Mathematical Biology Assignment 1

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Q1. Population genetics and the Fisher-Haldane-Wright equation

In this question we consider the Fisher-Haldane-Wright (FHW) equation,

$$p^A(n+1) = \frac{w^{AA}p^A(n)^2 + w^{Aa}p^A(n)[1-p^A(n)]}{w^{AA}p^A(n)^2 + 2w^{Aa}p^A(n)[1-p^A(n)] + w^{aa}[1-p^A(n)]^2}\,, \tag{1.1}$$

where $p^A(n)$ denotes the frequency of allele A in the population at generation n, and $w^{AA}, w^{Aa}, w^{aa} \in [0,1]$ represents the "absolute fitness" of each respective genotype. Note that we also have $p^a(n) = 1 - p^A(n)$.

Part a)

We first note that in factoring out w^{AA},

$$p^A(n+1) = \frac{w^{AA}\left(p^A(n)^2 + \frac{w^{Aa}}{w^{AA}}p^A(n)[1-p^A(n)]\right)}{w^{AA}\left(p^A(n)^2 + 2\frac{w^{Aa}}{w^{AA}}p^A(n)[1-p^A(n)] + \frac{w^{aa}}{w^{AA}}[1-p^A(n)]^2\right)}\,,$$

and then introducing the relative fitness of genotypes Aa and aa,

$$\hat{w}^{Aa} = \frac{w^{Aa}}{w^{AA}} \qquad \text{and} \qquad \hat{w}^{aa} = \frac{w^{aa}}{w^{AA}}\,, \tag{1.2}$$

we can rewrite the FHW equation in terms of these two relative fitness parameters,

$$p^A(n+1) = \frac{p^A(n)^2 + \hat{w}^{Aa}p^A(n)[1-p^A(n)]}{p^A(n)^2 + 2\hat{w}^{Aa}p^A(n)[1-p^A(n)] + \hat{w}^{aa}[1-p^A(n)]^2}\,. \tag{1.3}$$

Part b)

In order to keep some cleaner notation, let

$$p_n = p^A(n) \qquad \text{and} \qquad q_n = p^a(n) = 1 - p^A(n)\,. \tag{1.4}$$

Let s, h be new variables (we will deal with their domains later) and define

$$\hat{w}^{aa} = 1 - s \qquad \text{and} \qquad \hat{w}^{Aa} = 1 - hs\,. \tag{1.5}$$

Substituting these into (1.3), we can write (where $\bar{w}$ is the first denominator)

$$p_{n+1} = \frac{p_n^2 + (1-hs)p_nq_n}{p_n^2 + 2(1-hs)p_nq_n + (1-s)q_n^2} = \frac{p_n^2 + (1-hs)p_nq_n}{\bar{w}}\,. \tag{1.6}$$

Part c)

For simplicity, we assume that $w^{AA} > w^{aa}$, and assume that all genotypes have non-zero fitness. This firstly tells us that $0 < \hat{w}^{aa} < 1$, hence

$$0 < 1 - s < 1\,, \qquad \text{so} \quad 0 < s < 1\,. \tag{1.7}$$

We then know by definition that $\hat{w}^{Aa} > 0$ which gives us

$$0 < 1 - hs < \infty\,, \qquad \text{so} \quad -\infty < h < \frac{1}{s}\,. \tag{1.8}$$

We will see later in the question that the bound is important on $1/s$ in order to ensure that p_n^A does not become negative.

Part d)

In order to perform the equilibrium analysis, we first set $f(p_n) = p_{n+1} - p_n$ and then solve for $f(p_n) = 0$. We calculate

$$f(p_n) = p_{n+1} - p_n = p_n \left(\frac{p_n + (1-hs)q_n}{\bar{w}} - 1 \right) = 0\,, \tag{1.9}$$

which clearly yields $p^* = 0$ as a preliminary solution. We then solve for the bracket term,

$$\begin{aligned} 0 &= p_n + (1-hs)(1-p_n) - \left(p_n^2 + 2(1-hs)p_n(1-p_n) + (1-s)(1-p_n)^2 \right) \\ &= (2hs - s)p_n^2 + (2s - 3hs)p_n + (hs - s)\,, \end{aligned}$$

and so after dividing both sides by s, we can use the quadratic equation to solve

$$p_n = \frac{3h - 2 \pm \sqrt{(3h-2)^2 - 4(2h-1)(h-1)}}{2(2h-1)} = \frac{3h - 2 \pm h}{2(2h-1)}\,,$$

which yields our three equilibrium solutions

$$p^* = 0\,, \qquad p^* = 1\,, \qquad p^* = \frac{h-1}{2h-1} = P\,. \tag{1.10}$$

Part e)

i] For the equilibria $p^* = 0$, this represents the case where there are no A alleles in the population at time n, hence meaning there is no potential for any more to be produced at the next time step. Likewise the $p^* = 1$ case is indicative of a population of only A alleles, hence no a alleles, meaning that at each subsequent time-step the population will remain as only A alleles.

ii] In order to guarantee its biological existence, we require that $P \in [0, 1]$, hence we can solve

$$0 \leq \frac{h-1}{2h-1} \leq 1\,, \qquad \text{so} \quad h \in (-\infty, 0] \cup [1, 1/s)\,. \tag{1.11}$$

As in part c) we still require $0 < s < 1$.

iii] In the case of $h < 0$, we see that this corresponds to $\hat{w}^{Aa} > 1$, so $w^{Aa} > w^{AA}$. Hence, it corresponds to the scenario in which A and a alleles are able to coexist (remembering that $w^{AA} > w^{aa}$ by assumption) in the population, since the fitness of Aa is greater than that of AA so A will not completely dominate the system over time.

