**Mathematical physiology**

PROBLEM SHEET 0. [2018]

1. The Lotka–Volterra system is given by

$$\dot{x} = x(1-y),$$

$$\dot{y} = \mu y(x-1).$$

Write the equations in terms of $X = x-1$ and $Y = y-1$, and show that there is a first integral of the equation of the form

$$\mu w(X) + w(Y) = E, \quad (*)$$

where $E$ is constant. If the minimum value of $E = 0$, give the definition of $w(X)$, and draw its graph.

We now wish to show that the trajectories satisfying $(*)$ form closed loops in the $(X, Y)$ plane. To show this, define a function $r(\xi)$ by

$$\xi = +\sqrt{w(r)} \quad \text{if} \quad r > 0,$$

$$\xi = -\sqrt{w(r)} \quad \text{if} \quad r < 0,$$

and show that $r(\xi)$ is a smooth, monotonically increasing function, give its behaviour as $\xi \to \pm\infty$, and draw its graph.

Now consider the transformation from $(X, Y)$ to $(\xi, \eta)$ space given by $X = r(\xi)$, $Y = r(\eta)$. Show that the trajectories in $(X, Y)$ space are mapped to the curves

$$\mu\xi^2 + \eta^2 = E,$$

and deduce that these form closed loops in $(\xi, \eta)$ space and hence also $(X, Y)$ space.

2. For the system

$$\dot{x} = \frac{x}{1+x}\left[F(x) - y\right],$$

$$\dot{y} = \beta[G(x) - y],$$

where

$$F(x) = (k-x)(1+x), \quad G(x) = \frac{bx}{1+x},$$

where $k > 1$, $b > k^2$ and $\beta > 0$, show that there is at least one fixed point $(x_0, y_0)$ in the first quadrant. Assuming that $F'(x_0) > 0$, that this fixed point is unique, and that it is oscillatorily unstable, draw the nullclines of the system, and draw the trajectories in the phase plane.

Construct a bounding box for the trajectories, and show using the Poincaré–Bendixson theorem that the system has at least one stable limit cycle.

[*Hint: you can assume there is a small circle $C$ surrounding the fixed point on which all trajectories are directed outwards; the bounding box then consists of an inner curve $C$, and an outer curve which consists of straight (horizontal or vertical) lines, together with a curve $A$ in the part of the quadrant where $\dot{x} < 0$, $\dot{y} < 0$. Show that in this region, when $x$ is small,*

$$\frac{dy}{dx} \approx \frac{\beta y}{x(y-k)} > \frac{\beta k}{x(y-k)},$$

*and use this information to construct a suitable curve $A$ to complete the construction of $B$.*]

3. For a cubic nonlinearity, the travelling wave solutions of the nonlinear diffusion equation

$$u_t = f(u) + u_{xx}$$

satisfy the phase plane equations

$$U' = -V,$$

$$V' = f(U) - V,$$

where $U' = \dfrac{dU}{d\xi}$, $V' = \dfrac{dV}{d\xi}$, and

$$(U, V) \to (1, 0) \quad \text{as} \quad \xi \to -\infty,$$

$$(U, V) \to (0, 0) \quad \text{as} \quad \xi \to \infty,$$

where we take

$$f(U) = 2U(U-1)(a-U),$$

with $0 < a < 1$.

Carry out a phase plane analysis in the case $a < \frac{1}{2}$, assuming that $c > 0$ and that a connecting trajectory exists, and draw the phase plane trajectories.

[*Harder.*] In order to prove that there is a unique connecting trajectory, we can use a monotonicity argument.

Show that the separatrix arriving at $(0, 0)$ is determined by

$$\frac{dV}{dU} = c - \frac{f(U)}{V}, \quad V \approx \lambda_0 U \quad \text{as} \quad U \to 0, \quad (*)$$

where

$$\lambda_0 = \tfrac{1}{2}[c + \{c^2 - 4f'(0)\}^{1/2}].$$

Show that $\lambda_0$ is a monotonically increasing function of $c$. Deduce that if two solutions of $(*)$ are denoted $V_1$ and $V_2$, corresponding to two values $c_1 < c_2$, then for small $U$, $V_1 < V_2$.

Show that if $V_1 = V_2$ at some $U > 0$, then necessarily $V_1' \geq V_2'$ at that point. Using $(*)$, show that this contradicts the assumption that $c_1 < c_2$. Hence deduce that $V(U;c)$ is a monotonically increasing function of $c > 0$.

Show that for large $c$, $V \approx cU$, so that in particular $V(1,c) > 0$ and the arriving separatrix at the origin is above the leaving separatrix at $(1,0)$ for large $c$.

