Problem sheet 3

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1 Michaelis-Menten Enzyme dynamics

Enzymes are biological molecules (typically proteins) that significantly speed up the rate of virtually all of the chemical reactions that take place within cells. They are vital for life and serve a wide range of important functions in the body, such as aiding in digestion and metabolism.

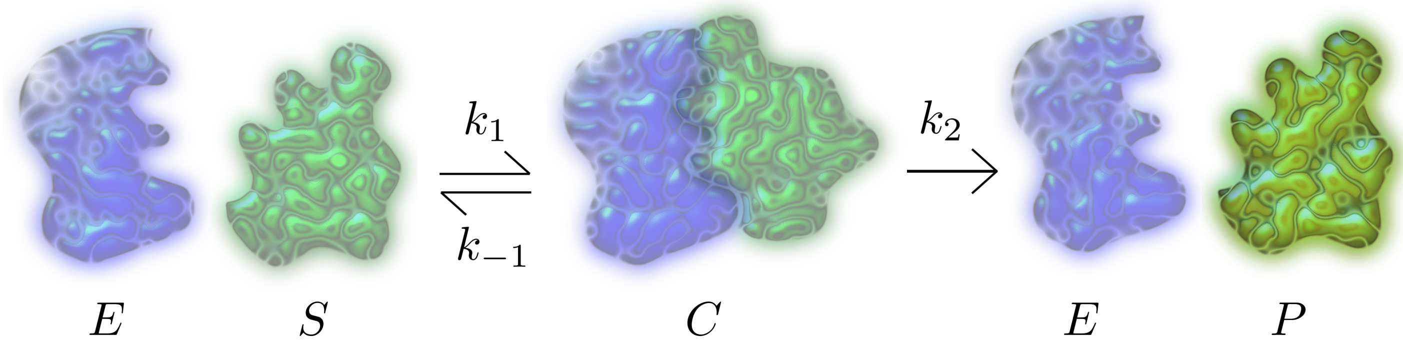

Figure 1: Schematic diagram of the Michaelis-Menten enzyme-substrate reaction.

In 1913 Leonor Michaelis and Maud Menten proposed a mathematical model of how enzymes work. The process involves an enzyme, E, binding to a substrate, S, to form a complex, C, which in turn releases a product, P, regenerating the original enzyme. This may be represented schematically as (see Figure 1)

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

1. Use the Law of Mass Action to write down the ODE formulation of the dynamics. The initial conditions are

$$S(0) = S_0, \quad E(0) = E_0, \quad C(0) = 0, \quad P(0) = 0. \tag{2}$$

2. Show $E + C$ =constant= E_0.
3. Why can we ignore the equations for $\dot{P}$ and $\dot{E}$? Specifically, show that we only need to consider the equations

$$\dot{S} = -k_1(E_0 - C)S + k_{-1}C, \tag{3}$$
$$\dot{C} = k_1(E_0 - C)S - (k_{-1} + k_2)C. \tag{4}$$

4. Use the following scales to non-dimensionalise the equations

$$t = \frac{\tau}{k_1 E_0}, \quad S = uS_0, \quad C = vE_0, \tag{5}$$

to produce the following system

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -u + (u + K - \lambda)v, \tag{6}$$
$$\epsilon\frac{\mathrm{d}v}{\mathrm{d}\tau} = u - (u + K)v. \tag{7}$$

What are ϵ, λ and K? Show that ϵ, λ and K are non-dimensional.

5. What are the initial conditions?
6. Suppose $E_0 \ll S_0$ (what does this mean?) and so let $\epsilon \to 0$. Show that we can write v as a function of u, which simplifies the $\mathrm{d}u/\mathrm{d}\tau$ equation to

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -u + (u + K - \lambda)\frac{u}{(u+K)}, \quad u(0) = 1. \tag{8}$$

This is known as the system on the 'outer' time-scale.

7. Substitute the time scale $\sigma = \tau/\epsilon$ into equations (6) and (7). Rearrange the system and, once again, let $\epsilon \to 0$. You should be able to show that the solution of the system is

$$\begin{aligned} u(\sigma) &= 1, \\ v(\sigma) &= \frac{1}{1+K}\left(1 - \exp(-(1+K)\sigma)\right). \end{aligned} \tag{9}$$

This is known as the system on the 'inner' time-scale.