By contrast, the case of $1 < h < 1/s$ corresponds to $\hat{w}^{Aa} < \hat{w}^{aa}$, so $w^{Aa} < w^{aa}$. Since our previous assumption still holds, we have $w^{AA} > w^{aa} > w^{Aa}$, which will cause some interesting dynamics in the system. Ultimately the A allele should dominate for the most part, but both w^{AA} and w^{aa} being greater than w^{Aa} basically means the opposite of the first case of h; that is, the system will tend to exterminate one of the alleles, not allowing them to both survive simultaneously.

Both of these predictions shall be borne out in parts g) and h).

Part f)

Consider $0 < h < 1$. We will use a standard linear stability analysis argument to show the stability, or lack thereof, of $p^* = 0, 1$. Let $p_{n+1} = g(p_n)$, where

$$g(p_n) = \frac{p_n^2 + (1-hs)p_n(1-p_n)}{p_n^2 + 2(1-hs)p_n(1-p_n) + (1-s)(1-p_n)^2}\,. \tag{1.12}$$

Consider a small deviation $p_n' = p^* + \varepsilon p_n$ around the fixed point p^*. By considering a Taylor series of g centred at p^*, we can write

$$p^* + \varepsilon p_{n+1} = g(p^* + \varepsilon p_n) = g(p^*) + g'(p^*)\varepsilon p_n + O(\varepsilon^2)\,,$$

and since $g(p^*) = p^*$ and ε is small, rearranging we see that

$$p_{n+1} = g'(p^*)p_n\,, \qquad \text{so} \quad p_n = g'(p^*)^n\,. \tag{1.13}$$

This tells us that p^* is a stable fixed point if $|g'(p^*)| < 1$, an unstable fixed point if $|g'(p^*)| > 1$ and indeterminate (to first order) if $|g'(p^*)| = 1$.

Clearly our next task is to calculate $g'(p_n)$ - this can be achieved by handing it to a Year 12 student and saying "it's character building". One just needs judicious algebra skills and the use of the quotient rule - we spare the reader such horrendous simplification details (needless to say, it truly is character building) and instead present the final derivative of g after performing such steps,

$$g'(p_n) = \frac{\Big(2hs^2(1-h) - s(1-hs)(2h-1)\Big)p_n^2 + 2hs(1-s)p_n + (1-s)(1-hs)}{\Big(s(2h-1)p_n^2 + 2s(1-h)p_n + (1-s)\Big)^2}\,. \tag{1.14}$$

Hence, we have

$$g'(0) = \frac{(1-s)(1-hs)}{(1-s)^2} = \frac{1-hs}{1-s} = 1 + \frac{(1-h)s}{1-s} \tag{1.15}$$

and with yet more judicious algebra (this time handing it to a Year 10), we have

$$g'(1) = 1 - hs\,. \tag{1.16}$$

Since by assumption $s, h \in (0,1)$, we see that $\frac{(1-h)s}{1-s} > 0$ and so $|g'(0)| > 1$, hence by (1.13) we see that $p^* = 0$ is an unstable fixed point. Further, we see that $0 < hs < 1$ and so $|g'(1)| < 1$, hence $p^* = 1$ is a stable fixed point.

Placing this back into a biological context, this tells us that for $h \in (0,1)$, the frequency of the A alleles will tend to dominate the population as $n \to \infty$, ultimately leaving the a alleles to die out. This is largely a result of our assumption that $w^{AA} > w^{aa}$ which dominates the behaviour of the system in this regime. Even if we started from $p_0 \approx 0$ (but not precisely zero), the A alleles would eventually take over due to their greater fitness, hence propensity to survive subsequent generations, and $p_n \to 1$ as $n \to \infty$.

Part g)

We can rewrite (1.6) as

$$h(p_n) = p_{n+1} = p_n + \frac{p_n q_n s(2h-1)}{\bar{w}}(p_n - P)\,. \tag{1.17}$$

In order to perform the linear stability analysis we again need to calculate $h'(P)$, but because of our clever rewriting above, this is now a simple task:

$$h'(p_n) = 1 + \frac{d}{dp_n}\left(\frac{p_n q_n s(2h-1)}{\bar{w}}\right)(p_n - P) + \frac{p_n q_n s(2h-1)}{\bar{w}}\,, \tag{1.18}$$

and we now see that the horrendous quotient derivative term will drop off when calculating $h'(P)$! Hence, we calculate

$$h'(P) = 1 + \frac{P(1-P)s(2h-1)}{P^2 + 2(1-hs)P(1-P) + (1-s)(1-P)^2}\,. \tag{1.19}$$

By simple analysis we see that for $P = \frac{h-1}{2h-1}$ we have

$$\text{if } h < 0 \text{ then } P \in (1/2, 1) \text{ and;} \qquad \text{if } h > 1 \text{ then } P \in (0, 1/2)\,. \tag{1.20}$$

Applying this to (1.19), we see that for $h < 0$ (and knowing that we always have $0 < s < 1$) there is one negative term, $(2h-1)$, hence meaning that $h'(P) < 1$. Showing $h'(P) > -1$ is a much more brutal exercise however, which we relegate to Desmos in the interest of time. Indeed, we see that $h'(P) = 1$ for $h = 0$, and $h'(P) \to 0$ monotonically as $h \to -\infty$, hence using proof by Desmos (the correct proof procedure for an Applied Mathematician, right?) we see that $|h'(P)| < 1$ and so P is stable.

Further, this behaviour is confirmed by our cobweb diagram seen in Figure 1.1 for two different trajectories beginning either side of P.

Since $\hat{w}^{Aa} = 1 - hs$, $h < 0$ corresponds to the case where $\hat{w}^{Aa} > \hat{w}^{AA}$, and so over time we see that the frequency of the A allele stabilises to a non-trivial value, but importantly so does the a allele since $p_n^a = 1 - p_n^A$ - in other words, P is an equilibrium for which both A and a exist in harmony in the population, unlike the other steady states where one ultimately dies out.

