Modelling within host infection dynamics - Tutorial to Lecture 8

Accompanying R codes: WoodsModels.R (Section 1), BasicInfectionModel.R (Section 3.2) and InfectionModelWithIR (Section 3.3 & 3.4).

Estimated time: 1.5 hours

Outline:

In this tutorial you will

- Learn to code and analyse different types of within host infection models.
- Explore properties of the Woods model as an empirical model of virus load profile over time
- Develop hypotheses for process based models
- Explore the behaviour of deterministic mechanistic models for within host virus dynamics

1. The Woods functions as mathematical models for PRRS viremia profiles

1. 1 Uni-modal Woods function

The unimodal Woods function is defined as

$$f(t) = at^b exp(-ct)$$

where t refers to time post infection and a, b, c are function parameters. The Woods function has been widely used for modelling lactation curves in dairy cows. In order determine whether the function is also suitable for modelling virus load profiles in infected individuals, we need to explore the properties of the function. In particular we want to determine what kind of profiles can be generated with this function, and provide a biological interpretation of the function parameters.

Use the R-script *WoodsModels.R* to answer the following questions:

1a: What role does each of the parameters have for determining the shape of the profile? Which parameters determine the time of peak virus load and the peak virus load itself? Tip: to test the effect of e.g. parameter a, generate plots with different values for a, keeping b and c fixed. This can be achieved by typing: WoodsFunction(a = c(1, 5, 10,15), b = 0.8, c = 0.1, time = 50)

1b: Derive an analytical expression for the time of peak virus load and for the actual peak virus load (in log units) (Tip: remember that the derivative of a function is zero at its maximum). **What are their values for a = 3.8, b=0.5 and c = 0.08? Check your analytical solution by plotting the corresponding curve in R. How long does it take before the virus load is below the detection level of 1 log unit?**

1c: What do all curves corresponding to different parameter values (a, b, c>0) have in common? Is the Woods function a realistic description of virus load at the very early and late stages of infection?

1.2 Extended Woods model

Experimental data show that virus load profiles of some pigs exhibit a bi-modal behaviour (2 peaks). This can be represented by the extended Woods function, given by the equation

$$V(t) = a_1 t^{b_1} e^{-c_1 t} + max(0, a_2(t - t_0)^{b_2} e^{-c_2(t-t_0)}$$

Call the *ExtendedWoodsFunction* in the R-script WoodsModels.R to generate plots and values for the parameters (a1, b1, c1, a2, b2, c2, t0) for 3 different virus load profiles that differ in the characteristics below:

i. **Profile 1: The first peak occurs within the first week of infection and the second peak occurs within 30-40 days post infection. The first phase of infection (i.e. until onset of rebound) is much longer than the rebound phase.**
ii. **Profile 2: The rebound peak is much higher than the first peak**
iii. **Profile 3: The first and rebound peak have the same value (rounded to the first decimal)**

1.3 Optional Question:

Fitting the extended Woods model to data from 1000 pigs provided for each pig estimates for the parameter values a1, b1, c1, t0, a2, b2, c2. When calculating correlations between the different parameter values, the following was found:

a) A strong positive correlation between the parameter values for b1 and c1
b) A weak correlation between a1 and a2
c) A strong negative correlation between c1 and c2
d) A strong positive correlation between t0 and c1

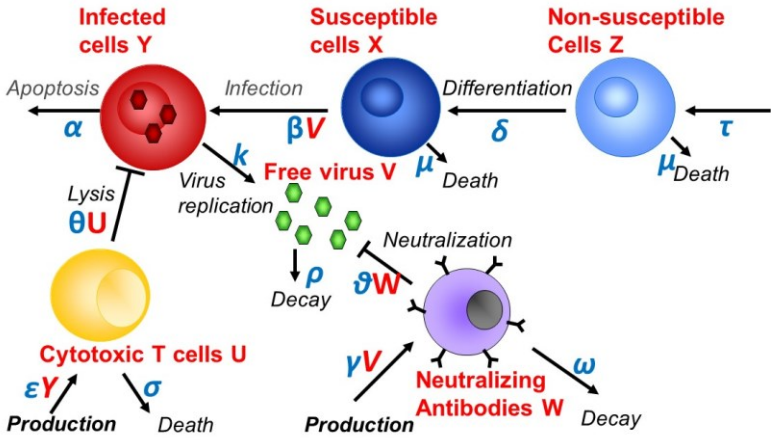
Describe in your own words what these correlations imply in terms of common shape characteristics.

2. Formulating hypotheses underlying the 'rebound' phenomenon – group discussion

The uni-and bi-modal Woods model was fit to virus load measures of 1000 pigs, all of which had been artificially infected with the same virus challenge dose at the same time before placing them into pens of 20 pigs per pen. The model fit statistics identified almost ¼ of the pigs as 'rebounders' (i.e. viremia curves had 2 peaks rather than one). **Can you think of potential reasons that could lead to rebound and would explain that only a proportion of pigs experienced rebound?**

3. Exploring the mechanistic within host infection model:

The figure below illustrates a simple model for virus infections (see also lecture notes):



Mathematically, the model can be represented by a system of ordinary differential equations (see lecture and R code)

3.1. Understanding the model

a. How many variables and how many parameters does the above model have?

b. How many predator-prey types interactions are embedded in this model?

c. What are the units of the parameters α and μ and which of the two parameters would you expect to have a greater value? (Justify)

d. What can be said about the value of the parameters γ,ϑ,ω if a host does not elicit a neutralizing antibody response?

3.2 The basic infection model without immune response

Open the R file BasicInfectionModel.R. It codes the above model assuming that target cells get fully replenished (i.e. total cell number is constant) and that a host does not produce any Tcell or neutralizing antibody response. Before we start exploring the behaviour of this model **take some time to familiarize yourself with the code.** Note, you don't need to understand what each exact line of the code means, but read the comments to get an idea what the code does. **Run this model with the default parameters first** by copying the entire code into the R command window. Then follow the instructions at the bottom of the R-code to answer the questions below.

a) What kind of shapes of virus load profiles can be generated with this model?

b) The basic reproductive ratio R_0 of the model above is

$$R_0 = \frac{\tau\beta k\delta}{\mu\alpha\rho(\delta+\mu)}$$

Use the simulations to verify that the infection persists if $R_0>1$ and dies out if $R_0<1$.

c) Use the simulations to verify that $R_0 > 1$ is equivalent to virus load converging to the steady state $V^* = \frac{\delta\tau k}{(\delta+\mu)\alpha\varphi} - \frac{\mu}{\beta} > 0$.

3.3 The full model including immune response

Open the R file InfectionModelWithIR.R. It codes the above model assuming that target cells get fully replenished (i.e. total cell number is constant) and that a host may elicit a T cell or neutralizing antibody response, or both. As before **take some time to familiarize yourself with the code** before using it to answer the following questions.

a) **What kind of virus load profile can you generate with this model? Can you find model parameter values corresponding to the five different equilibrium states mentioned in the lecture? What do the corresponding profile shapes look like?**
b) **Are both T-cell and neutralizing antibody response needed to clear the infection? Do they work independently or what can be said about their relationship?**

3.4. Optional section

Can the above mechanistic model generate virus load rebound? If yes, what does this tell us about potential mechanisms for generating rebound? Look back at your answers to section 2. How would you need to expand the current mechanistic model to implement the proposed mechanisms. Draw a flow chart of this model.