{dt} = f(u_n) - k_1 u_1 \to \frac{du_1}{dt} = \frac{a+u_n^m}{1+u_n^m} - k_1 A u_n = 0, K = k_1 A$

$\frac{a+u_n^m}{1+u_n^m} - K u_n = 0 \to \frac{a+u_n^m}{1+u_n^m} = K u_n \to a + u_n^m = K u_n (1 + u_n^m) \to 0 = K u_n (1 + u_n^m) - (a + u^m) \to$

$0 = K u_n + K u_n u_n^m - a - u_n^m \to 0 = K u_n u_n^m - u_n^m + K u_n - a \to$

$0 = K u_n^{m+1} - u_n^m + K u_n - a, \quad K > 0, m > 0, a > 0.$

m+1 polynomial with no exact solution available.

2. Consider the system of nonlinear chemical reaction

$$A \xrightarrow{k_1} B,\ B + X \xrightarrow{k_2} Y,\ 2X + Y \xrightarrow{k_3} 3X,\ X \xrightarrow{k_4} C, \tag{4}$$

where ks are the rate constants, and the reactant concentrations of chemical species A and B are kept at constant values of a and b, respectively, for all time.

(a) Write the governing differential equation system, according to the law of mass action, for the concentrations of X and Y ; nondimensionalize the equation so that they becomes

$$\frac{du}{d\tau} = 1 - (\beta + 1)u + \alpha u^2 v,\ \frac{dv}{d\tau} = \beta u - \alpha u^2 v, \tag{5}$$

in which u and v are the corresponding variables for the concentrations of X and Y, $\tau = k_4 t, \alpha = (k_1 a)^2 k_3 / k_4^3$ and $\beta = k_2 b / k_4$.

$\frac{dX}{dt} = +k_1 A - k_2 BX + k_3 X^2 Y - k_4 X$
$\frac{dY}{dt} = +k_2 BX - k_3 X^2 Y$
$\tau = k_4 t \longrightarrow d\tau = k_4 dt \longrightarrow \frac{dt}{d\tau} = \frac{1}{k_4}$
Multiple both sides of $\frac{dY}{dt}$ by $\frac{dt}{d\tau}$
$\frac{dY}{dt}\frac{dt}{d\tau} = \left(k_2 BX - k_3 X^2 Y\right)\frac{dt}{d\tau} \longrightarrow \frac{dY}{d\tau} = \left(k_2 BX - k_3 X^2 Y\right)\frac{1}{k_4} \longrightarrow \frac{dY}{d\tau} = \frac{k_2}{k_4} BX - \frac{k_3}{k_4} X^2 Y$
With $\beta = k_2 b / k_4 \longrightarrow \frac{dY}{d\tau} = \beta X - \frac{k_3}{k_4} X^2 Y$
$Y = C_1 v \longrightarrow dY = C_1 dv \longrightarrow \frac{dv}{dY} = \frac{1}{C_1}$
Multiple both sides of $\frac{dY}{d\tau}$ by $\frac{dv}{dY}$ to find C_1
$\frac{dY}{d\tau}\frac{dv}{dY} = \left(\beta X - \frac{k_3}{k_4} X^2 Y\right)\frac{dv}{dY} \longrightarrow \frac{dv}{d\tau} = \left(\beta X - \frac{k_3}{k_4} X^2 Y\right)\frac{1}{C_1} \longrightarrow \frac{dv}{d\tau} = \frac{\beta}{C_1} X - \frac{k_3}{k_4 C_1} X^2 Y$
Separate into the form I want it to become:
$\frac{\beta}{C_1} X = \beta u \longrightarrow \frac{1}{C_1} X = u \longrightarrow X = C_1 u$
I know from the given equation the nondimensionalization will turn it into this one.
$\frac{k_3}{k_4 C_1} X^2 Y = \alpha u^2 v$
Plug in α, u, v
$\alpha = \frac{(k_1 a)^2 k_3}{k_4^3}, \frac{1}{C_1} Y = v, \frac{1}{C_1} X = u$
$\frac{k_3}{k_4 C_1} X^2 Y = \left(\frac{(k_1 a)^2 k_3}{k_4^3}\right)(\frac{1}{C_1} X)^2 (\frac{1}{C_1} Y)$
Solve for C_1 and cancel similar terms
$X^2 Y = \left(\frac{k_1^2 a^2}{k_4^2}\right)\frac{1}{C_1^2} X^2 Y \longrightarrow 1 = \frac{k_1^2 a^2}{k_4^2}\frac{1}{C_1^2} \longrightarrow C_1^2 = \frac{k_1^2 a^2}{k_4^2} \longrightarrow C_1 = \pm\frac{k_1 a}{k_4} \longrightarrow C_1 = \frac{k_1 a}{k_4}$