Part h)

Now consider $h > 1$. Again referring to (1.19), we see that every term of the fraction is now positive meaning that it is immediate that $|h'(P)| > 1$, hence showing that P is unstable. Again, the cobweb diagram in Figure 1.2 shows this. Looking at this cobweb, we see that the value of the starting position p_0 is highly indicative of which equilibrium the system converges towards. In particular, if $p_0 < P$, the system converges towards $p^* = 0$, leading to the extinction of A; alternatively if $p_0 > P$ then the system converges towards $p^* = 1$, so the domination of A (and extinction of a). In other words, we see that P acts as a sort of threshold value that succinctly describes how the system will evolve depending on what the starting value is.

Part i)

The main benefit of using this parametrisation with s and h is that it gave us very easy intervals for h from which we could analyse the system. As we saw in part h), this ultimately translates into having a single parameter, h, whose values describe how the the relationship between w^{AA}, w^{Aa} and w^{aa} impact the dynamics of the system in a highly non-trivial way (the parameter s is not as important and basically just corresponds to a shape parameter). Noting the different behaviour we saw for $h < 0$ and $0 < h < 1$ and $h > 1$, we see that having such simple intervals that can synthesise this relationship between fitnesses is very helpful in analysing the system. Because such bounds do not correspond to easy bounds on the fitnesses (i.e. they have complicated relations between one another), this clearly shows the benefit compared to an alternative analysis.

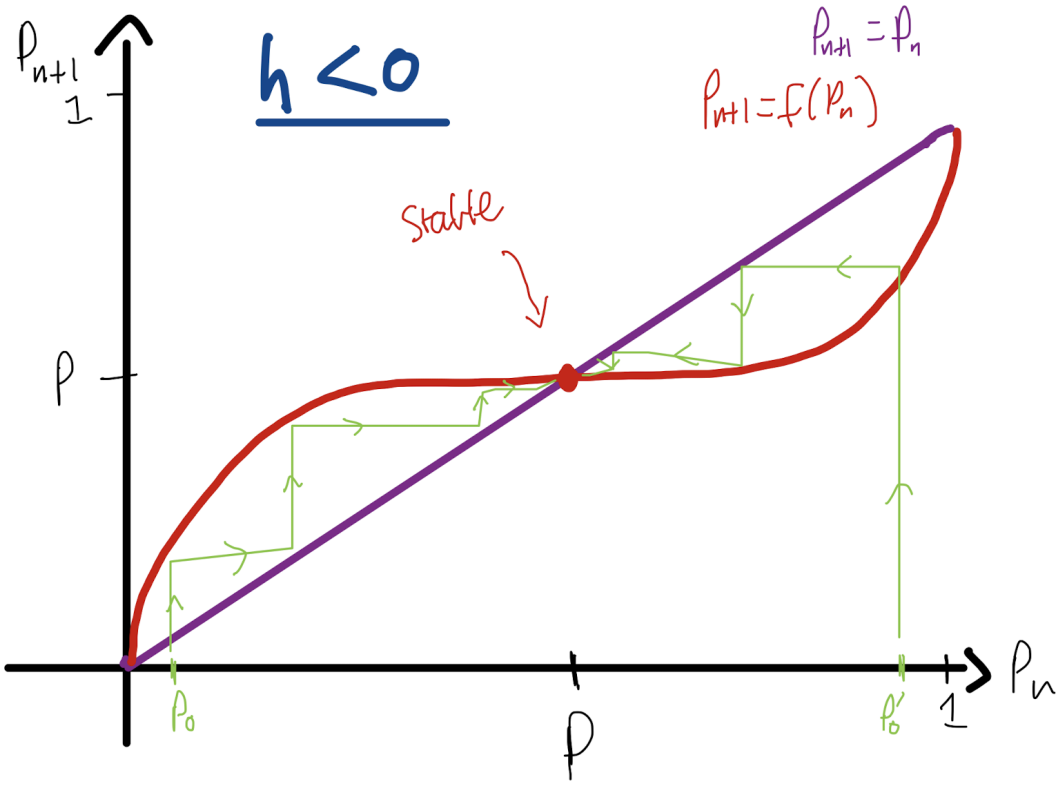

Figure 1.1: Cobweb diagram for $h < 0$ showing the stability of P for different initial values p_0 and p_0'.

