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# Mathematical modelling of the long-term dynamics of Cyprinid herpes virus 3

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## Abstract

The use of Cyprinid herpes virus 3 (CyHV-3), as a control measure for common carp in Australian rivers, is highly controversial. Little is known about the long-term dynamics of the virus or the development of innate resistance in wild carp populations. In this report we investigate competing assumptions about progression of individual carp through various immunological states when exposed to CyHV-3. In particular, whether exposure for some fish leads to the development of innate resistance (progression into a resistant class), and whether carp enter a latent or chronically infected state whereby reactivation of the virus can be triggered by stress and lead to onward transmission to other susceptible carp. The important findings of the study were that the assumptions of reactivation and resistance can drastically change the dynamics of the virus after the first mass die-off event however do not appear to have a significant effect on the initial epidemic. Three structurally different models were tested and determined to have the potential to replicate observations seen in the Northern Hemisphere. In conclusion, it is not possible at present to confidently predict the long-term consequences of releasing CyHV-3 in Australia.


# Introduction

Common carp are considered an invasive pest in Australia, as they decrease the water quality of our rivers and adversely affect native fish populations. The deliberate release of Cyprinid herpes virus 3 (CyHV-3) has been suggested as a control measure for carp and was dubbed ‘Carpageddon’ by the Australian government (‘Carpageddon: Australia plans…’, 2016). CyHV-3 is a strain of herpes which infects common carp and causes mortality for the majority of infected fish. Its proposed use as a control measure is highly controversial as concerns have been raised about its efficacy and potential to further decrease water quality. By studying the virus dynamics over times frames of the order of 30 years, we provide insight into the concerns around virus efficacy.

Studies of previous outbreaks in North America (Thresher et al, 2018) suggest low efficacy, as no subsequent mortality events were observed after the initial mass die-off

events. These studies imply that the virus goes extinct after the first outbreak or that wild carp populations quickly become resistant. However, consideration must be given to the idea of an observation threshold, that is the idea that the impact of the virus is in fact ongoing but the abundance of infected carp is low enough that die offs are not observed.

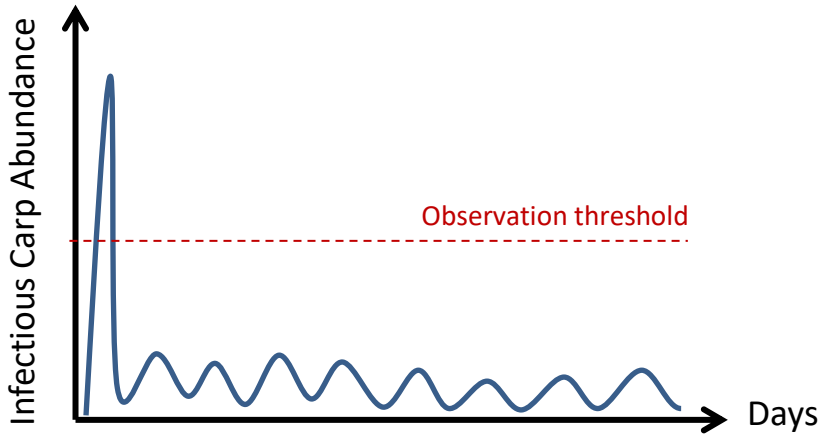


**Figure 1**: Infection abundance (blue) in relation to the observation threshold (red)

## Statement of authorship

Under the direction of my academic supervisor I developed the set of mathematical models for the spread of CyHV-3 presented in this report. I wrote MATLAB code that produced and visualised numerical solutions to the various differential equation models. I explored parts of the parameter space to help find reasonable parameter values, and I contributed to the interpretation of the results, made the figures and tables and drafted the report.

# Assumptions

## Base model

An initial model was constructed with underlying assumptions supported by observations of outbreaks of CyHV-3 in wild carp populations and experimental work on the virus (Thresher et al, 2018). We have five disease states, starting with all new individuals appearing in the susceptible class. Significant physical contact between a susceptible

fish and an infectious fish results in a probability of the susceptible fish becoming exposed; that is transmission of the virus occurs when susceptible fish have physical contact with an infectious class (see Figure 2; fish in class I or A). Once in the exposed class, individual carp go through an incubation period before becoming infected and infectious. In the based model 20% of infected fish recover, while the other 80% enter an ailing state leading to death.

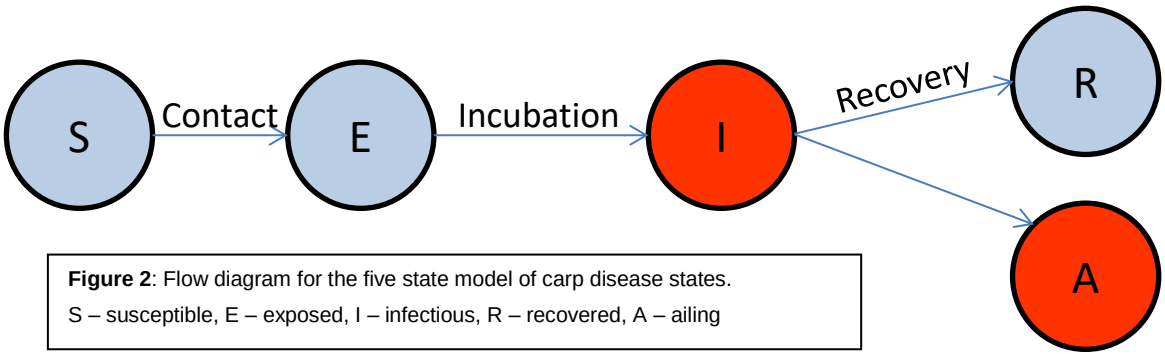


**Figure 2**: Flow diagram for the five state model of carp disease states.
S – susceptible, E – exposed, I – infectious, R – recovered, A – ailing