$\boxed{u = \frac{k_4}{k_1 a} X}$ $\boxed{v = \frac{k_4}{k_1 a} Y}$ $\boxed{\alpha = \frac{(k_1 a)^2 k_3}{k_4^3}}$ $\boxed{\beta = \frac{k_2 b}{k_4}}$ $\boxed{\tau = k_4 t}$

(b) Determine the positive steady state and show that there is a bifurcation value $\beta_c = 1 + \alpha$ at which the steady state becomes unstable in a Hopf bifurcation way.

Positive steady state when both derivatives equal zero.
$\frac{du}{dt} = 1 - (\beta+1)u + \alpha u^2 v = 0$
$\frac{dv}{dt} = \beta u - \alpha u^2 v = 0$
$\beta u - \alpha u^2 v = 0 \to \beta u = \alpha u^2 v \to \beta = \alpha u v \to v = \frac{\beta}{\alpha u}$
$1 - (\beta+1)u + \alpha u^2 v = 0 \to 1 - (\beta+1)u + \alpha u^2(\frac{\beta}{\alpha u}) = 0 \to 1 - (\beta+1)u + u\beta = 0 \to 1 - \beta u + u + u\beta = 0 \to 1 - u = 0 \to u = 1$
Steady state at $(1, \frac{\beta}{\alpha})$
Compute Jacobian Matrix
$\begin{pmatrix} \frac{df}{du} & \frac{df}{dv} \\ \frac{dg}{du} & \frac{dg}{dv} \end{pmatrix} \to \begin{pmatrix} -\beta - 1 + 2\alpha u v & +\alpha u^2 \\ \beta - 2\alpha u v & -\alpha u^2 \end{pmatrix}$ Evaluate at $(1, \frac{\beta}{\alpha})$
$\begin{pmatrix} -\beta - 1 + 2\alpha(1)(\frac{\beta}{\alpha}) & +\alpha(1)^2 \\ \beta - 2\alpha(1)\frac{\beta}{\alpha} & -\alpha(1)^2 \end{pmatrix} \to \begin{pmatrix} -\beta - 1 + 2\beta & +\alpha \\ \beta - 2\beta & -\alpha \end{pmatrix} \to \begin{pmatrix} \beta - 1 & +\alpha \\ -\beta & -\alpha \end{pmatrix}$
Plug in $\beta_c = \alpha + 1$
$\begin{pmatrix} (\alpha+1) - 1 & +\alpha \\ -(\alpha+1) & -\alpha \end{pmatrix} \to \begin{pmatrix} \alpha & +\alpha \\ -\alpha - 1 & -\alpha \end{pmatrix}$
Characteristic Polynomial for $\beta_c = \alpha + 1$:
$(\alpha - \lambda)(-\alpha - \lambda) - (\alpha)(-\alpha - 1) = 0 \to -\alpha^2 - \alpha\lambda + \lambda\alpha + \lambda^2 + \alpha^2 + \alpha = 0 \to \lambda^2 + \alpha = 0 \to \lambda^2 = -\alpha \to \lambda = \sqrt{-\alpha} \to \lambda = \pm i\sqrt{\alpha}, \quad a > 0$
Two imaginary eigenvalues. This corresponds to a solution of center point with spirals at the bifurcation point.
Characteristic Polynomial for β:
$(\beta - 1 - \lambda)(-\alpha - \lambda) - (\alpha)(-\beta) = 0 \to -\beta\alpha - \beta\lambda + \alpha + \lambda + \lambda\alpha + \lambda^2 + \beta\alpha = 0 \to \lambda^2 - \beta\lambda + \lambda\alpha + \lambda + \alpha = 0 \to \lambda^2 + (1 - \beta + \alpha)\lambda + \alpha = 0$
When $\beta = \beta_c = \alpha + 1$
$\lambda^2 + (1 - (\alpha+1) + \alpha)\lambda + \alpha = 0 \to \lambda = \pm i\sqrt{\alpha}$
This is the bifurcation value, where the dynamical system switches from a stable equilibrium to an oscillatory equilibrium.
When $\beta > \beta_c = \alpha + 1$
$\lambda^2 + (1 - \beta + \alpha)\lambda + \alpha = 0$
The b term is now negative. Meaning there are two real negative solutions. Meaning the solution has two stable solutions.
When $\beta < \beta_c = \alpha + 1$
$\lambda^2 + (1 - \beta + \alpha)\lambda + \alpha = 0$
The b term becomes positive. Meaning there are now two imaginary solutions. Meaning the solution oscillates.
This is characteristic of a hopf bifurcation, where at the point two real stable solutions turn into two oscillatory solutions.

