Modelling within host infection dynamics

Lecture 8

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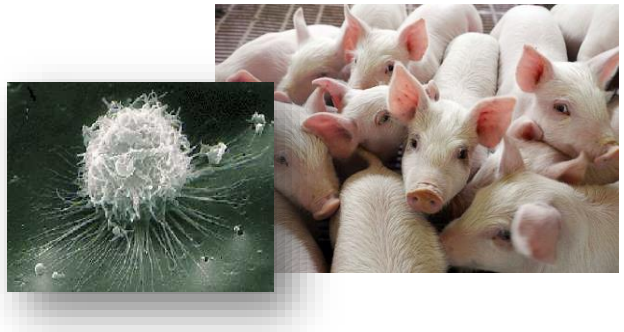
Purpose and Overview



We will use PRRS virus infections in pigs as a case study to discover the strengths & weaknesses, and synergy of empirical vs mechanistic models

1. Empirical modelling approach
   - Provide a mathematical description of virus load profile characteristics
2. Mechanistic modelling approach
   - Determine underlying mechanisms for PRRS virus load profiles

We use similar mathematical modelling tools as for epidemic models (universal language of mathematics), but different biological understanding (immunology vs. epidemiology)

Recap from Lecture 1: Empirical vs mechanistic models

We will use both types of approaches to model PRRS virus infections

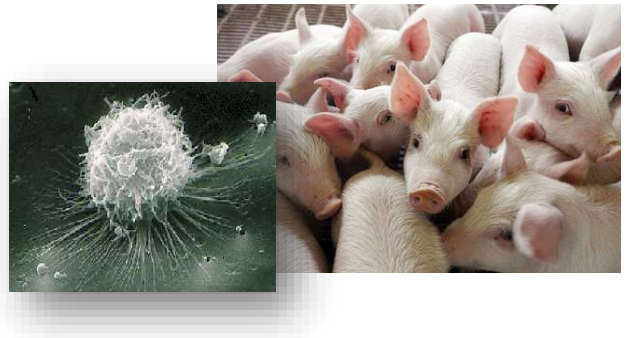
Empirical Models (also called Statistical Models):

- Data driven modelling approach
- Starting point: data obtained from empirical studies
- Aim: to determine patterns & relationships between data (model variables)
- Require no prior knowledge of the underlying biology

Mechanistic Models (also called Process Based Models):

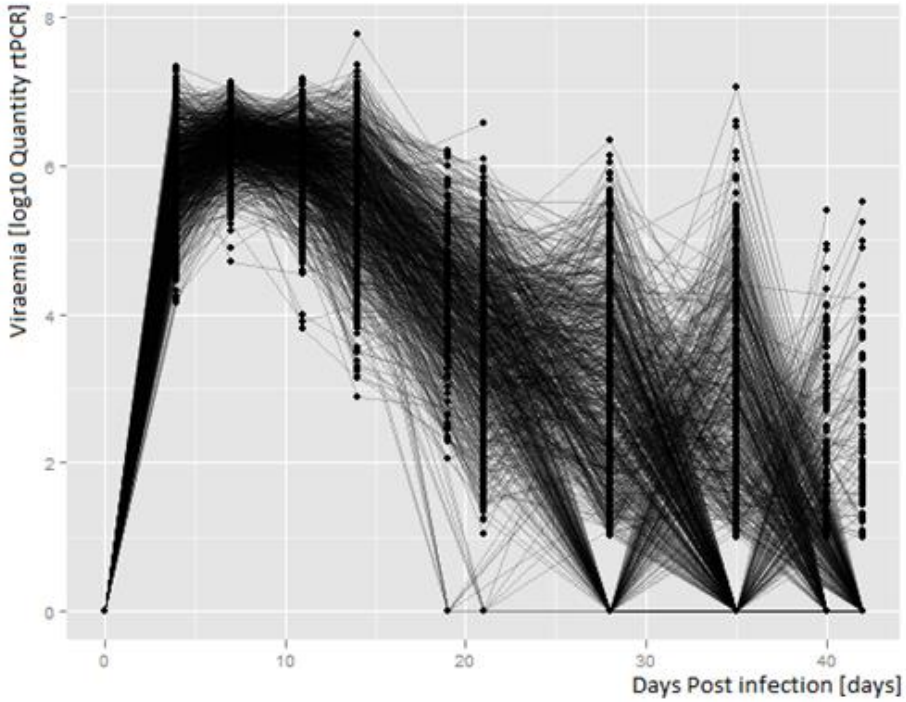
- Hypothesis driven modelling approach
- Starting point: specific phenomena of interest – observed from data
- Aim: to provide understanding for underlying mechanisms of this phenomenon
- Require prior understanding of system
- Data are used to parameterise / validate the model

