Part II Mathematical Biology - Section 1

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Contents

0 Introduction

Acknowledgements

Much of the content and the starting point for these notes comes from Prof. Peter Haynes's version of the notes from 2012. Any typos are, however, likely to be the fault of the present lecturer. If you spot any errors or have suggestions for improvements or other comments on these notes, please send them my way.

Practicalities

- Comments and corrections here please: `jrg20@cam.ac.uk`
- Online base via Moodle: `http://tinyurl.com/mathbio16`
- Examples sheets will appear online in the usual place
- Scans of handwritten notes from lecture itself will appear online after each lecture - these may be useful for repairing any gaps or errors in your own notes. I do not recommend using these *instead* of attending lectures.
- These fuller typed notes will appear eventually for at least the first two sections of the course - these are for you to check anything which you didn't fully follow in lectures, or to patch a missed lecture (but again, better to attend lectures...)
- Exercises will also be set during lectures: these should be doable without any supervision and I recommend doing them while reviewing your notes between lectures, solutions will appear online.

Preparation for this course

Part II Dynamical Systems is 'helpful' for parts of this course but certainly not essential. If you did not do Dynamical Systems, then it might be wise to do a little revision of parts of Ia Differential Equations: stability of equilibria of discrete and continuous time systems (Jacobians, saddles/focus/node, phase-plane diagrams). Indeed *'Ordinary Differential Equations'* by Robinson (see schedules for Ia Differential Equations) chapters 32 and 33 ('coupled nonlinear equations' and 'ecological models') will put you right on track for this course. The middle part of the course on stochastic systems will use some knowledge from Ia Probability, including generating functions. It would be a good idea to revise separable solutions from Ib Methods for the last part of the course on diffusion.

Interesting reading

None of these are essential to follow this course, but should be of interest:

- J.D. Murray *Mathematical Biology (3rd edition)* (see schedules) - the classic text on mathematical biology, covering a range of applications
- D. Neal *Introduction to Population Biology* - much overlap with this course in mathematical detail, but explores the biological principles in rather more depth and includes many real examples. Should be completely readable by you during or after this course.
- *Mathematics is biology's next microscope, only better; Biology is mathematics' next physics, only better* - article by Joel E. Cohen in PLoS Biology 2004 DOI: 10.1371/journal.pbio.0020439

1 Deterministic systems, no spatial structure

1.1 Single population models

1.1.1 Simple birth and death models

The simplest model?

Let $x(t)$ be population size as a function of time t. Assume that the number of offspring produced per individual per unit time is a constant $b > 0$. Similarly assume that the death rate (number of deaths per unit time per individual) is a constant $d > 0$.

$$x(t + \delta t) = -x(t) + b\,x\,\delta t - d\,x\,\delta t$$

Divide by δt and take the limit as $\delta t \to 0$.

$$\frac{dx}{dt} = (b - d)x = rx \quad \text{where} \quad r = b - d.$$

Solution is $x(t) = x_0 e^{rt}$, where $x(0) = x_0$, so the population grows indefinitely if $r > 0$ and decays towards zero (implying extinction) if $r < 0$.

Exercise 1: In the case when $r < 0$, find the half-life of the population

Exercise 2: Actually, this simple model is pretty good for invasions of new populations. Suppose a new disease is discovered and there are 1000 cases last week and 1500 cases this week, roughly when did the disease first appear?

Note that in a deterministic system, only the difference between b and d matters, e.g. $b = 21$, $d = 20$ gives entirely the same dynamics as $b = 1,000,001$, $d = 1,000,000$. These will differ in an analogous stochastic model (the ones with higher rates will fluctuate wildly).

Birth and death rates depend on population size Rather than constant, allow the number of offspring per individual per unit time to depend on population size, $a(x)$, and similarly the death rate $b(x)$. Then we have:

$$\frac{dx}{dt} = [b(x) - d(x)]x$$

Again, only the difference between birth and death rates matter in the deterministic system.

Typically, one might expect the birth rate per capita to decrease and/or death rate to increase for very large population size, as resources become scarce. For example here we could take the birth rate to be constant ($b(x) = B$) and the death rate to be proportional to population size ($d(x) = D\,x$):

$$\frac{dx}{dt} = [B - D\,x]x$$

By rescaling the population size and renaming parameters, we have the *logistic equation*:

$$\frac{dx}{dt} = \alpha x(1 - x)$$

Exercise 3: Find the rescaling.

For $x < 1$, births outnumber the deaths and the population grows. For $x > 1$, the opposite occurs and the population shrinks. The equilibrium population size (scaled) is one.

The logistic model

$$\frac{dx}{dt} = \alpha x(1 - x)$$

This is easy to solve:

$$\int \frac{1}{x(1-x)}dx = \int \frac{1}{x} + \frac{1}{1-x}dx = \log\left|\frac{x}{1-x}\right| + C = \alpha t$$

So putting $x = x_0$ at $t = 0$ we have:

$$\frac{x}{1-x} = \frac{x_0}{1-x_0}e^{\alpha t}$$

Which rearranges to:

$$x = \frac{x_0 e^{\alpha t}}{(1-x_0) + x_0 e^{\alpha t}}$$

Reassuringly, our steady population size is there: $x_0 = 1$ gives $x(t) = 1$. Also, it is always sensible to check zero initial conditions: $x_0 = 0$ gives $x(t) = 0$.

Exercise 4: show that the solution to the logistic equation can be rewritten for some t_0 as:

$$x = \begin{cases} \frac{1}{2} + \frac{1}{2}\tanh\left(\frac{1}{2}\alpha(t - t_0)\right) & \text{for } x_0 < 1 \\ \frac{1}{2} + \frac{1}{2}\coth\left(\frac{1}{2}\alpha(t - t_0)\right) & \text{for } x_0 > 1 \end{cases}$$

Note that for positive initial population size ($x_0 > 0$), $x \to 1$ as $t \to \infty$ (from above if $x_0 > 1$ and from below if $x_0 < 1$). There is a stable equilibrium, achieved for all positive initial conditions. The zero equilibrium $x = 0$, b is unstable.

One-dimensional stability recap

Consider:

$$\frac{dx}{dt} = f(x)$$

The steady-states are the values of x^* for which $f(x^*) = 0$. These may be interchangeably referred to as equilibria, fixed points, steady states or constant solutions. Stability is determined by behaviour near the fixed point, which can be found by linearisation around x^*. Set $x(t) = x^* + \epsilon(t)$. Then:

$$\frac{dx}{dt} = \frac{d\epsilon}{dt} = f(x^* + \epsilon) = \underbrace{f(x^*)}_{=0} + \epsilon f'(x^*) + \underbrace{\mathcal{O}(\epsilon^2)}_{\text{ignore}}$$

Hence:

$$\frac{d\epsilon}{dt} \simeq f'(x^*)\epsilon \quad \text{which has solution} \quad \epsilon(t) \simeq \epsilon_0 \exp[f'(x^*)t].$$

So ϵ, the perturbation away from x^* grows if $f'(x^*) > 0$ (unstable) and shrinks if $f'(x^*) < 0$ (stable).

In practice, just check sign of f' at fixed points. For simple biological models, this can usually be done easily by plotting f.

Exercise 5: check stability of the fixed points of the logistic model

1.1.2 Delay models

So far, we have $x'(t)$ depending on $x(t)$, i.e. the instantaneous current population size. Of course this is not always realistic. For example, offspring are not really produced instantaneously, there may be a significant gestation period, or time for eggs to hatch. Even then, new offspring may need further time to mature to adulthood, before they can in turn produce offspring. So, we might want $x(t)$ to denote adults, and births and/or deaths may depend on the population size at some past time point. In physiological models, there is often some form of delay, for example heart rate does not respond instantly to exercise. In biochemical signalling, there can be many steps between a trigger and effect, which can sometimes be modelled relatively simply as a time lag.

end of lecture 1

Mathematically, this leads to *delay-differential equations* (DDEs). Here is an example, the *Hutchinson-Wright* equation, which can be viewed as an extension to the logistic equation:

$$\frac{dx}{dt} = \alpha\, x(t)\,[1 - x(t-T)]$$

where the delay time T is a new parameter in the model (assume $T > 0$, note $T = 0$ was logisitic equation).

We can analyse its dynamics with much the same ideas as before: find the interesting fixed points and look at their stability by considering a small perturbation. Clearly $x(t) = 1$ is still the non-trivial steady state. Now set $x(t) = 1 + \epsilon(t)$ and sub in:

$$\begin{aligned} \frac{d\epsilon}{dt} &= \alpha(1+\epsilon(t))(-\epsilon(t-T)) \\ \frac{d\epsilon}{dt} &= -\alpha\epsilon(t-T) + O(\epsilon^2) \end{aligned}$$

And drop $O(\epsilon^2)$ from here.

This is still linear, so reasonable to seek a solution of the form $\epsilon = \epsilon_0 e^{st}$:

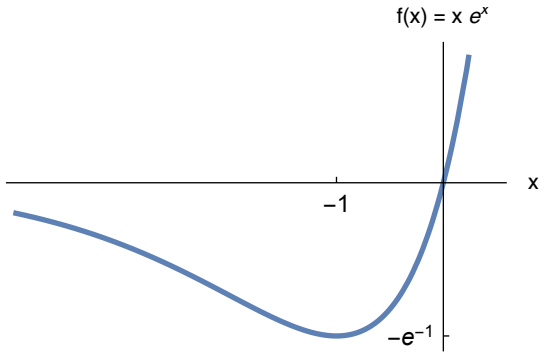
$$s = -\alpha\, e^{-sT} \tag{1}$$

We would like know the solutions for s. We see that if $T = 0$, then this just returns $s = -\alpha$, which corresponds to the stable fixed point of the logistic equation. If $T > 0$, then we need to look a bit more carefully.

First we might reasonably seek real s solutions. Rearranging:

$$sTe^{sT} = -\alpha T$$

Consider the shape of the LHS as a function of sT. It has a single minimum at $sT = -1$ when the LHS is equal to $-e^{-1}$. So, there are negative real roots for $\alpha T < e^{-1}$ and no real roots otherwise.



If we look at the solution near $sT = 0$, for small αT, the gradient is approximately 1, so we have $sT \approx -\alpha T$ so this is a continuation of the solution $s = -\alpha$, which is what we would have got with the logistic equation.

So far we have only considered real roots for s, but we might (correctly) suspect there could be complex roots of 1 for s. What would this mean? Our perturbation would follow $\epsilon_0 e^{st}$, so a complex solution would just give a solution that grows or decays but with oscillations (think back to complimentary functions in second order linear ODEs). We are now interested in the sign of the real part of s. If $Re(s) > 0$ we say it is unstable, if $Re(s) < 0$ we say it is stable. It is not usually possible to solve explicitly for s, but we can see now that it would be sensible to find when stability might change, i.e. $Re(s) = 0$.

Now lets seek complex roots of (1) by setting $s = \sigma + i\omega$ (where σ and ω are the real and imaginary parts of s). Sub in:

$$\sigma + i\omega = -\alpha e^{-s\sigma} e^{-is\omega} = -\alpha e^{-s\sigma} \left[\cos(\omega T) - i \sin(\omega T)\right]$$

Take real and imaginary parts:

$$\begin{aligned} \sigma &= -\alpha e^{-\sigma T} \cos(\omega T) \qquad \text{real part} \\ \omega &= +\alpha e^{-\sigma T} \sin(\omega T) \qquad \text{imaginary part} \end{aligned}$$

Seek a solution with $\sigma = 0$. Things simplify quite a bit:

$$\begin{aligned} 0 &= -\alpha \cos(\omega T) \\ \omega &= +\alpha \sin(\omega T) \end{aligned}$$

Squaring and adding gives $\omega^2 = \alpha^2$ so $\omega = \pm\alpha$. This is not too surprising: we should expect complex conjugate pairs of solutions. Could limit calculuations to $\omega > 0$ if it helped, and just remember the complex conjugates are also there. In any case, subbing in either solution to the second equation, gives the same outcome:

$$\sin(\alpha T) = 1 \quad \text{so } \alpha T = \frac{\pi}{2}, \frac{5\pi}{2}, \frac{9\pi}{2}, \ldots$$

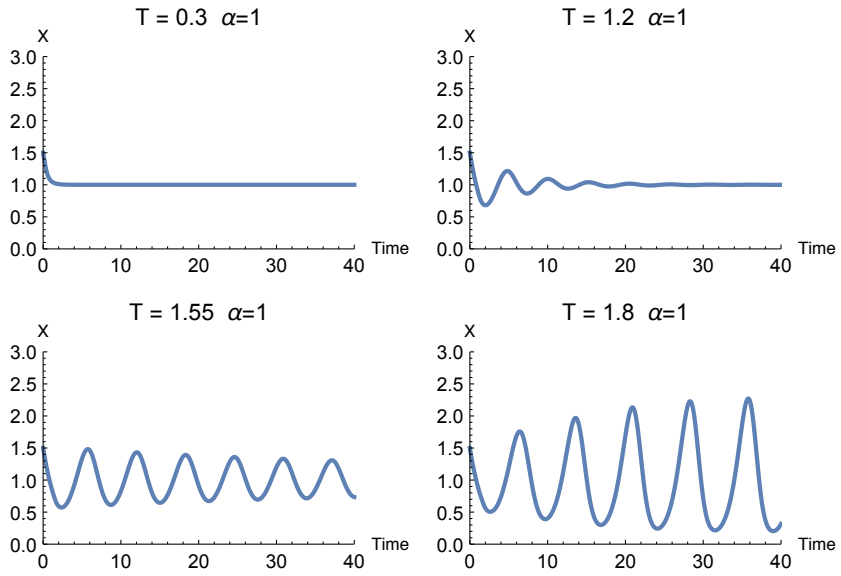
and no need to worry about negative solutions, as both $\alpha > 0$ and $T > 0$. So thinking about increasing T up from zero, we have a complex root switch real part sign many times. We are interested in the first one: $\alpha T = \pi/2$.

This is optional, but as this is the first example, we will check that we really do have stable solutions when $0 < T < \frac{\pi}{2\alpha}$. It turns out to be sensible to split into two cases according to modulus of ω

- For $|\omega| > \alpha$, from considering modulus in the equation for the real part we see that $\exp(-\sigma T) > 1$ hence $\sigma < 0$.
- For $|\omega| \leq \alpha$, $|\omega T| \leq \alpha T < \pi/2$ so $\cos(\omega T) > 0$. From the equation for the real part, we see $\sigma < 0$ again.

So either way, we have negative σ and hence stable solutions. Note we have not actually found any values for s, but we have shown they will have negative real part in this range.

Numerical simulation is consistent with $0 < T < \frac{1}{\alpha e}$ solutions decay exponentially to the fixed point; for $\frac{1}{\alpha e} < T < \frac{\pi}{2\alpha}$ solutions decay and oscillate to the fixed point, and for $T > \frac{\pi}{2\alpha}$ the solution is unstable and heads to a cycle. This is typical: delay-differential equation models often lead to oscillatory solutions.



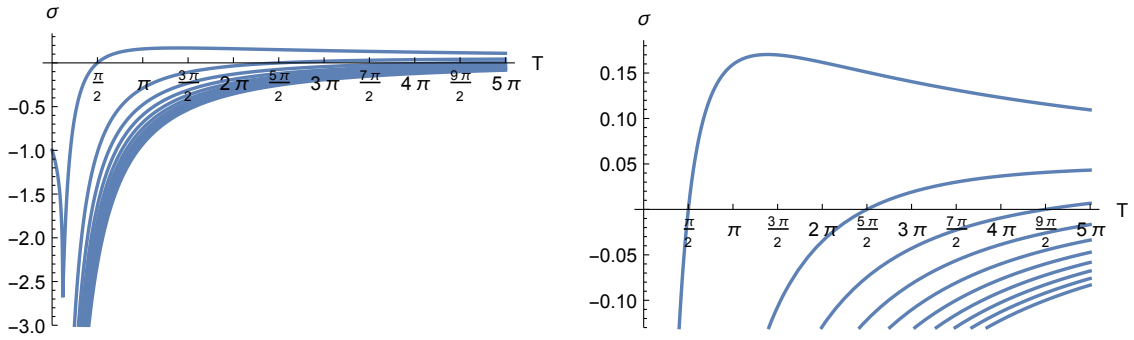
(See Mathematica: Delay Logistic Equation)

Under the carpet

Treat this note as starred. If you are happy with DDEs already, then skip it. If you are concerned that something might have been swept under the carpet here, you are right, so read on. What we have actually done is

- Found where there are real solutions for s and shown they are negative.
- For first range of T showed that any solution for s has negative real part
- Found all the values of $T > 0$ where a solution has real part zero

We can actually know more about the solutions for s of $sTe^{sT} = -\alpha T$ if we read up on 'Lambert W-Functions'. There are many solutions. Mathematica has a built-in function that can be used to give them numerically, and we can plot their real part as a function of T (set $\alpha = 1$ for simplicity).



$\sigma = Re(s)$ against T for $\alpha = 1$ for top 10 solutions
(same plot each side, just different vertical scale)

The root with the largest real part (top line on graph) actually corresponds to that largest real solution to start with, and you can see the sharp change of direction as it becomes complex. The vertical zoom-in on the right shows more clearly that successive (pairs of) solutions pass upwards into positive σ.

For $T = 0$ we only had one value of s (namely $s = -\alpha$). This was enough to determine the linear behaviour of any small perturbation: $\epsilon = \epsilon_0 \exp(-\alpha t)$, and we'd just need to put in the appropriate single constant ϵ_0. Now, for a perturbation, we should specify not just $\epsilon(0)$ but also $\epsilon(t)$ for the interval $t \in [-T, 0]$. And the resultant dynamics will be as a sum of these types of solution with different s:

$$\epsilon(t) = \sum_i a_i e^{s_i t}$$

where the a_i are determined by the initial conditions. The s_i with the largest real part will end up dominating as t increases.

So, actually we have got the dynamics right from the simple approach we first took: the real solution dominated when it existed, the we had an oscillatory but decaying solution until we found the lowest T where things could lose stability. For math bio, treat this simple approach as sufficient.

Be a bit careful when rescaling DDEs

This is just a word of caution about rescaling delay differential equations with respect to time. In short, you must remember to rescale any time lag also. In long, we will use the above as an example:

$$\frac{d\epsilon(t)}{dt} = -\alpha\epsilon(t-T)$$

There are two parameters here, α and T. It is tempting to try and get rid of α by rescaling time. We set $\hat{t} = \alpha t$ to cancel out with the α:

$$\frac{d\epsilon(t)}{dt} = \alpha\frac{d\epsilon}{d\hat{t}} = -\alpha\epsilon(t-T)$$

so

$$\frac{d\eta(\hat{t})}{d\hat{t}} = -\epsilon(t-T) = -\eta(\alpha(t-T)) = -\eta(\hat{t}-\alpha T)$$

and finally:

$$\frac{d\eta(\hat{t})}{d\hat{t}} = -\eta(\hat{t}-\alpha T).$$

So really we have not eliminated α but we have compounded our two parameters to a single parameter combination αT.

In general, be aware that the lag needs to rescale with time also. It is not usual in practice to write out all of these steps. It is usually acceptable to reuse the original variable name (ϵ here), but the change was made explicit just this once.

Exercise 6: Find the equivalent of equation (1) for this rescaled DDE. (It turns out to be slightly different, but it ought to give us the same conditions for stability.)