(c) Show that in the vincinty of $\beta = \beta_c$, the limit cycle has a period of $2\pi\sqrt{\alpha}$

The period is proportional is its angular velocity. The angular velocity for this is equal to the equivalent to the imaginary part of the eigenvalues.
Period $= \frac{2\pi}{\text{Imaginay}(\lambda)} \to$ Period $= \frac{2\pi}{\sqrt{\alpha}} \to \boxed{\text{Period} = 2\pi\sqrt{\alpha}}$

3. The 3-state Markov system

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A \tag{6}$$

has been widely used in biochemistry to model the conformational changes of a single protein undergoing though its three different states A, B, and C. For example, A is nonactive, B is partially active, and C is fully active.

(a) The probabilities for the states, $\vec{p} = (p_A, p_B, p_C)$ satisfies a differential equation

$$\frac{d}{dt}\vec{p}(t) = \vec{p}(t)Q \tag{7}$$

where Q is a 3×3 matrix. (See Sec. 6.2.5.1 of Qian's book chapter Mathematicothermodynamics.) Write the Q out in terms of the k's. Show that the sum of each and every row is zero. Discuss in probabilistic terms, what is the meaning of this result?

$$Q = \begin{pmatrix} (-k_{-1} - k_{-3}) & k_1 & k_{-3} \\ k_{-1} & (-k_{-1} - k_2) & k_2 \\ k_3 & k_{-2} & (-k_3 - k_{-2}) \end{pmatrix}$$

The rows sum to zero because in a continuous-time Markov chain, this generator matrices Q, describes transition rates, not the probabilities of being in a spot, and as such the rows must sum to zero to properly model how probability flows between states over time.

(b) Compute the steady state probabilities $p_A^{ss}, p_B^{ss}, p_C^{ss}$ and show that, in the steady state, the net (probabilistic) flux from state A to B,

$$J^{ss}_{A \to B} = k_1 p_A^{SS} - k_{-1} p_B^{SS} \tag{8}$$

is the same as the net flux from state $B \longrightarrow$ state C, and also the net flux from $C \longrightarrow A$. Since they are all the same, it is called the steady state flux J^{ss} of the biochemical reaction cycle in (1).

1. Compute the steady state probabilities:
Total probability must sum to one, so $p_A^{ss} + p_B^{ss} + p_C^{ss} = 1$.
Steady state flux in this situation means the rate of formation of B is the same as the rate of destruction of A. The system is a loop.
The steady state equations are:
$k_{-1}p_B^{ss} + k_3 p_C^{ss} = k_1 p_A^{ss} + k_{-3} p_A^{ss}$
$k_1 p_A^{ss} + k_{-2} p_C^{ss} = k_{-1} p_B^{ss} + k_2 p_B^{ss}$
$k_2 p_B^{ss} + k_{-3} p_A^{ss} = k_{-2} p_C^{ss} + k_3 p_C^{ss}$

Under the assumption of a completely looped cycle, where all transitions are equally probable, the steady-state probabilities must be equal. Therefore the probability of being at A, B, or C, must all be equivalent.
$\boxed{p_A^{ss} = p_B^{ss} = p_C^{ss} = \frac{1}{3}}$.

