Exercises for Tumor Dynamics Module *

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Exercises for Equation Development Module

1. **Purpose:** To interpret model equations biologically and to go through the preliminary steps of qualitative analysis.

   This model is derived from the paper by Panetta ([Pan96]). It is developed further in the Projects.

   Exercise: Another simple model of tumor/host interaction describes the growth of two populations, each growing according to a logistic law and competing with each other for resources. In this model, we lump together all non-tumor cells which are at the tumor site, including normal tissue as well as immune cells. We do *not* assume a constant source of immune cells.

   Let $X(t)$ denote the normal cell population at time t, (including immune cells), and let $Y(t)$ denote the tumor cell population at time t. The system of differential equations which describes the model is:

$$\begin{aligned} \frac{dX}{dt} &= a_1 X(1 - b_1 X) - c_1 XY \\ \frac{dY}{dt} &= a_2 Y(1 - b_2 Y) - c_2 XY \end{aligned}$$

   (a) What is the biological interpretation of each of the parameters a_1, a_2, b_1, b_2, c_1, and c_2? Are they all necessarily positive or negative?

   (b) Describe hypothetical experiments which would allow the determination of these parameters.

   (c) Determine the nullclines of this system. Use these nullclines to sketch a few representative phase portraits. Find and label all of the equilibria.

   (d) What condition must the parameters satisfy in order that the tumor-free equilibrium be stable?

   Solution:

   (a) The biological interpretation of the parameters is as follows:

   a_1, a_2 : Growth rates of the normal and tumor cells

   b_1, b_2 : Carrying capacity of the normal and tumor cells

   c_1, c_2 : Competition rate parameters of the normal and tumor cells

   They are all necessarily positive since the specified system of equations has the required negative signs to account for decrease in numbers wherever necessary.

   (b) The growth rate could be determined by examining a fixed number of cells (normal and tumor cells in different dishes) with an infinite nutrient supply, while the carrying capacity could be determined by by a similar experiment in which the nutrient supply was limited. The competition rate parameters may be determined using an assay procedure. This involves setting up different ratios of tumor cells to normal cells, wherein the normal cells take in a fixed amount

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of chromium. Varying amounts of tumor cells will kill proportional amounts of normal cells and release chromium, which is then measured using centrifugation and other processes. Thus the parameters c_1 and c_2 may be determined.

(c) The four cases that result depend on parameters are shown in Figure 1 (adapted from Boyce and DiPrima, Sixth Edition).

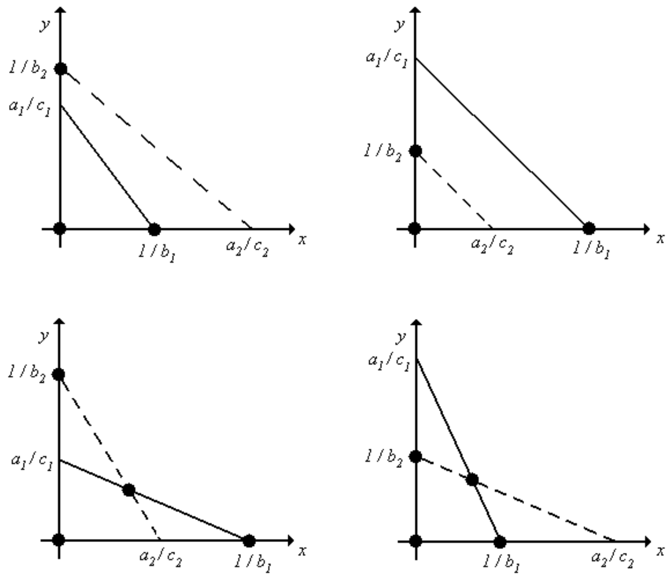

Figure 1: The various cases for the competing species system

(d) For the case that the tumor-free equlibrium $(1/b_1,0)$ is to be stable, linearize about this equilibrium point ($X = 1/b_1 + \epsilon u$ and $Y = 0 - \epsilon v$, where ϵ is small compared to $1/b_1$) to obtain,

$$\begin{pmatrix} u' \\ v' \end{pmatrix} = \begin{pmatrix} -a_1 & -\frac{c_1}{b_1} \\ 0 & a_2(1 - \frac{c_2}{b_1 a_2}) \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix}.$$

It is now seen that the tumor *cannot* recur if the eigenvalue $1 - c_2/b_1a_2$ is negative, and thus the condition for the tumor-free equilibrium to be stable is

$$\frac{c_2}{b_1 a_2} > 1.$$

2. **Purpose:** To explore another model equation using a more complicated tumor growth function, in an attempt to include the effects of angiogenesis.

The comparison of tumor growth curves is, continued in the Projects, using published data. See also Exercise 3. Research on tumor angiogenesis is a hot topic, and a literature search on current theories and proposed mechanisms would be an interesting research project.

Exercise: It has been observed both *in vivo* and *in vitro* that solid tumors experience an initial period of quick growth,followed by a period when growth slows or stops, follwed by another period of growth. It has been suggested that the first period of growth is during the 'avascular' phase, when the tumor has not yet developed any internal vasculature, so that the cells must acquire nutrients through diffusion from outside the tumor. Once the tumor reaches a certain size, the tumor cells release 'angiogenic growth factors', which stimulate the growth of blood vessels towards the tumor, and finally reaching into the interior of the tumor. After the tumor has been 'vascularized', another period of growth occurs.

In this exercise, the angiogenic process will be modelled by a drastic *slowing* in the growth rate when the tumor reaches a certain size, denoted by T_a.

(a) Sketch a graph of a possible growth function, $F(T) = \frac{dT}{dt}$, which is positive for $0 < T < T_{\text{MAX}}$, and is very small for T near $T_a < T_{\text{MAX}}$. In the spirit of generating tractable models, the function should be as simple as possible, within the prescribed constraints.

(b) Write a differential equation for $T(t)$, after writing an equation for the function $F(T)$ you graphed in 2a.

(c) Solve the differential equation in part 2b, and compare the result to logisitc tumor growth by plotting solution curves for the two types of growth, using the same initial conditions. (Depending on the form of $F(T)$, you may or may not be able to find an *explicit* solution for the differential equation. If an explicit solution is not available, use a numeric solver.) The comparison will be most meaningful if the same initial growth rates (when T is close to zero), and the same carrying capacity are used.

Comment on the effect of varying the tumor size during vascularization, i.e. T_{MAX}.

Solution:

(a) Within the prescribed constraints of the growth function $F(T) = \frac{dT}{dt}$, three different graphs ($F_1(T)$, $F_2(T)$, $F_3(T)$) are shown, each increasing in complexity. Any one of these graphs (and others not shown here) would be a sufficient answer to this question. These solutions will follow through and individually examine these graphs parts (b) and (c) of the question.

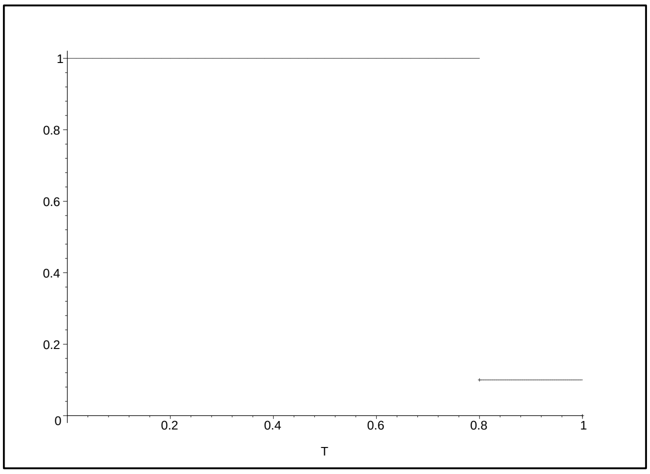

Figure 2: $F_1(T)$ - The simplest graph possible given the prescribed constraints.

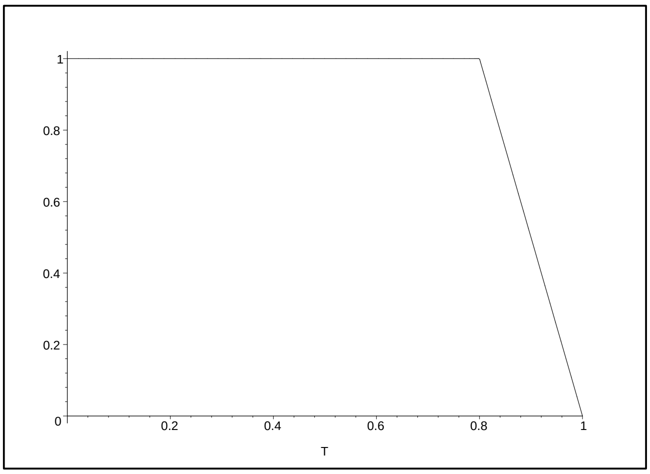

Figure 3: $F_2(T)$ - A slightly more complicated graphical representation for Exercise 2a.

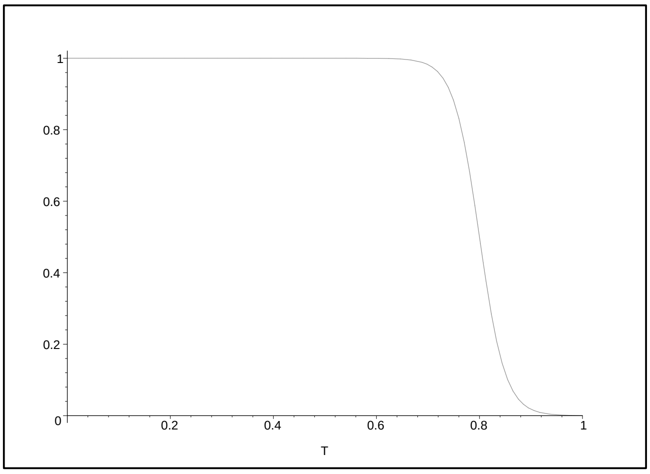

Figure 4: $F_3(T)$ - An even more complex possible graphical representation for Exercise 2a.