## Water Temperature Dependence

Since carp are a cold-blooded host, the activity of the virus depends on the temperature of the surrounding environment, i.e. the water temperature. Observations from field experiments (Omori & Adams, 2011) concluded that the virus actively replicates only when water temperatures are within a fixed temperature range. Propagation of the virus and progression of individuals infected with the virus therefore only occurs when temperatures are permissive and the effect of this is that outbreaks tend to occur in Spring and not at other times of the year.

For simplicity, all dependencies for water temperature in this report are modeled with a simple switch function, i.e. a combination of Heaviside step functions. When the water temperature is between 16 and 28°C, transmission and transition terms are switched on and at a fixed rate, otherwise their values are zero.

Equation (1) models the water temperature of the river and equation (2) is the simple switch for the transmission term, with $\beta_{permissive}$ being the value chosen for the transmission rate of the virus when in the active temperature range.

$$T(t) = a + b\cos\left(\frac{2\pi t}{365}\right) \qquad (1)$$

$$\beta(T) = \beta_{permissive}(H(T-16) - H(T-28)) \qquad (2)$$

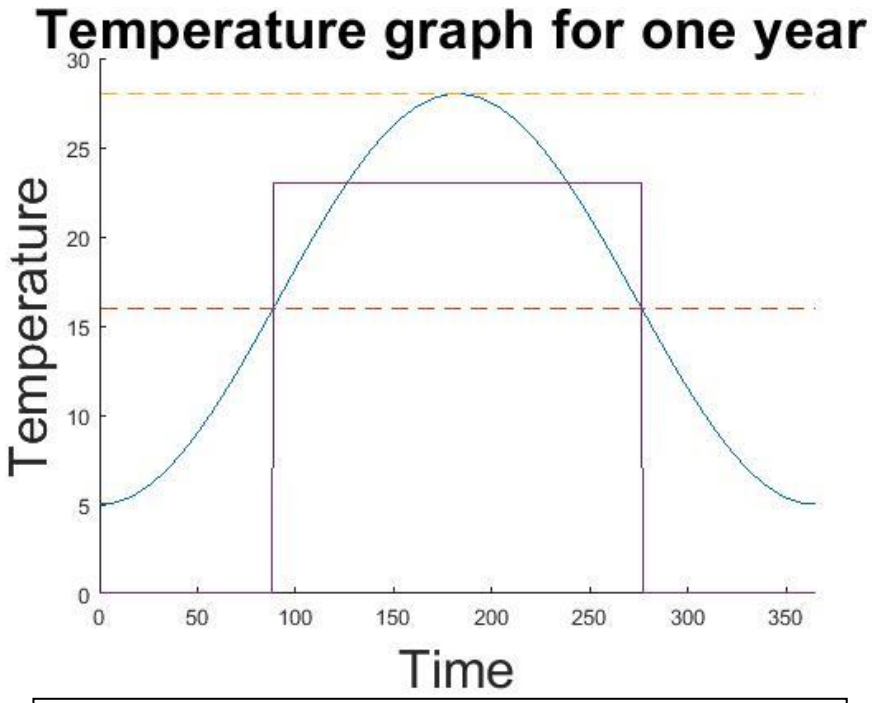


**Figure 3**: Water temperature (blue) over a one year timespan. The active temperatures limits of the virus (dotted yellow and dotted orange line) are shown and a representative step function (purple) is featured to depict the time of year the virus is active.

## Density Dependence

Assumptions about the density dependence of transmission and demography were tested. In the case of CyHV-3 whether transmission of the virus is density dependent or independent is difficult to determine since so little is known about the behaviour and contact rates of wild carp. Usually researchers will use density independent transmission for sexually transmitted diseases like AIDS and density dependent transmission for diseases like the flu. However, herpes viruses can be transmitted through a combination of both sexual and physical contacts, so neither assumption can be easily ruled out.

*Density dependent transmission* means that the more fish the higher the rate of contact will be, so the virus will propagate more quickly amongst high density carp populations. On the other hand, *density independent transmission* refers to assuming

a fixed rate of contact and therefore the propagation of the virus will occur at the same rate, no matter how many fish there are.

For the modelling of births and deaths in a population, *density independent demography* means that new individuals will appear in the population at a fixed rate regardless of the current size of the population. *Density dependent demography* means that the number of births and deaths depends on the density of carp in the population, i.e. there is a per capita birth rate and mortality rate.

