ODE Assignment 17

To present Sunday, June 19

1. p. 244 #1; 2. p. 245 #3; 3. p. 246 #8

Problem 1 Logan p. 244 #1

A proof: $\vec{x}_1 = \begin{pmatrix} \phi_1(t) \\ \phi_2(t) \end{pmatrix}$ $\vec{x}_2 = \begin{pmatrix} \psi_1(t) \\ \psi_2(t) \end{pmatrix}$

$\vec{x}_1$ and $\vec{x}_2$ are independent.

Let $\Phi(t) = \begin{pmatrix} \phi_1(t) & \psi_1(t) \\ \phi_2(t) & \psi_2(t) \end{pmatrix}$

be a fundamental matrix.

Compute $\Phi'(t)$:

$$\Phi'(t) = \begin{pmatrix} \phi_1'(t) & \psi_1'(t) \\ \phi_2'(t) & \psi_2'(t) \end{pmatrix} = \begin{pmatrix} A_{11}\phi_1 + A_{12}\phi_2 & A_{11}\psi_1 + A_{12}\psi_2 \\ A_{21}\phi_1 + A_{22}\phi_2 & A_{22}\psi_1 + A_{22}\psi_2 \end{pmatrix}$$

Compute

$$A\Phi(t) = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix} \begin{pmatrix} \phi_1 & \psi_1 \\ \phi_2 & \psi_2 \end{pmatrix} = \begin{pmatrix} A_{11}\phi_1 + A_{12}\phi_2 & A_{12}\psi_1 + A_{12}\psi_2 \\ A_{21}\phi_1 + A_{22}\phi_2 & A_{21}\psi_1 + A_{22}\psi_2 \end{pmatrix}$$

These are the same. E.g., $\Phi' = A\Phi$.

Also, the general solution is of course

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = c_1\vec{x}_1 + c_2\vec{x}_2 = c_1\begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix} + c_2\begin{pmatrix} \psi_1 \\ \psi_2 \end{pmatrix} = \begin{pmatrix} c_1\phi_1 + c_2\psi_1 \\ c_1\phi_2 + c_2\psi_2 \end{pmatrix}$$

But consider

$$\Phi\vec{C} = \begin{pmatrix} \phi_1 & \psi_1 \\ \phi_2 & \psi_2 \end{pmatrix}\begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = \begin{pmatrix} \phi_1 c_1 + \psi_1 c_2 \\ \phi_2 c_1 + \psi_2 c_2 \end{pmatrix}$$

These are also the same. E.g., $\Phi\vec{C} = c_1\vec{x}_1 + c_2\vec{x}_2$.

Problem 2 Logan p. 245 #3

Solve $\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} 3 & -1 \\ 1 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} 1 \\ 2 \end{pmatrix}$

$$\Phi = \begin{pmatrix} \phi_1 & \psi_1 \\ \phi_2 & \psi_2 \end{pmatrix} = \begin{pmatrix} 1+t & -t \\ t & 1-t \end{pmatrix} e^{2t}$$

$$\Phi^{-1} = \begin{pmatrix} 1-t & t \\ -t & 1+t \end{pmatrix} e^{-2t}$$

how convenient that Logan made the determinant be 1

The general solution is

$$\vec{x}(t) = \Phi \vec{k} + \Phi \int_0^t \Phi^{-1}(s) f(s)\, ds$$

$$= \Phi \vec{k} + \Phi \int_0^t \begin{pmatrix} 1-s & s \\ -s & 1+s \end{pmatrix} e^{-2s} \begin{pmatrix} 1 \\ 2 \end{pmatrix} ds$$

$$= \Phi \vec{k} + \Phi \int_0^t \begin{pmatrix} 1-s+2s \\ -s+2(1+s) \end{pmatrix} e^{-2s} ds$$

$$= \Phi \vec{k} + \Phi \int_0^t \begin{pmatrix} 1+s \\ 2+s \end{pmatrix} e^{-2s} ds$$

let $r = 2s$
$ds = \frac{1}{2} dr$

$$= \Phi \vec{k} + \frac{\Phi}{2} \int_0^{2t} \begin{pmatrix} 1+\frac{1}{2}r \\ 2+\frac{1}{2}r \end{pmatrix} e^{-r} dr$$