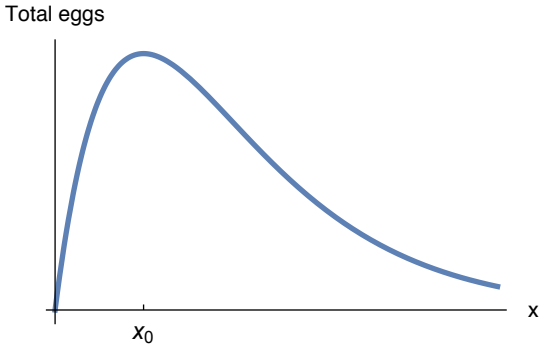
DDE Example: Blowflies

This example stems from classic experimental work by Nicholson and others in the 1950s on the Australian sheep blowfly. Populations of flies were kept in the lab and population size was tracked over time, showing some quite spectacular fluctuations despite the available food and other external factors being kept steady. The full life cycle of these flies is a few weeks (eggs, larval stages, then adult). Mathematical biologists have modelled this using delay differential equations.

The unusual thing here is that the number of eggs produced by adult flies is very strongly regulated by population size, in fact we assume that the per capita rate of egg production is exponentially decreasing with population size. This means that the total number of eggs produced is no longer monotonic increasing with population size, but now is unimodal with a peak at $x = x_0$.

end of lecture 2

Per capita egg production if population has size x: $\quad Pe^{-x/x_0}$
Total egg production from population of size x: $\quad p(x) = Pxe^{-x/x_0}$



Now assume that eggs turn into adults after a delay t_D, and that the per capita death rate δ does not depend on population size, and we have our model:

$$\frac{dx(t)}{dt} = \underbrace{P\,x(t-t_D)\,Exp\left(-\frac{1}{x_0}x(t-t_D)\right)}_{\text{new eggs at time } t-t_D} - \underbrace{\delta\,x(t)}_{\text{death}} \tag{2}$$

Note that $x(\mathrm{blah})$ denotes x evaluated at blah (as opposed to multiplied by), and similarly for $\hat{x}$ below.

This system has four parameters[1]: P, t_D, x_0 and δ. By strategic rescaling, this can be reduced to two. As usual, we can rescale time to adsorb a parameter, and here we'll choose the death rate. Set $\hat{t} = \delta \times t$ to make $\frac{d}{dt} = \delta \frac{d}{d\hat{t}}$.

We can also rescale x to tidy the exponent: set $\hat{x} = x/x_0$. We will consider $\hat{x}$ as a

[1] and as usual in mathematical biology, assume everything is positive unless you have a good reason to think otherwise

function in our rescaled time: $\hat{t}$. So we are setting this

$$x(t) = x_0\,\hat{x}\left(\hat{t}\right) = x_0\,\hat{x}\left(\delta\,t\right),$$

so in particular

$$x(t - t_D) = x_0\,\hat{x}\left(\delta \times (t - t_D)\right) = x_0\,\hat{x}\left(\hat{t} - \delta\,t_D\right).$$

Hence making these changes and also dividing through by x_0:

$$\frac{d\hat{x}(\hat{t}\,)}{d\hat{t}} = \frac{P}{\delta}\hat{x}(\hat{t} - \delta\,t_D)e^{-\hat{x}(\hat{t}-\delta\,t_D)} - \hat{x}(\hat{t}\,)$$

From this we can see that the model really only depends on two parameter combinations. Set $a = \delta t_D$ and $b = Pt_D$ (turns out to be sensible to think of them both as increasing in t_D, so use these and then drop the hats to get the system in a suitable form to analyse:

$$\frac{dx(t)}{dt} = \frac{b}{a}\,x(t - a)\,e^{-x(t-a)} - x(t) \tag{3}$$

Exercise 7: get from equation 2 to equation 3 (without using notes!)

To find any equilibria, we solve for $x(t) = x^*$ where x^* is constant:

$$0 = \frac{b}{a}\,x^*e^{-x^*} - x^*$$

Which gives $x^* = \log\frac{b}{a}$ as the non-trivial solution. Assume $b > a$ so that this solution is positive.

For stability, look at dynamics close to this fixed point, i.e. ϵ small[2]:

$$x(t) = x^* + \epsilon y(t)$$

Sub this into equation 3:

$$\begin{aligned}
\epsilon\,y'(t) &= \frac{b}{a}\,(x^* + \epsilon\,y(t - a))\underbrace{e^{-x^*}}_{=a/b}e^{-\epsilon\,y(t-a)} - (x^* + \epsilon\,y(t))) \\
&= (x^* + \epsilon\,y(t - a))\,e^{-\epsilon\,y(t-a)} - (x^* + \epsilon\,y(t)) \\
&= (x^* + \epsilon\,y(t - a))\,(1 - \epsilon\,y(t - a)) - (x^* + \epsilon\,y(t)) + \mathcal{O}(\epsilon^2)
\end{aligned}$$

[2]We don't really need ϵ and $y(t)$ (lectures just used $\epsilon(t)$). Just need some function of time which is assumed to be small, but sometimes it is easier to put ϵ in as a constant to explicitly to keep track of what is small.

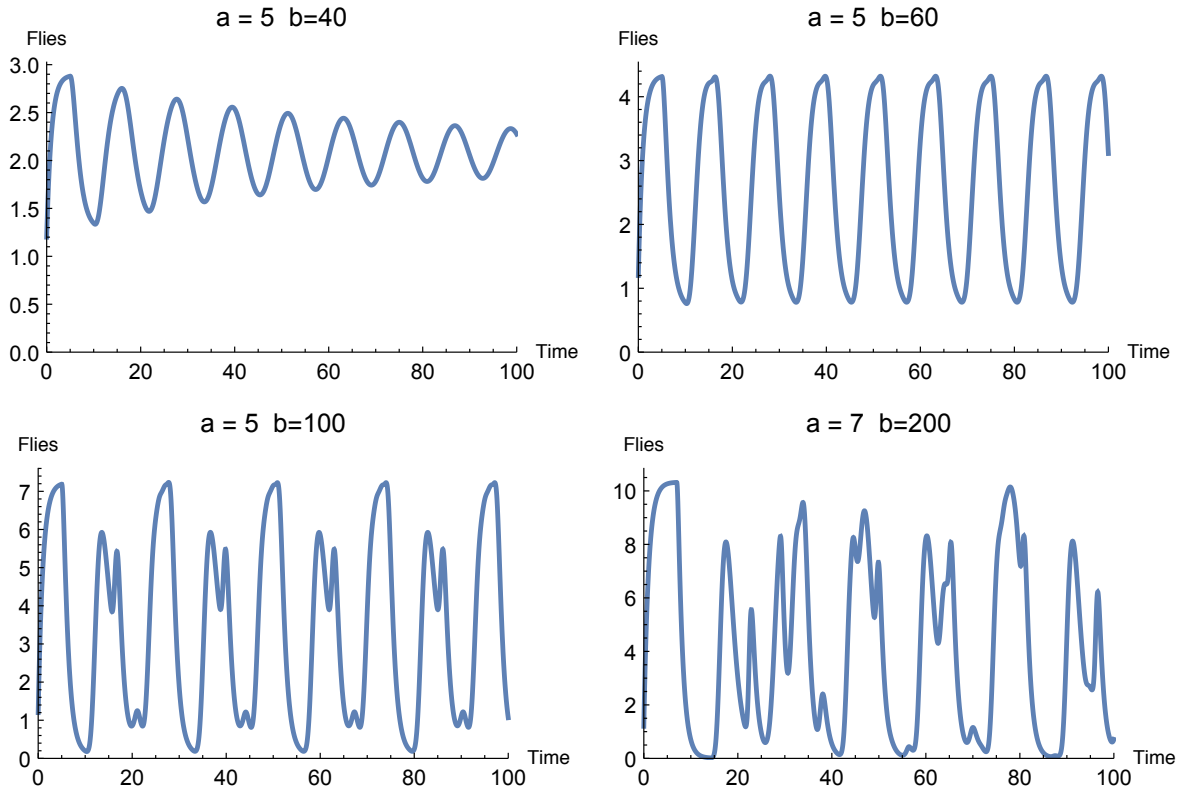
And the order 1 terms cancel (which is reassuring, as it was supposed to be a fixed point) and then taking just order ϵ:

$$y'(t) = (1 - x^*)\, y(t - a) - y(t)$$

Exercise 8: Continue from here to get to:

$$\begin{aligned} \sigma &= (1 - x^*)\, e^{-a\sigma} \cos(a\omega) - 1 \\ \omega &= (1 - x^*)\, e^{-a\sigma} (-\sin(a\omega))\,. \end{aligned}$$

Exercise 9: Show the system is datable for $b < e^2 a$.



(See Mathematica: Blowflies, and keep $b \gg a$)

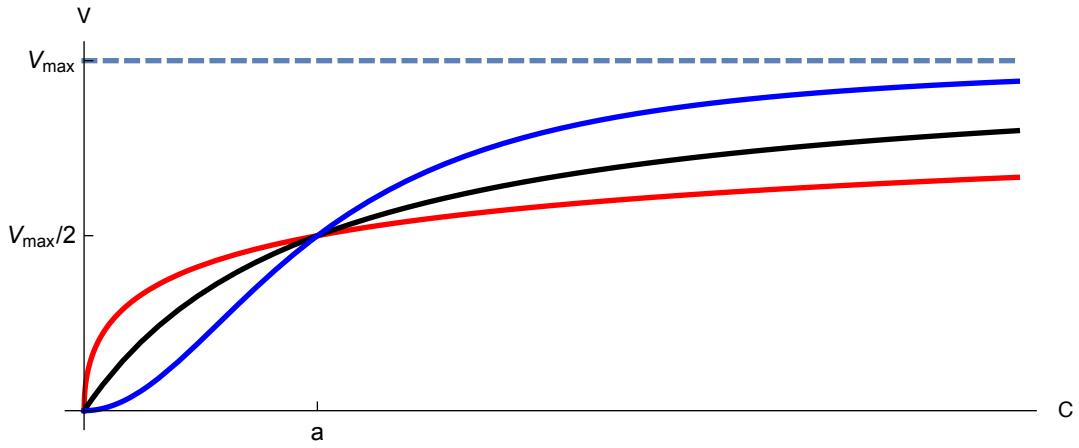
Physiological Example: Breathing

This is a simple model of respiration (breathing) where we focus on one particular function of breathing: to remove carbon dioxide from the blood. We assume there is a feedback system where the volume of breath depends positively on the level of carbon-dioxide in the blood.

$$\begin{aligned} V &= \text{air inhaled (per breath)} \\ C(t) &= \text{concentration of carbon dioxide in the blood at time } t \end{aligned}$$

And we use a Hill[3] function to model how V depends on C:

$$V(C) = V_{max}\frac{C^m}{a^m + C^m}$$



Hill function for various m: red $m = 1/2$, black $m = 1$, blue $m = 2$. They all pass though the same point at $C = a$: half of the maximum V_{max}.

However, there will be a lag between the level of carbon dioxide being detected and the time until the breath volume is adjusted. This will involve a series of chemical reactions, and communication with the brainstem, but we do not need to know all the details, just that there is some time difference, call it T. Also assume that the amount of carbon dioxide breathed out is proportional both to its current concentration and to the breath volume, with multiplicative constant b. Finally, assume that carbon dioxide in the blood is added at a constant rate p (from other physiological processes around the body). This gives us the folioing equation:

[3]Archibald Hill 1886-1977: Trinity mathmo and Nobel Prize winning Physiologist, among many other things: `http://www.nobelprize.org/nobel_prizes/medicine/laureates/1922/hill-bio.html`

$$\frac{dC}{dt} = \underbrace{+p}_{CO_2 \text{ in to blood}} \quad \underbrace{-b\,C(t)V\left(C(t-T)\right)}_{\text{breathed out}}$$

$$= \quad p \quad -b\,C(t)V_{max}\frac{C(t-T)^m}{a^m + C(t-T)^m}$$

end of lecture 3

And we go ahead and rescale in the same way as before. We can pick up a good rescaling for C by tidying the Hill function: set $\hat{C} = C/a$. Again, we can choose to eliminate something else by rescaling time, so go for making that first term into 1. Set $\hat{t} = \frac{p}{a}t$ so that $\frac{d}{dt} = \frac{p}{a}\frac{d}{d\hat{t}}$:

$$\frac{d\hat{C}}{d\hat{t}} = 1 - \frac{abV_{max}}{p}\,\hat{C}(\hat{t}\,)\frac{\hat{C}(\hat{t} - pT/a)^m}{1 + \hat{C}(\hat{t} - pT/a)^m}$$

Again, note how the time lag also is rescaled as we are now working with $\hat{C}$ as a function of $\hat{t}$. Now we can see there are essentially two new parameter combinations emerging here, $\tau = pT/a$ and $\alpha = abV_{max}/p$, so work in terms of those and also we can drop the hats at this point[4]:

$$\frac{dC}{dt} = 1 - \alpha\,C(t)\frac{C(t-\tau)^m}{1 + C(t-\tau)^m}$$

This could be tidied a little further by defining $f(x) = x^m/(1+x^m)$:

$$\frac{dC}{dt} = 1 - \alpha\,C(t)f(C(t-\tau))$$

Seek a constant equilibrium solution:

$$0 = 1 - \alpha C^* f(C^*)$$

$$1 = \alpha C^* f(C^*)$$

The function f increases from zero to one. While we can't write down an explicit solution for this (at least not for general m in the Hill function), we can easily see that the right-hand side is unboundedly monotonically increasing, starting from zero, so there will be a unique solution C^*. Also, as $f < 1$ we know that C^* will satisfy $C^* > 1/\alpha$, which will turn out to be useful later.

For stability, as usual we set $C = C^* + \epsilon y(t)$.

[4] in lectures, we just reused T, but done with τ here

$$\begin{aligned}
\epsilon y'(t) &= 1 - \alpha\,(C^* + \epsilon y(t)) f(C^* + \epsilon y(t-\tau)) \\
&= 1 - \alpha\,(C^* + \epsilon y(t))\,(f(C^*) + \epsilon y(t-\tau) f'(C^*)) + \mathcal{O}(\epsilon^2) \\
&= 1 - \alpha\,[C^* f(C^*) + \epsilon y(t) f(C^*) + C^* \epsilon y(t-\tau) f'(C^*)] + \mathcal{O}(\epsilon^2) \\
&= \underbrace{1 - \alpha\, C^* f(C^*)}_{=0} - \epsilon\alpha [y(t) f(C^*) + C^* y(t-\tau) f'(C^*)] + \mathcal{O}(\epsilon^2)
\end{aligned}$$

And so to order ϵ (in other words, linearising):

$$y'(t) = -\underbrace{\alpha f(C^*)}_{A}\, y(t) - \underbrace{\alpha C^* f'(C^*)}_{B}\, y(t-\tau)$$

for some constants A and B.

Exercise 10 : show that

$$A = \frac{1}{C^*}\,, \quad B = \left(1 - \frac{1}{\alpha C^*}\right) \frac{m}{C^*}.$$

and check that B is positive

So, in essence:

$$y'(t) = -Ay(t) - By(t-\tau)$$

Now we have an equation which is linear in y, though it is still a delay equation, so we try a solution of the form $y = e^{st}$:

$$s = -A - Be^{-s\tau}$$

We can immediately see that for $\tau = 0$ that $s = -A - B$, so C^* is stable. For more general parameters, we explore this as usual by setting $s = \sigma + i\omega$ (where we always take σ and ω to be real).

$$\begin{aligned}
\sigma &= -A - Be^{-\sigma\tau} \cos\omega\tau \\
\omega &= Be^{-\sigma\tau} \sin\omega\tau
\end{aligned}$$

Note that the equations are symmetric in $\pm\omega$, which is not surprising: the roots for s should be in complex conjugate pairs. We could restrict attention to $\omega > 0$.

There's a few things we could argue through now. With a bit of work, we could show for small τ (actually not very small needed), we should show $\sigma > 0$ impossible, so still stable.

Actually, we might be interested in the shape parameter of the Hill function m. We can show that if m is small, then B will be small (need to be a bit careful as m is implicitly

in c^*, but that can be bounded). If B is small, we can also see $\sigma > 0$ impossible. Now think about larger m, as it increases from small. To try and find a boundary when the real part goes through zero (which should give us the edge of instability), set $\sigma = 0$:

$$\begin{aligned} 0 &= -A - B\cos\omega\tau \\ \omega &= B\sin\omega\tau \end{aligned}$$

Which rearranges to:

$$-A\tau\tan(\omega\tau) = \omega\tau \quad (4)$$
$$B^2 = bA^2 + \omega^2 \quad (5)$$

Equation 4 has a root for ωT in $(\pi/2, \pi)$, and its exact value will depend on $A\tau$. Call it $g(A\tau)$. There are other roots further on, but this lowest one turns out to be the one of interest. Equation 5 gives an implicit expression that must be satisfied by A, B and τ:

$$B^2 = A^2 + \tau^{-2}g(A\tau)^2$$

Exercise 11: Consider varying the parameter m. Show that this boundary for instability means that:

$$1 + \frac{\pi^2 C^{*2}}{4\tau^2} \leq m^2\left(1 - \frac{1}{\alpha C^*}\right)^2 \leq 1 + \frac{\pi^2 C^{*2}}{\tau^2}$$

And in particular, this means that this critical m is greater than 1.

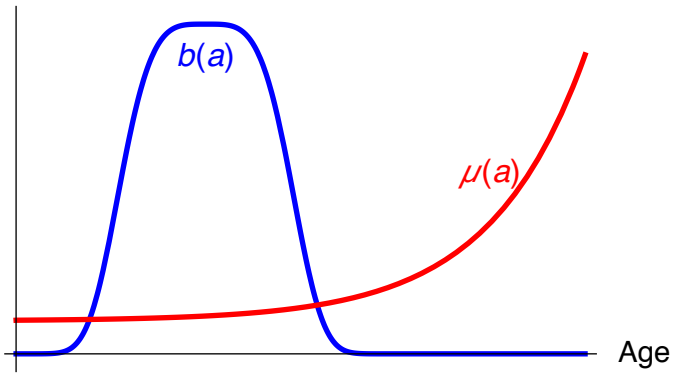
1.1.3 Populations with age structure

So far, we have just been considering the population size (usually x). However, when thinking about birth and death rates, it would often be important to consider the age of individuals. Now, set $n(a,t)$ to be the number of individuals at time t who are age a [5]. The *total* population at time t can be found by integrating over all ages:

$$N(t) = \int_0^\infty n(a,t)da$$

Now we set up birth and death rates as functions of age. Let $b(a)$ be the birth rate *from* individuals of age a. Let $\mu(a)$ be the death rate *of* individuals of age a.

[5] Strictly, this is a density function in a. So this should really be $n(a,t)\delta a$ is the number of individuals aged between a and $a + \delta a$. We don't usually need to say all of this though.



Example for $b(a)$ and $\mu(a)$. Birth rate might be highest from a particular age group, while the death rate may increase with age.

Now start to build the equations that govern n. Consider how a chunk[6] of population ages as time increases from t to $t + \delta t$. They will age by δt, but a small number might have die in that time:

$$n(a + \delta t, t + \delta t) = n(a, t) - \mu(a)\delta t\, n(a, t) + \mathcal{O}(\delta t^2) \tag{6}$$

The left hand side can be expanded by Taylor series, again to first order in δt:

$$n(a + \delta t, t + \delta t) = n(a, t) + \delta t \frac{\partial n}{\partial a}(a, t) + \delta t \frac{\partial n}{\partial t}(a, t) + \mathcal{O}(\delta t^2)$$

Sub this in to equation 6, cancel the $n(a, t)$, divide by δt and take limit $\delta t \to 0$:

$$\frac{\partial n}{\partial t}(a, t) + \frac{\partial n}{\partial a}(a, t) = -\mu(a)\, n(a, t)$$

Or we usually write:

$$\boxed{\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)\, n(a, t)} \tag{7}$$

With an initial condition in time, this is most of the story, but we also need a boundary condition in age, i.e. the newborns that appear at age zero:

$$\boxed{n(0, t) = \int_0^\infty b(a) n(a, t) da} \tag{8}$$

[6] c.f. fluids courses where we start with a blob of fluid. In fact this derivation is very similar if we replace space with age. The material derivative in fluids ($\frac{D}{Dt} = \frac{\partial}{\partial t} + u.\frac{\partial}{\partial x}$) is like the left hand side in equation 7 if we think about age rather than space, and our blob moves (ages) with velocity 1 in time. Note: don't try to think too hard about a fluids equivalent for the the boundary condition at age 0: that would be taking the analogy too far!