(b) The equations for ($F_1(T)$, $F_2(T)$, $F_3(T)$) respectively are:

$$F_1(T) = \begin{cases} k & 0 \leq T < T_a \\ \epsilon k & T_a \leq T \leq T_{MAX} \end{cases}$$

$$F_2(T) = \begin{cases} k & 0 \leq T < T_a \\ \frac{k(T_{MAX}-T)}{T_{MAX}-T_a} & T_a \leq T \leq T_{MAX} \end{cases}$$

$$F_3(T) = \frac{k}{2}\left(1 - \tanh(10(T - T_a))\right)$$

Finding an explicit solution, $T(t)$, for each of $F_1(T), F_2(T)$ and $F_3(T)$ is difficult, so a numerical solver is used. The solution found was used to plot the comparative graphs in part (c).

(c) The solution curves of $F_1(T), F_2(T)$ and $F_3(T)$ (thin line) compared to that of logistic tumor growth $F_G(T) = \frac{dT}{dt} = aT(b-T)$ (thick line) can be seen in Figure 5, 6 and 7 respectively. In these plots, $T_a = 0.8$, $T_{MAX} = 1$ and $t = 0..70$.

Varying the tumor size during vascularisation only seems to change the length of time taken to grow to T_{MAX}. No other changes could be detected.

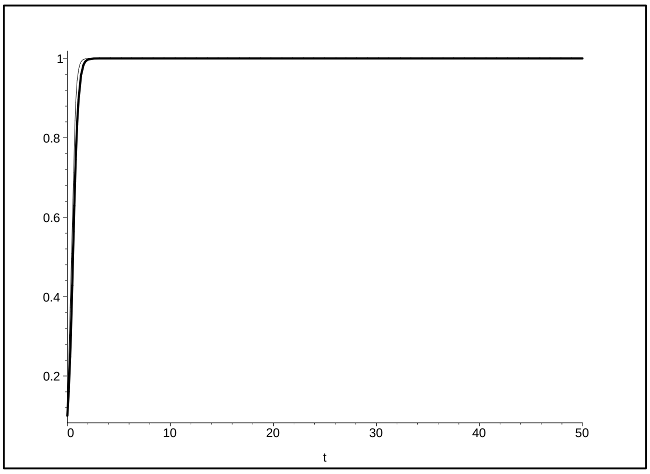

Figure 5: A comparison between $F_1(T)$ and the logistic equation, $F_G(T)$. Upon inspection, it can be seen that $F_1(T)$ closely follows the behavior of the logistic equation everywhere except for the region from approximately $t = 1$ to $t = 3$.

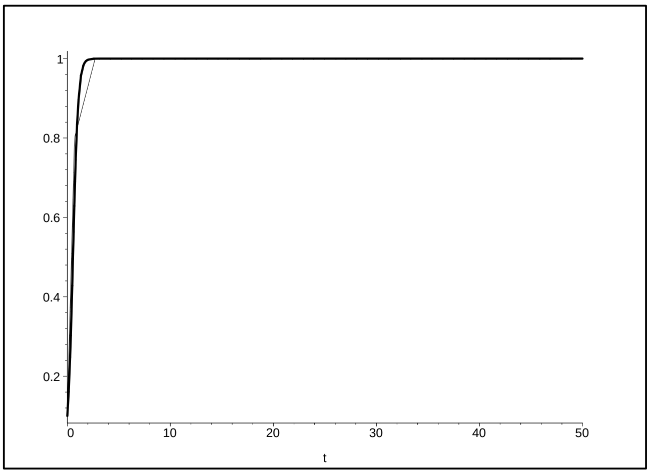

Figure 6: A comparative plot between $F_2(T)$ and the logistic equation. The behaviour of $F_2(T)$ is quite similar to that of the logistic equation, however there is a slightly more noticeable difference in behavior for the region $t = 1$ to $t = 2$.

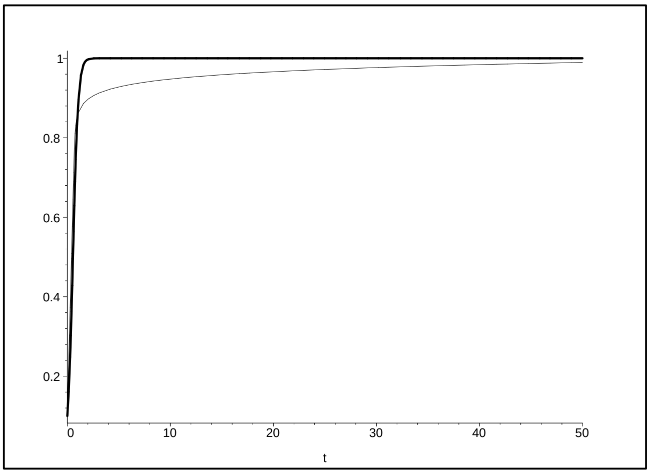

Figure 7: Plotting $F_3(T)$ with the logistic equation finds that its behavior varies greatly with that of the logistic equation.

3. **Purpose:** To come up with a model equation using a different tumor growth function. The solutions are compared with those derived from the logistic growth law.
The comparison of tumor growth curves is, continued in the Projects, using published data. See also Exercise 2

Exercise: It has been observed that in certain tumors grown *in vitro* only a thin layer of cells on the tumor's surface are actually proliferating.

Consider a perfectly spherical tumor, and let $T(t)$ denote the tumor population at time t.

(a) Write a differential equation for $T(t)$, assuming that only the cells on the surface of the sphere proliferate. (Assume that the number of cells, T, is proportional to volume, but that the number of proliferating cells is proportional to the surface area of the sphere. You'll need to express the number of proliferating cells as a function of T.) This is known as "Von Bertalanffy" growth.

(b) Solve the differential equation in part 3a, and compare the result to exponential tumor growth by plotting solution curves for the two types of growth, using the same initial conditions.

(c) Add a growth-limiting term to the differential equation in part 3a, analagous to the overcrowding term in the logistic growth equation. Again, compare numerical simulations of the two systems for, using the same initial conditions, the same proliferation rate, and the same initial conditions.

Solution:

(a) Since the only proliferating cells are those on the surface of the sphere, and that the number of cells T is proportional to the volume V of the sphere, we find

$$T = kV$$

, where k is a constant. Now since the number of proliferating cells, P is proportional to the surface area of the sphere, we get

$$P = k_2 4\pi R(t)^2$$

where k_2 is a constant and $R(t)$ is the radius of the sphere as a function of time, t. Recalling that the volume of a sphere is given by $V = \frac{4}{3}\pi R(t)^3$, rearrange for $R(t)$ and substitute into proliferating cells equation to find that $P = k_2 4\pi(\frac{3}{4\pi}V)^(\frac{2}{3})$. The differential equation for $T(t)$, assuming that only the cells on the surface of the sphere proliferate, can now be written as

$$\frac{dT}{dt} = kT^{\frac{2}{3}}.$$

(b) Solving the differential equation in part 3a, we find that

$$T(t) = \left(\frac{kt}{3} + C_1\right)^3$$

where C_1 is a constant of integration. Figure 8 plots this solution (thin line) and compares it with the solution curve for the exponential tumor growth (thick line), with $k = 1$.

(c) The addition of a growth limiting term to the differential equation in part 3a, analogous to the overcrowding term in the logistic growth equation, finds that the differential equation now becomes

$$\frac{dT}{dt} = kT^{\frac{2}{3}}(1 - bT).$$

Figure 9 plots the numerical solution to this equation (thin line) and compares it to the solution curve of the logistic growth equation (thick line), with $k = 1$ and $b = \frac{1}{100}$.

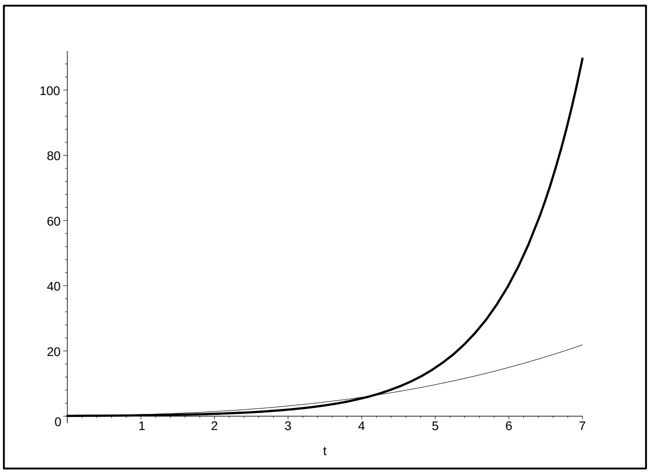

Figure 8: The solution curves for Exercise 3b.

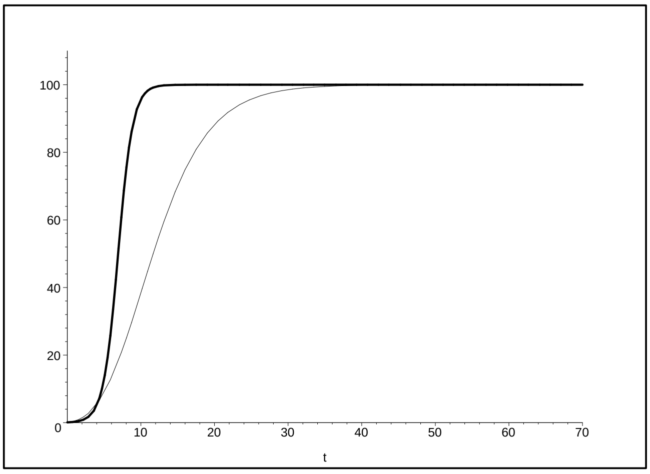

Figure 9: The solution curves for Exercise 3c.

4. **Purpose:** Compare the tumor-immune model using Von Bertalanffy growth to the one presented in class using a qualitative analysis.
   See Exercise 3

   Exercise: Use the Von Bertalanffy model of tumor growth in the absence of an immune response:

   $$\frac{dT}{dt} = aT^{2/3}(1 - bT).$$

   Add the immune population, with competition and response terms identical to those used in the model presented in class. Draw nullclines, determine the number of possible equilibria and their stability. Does the qualitative behavior differ from that of the model presented in class? If so, how?

