INTRODUCTION TO MATHEMATICAL BIOLOGY

HOMEWORK SOLUTIONS

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Exercise 4.1

(a) The reactions are described by the following equations

$$\begin{aligned}
\frac{ds_1}{dt} &= -k_1 e s_1 + k_{-1} x_1 \\
\frac{ds_2}{dt} &= -k_2 x_1 s_2 + k_{-2} x_2 \\
\frac{dx_1}{dt} &= +k_1 e s_1 - k_{-1} x_1 - k_2 x_1 s_2 + k_{-2} x_2 \\
\frac{dx_2}{dt} &= +k_2 x_1 s_2 - k_{-2} x_2 - k_3 x_2
\end{aligned}$$

We have the following conservation law:

$$e(t) + x_1(t) + x_2(t) = \text{constant} = e_0$$

and we assume that the enzyme concentration is much smaller than the substrate concentration:

$$e_0 \ll s_1(t), \quad e_0 \ll s_2(t).$$

In particular, we introduce a small parameter $\varepsilon > 0$ and we introduce the scaled variables x_1^*, x_2^* such that

$$e_0 = \varepsilon e_0^*, \quad x_1 = \varepsilon x_1^*, \quad x_2 = \varepsilon x_2^*$$

(hence $x_1^*, x_2^* = o(1)$ are comparable with s_1, s_2.)

The system becomes

$$\begin{aligned}
\frac{ds_1}{dt} &= \varepsilon[-k_1 e_0 s_1 + (x_1^* + x_2^*) s_1 + k_{-1} x_1^*] && \text{slow} \\
\frac{ds_2}{dt} &= \varepsilon[-k_2 x_1^* s_2 + k_{-2} x_2^*] && \text{slow} \\
\frac{dx_1^*}{dt} &= k_1 e_0^* s_1 - k_1 (x_1^* + x_2^*) s_1 - k_{-1} x_1^* - k_2 x_1^* s_2 + k_{-2} x_2^* && \text{fast} \\
\frac{dx_2^*}{dt} &= +k_2 x_1^* s_2 - k_{-2} x_2^* - k_3 x_2^* && \text{fast}
\end{aligned}$$

(b) We find the quasi-equilibrium of x_1^* and x_2^* as a function of s_1, s_2 and the total concentration of enzyme e_0.

$$\begin{cases} k_1 e_0 s_1 - k_1(x_1^* + x_2^*)s_1 - k_{-1}x_1^* - k_2 x_1^* s_2 + k_{-2}x_2^* = 0 \\ k_2 x_1^* s_2 - k_{-2}x_2^* - k_3 x_2^* = 0 \end{cases}$$

$$\Leftrightarrow \begin{cases} x_2^* = \dfrac{k_1 k_2 s_1 s_2 e_0}{(k_1 s_1 - k_{-2})k_2 s_2 + (k_{-2} + k_3)(k_1 s_1 + k_2 s_2 + k_{-1})} \\ x_1^* = \dfrac{(k_{-2} + k_3)k_1 s_1 e_0}{(k_1 s_1 - k_{-2})k_2 s_2 + (k_{-2} + k_3)(k_1 s_1 + k_2 s_2 + k_{-1})} \end{cases}$$

(c) Under the assumption that x_1^*, x_2^* equilibrate fast at their stable quasi-equilibrium, the dynamics of the product P is described by

$$\begin{aligned} \frac{dP}{dt} = k_3 x_2^* &= \frac{k_1 k_2 k_3 e_0 s_1 s_2}{(k_1 s_1 - k_{-2})k_2 s_2 + (k_{-2} + k_3)(k_1 s_1 + k_2 s_2 + k_{-1})} \\ &= \frac{k_1 k_2 k_3 e_0 s_1 s_2}{k_1 k_2 s_1 s_2 + (k_{-2} + k_3)k_1 s_1 + k_3 k_2 s_2 + (k_{-2} + k_3)k_{-1}} \end{aligned}$$

