HOMEWORK 6 ANSWER KEY

(1) The system in matrix form is

$$\begin{pmatrix} dP(t)/dt \\ dC(t)/dt \\ dI(t)/dt \end{pmatrix} = \begin{pmatrix} \rho - \delta_2 - \alpha & 0 & 0 \\ \alpha & -\beta - \delta_1 & 0 \\ 0 & \beta & \rho - \delta_2 \end{pmatrix} \begin{pmatrix} P(t) \\ C(t) \\ I(t) \end{pmatrix} \tag{1}$$

Because this matrix is lower triangular, the eigenvalues are the entries along the diagonal. Thus, the three eigenvalues are

$$\lambda_1 = \rho - \delta_2 - \alpha, \tag{2}$$
$$\lambda_2 = -\beta - \delta_1, \tag{3}$$
$$\lambda_3 = \rho - \delta_2. \tag{4}$$

For the cancer-free equilibrium (0, 0, 0) to be stable, we require that all three eigenvalues are negative. λ_2 will always be negative, and λ_1 and λ_3 will be negative if $\rho - \delta_2 < 0$. Connecting this result with what we found in class, we see that the conditions under which cancer metastasizes ($\rho - \delta_2 > 0$) also govern whether the primary tumor will be able to persist. Put another way, if conditions allow the primary tumor to develop, metastasis will always follow unless treatment is provided.

(2) Depending on how you interpreted the description of the system, there are two models that are plausible. The first assumes that the rate of uptake of drug by the tumor cells is $\mu N(t)$, and the second assumes that the rate of uptake is $\mu C(t)$. In reality, the rate of uptake of drug would probably depend on both $N(t)$ and $C(t)$ - we don't consider that possibility here only because it would make the model nonlinear!

The first model is:

$$\frac{dC(t)}{dt} = C_0 - \omega C(t) - \mu N(t), \tag{5}$$
$$\frac{dN(t)}{dt} = \rho N(t) - \mu N(t). \tag{6}$$

The first model is:

$$\frac{dC(t)}{dt} = C_0 - \omega C(t) - \mu C(t), \tag{7}$$
$$\frac{dN(t)}{dt} = \rho N(t) - \mu C(t). \tag{8}$$

(I should point out that there is a problem with both of these models: terms in the dC/dt equation should have units of "drug per time", whereas terms in the dN/dt equation should have units of "tumor cells per time." However, either $\mu N(t)$ (for the first model) or $\mu C(t)$ appear in both equations. This means that the units are incorrect for one of the two differential equations. The easiest way to handle this would be to add a term ϵ that has units of "tumor cells killed per drug," thus converting drug uptake by tumor cells into tumor cell mortality. That is, for the first model, if μ has units of "drug per tumor cell per time", then the units are correct for dC/dt; multiplying $\mu N(t)$ by ϵ in the dN/dt equation gives the dN/dt equation proper units. For the second model, if μ has units of "drug uptake per drug per time", then the units of dC/dt are correct; multiplying $\mu C(t)$ by ϵ in the dN/dt equation gives dN/dt correct units.)

For simplicity of presentation, I will analyze each model separately.

For the first model, the nullclines are given by finding the combination of $C(t)$ and $N(t)$ that cause $dC/dt = 0$ (for the C nullcline) and $dN/dt = 0$ (for the N nullcline). Thus the C

nullcline is

$$\frac{dC}{dt} = 0 \Rightarrow N(t) = \frac{C_0}{\mu} - \frac{\omega}{\mu}C(t), \tag{9}$$

which is a line in the C-N plane with intercept C_0/μ and slope $-\omega/\mu$. The N nullcline is

$$\frac{dN}{dt} = 0 \Rightarrow N(t)(\rho - \mu) = 0 \Rightarrow N(t) = 0, \tag{10}$$

which is a line along the C-axis in the C-N plane.

To find the direction of the vector field along each nullcline, we ask, "What is the sign of dN/dt along the C nullcline? What is the sign of dC/dt along the N nullcline?".

To find the sign of dN/dt along the C nullcline, we plug the equation for the C nullcline into the dN/dt equation.

$$\frac{dN}{dt} = N(t)(\rho - \mu) = \left(\frac{C_0}{\mu} - \frac{\omega}{\mu}C(t)\right)(\rho - \mu). \tag{11}$$

We need to consider two cases: $\rho - \mu > 0$ and $\rho - \mu < 0$. If $\rho - \mu > 0$, then $dN/dt > 0$ whenever $C_0/\mu > C(t)\omega/\mu$, that is, whenever $C(t) < C_0/\omega$. Conversely, $dN/dt < 0$ when $C(t) > C_0/\omega$. If $\rho - \mu < 0$, though, these conditions are reversed.

