

Systems Biology, Homework # 4

Mathematical Analysis

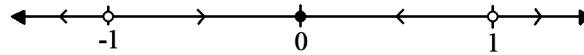
Grayson Gerlich

1. Phase Analysis

- (a) Sketch the phase line for the differential equation

$$\frac{d}{dt}V(t) = V^3(t) - V(t)$$

The phase line for this ODE is as follows:



- (b) Consider the simple model

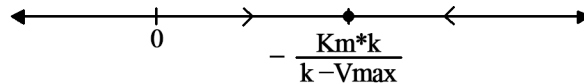
$$\frac{d}{dt}s(t) = k - \frac{V_{\max}s}{K_M + s}$$

in which species s is produced at a fixed rate and consumed via Michaelis-Menten kinetics. Sketch a phase line for this system. Verify that the steady state is stable for any non-negative parameter values, provided $V_{\max} > k$.

We can solve for the $s(t)_{ss}$ to find the steady state value, giving the following:

$$s(t)_{ss} = -\frac{K_M k}{k - V_{\max}}$$

By inspection, we can tell that if $V_{\max} < k$, the resulting value of $s(t)_{ss}$ will be negative. Otherwise, there will be a positive steady state solution (one independent of time dependent values) for all non-negative parameter values. The resulting phase line is as follows.



2. Network analysis in phase-space

- (a) Find general equations for the s_1 - and s_2 -nullclines.

We can express the differential equations for this system as follows:

$$\frac{ds_1}{dt} = k_1 + k_5 s_2 - k_3 s_2$$

$$\frac{ds_2}{dt} = \frac{k_2}{1+s_1^2} - k_5 s_2 - k_4$$

The nullcline equations for s_1 and s_2 satisfy the equations $\frac{ds_1}{dt} = 0$ and $\frac{ds_2}{dt} = 0$ respectively. Solving for these gives:

$$s_1 = \frac{k_1 + k_5 s_2}{k_3}$$

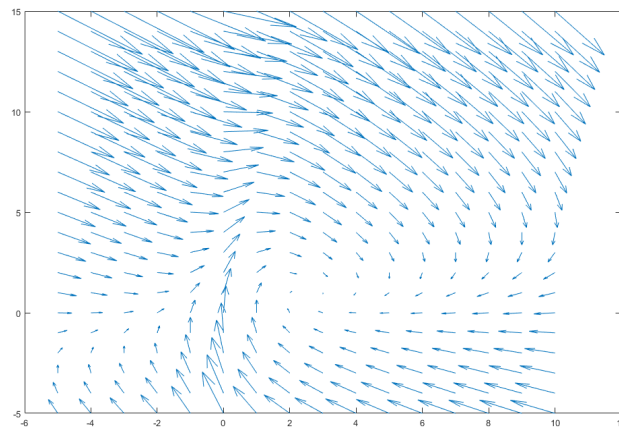
$$s_2 = \frac{\frac{k_2}{1+s_1^2} - k_4}{k_5}$$

(b) Sketch, by hand, the phase portrait.

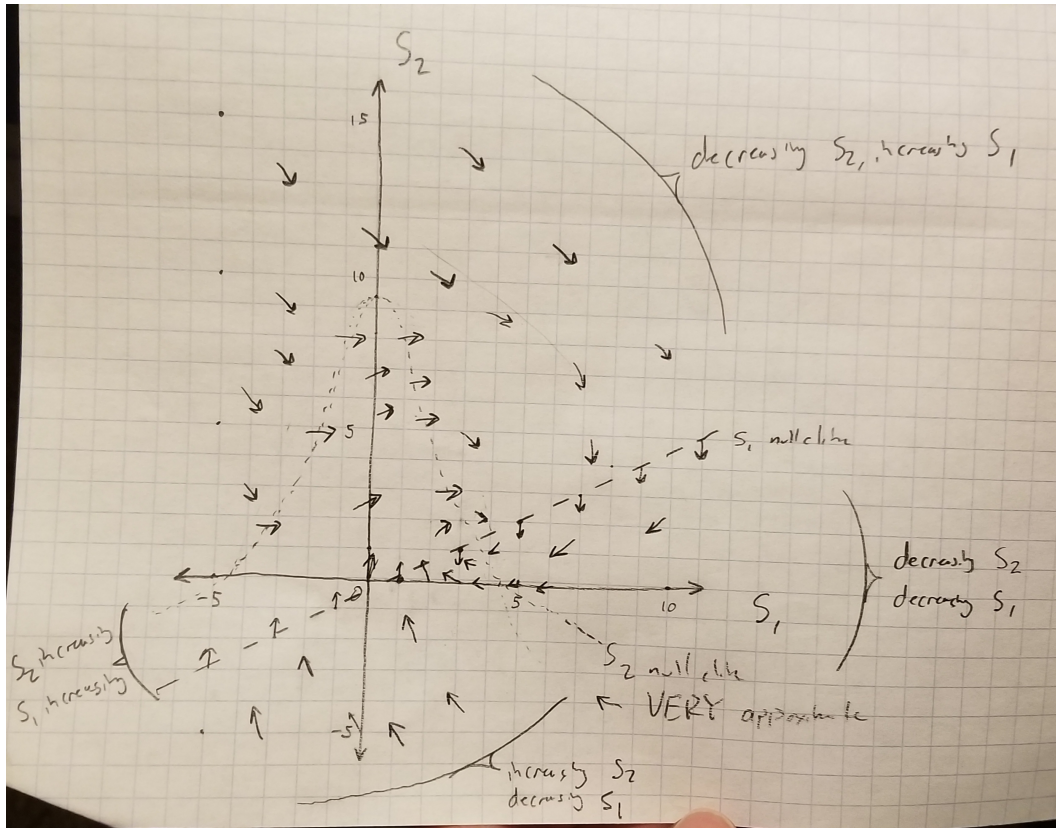
I'll admit, I didn't look forward to generating this plot by hand, so I made it matlab first using the following code.

```
1 [s1, s2] = meshgrid(-5:1:10, -5:1:15); %create grid to work on
2 ds1dt = 1+2.*s2-s1; %define ds1dt
3 ds2dt = 20./(1+s1.^2)-2.*s2-1; %define ds2dt
4
5 %define nullclines (not shown on quiver plot)
6 %s1null = 1 + 2.*s2;
7 %s2null = ((20./(1+s1.^2))-1)/2;
8
9 %plot phase portrait
10 quiver(s1,s2,ds1dt, ds2dt, 2.5)
```