Remember that the equation for the product in the classical Michaelis–Menten process is

$$\frac{dP}{dt} = k_2 x^* = \frac{k_1 k_2 e_0 s}{k_1 s + k_{-1} + k_2}.$$

(i) If $s_1 \to \infty$, then the dynamics is dominated by the term

$$\frac{dP}{dt} = \frac{k_2 k_3 e_0 s_2}{k_2 s_2 + k_{-2} + k_3}$$

hence it correspond to the simple Michaelis–Menten process with

$$E + S_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} X_2 \overset{k_3}{\to} P$$

(ii) Analogously, for $s_2 \to \infty$, we have

$$\frac{dP}{dt} = \frac{k_1 k_3 e_0 s_1}{k_1 s_1 + k_3}$$

which corresponds to

$$E + S_1 \overset{k_1}{\longrightarrow} X_1 \overset{k_3}{\longrightarrow} P$$

Notice that, in this limiting case, the reaction $E + S_1$ is effectively non-reversible. This is because the complex X_1 gets an S_2 at once, before it would have time to dissociate back to E and S_1.

Exercise 4.2

Let $f(x) = xg(x)$ with

$$g(x) = (a + bx)(c_0 - kx) - \mu = -bkx^2 + (bc_0 - ak)x + ac_0 - \mu$$

Hence g is a downward parabola which is translated along the vertical axis when varying μ.

The equilibria of the system are $x = 0$ and $\hat{x}$ such that $g(\hat{x}) = 0$, i.e.,

$$\hat{x} = \frac{bc_0 - ak \pm \sqrt{(bc_0 - ak)^2 + 4bk(ac_0 - \mu)}}{2bk} = \frac{bc_0 - ak \pm \sqrt{(bc_0 + ak)^2 - 4bk\mu}}{2bk}$$

The solutions exist real iff

$$\mu < \frac{(bc_0 + ak)^2}{4bk} =: \mu^*$$

corresponding to

$$\hat{x} = \hat{x} = \frac{bc_0 - ak}{2bk},$$

and the equilibrium curve $\hat{x}$ intersects the axis $x = 0$ at $\mu = ac_0$. Moreover, if $\mu < ac_0$ there is always at least one positive root $\hat{x}_1$. The sign of the second root depends on the value of the parameters a, b, c_0, k, and they will determine different bifurcation diagrams.

Let us study the stability of equilibria. We have

$$f'(x) = xg'(x) + g(x).$$

In particular,

$$f'(0) = g(0) = ac_0 - \mu,$$

hence the zero equilibrium is asymptotically stable for $\mu > ac_0$. We can conclude about the stability of the other equilibria (when they exist) by the principle of alternating stability. In particular:

If $bc_0 - ak > 0$, then the fold bifurcation takes place in the positive half-plane at $\mu = \mu^*$, and the 0 equilibrium undergoes a (subcritical) transcritical bifurcation at $\mu = ac_0$.

If $bc_0 - ak < 0$, the the fold bifurcation takes place in the negative half-plane at $\mu = \mu^*$, and the 0 equilibrium undergoes a (supercritical) transcritical bifurcation at $\mu = ac_0$.

Exercise 4.3

We rewrite the model in terms of the relative density of individuals $x_i = N_i/N$, where $N = \sum N_i$ is the total population density.

$$\begin{aligned}\frac{dx_i}{dt} &= \frac{1}{N}\frac{dN_i}{dt} - \frac{N_i}{N^2}\sum \frac{dN_i}{dt} \\ &= (b_i[c_0 - \sum_j k_j N_j] - \mu_i)x_i - x_i \sum_k (b_k[c_0 - \sum_j k_j N_j] - \mu_k)x_k\end{aligned}$$

Define the average growth rate of the population (which depends on the vector of population sizes $\underline{N}$ as

$$\overline{r}(\underline{N}) := \sum_k (b_k[c_0 - \sum_j k_j N_j] - \mu_k)x_k.$$

Hence,

$$\frac{dx_i}{dt} = (b_i[c_0 - \sum_j k_j N_j] - \mu_i - \overline{r}(\underline{N}))x_i$$