Problem 2 (CONT'D)

We got as far as:

$$\vec{x}(t) = \Phi\vec{k} + \frac{1}{2}\Phi\int_0^{2t}\begin{pmatrix}1+\frac{1}{2}r\\ 2+\frac{1}{2}r\end{pmatrix}e^{-r}\,dr$$

We have to determine $\vec{k}$ from the initial conditions and we have to do the integral.

$\Phi(0) = \begin{pmatrix}1 & 0\\ 0 & 1\end{pmatrix} \leftarrow$ how convenient again!

So we can just read off that $\vec{k} = \begin{pmatrix}x(0)\\ y(0)\end{pmatrix} = \begin{pmatrix}1\\ 2\end{pmatrix}$.

To do the integral, we need

$$\int_0^{2t} e^{-r}\,dr = -e^{-r}\Big]_0^{2t} = 1-e^{-2t}$$

and

$$\int_0^{2t} re^{-r}\,dr = -\frac{d}{d\alpha}\int_0^{2t}e^{-\alpha r}\,dr\Big|_{\alpha=1} = -\frac{d}{d\alpha}\left(\frac{1}{\alpha}\left(1-e^{-2\alpha t}\right)\right)\Big|_{\alpha=1}$$

$$= \left(\frac{1}{\alpha^2}\left(1-e^{-2\alpha t}\right) + \frac{1}{\alpha}(-2\alpha)e^{-2\alpha t}\right)\Big|_{\alpha=1} = 1-e^{-2t}-2te^{-2t}$$

So

$$2+1+\tfrac{1}{2}$$

$$\vec{x}(t) = \Phi\begin{pmatrix}1\\ 2\end{pmatrix} + \frac{1}{2}\Phi\begin{pmatrix}1-e^{-2t}+\frac{1}{2}\left(1-e^{-2t}-2te^{-2t}\right)\\ 2\left(1-e^{-2t}\right)+\frac{1}{2}\left(1-e^{-2t}-2te^{-2t}\right)\end{pmatrix}$$

All these $\frac{1}{2}$'s are error prone. Let us rewrite:

$$\vec{x}(t) = \frac{1}{4}\Phi\begin{pmatrix}4+2-2e^{-2t}+1-e^{-2t}-2te^{-2t}\\ 8+4-4e^{-2t}+1-e^{-2t}-2te^{-2t}\end{pmatrix}$$

$$= \frac{1}{4}\Phi\begin{pmatrix}7-3e^{-2t}-2te^{-2t}\\ 13-5e^{-2t}-2te^{-2t}\end{pmatrix}$$

Now let's put in

$$\Phi = \begin{pmatrix}1+t & -t\\ t & 1-t\end{pmatrix}e^{2t}$$

and bring it home.

Problem 2 (CONT'D)

$$\vec{x}(t) = \frac{1}{4}\begin{pmatrix} 1+t & -t \\ t & 1-t \end{pmatrix}\begin{pmatrix} 7e^{2t}-3-2t \\ 13e^{2t}-5-2t \end{pmatrix}$$

$$= \frac{1}{4}\begin{pmatrix} (1+t)(7e^{2t}-3-2t) - t(13e^{2t}-5-2t) \\ t(7e^{2t}-3-2t) + (1-t)(13e^{2t}-5-2t) \end{pmatrix}$$

$$= \frac{1}{4}\begin{pmatrix} 7e^{2t} - 6te^{2t} - 3 - \cancel{5t} - \cancel{2t^2} + \cancel{5t} + \cancel{2t^2} \\ 13e^{2t} - 6te^{2t} - \cancel{3t} - \cancel{2t^2} - 5 + \cancel{3t} + \cancel{2t^2} \end{pmatrix}$$

$$= \frac{1}{4}\begin{pmatrix} (7-6t)e^{2t} - 3 \\ (13-6t)e^{2t} - 5 \end{pmatrix} \longleftarrow$$

wow, our lives were made easy because the t and t^2 terms cancelled out.