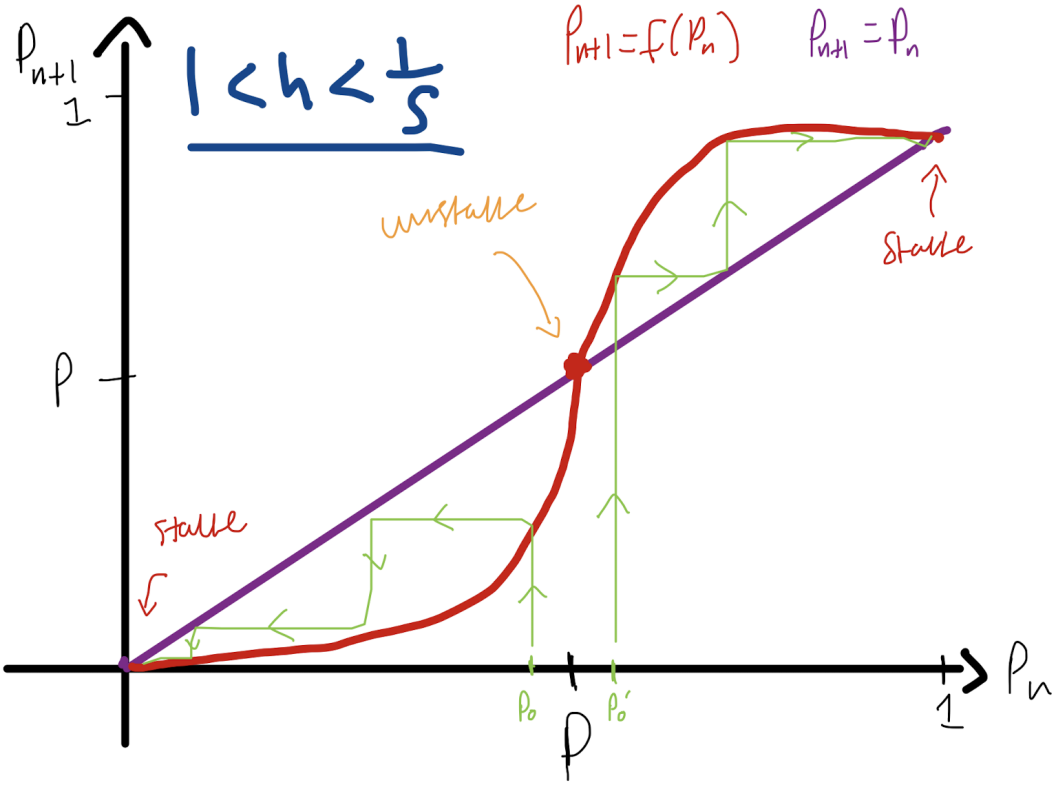

Figure 1.2: Cobweb diagram for $1 < h < 1/s$ showing the instability of P for different initial values p_0 and p_0'.

Q2. Brushtailed possums in Middle Earth

We will study brushtailed possums with bovine tuberculosis (TB) in New Zealand. Consider a possum population to have density $N(t)$ per hectare. This population divides into the contagious infectives $C(t)$ and those without disease, the susceptibles $S(t)$, hence $N(t) = S(t)+C(t)$. Let β denote a simple natural birth rate, α denote a natural death rate, α_d denote a death rate attributable to the disease, and b denote the cross-infection rate. Measured estimates have $\alpha_d > \beta - \alpha > 0$, which also says that $\alpha_d - (\beta - \alpha) > 0$ (this will be useful). We can use the following equations to describe the dynamics of the population:

$$f_1(S, C) = \frac{dS}{dt} = (\beta - \alpha)S + \beta C - bCS\,, \tag{2.1}$$

$$f_2(S, C) = \frac{dC}{dt} = bCS - (\alpha_d + \alpha)C\,. \tag{2.2}$$

Let $F(S, C) = (f_1(S, C), f_2(S, C))$ as defined above.

Part a)

To determine the steady states (S^*, C^*) such that $F(S^*, C^*) = 0$ we set $\frac{dS}{dt} = 0$ and $\frac{dC}{dt} = 0$ and solve for S and C. Using $bCS = (\alpha_d+\alpha)C$ from (2.2), we can substitute this into (2.1) and get

$$(\beta - \alpha)S + \beta C - (\alpha_d + \alpha)C = 0\,, \qquad \text{so} \quad S = \frac{\alpha_d - (\beta - \alpha)}{\beta - \alpha}C\,. \tag{2.3}$$

Hence, substituting this back into (2.2) we get

$$\frac{b(\alpha_d - (\beta - \alpha))}{(\beta - \alpha)}C^2 - (\alpha_d + \alpha)C = 0\,,$$

which leads to the two solutions

$$C = 0 \quad \text{and} \quad C = \frac{(\alpha_d + \alpha)(\beta - \alpha)}{b(\alpha_d - (\beta - \alpha))}\,. \tag{2.4}$$

Putting these back into (2.3), we see that our two steady state solutions are

$$(S_0^*, C_0^*) = (0, 0) \quad \text{and} \quad (S^*, C^*) = \left(\frac{\alpha_d + \alpha}{b},\ \frac{(\alpha_d + \alpha)(\beta - \alpha)}{b(\alpha_d - (\beta - \alpha))}\right)\,. \tag{2.5}$$

Clearly the first steady state is trivial since this gives $N(t) = 0$, hence just amounts to a system with no possums in it.

In order to determine the stability of (S^*, C^*), we will again use a linear stability analysis. Let $g(S, C) = (S, C)$, hence $\dot{g}(S, C) = (\dot{S}, \dot{C})$. Then by considering a small perturbation around the steady state (S^*, C^*), where $F(S^*, C^*) = 0$ by definition, we use a standard Taylor series argument to say that

$$\dot{g}(S, C) \approx J_F(S^*, C^*)g(S, C)\,, \tag{2.6}$$

where $J_F(S^*, C^*)$ is the Jacobian of F evaluated at the steady state. The Jacobian then takes the form

$$J_F(S, C) = \begin{pmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial C} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial C} \end{pmatrix} = \begin{pmatrix} (\beta - \alpha) - bC & \beta - bS \\ bC & bS - (\alpha_d + \alpha) \end{pmatrix} . \tag{2.7}$$

As a warm-up, we calculate the Jacobian of the trivial steady state

$$J_F(0, 0) = \begin{pmatrix} \beta - \alpha & \beta \\ 0 & -(\alpha_d + \alpha) \end{pmatrix} . \tag{2.8}$$

With some easy calculations, we calculate the eigenvalues λ and corresponding eigenvectors v of this matrix as

$$\lambda_1 = \beta - \alpha \text{ with } v_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \text{ and;} \tag{2.9}$$

$$\lambda_2 = -(\alpha_d + \alpha) \text{ with } v_2 = \begin{pmatrix} -\frac{\beta}{\beta + \alpha_d} \\ 1 \end{pmatrix} . \tag{2.10}$$

Hence we see that since $\beta - \alpha > 0$ by assumption, by the stability theorem of (4.9 Edelstein-Keshart, 2005), one eigenvalue has positive real part and hence $(0, 0)$ is an unstable fixed point.