Translating the flow diagram in Figure 2 into a set of differential equations with the mentioned assumptions above gives (3) and (4).

$$\frac{dS}{dt} = B - \beta(T)S(I + A)/N - \mu S$$
$$\frac{dE}{dt} = \beta(T)S(I + A/N) - \gamma(T)E - \mu E$$
$$\frac{dI}{dt} = \gamma(T)E - \eta(T)I - \mu I$$
$$\frac{dR}{dt} = f\eta(T)I - \mu R$$
$$\frac{dA}{dt} = (1 - f)\eta(T)I - \xi A - \mu A \qquad (3)$$

The system of equations given by (3) represents density independence for both demography and transmission. *B* is the fixed birth rate and μ is the mortality. *β* represents the transmission rate of the virus and is water temperature dependent. *γ* represents the incubation period, that is *1/γ* is the number of days spent in the exposed state. Similarly, *η* denotes the rate at which an infectious fish either recovers or becomes ailing, so that *1/η* is the number of days a carp is infectious. Both are also water temperature dependent. f determines the proportion of fish that will recover and *(1-f)* is the proportion that will become ailing. *ξ* represents the higher mortality rate for ailing fish.

The system of differential equations given by (4) represent density dependent demography and transmission. Now we replace *B* with $b_1$ denoting the per capita birth rate. $\mu_0$ is the underlying death rate and $\mu_1$ is the per capita death rate.

Four combinations of demography and transmission were tested. Differential equations are not shown for density dependent demography with density independent transmission and vice versa, however were also tested.

$$\frac{dS}{dt} = b_1 N - \beta(T)S(I+A) - \mu_1 NS - \mu_0 S$$
$$\frac{dE}{dt} = \beta(T)S(I+A) - \gamma(T)E - \mu_1 NE - \mu_0 E$$
$$\frac{dI}{dt} = \gamma(T)E - \eta(T)I - \mu_1 NI - \mu_0 I$$
$$\frac{dR}{dt} = f\eta(T)I - \mu_1 NR - \mu_0 R$$
$$\frac{dA}{dt} = (1-f)\eta(T)I - \xi A - \mu_1 NA - \mu_0 A \quad (4)$$

## Reactivation – latently infected carp

Herpes virus is known to persist within a host indefinitely. This assumption was modeled as a sixth state added to the flow diagram representing latently infected fish. When the water temperature is within the permissive range, a proportion of recovered fish can become infected through reactivation of the virus and either recover or become ailing. Since they are now infectious again, this class of latently infected carp can contribute to the transmission term, however latently infected fish are distinguishable from carp experiencing a first infection by their higher recovery rate.

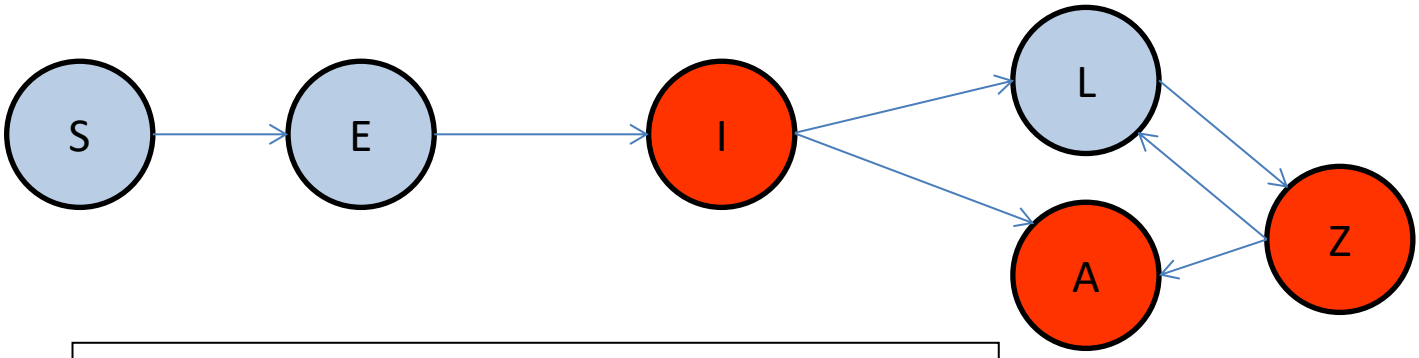


**Figure 4**: Flow diagram for the reactivation model of CyHV-3 in carp.
S – susceptible, E – exposed, I – infectious, L – latent, A – ailing, Z - latently infected

The system of equations given by (5) show the addition of the latently infected state, Z. Now, we have an additional parameter $\sigma$, representing the rate at which the infection in latent fish reactivates. $\sigma$ is water temperature dependent so $1/\sigma$ is the average number of water temperature permissive days that carp spend in the latent/chronic state before becoming infected again. Due to the higher survival rate of secondary infections, we also have an additional recovery rate term, $\alpha$, representing the proportion of latently infected carp that recover.

$$\frac{dS}{dt} = b_1 N - \beta(T)S(I+A) - \mu_0 S - \mu_1 NS$$
$$\frac{dE}{dt} = \beta(T)S(I+A) - \gamma(T)E - \mu_0 E - \mu_1 NE$$
$$\frac{dI}{dt} = \gamma(T)E - \eta(T)I - \mu_0 I - \mu_1 NI$$
$$\frac{dL}{dt} = \eta(T)(fI + \alpha Z) - \sigma(T)L - \mu_0 R - \mu_1 NR$$
$$\frac{dA}{dt} = \eta(T)\left((1-f)I + (1-\alpha)Z\right) - \xi A - \mu_0 A - \mu_1 NA$$
$$\frac{dZ}{dt} = \sigma(T)L - \eta(T)Z - \mu_0 Z - \mu_1 ZN \qquad (5)$$

