Cellular Biophysics and Modeling — Fall 2025

Problem Set #3

1. Use the Hodgkin-Huxley Simulation with Javascript that you can find at `https://www.andrewkrause.org/tools-code/hodgkin-huxley-simulation-with-javascript` to explore the Hodgkin-Huxley model and answer the following questions.

   Begin with default parameters. Press `Start` and notice that the random applied current generates action potentials. Now set `IRand` to $0\,\mathsf{nA/cm^2}$. This parameter will remain 0 for the rest of these questions. As a consequence, your numerical exploration of the Hodgkin-Huxley model will be deterministic.

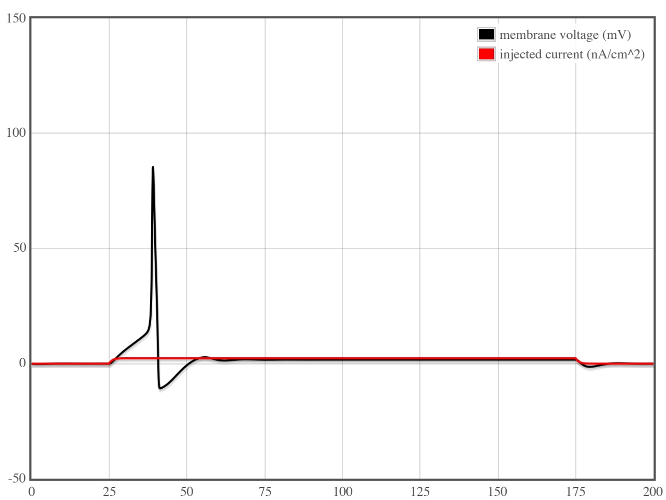
   Document your work by printing out PDFs of the simulations performed to answer each question. Alternatively, you may sketch a qualitatively correct representation of the simulation results for each question.[1]

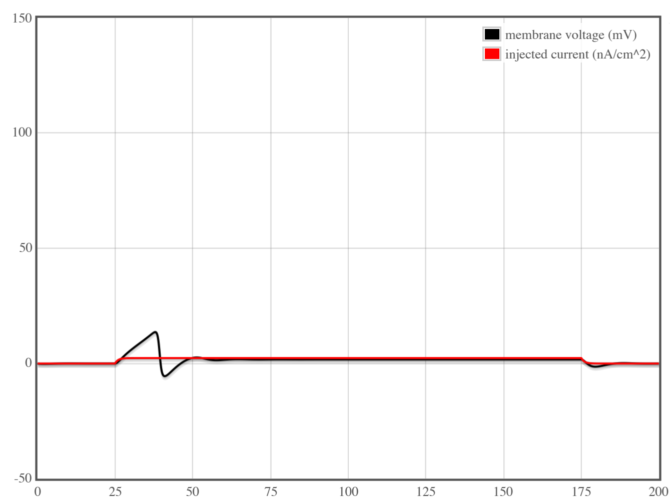
   (a) Find the minimum integer-value current (`IDC`, in units of $\mathsf{nA/cm^2}$) for eliciting a single action potential.

   The minimum integer-value current is `IDC` $= 3\,\mathsf{nA/cm^2}$ (see answer to next question).

   (b) Explore the "sharpness" of the threshold phenomenon. Is the threshold "graded" or "all-or-none"? If the threshold is "all-or-none," determine a **superthreshold** and **subthreshold** applied currents that are separated by $0.01\,\mathsf{nA/cm^2}$ or less.

   Left: `IDC` $= 2.355298\,\mathsf{nA/cm^2}$ results in a spike (is a superthreshold current). Right: `IDC` $= 2.355297\,\mathsf{nA/cm^2}$ does not yield a spike (is a subthreshold current).

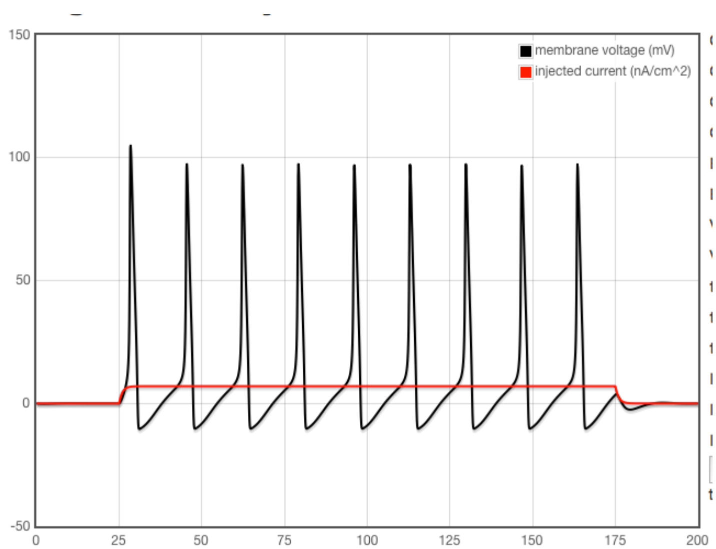




[1]Adapted from exercises at the end of Nelson and Rinzel 2003 *The Hodgkin-Huxley Model.*

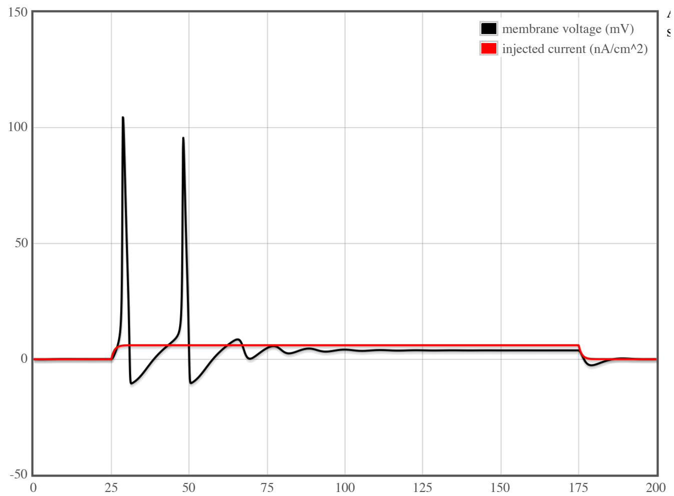
(c) The **rheobase** current is the minimum (integer-valued) current that will elicit repetitive firing (i.e., generate a train of action potentials). What is the rheobase current for the model?