Next consider the non-trivial fixed point of (2.5). After suitable simplification, we calculate

$$J_F(S^*, C^*) = \begin{pmatrix} -\dfrac{\beta(\beta - \alpha)}{\alpha_d - (\beta - \alpha)} & -(\alpha_d - (\beta - \alpha)) \\ \dfrac{(\alpha_d + \alpha)(\beta - \alpha)}{\alpha_d - (\beta - \alpha)} & 0 \end{pmatrix} . \tag{2.11}$$

Solving for $\det(J_F - \lambda) = 0$ yields a quadratic of the form

$$\lambda^2 + \frac{\beta(\beta - \alpha)}{\alpha_d - (\beta - \alpha)}\lambda + (\alpha_d + \alpha)(\beta - \alpha) = 0 \, , \tag{2.12}$$

which has unwieldy solutions. From lectures, the Routh-Hurwitz conditions tell us that a necessary and sufficient condition for both eigenvalues of a two-dimensional Jacobian matrix to have negative real parts is if $\mathrm{tr} J < 0$ and $\det J > 0$. Due to our parameter constraints, this is clearly satisfied in (2.11), hence it is *guaranteed* that (S^*, C^*) is a stable steady state. However, the roots of the quadratic in (2.12) are clearly non-trivial, so we will classify the type of steady state based on a condition.

We see that (2.12) has solution

$$\lambda = \frac{1}{2} \left(-\frac{\beta(\beta - \alpha)}{\alpha_d - (\beta - \alpha)} \pm \sqrt{\left(\frac{\beta(\beta - \alpha)}{\alpha_d - (\beta - \alpha)} \right)^2 - 4(\alpha_d + \alpha)(\beta - \alpha)} \right) , \tag{2.13}$$

and so clearly the necessary condition comes down to whether the square root term produces a non-zero imaginary part (spiral) or a zero imaginary part (sink). Hence, noting that we can factor out a $(\beta - \alpha)$ term for the condition, we have

$$(S^*, C^*) \text{ is a stable } \begin{cases} \text{spiral} & \text{if } \frac{\beta^2(\beta-\alpha)}{(\alpha_d-(\beta-\alpha))^2} - 4(\alpha_d + \alpha) < 0 \\ \text{sink} & \text{if } \frac{\beta^2(\beta-\alpha)}{(\alpha_d-(\beta-\alpha))^2} - 4(\alpha_d + \alpha) > 0 \end{cases} . \tag{2.14}$$

Part b)

Let our parameters take the following values:

$$\beta = 0.305\,, \quad \alpha = 0.105\,, \quad \alpha_d = 3\,, \quad b = 0.7\,. \tag{2.15}$$

We first note that with these values our (non-trivial) steady state, using (2.5), will be $(S^*, C^*) = (4.436, 0.317)$. Further, these values satisfy the spiral condition of (2.14).

Indeed, observing Figure 2.1 we see that our predicted stable spiral at the specified steady state is the correct description of the dynamics. The spiral takes on an interesting oblong shape, whereby the number of contagious possums increases to significant values (such as $C = 7$ that can be seen in the left hand plot), and then decreases rather sharply when the death rate due to contagion, α_d, overwhelms the system. Since we have $\beta > \alpha$, i.e. more births than deaths, this allows the number of susceptibles to grow whilst C is still low. However, as can be seen in Figure 2.2, we always have $C(t) > 0$ which means that there is always just enough TB in the system to allow for further infection spikes, thus beginning the cycle again. Figure 2.2 also demonstrates the stable spiral phenomenon in the form of damped oscillations of both $S(t)$ and $C(t)$, ultimately converging to the steady state $(S^*, C^*) = (4.436, 0.317)$.

The dynamics of $N(t) = S(t) + C(t)$ are ultimately quite volatile, as indicated by the oblong shape (a more circular one would imply more constant $N(t)$ values) and depend heavily on which stage of the cycle the population is in. The right hand plot of Figure 2.2 demonstrates how $N(t) \approx S(t)$ due to the relatively small size of $C(t)$ at any time value which only provides small fluctuations to $N(t)$ not encapsulated by $S(t)$. Again, this is largely down to the substantial size of $\alpha_d = 3 >> \beta - \alpha = 0.2$, so once a possum is contagious it dies quite rapidly. Ultimately, $N^* = S^* + C^* = 4.753$ is the long-term equilibrium of the possum population which becomes highly stable as $S(t)$ and $C(t)$ stabilise themselves.

Part c)

Suppose we want to ensure possum extinction by replacing $\alpha \mapsto \alpha + \kappa$ for some cull rate κ. Observing (2.1), we see that the pivotal term that causes stable possum numbers in the longrun is $(\beta - \alpha)S$, therefore to ensure possum extinction we need $\beta - \alpha < 0$. Clearly, if we then set $\kappa > \beta - \alpha$, hence $\beta - (\alpha + \kappa) < 0$, we will ensure that the possums will eventually be extinct. Plotting this scenario with $\alpha + \kappa = 0.400 > \beta = 0.305$ on pplot8 demonstrates that this does incur the desired outcome of eventual extinction, $N(t) \to 0$, as $(0, 0)$ becomes a sink as predicted with the eigenvalues in (2.9) since we now have $\beta - \alpha < 0$.