## Resistant Carp

In many disease systems, the host and virus will evolve so that the virus is less harmful. One way this can occur is through the existence of a resistance class. There is very little information currently about the assumption of resistance to CyHV-3. Different scenarios of assumptions regarding the development of resistance are modeled in this paper as a preliminary investigation into the dynamics of resistant carp. Three approaches to the development of resistance were considered; a small proportion of exposed fish become resistant (perhaps as a result of past exposure to a similar virus), exposure during suboptimal temperatures leading to the development of resistance (inactive virus exposure similar to a vaccine), and heritable resistance.

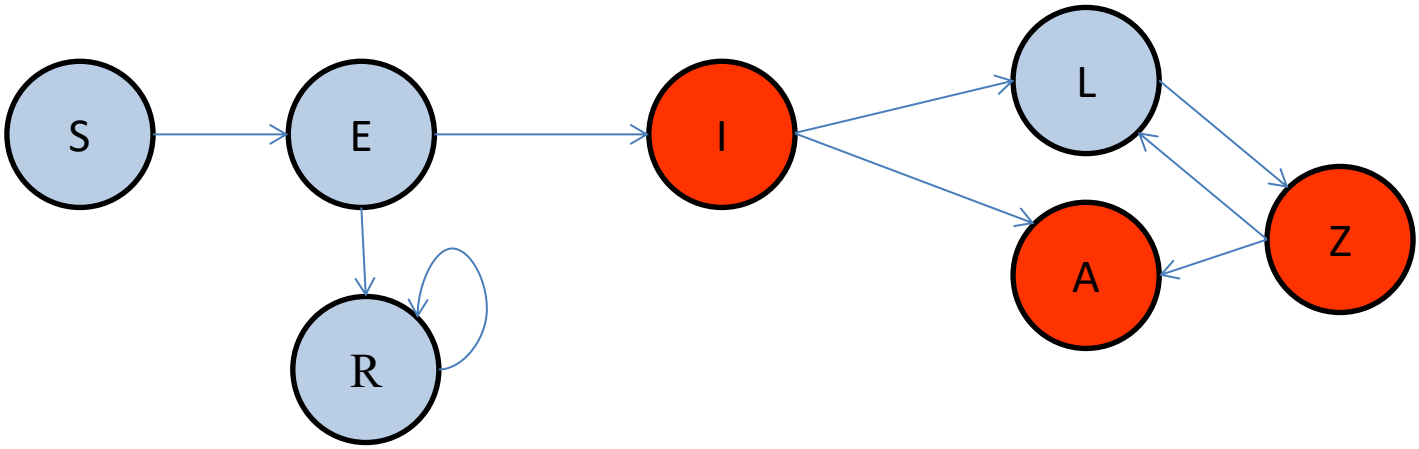


**Figure 5**: Flow diagram for the development of resistance.
S – susceptible, E – exposed, I – infectious, L – latent, A – ailing, Z - latently infected, R - resistant

$$\frac{dS}{dt} = b_1(N-R) - \beta S(I+A+Z) - \mu_0 S - \mu_1 SN$$
$$\frac{dE}{dt} = \beta S(I+A+Z) - \gamma E - \mu_0 E - \mu_1 EN$$
$$\frac{dI}{dt} = (1-\varphi)\gamma E - \eta I - \mu_0 I - \mu_1 IN$$
$$\frac{dL}{dt} = \eta(fI+\alpha Z) - \sigma L - \mu_0 L - \mu_1 LN$$
$$\frac{dA}{dt} = \eta\left((1-f)I + (1-\alpha)Z\right) - \xi A - \mu_0 A - \mu_1 AN$$
$$\frac{dZ}{dt} = \sigma L - \eta Z - \mu_0 Z - \mu_1 ZN$$
$$\frac{dR}{dt} = b_1 R + \varphi\gamma E - \mu_0 R - \mu_1 RN \quad (6)$$

$$\frac{dS}{dt} = b_1 N - \beta S(I+A+Z) - \mu_0 S - \mu_1 SN$$
$$\frac{dE}{dt} = \beta_{permissive} S(I+A+Z) - \gamma E - \mu_0 E - \mu_1 EN$$
$$\frac{dI}{dt} = \gamma E - \eta I - \mu_0 I - \mu_1 IN$$
$$\frac{dL}{dt} = \eta(fI+\alpha Z) - \sigma L - \mu_0 L - \mu_1 LN$$
$$\frac{dA}{dt} = \eta\left((1-f)I + (1-\alpha)Z\right) - \xi A - \mu_0 A - \mu_1 AN$$
$$\frac{dZ}{dt} = \sigma L - \eta Z - \mu_0 Z - \mu_1 ZN$$
$$\frac{dR}{dt} = \beta_{suboptimal} S(I+A+Z) - \mu_0 R - \mu_1 RN \quad (7)$$