   Recall the system of equations presented in class: T denotes tumor cells, and E denotes effector (cytotoxic immune) cells. The equations are

   $$\begin{aligned} \frac{dE}{dt} &= s + \frac{pET}{g+T} - dE - mET \\ \frac{dT}{dt} &= aT(1-bT) - cET \end{aligned}$$

   Solution:

   The Von Bertalanffy model of tumor growth in the presence of an immune population, competition and response terms identical to the those used in class finds the system of equations to be

   $$\begin{aligned} \frac{dE}{dt} &= s + \frac{pET}{g+T} - dE - mET \\ \frac{dT}{dt} &= aT^{2/3}(1-bT) - cET \end{aligned}$$

   where s, p, g, d, m, a, b, c are constants, T denotes tumor cells and E denotes effector (cytotoxic immune) cells. The T nullclines are found to be at

   $$\begin{aligned} T &= 0 \\ E &= \frac{a(1-bT)}{cT^{\frac{1}{3}}}, \end{aligned}$$

   and the E nullcline is at

   $$E = \frac{s(g+T)}{(d+mT)(g+T) - pT}.$$

   These nullclines are plotted in Figure 10. There are 2 possible equilibria for this system. One is located at $(T, E) = (0, \frac{s}{d})$, while the other is at $E = \frac{a(1-bT)}{cT^{\frac{1}{3}}}$ given that T is a solution of the nonlinear equation $\frac{a(1-bT)}{cT^{\frac{1}{3}}} = \frac{s(g+T)}{(d+mT)(g+T)-pT}$, which can be solved numerically using, for example, the Newton-Raphson Method.

   The Jacobian for the system at $(T, E) = (0, \frac{s}{d})$ is singular, hence the stability of the equilibrium point cannot be determined using linear stability analysis. From Maple plots, it appears that this equilibrium point is a saddle with an extremely unstable manifold. The stability of the other equilibrium point is also difficult to determine, however using Maple, it is found to be a stable node. The parameter values used to determine the stability of these points are the same as those used in the Kuznetsov paper [KMTP94]. The qualitative behaviour of the model differs slightly to the one presented in class due to the $T^{\frac{2}{3}}$ term in the Von Bertalanffy equation. The equilibria at A and B in the model presented in class still exist in this model, however due to the behaviour of the term mention above, the two equilibria at C and D no longer exist.

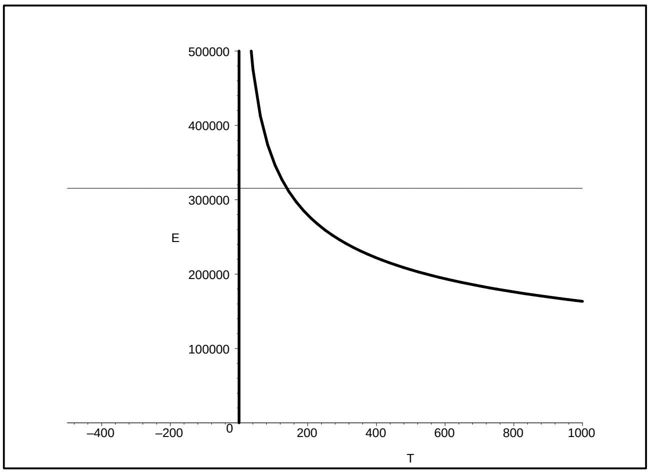

Figure 10: The T nullclines (thick line) and E nullcline (thin line) for Exercise 4.

Exercises for Qualitative Analysis Module

1. **Purpose:** To study non-linear centers.
   Notes: Define a **reversible system** to be any second-order system that is invariant under $t \to -t$ and $y \to -y$. For example, any system ofthe form

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= g(x, y), \end{aligned}$$

   where f is odd in y and g is even in y(i.e., $f(x, -y) = -f(x, y)$ and $g(x, -y) = g(x, y)$) is reversible.

   Theorem: (Nonlinear centers for reversible systems) Suppose the origin $\mathbf{x}* = \mathbf{0}$ is a linear center for the continously differentiable system

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= g(x, y), \end{aligned}$$

   and suppose that the system is reversible. Then sufficiently close to the origin, all trajectories are closed curves. from[Str94], Example 6.6.1

   Exercise: Show that the system

$$\begin{aligned} \dot{x} &= y - y^3 \\ \dot{y} &= -x - y^2 \end{aligned}$$

   has a nonlinear center at the origin, and plot the phase portrait.

   Solution: For the system

$$\dot{x} = y - y^3 = f(x, y)$$
$$\dot{y} = -x - y^2 = g(x, y)$$

   the fixed point x^* is $(0, 0)$. Compute the Jacobian for the system and evaluate it at the fixed point,

$$\mathbf{A} = \begin{bmatrix} 0 & 1 - 3y^2 \\ -1 & -2y \end{bmatrix}\Bigg|_{(0,0)} = \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix}.$$

   The eigenvalues of A are i and $-i$; purely imaginary eigenvalues are characteristic of a center; thus $x^* = 0$ is a center. To show that the system is reversible, consider

$$f(x, -y) = -y - (-y)^3 = -y + y^3 = -(y - y^3) = -f(x, y)$$
$$g(x, -y) = -x - (-y)^2 = -x - y^2 = g(x, y)$$

   which illustrates that f is odd in y and g is even in y. Thus all trajectories sufficiently close to the origin are closed curves. The phase portrait is shown in Figure 11.

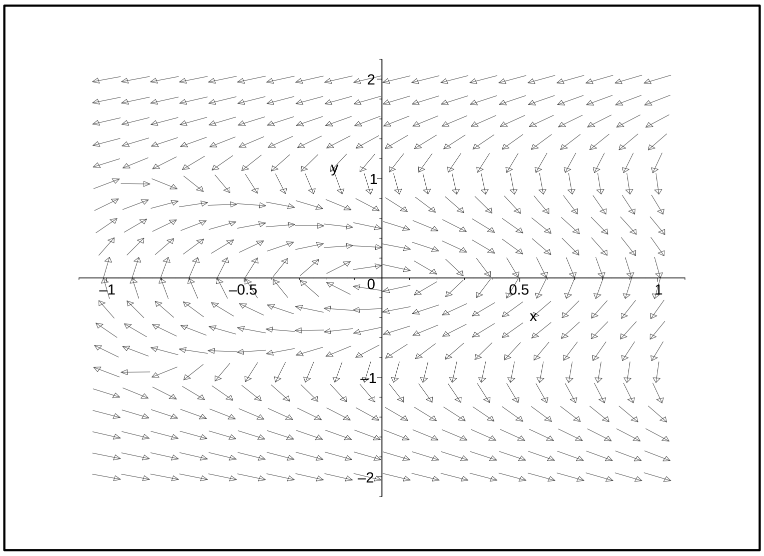

Figure 11: Phase plot of system for Problem 1

2. **Purpose:** To study fixed points and linearizations. From [Str94], 6.3.

   Excercise: For each of the following systems, find the fixed points, classify them, sketch the neighboring trajectories, and try to fill in the rest of the phase portrait.

   (a) $\dot{x} = x - y, \dot{y} = x^2 - 4$
   (b) $\dot{x} = \sin y, \dot{y} = x - x^3$
   (c) $\dot{x} = 1 + y - e^{-x}, \dot{y} = x^3 - y$
   (d) $\dot{x} = y + x - x^3, \dot{y} = -y$
   (e) $\dot{x} = \sin y, \dot{y} = \cos x$
   (f) $\dot{x} = xy - 1, \dot{y} = x - y^3$

   Solution:
   For the following systems, the fixed points are found by solving $\dot{x} = 0$, $\dot{y} = 0$. The linearized system about the fixed point(s) is obtained by evaluating the Jacobian at those point(s). The eigenvalues of the resulting matrix are used to classify the fixed point(s). The phase portrait for each system in shown in the solution to Exercise 3.

   (a) $\dot{x} = x - y, \dot{y} = x^2 - 4$
   The fixed points are $(2, 2)$ and $(-2, -2)$. The Jacobian of the system is $\begin{bmatrix} 1 & -1 \\ 2x & 0 \end{bmatrix}$. Classifying the fixed points using the eigenvalues,
   $(2, 2) : \begin{bmatrix} 1 & -1 \\ 4 & 0 \end{bmatrix}$. Eigenvalues are $\frac{1}{2} \pm \frac{1}{2} I\sqrt{15}$, and thus $(2, 2)$ is an *unstable spiral*.
   $(-2, -2) : \begin{bmatrix} 1 & -1 \\ -4 & 0 \end{bmatrix}$. Eigenvalues are 2.5616 and -1.5616, and thus $(-2, -2)$ is a *saddle point*.

   (b) $\dot{x} = \sin y, \dot{y} = x - x^3$
   The fixed points are $(0, n\pi)$, $(0, (2n + 1)\pi)$, $(1, n\pi)$, $(1, (2n + 1)\pi)$, $(-1, n\pi)$, and $(-1, (2n + 1)\pi)$. The Jacobian of the system is $\begin{bmatrix} 0 & \cos y \\ 1 - 3x^2 & 0 \end{bmatrix}$. Classifying the fixed points using the eigenvalues,
   $(0, n\pi) : \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$. Eigenvalues are 1 and -1, and thus $(0, n\pi)$ is a *saddle point*.
   $(1, n\pi), (-1, n\pi) : \begin{bmatrix} 0 & 1 \\ -2 & 0 \end{bmatrix}$. Eigenvalues are $I\sqrt{2}$ and $-I\sqrt{2}$, and thus a fixed point of this form is a *center*.
   $(0, (2n + 1)\pi) : \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix}$. Eigenvalues are I and $-I$, and thus $(0, (2n + 1)\pi)$ is a *center*.
   $(1, (2n + 1)\pi), (-1, (2n + 1)\pi) : \begin{bmatrix} 0 & -1 \\ -2 & 0 \end{bmatrix}$. Eigenvalues are $\sqrt{2}$ and $-\sqrt{2}$, and thus a fixed point of this form is a *center*.

   (c) $\dot{x} = 1 + y - e^{-x}, \dot{y} = x^3 - y$
   The only fixed point is $(0, 0)$. The Jacobian of the system is $\begin{bmatrix} e^{-x} & 1 \\ 3x^2 & -1 \end{bmatrix}$. Classifying the fixed points using the eigenvalues,
   $(0, 0) : \begin{bmatrix} 1 & 1 \\ 0 & -1 \end{bmatrix}$. Eigenvalues are 1 and -1, and thus $(0, 0)$ is a *saddle point*.