In questions 7-6 you have done a multiple scales simplification of the Michaelis-Menton problem. Namely, the whole equation is hard to solve. However, we can solve for what the equation looks like for small time, σ (question 7) and we can solve for what the equations looks like for large time, question (6). In the computation question, which is next, we check these approximations.

1.1 Answers

1.1.1

$$\begin{aligned} \dot{E} &= -k_1 ES + (k_{-1} + k_2) C, \\ \dot{S} &= -k_1 ES + k_{-1} C, \\ \dot{C} &= k_1 ES - (k_{-1} + k_2) C, \\ \dot{P} &= k_2 C. \end{aligned}$$

1.1.2

$$\mathrm{d}(E + C)/\mathrm{d}t = 0 \implies E + C = \text{ constant } = E_0, \tag{10}$$

using the initial conditions.

1.1.3

$\dot{P}$ depends on C, but none of the other equations depend on P, thus, $\dot{P}$ decouples from the system, in that once we solved the rest of the system we can produce P through integration C. This leaves equations for E, S and C. Using $E+C = E_0$ we can eliminate E as well, leaving just equations for S and C. Substituting in $E = E_0 - C$ we generate

$$\dot{S} = -k_1(E_0 - C)S + k_{-1}C, \tag{11}$$

$$\dot{C} = k_1(E_0 - C)S - (k_{-1} + k_2)C. \tag{12}$$

1.1.4

We should find that

$$\begin{aligned} \epsilon &= \frac{E_0}{S_0}, \\ \lambda &= \frac{k_2}{k_1 S_0}, \\ K &= \frac{k_{-1} + k_2}{k_1 S_0}. \end{aligned}$$

The units are:
dim(ϵ)=density/density=1,
dim(λ)=$\frac{1/\text{time}}{1/(\text{density}\times\text{time})\times\text{density}} = 1$ =dim(K).

1.1.5

The initial conditions are $u(0) = S_0/S_0 = 1$ and $v(0) = 0/E_0 = 0$.

1.1.6

$E_0 \ll S_0$ means that there is very little enzyme compared to substrate.

Setting $\epsilon = 0$ in equation (7) gives

$$0 = u - (u+K)v \implies v = u/(u+K), \tag{13}$$

which can be substituted into equation (6) to produce

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -u + (u + K - \lambda)u/(u+K), \quad u(0) = 1. \tag{14}$$

1.1.7

On substituting $\sigma = \tau/\epsilon$ into equations (6) and (7) we have

$$\frac{\mathrm{d}u}{\mathrm{d}\sigma} = \epsilon\left(-u + (u + K - \lambda)v\right) \approx 0, \quad u(0) = 1 \tag{15}$$

$$\frac{\mathrm{d}v}{\mathrm{d}\sigma} = u - (u+K)v \quad v(0) = 0. \tag{16}$$

Solve equation (15) provides $u = 1$, which is substituted into equation (16) to produce

$$\frac{\mathrm{d}v}{\mathrm{d}\sigma} = 1 - (1+K)v \quad v(0) = 0. \tag{17}$$

Solving this equations gives the final answer

$$v(\sigma) = \frac{1}{1+K}\left(1 - \exp(-(1+K)\sigma)\right). \tag{18}$$

2 Computer simulation

Let $K = 2$, $\lambda = 1$ and $\epsilon = 0.001$. Simulate

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -u + (u + K - \lambda)v, \quad u(0) = 1 \tag{19}$$

$$\epsilon\frac{\mathrm{d}v}{\mathrm{d}\tau} = u - (u+K)v \quad v(0) = 0. \tag{20}$$

and

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -u + (u + K - \lambda)u/(u+K), \quad u(0) = 1. \tag{21}$$

with $v = u/(u+K)$ over the time $t \in [0, 20]$. How well do these curves approximate each other?

2.1 Answer

The simulations are shown below.