The system of equations given by (6) represents heritable resistance and the development of resistance as a result of a small proportion of exposed becoming resistant. Comparatively, the system of equations given by (7) represents the development of resistance through suboptimal water temperatures and an absence of heritable resistance. Systems (6) with no heritable resistance and (7) with the addition of heritable resistance were also tested.

| Parameter | Meaning | Value | Units | Reference |
|---|---|---|---|---|
| ***B*** | Fixed birth rate | $\mu * 500000$ | /day | - |
| ***b1*** | Per capita birth rate | 0.001 | /day | - |
| ***$\mu_0$*** | Fixed death rates | $\frac{1}{15*365}$ | /day | - |
| ***$\mu_1$*** | Per capita death rate | $\frac{-\mu_0+b_1}{500000}$ | /day | - |
| ***β*** | Transmission rate | Density independent 0.88 Density dependent 0.00000176 | /day | 3 See appx.1 |
| ***1/γ*** | Incubation period | $\left(\frac{1}{\gamma_p}\right) * (\mathrm{H}(\mathrm{T}-16) - \mathrm{H}(\mathrm{T}-28))$ | Days | See appx.2 |

| | | | | |
|---|---|---|---|---|
| ***1/η*** | Infectious period | $\frac{4}{\gamma}$ | Days | - |
| ***f*** | Proportion of fish that recover | 0.2 | - | - |
| ***ξ*** | Virus induced mortality rate | 0.2 | /day | 3 |
| ***α*** | Proportion of fish with reactivation that recover | 0.95 | - | - |
| ***σ*** | Rate of reactivation | 0.002 | /day | - |
| ***φ*** | Fraction that develop resistance on exposure | 0.2 | - | - |
| ***a*** | Average water temperature | 16.5 | °C | 3 |
| ***b*** | Amplitude of water temperature fluctuation | 11.5 | °C | 3 |
| ***T(t)*** | Temperature equation | $a - bcos(\frac{2\pi t}{365})$ | °C | 3 |

**Table 1**: functions and parameter values used through this paper. Rates are expressed per day.

# Results

Comparing the five state models, different combinations of density dependence did not appear to have a significant effect on the dynamics of the virus. For the parameter values listed in table 1, the graphs in figure 6 were produced.

All four combinations of the assumptions had the potential to persist when the demographic turnover was high enough. By increasing the birth rate parameters, we can see dynamics with annual outbreaks and persistence of the virus. However, when the turnover is too high, the dynamics predict the virus will die out again. Figure 7 shows the values of the per capita death rate and birth rate for which the virus persists in the model with density dependent transmission and demography.