   (d) $\dot{x} = y + x - x^3, \dot{y} = -y$
   The fixed points are $(0, 0)$, $(1, 0)$, and $(-1, 0)$. The Jacobian of the system is $\begin{bmatrix} 1 - 3x^2 & 1 \\ 0 & -1 \end{bmatrix}$. Classifying the fixed points using the eigenvalues,
   $(0, 0) : \begin{bmatrix} 1 & 1 \\ 0 & -1 \end{bmatrix}$. Eigenvalues are 1 and -1, and thus $(0, 0)$ is a *saddle point*.

$(1,0),(-1,0):\begin{bmatrix} -2 & 1 \\ 0 & -1 \end{bmatrix}$. Eigenvalues are -2 and -1, and thus $(1,0)$ and $(-1,0)$ are *stable nodes.*

(e) $\dot{x} = \sin y, \dot{y} = \cos x$

The fixed points are $((2n+1)\pi/2, 2n\pi)$. The Jacobian of the system is $\begin{bmatrix} 0 & \cos y \\ -\sin x & 0 \end{bmatrix}$.
Classifying the fixed points using the eigenvalues,

$([3,7,11\ldots]\pi/2, 2n\pi):\begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$. Eigenvalues are 1 and -1, and thus the fixed point(s) is a *saddle point.*

$([1,5,9\ldots]\pi/2, 2n\pi):\begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix}$. Eigenvalues are I and $-I$, and thus the fixed point(s) is a *center.*

(f) $\dot{x} = xy - 1, \dot{y} = x - y^3$

The real fixed points are $(1,1)$, $(-1,-1)$ and $(I,-I)$. The Jacobian of the system is $\begin{bmatrix} y & x \\ 1 & -3y^2 \end{bmatrix}$.
Classifying the fixed points using the eigenvalues,

$(1,1):\begin{bmatrix} 1 & 1 \\ 1 & -3 \end{bmatrix}$. Eigenvalues are -3.2361 and 1.2361, and thus $(1,1)$ is a *saddle point.*

$(-1,-1):\begin{bmatrix} -1 & -1 \\ 1 & -3 \end{bmatrix}$. Eigenvalues are -2 and -2, and thus $(-1,-1)$ is a *stable node.*

3. **Purpose:** To compare computer generated phase portratis with initial sketches.

   Exercise: For each of the nonlinear systems in Exercise 2, plot a computer-generated phase portrait and compare to your approximate sketch.

   Solution:
   The required computer-generated phase portrait for each system was created in Maple and are shown below.

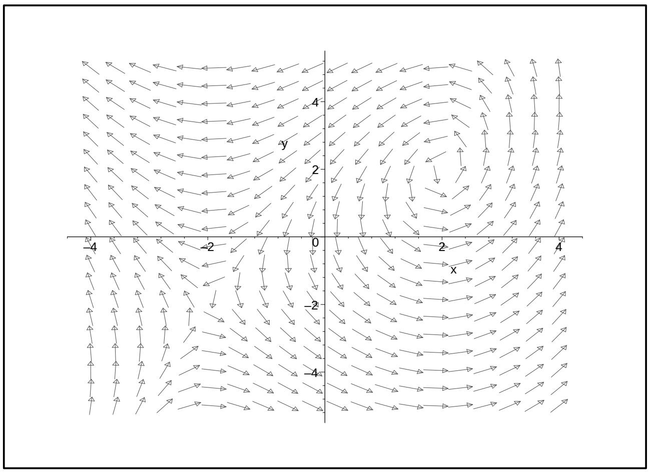

Figure 12: Phase portrait for Exercise 3a

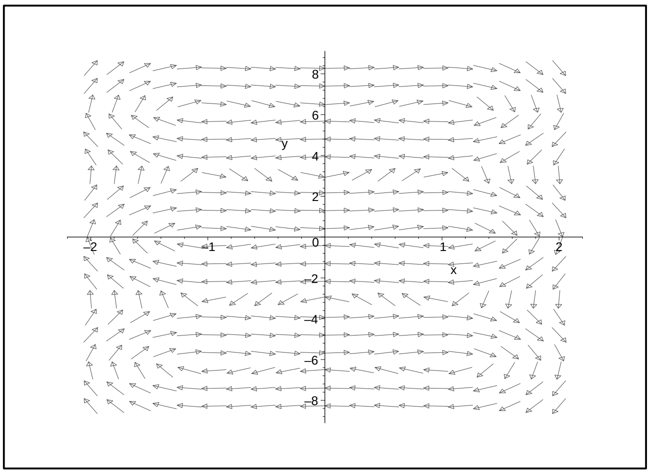

Figure 13: Phase portrait for Exercise 3b

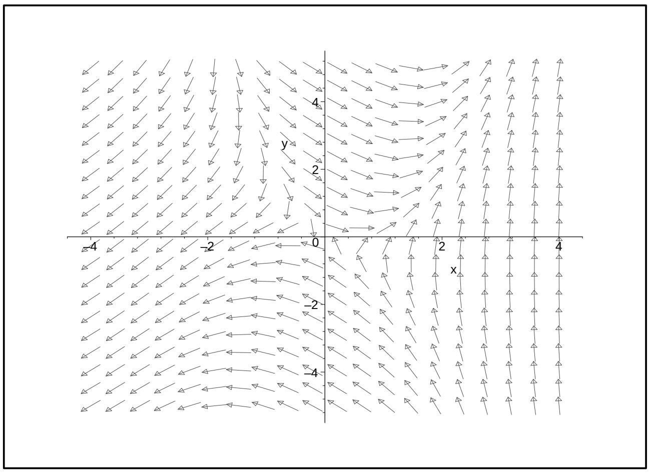

Figure 14: Phase portrait for Exercise 3c

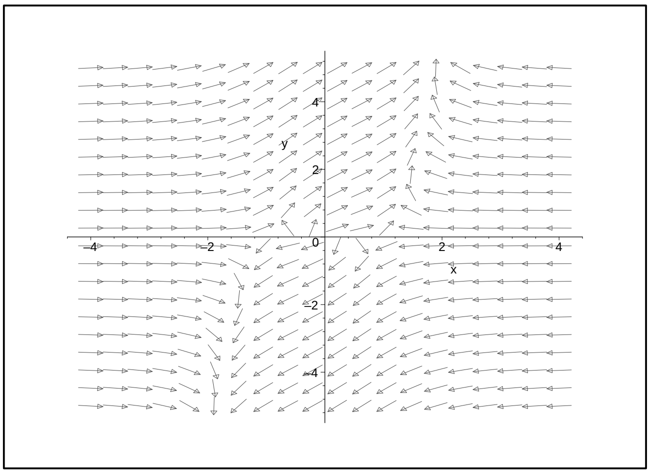

Figure 15: Phase portrait for Exercise 3d

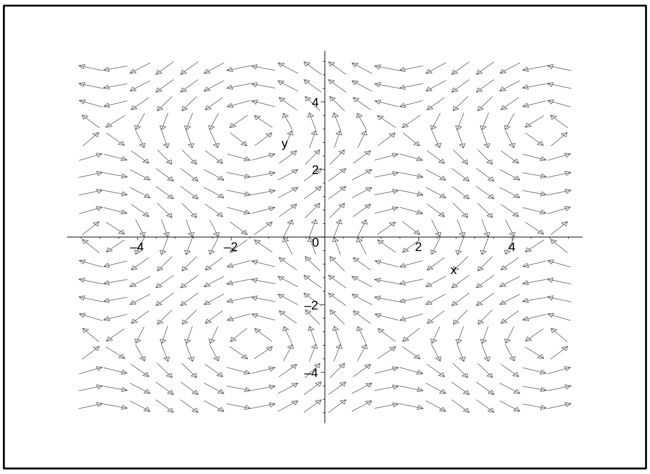

Figure 16: Phase portrait for Exercise 3e

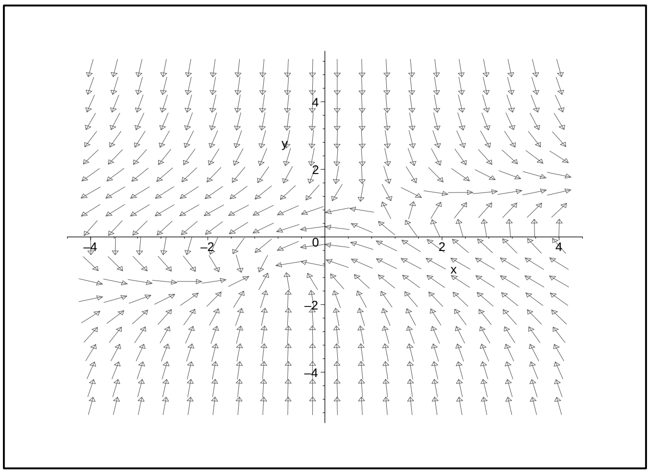

Figure 17: Phase portrait for Exercise 3f

4. **Purpose:** To use qualitative arguments to deduce the phase portrait of a system. From [Str94], Problem 6.6.6

Exercise: Consider the reversible system $\dot{x} = y(1-x^2), \dot{y} = 1-y^2$.

(a) Plot the nullclines $\dot{x} = 0$ and $\dot{y} = 0$.

(b) Find the sign of $\dot{x}, \dot{y}$ in different regions of the plane.

(c) Calculate the eigenvalues and eigenvectors of the saddle points at $(-1, \pm 1)$.

(d) Consider the unstable manifold of $(-1,-1)$. By making an argument about the signs of $\dot{x}, \dot{y}$, prove that this unstable manifold intersects the negative x-axis. Then use reversibility to prove the existence of a heteroclini trajectory connecting $(-1,-1)$ to $(-1,1)$.

(e) Using similar arguments, prove that another heteroclinis trajectory exists, and sketch several other trajectories to fill in thephase portrait.

Solution:

(a) The nullcline plot of $\dot{x} = 0$ and $\dot{y} = 0$ can be seen in Figure 18.

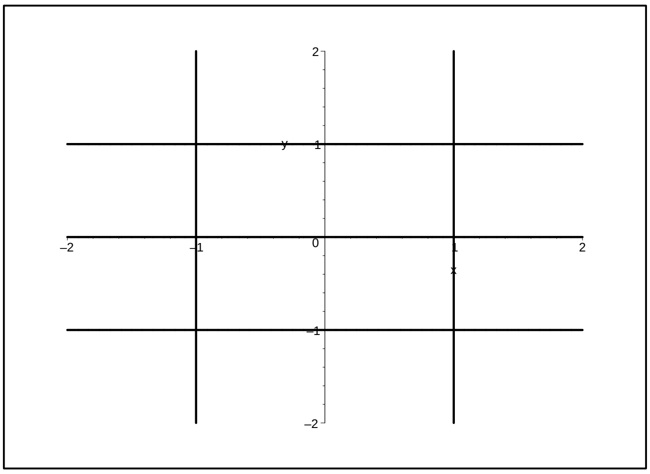

Figure 18: Nullcline plot for Exercise 4a

(b) Figure 19 shows the signs of $\dot{x}, \dot{y}$ in the different regions of the plane.