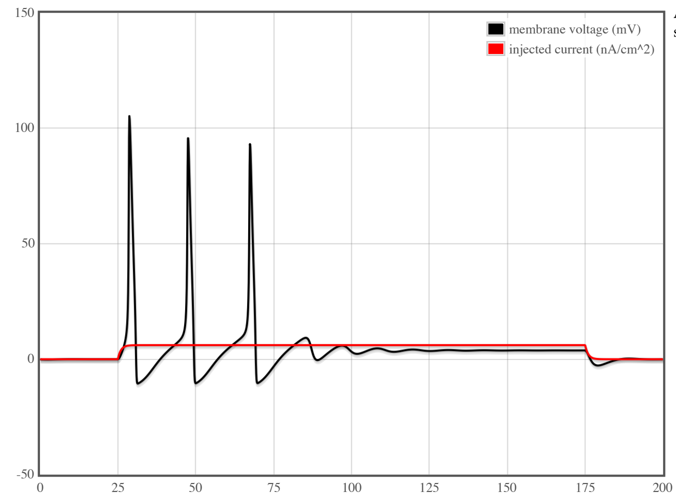
The rheobase for the mode is IDC $= 7\,\mathsf{nA/cm^2}$:



(d) How sharp is the transition from single spike generation to **repetitive firing**? Can you find a value of the injected current that generates two action potentials, but doesn't fire repetitively?

Left: IDC $= 6\,\mathsf{nA/cm^2}$. Right: IDC $= 6.1\,\mathsf{nA/cm^2}$.

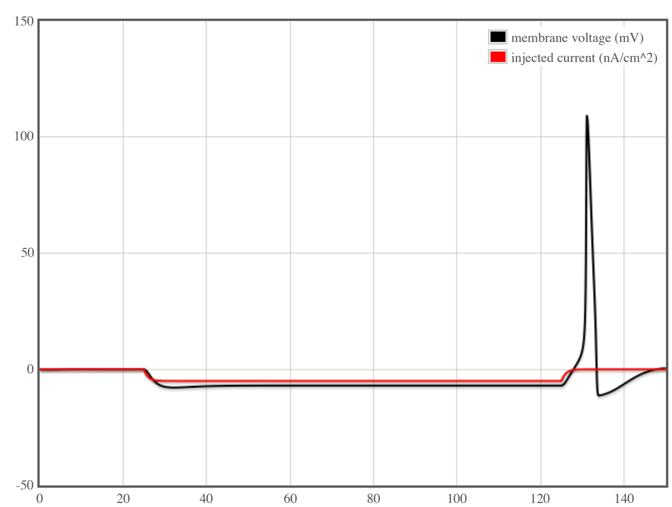




(e) Set `tStop` $= 150\,\mathsf{ms}$, `tInjStart` $= 25\,\mathsf{ms}$ and `tInjStop` $= 125\,\mathsf{ms}$.
By counting the number of spikes generated in a $100\,\mathsf{ms}$ window, construct a plot of firing frequency vs. injected current—that is, a **frequency-current relation**—starting at the rheobase current and working up to a value of about $IDC = 200\,\mathsf{nA/cm^2}$.

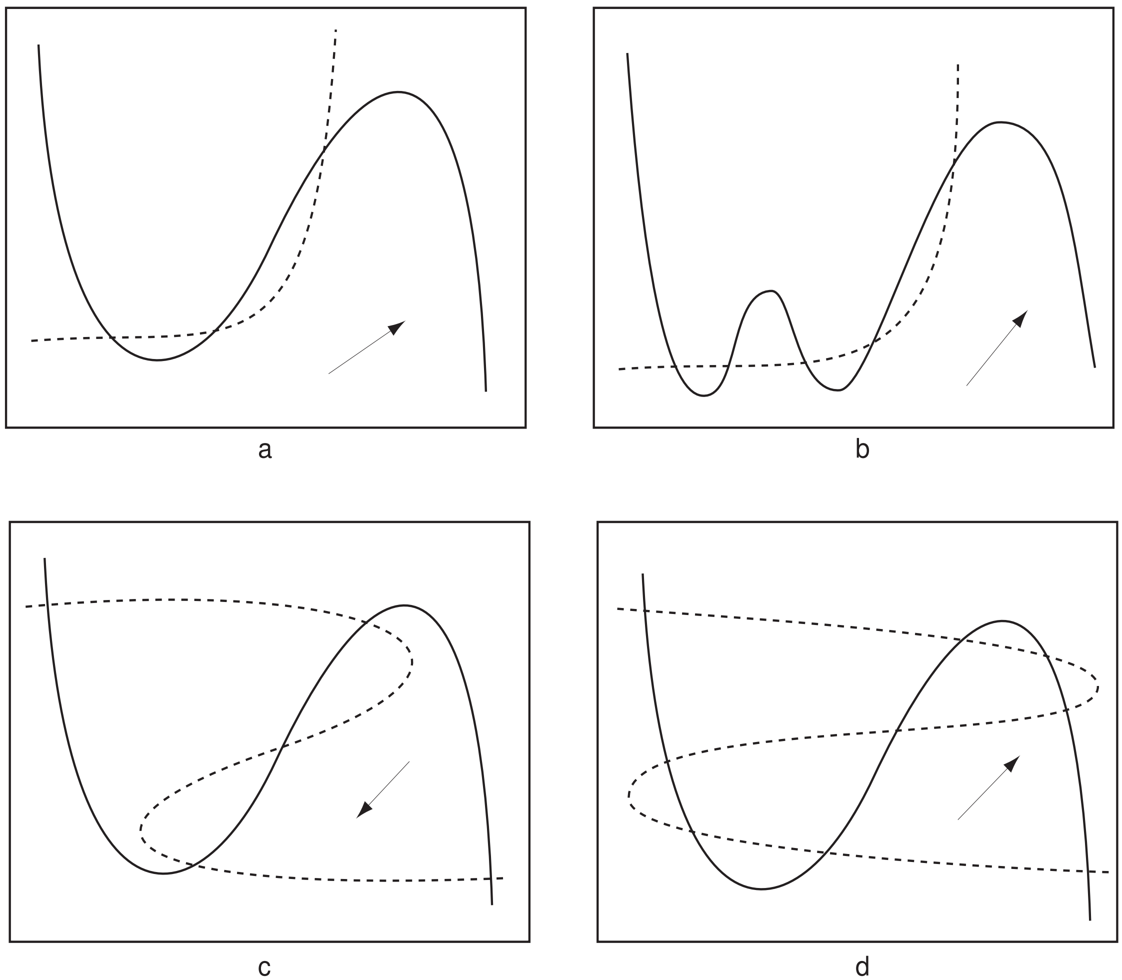
(f) What is the minimum firing frequency for repetitive spiking?