PRRS viraemia profiles



PRRS Host Genetics Consortium PRRSV challenge experiment on growing pigs:

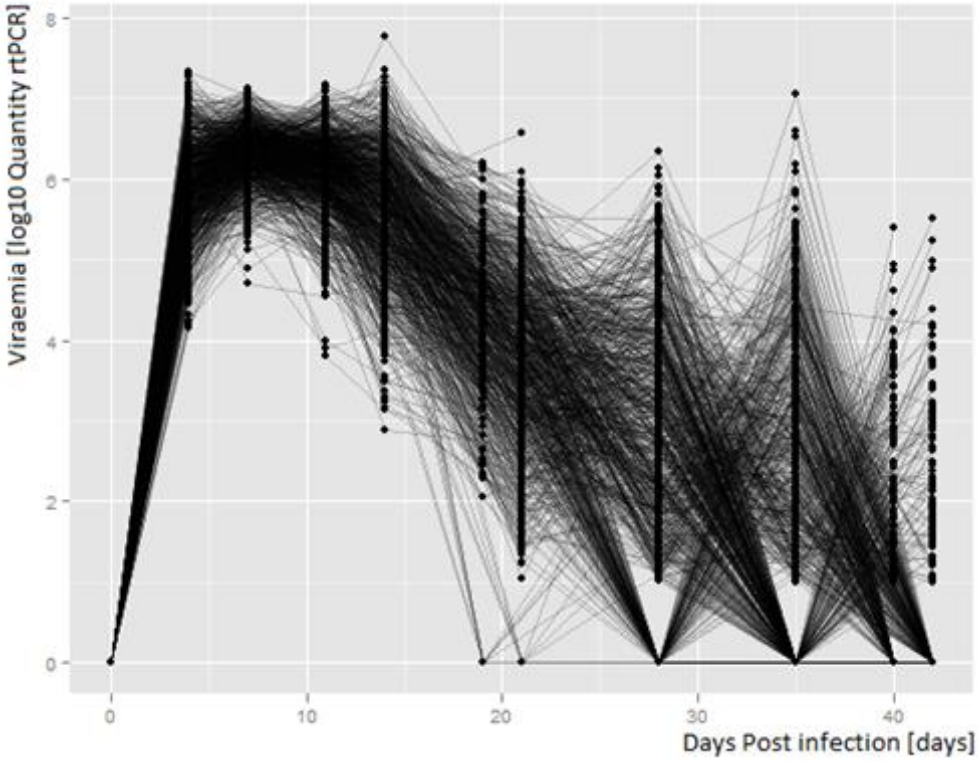
- ~1500 immunologically naïve piglets experimentally infected with same strain / dose of a virulent strain of PRRSV
- Repeated measurements of virus load in serum from rtPCR at 0, 4, 7, 11, 14, 21, 28, 35 & 42 days post infection



Steps of the empirical (statistical) modelling approach

1. Examine the viraemia data and find a mathematical function that describes the full range of virus load profiles
2. Explore the function
3. Fit the function to the data (see inference lectures)
4. Use the function to gain new insights into infection characteristics