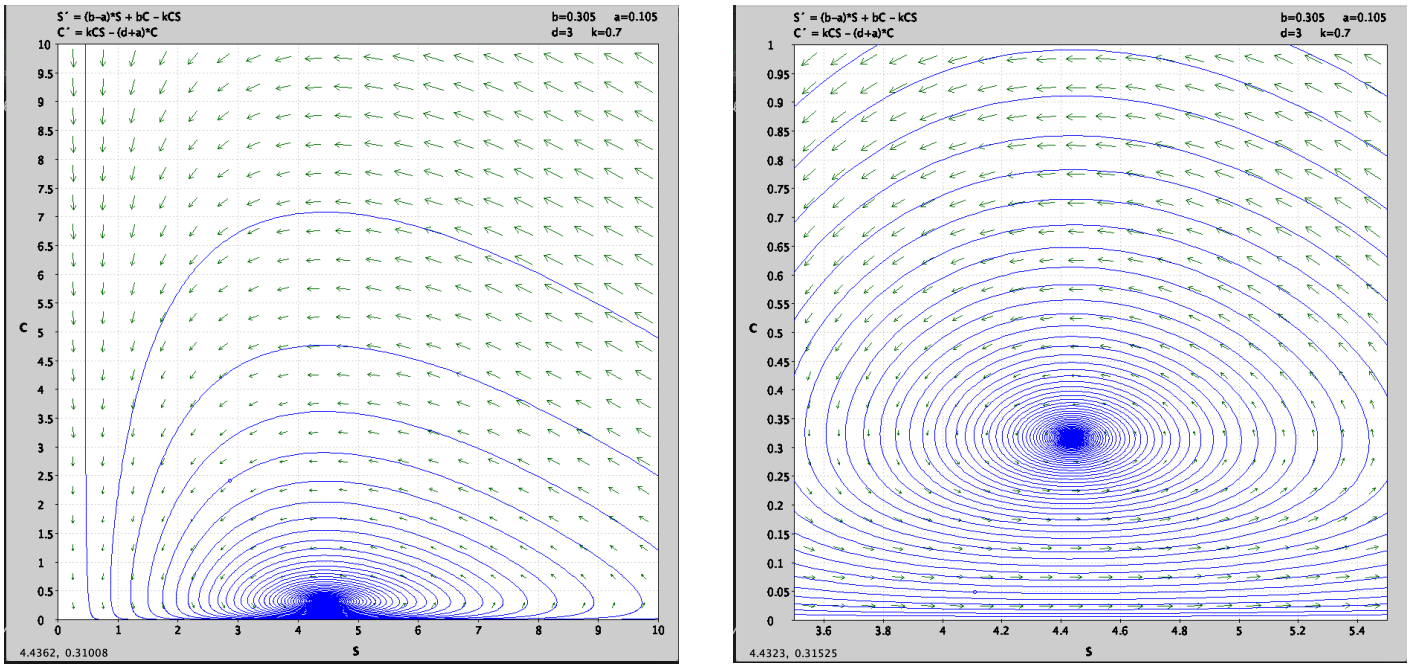

Figure 2.1: Phase plane portrait created using pplane8 with values specified by part b). Left hand side: $(S, C) \in [0, 10]^2$ and right hand side: $(S, C) \in [3.5, 5.5] \times [0, 1]$.

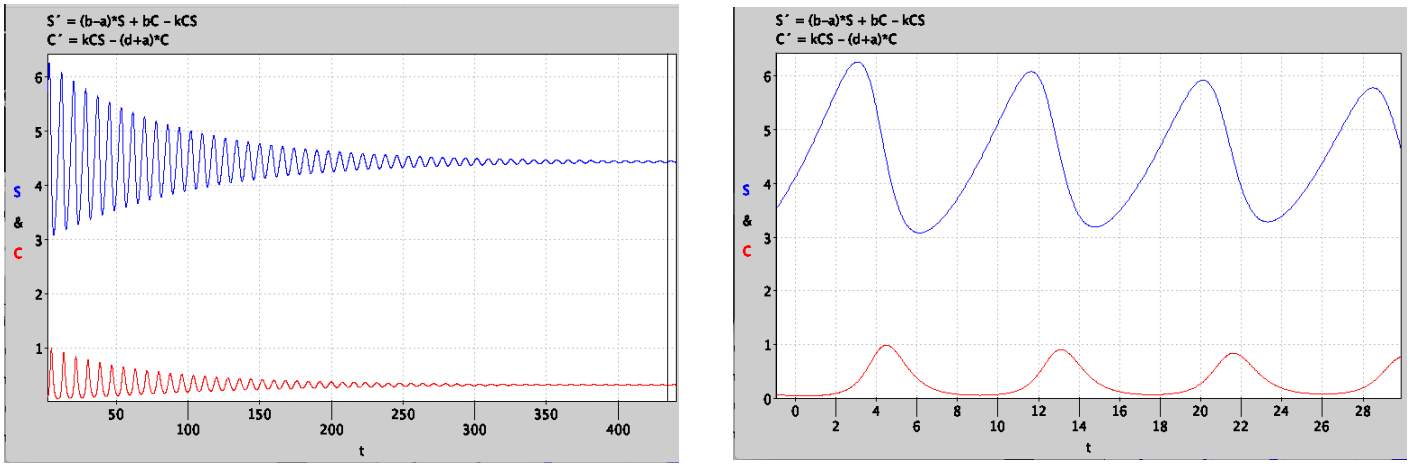

Figure 2.2: Numerical solutions for $S(t)$ (blue) and $C(t)$ (red) given some initial condition. LHS: $t \in [0, 450]$ and; RHS: $t \in [0, 30]$

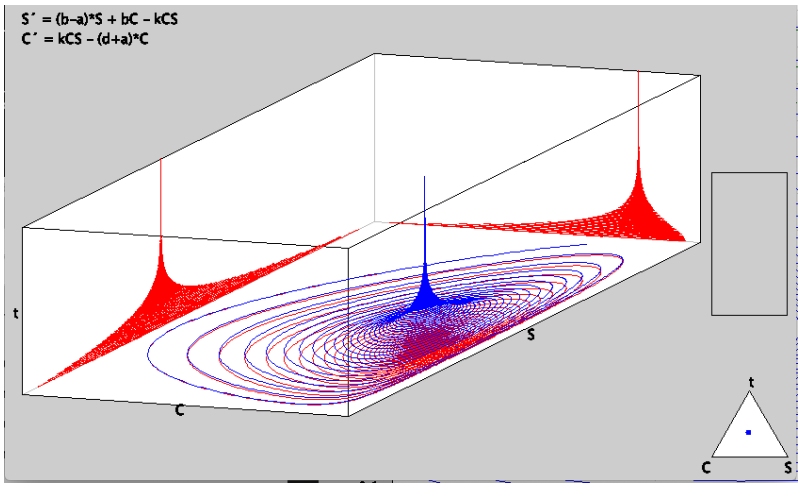

Figure 2.3: 3D Composite of trajectory of $S(t), C(t)$ as t varies, because it's fun to look at and why not?