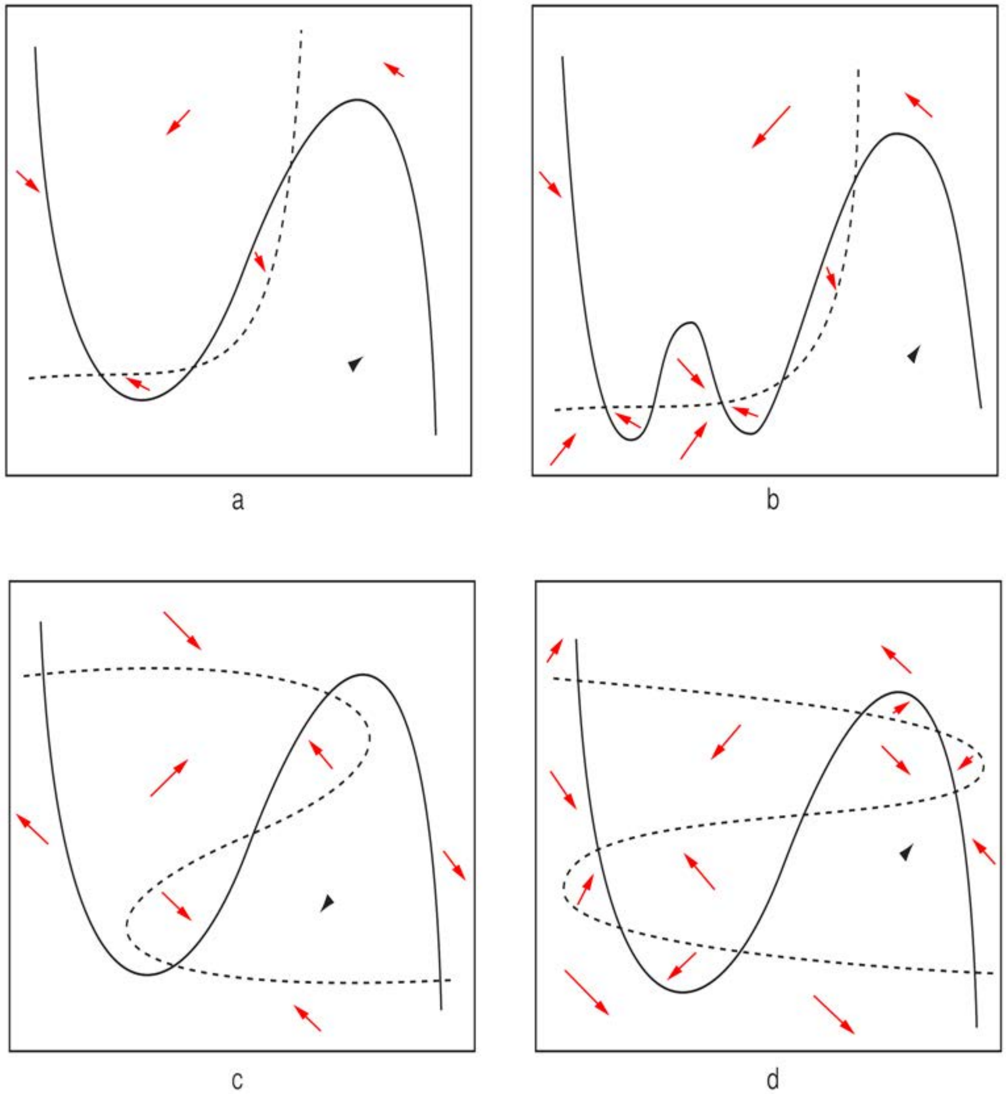
(g) All of the injection pulses in the previous current clamp problems have been depolarizing. Now consider the effect of hyperpolarizing current pulses. Set the pulse amplitude to $IDC = -5\,\mathsf{nA/cm^2}$. You will likely observe a single "rebound" spike after the hyperpolarizing current pulse ends. This phenomenon is called **post anodal break excitation**. What mechanism(s) in the model might be responsible for this behavior?

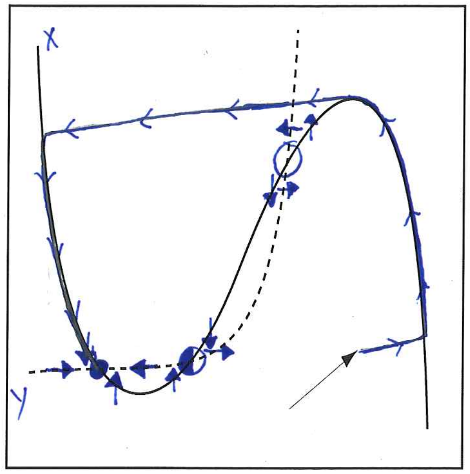


The hyperpolarization de-inactivates the sodium current, lowering the threshold voltage, which is achieved when the membrane is released from hyperpolarization.

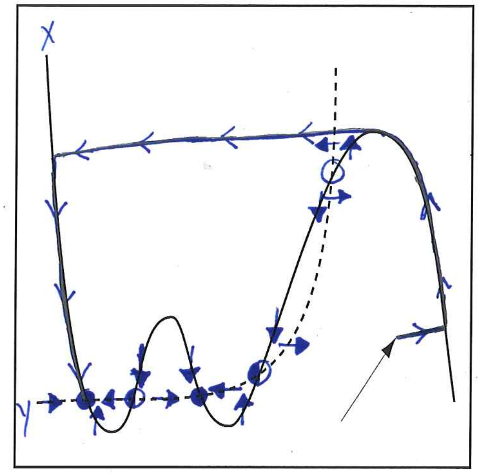
2. In the four phase planes below, y is the vertical axis, x is the horizontal axis, the solid curve is the x-nullcline, the dashed curve is the y-nullcline, and the direction of vector field at one particular value of (x, y) is indicated by a filled triangle (e.g., in panel (a), the arrow points northeast, so $dx/dt > 0$ and $dy/dt > 0$ in this region). For each phase plane, do (a), (b) and (c) below.