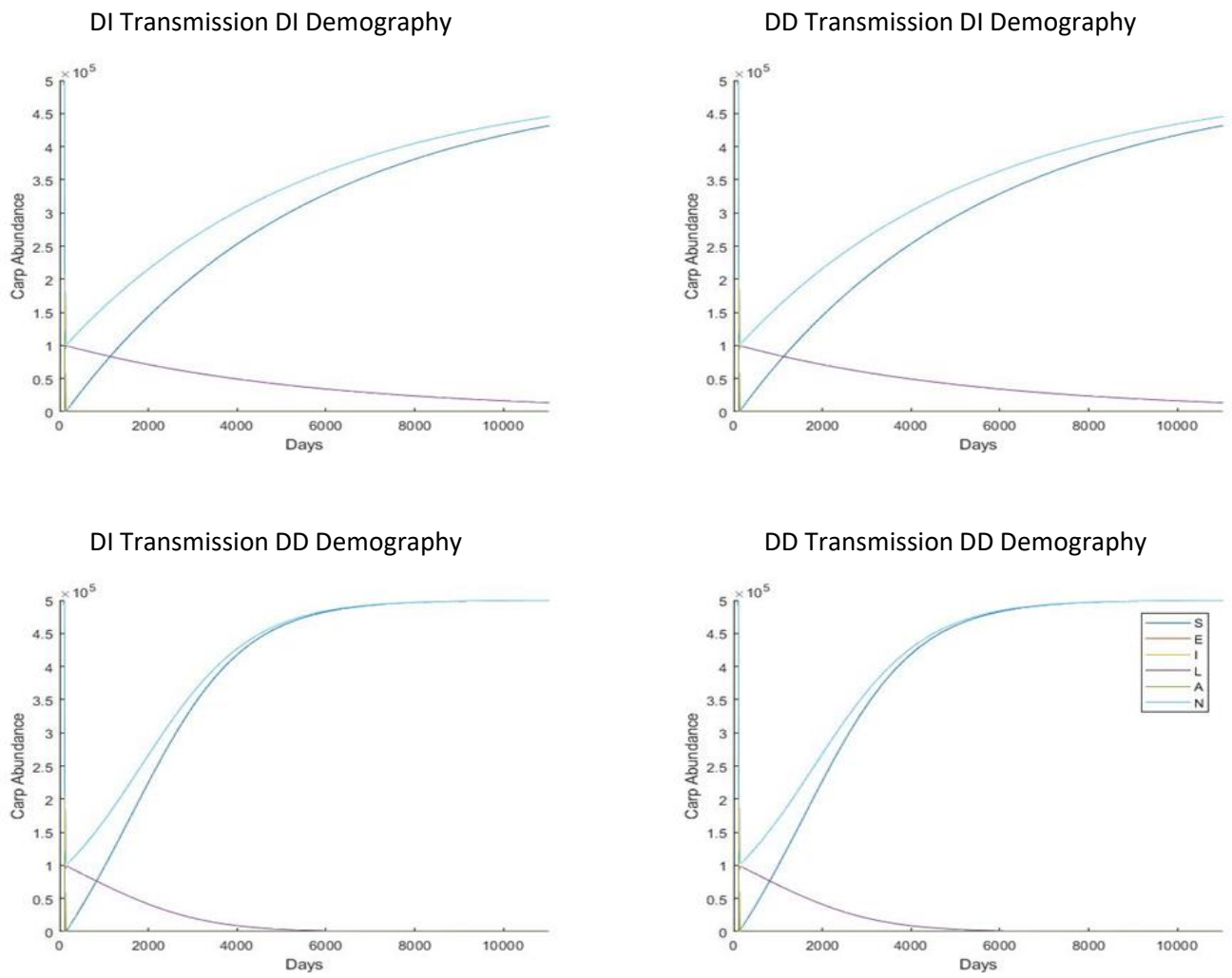


**Figure 6**: Disease dynamics over 30 years for density dependence/density independence in transmission and demography

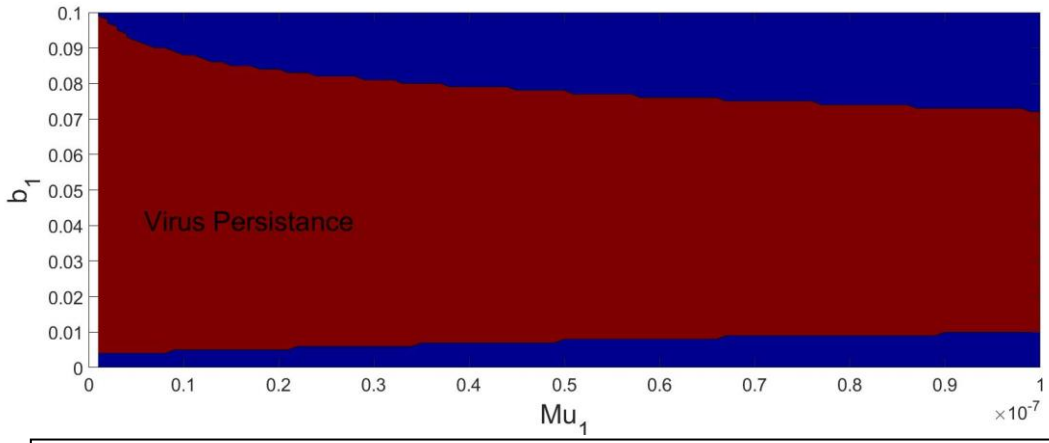


**Figure 7**: Persistence plot for varying values of $b_1$ and $\mu_1$ in the SEILA model with density dependent demography and transmission. Red is for persistence of the virus, i.e. after 30 years states E, I, A are not empty and blue means that the virus has died out, i.e. E, I and A abundances are all 0.

The addition of reactivation in latently infected fish favoured persistence of the virus for the parameter values in table 1. Infection abundance was extremely small in comparison to the total population abundance; however, the population size was significantly suppressed to less than 30% of the carrying capacity, which is 500000 carp.

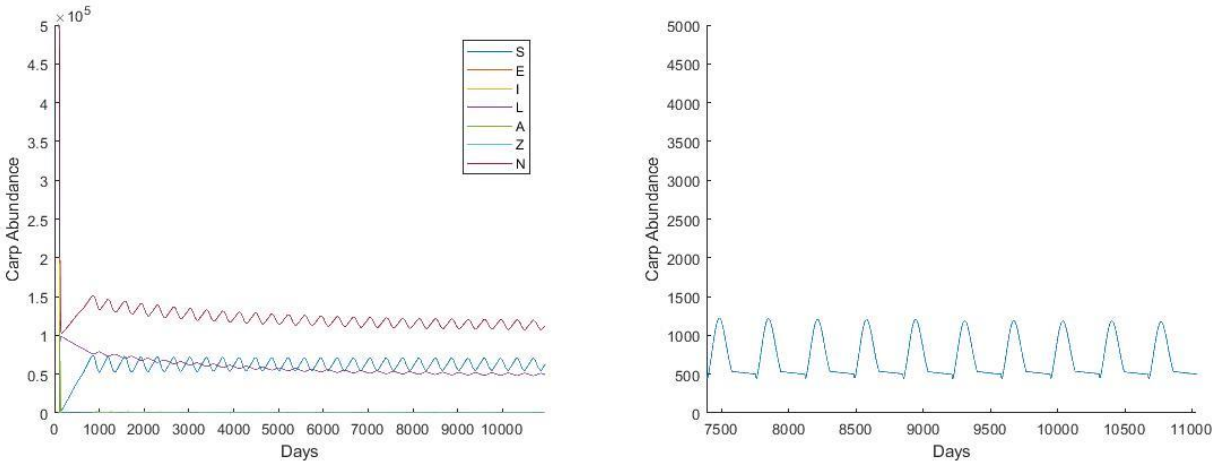


**Figure 8**: Left: State dynamics of SEILAZ model with density dependence in demography and transmission. N is the total population abundance of carp. Right: Infected state dynamics after 20 years.