To find the sign of dC/dt along the N nullcline, we plug in the equation for the N nullcline into the dC/dt equation.

$$\frac{dC}{dt} = C_0 - \omega C(t) - \mu(0) = C_0 - \omega C(t). \tag{12}$$

Thus $dC/dt > 0$ when $C(t) < C_0/\omega$ and $dC/dt < 0$ when $C(t) > C_0/\omega$.

Note that $C(t) = C_0/\omega$ features prominently in determining the direction of the vector fields along both nullclines. This is because $C(t) = C_0/\omega$ is the $C(t)$ value at the intersection of the nullclines and the direction of the vector field along each nullcline will switch directions at the intersection of the nullclines (Fig. 1).

Fig. 1 suggests that the equilibrium will be unstable if $\rho > \mu$ and stable if $\rho < \mu$. This suggests that, for this very simple and, in some ways, biologically implausible model, the rate of inflow of drug C_0 does not affect the outcome of chemotherapy.

This intersection is the equilibrium of the system. We can confirm this by solving the system of equations $dC/dt = 0$ and $dN/dt = 0$ for $\hat{C}$ and $\hat{N}$

$$\frac{dN}{dt} = 0 \Rightarrow \hat{N}(\rho - \mu) = 0 \Rightarrow \hat{N} = 0, \tag{13}$$

$$\frac{dC}{dt} = 0 \Rightarrow C_0 - \omega\hat{C} - \mu\hat{N} = 0 \Rightarrow \hat{C} = \frac{C_0}{\omega}. \tag{14}$$

For the second model, the C nullcline is

$$\frac{dC}{dt} = 0 \Rightarrow C_0 - C(t)(\omega + \mu) = 0 \Rightarrow C(t) = \frac{C_0}{\omega + \mu}, \tag{15}$$

which is a vertical line C-N plane with C-intercept $C_0/(\omega + \mu)$. The N nullcline is

$$\frac{dN}{dt} = 0 \Rightarrow \rho N(t) - \mu C(t) = 0 \Rightarrow N(t) = \frac{\mu C(t)}{\rho}, \tag{16}$$

which is a line in the C-N plane with slope μ/ρ and intercept 0.

To find the sign of dN/dt along the C nullcline, we plug the equation for the C nullcline into the dN/dt equation.

$$\frac{dN}{dt} = \rho N(t) - \mu C(t) = \rho N(t) - \mu\frac{C_0}{\omega + \mu}. \tag{17}$$

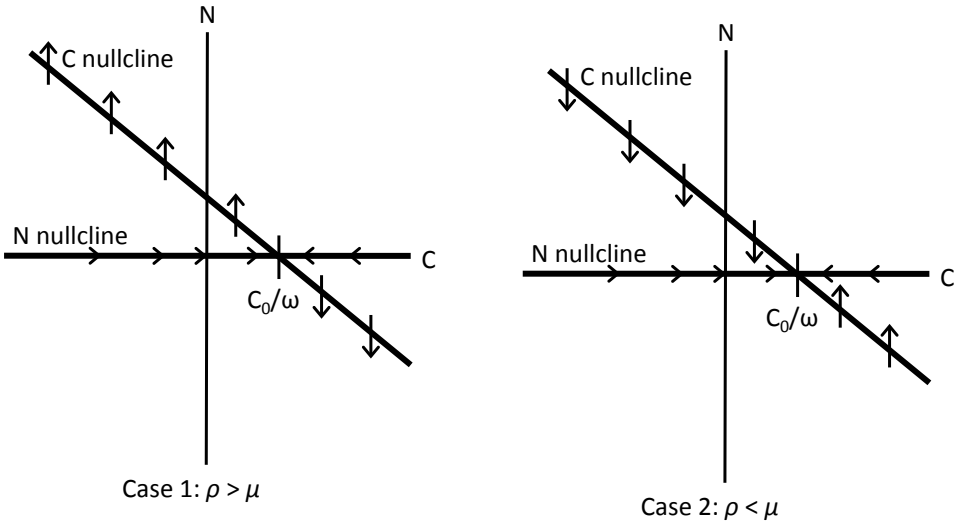

FIGURE 1. Nullclines and vector field direction for the system defined in question 2.