I also plotted the nullclines, but the interaction between matlab's quiver and plot functions is somewhat complex, so I didn't go through the trouble of plotting them together. The resultant plot looks like this.



I let this inform my plot by hand, which includes the nullclines drawn as best as I can. I chose the axes I did because the s_2 nullcline crests at $s_2 = 10$ or so and I wanted to capture the full behavior. My plot (done by hand) is as follows. I apologize for the size, but I put it in this document at full resolution, so you should be able to zoom in on it.



3. Turn in the problem that we did in class:

$$\begin{aligned}\frac{ds_1}{dt} &= V_0 - k_1 s_1 \\ \frac{ds_2}{dt} &= k_1 s_1 - \frac{V_2 s_2}{K_M + s_2}\end{aligned}$$

(a) Identify the steady state

Setting the above ODEs to 0, we can solve for s_1 ss:

$$s_1ss = \frac{V_0}{k_1}$$

Rearranging the above equation, we can substitute it to solve for s_2 ss:

$$s_2ss = \frac{V_0 K_m}{V_2 - V_0}$$

(b) Construct the system Jacobian

The Jacobian $J(s_1, s_2)$ can be found by taking simple partial derivatives, it is as follows:

$$J(s_1, s_2) = \begin{bmatrix} \frac{\partial f}{\partial s_1} & \frac{\partial f}{\partial s_2} \\ \frac{\partial g}{\partial s_1} & \frac{\partial g}{\partial s_2} \end{bmatrix} = \begin{bmatrix} -k_1 & 0 \\ k_1 & -\frac{K_M V_2}{(K_M + s_2)^2} \end{bmatrix}$$

(c) Compute the eigenvalues of the Jacobian

As there is a 0 off the diagonal of the Jacobian, the eigenvalues are simply $\lambda_1 = -k_1$ and $\lambda_2 = -\frac{V_0 K_m}{V_2 - V_0}$.

(d) Determine stability

Because both λ_1 and λ_2 are always negative (λ_2 is negative provided all parameters are positive, which they must be), the system is stable.

4. Sensitivity analysis: reversible reaction.

(a) Solve for the steady-state concentration of A^* and verify (just explain in words) that an increase in k_1 leads to an increase in $[A^*]^{ss}$.

The differential equations governing this system can be represented as follows.

$$\frac{dA}{dt} = k_2 A^* - k_1 A$$

$$\frac{dA^*}{dt} = k_1 A - k_2 A^*$$

We can solve for A_{ss}^* by setting the second equation to 0 and solving to get:

$$A_{ss}^* = \frac{k_1 A}{k_2}$$

It is clear from this equation, that as k_1 increases, so does A_{ss}^* .

(b) Parametric sensitivity analysis

I'm not sure exactly what Dr. Leiderman means by T in the directions in this question, I'm assuming its a typo. I'm not sure if she means k_2 or A , so I solved for both. With this in mind, we can represent the relative sensitivities of A_{ss}^* to k_2 , k_1 , and A respectively, as the following:

$$\frac{k_2}{A_{ss}^*} \frac{dA_{ss}^*}{dk_2}$$

$$\frac{k_1}{A_{ss}^*} \frac{dA_{ss}^*}{dk_1}$$

$$\frac{A}{A_{ss}^*} \frac{dA_{ss}^*}{dA}$$

These evaluate to the following expressions.

$$-\frac{Ak_1}{A_{ss}^*k_2}$$

$$\frac{Ak_1}{A_{ss}^*k_2}$$

$$\frac{A}{A_{ss}^*}$$

This indicates that the system is equally sensitive to changes in either k_1 or k_2 . This is easy enough to infer from the system as it is. Depending on the values of k_1 and k_2 , the system may or may not be more or less sensitive to changes in A . Of course, if you plug in the A_{ss}^* equation, all of these evaluate to 0, so the entire exercise is largely useless without data.