The age ∞ might look worrying, but in practice for any sensible model, the birth rate times population size is zero for a greater than some age, or at least mathematically the product tends to zero sufficiently fast for this integral to always be sensible.

Wave-like solutions

(Note: would be a good idea to have read through this once and understood the ideas, but otherwise treat it as starred)

The left hand side of equation 7 may remind you of characteristic or wave solutions from earlier courses (such as IB Methods). This works very easily for $\mu(a) = 0$ and ignoring age boundary condition. Any general function of $n(a,t) = g(a-t)$ solves $\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = 0$. This would be just a fixed population age distribution, just drifting upwards in age with time (which is fine only for no deaths).

We can extend this to account for the age-dependent death rate, and it can easily be checked that equation 7 is solved by:

$$n(a,t) = Exp\left[-\int_0^a \mu(s)ds\right] g(a-t)$$

The exponential term represents the probability of *surviving* to age a, where s is a dummy variable for age in the integration. We don't know much about g yet. This again is a wave-like solution, with some decay with age to account for deaths.

If we are given an initial condition i.e. $n(a,0) = n_0(a)$ then that is enough to specify $g(x)$ for $x > 0$:

$$n(a,0) = n_0(a) = e^{-\int_0^a \mu(s)ds} g(a)$$

$$\Rightarrow \quad g(a) = \frac{n_0(a)}{e^{-\int_0^a \mu(s)ds}}$$

Effectively, this is working out the number of births at time a ago, by consider those age a and scaling it up to account for the proportion that died before time zero.

To determine $g(x)$ for $x < 0$, we should use the newborn boundary condition (equation 8), which gives:

$$g(-t) = \int_0^\infty b(a) e^{-\int_0^a \mu(s)ds} g(a-t)da$$

And then split integral range at $a = t$ so when $a - t$ changes sign so we can use the initial condition in the second term:

$$
\begin{aligned}
g(-t) &= \int_0^t b(a)e^{-\int_0^a \mu(s)ds} g(a-t)da + \int_t^\infty b(a)e^{-\int_0^a \mu(s)ds} g(a-t)da \\
&= \int_0^t b(a)e^{-\int_0^a \mu(s)ds} g(a-t)da + \int_t^\infty b(a)e^{-\int_0^a \mu(s)ds} \left[e^{+\int_0^{a-t} \mu(s)ds} n_0(a-t)\right] da \\
&= \int_0^t b(a)e^{-\int_0^a \mu(s)ds} g(a-t)da + \int_t^\infty b(a)e^{-\int_{a-t}^a \mu(s)ds} n_0(a-t)da
\end{aligned}
$$

The first term is the births from those who were born after $t = 0$. The second term represents offspring from those individuals who were part of the initial condition population. They were age $a - t$ initially at $t = 0$, then they needed to survive from age $a - t$ to age a (which is the exponential term), and then give birth.

Under all sensible models with sensible initial conditions[7], this second term tends to zero as time increases (original population dies or doesn't contribute to birth rate). Then in principle $g(-t)$ can be determined by using the values for $g(x)$ for $-t < x < 0$. Essentially, this means that for large enough time, we can ignore the details of the initial condition (i.e. bin the second term above). It is this irrelevance of initial condition that we are exploiting in the next section.

(end of starred section)

Normal mode solutions

Without worrying about initial conditions (see previous section), we look for a 'normal mode' solution to equations 7 and 8. Set:

$$n(a,t) = r(a)e^{\gamma t}$$

Where r is the general shape of the population distribution, and the whole thing is scaled up or down in time, according to the exponent γ.

end of lecture 4

Sub it into equation 7:

$$
\begin{aligned}
\gamma\, r(a)e^{\gamma t} + r'(a)e^{\gamma t} &= -\mu(a)\, re^{\gamma t} \\
r'(a) &= -(\mu(a) + \gamma)\, r(a)
\end{aligned}
$$

Which we can solve by integrating with respect to a:

$$r(a) = r(0)e^{-\gamma a}e^{-\int_0^a \mu(s)ds}$$

[7] 'sensible' would certainly demand that the mean number of offspring is finite

The same exponential of an integral appears as in the previous section. Again, it is the probability of surviving from birth to age a. So we now have:

$$n(a,t) = r(0)e^{\gamma(t-a)}e^{-\int_0^a \mu(s)ds}$$

We can substitute the normal mode solution with this expression for r into equation 8:

$$r(0)e^{\gamma t} = \int_0^\infty b(a)\, r(0)\, e^{\gamma(t-a)}e^{-\int_0^a \mu(s)ds}\, da$$

Cancelling, and defining ϕ:

$$1 = \int_0^\infty b(a)\, e^{-\gamma a}e^{-\int_0^a \mu(s)ds}\, da := \phi(\gamma)$$

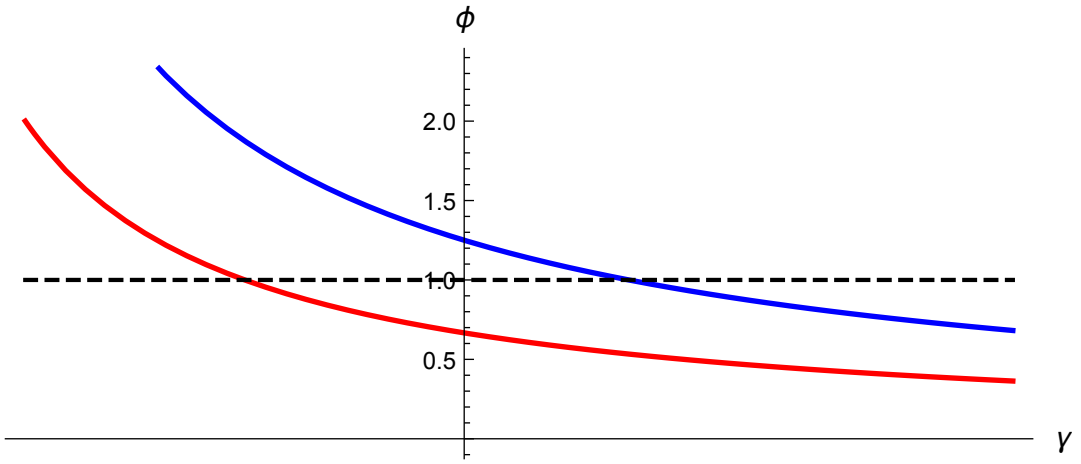
So if we can find a gamma that satisfies $\phi(\gamma) = 1$, we have a valid normal mode solution. How does ϕ depend on γ? We can see that it must be a decreasing function of γ and that it can be made as small as we like by taking very large γ, and as large as we like by making γ more negative[8]. So, there will be a unique root for $\phi(\gamma) = 1$. The question is whether it is for positive or negative gamma, which determines whether our population will grow or decay (shrink). Check $\phi(0)$ to see which side of 1 it is:

$$\phi(0) = \int_0^\infty b(a)\, e^{-\int_0^a \mu(s)ds}\, da$$

This is just the probability of being still alive at age a, the birth rate at that age, and then integrated over all ages. This must be the average number of births from one individual, i.e. the mean number of offspring from one individual.

$$\begin{aligned} \phi(0) > 1 &\Rightarrow \text{solution in } \gamma > 0 \quad \rightarrow \quad \text{growth} \\ \phi(0) < 1 &\Rightarrow \text{solution in } \gamma < 0 \quad \rightarrow \quad \text{decay} \end{aligned}$$

[8] Actually integral usually blows up for some $\gamma < 0$, but all we need to know is that there is a root to $\phi(\gamma) = 1$



Some example curves for $\phi(\gamma)$. The red corresponds to a population that will decay, and the blue to a population that will grow.

Exercise 12: Try this method for the case where births and deaths don't actually depend on age, i.e. $b(a) = b$ and $\mu(a) = \mu$.

- *Find an expression for $\phi(\gamma)$.*
- *Find $\phi(0)$ and check it makes biological sense.*
- *Find γ that solves $\phi(\gamma) = 1$ (can't always do this explicitly, but can in this case)*
- *Find the condition for population growth/decay.*

1.2 Discrete time

There is often good reason to consider time in discrete steps in biological models (as opposed to the continuous time and differential equations in previous sections). For example, it may be natural to consider some particular period such as a year as that is the natural life cycle for many species (annual plants, insects such as the monarch butterfly), or even if lifecycle is longer, it may make sense to think in terms of discrete step of a year (e.g. hibernating mammals). Another natural timescale is a day. Another use of discrete time is when consider a model with generations of population, and it might be natural to model the timestep as per generation.

However, we know (e.g from Part Ia Differential Equations) that discrete systems[9] can behave in a complicated way. In particular a first-order system can be 'chaotic'.

1.2.0 Revision: 1-D stability in difference equations (maps)

Consider the system where the number of individuals in the next generation is a function of the number in the current generation. Call this function f, so

$$x_{n+1} = f(x_n). \tag{9}$$

A fixed point x^* is a solution to

$$x^* = f(x^*).$$

To analyse stability, look at perturbations from the fixed point, i.e. set $x_n = x^* + \epsilon_n$ (where we think of ϵ_0 as small). Subbing this in to equation 9:

$$\begin{aligned} x^* + \epsilon_{n+1} &= f(x^* + \epsilon_n) \\ x^* + \epsilon_{n+1} &= f(x^*) + f'(x^*)\,\epsilon_n + \mathcal{O}(\epsilon^2) \\ \epsilon_{n+1} &= f'(x^*)\,\epsilon_n + \mathcal{O}(\epsilon) \end{aligned}$$

So the perturbation just grows geometrically, with ratio $f'(x^*)$.

In practice, we don't usually present all of this, just go from finding x^* to considering the modulus of $f'(x^*)$:

$$\begin{aligned} |f'(x^*)| &< 1 \qquad x^* \text{ is a stable fixed point} \\ |f'(x^*)| &> 1 \qquad x^* \text{ is an unstable fixed point} \end{aligned}$$

[9] or difference equations, or maps: means the same thing

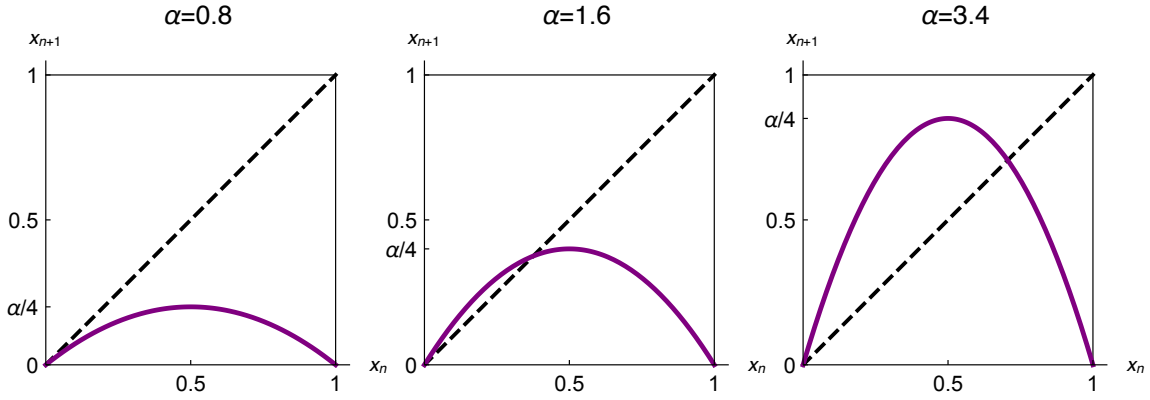
For the higher order discrete systems (see below), it is possible to come up with analogous tests for $f(x_n, x_{n-1}, \ldots)$, but in practice it is usual to just do the perturbation explicitly.

1.2.1 The logistic map

You will have encountered this example in other courses: it is probably the most studied discrete map. However, you should now note that it was first proposed as a population model, and the need to understand biologically-motivated systems has driven forward the mathematical area of chaos theory. The basic equation is wonderfully simple, but as you probably already know, the resultant dynamics are wonderfully rich:

$$x_{n+1} = \alpha\, x_n(1 - x_n) = f(x_n)$$

This just contains one parameter[10]. To make sure the map is from the interval $[0, 1]$ to itself, we restrict attention to $\alpha \in [0, 4]$.



The logistic map, for various α.

The fixed points satisfy $x = f(x)$, so seek:

$$\begin{aligned} f(x) - x &= 0 \\ \alpha\, x(1 - x) - x &= 0 \\ -x[\alpha x - \alpha + 1] &= 0 \end{aligned}$$

And we see that $x = 0$ is always a fixed point. In addition, we have $x^* = 1 - 1/\alpha$, which is in range when $\alpha > 1$.

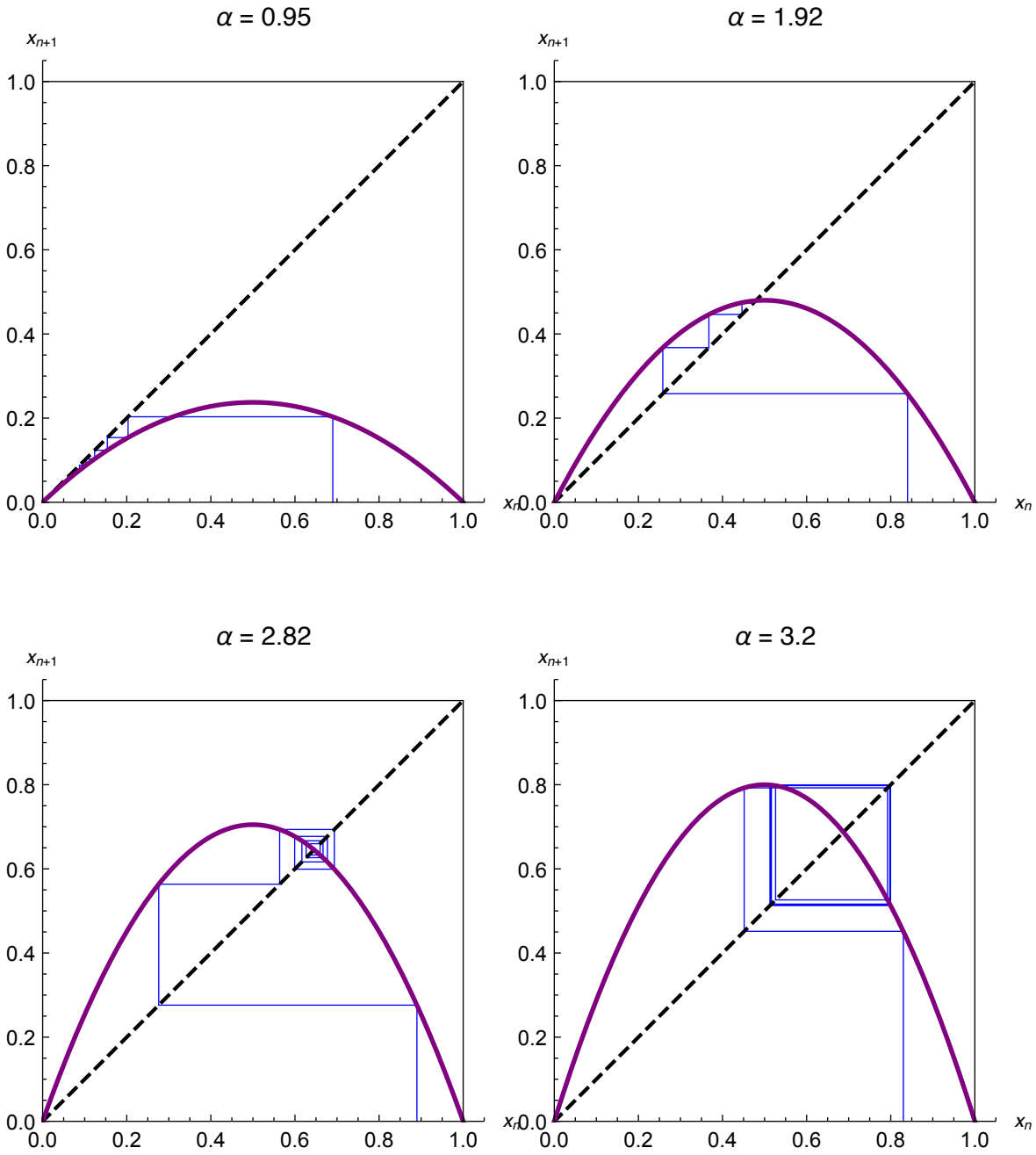
For stability, we have

$$f'(x) = \alpha(1 - 2x).$$

[10] we're calling it α here, but often it is r, μ or a and occasionally it is rescaled by a factor of 4

For $x^* = 1$, $f'(x^*) = \alpha$ so it is stable for $\alpha < 1$ and unstable for $\alpha > 1$.

For $x^* = 1 - 1/\alpha$, $f'(x^*) = 2 - \alpha$. So it is stable for $1 < \alpha < 3$ (doesn't exist for $\alpha < 1$) and unstable for $3 < \alpha$. We can break this down a little further to see when $f'(x^*)$ is positive and negative: it changes sign at 2, so $2 < \alpha < 3$ is stable, and nearby perturbations are jumping either side of the fixed point (and tending in). We can also note that $f'(x^*)$ goes through -1 at $\alpha = 3$, and this corresponds to a period-doubling bifurcation.



The logistic map, for various α. The blue lines show where successive iterates go, starting from an initial condition (line from the x- axis). See mathematica: logistic map.

At this point, it is a good idea to look at some numerical outputs, for example the cobweb figures here or see the mathematica file. What we can observe is that the

behaviour is straightforward to $\alpha < 3$. For $0 < \alpha < 1$ all trajectories head to the origin. For $1 < \alpha < 2$ all trajectories head into $x^* = 1 - 1/\alpha$ from one side (which side depends on initial conditions). For $2 < \alpha < 3$, trajectories still head to x^* but now in an oscillatory way, resulting in the blocky spirals in the cobweb diagram[11].

For α just a bit bigger than there, there looks to be a stable period-2 cycle, that is a pair of points where the map jumps from one to the other. Mathematically, x_1 and x_2 such that:

$$f(x_1) = x_2, \quad f(x_2) = x_1 \quad \text{and} \quad x_1 \neq x_2$$

Such x must satisfy $f^2(x) = x$, so we seek these solutions:

$$\begin{aligned} f^2(x) - x &= 0 \\ \alpha\, f(x)(1 - f(x)) - x &= 0 \\ \alpha^2 x(1-x)\,(1 - \alpha\, x(1-x)) - x &= 0 \\ -\alpha^3 x^4 + 2\alpha^3 x^3 - \alpha^2(1+\alpha)x^2 + (\alpha^2 - 1)x &= 0 \end{aligned}$$

Then at this point it looks a hit hopeless, but there is actually a way forward: any solution to $f(x) = x$ will also be a solution to $f^2(x) = x$. So, we should be able to factorise out $f(x) - x$, in fact exactly the expression we solved to find the fixed points. So working carefully, we can factorise out $x[\alpha x - \alpha + 1]$:

$$-x[\alpha x - \alpha + 1]\left(\alpha^2 x^2 - \alpha(\alpha+1)x + (\alpha+1)\right) = 0$$

We don't want these fixed point solutions though ($x_1 \neq x_2$ for a period-2 point), so can cancel these factors, leaving:

$$\alpha^2 x^2 - \alpha(\alpha+1)x + (\alpha+1) = 0 \tag{10}$$

And hence:

$$x_1, x_2 = \frac{1}{2\alpha}\left((1+\alpha) \pm \sqrt{(1+\alpha)(\alpha-3)}\right)$$

These can be assigned to x_1 and x_2 either way around. Looking at the square root, these exist for $\alpha > 3$. When they appear at $\alpha = 3$ they start at $x = 2/3$, i.e. where the fixed point is ($x^* = 1 - 1/\alpha$).