Let $\hat{N}_i$ be the size of the i-th population at equilibrium, and let $\underline{\hat{N}}$ be the vector of the total population at equilibrium. Then,

$$c_0 - \sum_j k_j \hat{N}_j = \tilde{c}(\underline{\hat{N}})$$

depends only on the population vector $\underline{\hat{N}}$. Moreover, at equilibrium the growth rate of the i-th population is zero for all $i = 1, \ldots, n$, and hence $\hat{N}_i = 0$ or

$$b_i[c_0 - \sum_j k_j \hat{N}_j] - \mu_i = 0 \Leftrightarrow \frac{b_i}{\mu_i} = \frac{1}{\tilde{c}(\underline{\hat{N}})}$$

It follows that all the strains that are persisting in the population at equilibrium have the same value b_i/μ_i. To check transversal stability of the equilibrium, assume that a new strain k is introduced in the population at equilibrium. Then, its growth rate is positive (i.e., the strain invades the population) iff

$$b_k \tilde{c}(\underline{\hat{N}}) - \mu_k > 0 \Leftrightarrow \frac{b_k}{\mu_k} > \frac{1}{\tilde{c}(\underline{\hat{N}})}.$$

So we can conclude that natural selection maximizes the value of b/μ.

Exercise 4.4

Assume that the dynamics of the toxin is fast. To represent this, we can introduce a small parameter $\varepsilon > 0$ and assume that the rates relevant to the toxin are very large ($o(1/\varepsilon)$) compared to the rates relevant to the bacteria ($o(1)$). In particular, we introduce the scaled rates α_i^*, δ^* such that

$$\alpha_i = \frac{\alpha_i^*}{\varepsilon}, \quad \delta = \frac{\delta^*}{\varepsilon}$$

(hence, α_i^* and δ^* are order $o(1)$).

(a) Consider only one strain ($n = 1$). The (fast) dynamics of T is

$$\varepsilon \frac{dT}{dt} = \alpha^* N - \delta^* T$$

and hence its quasi-equilibrium is

$$\hat{T}(N) = \frac{\alpha^*}{\delta^*} N = \frac{\alpha}{\delta} N$$

(and notice that it is asymptotically stable).

We plug $\hat{T}$ into the equation for N and get

$$\begin{aligned} \frac{dN}{dt} &= bN - (\mu - \rho \hat{T}(N))N = bN - \left(\mu - \frac{\rho \alpha N}{\delta}\right) N \\ &= rN \left(1 - \frac{N}{K}\right) N \end{aligned}$$

with

$$r = b - \mu, \quad K = \frac{\delta r}{\rho \alpha}.$$

(b) In presence of more strains ($n > 1$), the quasi-equilibrium is

$$\hat{T}(\underline{N}) = \frac{1}{\delta} \sum_j \alpha_j N_j = \frac{N}{\delta} \sum_j \alpha_j x_j$$

and

$$\frac{dN_i}{dt} = b_i N_i - (\mu_i - \rho \hat{T}) N_i.$$

In particular, the dynamics of the relative frequencies $x_i = N_i/N$ is

$$\begin{aligned} \frac{dx_i}{dt} &= (b_i - \mu_i - \rho \hat{T}(\underline{N}))x_i - x_i \sum_j (b_j - \mu_j - \rho \hat{T}) x_j \\ &= (b_i - \mu_i) x_i - \rho \hat{T} x_i - x_i \sum_j (b_j - \mu_j) x_j + x_i \rho \hat{T} \sum_j x_j \\ &= (r_i - \overline{r}) x_i \end{aligned}$$

(because $\sum_j x_j = 1$), where $r_i = b_i - \mu_i$ and $\overline{r}$ is the average over the total population. Hence, the density-dependence is nonselective, because the contribution $-\rho T$ describing the density dependence is not involved in the equation for the frequencies. Moreover, the dominating strain is the one maximizing the growth rate $r_i = b_i - \mu_i$.