3 Spruce budworm

Spruce budworm (see Figure 3) are preyed upon by spiders, miscellaneous insects, and birds. A model for their population size, N is given by

$$\dot{N} = RN\left(1 - \frac{N}{K}\right) - \frac{BN^2}{A^2 + N^2}. \tag{22}$$

1. What does each term in the equation mean?

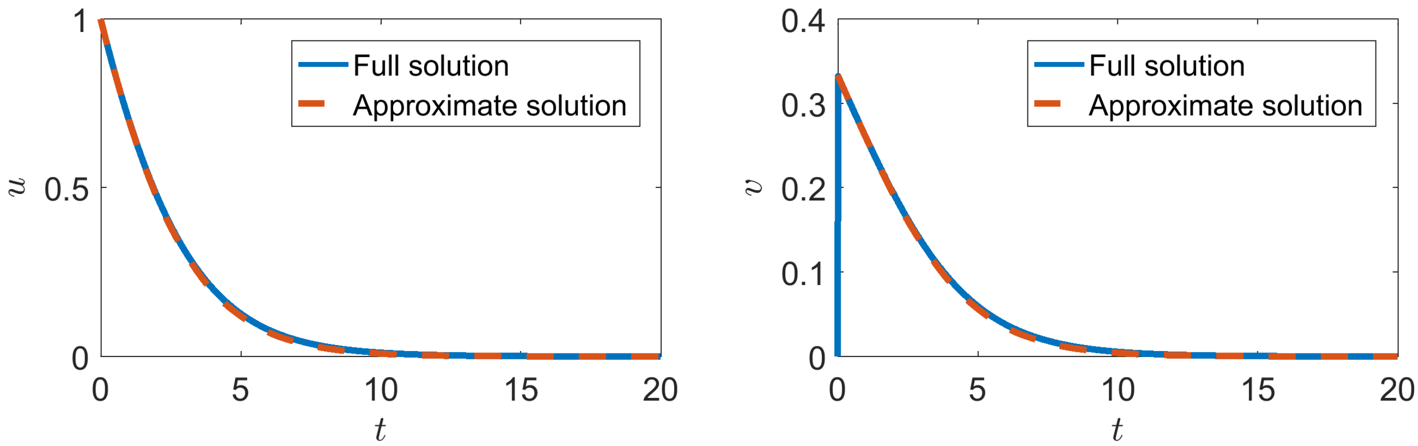

Figure 2: Full and approximate solutions to the Michaelis-Menten problem.

Figure 3: Spruce budworm in moth and larval stages.

2. Describe, with a sketch, three properties of the predation term
$$\frac{BN^2}{A^2+N^2}. \tag{23}$$
Hint: consider low, medium and high values of N.

3. Non-dimensionalise the equation to give the form
$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = ru\left(1-\frac{u}{k}\right) - \frac{u^2}{1+u^2}. \tag{24}$$
What are the scales of the population and time in terms of A, B, K and R? What are the parameters r, k in terms of A, B, K and R?

4. Show the population and time scales have the right dimension. Show that r and k are dimensionless.

3.1 Answers

3.1.1

$$\underbrace{\dot{N}}_{\text{Population evolution.}} = \underbrace{RN\left(1-\frac{N}{K}\right)}_{\text{Logistic growth, } \textit{i.e.} \text{ linear growth with competition.}} - \underbrace{\frac{BN^2}{A^2+N^2}}_{\text{Predation effects.}}. \tag{25}$$

3.1.2

For low populations there is little predation. As the population grows, so does the predation. The predation saturates at large population.

3.1.3

$$[N] = A, \quad [t] = \frac{A}{B}, \quad r = \frac{RA}{B}, \quad k = \frac{K}{A}. \tag{26}$$

3.1.4

A has units of density, B has units of density/time, R has units of 1/time and K has units of density.

Substituting these into the scales in Section 3.1.3 we find that $[N]$ and $[t]$ has units of density and time, respectively, whilst r and k are dimensionless.

4 Spruce budworm population stability

You can find more about the spruce budworm population equation and an online applet that allows you to simulate the system quickly and easily at the following website:

$$http://mathinsight.org/spruce\_budworm\_outbreak\_model \tag{27}$$

The above website may aid in the following questions as we are going to consider the steady states of

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = ru\left(1 - \frac{u}{k}\right) - \frac{u^2}{1+u^2} = f(u). \tag{28}$$

We could solve $f(u) = 0$, however, this leads to a cubic in u. This can be solved, but it is not very fun. Instead, we are going to consider sketches of the system.

We could sketch $f(u)$, directly, and draw arrows on the diagram, such that u is increasing if $f(u) > 0$ and u is decreasing if $f(u) < 0$. This will immediately tell us how many stationary states there are and inform us of their stability. We will do this towards the end of this question, however, going straight into the full sketch may cause us to miss certain cases, as we have two parameters, r and K, to worry about. However, if you feel confident shoot straight to question 3.