Where there was an absence of heritable resistance in the models, the virus did not die out in the 30-year timespan. However, resistance through suboptimal water temperature exposure favoured the survival of carp more than resistance by a small proportion of exposed fish.

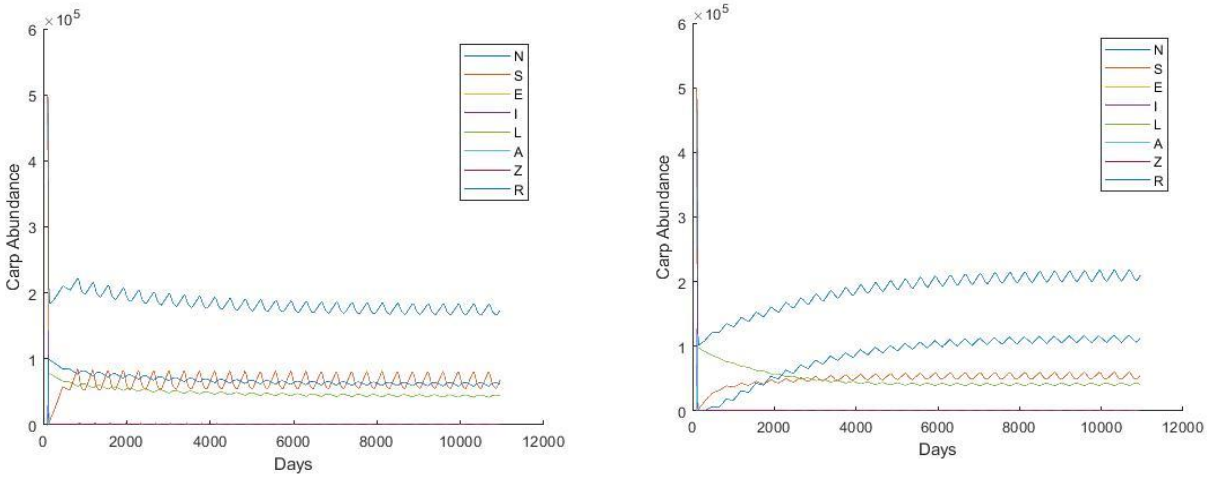


**Figure 9**: Left: Resistance for a small proportion of exposed and no heritable resistance. Right: Resistance as a result of being exposed during suboptimal temperatures. Both graphs are for the models with density dependent demography and transmission.

The addition of heritable resistance to both of these models, resulted in the virus dying out after a several small outbreaks for the parameter values in table 1.

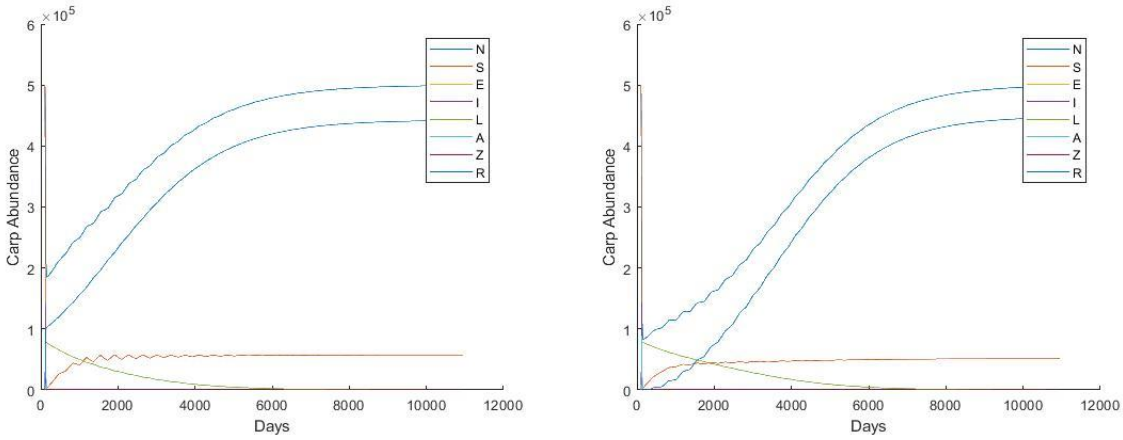


**Figure 10**: Resistant model dynamics with heritable resistance. Left: Resistance for a small proportion of exposed Right: Resistance as a result of being exposed during suboptimal temperatures.
Both models have density dependent demography and transmission.

# Discussion

Without heritable resistance, the effect of resistance in the population was surprisingly minimal. A small proportion of exposed fish becoming resistant had minimal effect on the dynamics of the virus. This seems to be a result of the simplicity in modelling this type of resistance. Since there is only one way to become resistant in this case, the number of carp in the resistant class is directly proportional to the number of fish that are exposed to the virus. Therefore, the maximum number of fish that can be resistant is 20% of the total number of exposed fish.