> *Exercise 13: Check that $f(x_1) = x_2$ and $f(x_2) = x_1$*

We can also check the stability of this period-2 cycle by considering f^2 (function applied twice) and checking if its derivative has modulus bigger than one or not, but there is a

[11] actually this must be why they are called 'cobweb diagrams', from the way oscillatory fixed points look like sort of like orb webs from spiders, but maybe only like that in minecraft.

nice technique to make this simple in terms of algebra. Rather than going back to the big expression for $f^2(x)$, just use the chain rule:

$$\frac{d}{dx}f^2(x) = \frac{d}{dx}f(f(x)) = f'\left(f(x)\right)\ f'(x)$$

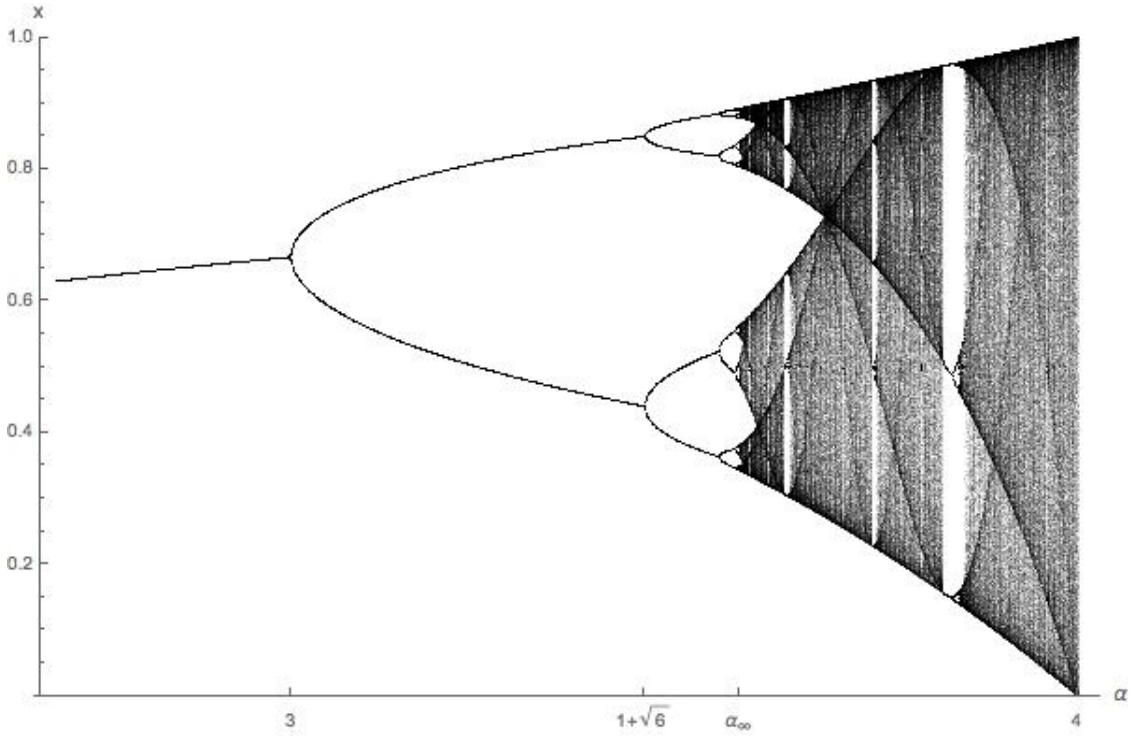
And at x_1 (or x_2), this gives is just $f'(x_1)f'(x_2)$. We have that $f'(x) = \alpha(1-2x)$ so

$$f'(x_1)f'(x_2) = \alpha(1-2x_1)\alpha(1-2x_2) = \alpha^2[1-2(x_1+x_2)+4x_1x_2]$$

and we can even read off the sum and product of x_1 and x_2 from the quadratic we solved to find them (equation 10).

Exercise 14: Show that the period-2 cycle of the logistic map becomes unstable at $\alpha = 1+\sqrt{6} \approx 3.45$

What happens for higher values of α? See Dynamical Systems course for more details, but in brief: there are a series of *period-doubling bifurcations*. We've found the first two, where the fixed point (a.k.a period-1) becomes unstable and a period-2 appears. Then the period-2 becomes unstable, and a period-4 will appear. This keeps going as α is increased, but these all accumulate at a certain value ($a_\infty \approx 3.5699$). For $\alpha > \alpha_\infty$ there are windows of 'chaos', but also windows where things settle to stable periodic orbits.



Bifurcation diagram, focusing on $\alpha > 3$. For each value of α, this is made just by picking random initial conditions for x and then iterating the map forward many times, throw the first few hundred iterates away, and then plot the results. Then keep doing this for lots of values of alpha.

end of lecture 5

1.2.2 Higher order discrete systems

So far we have considered the case when the value of x in the next time step or generation only depends on the current value. For many situations in biology, this is not enough: the dynamics may depend on earlier times also. We could develop some general theory, much like the box above but now for $x_{n+1} = f(x_n, x_{n-1}, \ldots, x_{n-p})$, but this is neither useful in practice nor informative. Instead we will explore a few examples, and see techniques which can be applied more generally.

Example: discrete version of breathing

Recall the physiological example from earlier where breathing is regulated to adjust for varying levels of carbon dioxide in the blood, with some lag. We can formulate a similar model in discrete time:

$$\underbrace{V_{n+1}}_{\text{Breath volume next step...}} = \underbrace{f\left(C_{n-k}\right)}_{\text{... depends on } CO_2 \text{ } k \text{ steps ago}} = \alpha C_{n-K}$$

One could imagine a more general f, but here we just consider a linear example. Then the equation for carbon dioxide change in blood:

$$\underbrace{C_{n+1} - C_n}_{\text{Change in } CO_2 \text{ in blood}} = \underbrace{M}_{CO_2 \text{ added}} - \underbrace{\beta V_{n+1}}_{\text{breathed out}}$$

and as usual α, β and M are real, constant and positive. Note that this is actually not just different from earlier breathing model by being discrete: the model for CO_2 being breathed out is now just proportional to V and does not depend on C at all[12]. The steps in n just represent some time step, e.g. minutes or breaths.

We can collapse this into a single variable:

$$C_{n+1} = C_n + M - \alpha\beta C_{n-k}. \tag{11}$$

Then seek constant solutions $C_n = C_*$:

$$C_* = C_* + M - \alpha\beta C_* \quad \implies c_* = \frac{M}{\alpha\beta}.$$

Now investigate stability of this steady state by perturbing[13] as $C_n = C_* + \delta_n$ and sub in to (11):

$$C_* + \delta_{n+1} = C_* + \delta_n + \underbrace{M - \alpha\beta C_*}_{=0} - \alpha\beta\delta_{n-k}$$

[12] Arguably, the earlier model is more sensible, where the higher the concentration in the blood, the higher the amount of CO_2 gets exchanged in lungs per volume of breath and expelled. This model is actually different, and chosen here just for convenient linearity later.

[13] not bothering with ϵ now, just think of δ_n as small

$$\delta_{n+1} - \delta_n + \alpha\beta\delta_{n-k} = 0$$

Normally we would then linearise in small δ, but this is already in right form here. Also, we could simplify slightly by making some compound parameter instead of $\alpha\beta$ but that is not essential.

Now we explore some different values of k. This is the time lag in steps between blood levels of CO_2 taking a value and the breathing volume adjusting. First, for $k = 0$ we simply have

$$\delta_{n+1} = (1 - \alpha\beta)\delta_n$$

and then it is clear that the steady state C_* is stable for $0 < \alpha\beta < 2$ and unstable for larger $\alpha\beta$.

Next, try $k = 1$:

$$\delta_{n+1} - \delta_n + \alpha\beta\delta_{n-1} = 0$$

To solve this linear difference equation, seek $\delta_n = p^n$ solutions:

$$p^2 - p + \alpha\beta = 0 \quad \implies p_\pm = \frac{1}{2} \pm \sqrt{\frac{1}{4} - \alpha\beta}.$$

and the general solution is a linear combination of these geometric solutions:

$$\delta_n = Ap_+^n + Bp_-^n.$$

For $0 < \alpha\beta < \frac{1}{4}$, both $p_\pm$ are real and $\in (0, 1)$, so p^n decays for both, and hence C_* is stable.

For $\frac{1}{4} < \alpha\beta$, both $p_\pm$ are complex[14]. This actually doesn't change our approach very much: we still need to know when solutions grow or decay and hence $|p| < 1$ or otherwise:

$$p_\pm = \frac{1}{2} \pm i\sqrt{\alpha\beta - \frac{1}{4}} \quad \implies |p|^2 = \left(\frac{1}{2}\right)^2 + \left(\alpha\beta - \frac{1}{4}\right) = \alpha\beta$$

hence for $\frac{1}{4} < \alpha\beta < 1$ the steady state is stable (and a perturbation decays in an oscillatory manner) and for $1 < \alpha\beta$ it is unstable. In summary, the steady state C_* is stable for $0 < \alpha\beta < 1$ and unstable for larger values. As expected, the longer lag decreases the range for stability (more parameter values are unstable).

This example worked out without too much difficulty as we could solve explicitly for p. This will be unlikely to work as we go up to higher order and therefore get something trickier than a quadratic to solve. Sticking with $k = 1$, we can explore an alternative strategy. For small $\alpha\beta$ we could see that our roots for p all had modulus less than one, so all we need to do is to imagine turning up $\alpha\beta$ until we the first time a root goes

[14]The $p_\pm$ are complex conjugates of each other. We will have real initial conditions for C and therefore δ. This will make A and B complex conjugates and this will give real δ_n for all n.

unstable. At the moment when this happens, a root will have modulus exactly one[15]. So, seek $p = e^{i\theta}$ for some $\theta \in [0, 2\pi)$.

$$p^2 - p + \alpha\beta = 0 : \quad e^{2i\theta} - e^{i\theta} + \alpha\beta$$

Then taking real and imaginary parts:

$$\cos 2\theta - \cos\theta + \alpha\beta = 0 \tag{12}$$

$$\sin 2\theta - \sin\theta = 0 \tag{13}$$

Start with the simpler one, the imaginary part (13):

$$\sin 2\theta = \sin\theta \implies 2\theta = \theta + 2n\pi \quad \text{or} \quad 2\theta = (\pi - \theta) + 2n\pi$$

for $n \in \mathbb{Z}$. Restricting attention to $\theta \in [0, 2\pi)$:

$$\theta = 0 \quad \text{or} \quad \frac{\pi}{3}, \frac{3\pi}{3}, \frac{5\pi}{3}$$

The real part will supply the corresponding values of $\alpha\beta$:

$$\alpha\beta = 0 \quad \text{or} \quad 1, -2, 1$$

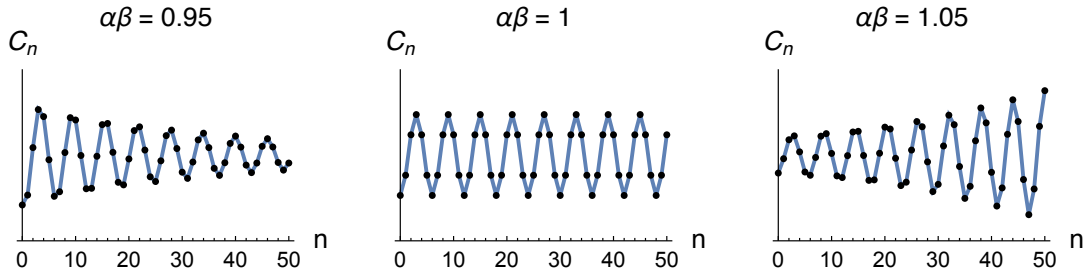
And as we are looking for the first positive[16] $\alpha\beta$, we see this is $\alpha\beta = 1$. This corresponds to $\theta = \pi/3$ or $\theta = 5\pi/3$. Equivalently, this is

$$p_\pm = e^{\pm\frac{i\pi}{3}} = \frac{1}{2} \pm i\,\frac{\sqrt{3}}{2}$$

which matches up with our first approach. Note that $p^6 = 1$ for both p_+ and p_-, so small perturbations satisfy:

$$\delta_{n+6} = Ap_+^{n+6} + Bp_-^{n+6} = Ap_+^n + Bp_-^n = \delta_n$$

so have period 6 at the boundary (at least to linear order), and close to period 6 just above and below.



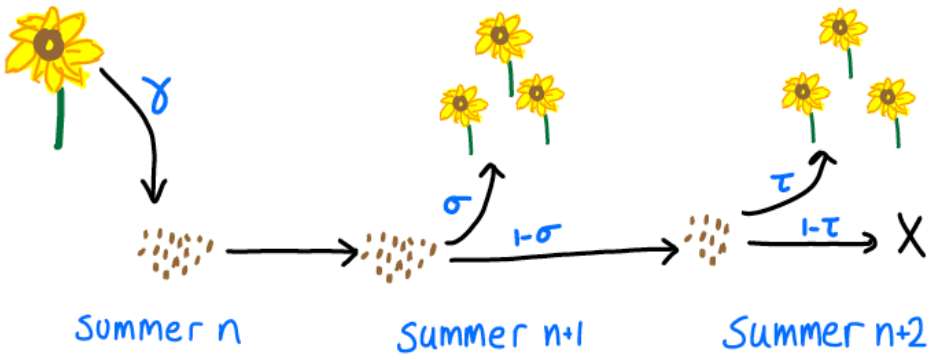
Typical solutions for $k = 1$ for various $\alpha\beta$ near to threshold for stability, starting from a perturbation away from steady state.

[15]Actually expect this to happen in complex conjugate pairs. We are implicitly assuming that roots are continuous in our model parameters (which does not seem too unreasonable in math bio). We are also assuming that the offending root(s) actually goes right *through* modulus one: technically it would be possible to just reach modulus one and then go back inside the unit circle. That would just be mean.

[16]actually the solution at zero corresponds to a root $p = 1$ exactly at $\alpha\beta = 0$, and this root edges just below one as we make $\alpha\beta$ small but positive. So this is moving into the region for stability, not moving out!

Example: Multi-generation model

Another set of problems which leads to higher order discrete systems is when the time steps are population generations and multiple generations need to be considered to find the next generation size. For example, a type of annual plant produces γ seeds in the summer and then dies. Those seeds stay in the ground over the winter. The next summer, each seed[17] has probability σ of successfully germinating and growing into a new adult plant. Failing that, the seed will germinate the summer after that with probability τ. Assume they cannot germinate after that.



We turn this wordy description into equations[18], accounting for number of adult plants at season n by x_n, seeds that have been waiting one year as $s_n^{(1)}$ and two years as $s_n^{(2)}$.

Then

$$\begin{aligned} x_n &= \sigma s_n^{(1)} + \tau s_n^{(2)} \\ s_n^{(1)} &= \gamma x_{n-1} \\ s_n^{(2)} &= (1-\sigma) s_{n-1}^{(1)} \end{aligned}$$

Then we can go from this system in multiple variables to one in a single variable, and here the only sensible choice is x_n:

$$x_n = \sigma\gamma x_{n-1} + \tau(1-\sigma)\gamma x_{n-2}. \tag{14}$$

Indeed, arguably it would be possible to go straight here from the description in words. Note $\gamma > 0$ and $\sigma, \tau \in [0,1]$ as they are proportions.

Note that equation (14) is linear in x and the steady state solution is $x_* = 0$. In theory we now propose a perturbation, sub it in, linearise, but of course in this case we just get the same equation back again. So, directly go for $x_n = p^n$:

$$p^2 - \sigma\gamma p - \tau(1-\sigma) = 0$$

[17] Think of this as proportion of seeds, as there are lots of seeds lots of seeds

[18] Indeed, this is half of the art of math bio in practice in research, except the wordy descriptions tend to be a lot more vague on crucial details and then there's a lot of decisions for the modeller to make.

$$p_{\pm} = \frac{\sigma\gamma}{2} \pm \frac{1}{2}\sqrt{\sigma^2\gamma^2 + 4\gamma\tau(1-\sigma)}$$

As the contents of the square root is positive, these roots are real. We can also see that the roots are positive and negative with the positive root having the larger modulus (i.e. $0 < -p_- < p_+$). Solutions will be of the form

$$x_n = A_1 p_+^n + A_2 p_-^n$$

and the first term will dominate as n increases. In fact, we just need to check p_+ for stability[19].

Seeking $p_+ = 1$ and a little algebra we arrive at

$$\gamma\left[\sigma + (1-\sigma)\tau\right] = 1$$

It is worth stepping back into original meaning of the parameters at this point. Considering this, the square bracket is the proportion of seeds that *ever* germinate, and the prefactor γ is the number of seeds produced by each adult plant ever. So $\gamma[..]$ is the mean number of offspring per plant. Call the whole thing K:

$$K = \gamma\left[\sigma + (1-\sigma)\tau\right]$$

It is not surprising that it determines the boundary for stability:

$$\begin{aligned} \text{mean offspring} = K &< 1, \quad x = 0 \quad \text{is stable} \\ \text{mean offspring} = K &> 1, \quad x = 0 \quad \text{is unstable} \end{aligned}$$

It is often the case that conditions on the boundary for stability has an intuitive explanation in terms of the original biological model. It is worth looking out for these as they are a good check that the algebra has come out correctly and the answer is sensible.

end of lecture 6

[19] If it is greater than one, then x_n grows eventually regardless of p_-. If it is less than one, then p_- also has modulus less than one, so x_n decays towards zero eventually.

1.3 Multi-species models

The dynamics of interacting populations (or biological substances) gives rise to the most interesting models in mathematical biology. In the next few sections, we will work through a series of examples, illustrating more general principles and techniques.

1.3.0 Revision: 2-D stability in continuous time

Consider the system:

$$\begin{aligned} \frac{du}{dt} &= f(u,v) \\ \frac{dv}{dt} &= g(u,v) \end{aligned}$$

A fixed point (u^*, v^*) satisfies $f(u^*, v^*) = 0$ and $g(u^*, v^*) = 0$.

To explore stability, consider a small perturbation to that fixed point. Set $u(t) = u^* + \xi(t)$, $v(t) = v^* + \eta(t)$ and expand in small ξ, η:

$$\frac{d\xi}{dt} = f\left(u^* + \xi, v^* + \eta\right) = \underbrace{f(u^*, v^*)}_{=0 \text{ at FP}} + \xi \left.\frac{\partial f}{\partial u}\right|_{\text{FP}} + \eta \left.\frac{\partial f}{\partial v}\right|_{\text{FP}} + \mathcal{O}(\xi^2, \xi\eta, \eta^2)$$

Similarly:

$$\frac{d\eta}{dt} = g\left(u^* + \xi, v^* + \eta\right) = \xi \left.\frac{\partial g}{\partial u}\right|_{\text{FP}} + \eta \left.\frac{\partial g}{\partial v}\right|_{\text{FP}} + \mathcal{O}(\xi^2, \xi\eta, \eta^2)$$

So the local dynamics comes down to the Jacobian:

$$\begin{pmatrix} \dot{\xi} \\ \dot{\eta} \end{pmatrix} = \left.\begin{pmatrix} \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \frac{\partial g}{\partial u} & \frac{\partial g}{\partial v} \end{pmatrix}\right|_{FP} \begin{pmatrix} \xi \\ \eta \end{pmatrix}$$

where the 2×2 matrix is the Jacobian. In practice, just find the Jacobian and start from there. We might sometimes want the eigenvectors to help draw phase-diagrams, but usually we just want the eigenvalues.