That was a fair amount of algebra. We better double-check.

First check initial conditions:

$$\vec{x}(0) = \frac{1}{4}\begin{pmatrix} 7-3 \\ 13-5 \end{pmatrix} = \frac{1}{4}\begin{pmatrix} 4 \\ 8 \end{pmatrix} = \begin{pmatrix} 1 \\ 2 \end{pmatrix} \quad ✓✓$$

Then take derivative:

$$\vec{x}' = \frac{1}{4}\begin{pmatrix} (7-6t)2e^{2t} - 6e^{2t} \\ (13-6t)2e^{2t} - 6e^{2t} \end{pmatrix}$$

$$= \frac{1}{4}\begin{pmatrix} (14-6)e^{2t} - 12te^{2t} \\ (26-6)e^{2t} - 12te^{2t} \end{pmatrix} = \begin{pmatrix} 2e^{2t} - 3te^{2t} \\ 5e^{2t} - 3te^{2t} \end{pmatrix}$$

Is this the same as

$$\frac{1}{4}\begin{pmatrix} 3 & -1 \\ 1 & 1 \end{pmatrix}\begin{pmatrix} (7-6t)e^{2t} - 3 \\ (13-6t)e^{2t} - 5 \end{pmatrix} + \begin{pmatrix} 1 \\ 2 \end{pmatrix} \quad ??$$

First the te^{2t} term. It is:

$$\frac{1}{4}\begin{pmatrix} -18+6 \\ -6-6 \end{pmatrix} te^{2t} = \begin{pmatrix} -3te^{2t} \\ -3te^{2t} \end{pmatrix} \quad ✓✓$$

Then the e^{2t} term. It is:

$$\frac{1}{4}\begin{pmatrix} 21-13 \\ 7+13 \end{pmatrix} e^{2t} = \begin{pmatrix} 2e^{2t} \\ 5e^{2t} \end{pmatrix} \quad ✓✓$$

Finally the constants are supposed to add up to zero:

$$\frac{1}{4}\begin{pmatrix} 3 & -1 \\ 1 & 1 \end{pmatrix}\begin{pmatrix} -3 \\ -5 \end{pmatrix} + \begin{pmatrix} 1 \\ 2 \end{pmatrix} = \frac{1}{4}\begin{pmatrix} -9+5 \\ -3-5 \end{pmatrix} + \begin{pmatrix} 1 \\ 2 \end{pmatrix} = \frac{1}{4}\begin{pmatrix} -4 \\ -8 \end{pmatrix} + \begin{pmatrix} 1 \\ 2 \end{pmatrix} = \begin{pmatrix} -1 \\ -2 \end{pmatrix} + \begin{pmatrix} 1 \\ 2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \quad ✓✓$$

Problem 3 Logan p. 246 #8

Part (a) is so straightforward, I couldn't think of anything to write down except the answer. For Part (c) where you have to start sketching, so that we have similar sketches, let's use r_1 = 3, r_2 = 1, and r_3 = 0.5, and in part (f) an initial concentration of x(0) = 2. The rates correspond to rapid transfer from blood to tissues, moderate transfer from tissues to blood, and slow elimination by the liver. The units could be mg/liter/hour for the rates and mg/liter for the initial value, but it doesn't really matter, since we are suppressing units. Maybe think about what you expect to happen to the drug before starting the problem.

If you want to do a bonus problem (especially if you are planning to be a pharmacologist), re-do Problem 3 but using that the tissues are something like 75 liters in volume whereas the blood is only 5 liters. Logan seems to have ignored the relative volumes. This would greatly slow the elimination process since the tissue will then harbor far more of the drug.

(a) As noted above, this part is so straightforward, there is nothing much to write down except the answer, but see my solution to the bonus problem.