2. The net probabilistic flux from state A to B
The net flux is the rate times the probability of amount of A or B. $J^{ss}_{A\to B} = k_1 p^{ss}_A - k_{-1} p^{ss}_B$
Using the steady state equations.
$k_{-1}p^{ss}_B + k_3 p^{ss}_C = k_1 p^{ss}_A + k_{-3} p^{ss}_A \longrightarrow k_3 p^{ss}_C - k_{-3} p^{ss}_A = k_1 p^{ss}_A - k_{-1} p^{ss}_B$
The flux from state A to state B in steady state when the rate of formation is equivalent to the rate of destruction is equivalent to the flux from state C to state A.
$J^{ss}_{A\to B} = k_1 p^{ss}_A - k_{-1} p^{ss}_B = k_3 p^{ss}_C - k_{-3} p^{ss}_A$
$J^{ss}_{C\to A} = k_3 p^{ss}_C - k_{-3} p^{ss}_A = k_1 p^{ss}_A - k_{-1} p^{ss}_B = J^{ss}_{A\to B}$
$k_2 p^{ss}_B + k_{-3} p^{ss}_A = k_{-2} p^{ss}_C + k_3 p^{ss}_C \longrightarrow J^{ss}_{B\to C} = k_2 p^{ss}_B - k_{-2} p^{ss}_C = k_3 p^{ss}_C - k_{-3} p^{ss}_A = J^{ss}_{C\to A}$
The flux from state B to state C is equivalent to state C to state A.
$\boxed{J^{ss} = J^{ss}_{A\to B} = J^{ss}_{B\to C} = J^{ss}_{C\to A}}$

(c) What is the condition, in terms of all the k's, for $J^{ss} = 0$?

The condition for the net flux to be equal to zero, this has the individual fluxes equal to zero.
$J^{ss} = J^{ss}_{A\to B} + J^{ss}_{B\to C} + J^{ss}_{C\to A}$
The fluxes in steady state can be defined as:
$J^{ss}_{A\to B} = k_1 p^{SS}_A - k_{-1} p^{SS}_B$, $J^{ss}_{B\to C} = k_2 p^{SS}_B - k_{-2} p^{SS}_C$, $J^{ss}_{C\to A} = k_3 p^{SS}_C - k_{-3} p^{SS}_A$
$p^{ss}_A = p^{ss}_B = p^{ss}_C = \frac{1}{3}$.

$J^{ss}_{A\to B} = 0 = k_1 p^{SS}_A - k_{-1} p^{SS}_B \longrightarrow J^{ss}_{A\to B} = 0 = k_1 \frac{1}{3} - k_{-1} \frac{1}{3} \longrightarrow k_1 - k_{-1} = 0 \longrightarrow k_1 = k_{-1}$
$J^{ss}_{B\to C} = 0 = k_2 p^{SS}_B - k_{-2} p^{SS}_C \longrightarrow J^{ss}_{B\to C} = 0 = k_2 \frac{1}{3} - k_{-2} \frac{1}{3} \longrightarrow k_2 - k_{-2} = 0 \longrightarrow k_2 = k_{-2}$
$J^{ss}_{C\to A} = 0 = k_3 p^{SS}_C - k_{-3} p^{SS}_A \longrightarrow J^{ss}_{C\to A} = 0 = k_3 \frac{1}{3} - k_{-3} \frac{1}{3} \longrightarrow k_3 - k_{-3} = 0 \longrightarrow k_3 = k_{-3}$
$\boxed{k_1 = k_{-1}}$ $\boxed{k_2 = k_{-2}}$ $\boxed{k_3 = k_{-3}}$
The condition for $J^{ss} = 0$ is for the forward reactions to be equal to the rate of the corresponding reverse reaction. This means the system must be in equilibrium for the system to have a net flux of zero.