Or even more basic, we just need to know the sign of the real parts of the eigenvalues. Let T be the trace and D the determinant of the Jacobian evaluated at some fixed point. Then (for 2-D), the eigenvalues are:

$$\lambda = -\frac{1}{2}T \pm \frac{1}{2}\sqrt{T^2 - 4D}$$

or alternatively the other way $T = \lambda_1 + \lambda_2$ and $D = \lambda_1\lambda_2$. So

$$\begin{aligned} D < 0 &: \text{saddle} \\ D > 0, T < 0 &: \text{stable} \\ D > 0, T = 0 &: \text{centre} \\ D > 0, T > 0 &: \text{unstable} \end{aligned}$$

We could then subdivide the stable and unstable cases according to focus or node (eigenvalues complex or real) by checking $T^2 - 4D$, but often in math bio we do not need to do this.

1.3.1 Competition models

The classic example is

$$\begin{aligned} \dot{N}_1 &= r_1 N_1 \left(1 - \frac{N_1}{K_1} - b_{12}\frac{N_2}{K_2}\right) \\ \dot{N}_2 &= r_2 N_2 \left(1 - \frac{N_2}{K_2} - b_{21}\frac{N_1}{K_1}\right). \end{aligned}$$

where there are two species N_1 and N_2. Each species alone has simple logistic dynamics (see lecture 1) with linear growth, and a negative quadratic term which means each species has some stable equilibrium size (K_1 and K_2 respectively: the carrying capacities for each species alone). The terms with the b_{12} and b_{21} are the interactions between the species: they each slightly 'harm' the other. An analysis of this system is one of the questions on examples sheet 1. The net outcome is not too surprising: if the negative interaction terms are not too big, then the two species will coexist at some stable equilibrium value. If the interaction terms are too strong, then the two species cannot stably coexist, and one or other species wins out.

Here we study instead a different competition system, motivated by recent research on controlling the spread of dengue. Dengue is a virus that causes disease in humans. Rather than being transmitted directly from human to human, it requires and intermediate vector: a mosquito. If the mosquito bites and takes blood from someone who is infected, the mosquito could go on to infect anyone they bite later.

You can read a lot more about the ideas on the Eliminate Dengue website[20], but in brief: *Wolbachia* are a type of bacteria that can infect a huge range of insect species. Researchers have developed a strain of *Wolbachia* that can infect the kind of mosquitos that can carry dengue. The bacteria seems to block transmission of dengue virus, so we would like to see if this would be a viable way to control dengue in practice[21]. If we introduce some mosquitos that carry *Wolbachia* into the wild, will eventually all mosquitos carry *Wolbachia*?

In mosquitos, *Wolbachia* is only transmitted vertically, which means to offspring mosquitos (as opposed to 'horizontal transmission': to general others in same species). If a female mosquito is infected, her eggs will certainly be infected, regardless of the carrier status of the male. She will also produce fewer eggs than usual. Here's the weird bit: if the female is uninfected but the male is infected, the eggs will not be viable at all, so no offspring at all. Now we start pulling this into a mathematical formulation.

[20] http://www.eliminatedengue.com/

[21] at time of writing, there is some hope that this might also apply to Zika virus, but far from clear yet

Let x be the number of uninfected female mosquitos, and y be the number of infected female mosquitos. Assume that the uninfected mosquitos have a per capita death rate d and a bonus per capita death rate of ϵ times the total number of female mosquitos (competition). The infected mosquitos have shorter lifespans on average, which we model here as a higher death rates by having an additional factor μ with d ($\mu > 1$).

We do not need to explicitly track the males: just assume their infection state is in proportion to the females (which you can check is the case by building full equations), so a proportion $x/(x+y)$ uninfected. Also assume there are enough males around for all eggs to be fertilised. Suppose that in a purely uninfected population, the rate of viable eggs for female mosquitos being produced is r per female capita. If the female is infected, assume that they produce λ times the normal number of eggs, so $\lambda < 1$.

Summarising the four possible crosses (female-male infection status combinations):

Cross	Frequency	Egg rate	State
F $\times$ M	$x.\frac{x}{x+y}$	r	Uninfected
F $\times$ M	$x.\frac{y}{x+y}$	0	$\nexists$
F $\times$ M	$y.\frac{x}{x+y}$	λr	Infected
F $\times$ M	$y.\frac{y}{x+y}$	λr	Infected

Where the F means infected and F is uninfected females, similarly for M and M for males.

Bringing this together, we get the following system:

$$\begin{aligned} \dot{x} &= r\,x\frac{x}{x+y} - d\,x - \epsilon\,x(x+y) \\ \dot{y} &= \lambda r\,y\frac{x}{x+y} + \lambda r\,y\frac{y}{x+y} - \mu d\,y - \epsilon\,y(x+y) \end{aligned}$$

By rescaling time by a factor r and both x and y by a factor ϵ/r, the system can be slightly tidied[22]:

$$\begin{aligned} \dot{x} &= x\left[\frac{x}{x+y} - \frac{d}{r} - (x+y)\right] \\ \dot{y} &= y\left[\lambda - \mu\frac{d}{r} - (x+y)\right] \end{aligned}$$

Looking at each population alone (i.e. forcibly setting $x = 0$ or $y = 0$), each is just logistic, and we can pick out the equilibrium single population sizes:

[22]There's a wording ambiguity about which direction is meant by 'rescale by a factor', but interpret here in the direction that tidies things up!

$$\text{Uninfected only}, y = 0: \quad \dot{x} = x\left(1 - \frac{d}{r} - x\right) = x\left(x_0 - x\right)$$

$$\text{Infected only}, x = 0: \quad \dot{y} = y\left(\lambda - \mu\frac{d}{r} - y\right) = y\left(y_0 - y\right)$$

where $x_0 = 1 - d/r$ and $y_0 = \lambda - \mu d/r$ are the equilibrium sizes of each population alone.

Now take some sensible assumptions, thinking about the case that we wish to model. We are imagining an uninfected resident population, so they are viable, i.e. $r > d$ so $x_0 > 0$. We also want to consider the case when the purely infected population is viable, otherwise the proposed introduction is hopeless anyway, so assume $\lambda r > \mu d$, i.e. $y_0 > 0$. We have already assumed that infection reduces the number of eggs ($\lambda < 1$) and infection increases the death rate ($\mu > 1$). So putting all these together, we have $0 < y_0 < x_0 < 1$.

This has demonstrated another strategy for rescaling parameters: discover a meaningful parameter combination by considering the relatively simple equilibrium points such as each population alone, then see if the system can be written out nicely in terms of these quantities. It works well for this example. Organising the parameters to be in terms of x_0 and y_0, the full system becomes:

$$\begin{aligned} \dot{x} &= x\left[x_0 - \frac{y}{x+y} - (x+y)\right] \\ \dot{y} &= y\left[y_0 \qquad\quad - (x+y)\right] \end{aligned}$$

There are four non-negative fixed points: no mosquitos $(0,0)$, purely uninfected $(x_0, 0)$ or purely infected $(0, y_0)$, and an interested mixed state one (x_1, y_1), where setting the square brackets to zero and working through:

$$x_1 = y_0(1 - x_0 + y_0) \quad \text{and} \quad y_1 = y_0(x_0 - y_0)$$

and as $0 < y_0 < x_0 < 1$, both x_1 and y_1 are positive.

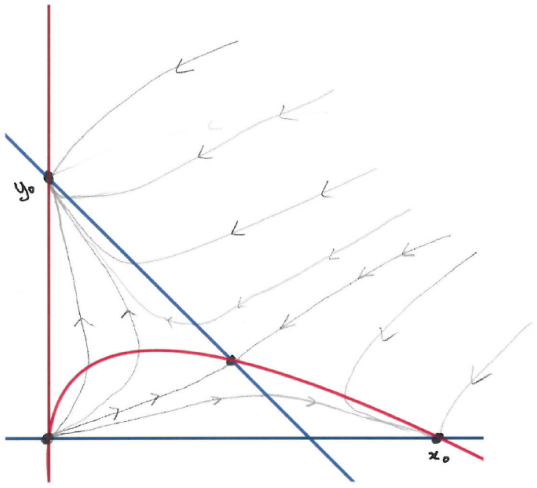
> *Exercise 15: Check the Jacobian at (x_1, y_1) and show that it corresponds to a saddle*

The next stage is to find the null clines and then put together the phase diagram. Nullclines are just when $\dot{x} = 0$ and when $\dot{y} = 0$. On these, the trajectories are pure vertical and pure horizontal respectively. But more usefully, these curves also divide up the phase plane into regions where the direction of trajectories is purely in one quadrant (e.g. up and left), which helps pulling the picture together.

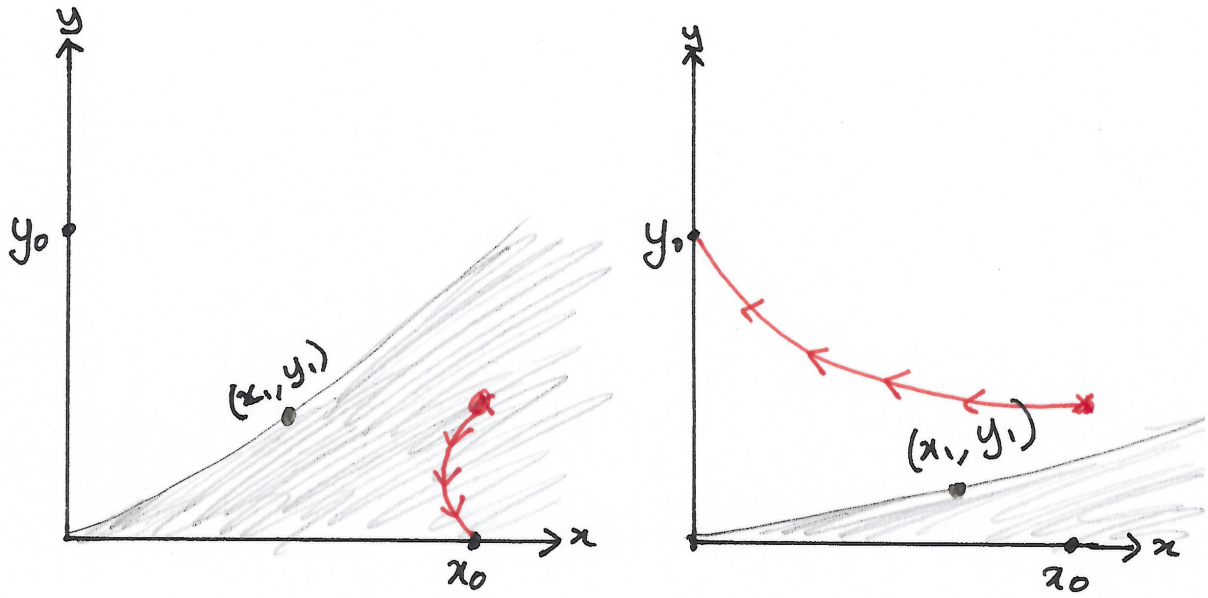
$$\dot{x} = 0 :$$

$$x = 0 \quad \text{or} \quad y = x_0(x+y) - (x+y)^2$$

$$\dot{y} = 0 : \quad y = 0 \quad \text{or} \quad x + y = y_0$$



Finally, we may answer our original question: what happens if we start at the uninfected equilibrium and introduce some infected mosquitos? This is sketched below: it really depends where the dividing line is between basins of attraction of the two stable fixed points. The dividing line (separatrix) goes through the saddle point (indeed it is the stable manifold of the saddle point).



A schematic of the different outcomes of an introduction of infected mosquitos. The shaded area in each case is the region where trajectories would head towards $(x_0, 0)$, drawn for two different examples. The red dot is where we are on the phase diagram after an introduction of a certain number of infected mosquitos. Clearly, if we want all mosquitos infected eventually, we would like to be in the righthand regime.

So introducing a very small number of mosquitos is not enough, there has to be quite a few infected mosquitos brought in. However, on the plus side, once the infected population is established, it won't easily revert back.

Exercise 16: Imagine you are a mathematical modeller advising on this project. The experimentalists can work to change the strain of Wolbachia *so as to make it less damaging to the mosquitos by softening the effect on the death rate (decrease μ towards 0) or the egg production rate (increase λ towards 1). We would like to make it so that a small introduction of infected mosquitos would be enough to make all mosquitos infected eventually. Would you advise them to concentrate their efforts on λ or μ or a combination of the two? (Hint: consider the impact on x_0 and y_0 and then the nullclines).*

We come back to this example later in the course, when we consider the spatial effects.

end of lecture 7

1.3.2 Predator-prey models

No course in math bio would be complete without this iconic system: the Lotka-Volterra model of predator-prey dynamics. The prey population (size N) would grow on its own, and the predator population (size P) would decay on its own. The interaction is predation which happens at rate proportion to the product of both population sizes: mass-action. The predation harms the prey and benefits the predators. This leads to the system

$$\begin{aligned} \frac{dN}{dt} &= aN - bNP = N(a - bP) \\ \frac{dP}{dt} &= cNP - dP = P(cN - d) \end{aligned}$$

where a, b, c and d are all positive. This can be rescaled to

$$\begin{aligned} \dot{u} &= u\,(1 - v) \\ \dot{v} &= -\alpha\, v\,(1 - u) \end{aligned}$$

Exercise 17: Carry out this rescaling and show that $\alpha = d/a$ (and also note $\alpha > 0$).

There are two fixed points: $(0, 0)$ and $(1, 1)$. The general Jacobian is given by

$$J = \begin{pmatrix} 1 - v & -u \\ \alpha v & -\alpha(1 - u) \end{pmatrix}$$

So evaluating at the fixed point at the origin:

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

And checking the eigenvalues[23] we see that the origin is a saddle. This is not a surprise as we geared the model so the prey would group on their own and the predators would decay.

The non-trivial fixed point gives

$$J_{(1,1)} = \begin{pmatrix} 0 & -1 \\ \alpha & 0 \end{pmatrix} \quad T = 0,\ D = \alpha \quad \lambda = \pm i\sqrt{\alpha}$$

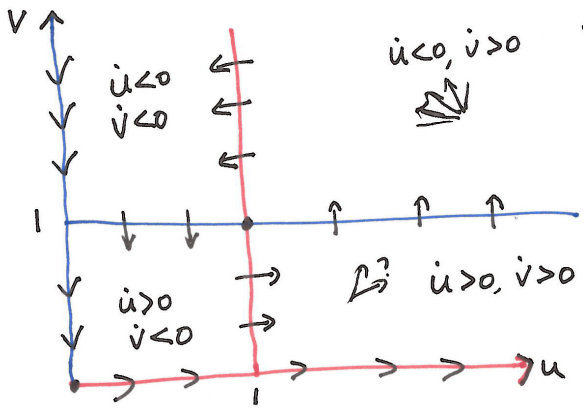
which corresponds to a centre. This is neither stable nor unstable to linear order, and in theory requires further work to determine non-linear stability (higher-order terms).

Nullclines In sketching phase diagrams, fixed point analysis gives us the dynamics close to equilibrium values, and we are left to join up the picture in between. Very often, it is useful to divide up space into regions where $\dot{u}$ and $\dot{v}$ are positive or negative. This means finding the *nullclines*: curves where one or other variable is unchanging.

For the Lotka-Volterra system:

$$\dot{u} = 0: \quad u = 0 \quad \text{or} \quad v = 1$$

$$\dot{v} = 0: \quad v = 0 \quad \text{or} \quad u = 1$$



This is starting to suggest that trajectories might be cycles: closed curves so the solution is periodic. However neither the Jacobian nor the diagram with the nullclines has conclusively shown that we have cycles. Luckily, we can explicitly find the trajectories for this system. Start by removing the time dependence to just think about curves in u, v space:

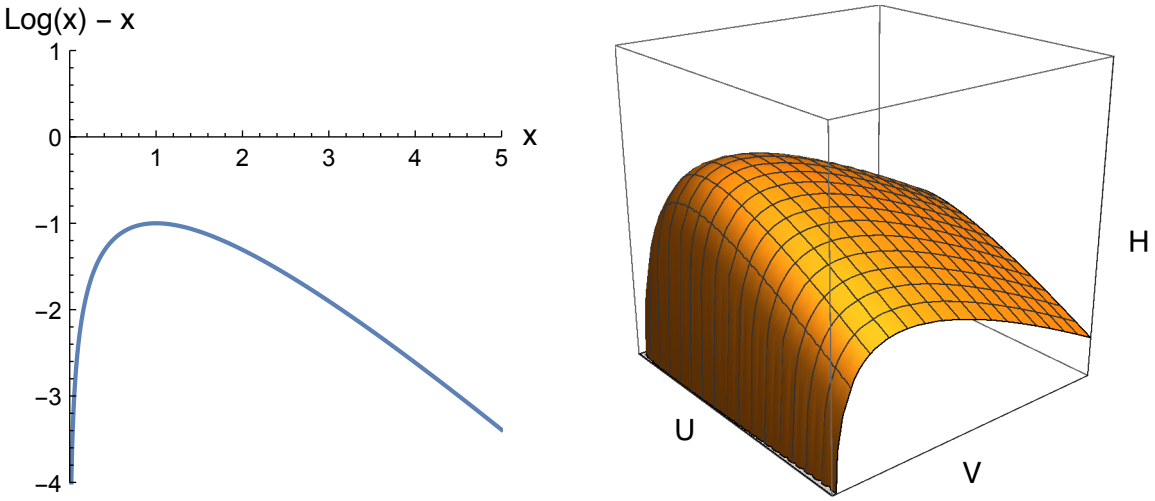
$$\frac{du}{dv} = \frac{\dot{u}}{\dot{v}} = \frac{-u(1-v)}{\alpha v(1-u)}$$

Then integrate:

$$\begin{aligned} \int \frac{\alpha(1-u)}{u} du &= -\int \frac{1-v}{v} dv \\ \alpha(\log u - u) &= -(\log v - v) + C \end{aligned}$$

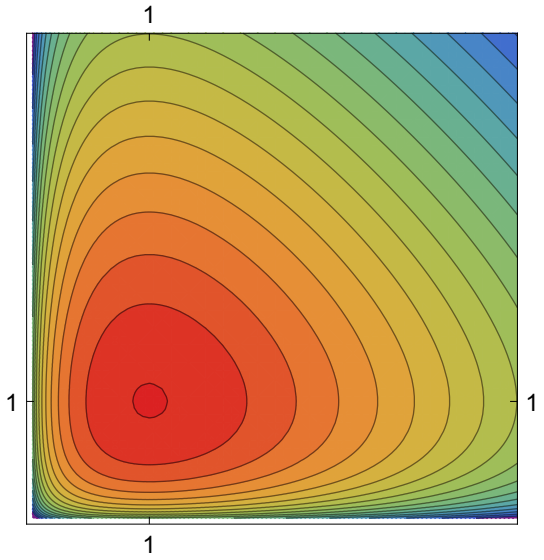
[23] The matrix is diagonal, so just read off the eigenvalues

In other words, we have $H(u,v) = \alpha(\log u - u) + (\log v - v)$ is a constant on trajectories[24].



Contours of constant $h(u,v)$, start by considering $\log x - x$. Then put into 3D by noting it is the sum of these in u and v.