1. Examining PRRS viraemia profiles

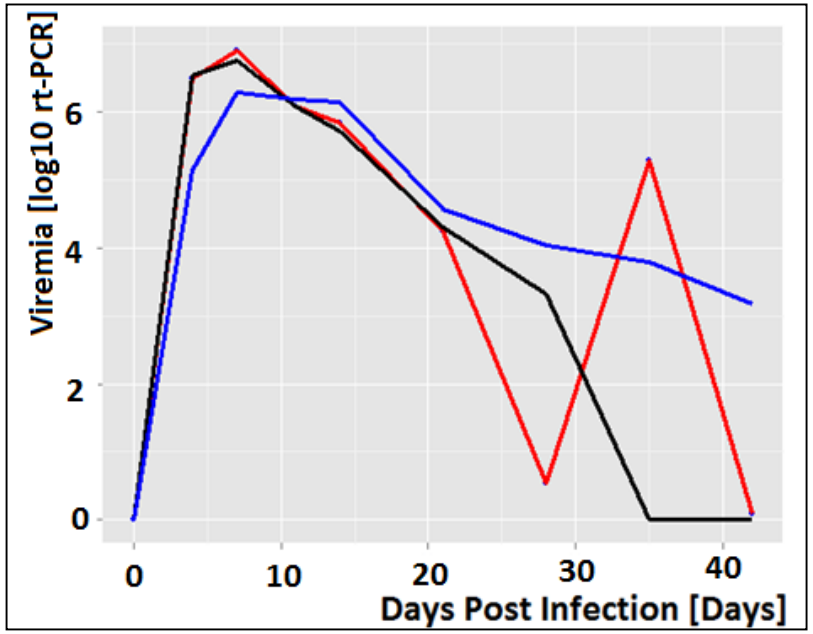


Huge variation in virus load trends:

- At a given point in time, virus loads can differ by 4-5 log differences
- Some clear the infection within 3-4 weeks
- Others have still high virus load after 6 weeks
- Some have a second phase of virus load increase

1. Is there one mathematical function that describes each of the observed profiles?
2. Can we distinguish systematic patterns from biological noise?
3. What is the relationship between early and late response?

Visual inspection indicates 3 response types:

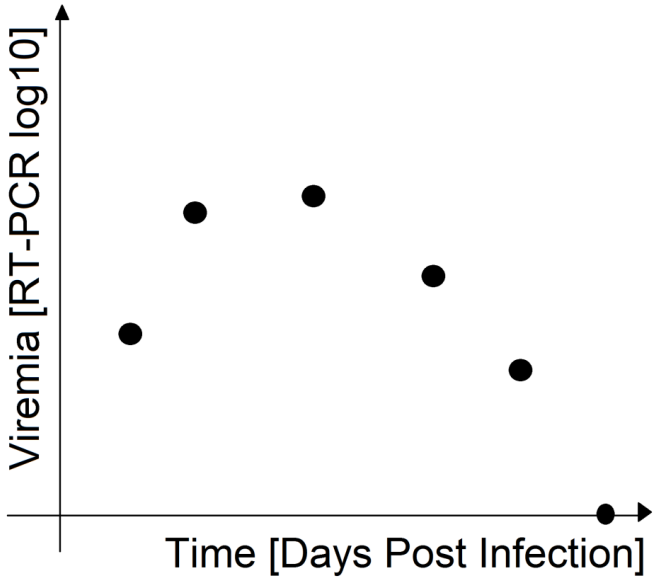


- There appear to be three types of virus load profiles:

  Clearance, Persistence, Rebound

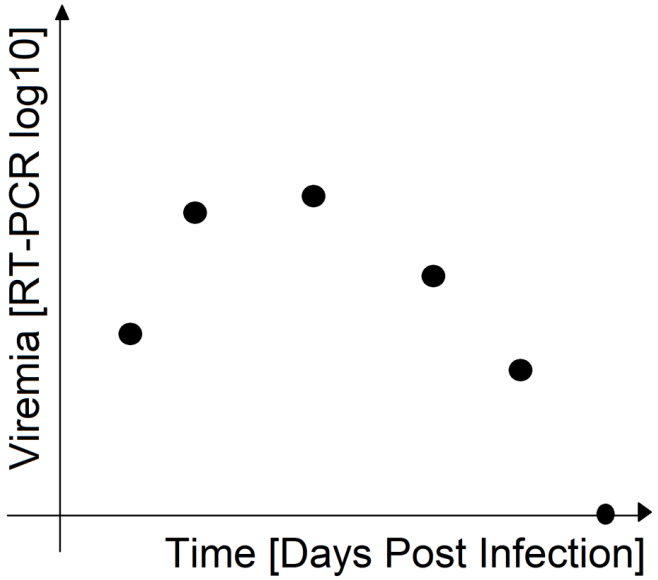
- Are these genuine or is rebound more likely the artefact of a measurement error?