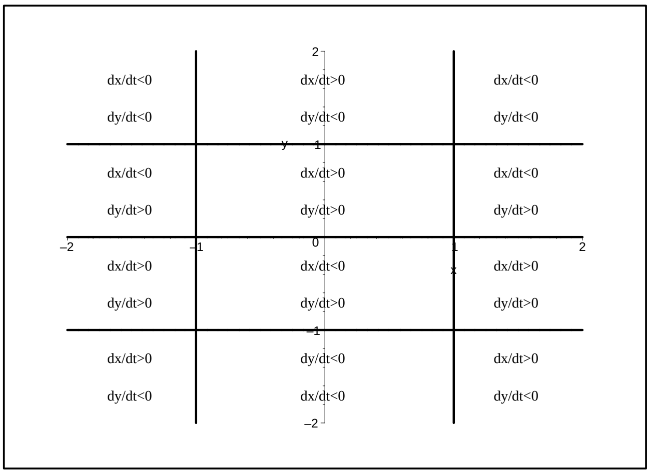

Figure 19: The sign of $\dot{x}, \dot{y}$ in different regions of the plane.

(c) The fixed points for the system are found by solving $\dot{x} = 0$, $\dot{y} = 0$. Their values are $(1, 1)$, $(-1, -1)$, $(1, -1)$ and $(-1, 1)$. The linearized system about these fixed points is obtained by evaluating the Jacobian at those points, and the eigenvalues and eigenvectors for the each of the fixed points in which we are interested are found.

The fixed points of interest are $(-1, 1)$ and $(-1, -1)$. The Jacobian of the system is $\begin{bmatrix} 2xy & 1-x^2 \\ 0 & -2y \end{bmatrix}$.

The Jacobian at the fixed point $(-1, 1)$ is $(-1, 1) : \begin{bmatrix} 2 & 0 \\ 2 & -2 \end{bmatrix}$. Eigenvalues are $\lambda_1 = -2$ and $\lambda_2 = 2$, and the eigenvectors are $\mathrm{e}_1 = [0, 1]$ and $\mathrm{e}_2 = [1, 0]$.

The Jacobian at the fixed point $(-1, -1)$ is $(-1, -1) : \begin{bmatrix} -2 & 0 \\ 2 & 2 \end{bmatrix}$. Eigenvalues are $\lambda_1 = -2$ and $\lambda_2 = 2$, and the eigenvectors are $\mathrm{e}_1 = [1, 0]$ and $\mathrm{e}_2 = [0, 1]$.

(d) At the fixed point $(-1, -1)$ the signs of $\dot{x}$ are such that the solutions are kept in towards the nullcline $x = -1$ and since the signs of $\dot{y} > 0$ the solutions move upwards, for all $-1 < y < 0$. The nullcline of $\dot{x}$, $y = 0$ make the solutions move vertically so solutions continue vertically across the axis. Therefore the manifold intersects the x-axis.
To show that the system is reversible, consider $\dot{x} = y(1 - x^2) = f(x, y), \dot{y} = 1 - y^2 = g(x, y)$. Now

$$f(x, -y) = y - x^2y = -y + x^2y = -y(1 - x^2) = -f(x, y)$$
$$g(x, -y) = 1 - (-y)^2 = 1 - y^2 = g(x, y)$$

which illustrates that f is odd in y and g is even in y. Thus there is existence of a heteroclinic trajectory connecting $(-1, -1)$ to $(-1, 1)$.

(e) Similarly, at the fixed point $(1, -1)$, the signs of $\dot{x}$ and $\dot{y}$ are such that the solutions move vertically from the fixed point toward the fixed point $(1, 1)$. As already shown above, f is odd in y and g is even in y so there is the existence of a heteroclinic trajectory connecting $(1, -1)$ to $(1, 1)$. The phase portrait of the system can be seen in Figure 20.

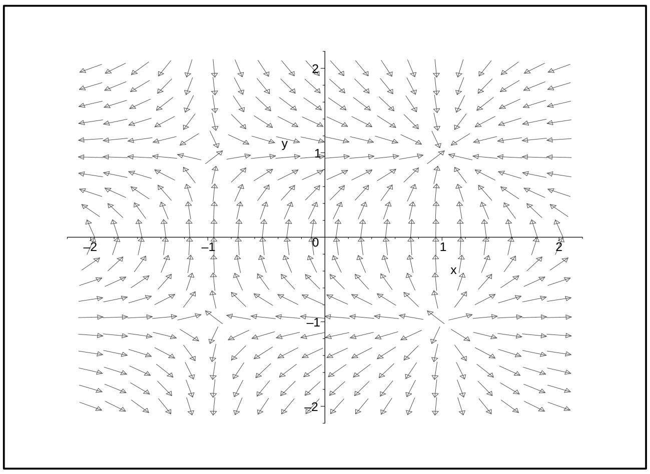

Figure 20: Phase portrait of the system in Exercise 4.

Exercises for Numerics Module

1. **Purpose:** Determining whether an IVP is well-posed.

   Exercise: For each of the following IVPs,determine whether or not it is well-posed, and explain why.

   (a) $y' = -5y$
   $y(0) = 1$ and $0 < t < 5$.

   (b) $y' = 2y^{1/2}$
   $y(0) = 0$ and $0 < t < 2$.

   Solution:

   (a) Well-posed. The general solution is $y(t) = Ce^{-5t}$, and here $C = 1$. $f(y) = -5y$, which is Lipschitz continuous with constant $L = 5$.

   (b) Not well-posed, solution is not unique. Two solutions: $y(t) = 0$ or $y(t) = t^2$. Furthermore, a small perturbation in the initial condition, say $y(0) = 1.01$ results in a significantly different solution $y(t) = t^2 \pm 0.2t + 0.1$.

2. **Purpose:** Understanding stability of solutions, stability of a numerical method, computing solutions for Forward and Backward Euler methods.

   Note to Instructor: If you have chosen not to present the slides on stability of an ODE solution, you may wish to skip part (a) of this exercise. From [Hea02, p.417,#9.4].

   Exercise: Consider the ODE with $y' = -5y$ with initial condition $y(0) = 1$. We will solve this ODE numerically using a step-size of $h = 0.5$.

   (a) Are solutions to this ODE stable?

   (b) Is Euler's method stable for this ODE using this step-size?

   (c) Compute the numerical value for the approximate solution at $t = 0.5$ given by Euler's method.

   (d) Is the backward Euler (BE) method stable for this ODE using this step-size?

   (e) Compute the numerical value for the approximate solution at $t = 0.5$ given by the backward Euler method.

   Solution:

   (a) The solution to this ODE is $y(t) = e^{-5t}$ and is stable since $\lambda = -5 < 0$ for the generic ODE $y' = \lambda y$ as discussed in class.

   (b) Verify that Euler's method is not stable for this ODE using a step-size of $h = 0.5$ by computing the amplification factor which is greater than 1,

   $$|1 + \lambda h| = |1 + (-5)(0.5)| = 1.5 > 1$$

   (c) The numerical value for the approximation solution at $t = 0.5$ is,

   $$y_1 = y_0 + hf(t_0, y_0) = 1 + 0.5(-5(1)) = -1.5$$

   (d) The Backward Euler method is stable for this ODE using a $h = 0.5$ step-size, and can be verified by computing the amplification factor,

   $$\left| \frac{1}{1 - \lambda h} \right| = 0.286 < 1$$

   In fact, the BE method is stable for this ODE for any step size.

   (e) The numerical value for the approximate solution using this method at $t = 0.5$ is,

   $$y_1 = y_0 + h(-5y_1) \Rightarrow y_1 = \frac{y_0}{1 + 5h} = 0.2857$$

3. **Purpose:** Comparing results for Forward Euler versus Backward Euler. From [Hea02, p.417,#9.5].

   Exercise: With the initial value of $y_0 = 1$ at $t_0 = 0$ and a time step of $h = 1$, compute the approximate solution value y_1 at time $t_1 = 1$ for the ODE $y' = -y$ using each of the following two numerical methods. (Your answers should be numbers, not formulas.)

   (a) Euler's method
   (b) Backward Euler method

   Solution:

   (a) Euler's method is defined as $y_{n+1} = y_n + \Delta t f(y_n)$.
   Thus, $y_1 = y_0 + h(-y) = 1 + 1(-0) = 1$
   (b) The Backward Euler method is defined as $y_{n+1} = y_n + \Delta t f(y_{n+1})$.
   Thus, $y_1 = y_0 + h(-y_1) \Rightarrow y_1(1+h) = y_0 \Rightarrow y_1 = \frac{1}{1+1} = \frac{1}{2}$

4. **Purpose:** Converting a second order ODE to a first order system, determining stability of solutions and stability of Euler's method and Backward Euler method on this system.

   Note to Instructor: If you have chosen not to present the slides on stability of an ODE solution, you may wish to skip part (c) of this exercise. From [Hea02, p.417,#9.7]. **Exercise:** Consider the IVP $y'' = y$ for $t \geq 0$ with initial values $y(0) = 1$ and $y'(0) = 2$.

   (a) Express this second-order ODE as an equivalent system of two first-order ODEs.
   (b) What are the corresponding intial conditions for the system of ODEs in part (a)?
   (c) Are solutions of this system stable?
   (d) Perform one step of Euler's method for this ODE system using a step size of $h = 0.5$.
   (e) Is Euler's method stable for this problem using this step size?
   (f) Is the backward Euler method stable for this problem using this step size?