Then plot contours of constant H:



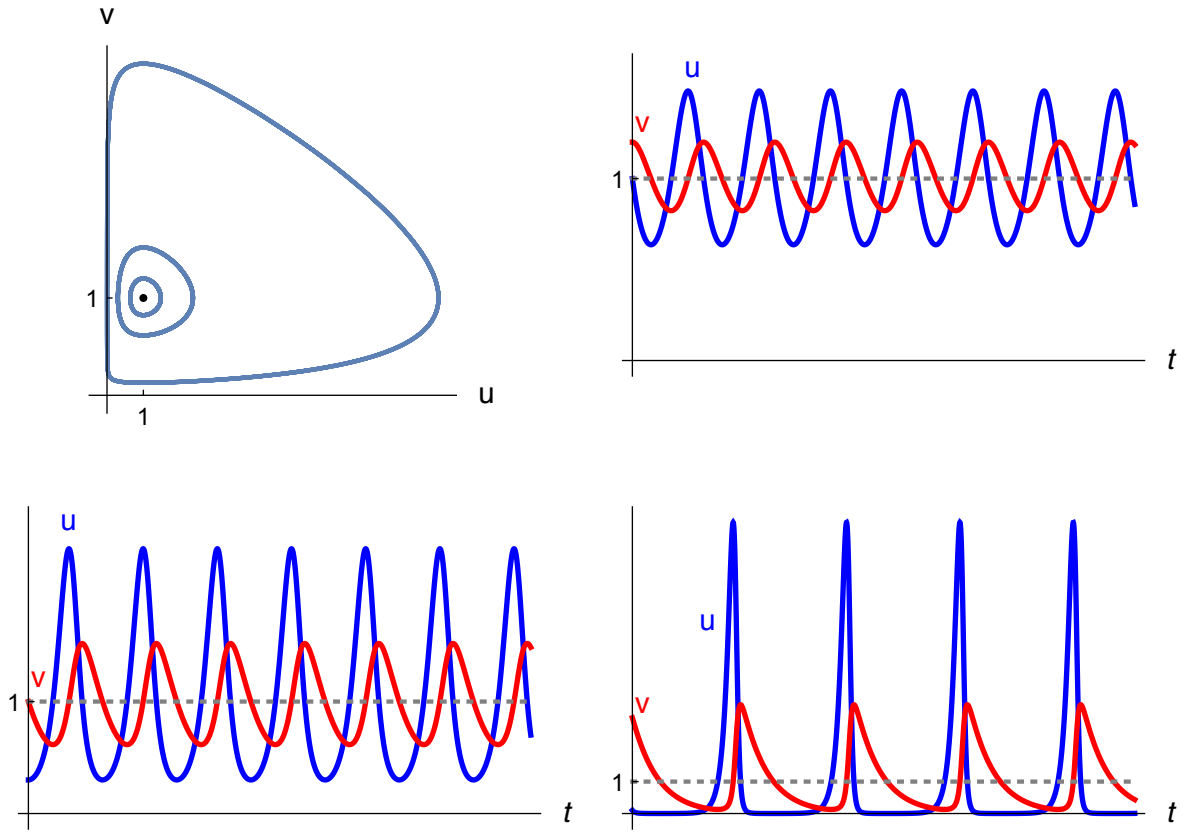
And we know trajectories must remain on constant contours, so just add some arrows and we are done.

For the Lotka-Volterra system, we can also show that the *time-average* of the period orbits are all equal to the values of the population size at the fixed point. These were both normalised to 1 here, but it still holds for the system before rescaling of course. Starting from $\dot{u} = u\,(1 - v)$ and integrating over one period:

[24] In language of dynamics systems this is like a Hamiltonian.

$$\int \frac{1}{u} du = \int 1 - v \, dt$$
$$\underbrace{[\log u]}_{=0 \text{ as same } u \text{ at each end}} = \underbrace{\int 1 \, dt}_{\text{period } T} - \underbrace{\int v \, dt}_{T \times \text{ average } v}$$

So the time-average value of v is 1. A similar calculation starting from $\dot{v}$ shows that the time-average of u is also 1. This is true no matter which contour of H we are on.



Solutions of the Lotka-Volterra system for assorted starting conditions, with the trajectories shown also together in the u, v plane. Note that the vertical scale changes between plots, but the dotted line marks 1, the time-average of both populations. It can also be seen from these solutions that the prey (blue) lead and the predators (red) follow.

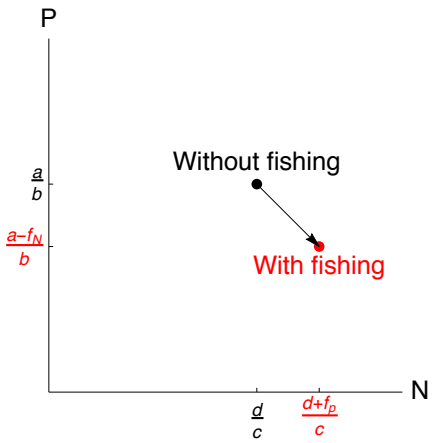
The effect of fishing Returning to the unscaled original system, we can ask the question: what is the effect of fishing on the system? We simulate this by introducing terms representing fishing of both populations at a constant per capita rate (but potentially different constants for predators and prey):

$$\dot{N} = N(a - bP) - f_N N = N\left((a - f_N) - bP\right)$$
$$\dot{P} = P(cN - d) - f_P P = P\left(cN - (d + f_P)\right)$$

And this is just the same system as before with just a tweak of parameters: a is replaced by $a - f_N$ and d is replaced by $d + f_P$ (taking care with the signs). So now no further serious work is needed: just look at the effect of shifting the parameters. The fixed point moves:

$$\text{Originally at} \quad \left(\frac{d}{c}, \frac{a}{b}\right) \qquad \text{Now:} \quad \left(\frac{d+f_P}{c}, \frac{a-f_N}{b}\right)$$

i.e. a higher number of prey and lower number of predators. We also know from above that the time-average of the cycles will similarly move.



This result is remarkably simple, but maybe slightly surprising: fishing is depleting both populations, yet the net result is actually an increase in the prey population. The effects of fishing are concentrated in the predators. In general, when we have multiple populations in balance with each other and their environment (an ecosystem) external interventions can have non-obvious effects. Mathematical models can help us understand these[25]. Vito Volterra used exactly the system we have studied here to understand the changes in fish population in the Adriatic. During war time, fishing was lower than usual but the proportion of the catch that were predators (sharks etc.) went up. This is rather elegantly explained by the above analysis.

The cycles are not robust! That we have cycles is pretty special. If we change the structure of the Lotka-Volterra system in almost any way[26] then the cycles will break. Here we look at the example of adding logistic-style quadratic terms, which represent interaction within each species alone: intra-specific competition adds to the death rate. Working now in the rescaled system:

$$\begin{aligned} \dot{u} &= u\,(1-v) - \epsilon_u u^2 \\ \dot{v} &= -\alpha\, v\,(1-u) - \alpha\,\epsilon_v v^2 \end{aligned}$$

[25] This is where mathematical biology has been historically most successful: at explaining observed phenomena.

[26] The parameter tweak of fishing was not a structural change.

Assume both rates $\epsilon_u, \epsilon_v \ll 1$ so the change to the system is small[27]. Note the factor of α in new term in the second equation: this is just to make the algebra tidier, as the system can now be written:

$$\begin{aligned} \dot{u} &= u\,[1 - v - \epsilon_u u] \\ \dot{v} &= -\alpha\, v\,[1 - u + \epsilon_v v] \end{aligned}$$

Look for fixed points, paying attention only to $u \geq 0$ and $v \geq 0$.

Exercise 18: Show that there are three fixed points now.

- *The usual trivial fixed point* $(0, 0)$
- *Prey population only (at their logistic equilibrium):* $(\epsilon_u^{-1}, 0)$
- *One with both populations present:* (u^*, v^*) *where*

$$u_* = \frac{1 + \epsilon_v}{1 + \epsilon_u \epsilon_v} \quad and \quad v_* = \frac{1 - \epsilon_u}{1 + \epsilon_u \epsilon_v}$$

and hence $u_* > 1$, $v_* < 1$.

Use the Jacobian[28] to analyse the stability of this fixed point.

$$J_{(u_*, v_*)} = \begin{pmatrix} \underbrace{[1 - v_* - \epsilon_u u_*]}_{=0} + u_*(-\epsilon_u) & -u_* \\ \alpha v_* & -\alpha \underbrace{[1 - u_* + \epsilon_v v_*]}_{=0} - \alpha v_* \epsilon_v \end{pmatrix}$$

$$= \begin{pmatrix} -\epsilon_u\, u_* & -u_* \\ \alpha v_* & -\alpha\, v_*\, \epsilon_v \end{pmatrix} = \begin{pmatrix} - & - \\ + & - \end{pmatrix}$$

And hence $T < 0$ and $D > 0$ and this is always a stable fixed point.

Exercise 19: Continue this example by using nullclines.

Hint: think about the competition terms and how their main effect is to 'push' large u and v inwards.

[27] Or at least it is small for sensible u, v, i.e. on scale of original fixed point

[28] Three useful tricks: (i) keep brackets intact as long as possible: for example in finding the fixed point you will have solved $(1 - v - \epsilon_u u) = 0$ so keep it together when differentiating and then it will be effortlessly zero at the fixed point; (ii) don't sub in the espressions for u_* and v_* too soon, just keep them as u_* and v_* as long as possible; (iii) often we don't even need the full Jacobian evaluated: it is enough to see the signs of the entries, sometimes.

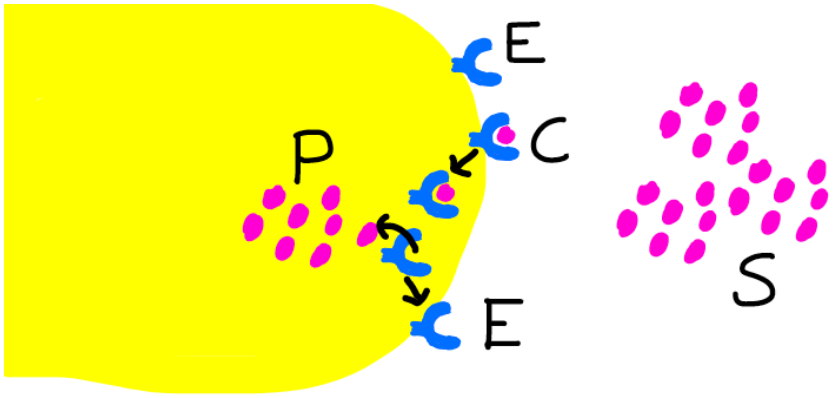
Exercise 20: For those who did dynamical systems[a]: construct a (strict) Lyapunov function to show (u^*, v^*) attracts all trajectories that start in $u, v > 0$.

Hint: $H(u, v)$ was constant before, so seems like a good place to start.

[a] for those that didn't but are unlikely to be put off by my warnings: good for you! All you need here is that a Lyapunov function $V(u, v)$ is such that it is strictly decreasing along trajectories in this domain, except at the fixed point (where is is constant). The function V should be continuous and zero at the fixed point, positive everywhere else. If you find such a function, trajectories have V decreasing and bounded below, so V tends to some constant, so trajectories tend to a some set where $\dot{V} = 0$, which here is just the fixed point.

end of lecture 8

1.3.3 Chemical kinetic models



The big yellow blob is the bacterium, the blue things are the receptors and the pink dots are the nutrients. OK so a bit of imagination required!

Imagine a single bacterium. It has receptors ready to pick up nutrients. The receptors start empty (E) and pick up nutrients in a substrate (S). Receptors then carry the nutrient so there is a complex (C) consisting of a reception and a nutrient particle. This goes into the bacterium where the nutrient is dropped off to be final product (P). We can describe this in terms of chemical kinetic notation as follows:

$$\begin{aligned} \mathrm{E} + \mathrm{S} &\underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \\ \mathrm{C} &\xrightarrow{k_3} \mathrm{E} + \mathrm{P} \end{aligned}$$

with three rates: k_1 is the rate that E and S combine, k_2 is the rate at which C can fail and fall apart back into E and S, and k_3 is the rate at which C is internalised and drops off P and becomes an empty E again.

To set up differential equations, suppose that everything is large numbers so that we can sensibly talk about concentrations. Let s be the concentration of S, and similarly

for e, p and c. Then in differential equations, our system can be described as

$$\begin{aligned}
\dot{s} &= -k_1\, e\, s + k_2\, c \\
\dot{e} &= -k_1\, e\, s + k_2\, c + k_3\, c \\
\dot{c} &= +k_1\, e\, s - k_2\, c - k_3\, c \\
\dot{p} &= + k_3\, c
\end{aligned}$$

For initial conditions, suppose that we start with all the nutrients outside and all receptors empty, so $s(0) = s_0$, $e(0) = e_0$, $c(0) = 0$ and $p(0) = 0$, for some $s_0, e_0 > 0$. Also suppose that there are a lot more nutrients than receptors, so that receptors are used many times before the substrate is fully depleted: $s_0 \gg e_0$.

From thinking about the original scenario, we can immediately see that there must be some invariant quantities. In particular, the number of receptors stays constant if we include both carrying (C) and empty (E). Also the nutrients are constant if we consider them outside (S), being carried (C) and inside (P).

We could also see this from the equations by spotting combinations that add to give no change:

$$\dot{e} + \dot{c} = 0\,, \quad \dot{s} + \dot{c} + \dot{p} = 0$$

so these are constant, and we can determine the constants by initial conditions:

$$e + c = e_0\,, \quad s + c + p = s_0\,.$$

We can use these to go from four differential equations down to two, substituting for e and p (in principle at least, p doesn't actually occur anywhere). This is our reduced system:

$$\begin{aligned}
\dot{s} &= -k_1(e_0 - c)s + k_2\, c &&= -k_1\, e_0\, s + (k_1\, s + k_2)c \\
\dot{c} &= +k_1(e_0 - c)s - k_2\, c - k_3\, c &&= +k_1\, e_0\, s - (k_1\, s + k_2 + k_3)c
\end{aligned}$$

This is already much better, but we can rescale further by strategic use of our initial conditions. We set $u = s/s_0$ and $v = c/e_0$ and then these have nice interpretations: u is the proportion of total nutrient still available (so u is one initially) and v is the proportion of receptors that are currently carrying nutrient (so v is zero initially). We could also rescale time to adsorb one of the rates.

Exercise 21: By a suitable rescaling, turn the system into:

$$\begin{aligned}
u' &= -u + (u + \mu - \lambda)v && u(0) = 1 \\
\epsilon v' &= +u - (u + \mu)v && v(0) = 0
\end{aligned}$$

where

$$\lambda = \frac{k_3}{k_1\, s_0}, \quad \mu = \frac{k_2 + k_3}{k_1\, s_0}, \quad \epsilon = \frac{e_0}{s_0} \ll 1\,.$$

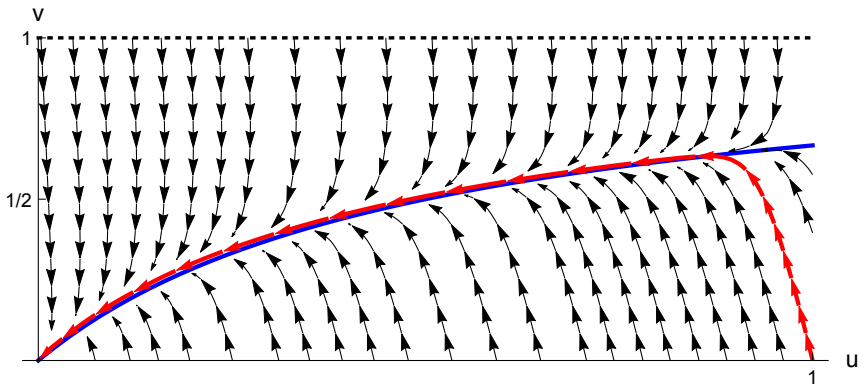
We see that the v dynamics are faster than the u dynamics (by an order of $1/\epsilon$). So we can see what the solutions will be like without doing too much more work. Do the v dynamics first imagining u to be almost fixed. We can see that it is exponential decay down to a constant:

$$v = \frac{u}{u+\mu}$$

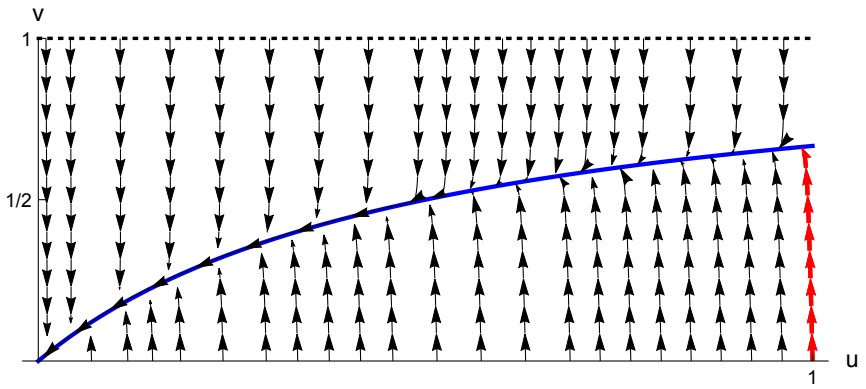
where the decay is fast (takes order ϵ time). So assume that has happened, and as we now slowly change u, the fast dynamics of v ensures it keeps moving quickly back to its equilibrium value again (which is itself a function of u). Substitute this value of v into the u' equation:

$$u' = -u + (u + \mu - \lambda)\frac{u}{u+\mu} = -\frac{\lambda\, u}{u+\mu}$$

so we can see that u just decays towards $u = 0$.



This is for $\epsilon = 0.1$ which is not super small, and even then it is clear the trajectories quickly move to $v = u/(u+\mu)$. The red trajectory is for the initial condition $u = 1$, $v = 0$.



Same but for $\epsilon = 0.01$, when the fast-slow dynamic is clearer: trajectories move vertically first until they are near the $v = u/(u+\mu)$ curve, then they move slowly along that curve

Thinking back to the original system, the v dynamics being fast just means that the proportion of receptors occupied quickly settles to some value and then slowly readjusts as the nutrient is depleted. This was all a consequence of our original assumption of there being much more nutrient out there than the total number of receptors.

This system is actually a classic model for enzyme kinetics used by biochemists (Michaelis-Menten).

Exercise 22: Work back to the original system and show that the inverse *of the rate of nutrient uptake is linear in the* inverse *of substrate. In other words:*

$$\left(\frac{dp}{dt}\right)^{-1} = A + B\,s^{-1}$$

for some constants A and B.

In principle this gives a test for whether a set of observations are consistent with Michaelis-Menten kinetics. In practice, one should probably be more than mildly concerned about issues with inverting small numbers, when those small numbers are hard-to-measure experimental quantities.

Exercise 23: Translate this to differential equations:

$$\mathrm{C} + \mathrm{X}_0 \underset{\mu_1}{\overset{k_1}{\rightleftharpoons}} \mathrm{X}_1 \xrightarrow{\lambda_1} \mathrm{X}_0 + \mathrm{P}$$

$$\mathrm{C} + \mathrm{X}_1 \underset{\mu_2}{\overset{k_2}{\rightleftharpoons}} \mathrm{X}_2 \xrightarrow{\lambda_2} \mathrm{X}_1 + \mathrm{P}$$

Also, find an invariant sum. You can do this by considering the reactions above directly, or by inspecting your differential equations (I think it is usually easier to spot these from the reactions directly.)

1.3.4 Epidemic models

There is a long and fruitful tradition of using mathematical models to capture how infectious disease spreads through a population. The most classic model (first published over a century ago) is so-called 'SIR' model. Here, the population is divided into three groups: susceptible (S), infected/infectious (I) and recovered/removed (R). This compartmental model is a little different to the population models we have seen already. In predator-prey and competition models that we have considered so far, the groups are really separate and it is not possible to move from one to another: you're there from birth to death. Here, it is possible to move between S, I and R. This type of model is usually called a 'compartmental model' where there are flows and interaction between compartments. It works for populations as well as chemical kinetics (see below) among many other things.