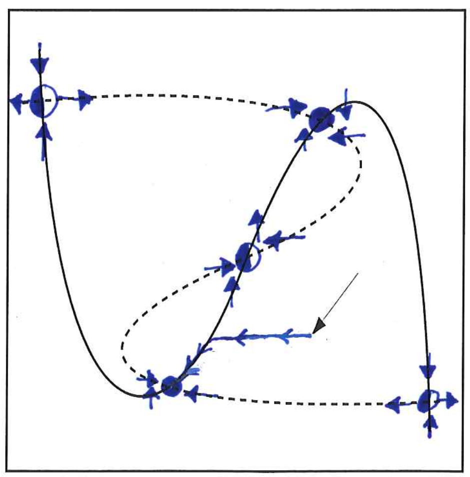

a
b
c
d



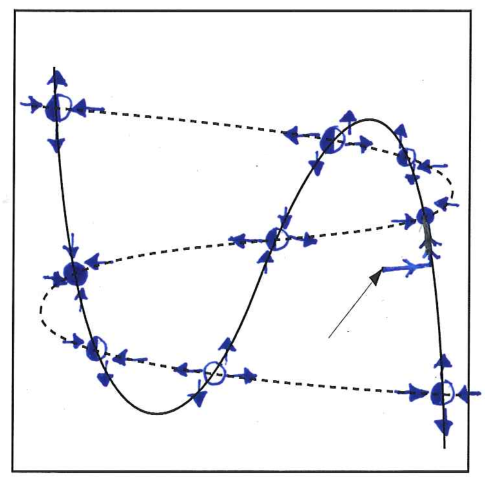
a



b



c



d

(a) Determine the direction of the vector field in each region of the phase plane delimited by the nullclines. Draw an arrow pointing either northeast ($dx/dt > 0$, $dy/dt > 0$), northwest ($dx/dt < 0$, $dy/dt > 0$), southwest ($dx/dt < 0$, $dy/dt < 0$) or southeast ($dx/dt > 0$, $dy/dt < 0$).

(b) Assuming x is a fast variable and y is a slow variable, sketch the solution (trajectory) beginning near the filled triangle.

(c) Assuming x is a fast variable and y is a slow variable, use an open or filled circle to indicate whether each steady-state is stable or unstable.

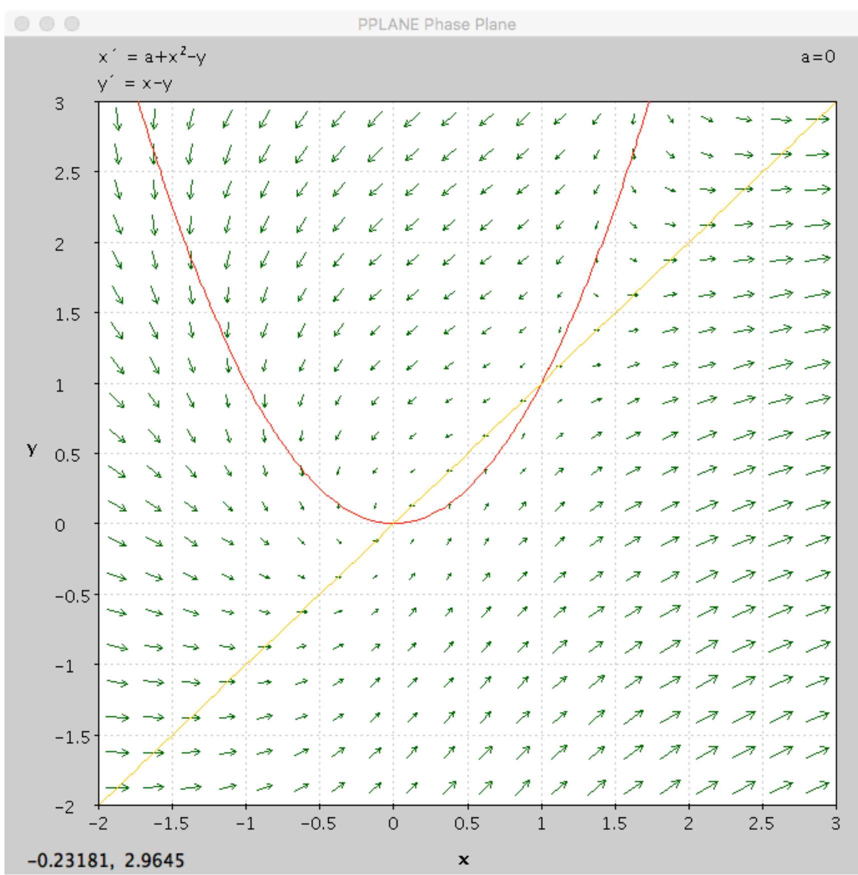
3. Consider the nonlinear system

$$\frac{dx}{dt} = a + x^2 - y$$
$$\frac{dy}{dt} = x - y$$

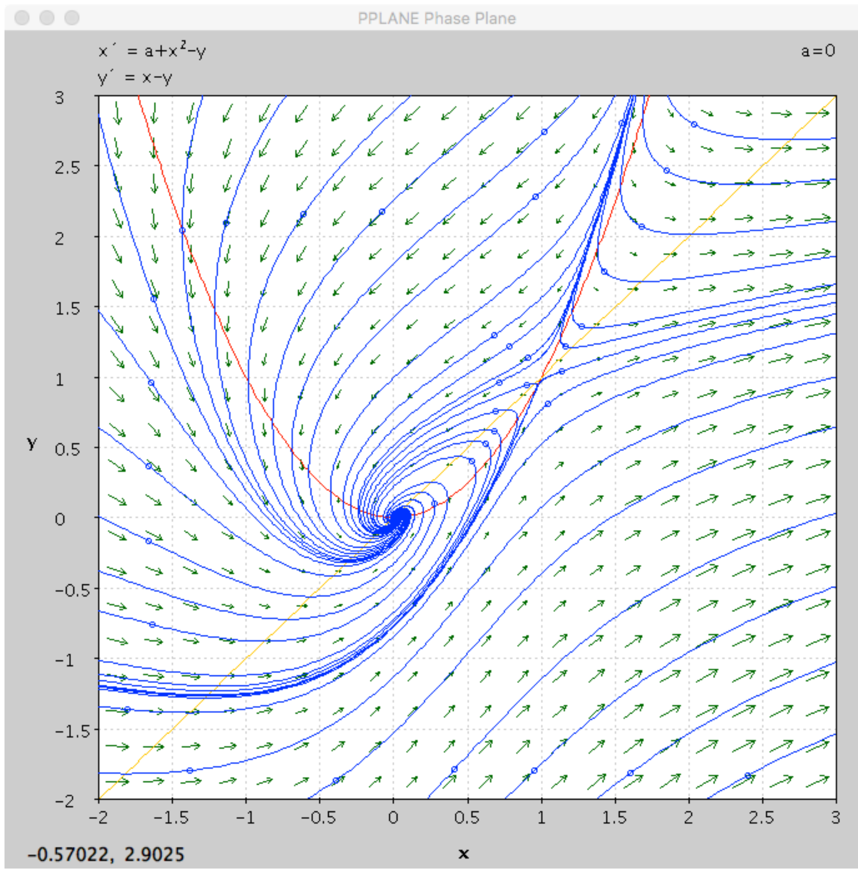
(a) Analytically determine the equations for the x- and y-nullclines.