Q3. Gene activation

Consider a gene G that is activated by the presence of a biochemical substance S. Let $g(t)$ be the concentration of the gene product at time t and assume that the concentration of S, denoted by s_0, is fixed. A model describing the dynamics of G is

$$\frac{dg}{dt} = k_1 s_0 - k_2 g + \frac{k_3 g^2}{k_4 + g^2}\,, \tag{3.1}$$

where each $k_1, k_2, k_3, k_4 > 0$ is constant and $s_0 \geq 0$.

Part a)

We first notice that the $P = \frac{k_3 g^2}{k_4 + g^2}$ term is a so-called "predation" term (J.D. Murray, 2002) though unlike how it is used in the spruce budworm example, the sign here is flipped. Importantly, this term saturates for large enough g values, which in our case means that for $g = 0$ we have $P = 0$, but then past some critical value, say $g \approx 3$ (in the case of $k_3, k_4 = 1$), we will have $P \approx 1$ as $g \to \infty$. The point is that P acts as a kind of "switch", and so in our case, once g reaches a particular level, this switch will be activated forever more, hence activating G. Here, k_3 represents a kind of velocity and has units g/t, whereas k_4 represents the threshold activation level beyond which the gene has well and truly been activated by S.

Of course, we can only reach this level of saturation if there is any gene activated at all, and this is where the $L = k_1 s_0 - k_2 g$ term comes into the picture. If we had $k_3 = 0$, then we would yield a solution of $g(t) = \frac{k_1 s_0}{k_2}(1 - e^{-k_2 t})$. This tells us that $k_1 s_0$ (where k_1 is some rate of substance parameter) is the natural bound on the activation, and asymptotic solution, before the P term kicks in, and k_2 is the velocity of this change in $g(t)$.

Part b)

Using dimensionless parameters (which we will take as gospel), we can rewrite (3.1) as

$$f(x|s,r) = \frac{dx}{d\tau} = s - rx + \frac{x^2}{1 + x^2}\,, \tag{3.2}$$

where $r = k_2\sqrt{k_4}/k_3$ and $s = k_1 s_0 / k_3$. We now set $r = 0.4$ for the remainder of the question. The plot asked for can be seen in Figure 3.1.

Part c)

Using Figure 3.1, and a slightly enhanced sketch displaying flow lines in Figure 3.2, we present a bifurcation diagram for $f(x|s,r)$ in Figure 3.3. As can be seen, the bifurcation point - a saddle node, where the stable and unstable points "collide" - occurs at $(s, \bar{x}) = (0.0418, 0.2198)$ which was found by finding the global minimum of $f(x|0, 0.3)$ and solving appropriately. Note that the line emanating from the top $\bar{x}$ value represents the fact that the third steady state is always stable for any $s \geq 0$.

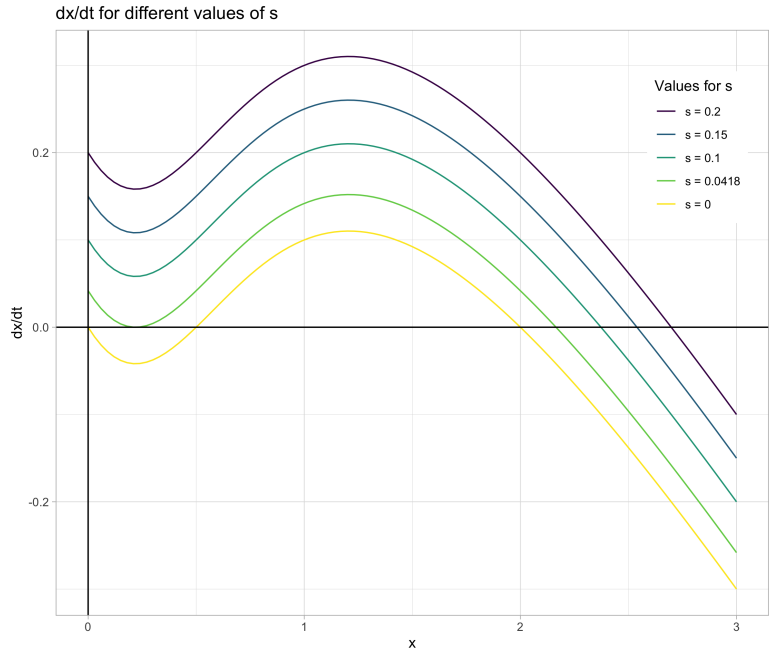

Figure 3.1: $\frac{dx}{d\tau}$ vs. x for different values of s

Part d)

Assume there is initially no gene product, so $x(0) = 0$. When the process begins with $s = 0$, we clearly have $dg/dt = 0$ hence there will be no activity. As we slowly increase the s value, say to $s = 0.01$, $x(\tau)$ will slowly move to the new stable saddle point $\bar{x}_1 > 0$, which clearly will shift slightly as we slowly increase s. Then, once $s > 0.0418$, the gene's activation level will very quickly move towards the other stable saddle point $\bar{x}_3$, where it will asymptote towards this value. It is past this bifurcation point when the gene activation "really kicks in", since the level of activation at $\bar{x}_3$ is far greater than that of the first few steady states, particularly as s increases well beyond 0.0418.

Part e)

If we instead suppose that $s = 1$ to start with (and still $x(0) = 0$), then we find that the speed of the reduction of s truly makes a difference. Supposing it is *slowly* decreased as in the question, then $x(\tau)$ will approach $\bar{x}_3$ and stabilise there. Even when $s < 0.0418$, it will still be attracted to $\bar{x}_3$ (since $\bar{x}_2$ is an unstable steady state), hence the gene will *not* turn off again but merely stay close to $\bar{x}_3$.