Here we have two processes causing a flow between compartments: infection takes individuals from S to I and recovery takes them from I to R. For now, we do not include any births or deaths: we are thinking of some short outbreak of disease in a

closed population. The fully system is:

$$\begin{aligned}\dot{S} &= -\beta IS \\ \dot{I} &= +\beta IS - \nu I \\ \dot{R} &= +\nu I\end{aligned}$$

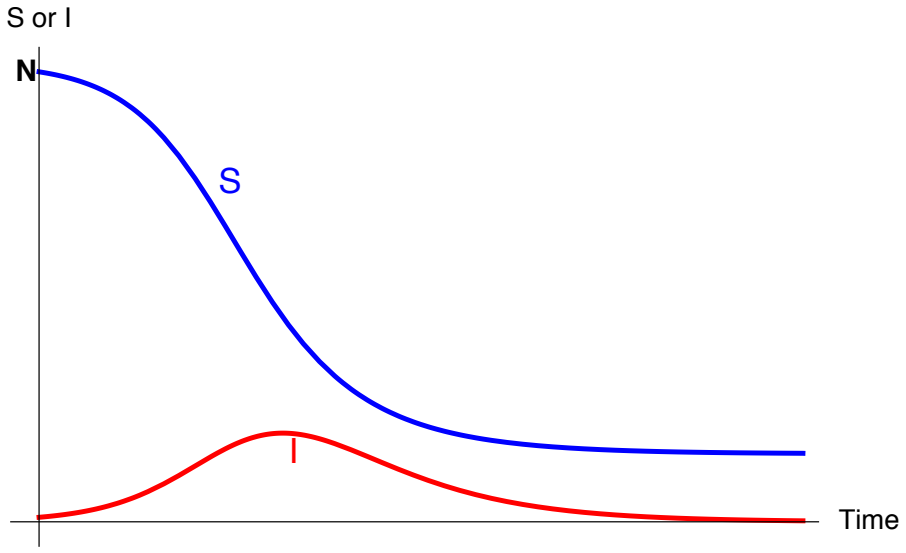
The total rate of infection is mass-action: proportional to the product of S and I. We have seen interaction terms like this before, for example in predation ($N \times P$). It corresponds to the frequency of the two groups encountering each other. Or another way to think about it is that the rate *per capita* of infection is proportional to the number of infected I, the number available to infect is S, so the total rate is proportional to $S \times I$. We call coefficient β the transmission rate. The recovery term is simpler, just simple rate per individual: ν.

It is easy to see that the total population size remains constant here[29]. We then denote total population size as $N = S + I + R$, and see $\dot{N} = 0$. So if we know N (think of as an extra parameter), then knowing any two of S, I and R is enough to determine the third. So, we might as well drop R from the system, and actually we don't even need to sub $R = N - I - S$ in anywhere as it does not occur in the other equations:

$$\begin{aligned}\dot{S} &= -\beta IS \\ \dot{I} &= +\beta IS - \nu I\end{aligned}$$

We can reconstruct R if we even need it, which we rarely do in practice. Usually I is most visible, perhaps followed by S.

We can solve for S and I numerically without much difficulty, and here is a typical output when we start with a few infecteds and the rest susceptible:



[29] Disturbingly, this all still works for fatal diseases: the R compartment serves equally well for those who have recovered and are now fit and well and now immune to the disease, as those who are in fact dead. Either way, they can't get the disease again. We just call them all 'removed', which always seems a bit uncaring.

When can an epidemic happen?

An 'epidemic' is simply when the cases increase, i.e. $\dot{I} > 0$. So initially $t = 0$ and

$$\dot{I}(0) = [\beta S(0) - \nu] I(0)$$

and assume that one or a few infected are introduced initially so that $I(0) > 0$. The we just need to check the sign of $[\beta S(0) - \nu]$ (where $S(0)$ is just the initial number of susceptibles). Imagine that we are starting from nearly everyone susceptible, and only a very small number infected, then $S(0) \approx N$. We see that an epidemic is possible if and only if

$$\frac{\beta}{\nu} N > 1 \,.$$

As always, we should try and interpret this inequality. Looking at the lefthand side, the trickiest bit is the $1/\nu$. We know ν is the recovery rate per individual. One way to imagine this is as a random process with event happening at rate ν if it hasn't happened already. This leads to an exponential distribution of time to recovery. The *expected* time to recovery is $1/\nu$, i.e. the duration of a infection. This is multiplied by β, which is the rate that one individual infects each susceptible[30]. Finally, N is roughly the number of susceptible individuals around. So, time infected, rate of on infected infecting each contact, number of contacts: the product is total number infected, on average, from one infection.

Actually this idea holds more generally in disease modelling, and this number is known as the *reproductive ratio*, or R_0[31]. Note this is an unfortunate piece of historical notation as this R_0 has nothing to do with the R of SIR. It is defined as *the mean number of secondary cases in an otherwise susceptible population*. In other words, if we drop one infected into our susceptible population, how many others will they directly infect? For this classic SIR model, we have found:

$$R_0 = \frac{\beta}{\nu} N \,.$$

and our threshold for an epidemic is $R_0 > 1$. This of course is also the threshold in more general models also, once we have identified R_0 (which is not always easy to do in practice[32]).

end of lecture 9

Vaccination We actually have enough to say quite a bit about the potential for vaccation as a control measure, without going into the differential equations in any further detail. Suppose that we intervene before a possible epidemic to vaccinate a proportion p of the population, and assume the vaccine gives total protection against the disease.

[30] a sort of *per capita per capita*

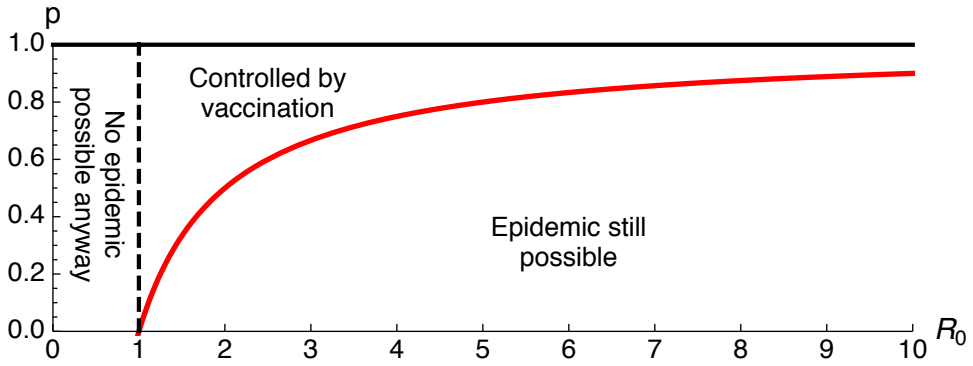
[31] pronounced R-nought

[32] There's plenty more to read and learn about R_0, and this paper by Heffernan *et al.* is a good place to start: `http://doi.org/10.1098/rsif.2005.0042`

This is equivalent[33] to moving a proportion p of the population straight into R and leaving $S(0) \approx (1-p)N$. Our condition for an epidemic to be possible is now

$$\frac{\beta}{\nu} S(0) = \frac{\beta}{\nu}(1-p)N = (1-p)R_0 > 1\,.$$

We can rearrange this to find the threshold for p in terms of R_0: $p < 1 - 1/R_0$ for an epidemic to be possible:



If R_0 is less than one, there's no chance of an epidemic anyway, so no need to vaccinate. For $R_0 > 1$, there is some $p_c \in (0,1)$ which is the vaccination threshold. It is not too hard to understand this intuitively, and to see why it depends on R_0 only. We'd like to vaccinate enough individuals so that the disease cannot spread through the population. We'd like to make the *effective* reproduction ratio less than 1. If we introduce one infected and they would infect R_0 others, we'd like to vaccinate at least $R_0 - 1$ of those R_0. That's just the proportion p_c.

This is all interlinked with the idea of *herd immunity* which is the idea that having many individuals immune can even protect other individuals. For each person vaccinated, it protects not just that person, but all the people they would have gone on to infect, and even later generations of infection onwards. These ideas are not new to mathematicians, and can be thought about more generally in terms of percolation theory.

Epidemic and final size

We can go further with this simple model and learn something of the trajectory of an epidemic once it does start. Here, it does not make sense to do a traditional fixed point analysis: the whole the epidemic is itself transient behaviour.

At the end of an epidemic, the susceptibles are *not* fully depleted: S seems to plateau to some positive value. Actually, we can understand this by considering the $S - I$ phase-plane. The whole of $I = 0$ is a line of fixed points, but it is not so much these we

[33] All of this is for a perfect vaccine, so being vaccinated means you truly in R. One can easily extend this to think about imperfect vaccines.

are interested in as the trajectories that arrive at them. We can explicitly solve for I as a function of S in this case:

$$\frac{dI}{dS} = \frac{\dot{I}}{\dot{S}} = \frac{+\beta IS - \nu I}{-\beta IS} = -1\frac{\nu}{\beta S} = -1 + \frac{N}{R_0}\frac{1}{S}$$

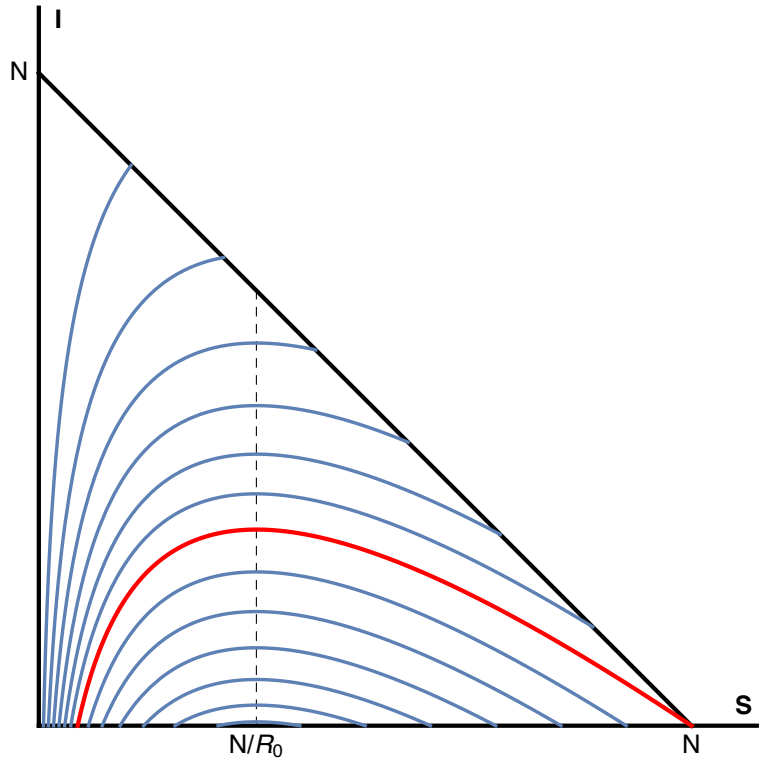
And integrating with respect to S:

$$I = -S + \frac{N}{R_0}\log S + C$$

for some constant C which is determined by initial conditions (now thinking about I and S as functions of time again):

$$[I(t) - I(0)] = -[S(t) - S(0)] + \frac{N}{R_0}\log\left[\frac{S(t)}{S(0)}\right] \tag{15}$$

The phase plane for this system should be restricted to the triangle in the $S - I$ plane where $S \geq 0$, $I \geq 0$, and $S + I \leq N$. We can see from above that $dI/dS > -1$ so the trajectories never go as steep downwards as the diagonal line. If we now consider things as a function of time, we see that trajectories can start anywhere, and head to the $I = 0$ line.



Solutions $I(S)$. To make this a phase diagram for the system in time, put some arrows on the curves (all will have S decreasing). The trajectory in red is the one which has $S \approx N$

and $I \approx 0$ initially, corresponding to an epidemic starting after a few infecteds introduced into an otherwise susceptible population.

> *Exercise 24: Show that trajectories have a maximum number of infecteds as $S = N/R_0$, and explain why this is. Hint: it might be useful to use the idea of 'effective' reproduction ratio (often labelled R_{eff} or r) which is the equivalent of R_0 but at some general value of S).*

Suppose we know $I(0)$ and $S(0)$, can we work out where exactly on the $I = 0$ line that the trajectory will head to? In other words, can we work out what value S will tend to? It turns out we can, at least implicitly. Consider in particular the case when we introduce a small number of infecteds into an otherwise susceptible population ($I(0) \ll N$, $S(0) \approx N$). Let time go to infinity, and we know $I(t) \to 0$. Suppose $S(t)$ tends to some value which we write as σN (which is the definition of σ). We see that σ is the proportion of the population that escape the epidemic and actually never get infected. We can find an implicit equation for σ by substituting all our initial and final values into 15:

$$0 = -[\sigma N - NB] + \frac{N}{R_0} \log \left[\frac{\sigma N}{N} \right]$$

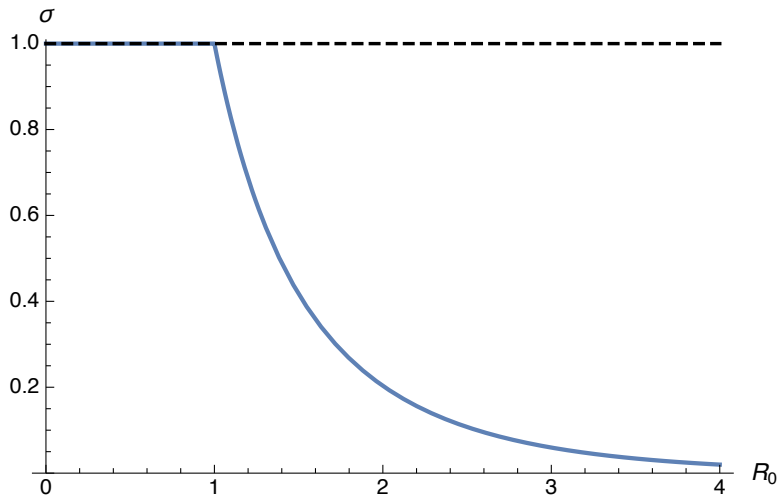
and rearranging:

$$\sigma - \frac{1}{R_0} \log \sigma = 1 \,. \tag{16}$$

> *Exercise 25: Start from the equations for $\dot{S}$ and $\dot{I}$ and get to equation 16 (without any notes).*

Note that N has cancelled out: our escape proportion σ only depends on R_0. This equation always has $\sigma = 1$ as a solution. This corresponds to nothing happens: final values and initial values the same, i.e. no epidemic. This is not the interesting solution. For $R_0 > 1$, there is a solution for $\sigma \in (0, 1)$, and that is the one that we want[34].

[34] Actually for R_0 securely above 1, $\sigma \approx e^{-R_0}$, so proportion escaping gets very small, but non-zero still.



This was an important early result of disease modelling (about a century ago): epidemics burn out leaving some proportion still susceptible. Before the concept of herd immunity, this would have been a non-trivial result. Without this understanding, epidemiologists would need to invoke some special reason for the epidemic ending before it got everyone, for example some people are naturally protected, or the virus has changed, or the weather changed and stopped the epidemic. What this very basic model showed was that none of this was necessary: epidemics will just burn themselves out before they get to everyone.

Exercise 26: Show that if $R_0 = 1 + \epsilon$, then $\sigma = 1 - 2\epsilon + \mathcal{O}(\epsilon^2)$.

Extensions to the SIR model (not lectured, but not beyond course!)

There are a lot of ways to extend the SIR model [35]. Indeed it is a whole research area. It is tempting just to add more and more detail in the hopes of making something more 'realistic', but in doing that, we lose model parsimony. Simple models are good as they are tractable enough to draw some general insights (such as R_0 above, which is a useful concept far more generally). But sometimes there are some parts of the dynamics that we really need to add to understand some particular problem.

One more example here: we have looked at the simple SIR model which is a one-off epidemic. What about something like measles in the UK before vaccination? It seemed

[35] And maybe one way to simplify: if there is no recovery, then we have the SI model. This might be appropriate for an extreme zombie invasion. As before, the total population size is constant so $S = N - Z$. The dynamics is now just 1D, and is given by

$$\dot{Z} = \beta Z(N - Z)$$

and hence zombies are logistic. Surprisingly, there is a whole book on the 'Mathematical Modelling of Zombies' by 'Robert Smith?' (yes, that is really his name).

to cause large epidemics every two years or so. To consider this longer term dynamic, we absolutely must add in some host turnover, i.e. natural births and deaths (not due to the disease), to keep a trickle of new susceptibles coming into the system. Easiest way to do that is a constant birth/death rate per capita (μ):

$$\begin{aligned} \dot{S} &= -\beta IS \qquad -\mu S + \mu N \\ \dot{I} &= +\beta IS - \nu I - \mu I \end{aligned}$$

And if we did put the $\dot{R}$ equation, it would have $-\mu R$ representing deaths. The births are all going into S: we assume everyone is born susceptible.

We can see by checking the $\dot{I}$ equation as above that we have a slightly modified expression for R_0 in this model:

$$R_0 = \frac{\beta}{\nu + \mu} N$$

(which is reassuring the same as before if $\mu = 0$). Now we are going to focus on acute (short) infection, i.e. the infectious period is much shorter than host lifetime. Or put another way, the recovery rate is far higher than the natural death rate: $\nu \gg \mu$.

The births and deaths mean that there is a balance to the epidemic dynamics: susceptibles are depleted by the epidemic, but replenished by natural population turnover. So, now there is actually a fixed point with disease present ($I^* > 0$):

$$S^* = \frac{\mu + \nu}{\beta} = \frac{N}{R_0}, \quad I^* = \frac{\mu(N - S^*)}{\beta S^*} = \frac{\mu}{\beta}(R_0 - 1)$$

and note attempt to write things in terms of R_0 whenever we see likely-looking expressions appear. We really should not be surprised by the factor of $R_0 - 1$. It means this fixed point only makes sense when $R_0 > 1$, which seems sensible.

The Jacobian is given by

$$J = \begin{pmatrix} -\beta I - \mu & -\beta S \\ \beta I & [\beta S - \nu - \mu] \end{pmatrix}$$

so evaluating at fixed point (noting that once again the square bracket is zero):

$$J_{(S^*, I^*)} = \begin{pmatrix} -\mu R_0 & -(\mu + \nu) \\ \beta(R_0 - 1) & 0 \end{pmatrix}$$

and for once, we are actually going to find the eigenvalues, as there is more we can learn here than just stability or otherwise. The eigenvalues λ satisfy

$$\lambda^2 - tr(J)\lambda + det(J) = \lambda^2 + \mu R_0 \lambda + \mu(\mu - \nu)(R_0 - 1)$$

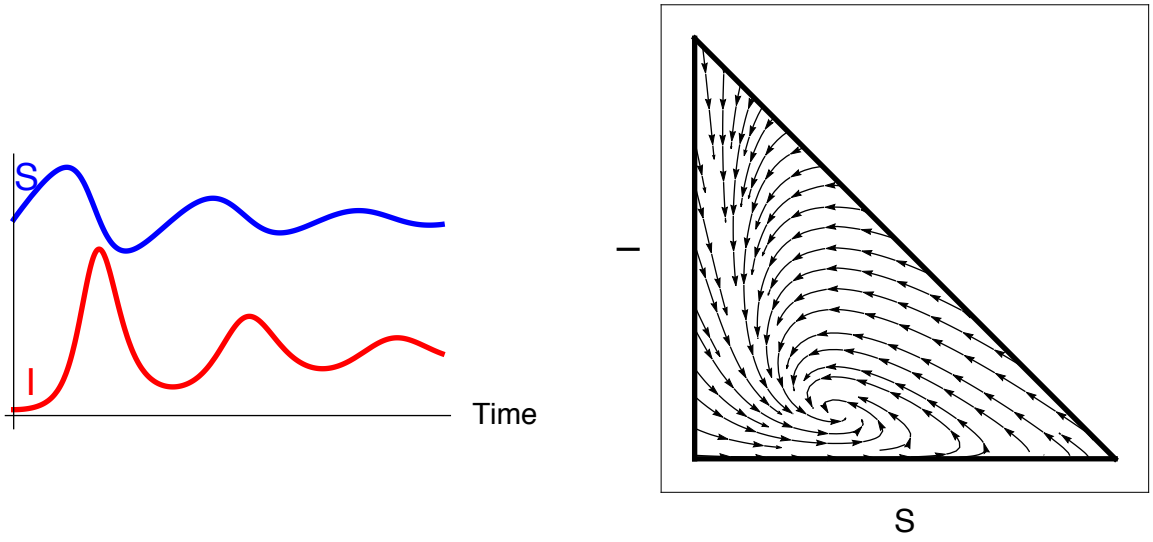
which has solutions

$$\lambda = -\frac{1}{2}\mu R_0 \pm \sqrt{\frac{1}{4}\mu^2 R_0^2 - \mu(\mu+\nu)(R_0-1)}.$$

This looks like a terrible mess for a moment, and then we realise that the square root contains μ^2 and $\mu\nu$ terms. We were considering the case when $\nu \gg \mu$, so this simplifies (taking factor of -1 out of square root to get i):

$$\lambda \approx -\frac{1}{2}\mu R_0 \pm i \underbrace{\sqrt{\mu\nu(R_0-1)}}_{=\omega}.$$

The eigenvalues are a complex pair with negative real part, so the fixed point is a stable focus (inwards spirals). This is not too hard to think about if, we suppose the epidemics happen and then host turnover refills S gradually. From these considerations, we can draw a phase diagram, and typical dynamics against time:



I have cheated here to make the diagrams a bit clearer. On the left, I have scaled S down somewhat to fit it on same plot. On right, I've taken a different $\nu : \mu$ ratio, to move the fixed point away from the S axis, so swirly dynamics is clearer.