$dN/dt > 0$ if $N(t) > \frac{\mu C_0}{\rho(\omega+\mu)}$. $dN/dt < 0$ if $N(t) < \frac{\mu C_0}{\rho(\omega+\mu)}$.

To find the sign of dC/dt along the N nullcline, we plug in the equation for the N nullcline into the dC/dt equation.

$$\frac{dC}{dt} = C_0 - (\omega+\mu)C(t) = C_0 - (\omega+\mu)\frac{\rho N(t)}{\mu}. \tag{18}$$

$dC/dt > 0$ if $N(t) < \frac{\mu C_0}{\rho(\omega+\mu)}$. $dC/dt < 0$ if $N(t) > \frac{\mu C_0}{\rho(\omega+\mu)}$.

Note that $N(t) = \frac{\mu C_0}{\rho(\omega+\mu)}$ features prominently in determining the direction of the vector fields along both nullclines. Again, this is because this is the equilibrium $N(t)$ value, which you can see by solving both $dC/dt = 0$ and $dN/dt = 0$ simultaneously. Clearly, based on the nullclines, the equilibrium $\hat{C} = \frac{C_0}{\omega+\mu}$. Plugging that value into the $dN/dt = 0$ equation and solving for $\hat{N}$, you find that $\hat{N} = \frac{\mu C_0}{\rho(\omega+\mu)}$.

Fig. 2 suggests that the equilibrium is unstable, and that where the system will end up depends on where it starts. Focusing on the biologically relevant quadrant of the C-N plane, where both $N(t) > 0$ and $C(t) > 0$, the nullclines divide this quadrant into four regions. If the system starts above the N nullcline, it appears that the system dynamics will eventually settle on the eigenvector defined by N nullcline, with an exponentially growing tumor population and a fixed

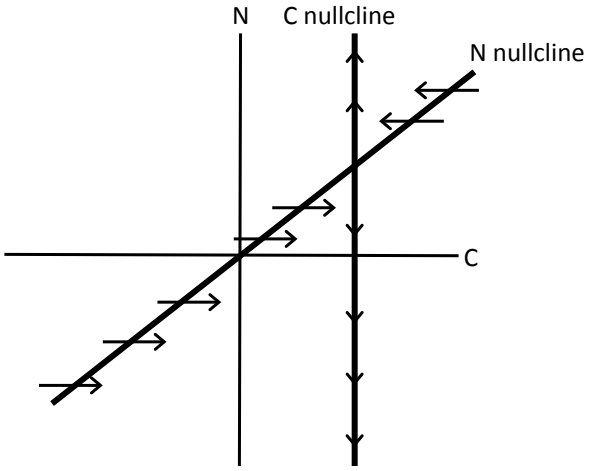

FIGURE 2. Nullclines and vector field direction for the second possible system suggested by the diagram in question 2.

amount of drug. If the system starts below the N nullcline, the dynamics will also settle on this eigenvector, but with no tumor cells (actually, with negative tumor cells, since there is nothing preventing tumor cell abundance from becoming negative).