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} -r_1 - r_3 & r_2 \\ r_1 & -r_2 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

(b) The critical point is where $x' = y' = 0$

$\Rightarrow (-r_1 - r_3)x - r_2 y = 0$ and $r_1 x - r_2 y = 0$.

Add these two equations and you get $-r_3 x = 0$. So $x = 0$. Put that into the second equation and you get $y = 0$. I am assuming that all of r_1, r_2, and r_3 are non-zero.

Problem 3 (CONT'D)

(c) The x-nullcline is where

$$-r_1 x - r_3 x + r_2 y = 0 \quad \text{or} \quad y = \frac{r_1 + r_3}{r_2} x.$$

The y-nullcline is where

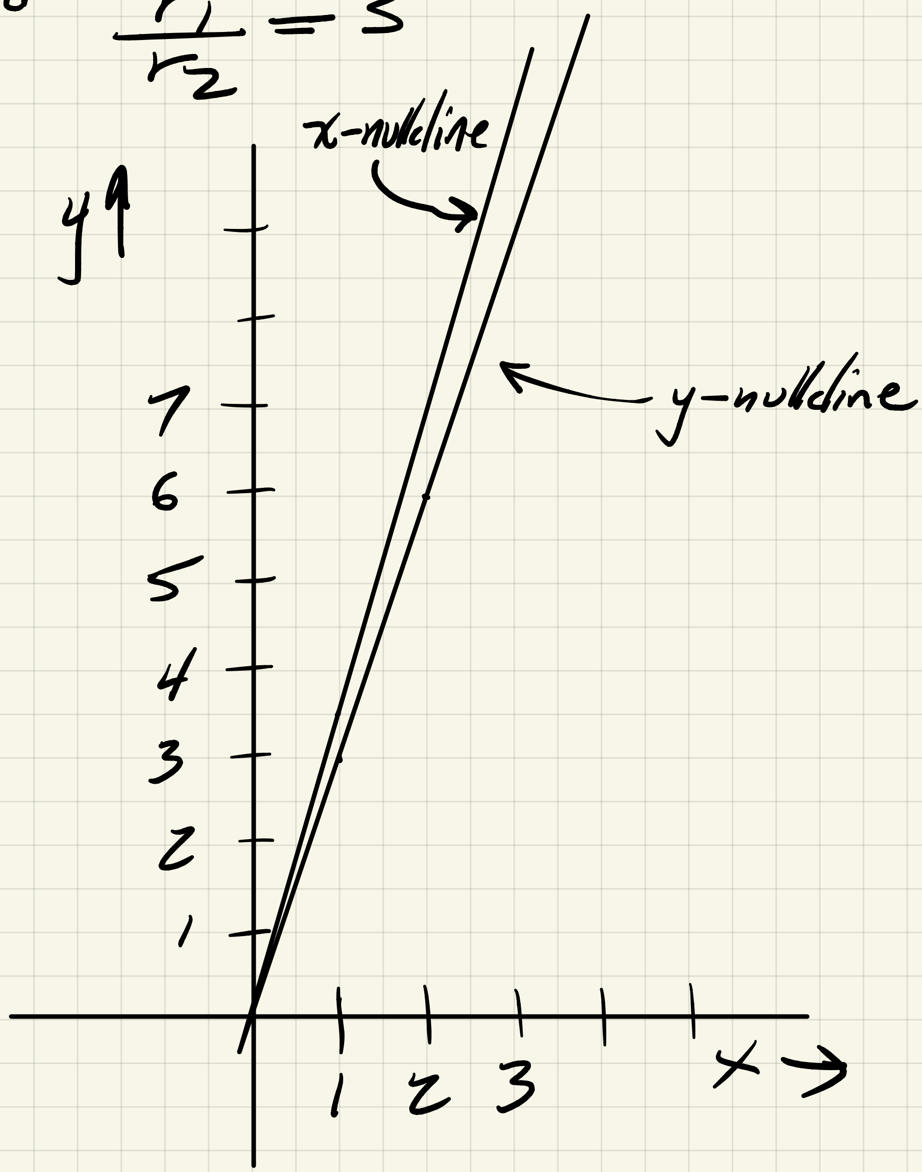
$$r_1 x - r_2 y = 0 \quad \text{or} \quad y = \frac{r_1}{r_2} x$$