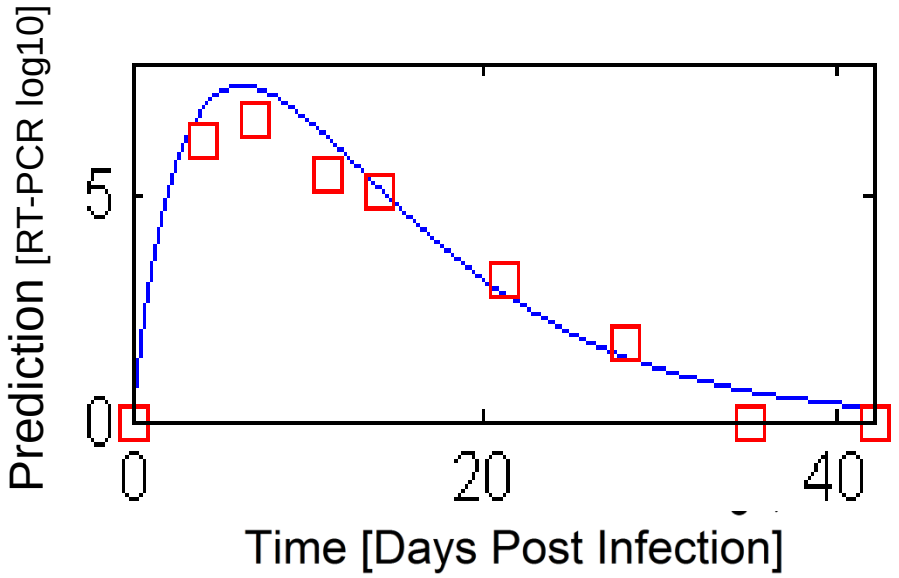
Examining individual viraemia profiles



1. Characteristics of individual (uni-modal) profiles
- Steep increase in virus load towards peak viraemia ~7-14 days post infection
- Gradual viraemia decline, often sigmoidal shape

