Homework # 4

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

$$\frac{\mathrm{d}u_1}{\mathrm{d}t} = f(u_n) - k_1 u_1,$$
$$\frac{\mathrm{d}u_j}{\mathrm{d}t} = u_{j-1} - k_j u_j, j = 2, 3, \cdots, n;$$

in which the functional form for the feedback regulation of the n^{th} species on the 1^{st} species is given as

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

where constants $a, m > 0$.

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

(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.

2. Consider the system of nonlinear chemical reaction

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

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

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

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 $\beta = k_2 b / k_4$.

(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.

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

3. The 3-state Markov system,

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

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 non-active, 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

$$\frac{\mathrm{d}}{\mathrm{d}t}\vec{p}(t) = \vec{p}(t)\mathbf{Q},$$

where $\mathbf{Q}$ is a 3×3 matrix. (See Sec. 6.2.5.1 of Qian's book chapter ***Mathematicothermodynamics***.) Write the $\mathbf{Q}$ 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?

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

$$J_{A\to B}^{ss} = k_1 p_A^{ss} - k_{-1} p_B^{ss},$$

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

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

Additional Problems for AMATH 523

4. Consider the reaction system with two biochemical species X and Y which degrade linearly, with rate constants b and d respectively, and X actives the synthesis of Y and Y actives the synthesis of X according to

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \frac{ay^2}{k^2 + y^2} - bx,$$
$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = \frac{cx^2}{h^2 + x^2} - dy,$$

where $x(t)$, $y(t)$ are the concentrations of X, Y at time t, and a, b, c, d, k and h are positive constants. Nondimensionalize the system to reduce the relevant number of parameters. Show that there can be two or zero positive steady states. [Hint: You might need to use Descartes' rule of signs, which can be found from online wikipedia.]

Studying simple mathematical models like this was an active area of biological research. For examples see

`https://doi.org/10.1103/PhysRevLett.84.5447`
`https://doi.org/10.1073/pnas.110057697`