If, however, the turning-off process happens quite quickly, then (without having done the formal analysis), it is possible that $x(\tau)$ hasn't made it that far along the x-axis, and so if $s < 0.0418$ rather quickly then x may become trapped in the region between $\bar{x}_1 < x(\tau) < \bar{x}_2$, where it would hence be attracted to the stable node $\bar{x}_1$ as it didn't have enough time to make it close to $\bar{x}_3$, hence meaning the gene would turn off again.

We also note that we could again use pplane8 to perform this analysis by setting something like $ds/dt = -0.05s$ and observing the dynamics with $s(0) = 1$ and $x(0) = 0$. We leave this as an exercise to the reader.

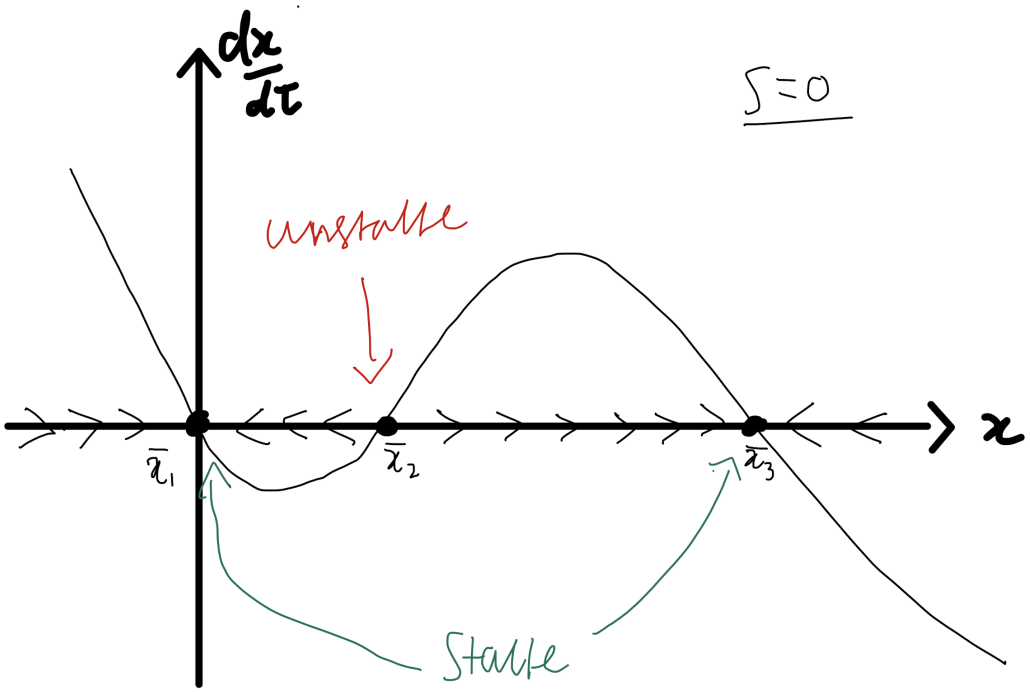

Figure 3.2: $\frac{dx}{d\tau}$ vs. x for $s = 0$ with flow lines

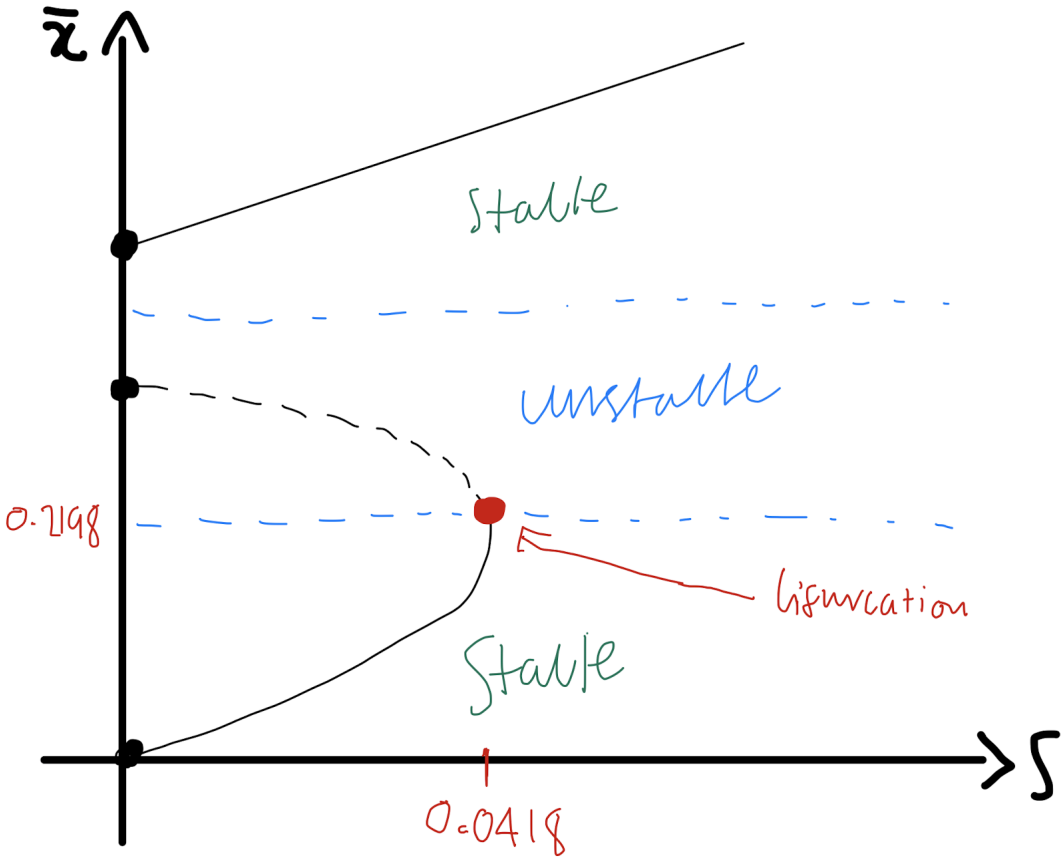

Figure 3.3: Bifurcation diagram for (3.2) as s varies