To do the sketches, we'll use

$r_1 = 3$
$r_2 = 1$
$r_3 = 0.5$

Then $\frac{r_1 + r_3}{r_2} = 3.5$

and $\frac{r_1}{r_2} = 3$



NB:
we are only interested in
$x \geq 0$
and
$y \geq 0$
(negative concentrations make no sense)

Problem 3 (CONT'D)

(d) The region between the nullclines is the narrow wedge defined by

$$\frac{r_1}{r_2}x < y < \frac{r_1+r_3}{r_2}x$$

true everywhere

used $x > \frac{r_2}{r_1+r_3}y$

In this region $\quad x' = -r_1 x - r_3 x + r_2 y$

$$< -\cancel{(r_1+r_3)}\frac{r_2}{\cancel{r_1+r_3}}y + r_2 y = 0$$

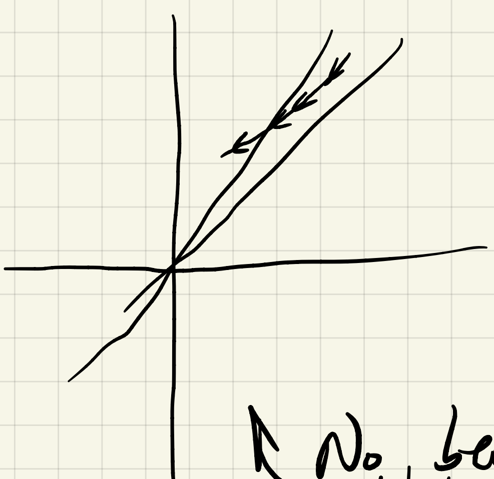
true everywhere

used $x < \frac{r_2 y}{r_1}$

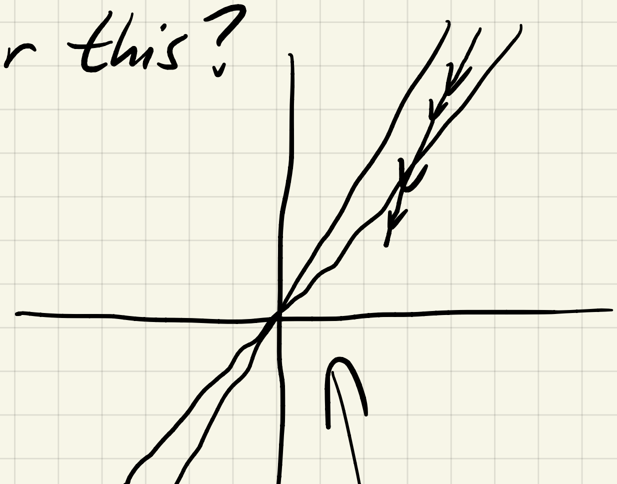
Also in this region $\quad y' = r_1 x - r_2 y$

$$< \cancel{r_1}\frac{r_2}{\cancel{r_1}}y - r_2 y = 0$$

So we have shown that $x' < 0$ and $y' < 0$ in the wedge. That isn't quite enough. Couldn't it escape the wedge while still going down and to the left like this? Or this?



No, because it would have to be going straight down at the point it crossed the x-nullcline



No, because it would have to be going straight left at the point it hit the y-nullcline

Problem 3 (CONT'D)

(e) Analytical approach

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} -r_1 - r_3 & r_2 \\ r_1 & -r_2 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

$$\det \begin{pmatrix} -r_1 - r_3 - \lambda & r_2 \\ r_1 & -r_2 - \lambda \end{pmatrix} = \cancel{r_1 r_2} + r_3 r_2 + (r_1 + r_2 + r_3)\lambda + \lambda^2 - \cancel{r_1 r_2} = 0$$

$$\lambda^2 + (r_1 + r_2 + r_3)\lambda + r_3 r_2 = 0$$

$$\lambda = \frac{-(r_1 + r_2 + r_3) \pm \sqrt{(r_1 + r_2 + r_3)^2 - 4 r_2 r_3}}{2}$$