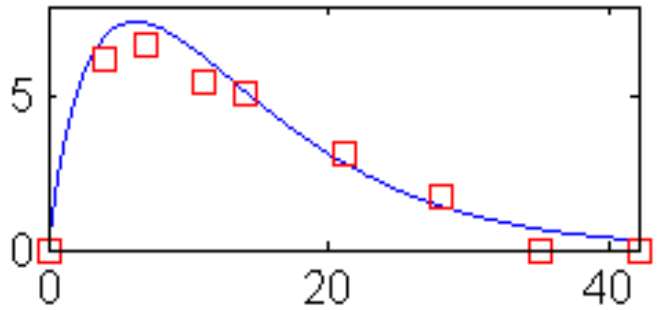
Candidate Model: The Woods function





$$V(t) = a_1 t^{b_1} e^{-c_1 t}$$

2. Exploring the Woods function

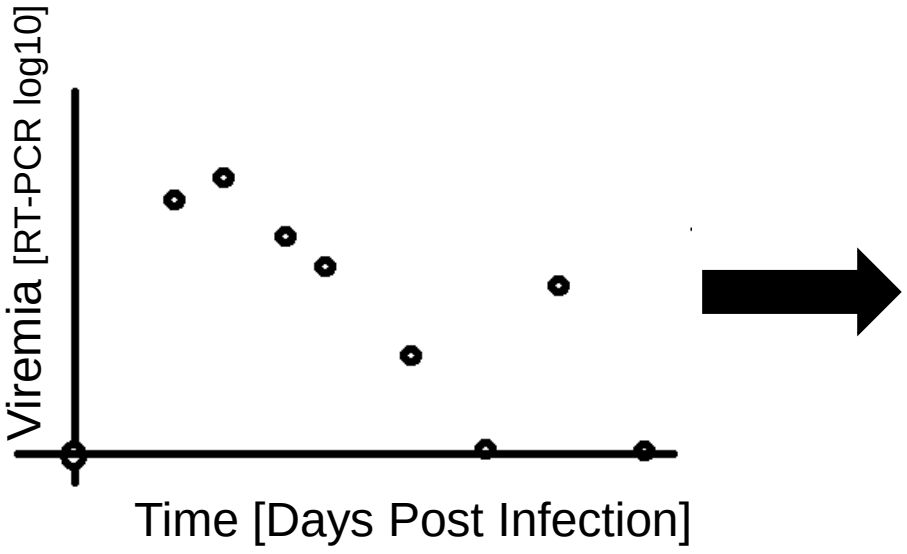


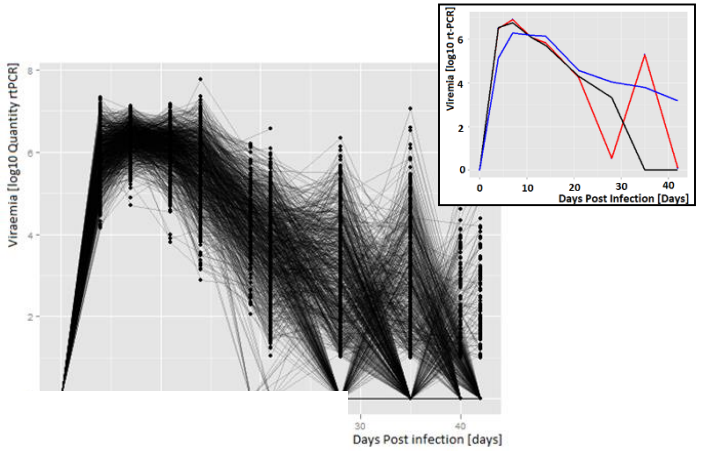
- The Woods function is given by the equation

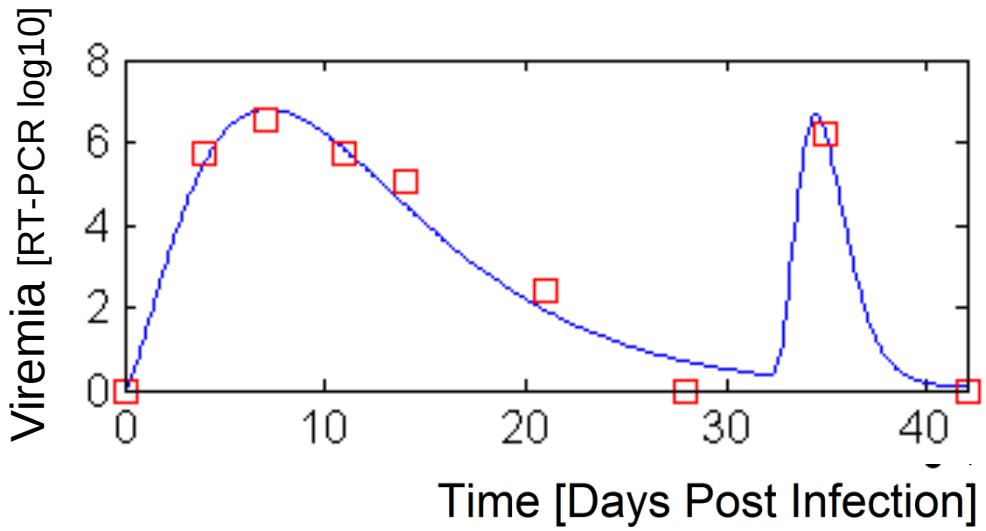
$$V(t) = a_1 t^{b_1} e^{-c_1 t}$$

- It produces uni-modal viraemia profiles
- The profile is completely specified by 3 parameters (a_1, b_1, c_1) that are easy to interpret (see tutorial)
- Estimates for parameter values and goodness of fit are obtained via statistical inference (see tutorial)