   Solution:

   (a) Recall the given equation $y'' = y$. Let $u = y'$. Differentiating the latter equation, we get $u' = y''$. Substituting this into the given equation, gives $u' = y$. So the system of two first order ODEs is given by
   $$y' = u$$
   $$u' = y.$$
   (b) The corresponding initial conditions for the system of ODEs in part (a) are: $y(0) = 1$ and $u(0) = 2$.
   (c) We find the solution of this system and consider the behaviour as t increases:
   $$\begin{aligned} \begin{bmatrix} y' \\ u' \end{bmatrix} &= \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} y \\ u \end{bmatrix} \\ &= \alpha \begin{bmatrix} 1 \\ 1 \end{bmatrix} \mathrm{e}^{t} + \beta \begin{bmatrix} 1 \\ -1 \end{bmatrix} \mathrm{e}^{-t} \end{aligned}$$
   So we find that
   $$y = \alpha \mathrm{e}^{t} + \beta \mathrm{e}^{-t}$$
   $$u = \alpha \mathrm{e}^{t} - \beta \mathrm{e}^{-t}$$
   . Using the initial conditions, $\alpha = \frac{3}{2}$ and $\beta = \frac{-1}{2}$, so the solution of the system is
   $$y = \frac{3}{2}\mathrm{e}^{t} - \frac{1}{2}\mathrm{e}^{-t}$$
   . From this, it can be seen that the solutions of the system are unstable because as $t \to \infty$, $y \to \infty$.

(d) Euler's method state that, given $y(t_0) = y_0$, t_0 and h, then $y(t_1) = y(t_0) + hf(t_0, y_0)$. In this case, we have that $f : \mathrm{Y} = \begin{bmatrix} y \\ u \end{bmatrix}$, $y(t_0) : \mathrm{Y}(0) = \begin{bmatrix} 2 \\ 1 \end{bmatrix} = \mathrm{Y}_0$, $t_0 : t_0 = 0$, $h = 0.5$. Now since $\mathrm{Y}(0) = \begin{bmatrix} 2 \\ 1 \end{bmatrix}$, then

$$\begin{aligned} \mathrm{Y}_1 &= \mathrm{Y}_0 + h\mathrm{Y}_0 \\ &= \begin{bmatrix} 2 \\ 1 \end{bmatrix} + 0.5 \begin{bmatrix} 2 \\ 1 \end{bmatrix} \\ &= \begin{bmatrix} \frac{3}{2} \\ 3 \end{bmatrix} \end{aligned}$$

, so $y(0.5) = 3$ and $u(0.5) = \frac{3}{2}$.

(e) With the step size $h = 0.5$, Euler's method takes the form

$$\begin{aligned} \mathrm{Y}_{k+1} &= \mathrm{Y}_k + 0.5\mathrm{Y}_k \\ &= \frac{3}{2}\mathrm{Y}_k. \end{aligned}$$

In this case, the amplication factor is $\frac{3}{2}$, which is greater than one so Euler's method will be unstable with $h = 0.5$.

(f) For backward Euler,

$$\begin{aligned} \mathrm{Y}_{k+1} &= \mathrm{Y}_k + 0.5\mathrm{Y}_{k+1} \\ &= -2\mathrm{Y}_k \\ &= (-2)^{k+1}\mathrm{Y}_0. \end{aligned}$$

Since $|(-2)| > 1$, then backward Euler will be unstable for this problem with $h = 0.5$.

5. **Purpose:** Identifying properties of methods. From [Hea02, pp.417–418,#9.9]. **Exercise:** For each property listed below, state which of the following two ODE methods has or have the given property:

$$y_{k+1} = y_k + \frac{h}{2}(3f(t_k, y_k) - f(t_{k-1}, y_{k-1})) \quad (1)$$

$$y_{k+1} = y_k + \frac{h}{2}(f(t_k, y_k) - f(t_{k+1}, y_{k+1})) \quad (2)$$

Properties:

(a) Second-order accurate

(b) Single-step method

(c) Implicit method

(d) Unconditionally stable

(e) Good for solving stiff ODEs

6. **Purpose**: Determining the accuracy of a method through Taylor expansions. Note to Instructor: You may need to help the students by giving them a bit more background on how to Taylor expand about points other than t_{n+1}. For example,

$$y(t_{n-1}) = y(t_n) - hy'(t_n) + \frac{h^2}{2}y''(t_n) - \frac{h^3}{3!}h'''(t_n) + \mathcal{O}(h^4)$$

From [Hea02, pp.418,#9.12].

Exercise: The centered difference approximation

$$y' \equiv \frac{y_{k+1} - y_{k-1}}{2h}$$

leads to the two-step *leapfrog method*

$$y_{k+1} = y_{k-1} + 2hf(t_k, y_k)$$

for solving the ODE $y' = f(t, y)$. Determine the order of accuracy for this method.

Solution:

Write expressions for y_{k+1} and y_{k-1} as follows,

$$y_{k-1} = y_k - hy_k' + \frac{h^2}{2}y_k'' - \frac{h^3}{3!}y_k''' + \mathcal{O}(h^4)$$

$$y_{k+1} = y_k + hy_k' + \frac{h^2}{2}y_k'' + \frac{h^3}{3!}y_k''' + \mathcal{O}(h^4)$$

Thus we can compute y' using the *leapfrog method* as shown,

$$y' = \frac{y_{k+1} - y_{k-1}}{2h} = \frac{2hy_k' + \frac{h^3}{3!}y_k''' + \mathcal{O}(h^4)}{2h} = y_k' + \frac{h^2}{3!}y_k''' + \mathcal{O}(h^4) = y_k' + \mathcal{O}(h^2)$$

Thus, the accuracy for this method is $\mathcal{O}(h^2)$.

7. **Purpose**: Computing project. Using packaged software to compute the solution to a system of ODEs representing an SIR epidemic model. Understanding the meaning of the model and experimenting with parameter values to determine different outcomes.

From [Hea02, pp.418–419,#9.2]. **Exercise:** The *Kermack-McKendrick model* for the course of an epidemic in a population is given by the system of ODEs

$$\begin{aligned} y_1' &= -cy_1y_2 \\ y_2' &= cy_1y_2 - dy_2 \\ y_3' &= dy_2 \end{aligned}$$

where y_1 represents susceptibles, y_2 represents infectives in circulation, and y_3 respresents infectives removed by isolation, death, or recovery and immunity. The parameters c and d represent the infection rate and removal rate, respectively. Use a library routine to solve this system numerically, with the parameter values $c = 1$ and $d = 5$, and initial values $y_1(0) = 95$, $y_2(0) = 5$, and $y_3(0) = 0$. Integrate from $t = 0$ to $t = 1$. Plot each solution component on the same graph as a function of t. As expected with an epidemic, you should see the number of infectives grow at first, then diminish to zero. Experiment with other values for the parameters and initial conditions. Can you find values for which the epidemic does not grow, or for which the entire population is wiped out?

Solution:

A plot of each component on the same graph, as a function of t can be seen in Figure 21. In the plot, y_1, the susceptibles is represented by the thin solid line, y_2, the infectives in circulation represented by thin dashed line, and y_3, the infectives removed is represented by the thick solid line.

Examples of values for which the epidemic does not grow include $c = 0.5, d = 5$ and $c = 1, d = 100$. An example value for which the entire population is wiped out is $c = 10, d = 10$.

8. **Purpose**: Computing project. Using packaged software to compare efficiency of various library routines. Note to Instructor: You may ask the students first to catalog the ODE solving routines available in whichever numerical package you choose to have them use. Or you may wish to specify a particular set of ODE solvers the students should implement. From [Hea02, p.419,#9.3].

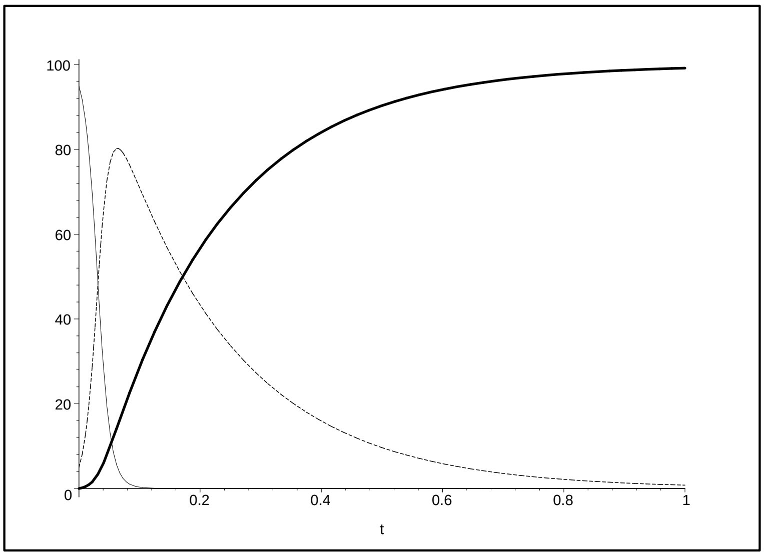

Figure 21: Phase portrait of the system in Exercise 4.

Exercise: Experiment with several different library routines having automatic step-size selection to solve the ODE

$$y' = -200ty^2$$

numerically. Consider two different initial conditions, $y(0) = 1$ and $y(-3) = 1/901$, and in each case compute the solution until $t = 1$. Monitor the step size used by the routines and discuss how and why it changes as the solution progresses. Explain the difference in behavior for the two intial conditions. Compare the different routines with respect to efficiency for a given accuracy requirement.

9. **Purpose**: Computing project. Using packaged or self-written software to compare stiff and non-stiff numerical solution methods. Note to Instructor: You may choose to ask the students to compare forward Euler with backward Euler, in addition to comparing the packaged routines. From [Hea02, p.419,#9.5]. **Exercise:** The following system of ODEs models nonlinear chemical reactions

$$\begin{aligned} y_1' &= -\alpha y_1 + \beta y_2 y_3 \\ y_2' &= \alpha y_1 - \beta y_2 y_3 - \gamma {y_2}^2 \\ y_3' &= \gamma {y_2}^2 \end{aligned}$$

where $\alpha = 4 \times 10^{-2}$, $\beta = 10^4$, and $\gamma = 3 \times 10^7$. Starting with initial conditions $y_1(0) = 1$ and $y_2(0) = y_3(0) = 0$, integrate this ODE from $t = 0$ to $t = 3$. You may use either a library routine or an ODE solver of your own design. Try both stiff and non-stiff methods, and experiment with various error tolerances. Compare the efficiencies of the stiff and non-stiff methods as a function of error tolerance.

Solution:
The following results were found using MATLAB ODE23 (nonstiff method)

The following results were found using MATLAB ODE23s (stiff method)

From these results, it can be seen that the stiff method seems to be more efficient than the non-stiff method, requiring less time steps and generally less CPU time.