Critically, the following questions only deal with sketches. Thus, you do not have to be exactly accurate in your plotted values. We are just need to provide the general shape of the curve. This means little, if any, calculation should be required. Namely, an exact analytical result is not required, only approximate sketches backed up by logical thought.

1. By inspection $u_0 = 0$ is always a steady state of $f(u)$ (make sure you understand why). Instead of considering $f(u)$ let us consider the two functions
$$f_1(u) = r\left(1 - \frac{u}{k}\right), \quad f_2(u) = \frac{u}{1+u^2}. \tag{29}$$
Sketch f_2 on three different axes. Fix the value of r/k to be greater than zero (say $r/k = 0.05$), but allow r to vary (with k being defined by, say, $k = 0.05/r$). Sketch on these three different plots f_1 for different values of r, namely consider r small, medium and large[1]

2. Draw on your above diagrams regions where $f_1 > f_2$ and regions where $f_2 > f_1$.

3. Noting that a steady state, u', satisfies
$$f(u') = 0 = u'(f_1(u') - f_2(u')), \tag{30}$$
use your sketches of f_1 and f_2 to plot three situations of $f(u)$.

4. You should be able to show that (depending on the value of the parameters) there can be as few as two steady states and as many as 4 steady states. Name the four steady states $0 = u_0 < u_- < u_s < u_+$, in the obvious way. Specify on your diagrams these four steady states. The middling value of r sketch is given in Figure 4.

5. Use each sketch of $f(u)$ to state the stability of each steady state, u_0, u_-, u_s and u_+ (when they exist).

6. Does the system exhibit hysteresis? To solve this follow these steps:

[1] Note that small, medium and large values are ill-defined. Specifically, when saying such terms you should always specify compared to what. Namely, small, or large, compared to what value? Thus, if you are plotting these accurately consider $r \in [0.4, 0.6]$.

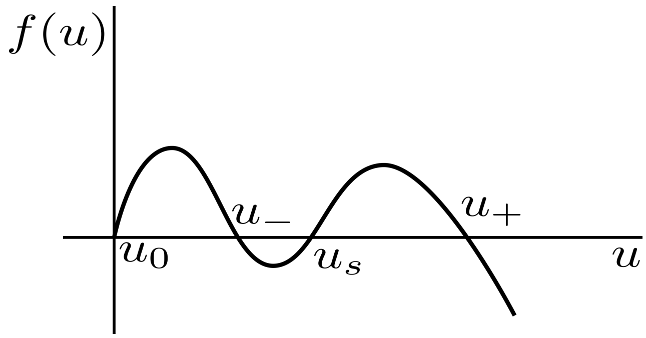

Figure 4: Plots of f for a middling value of r.

(a) start with a low value of r, such that only u_0 and u_- exist. Suppose we start with a small initial condition, where do you evolve to?

(b) increase r until u_0, u_-, u_s, u_+ all exist, what happens to the point you evolve to?

(c) increase r further until only u_0 u_+ exist, what happens to the point you evolve to?

(d) decrease r until u_0, u_-, u_s, u_+ all exist, what happens to the point you evolve to?

(e) is the point you evolve to in step 6b the same as the point you evolve to in step 6d? Use this to answer the original question.

4.1 Answer

4.1.1

$u = 0$ is a solution of $f(u) = 0$, thus, it is always a steady state. See Figure 5 for the sketches.