There are three possibilities $\quad r_1 + r_2 + r_3 \begin{array}{l} > 2\sqrt{r_2 r_3} \\ = 2\sqrt{r_2 r_3} \\ < 2\sqrt{r_2 r_3} \end{array}$

If the first, we have two different <u>negative</u> eigenvalues.
If the second, we have two equal negative eigenvalues.
If the third, we have two complex conjugate eigenvalues, but the important thing is that the real part is negative.

In all three cases, both solutions go as $e^{-\alpha t}$ where α is one or two positive numbers.

So all solutions are driven toward the origin for large t.

Problem 3 (CONT'D)

(f) Do a phase plane diagram and sketch the trajectory with $x(0) = x_0 = 2$, $y(0) = y_0 = 0$

Phase Diagrams for Logan p. 246 #8(f)

Focusing on the region between the nullclines first:

In[25]:=
```
r1 = 3; r2 = 1; r3 = 0.5;
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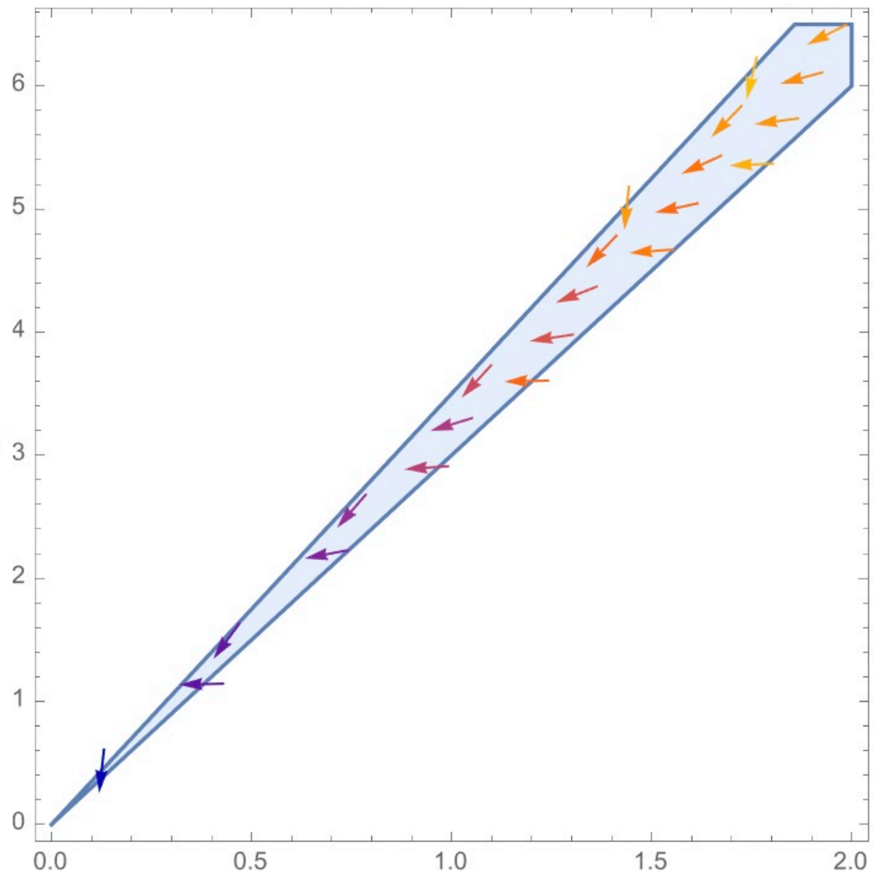
In[26]:=
```
VectorPlot[{-r1 x - r3 x + r2 y, r1 x - r2 y}, {x, 0, 2}, {y, 0, 6.5},
 RegionFunction → Function[{x, y}, x r1 / r2 < y < (r1 + r3) x / r2]]
```

Out[26]=



So our arguments that between the nullclines, the concentrations stay between them and are driven towards zero is confirmed.

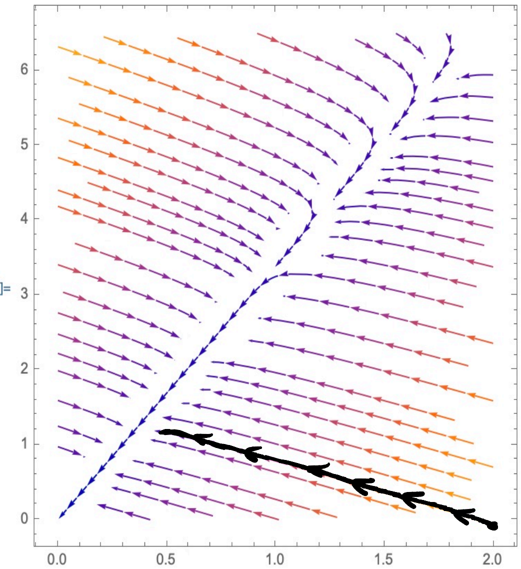
Problem 3 (CONT'D)

Now we will study the trajectory that begins with $x(0)=2$, $y(0)=0$.