Error tolerance	t steps	Failures	CPU time (secs)
1e-12	2921	10	2.703
1e-10	2683	11	2.624
1e-8	2633	11	2.644
1e-6	2623	9	2.994
1e-4	2623	32	0.47

Error tolerance	t steps	Failures	CPU time (secs)
1e-12	1690	4	5.387
1e-10	266	3	0.941
1e-8	50	3	0.43
1e-6	19	3	0.141
1e-4	15	3	0.741

Exercises for Bifurcation Module

1. **Purpose:** To study saddle node bifurcations in a model. From [Str94], Example 8.1.1.

   Exercise: The following system has been discussed by [Gri71] as a model for a genetic control system. The activity of a certain gene is assumed to be directly induced by two copies of the protein for which it codes. In other words, the gene is stimulated by its own product, potentially leading to an autocatalytic feedback process. In dimensionless form, the equations are

$$\dot{x} = -ax + y$$
$$\dot{y} = \frac{x^2}{1+x^2} - by$$

   where x and y are proportional tothe concentrations of the protein and the messenger RNA from which it is translated, respectively, and $a, b > 0$ are parameters that govern the rate of degradation of x and y. Show that the system has three fixed points when $a < a_c$, where a_c is to be determined. Show that two of these fixed points coalesce in a saddle-node bifurcation when $a = a_c$. Then sketch the phase portrait for $a < a_c$, and give a biological interpretation.

   Solution: The fixed points of a system are found by solving $\dot{x} = 0$ and $\dot{y} = 0$. For this particular system, solve:

$$y = ax \quad \text{and} \quad y = \frac{1}{b}\frac{x^2}{1+x^2}\ , \quad \Rightarrow ax = \frac{x^2}{b(1+x^2)}$$
$$\text{for} \quad x^* = 0, \frac{1 \pm \sqrt{1-4a^2b^2}}{2ab}$$

   which illustrates the required three fixed points. Notice that if $1 - 4a^2b^2 = 0$, or rather $2ab = 1$, the two latter fixed points coalesce into one. Thus we can determine $a_c = 1/2b$, below which value three fixed points exist.

   At $a = a_c$, the non-zero fixed point is $x^* = 1/2ab$. The presence of the saddle-node bifurcation can be confirmed by evaluating the Jacobian matrix,

$$A = \left(\begin{array}{cc} -a & 1 \\ \frac{2x}{(1+x^2)^2} & -b \end{array} \right)\Bigg|_{x=x^*} = ab - \frac{2x^*}{(1+(x^*)^2)^2}$$

   at the fixed point. Since two fixed points coalesce at $a = a_c$, and the eigenvalues of A are both real positive and negative, there exists a saddle-node bifurcation. The phase portrait for $a < a_c$ is shown in Figure 22.

   The biological interpretation is that the system can act like a *biochemical switch*, but only if the MRNA and protein degrade slowly enough - specifically, their decay rates must satisfy $ab < 1/2$. In this case, there are two stable steady states: one at the origin, meaning the gene is silent and there is no protein around to turn it on; and one where x and y are large, meaning that the gene is active and sustained by the high level of protein. The stable manifold of the saddle acts as a threshold; it determines whether the gene turns on or off, depending on the intial values of x and y.

2. **Purpose:** To study homoclinic bifurcations. From [Str94], pp 262-263

   Notes: This is similar to a heteroclinic bifurcation, in that it involves the unstable manifold of a saddle point.

   Exercise: Consider the system

$$\dot{x} = y$$
$$\dot{y} = \mu y + x - x^2 + xy$$

   (a) Show that the origin is a saddle point for all values of μ.

   (b) Find any other equilibria and determine their stability.

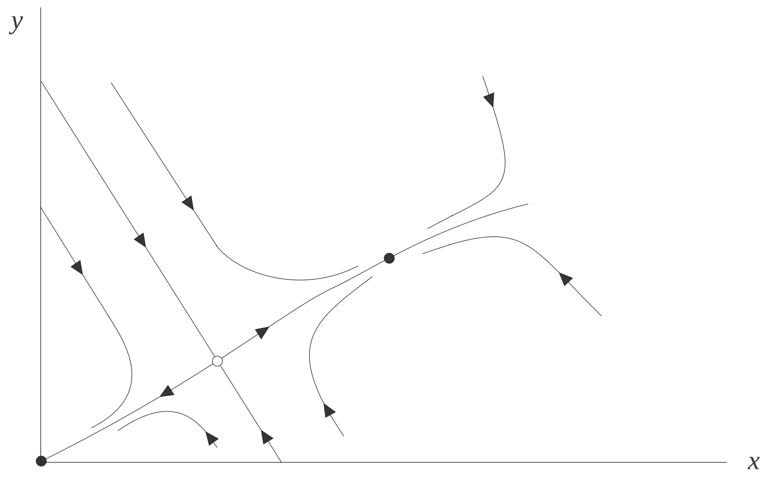

Figure 22: Phase portrait for the $a < a_c$ case

(c) Numerically plot phase portraits for values of μ between -1 and -0.5. What happens to the unstable manifold through the origin as μ is varied?

(d) Numerically find the critical μ-value at which the stable and unstable manifolds through the origin intersect. (This is called a *homoclinic connection* or *homoclinic orbit*.)

(e) Plot a few phase portraits for μ-values above and below this critical value and describe what happens to the unstable manifold through the origin.

This type of bifurcation is called a *homoclinic bifurcation*.

Solution:

(a) The Jacobian of the system at the origin is $J = \begin{bmatrix} 0 & 1 \\ 1 - 2x + y & \mu + x \end{bmatrix}\Bigg|_{0,0} = \begin{bmatrix} 0 & 1 \\ 1 & \mu \end{bmatrix}$. The eigenvalues are given by $\lambda_{1,2} = \frac{\mu}{2} \pm \frac{\sqrt{\mu^2+4}}{2}$. Now since $\mu^2 + 4 > \mu^2 \ \forall \mu$, then it must hold that $\sqrt{\mu^2 + 4} > \mu \ \forall \mu$. Therefore $\lambda_1 = \frac{\mu}{2} + \frac{\sqrt{\mu^2+4}}{2} > 0 \ \forall \mu$ and $\lambda_2 = \frac{\mu}{2} - \frac{\sqrt{\mu^2+4}}{2} > 0 \ \forall \mu$. Since both eigenvalues are real and are of opposite signs, then the origin is a saddle for all values of μ.

(b) The other fixed point, $(1, 0)$ can be found by solving $\dot{x} = 0$ and $\dot{y} = 0$. The Jacobian evaluated at this point is $J = \begin{bmatrix} 0 & 1 \\ -1 & \mu + 1 \end{bmatrix}$, and it has eigenvalues $\lambda_{1,2} = \frac{(\mu+1) \pm \sqrt{(\mu+1)^2 - 4}}{2}$.
If $(\mu + 1)^2 > 4, \lambda_{1,2} \in \mathbb{R}$ and $\lambda_{1,2} > 0$ if $\mu > -1$. Therefore, need $\mu > 1$, which then makes this fixed point an unstable node.
If $(\mu + 1)^2 < 4, \lambda_{1,2} \in \mathbb{R}$ and $\lambda_{1,2}$ are complex conjugates. For $\mu < -1$, the real parts of λ are negative, therefore the fixed point is a stable spiral. For $-1 < \mu < 1$, the real parts of λ are positive, therefore the fixed point is an unstable spiral.

(c) Figure 23 shows different phase portraits for the system for $\mu = -0.55, -0.75, -0.8$ and $\mu = -0.95$.

(d) Using Maple, it is possible to numerically determine the critical μ-value, μ_c. This critical value, where the stable and unstable manifolds through the origin intersect occurs at $\mu_c = -0.8645$.

(e) Figure 24 shows different phase portraits for the system for various values of μ above and below the critical value $\mu = -0.8645$.

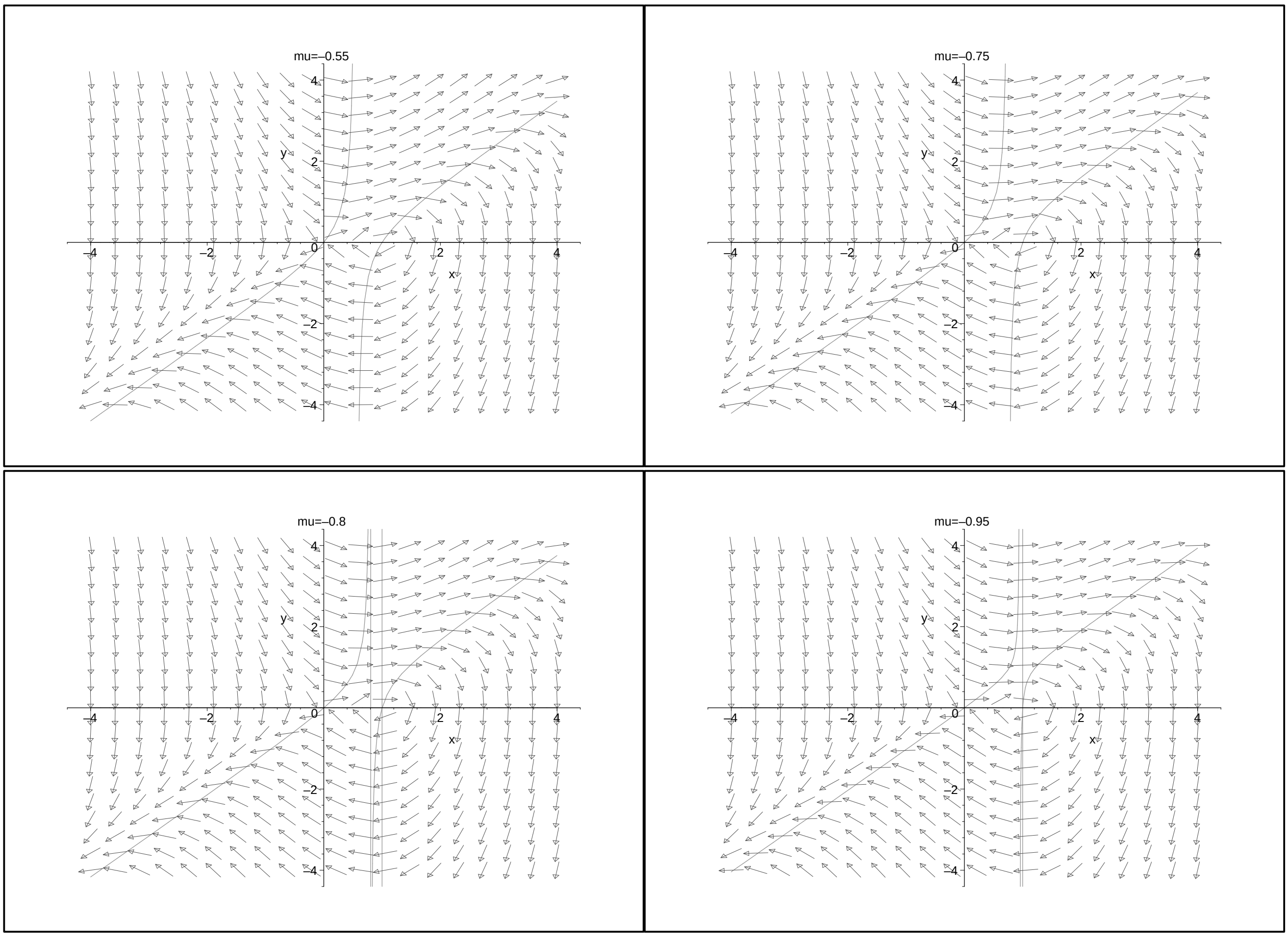

Figure 23: Phase portraits for Exercise 2c for various values of μ between -1 and -0.5.