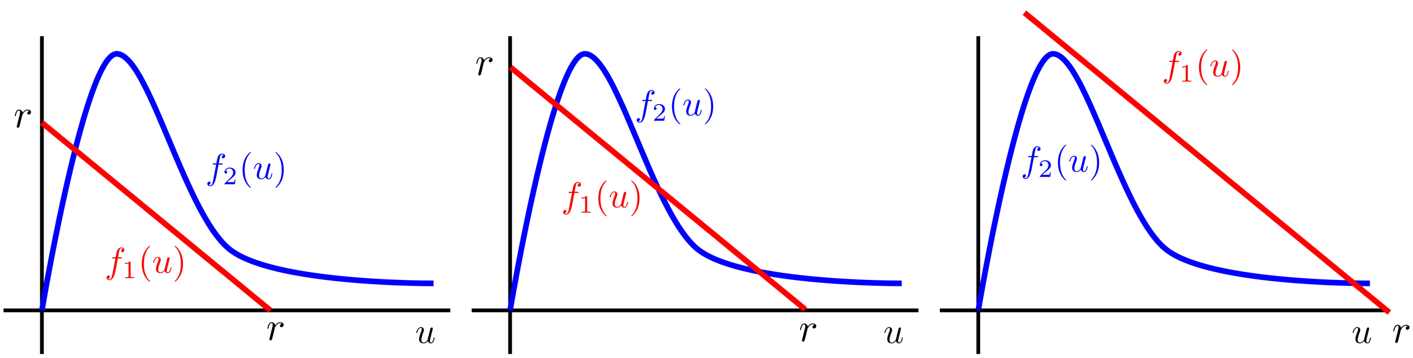

Figure 5: Plots of f_1 and f_2, for varying r and fixed r/k. r increases left to right.

4.1.2

See Figure 6 for the sketches.

4.1.3

See Figure 7 for the sketches.

4.1.4

The steady states have been specified on Figure 7.

4.1.5

Using Figure 7 u_0 is always unstable and always exists. u_- and u_+ are always stable when they exist. u_s is always unstable when it exists.

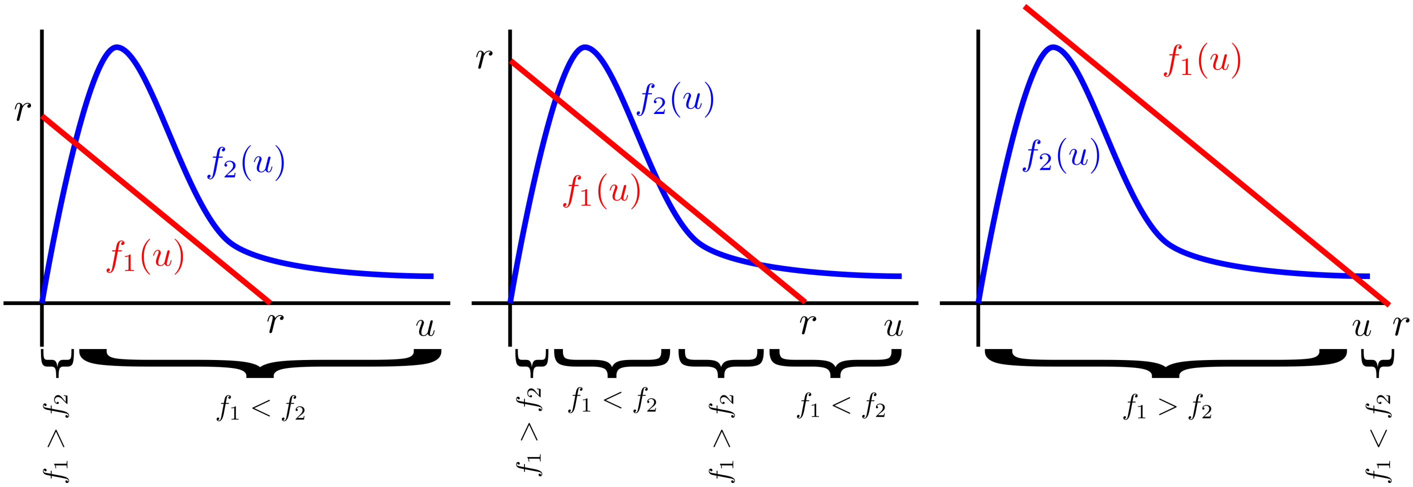

Figure 6: Plots of f_1 and f_2, for varying r and fixed r/k. r increases left to right. The brackets along the u axis delineate the regions over which $f_1 > f_2$ and $f_2 > f_1$.