Here's a streamplot that includes the initial value condition that Logan asked us to consider (with $x_0 = 2$).

In[34]:=
```
StreamPlot[{-r1 x - r3 x + r2 y, r1 x - r2 y}, {x, 0, 2}, {y, 0, 6.5}]
```

Out[34]=

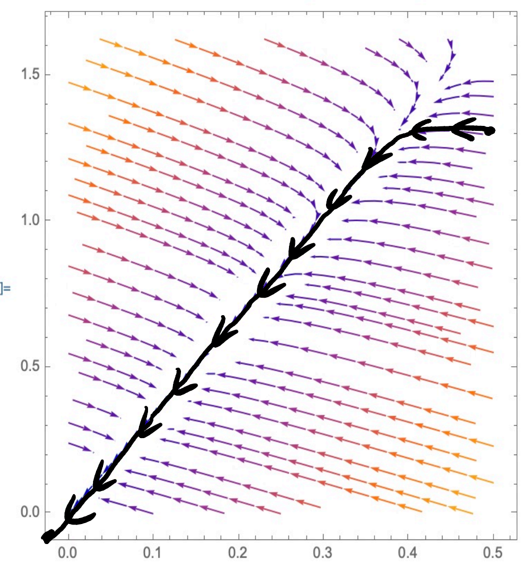


I have inked in the relevant trajectory from (2.0, 0) down to about (0.5, 1.25)

Let's zero in on the region where the concentrations enters the wedge between the nullclines. It looks the same (there is some kind of scale invariance at work), but notice the axes are changed.

In[35]:=
```
StreamPlot[{-r1 x - r3 x + r2 y, r1 x - r2 y}, {x, 0, 0.5}, {y, 0, 1.625}]
```

Out[35]=



Here I have continued inking it in from about (0.5, 1.25) down to (0, 0)

Interpretation: The blood and tissues quickly equalize to an approximately constant ratio that is controlled just by $\frac{r_1}{r_2}$. The small value of r_3 slowly removes the drug from the blood, but the ratio remains approximately constant.

Bonus Problem

Let's redo part (a) in particular of the previous problem, but allowing for the fact that the volume of the tissues is far larger than the volume of the blood.

So, let x be concentration in blood,
y be " " tissue,

V_b = volume of blood
V_t = " " tissue

r_1 = blood-to-tissue rate
r_2 = tissue-to-blood rate