Show that for small $c$,

$$\tfrac{1}{2}V^2 + \int_0^U f(U)\,dU \approx 0,$$

and deduce that the separatrix arriving at $(0,0)$ passes through $(U_0, 0)$ where $U_0$ is the minimum positive value such that $\displaystyle\int_0^{U_0} f(U)\,dU = 0$. Deduce that if $U_0 < 1$, the arriving separatrix is below the leaving separatrix for small $c$.

Show that

$$U_0 = \tfrac{2}{3}(a+1) - \tfrac{2}{3}\left[\left(\tfrac{1}{2} - a\right)(2-a)\right]^{1/2},$$

and deduce that $U_0$ exists and is $< 1$ iff $a < \frac{1}{2}$. Hence show that there is a unique connecting trajectory between $(1,0)$ and $(0,0)$ with $c > 0$ if $a < \frac{1}{2}$, but no such trajectory exists for any $c > 0$ if $a > \frac{1}{2}$.

4. Derive a suitably scaled form of the Michaelis-Menten model for the reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} E + P,$$

and show that it depends on the parameters

$$K = \frac{k_{-1} + k_2}{k_1 S_0}, \quad \lambda = \frac{k_2}{k_1 S_0}, \quad \varepsilon = \frac{E_0}{S_0},$$

where $S_0$ and $E_0$ are the initial values of $S$ and $E$. If $\varepsilon \ll 1$, show that the solution consists of an outer layer in which $t = O(1)$, and an inner layer in which $t = O(\varepsilon)$, and find explicit approximations for these. Hence show that $S$ decreases linearly initially, but exponentially at large times.

5. An enzyme has $n$ binding sites for a substrate $S$. If the enzyme complexes with $j$ bound sites are denoted as $C_j$, write down the rate equations for the concentrations of $S$, $P$ and $C_j$, $j = 0, 1, \ldots, n$, where $C_0 = E$, satisfying the reactions

$$S + C_{i-1} \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} C_i \overset{k_i^+}{\rightarrow} C_{i-1} + P.$$

Deduce that

$$C_0 = E_0 - \sum_1^n C_i,$$

where $E_0$ is the initial enzyme present. Use the quasi-steady state assumption to show that $R_i = 0$, $i = 1, \ldots, n$, where

$$R_i = k_i S C_{i-1} - (k_{-i} + k_i^+) C_i,$$

and deduce that the reaction rate $r = dP/dt$ is given approximately by

$$r = \frac{E_0 \sum_{r=1}^{n} k_r^+ \phi_r S^r}{1 + \sum_{j=1}^{n} \phi_j S^j},$$

where

$$\phi_j = \prod_{i=1}^{j} \frac{1}{K_i}, \quad K_i = \frac{k_{-i} + k_i^+}{k_i}.$$

Deduce that if $k_1 \to 0$ with $k_1 k_n$ finite, the reaction rate is approximated by the Hill equation

$$r = \frac{k_n^+ E_0 S^n}{\prod_{i=1}^{n} K_i + S^n}.$$

6. Suppose a population has a size distribution $\phi(a, t)$, where $a$ is age and $t$ is time: $\phi\, \delta a$ is the number of individuals with ages between $a$ and $a + \delta a$. The birth rate $b(a)$ depends on age, as does the mortality rate $m(a)$. Show that

$$\phi_t + \phi_a = -m\phi,$$

and explain why the birth rate appears in the boundary condition

$$\phi(0, t) = \int_0^\infty b(a)\phi(a, t)\, da.$$

What is assumed about $\phi$ as $a \to \infty$?

Show that the steady size distribution with age of a population is given by the solution of the linear integral equation

$$\phi(a) = \int_0^\infty G(a, \xi)\phi(\xi)\, d\xi,$$

where $G(a, \xi)$ should be specified.

Use the method of characteristics to show that for $t > a$, the solution for $\phi$ is

$$\phi = \int_0^\infty b(\xi)\phi(\xi, t - a)\, d\xi \exp\left[-\int_0^a m(\eta)\, d\eta\right].$$

Deduce an approximate equation for $\phi$ if $b(\xi) = 0$ for $\xi < t_m$, $b = B$ (constant) for $t_m < \xi < t_m + t_b$, $b = 0$ for $\xi > t_m + t_b$, where $t_b$ is small, and hence show that if $x(t) = \phi(t_m, t)$, then

$$x(t) \approx \Lambda x(t - t_m),$$

where $\Lambda = B t_b \exp\left[-\int_0^{t_m} m(\eta)\, d\eta\right]$. Why is this obvious?