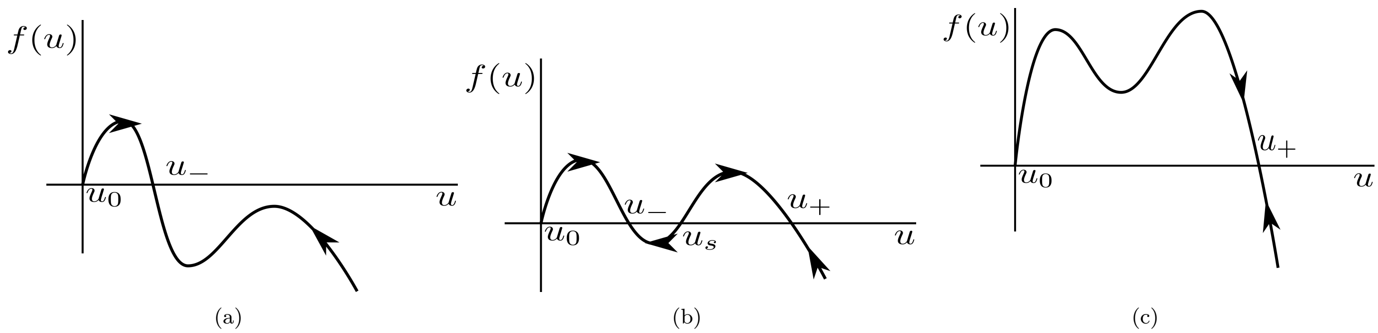

Figure 7: Three potential sketches of the spruce budworm phase plane depending on the parameter r, with fixed r/k. r increases left to right.

4.1.6

(a) when r is small only u_0 and u_- exist and, so, the system will tend to u_-.

(b) as r increase u_s and u_+ will appear, but u_- is still stable and so the system stays where it is, as u_-.

(c) for large r u_- disappears. The system then evolves to u_+.

(d) reducing r to the previous value brings back u_-, but u_+ still exists and is stable so the system stays at u_+.

(e) originally we were at u_- now we are at u_+, even though we have reduced r back to the previous position. Since these are different steady states the model presents hysteresis.

Exam revision

5 Stability of a one variable system

Consider the following equation

$$\dot{u} = u(1-u)^3(u-2)^2(3-u)(4-u). \tag{31}$$

1. What are the steady states?
2. Linearise around each steady state. Which steady states are stable and which are unstable? Why can you not categorise the stability of $u = 1$ and $u = 2$?
3. Sketch the phase plane $(u, \dot{u})$ and show that your linear analysis tallies with the stability information gained from the sketch.
4. Use the sketch to categorise the stability of $u = 1$ and $u = 2$.

5.1 Answer

5.1.1

Steady states are $u_s = 0, 1, 2, 3, 4$.

5.1.2

For linear stability analysis we need to check the sign of $\mathrm{d}f(u_s)/\,\mathrm{d}u$.

$$\frac{\mathrm{d}f}{\mathrm{d}u} = -2(u-1)^2(u-2)(4u^4 - 33u^3 + 88u^2 - 80u + 12). \tag{32}$$

and, so,

$$\begin{aligned}
\frac{\mathrm{d}f}{\mathrm{d}u}(0) &= 48 > 0 \\
\frac{\mathrm{d}f}{\mathrm{d}u}(1) &= 0 \\
\frac{\mathrm{d}f}{\mathrm{d}u}(2) &= 0 \\
\frac{\mathrm{d}f}{\mathrm{d}u}(3) &= 24 > 0 \\
\frac{\mathrm{d}f}{\mathrm{d}u}(4) &= -432 < 0.
\end{aligned}$$

Thus, $u_s = 0, 3$ are unstable, $u_s = 4$ is stable and we can not categorise $u_s = 1, 2$ because the equation has at least a double root at these points and, as such, the derivative evaluates to zero.

5.1.3

Figure 8 illustrates that $u_s = 0, 2, 3$ are unstable, whilst $u_s = 1, 4$ are stable.

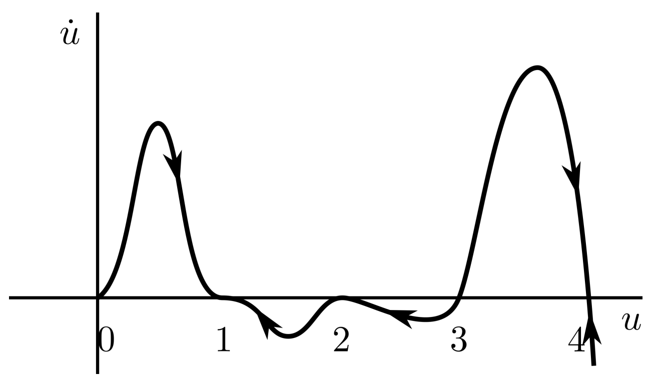

Figure 8: Phase plane plot of equation (31).

6 Infections

The interaction dynamics of any disease can be understood by modelling three sections of the population: the susceptible population, S; the infected population, I and the recovered population, R. They interact through the following rules:

- whenever a susceptible agent interacts with an infective agent the result is two infective agents at a rate r_1;
- the infected population recovers at a rate proportional to the size of the infected population, the rate of proportionality is r_2.