$$0 = a + x^2 - y \Longrightarrow y = x^2 + a \quad (x\text{-nulline})$$
$$0 = x - y \Longrightarrow y = x \quad (y\text{-nullcline})$$

(b) Use the phase plane analysis software package "pplane" found at `https://www.cs.unm.edu/~joel/dfield/` to plot the nullclines of this ODE system. There is a menu option `Solution / Show Nullclines`. I recommend setting the x and y limits to -2 (min) to 3 (max).



(c) Using the mouse to select initial conditions, produce a phase plane with enough trajectories to give a sense of the flow.



(d) Assuming that $a = 0$, analytically find the x and y values for two steady-states.

Steady-states are given by intersections of the nullclines. Solving $y_{ss} = x_{ss}^2 + a$ and $y_{ss} = x_{ss}$ simultaneously gives

$$x_{ss} = x_{ss}^2 + a \quad \Longrightarrow x_{ss} = \frac{1 \pm \sqrt{1-4a}}{2}.$$

When $a = 0$, we have $\sqrt{1-4a} = \sqrt{1-4\cdot 0} = \sqrt{1} = 1$, so the steady-state values of x are

$$x_{ss} = \frac{1 \pm 1}{2} \Longrightarrow x_{ss} = 0 \text{ or } 1.$$

Because $y = x$ is one of the nullclines, $y_{ss} = x_{ss}$ where the nullclines intersect; thus, steady-states are $(x_{ss}, y_{ss}) = (0,0)$ and $(x_{ss}, y_{ss}) = (1,1)$.

(e) Consider the flow in the phase plane near each of the two steady states. Classify each steady state as either stable or unstable. Check your answer using the software: `PPLANE Phane Plane / Solution / Find an Equilibrium Point`.

From the trajectories in the phase plane one can see that the steady state $(x_{ss}, y_{ss}) = (0, 0)$ is a stable spiral and $(x_{ss}, y_{ss}) = (1, 1)$ is a saddle (unstable).
This can also be shown using linear stability analysis. The Jacobian of the 2D system is

$$J(x, y) = \begin{pmatrix} 2x & -1 \\ 1 & -1 \end{pmatrix}$$

Evaluating the Jacobian at the steady state $(x_{ss}, y_{ss}) = (0, 0)$ we have

$$J(0, 0) = \begin{pmatrix} 0 & -1 \\ 1 & -1 \end{pmatrix}$$

The trace of the Jacobian is $\mathrm{tr}(J) = -1$ and the determinant of J is $\det(J) = 1$, which satisfies the condition for stability. Because $\det(J) > \mathrm{tr}(J)^2/4$, the stable steady state is a spiral.
Evaluating the Jacobian at the steady state $(x_{ss}, y_{ss}) = (1, 1)$ we have

$$J(1, 1) = \begin{pmatrix} 2 & -1 \\ 1 & -1 \end{pmatrix}$$

The trace of the Jacobian is $\mathrm{tr}(J) = 1$ and the determinant of J is $\det(J) = -1$. Because the determinant is negative the steady state at $(1, 1)$ can be classified as a saddle (unstable).

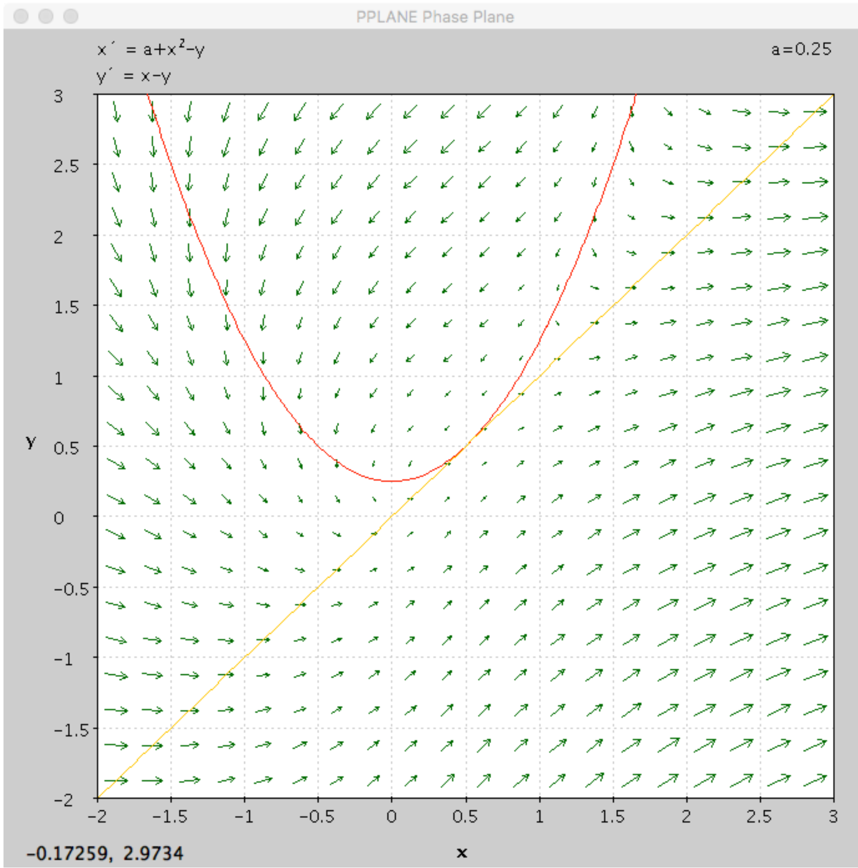
(f) Determine the Jacobian of this nonlinear system. Evaluate the Jacobian at each steady state. By calculating the determinant and trace of these matrices, confirm PPLANE's stability analysis (answer to previous question).