The dynamics for resistance through suboptimal water temperature exposure appears to be slightly more effective. Exposure is less likely to occur during suboptimal temperatures since the abundance of infectious carp peaks when the water temperature is permissive. The abundance of infectious carp in suboptimal temperatures is therefore at a minimum, so the impacts of resistance on the dynamics are also minimal. However, in comparison to the prior resistance assumption, there is no limiting factor for resistance. All susceptible carp that are exposed during

suboptimal temperatures become resistant, suggesting that eventually all carp become resistant if the virus is not eradicated, just not in the modeled 30 year timespan.

Unsurprisingly, the addition of heritable resistance resulted in an eradication of the virus for both methods of developing resistance. Natural selection means that resistant fish are strongly favoured because they avoid an important source of mortality. Also, since resistant carp give birth to resistant carp, resistance abundance grows exponentially and the large proportion of resistant fish creates a protective effect for the entire population of carp. Now we have herd immunity and susceptible carp escape infection as a result.

Each model shares a key attribute in the dynamics of CyHV-3; that is the initial mass-die off event created by the first outbreak of CyHv-3 in the population. Despite the persistence of the virus in some models containing reactivation, none of the models predict subsequent mass die-off events. These dynamics suggest that for the models where the virus persists, it is probable that the infection abundance escapes the observation threshold. Therefore, all three models have the potential to match the observed dynamics of CyHV-3 in the northern hemisphere.

In conclusion, it is not possible to confidently predict the dynamics of cyprinid herpes virus 3 in wild carp in the long-term. Improvements need to be made with more information on the biology of carp and the characteristics of cyprinid herpes virus 3. For example the true parameter values of the density dependent birth rate, the transmission term and the rate of reactivation. Most importantly, more research is needed on the development of resistance, without which we cannot determine which model is the most biologically accurate.

# Acknowledgements

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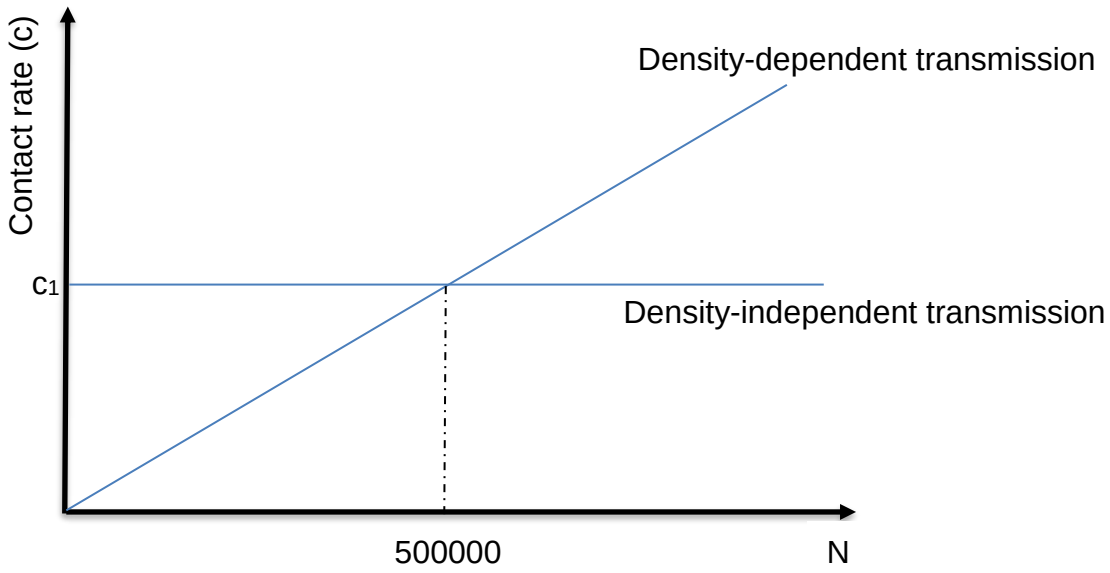
# Appendices

## Appendix 1




$slope = k = \frac{c_1}{500000}$

**Density-dependent:**

Force of infection, $\lambda$, is calculated as:

$\lambda = -cvp$

*c* is the contact rate, *v* is the probability that the virus is transmitted given contact and *p* is the probability that the contact is with an infected fish.

The contact rate is proportional to the population size, *N*, for density dependent transmission.

$c \propto N,\ p = \frac{I}{N},\ => \lambda = -kNv\frac{I}{N}$

$\lambda = -kvI = -\beta I$

$\therefore\ \beta_1 = kv$

**Density-independent:**

$\lambda = -cvp$

$\lambda = -cv\frac{I}{N}$

$\lambda = -\beta\frac{I}{N}$

$\therefore\ \beta_2 = cv$

$\beta_2 = 0.88$ (Omori & Adams 2011)

$v = 0.88/c_1$

$\beta_1 = \frac{c_1}{500000}\frac{0.88}{c_1} = \frac{0.88}{500000}$

## Appendix 2

$\gamma(T(t)) = w_3 \exp\left(-\left(\frac{T}{w_2}\right)^{w_1}\right) T^{w_1-1} w_1 w_2^{-w_1}$

$w_1 = 8.11\ w_2 = 25.15\ w_3 = 9.75$ (Omori & Adams, 2011)

$$\gamma_p = \frac{\int w_3 \exp\left(-\left(\frac{T}{w_2}\right)^{w_1}\right) T^{w_1-1} w_1 w_2^{-w_1}}{28-16}$$

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