Finally, suppose that the initial densities of the susceptible and infectives are S_0 and I_0, respectively, and that there are no initially recovered people.

1. Convert the above rules into interaction equations.

2. Use the Law of Mass Action to convert the interaction equations into ODEs.
3. Show that $S + I + R = \text{constant} = S_0 + I_0$. What does this mean?
4. What are the dimensions of S, I, R, $\dot{S}$, $\dot{I}$, $\dot{R}$, r_1 and r_2 in terms of density and time?
5. Let $S = [S]S'$, $I = [I]I'$, $R = [R]R'$ and $t = [t]t'$ where the bracketed variable is the dimensional part and the primed variable be the non-dimensional part. Further, suppose we non-dimensionalise the system as

$$\begin{aligned}\dot{S}' &= -S'I', \quad S'(0) = S_0',\\ \dot{I}' &= S'I' - I', \quad I'(0) = I_0',\\ \dot{R}' &= I', \quad R'(0) = 0,\end{aligned}$$

where the $\dot{}$ symbol now stands for $\mathrm{d}/\mathrm{d}t'$. What are the scales $[S]$, $[I]$, $[R]$ and $[t]$ in terms of r_1 and r_2? Show that they have the right dimension, *i.e.* $[S]$ has the same dimension as S, as specified in question 4.
6. What are the forms of S_0' and I_0' in terms of r_1, r_2, S_0 and I_0?
7. By integrating

$$\frac{\mathrm{d}I'}{\mathrm{d}S'} = \frac{\dot{I}'}{\dot{S}'}, \quad \frac{\mathrm{d}R'}{\mathrm{d}S'} = \frac{\dot{R}'}{\dot{S}'}, \tag{33}$$

find expressions for $I'(S')$ and $R'(S')$. Do not forget about the initial conditions.

6.1 Answers

6.1.1

$$S + I \xrightarrow{r_1} 2I, \tag{34}$$
$$I \xrightarrow{r_2} R. \tag{35}$$

6.1.2

$$\dot{S} = -r_1 SI, \quad S(0) = S_0, \tag{36}$$
$$\dot{I} = r_1 SI - r_2 I, \quad I(0) = I_0, \tag{37}$$
$$\dot{R} = r_2 I, \quad R(0) = 0. \tag{38}$$

6.1.3

Adding equations (36)-(38) we get $\mathrm{d}(S + I + R)/\mathrm{d}t = 0$. Integrating and using the initial conditions produces the result $S + I + R = S_0 + I_0$. This means that the total number of humans is conserved, namely they are either susceptible, infected, or removed. There is no leakage from the system.

6.1.4

dim(S)=dim(I)=dim(R)=density.
dim($\dot{S}$)=dim($\dot{I}$)=dim($\dot{R}$)=density/time.
dim(r_1)=1/(density×time).
dim(r_2)=1/time.

6.1.5

Substituting $S = [S]S'$, $I = [I]I'$, $R = [R]R'$ and $t = [t]t'$, into the system we find that

$$\frac{[S]}{[t]} = r_1[S][I], \tag{39}$$
$$\frac{[I]}{[t]} = r_1[S][I] = r_2[I], \tag{40}$$
$$\frac{[R]}{[t]} = r_2[I], \tag{41}$$

from which we rapidly find that $[S] = [I] = [R] = r_2/r_1$ and $[t] = 1/r_2$. Using the results from question 4 we find that r_2/r_1 =density and $1/r_2$ =time. Thus, units are consistent.

6.1.6

$S_0' = S_0/[S] = r_1 S_0/r_2$.
$I_0' = I_0/[I] = r_1 I_0/r_2$.

6.1.7

$$\frac{\mathrm{d}I'}{\mathrm{d}S'} = \frac{\dot{I}'}{\dot{S}'} = 1 - \frac{1}{S'},$$
$$\frac{\mathrm{d}R'}{\mathrm{d}S'} = \frac{\dot{R}'}{\dot{S}'} = \frac{1}{S'},$$

Integrating the above equations with initial conditions $I'(S_0') = I_0'$ gives

$$I'(S') = \log\left(\frac{S'}{S_0'}\right) + I_0' + S' - S_0'. \tag{42}$$

and

$$R' = \log\left(\frac{S'}{S_0'}\right). \tag{43}$$