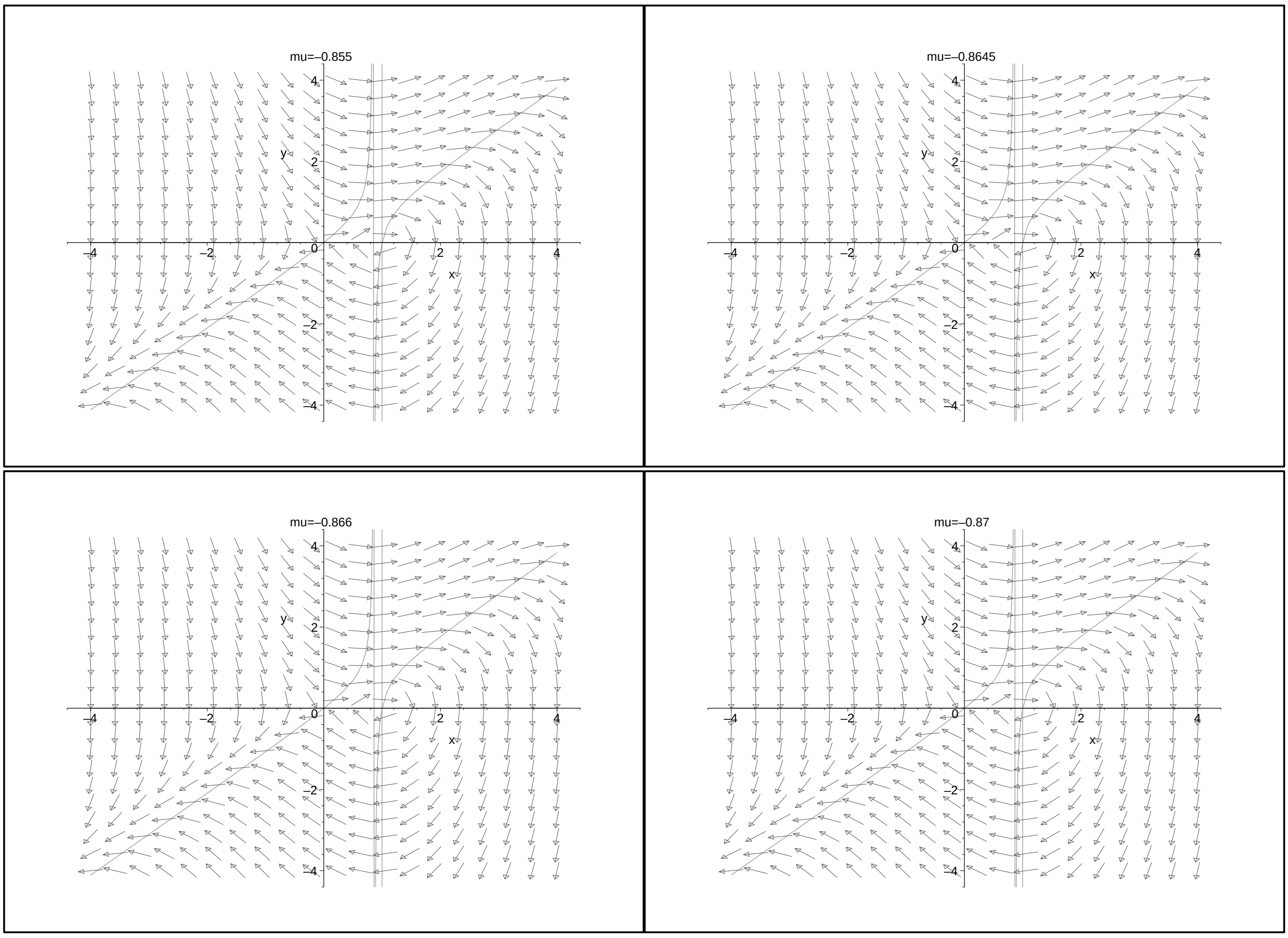

Figure 24: Phase portraits for Exercise 2e for various values of μ above and below the critical value of $\mu_c = -0.8645$.

3. **Purpose:** To determine the type of bifurcation. From [Str94], Problem 8.1.6.

Exercise: Consider the system $\dot{x} = y - 2x, \dot{y} = \mu + x^2 - y$.

(a) Sketch the nullclines.

(b) Find and classify the bifurcations that occur as μ varies.

(c) Sketch the phase portrait as a function of μ.

Solution:

(a) The nullclines for this system are given by $y = 2x$ and $y = \mu + x^2$, however the number of fixed points varies depending on the value of μ. If $\mu > 1$, the there are no fixed points for the system (see Figure 25). For $\mu = 1$, one fixed point occurs (see Figure 26), and for $\mu < 1$, there are 2 fixed points for the system (see Figure 27).

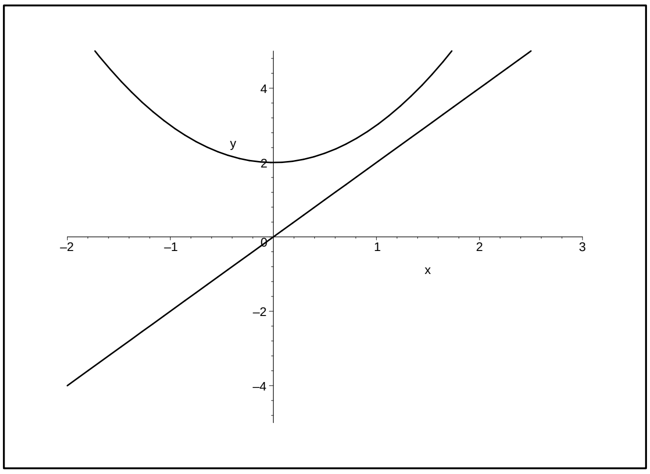

Figure 25: The nullclines for the $\mu > 1$ case

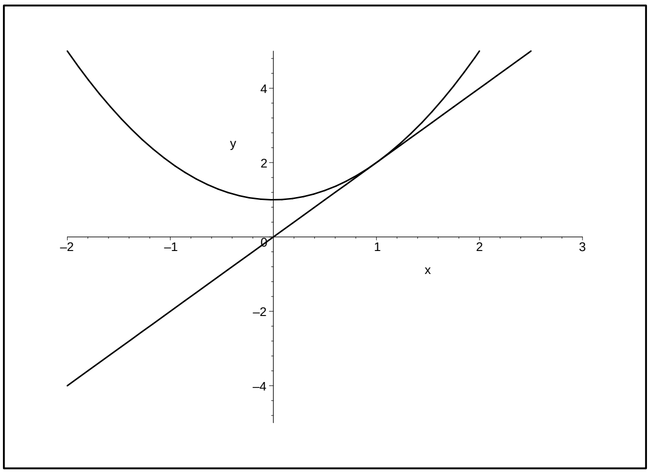

Figure 26: The nullclines for the $\mu = 1$ case

(b) The bifurcations of the system occur at the critical value of $\mu_c = 1$, and is a saddle-node bifurcation. This can be found by evaluating the Jacobian, finding the eigenvalues and classifying the fixed points for $\mu \leq 1$.

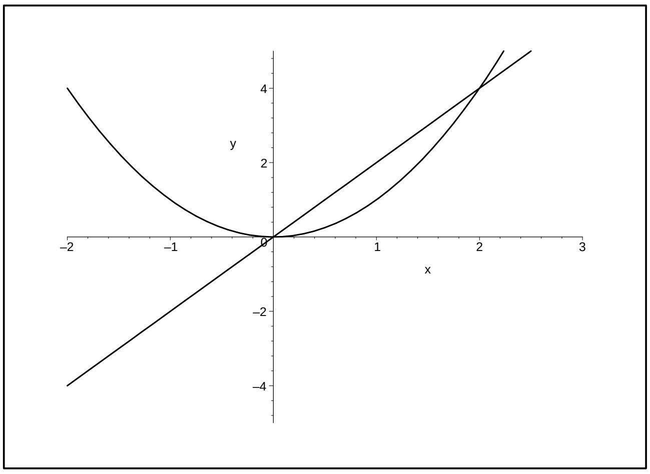

Figure 27: The nullclines for the $\mu < 1$ case

References

[Gri71] J.S. Griffith. *Mathematical Neurobiology.* Academic Press, 1971.

[Hea02] Michael T. Heath. *Scientific Computing: An Introductory Survey.* McGraw Hill, second edition, 2002.

[KMTP94] Vladmir A. Kuznetsov, Iliya A. Makalkin, Mark A. Taylor, and Alan S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2), 1994.

[Pan96] John Carl Panetta. A mathematical model of periodically pulsed chemotherapy: Tumor recurrence and metastasis in a competitive environment. *Bulletin of Mathematical Biology*, 58(3):425–227, 1996.

[Str94] Steven H. Strogatz. *Nonlinear Dynamics and Chaos.* Addison-Wesley, 1994.