r_3 = excretion from liver rate

all three of these will be measured as a change in <u>blood</u> concentration

$$(xV_b)' = -r_1 V_b x + r_2 V_b y - r_3 V_b x$$

$$(yV_t)' = r_1 V_b x - r_2 V_b y$$

Divide the first equation through by V_b. Get same equation as in Problem 3.

$$x' = -r_1 x + r_2 y - r_3 x$$

Divide the second equation through by V_b. Get

$$y' = \frac{r_1}{r} x - \frac{r_2}{r} y \qquad \text{where } r = \frac{V_t}{V_b} \approx 15$$

Bonus Problem (cont'd)

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} -r_1 - r_3 & r_2 \\ r_1/v & -r_2/v \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

$r_1 = 3$
$r_2 = 1$
$r_3 = 0.5$
$v = 15$

Nullcline locations are unchanged!

Phase Diagram for Bonus Problem

In[31]:=
```
v = 15;
```

In[32]:=
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StreamPlot[{-r1 x - r3 x + r2 y, r1 x / v - r2 y / v}, {x, 0, 2}, {y, 0, 6.5}]
```
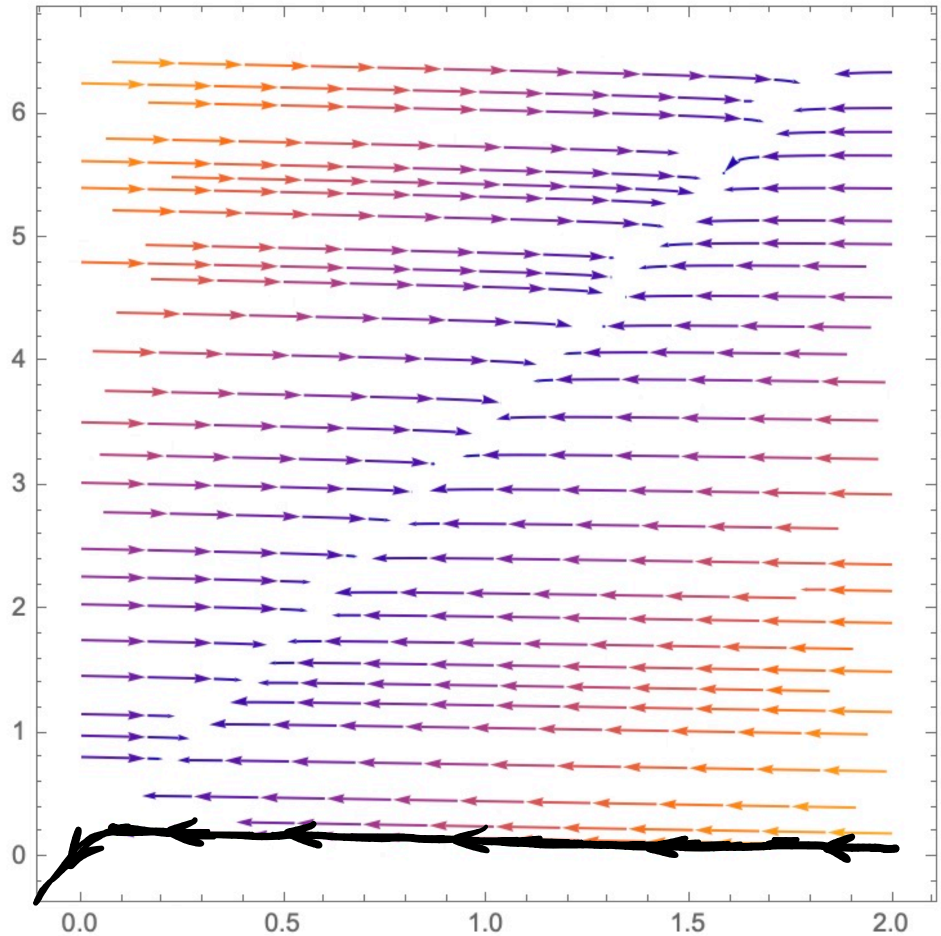

Out[32]=



I have again inked in the trajectory beginning with $x(0)=2$, $y(0)=0$.

Interpretation: Same as before, but now as the blood and tissue equalize (with a ratio that is still controlled by r_1/r_2) we get a much less pronounced rise in the tissue concentration, simply because there is so much more tissue than blood.