(g) Consider a to be a bifurcation parameter. What is the critical value of a? Over what range of values for a does the system have 2, 1 or 0 equilibria? What type of bifurcation occurs when a is at the critical value?

We already found that steady states are given by (x, y) where $y = x$ and

$$x = \frac{1 \pm \sqrt{1 - 4a}}{2}.$$

The critical value of a is that value that leads to 1 steady state, as opposed to 0 or 2. This occurs when $1 - 4a = 0$; thus, the critical value is $a = 1/4$.



The bifurcation that occurs is a saddle-node bifurcation, i.e., the coalescence of a stable node and an unstable saddle.

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4. The Fitzhugh-Nagumo (FHN) equations are:

$$\begin{aligned}\frac{dx}{dt} &= x - x^3/3 - y + \gamma \\ \frac{dy}{dt} &= \epsilon(x + \alpha + \beta y)\end{aligned}$$

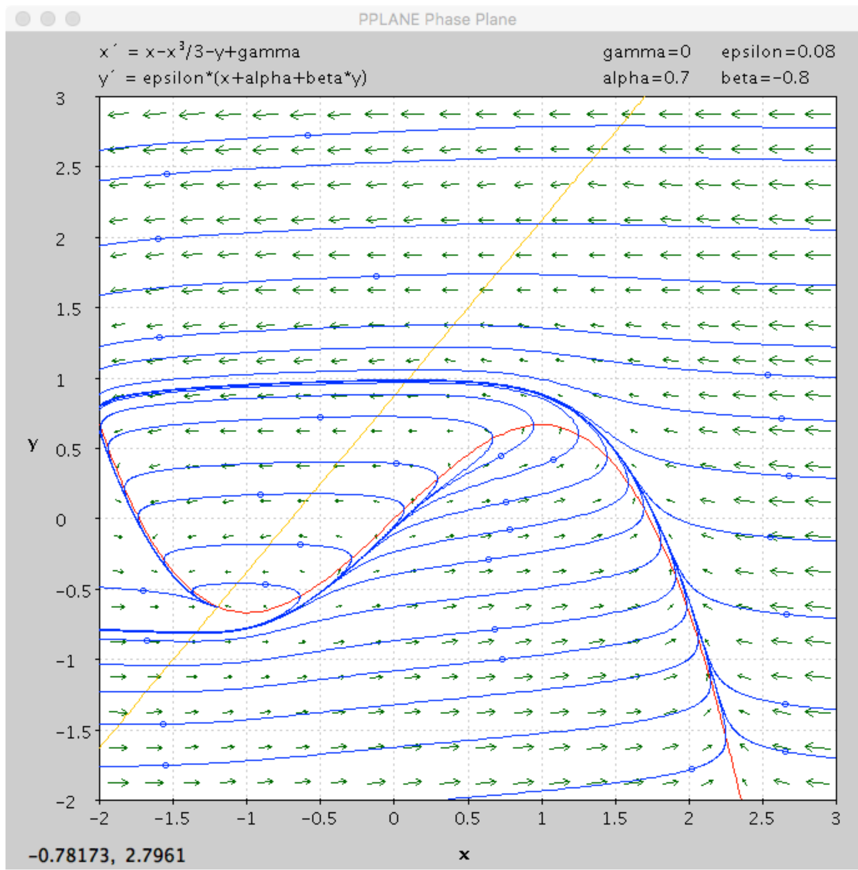
where $\epsilon = 0.08$, $\alpha = 0.7$, and $\beta = -0.8$. Comparing these equations to the Morris-Lecar model discussed in class, notice that the variable y is a 'recovery variable' and γ enters into the equations like an applied current.

(a) Analytically determine formula for the x- and y-nullclines. Your answer will be a function of ϵ, α, β and γ. Which nullcline is cubic and which is linear?

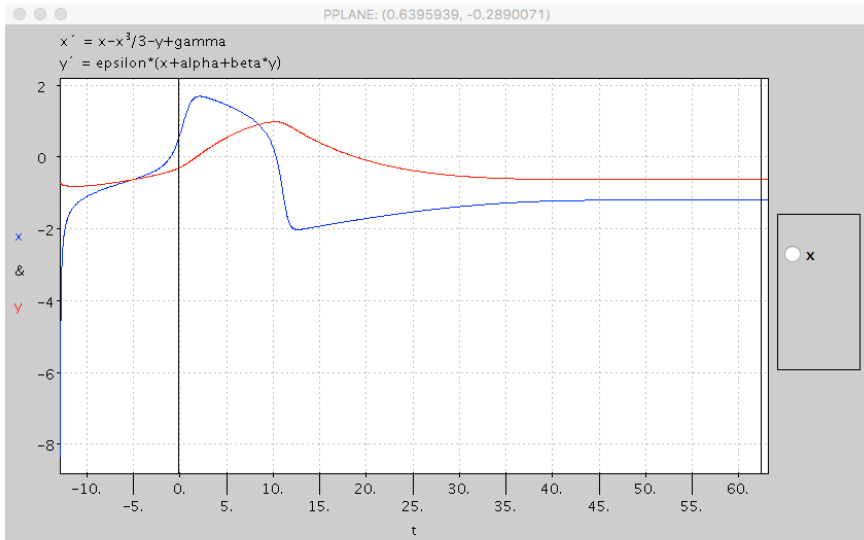
$$\begin{aligned}0 &= x - x^3/3 - y + \gamma \Longrightarrow y = x - x^3/3 + \gamma \quad (x\text{-nulline}) \\ 0 &= \epsilon(x + \alpha + \beta y) \Longrightarrow y = -\frac{x+\alpha}{\beta} \quad (y\text{-nullcline})\end{aligned}$$

The y-nullcline is linear and the x-nullcline is cubic.