This is like a damped pendulum, settling down to some endemic equilibrium. Looking at the these epidemics as we settle down, we can work out their approximate period from the imaginary part of the eigenvalues. The dynamics will be like $\cos(\omega t)$, and some decaying exponential. So the period T is

$$T \approx \frac{2\pi}{\omega} = \frac{2\pi}{\sqrt{\mu\nu(R_0-1)}}$$

and it is of note that $(\mu\nu)^{-\frac{1}{2}}$ is just the geometric mean of host lifetime and disease infectious period. The $R_0 - 1$ is back again. If R_0 is only just above threshold, the

period between epidemics is large. If R_0 is huge, then short period (bit like a pendulum in very strong gravity).

To finish the measles story, here we have period epidemics settling down. But real life is not like this model in one crucial way. The dynamics of measles in UK before vaccination involved much of the spread being in school-age children. And of course then, we should think about how schools worked. Kids aged 5 or so start school together in September, at the start of their first academic year. So, rather than there being a gentle trickle of susceptibles into the system, there is a huge kick once a year. This is enough to stop our damped pendulum settling down. The estimated T for measles (using the expression above, put $R_0 = 20$, infectious period about 12 days, lifetime about 70 years) is about 2.18 years. The forcing rounds this to a whole number of years, and so we end up with our epidemics every two years.

The author of these notes is probably biased (this is JRG's research area), but the field of disease modelling is very rich in terms of both mathematical interest and practical importance. However, we have some other interesting topics to cover in this course, so we will move on. If you want to read more, then do have a look at the book called 'Modeling Infectious Diseases in Humans and Animals' by Keeling and Rohani.

end of lecture 9

1.3.5 Excitable systems

In this section we consider *excitable systems* where a biological system can 'fire' following a small impulse. Heart muscle cells are one example of this: these are primed to contract in response to small electrical impulses. At the huge scale we could also consider large population phenomena such as plankton blooms, where relatively small environmental effects can lead to a dramatic burst of plankton growth. Arguably, some epidemic models should be considered also as excitable systems: a small number of initial infecteds can spark off a major epidemic. However for contrast here we will focus on a small physiological system: a neuron (nerve or brain cell) which receives a small input signal and can then fire an onwards signal to other cells.

The biochemical basis for signal propagation by neurons is well understood. It comes down to considering the difference in electrical potential (voltage) between the inside and outside of the cell, and how positively charged sodium and potassium ions are transported across the membrane by pumps. These pumps themselves change their behaviour according to the voltage difference. It is possible to develop a set of equations to represent these quantities (the Hodgkin-Huxley model of the action potential). While this system behaves in the right sort of way, it is not very easy to use it to gain mathematical insight as to why there is a threshold where an initial impulse is large enough to cause a 'spike'.

Here we move to a second layer of models (so this is a really a model of a model[36]). This type of model was developed independently by two researchers, hence it is the

[36] one could argue it is actually models all of the way down: the Hodgkin-Huxley model is itself a simple mathematical description of our understanding of the electrochemistry, and of course our understanding is an idealised model of how some imagined neuron might fire, and 'neuron' is catch-all term for a variety

Fitzhugh-Nagumo model. Students of dynamical systems will see similarities with the van der Pol oscillator, but this has a subtle but important modification.

Here is the Fitzhugh-Nagumo model:

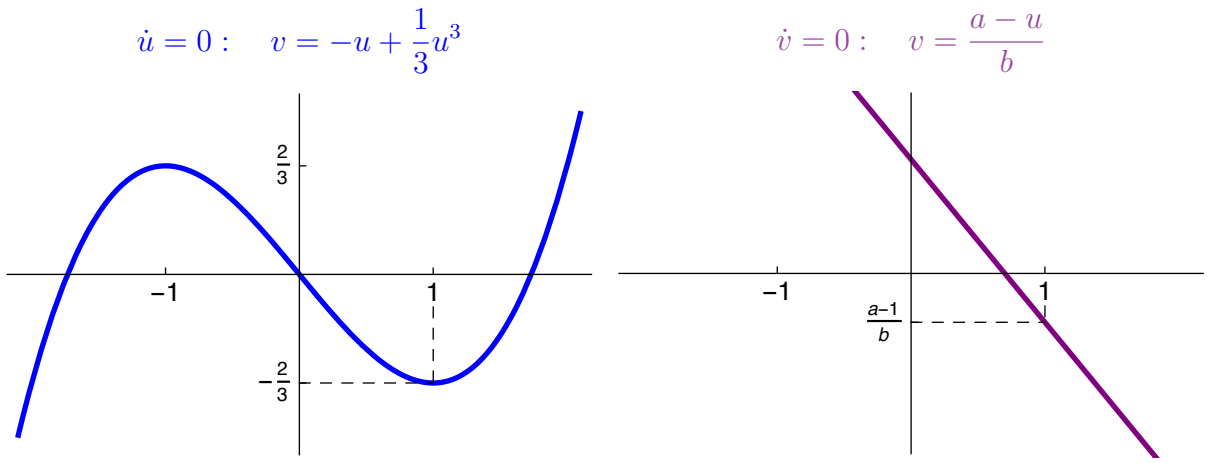
$$\begin{aligned} \dot{u} &= c\left(v + u - \frac{1}{3}u^3 + z(t)\right) \\ \dot{v} &= -\frac{1}{c}\left(u - a + b\,v\right) \end{aligned}$$

where

$$0 < b \leq 1, \quad 1 - \frac{2}{3}b < a < 1, \quad c \gg 1\,.$$

The term $z(t)$ represents external input, which might be applied at some time and not at others. To start with, we analyse the system with $z(t) = 0$. Note that the u and v are not quantities that we can easily relate back to the original biochemical model: they are not directly comparable to potassium levels, voltage difference or other physical quantities, but the idea is that this model will illustrate the mathematical processes at work.

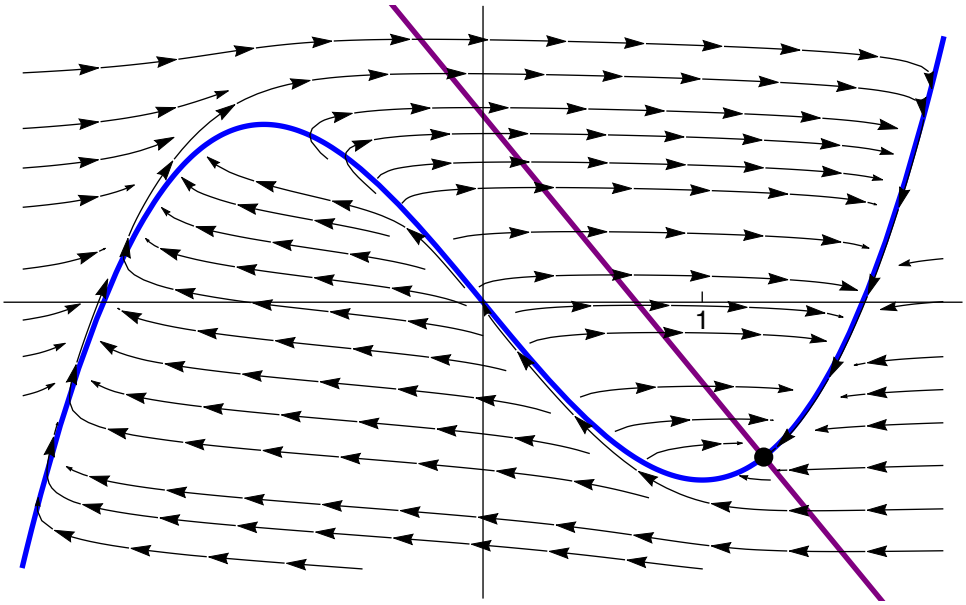
The nullclines are themselves fairly simple (u on horizontal axis, v on vertical):



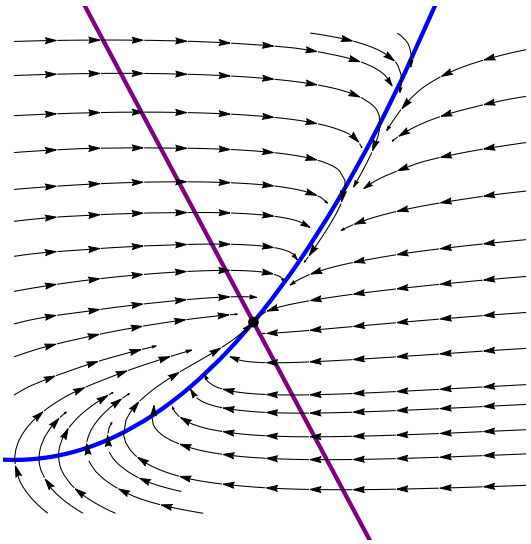
However we must check how they sit relative to each other. Given the $\dot{v} = 0$ nullcline (in purple above) has gradient $-1/b$ it is not too hard to check this is steeper than the downwards section of the $\dot{u} = 0$ nullcline. So there must be a single intersection. The range in a above is rigged to ensure that at $u = 1$ the $\dot{v} = 0$ nullcline is between $-2/3$ and 0.

For $c \gg 1$, we have fast-slow dynamics again. The u dynamics are fast and so we move quickly near-horizonal away from the $\dot{u} = 0$ nullclines. The vertical adjustment happens more slowly. This means we crawl along just outside the cubic nullcline much of the time, but if we reach the maximum or the minimum, then we 'fall off' and zip across until we hit another section of the cubic.

of cells, and so it goes on until we are in the land of philosophy, which means we probably should have stopped a while back, probably before reading this footnote.



For this plot, $a = 0.7$, $b = 1$ and $c = 5$.



Same parameters, just a zoom-in on the fixed point showing how all trajectories head to it.

Depending on where we start, we might first do a stint moving up the left side of the cubic, then a hop across, and then drift down to the single fixed point. Unlike the van der Pol oscillator, that's it! So long as $z(t) = 0$ we just stay there.

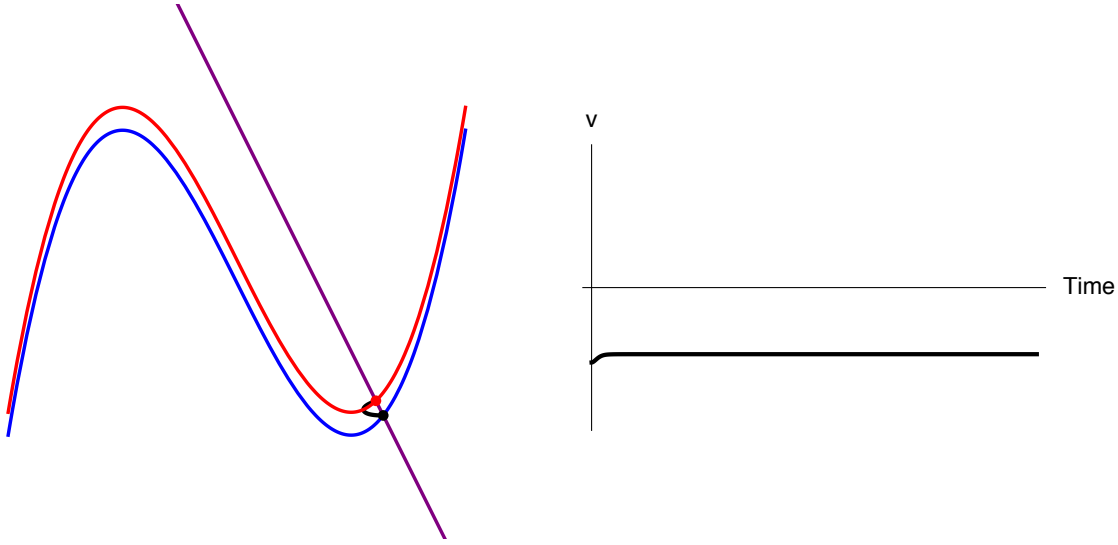
Finding the value of u and v at the fixed point involves solving a cubic of course, but luckily we do not actually need to do this. It suffice to say the fixed point is at (u^*, v^*) and to note that by the arrangement of nullclines, we see that $u^* > 1$. Check the Jacobian at the fixed point to confirm stability (though we are already sure it must be stable):

$$J_{(u_*,v_*)} = \begin{pmatrix} c\,(1-u^{*2}) & c \\ -1/c & -b/c \end{pmatrix} = \begin{pmatrix} - & + \\ - & - \end{pmatrix}$$

which is clearly a matrix with negative trace and positive determinant, so indeed the fixed point is stable.

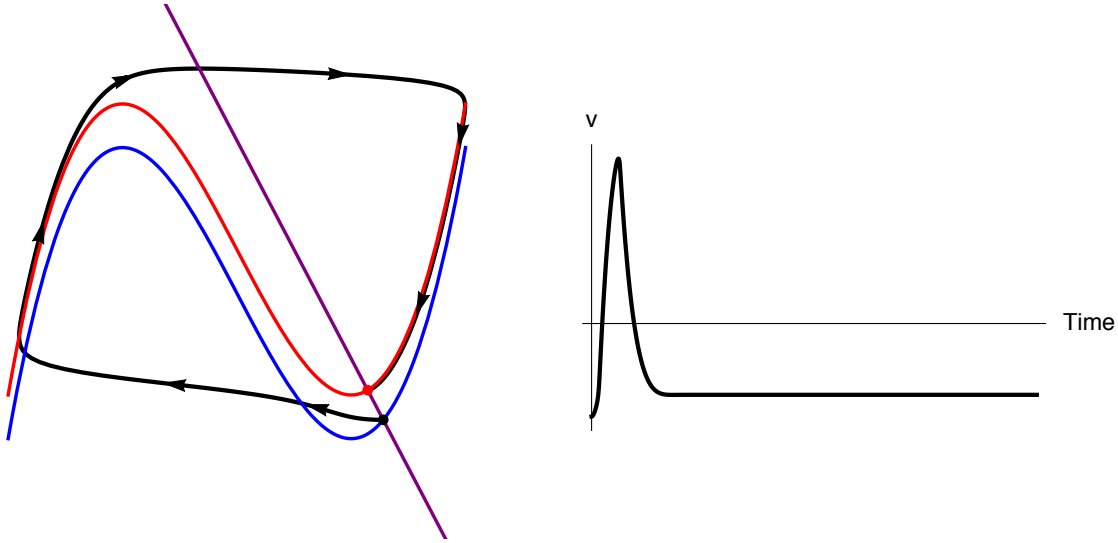
Suppose now that the system has settled to the fixed point, i.e. suppose the neuron is at rest. Now apply some input: $z(t) = -V_0$, where V_0 is a (possibly small) positive constant. We can see that the $\dot{v} = 0$ nullcline is completely unchanged, but the $\dot{u} = 0$ nullcline shifts up by that constant. There are now three cases we must consider. In each of the plots for the cases below, the original cubic nullcline is shown in blue, and the new shifted one in red, with the new fixed point in red. For the phase diagrams on the left, the axes have been left out for clarity. The plot on the right shows v against time.

(i) No spike:



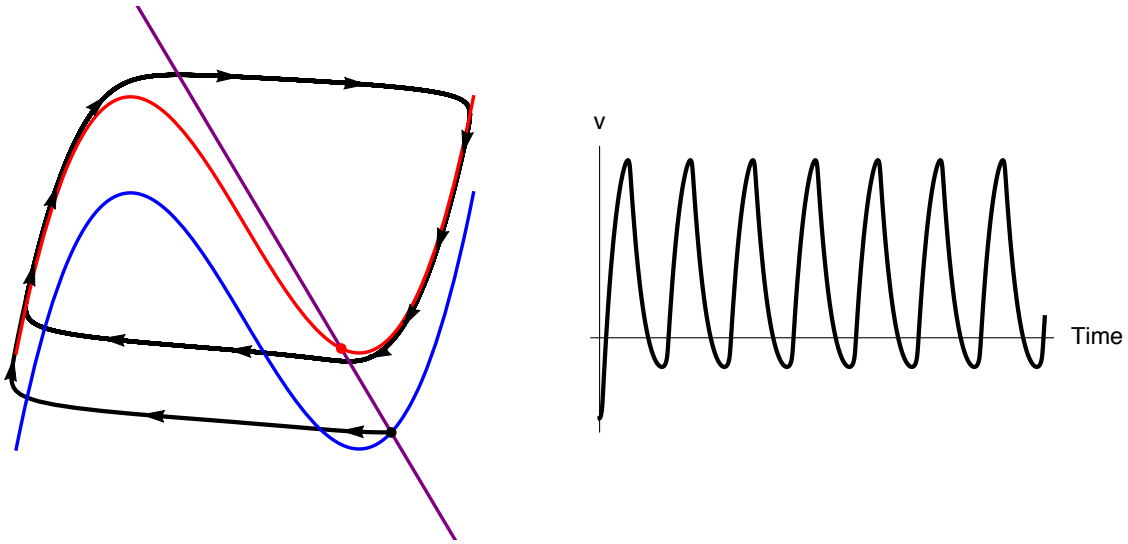
Quite a dull case: basically the fixed point has not moved too much and the system just corrects to the new system (same for $V_0 < 0$).

(ii) Enough impulse for one spike:



This is the excitable behaviour! The trajectory from the old fixed point skims below the new nullcline and thus has to go the whole way across to the other branch of the cubic, climb up and then back to the right and climb down. This corresponds to spike in v. After that, we arrive at the new fixed point, which is much as before.

(iii) Enough impulse for multiple spikes:



Now V_0 is large enough that it is actually a structural chance to the system. The new fixed point is not stable: the nullcline is now shifted so far that the fixed point has moved beyond the minimum to the middle portion of the cubic. So, we start off as in case (ii): from the original fixed point and do a loop, but now there is no fixed point to land on, so it goes around again, and again, and again. It will keep going until $z(t)$ is switched off again.

Exercise 27: Find the threshold for V_0 for repeated firing (case (iii)).

So this Fitzhugh-Nagumo model illustrates how a mathematical system can be excitable. We can gain the insight that we need a nullcline which is like a cubic, with multiple branches for a fast-slow solutions to follow. We can also see how a small external input can shift the system so that there is a large single transient, or even so that the system itself has changed and there are cycles. The fast-slow dynamics make it easy to illustrate what is going on, but it turns out that a large value of c is not required[37].

end of lecture 10

[37] Have a go with the mathematica simulation.