Introduction to Mathematical Biology
Exercises 10.1-10.5

10.1. *Migration into a black hole.* Consider a population that would grow according to the logistic model if all individuals stayed in the favourable habitat. Some individuals, however, migrate to an unfavourable habitat where reproduction is not possible, and death occurs at rate μ. Migration occurs at rate m in both directions. With N_1 and N_2 denoting population size in the favourable and in the unfavourable habitat, respectively, these assumptions lead to the model

$$\begin{aligned} \frac{dN_1}{dt} &= rN_1(1-cN_1) - mN_1 + mN_2 \\ \frac{dN_2}{dt} &= -\mu N_2 - mN_2 + mN_1 \end{aligned}$$

where r and c are the parameters of logistic growth (the carrying capacity is $K = 1/c$). Find the conditions under which the extinction equilibrium $(N_1, N_2) = (0, 0)$ is unstable. If these conditions are met, the population is said to be viable.

10.2. *Discrete structure in continuous time.* A population of frogs consists of tadpoles (juveniles, density N_1) and adult frogs (N_2). Adults produce juveniles at a *per capita* birth rate $b(N_2) = [b_0 - cN_2]_+$ (where $[x]_+ = \max(x, 0)$, cf. the birth rate cannot be negative). The birth rate depends only on the density of the adults themselves because the juveniles live in a different habitat and therefore use other resources than the adults. The juveniles die at a constant mortality rate μ_1 and mature (become adult) at a constant rate γ. The adults die at a constant rate μ_2. These assumptions lead to the model

$$\begin{aligned} \frac{dN_1}{dt} &= b(N_2)N_2 - \mu_1 N_1 - \gamma N_1 \\ \frac{dN_2}{dt} &= \gamma N_1 - \mu_2 N_2 \end{aligned}$$

(a) Calculate R_0 in a virgin environment and derive the condition for viability. *Hint:* use results from the first set of homework exercises.
(b) Calculate the population vector at equilibrium.
(c) Establish whether the equilibrium is stable.

10.3. *Chemostat dynamics.* Here we revisit the dynamics of the chemostat already considered in exercise 4.1 (see details there). Recall that the concentrations of bacteria (x) and of the nutrient (c) change in the chemostat according to the differential equations

$$\begin{aligned} \frac{dx}{dt} &= r(c)x - fx \\ \frac{dc}{dt} &= -kr(c)x - f(c - c_0) \end{aligned}$$

where $f = F/V$, with F being the inflow of a nutrient solution of concentration c_0 as well as the outflow of the chemostat content and V the volume of the chemostat. r is a strictly increasing function that describes the growth rate of the bacteria as a function of the nutrient concentration, and k is the number of nutrient particles necessary to make a new bacterium. Prove that the positive equilibrium of this system, when it exists, is always a stable node.

10.4. *Bacterial growth limited by the accumulation of a toxin.* Suppose that a population of bacteria would grow exponentially at a rate $r > 0$, but the bacteria produce a toxin at a per capita rate p, and the toxin kills the bacteria proportionally to its concentration T leading to a *per capita* death rate cT . The toxin decays at a constant rate α. The population density of the bacteria (N) and the concentration of the toxin (T) thus obey the differential equations

$$\begin{aligned} \frac{dN}{dt} &= rN - cTN \\ \frac{dT}{dt} &= pN - \alpha T \end{aligned}$$

(a) Show that this model has a single nontrivial equilibrium, which is always stable when it is positive.
(b) Investigate when the nontrivial equilibrium is a stable node and when it is a stable focus. Interpret the result biologically: do oscillations occur when the toxin decays fast or when it decays slowly? Can you explain why?
(c) Suppose now that the production and the decay of the toxin is much faster than the population growth of the bacteria, i.e., p and α are large compared to r and cT. Show that in this case, the bacteria follow logistic population growth, and derive the carrying capacity.

10.5. *A genetic switch.* Each cell of a multicellular organism contains the same set of genes, but not all genes are active in all cells: Cells in different tissues or organs are different because they express different sets of genes. During embryonic development, sets of genes thus need to be switched on or off. This switching is done by so-called transcription factors, proteins that bind to DNA and either activate or repress a set of genes. The question is, of course, what regulates the production of transcription factors and how can

the cell achieve alternative stable equilibria such that it either expresses one set of genes or another.

In a model of a simple genetic switch, consider two transcription factors U and V. The two transcription factors belong to two different sets of genes under separate regulating DNA sequences R_U and R_V, respectively. Both transcription factors can bind to both regulating sequences, but with different results: When U binds to R_U, the DNA where U itself is coded, then it activates the set of genes which, among other things, produce U. When V binds to R_U, then it does not activate and moreover it prevents U binding (simply takes away the binding place, which is called "competitive inhibition"). The roles are reversed for the set of genes that include the gene for V: R_V is activated by binding V and not activated by binding U. Only activated genes work and produce the corresponding proteins, including the transcription factors U and V themselves, at constant rates. The transcription factors decay at a constant rate. Binding the transcription factors U and V to R_U and R_V and releasing them happen much faster than the production and decay of U and V.

(a) Let us first investigate the fast reactions involved in the genetic switch. Binding and releasing the transcription factors U and V to and from the regulating sequence R_U happen according to the chemical reaction

$$R_U + U \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_U U$$

$$R_U + V \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_U V$$

and, analogously, the same reactions involving the regulating sequence R_V are

$$R_V + U \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_V U$$

$$R_V + V \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_V V$$

Notice that, for simplicity, we have made the assumption that R_V binds its own activating factor V at the same rate k_1 at which R_U binds U; and so forth, each pair of analogous reactions has the same rate for the two regulating sequences. This need not be so in reality, but nevertheless this simplified model will serve as a useful illustration of the processes underlying a genetic switch.

Denote the concentrations of U and V respectively by u and v; on the fast time scale, we consider these concentrations to be constants. Binding and releasing U and V does in fact change the number of free molecules of U and V, but since U and V are present in relatively large numbers whereas each cell has only one copy of R_U and one copy of R_V, the change of u and v from binding or releasing a single molecule is negligible.

Let x denote the probability that (or fraction of time while) R_U binds U and is therefore active; and let y denote the probability R_U that binds V. With probability $1-x-y$, the regulating sequence is free and is available for binding either U or V. Construct differential equations to describe the dynamics of x and y, and determine their quasi-equilibrium values for given u and v. Verify that this quasi-equilibrium is stable. Next, let p and q denote the probabilities that R_V binds U and that it binds V, respectively. Determine the quasi-equilibrium of p and q as well.

(b) Let us now turn to the slow time scale of the genetic switch. Asseme that R_U and R_V, when active, produce respectively U and V at the same constant rate a. Construct differential equations for the change of u and v using the quasi-equilibria obtained above, and verify thereby that the slow dynamics can be written in the form

$$\begin{aligned} \frac{du}{dt} &= \frac{\phi u}{1+\alpha u+\beta v} - \mu u \\ \frac{dv}{dt} &= \frac{\phi v}{1+\beta u+\alpha v} - \mu v \end{aligned}$$

where μ is the rate of decay (for simplicity, assumed to be the same for U and V) and ϕ, α and β are parameters derived from the binding rates and from a. Find all biologically relevant equilibria of the slow system and establish their stability. Under which condition does this system have multiple stable equilibria, i.e., when can it function as a genetic switch?