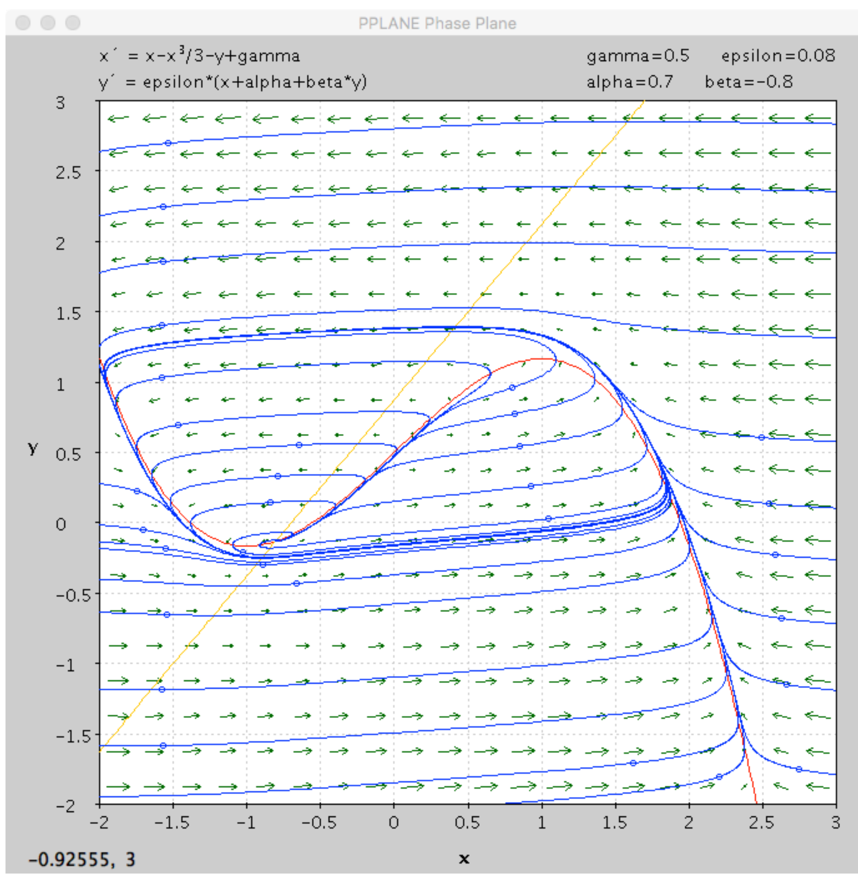
(b) Using pplane and the above values for ϵ, α, β and $\gamma = 0$, plot the x- and y-nullclines. Using the mouse to select initial conditions, produce a phase plane of the **subthreshold** Fitzhugh-Nagumo model with enough trajectories to give a sense of the flow.

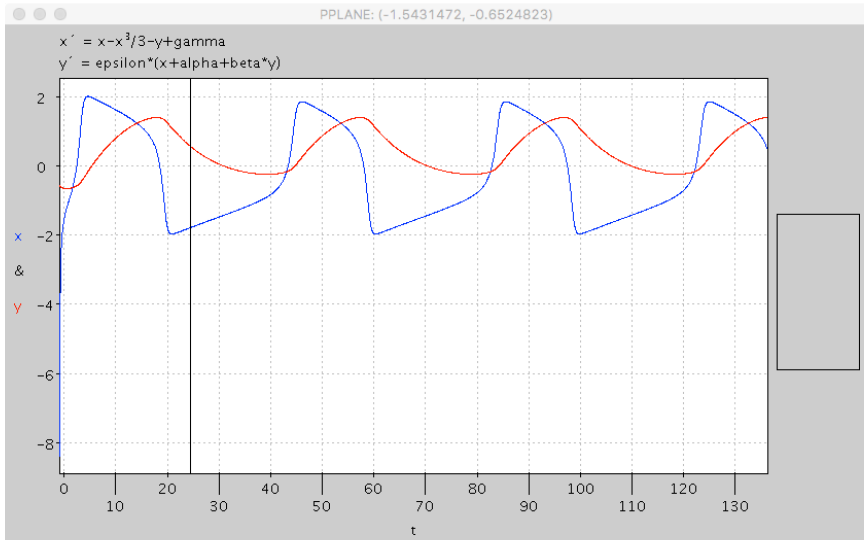


(c) Using the initial condition of $(x, y) = (-0.5, -0.5)$ and the menu options
`PPLANE Phane Plane / Options / Solution Direct / Forward`
`PPLANE Phane Plane / Graph / Both x-t & y-t`
produce a plot of $x(t)$ and $y(t)$ that shows the Fitzhugh-Nagumo model is excitable when $\gamma = 0$ (a single action potential).



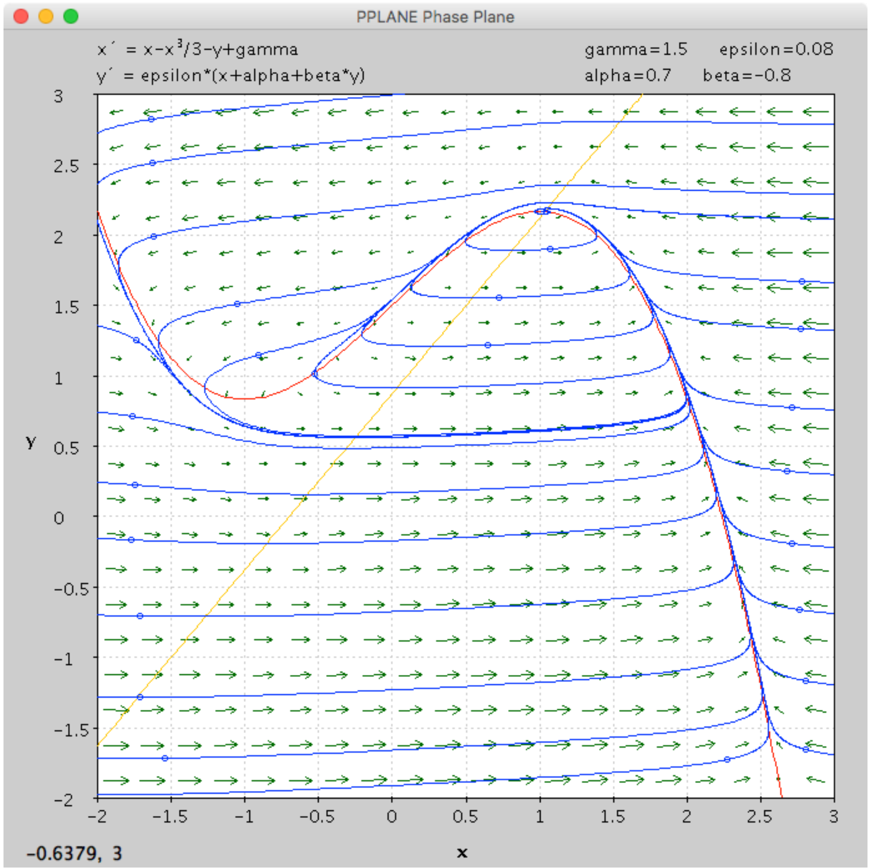
(d) Repeat the previous two questions using $\gamma = 0.5$. This superthreshold applied current leads to repetitive action potentials.