Modelling rebound

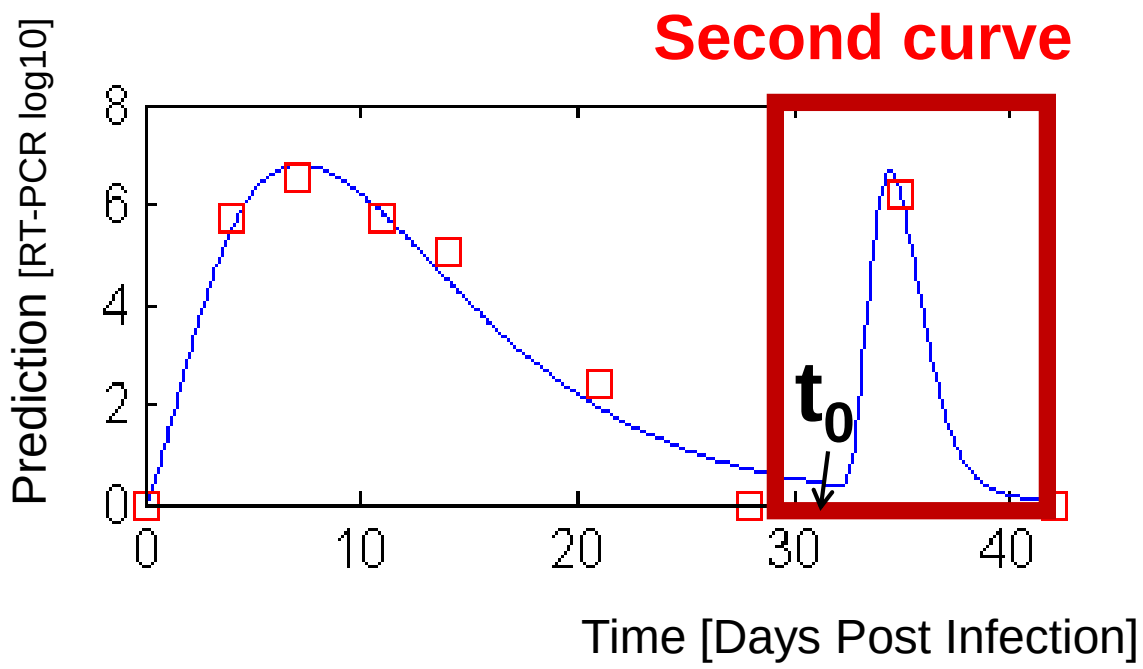






Extended Woods model

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



The extended Woods function overlays 2 Woods functions

1. The unimodal Woods function

   $V_1(t) = a_1 t^{b_1} e^{-c_1 t}$ for $t \leq t_0$

2. A shifted Woods function with origin at t_0

   $V_2(t) = a_2 (t - t_0)^{b_2} e^{-c_2 (t - t_0)}$ for $t \geq t_0$

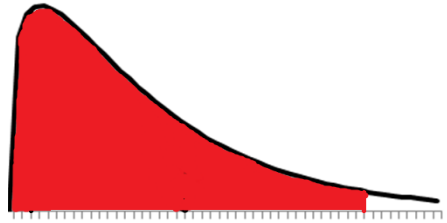
   (note that $a_1 t^{b_1} e^{-c_1 t} \approx 0$ for $t \geq 20$ days)