(3) The SIR model can be simulated using the code below. Fig. 3 shows the results. You can see clear differences in the dynamics as w, the rate that immunity is lost, is varied. First, when immunity is lost rapidly, the system approaches equilibrium much more quickly. Both the period (time between cycle peaks) and amplitude (height of the oscillations) increase when the rate of loss of immunity is slowed down (or, to say it another way, period and amplitude increase as the duration of immunity increases). Increasing the duration of immunity also decreases the the equilibrium prevalence of infection, from around 1% prevelance when $w = 0.25$ to a prevalence that is very close to 0 when $w = 0.01$. The equilibrium number of susceptible hosts, however, is unchanged. Since the total population size is constant, the fact that the number of susceptibles are unchanged but the number of infecteds decrease as immune duration increases, it is clear that the equilibrium number of temporarily immune individuals ($\hat{R}$) must be increasing, a result that is intuitive.

```
library(deSolve)

sirs_model <- function(t, state, parameters) {
```

```
    ## assign parameter values to parameter variables the function 'unname()'
    ## just removes the name of the parameter - this is unnecessary, it just
    ## cleans things up a bit
    m <- unname(parameters["m"])
    B <- unname(parameters["B"])
    w <- unname(parameters["w"])
    g <- unname(parameters["g"])  ## add recovery rate as a parameter

    ## assign state variables to names
    S <- unname(state["S"])
    I <- unname(state["I"])
    R <- unname(state["R"])  ## add in the new state variable

    ## compute the rates of change
    dSdt <- m - B * S * I - m * S + w * R
    dIdt <- B * S * I - (m + g) * I
    dRdt <- g * I - m * R - w * R  ## and keep track of its dynamics

    ## return as a list object, with the first element of the list being the
    ## derivatives. The order of derivatives must be the same as the order in the
    ## initial condition vector!
    return(list(c(dSdt, dIdt, dRdt)))
}
## The three different parameter sets are:
pars1 = c(m = 1/30, g = 6, B = 8, w = 0.01)
pars2 = c(m = 1/30, g = 6, B = 8, w = 0.05)
pars3 = c(m = 1/30, g = 6, B = 8, w = 0.25)
## The initial conditions are:
y0 = c(S = 0.99, I = 0.01, R = 0)
## Simulate for each parameter set
out1 <- ode(y0, seq(0, 100, 0.1), sirs_model, pars1)
out2 <- ode(y0, seq(0, 100, 0.1), sirs_model, pars2)
out3 <- ode(y0, seq(0, 100, 0.1), sirs_model, pars3)

## Plot the results, first for S, and then for I (the call to 'par' sets the
## plot window up so I can create both plots at the same time - see ?par to
## learn more)
par(mfrow = c(1, 2), mar = c(5, 5, 0, 0), oma = c(0, 0, 1, 1))
plot(out1[, c("time", "S")], type = "l", lwd = 2, lty = 1, xlab = "Time", ylab = "Number of susceptible ho
points(out2[, c("time", "S")], type = "l", lwd = 2, lty = 2)
points(out3[, c("time", "S")], type = "l", lwd = 2, lty = 3)
legend(x = "topright", c("w=0.01", "w=0.05", "w=0.25"), lty = c(1, 2, 3))

plot(out1[, c("time", "I")], type = "l", lwd = 2, lty = 1, xlab = "Time", ylab = "Number of infected hosts
points(out2[, c("time", "I")], type = "l", lwd = 2, lty = 2)
points(out3[, c("time", "I")], type = "l", lwd = 2, lty = 3)
```

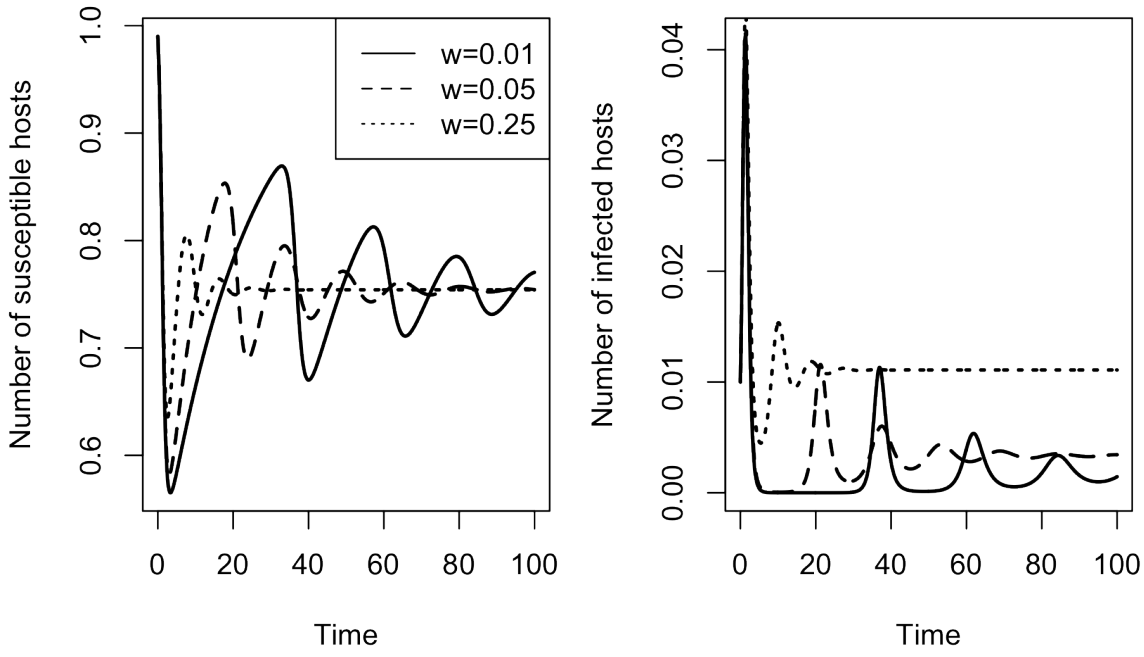

FIGURE 3. Dynamics of susceptible and infected hosts as the rate that immunity is lost increases.