(e) Determine the value of γ that leads to over-stimulation (depolarization block).

$\gamma = 1.4$ does not lead to depolarization block, while $\gamma = 1.5$ does (the phase plane is shown below).



5. Find the general solution of the form

$$\vec{\mathbf{z}}(t) = c_1\vec{\mathbf{v_1}}e^{\lambda_1 t} + c_2\vec{\mathbf{v_2}}e^{\lambda_2 t}$$

for the 2D linear system

$$\begin{aligned} \frac{dx}{dt} &= 3x - y \\ \frac{dy}{dt} &= 6x - 4y \end{aligned}$$

and sketch a graph of the flow in the (x, y)-plane based on your calculation of the eigenvectors $\vec{\mathbf{v_1}}$ and $\vec{\mathbf{v_2}}$.

6. Sketch the phase-plane behavior of the following systems of linear equations and classify the equilibrium at the origin $(0, 0)$. First do this "by hand" as discussed in class (calculating eigenvalues and eigenvectors associated with the 2D linear system). Then check your work using an online 2D linear system solver.

(a)

$$\begin{aligned} \frac{dx}{dt} &= 2x + y \\ \frac{dy}{dt} &= x + 2y \end{aligned}$$

(c)

$$\begin{aligned} \frac{dx}{dt} &= 2x + y \\ \frac{dy}{dt} &= x - 2y \end{aligned}$$

(b)

$$\begin{aligned} \frac{dx}{dt} &= -4x - 2y \\ \frac{dy}{dt} &= 3x - y \end{aligned}$$

(d)

$$\begin{aligned} \frac{dx}{dt} &= x - 4y \\ \frac{dy}{dt} &= x + y \end{aligned}$$

Problem 5

Solve the 2D linear system

$$\dot{x} = 3x - y, \qquad \dot{y} = 6x - 4y.$$

Matrix form: $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ with

$$A = \begin{pmatrix} 3 & -1 \\ 6 & -4 \end{pmatrix}.$$

Compute trace and determinant:

$$\operatorname{tr} A = 3 + (-4) = -1, \qquad \det A = 3 \cdot (-4) - (-1) \cdot 6 = -12 + 6 = -6.$$

Characteristic polynomial:

$$\lambda^2 - (\operatorname{tr} A)\lambda + \det A = \lambda^2 + \lambda - 6 = 0,$$

so

$$\lambda = \frac{-1 \pm \sqrt{1+24}}{2} = \frac{-1 \pm 5}{2}.$$

Thus $\lambda_1 = 2$, $\lambda_2 = -3$.

Eigenvectors:

- $\lambda_1 = 2$: solve $(A - 2I)v = 0$:

$$\begin{pmatrix} 1 & -1 \\ 6 & -6 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = 0 \Rightarrow v_2 = v_1.$$

  Take $v^{(1)} = (1, 1)^T$.

- $\lambda_2 = -3$: solve $(A + 3I)v = 0$:

$$\begin{pmatrix} 6 & -1 \\ 6 & -1 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = 0 \Rightarrow -v_2 + 6v_1 = 0 \Rightarrow v_2 = 6v_1.$$

  Take $v^{(2)} = (1, 6)^T$.

General solution:

$$\boldsymbol{z}(t) = c_1 \begin{pmatrix} 1 \\ 1 \end{pmatrix} e^{2t} + c_2 \begin{pmatrix} 1 \\ 6 \end{pmatrix} e^{-3t}.$$

Phase-plane: one eigenvalue positive, one negative ⇒ a *saddle* at the origin. Trajectories move away along the unstable eigendirection $v^{(1)}$ as $t \to +\infty$ and approach the origin along the stable eigendirection $v^{(2)}$.

Problem 6

For each linear system, classify the equilibrium at the origin and sketch the phase portrait.

(a)

$$\dot{x} = 2x + y, \quad \dot{y} = x + 2y.$$

Matrix $A = \begin{pmatrix} 2 & 1 \\ 1 & 2 \end{pmatrix}$. Trace = 4, determinant = 3. Characteristic: $\lambda^2 - 4\lambda + 3 = 0 \Rightarrow \lambda = 3, 1$ (both positive, real, distinct).

$$\Rightarrow \textbf{Unstable node (source)}.$$

Eigenvectors: $\lambda = 3$ gives $y = x$; $\lambda = 1$ gives $y = -x$.

(b)

$$\dot{x} = -4x - 2y, \quad \dot{y} = 3x - y.$$

Matrix $A = \begin{pmatrix} -4 & -2 \\ 3 & -1 \end{pmatrix}$. Trace = -5, determinant = 10. Compute discriminant: $\operatorname{tr}^2 - 4\det = 25 - 40 = -15 < 0$.

$\Rightarrow$ **Stable spiral (spiral sink)** (complex eigenvalues, negative real part).

(c)

$$\dot{x} = 2x + y, \quad \dot{y} = x - 2y.$$

Matrix $A = \begin{pmatrix} 2 & 1 \\ 1 & -2 \end{pmatrix}$. Trace = 0, determinant = -5.

$$\Rightarrow \textbf{Saddle (unstable)} \quad (\det < 0).$$

(d)

$$\dot{x} = x - 4y, \quad \dot{y} = x + y.$$

Matrix $A = \begin{pmatrix} 1 & -4 \\ 1 & 1 \end{pmatrix}$. Trace = 2, determinant = 5. Discriminant = $4 - 20 = -16 < 0$ so complex eigenvalues with positive real part.

$$\Rightarrow \textbf{Unstable spiral (spiral source).}$$

Eigenvalues $\lambda = 1 \pm 2i$ (check via characteristic polynomial).

For each subproblem the student should sketch the eigendirections (real eigenvectors) or spirals and annotate "stable/unstable" as above.