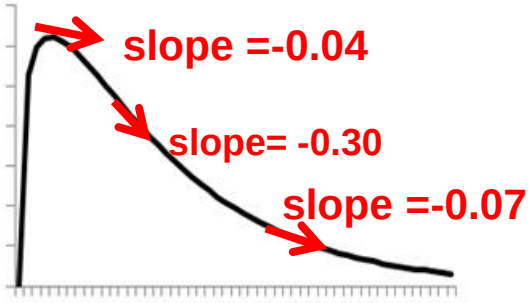
Benefits of fitting functions to data

1. Removes noise from the data

2. Provides estimates (new phenotypes) for

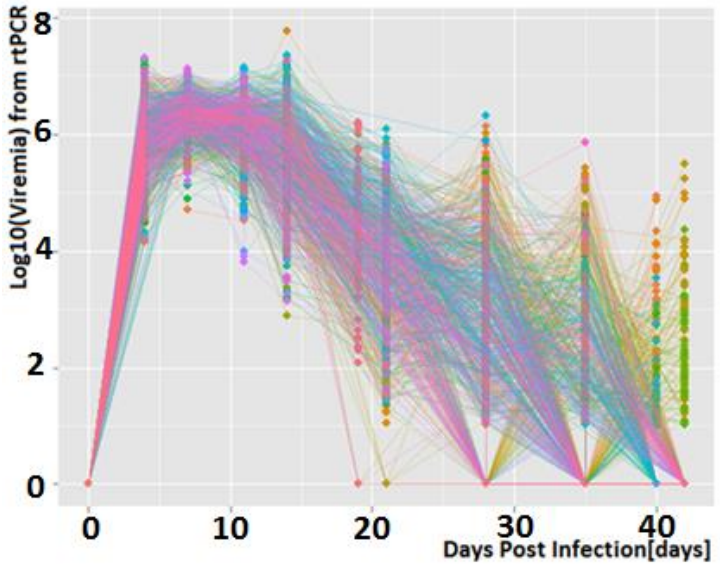
- **Viraemia levels at any time point** post infection: evaluate V(t)
- **Time of peak virus load**: obtained by setting $\frac{dV}{dt} = 0$
- **Peak virus load:** obtained by setting $\frac{dV}{dt} = 0$
- **Duration of infection**: calculate T, when $V(T)$ < detection level
- **Severity of infection**, described by cumulative virus load over the infection period: obtained by integrating $\int_{t=0}^{T} V(t)dt$
- **Rate of change in viraemia** at any stage of infection, described by the local slopes: obtained by calculating the derivative $\frac{dV}{dt}$ at times t_i



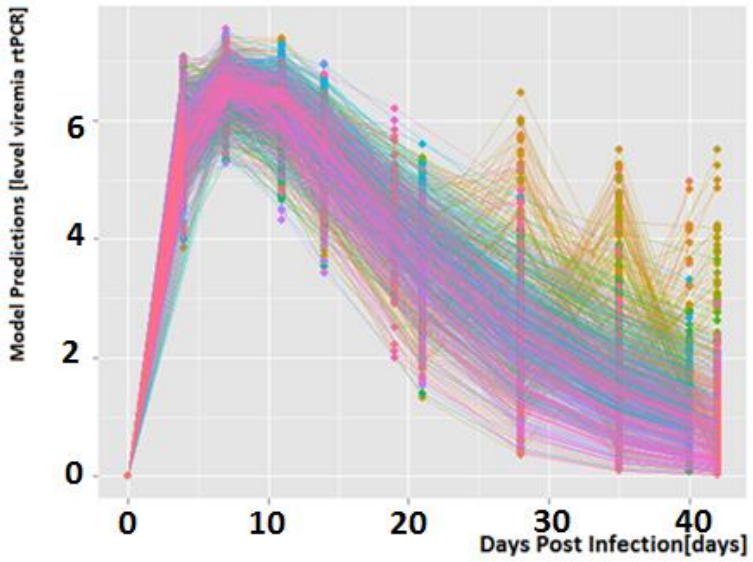


3. Fit the function to individual viraemia data profiles

- We use statistical inference (see Lecture & tutorial on Thursday) to fit the Woods models to the data
- This provides for every pig estimates (with measure of certainty) of the function parameter values & a measure for goodness of fit



Raw PRRS viremia data



Predicted viremia (extended Woods model predictions)

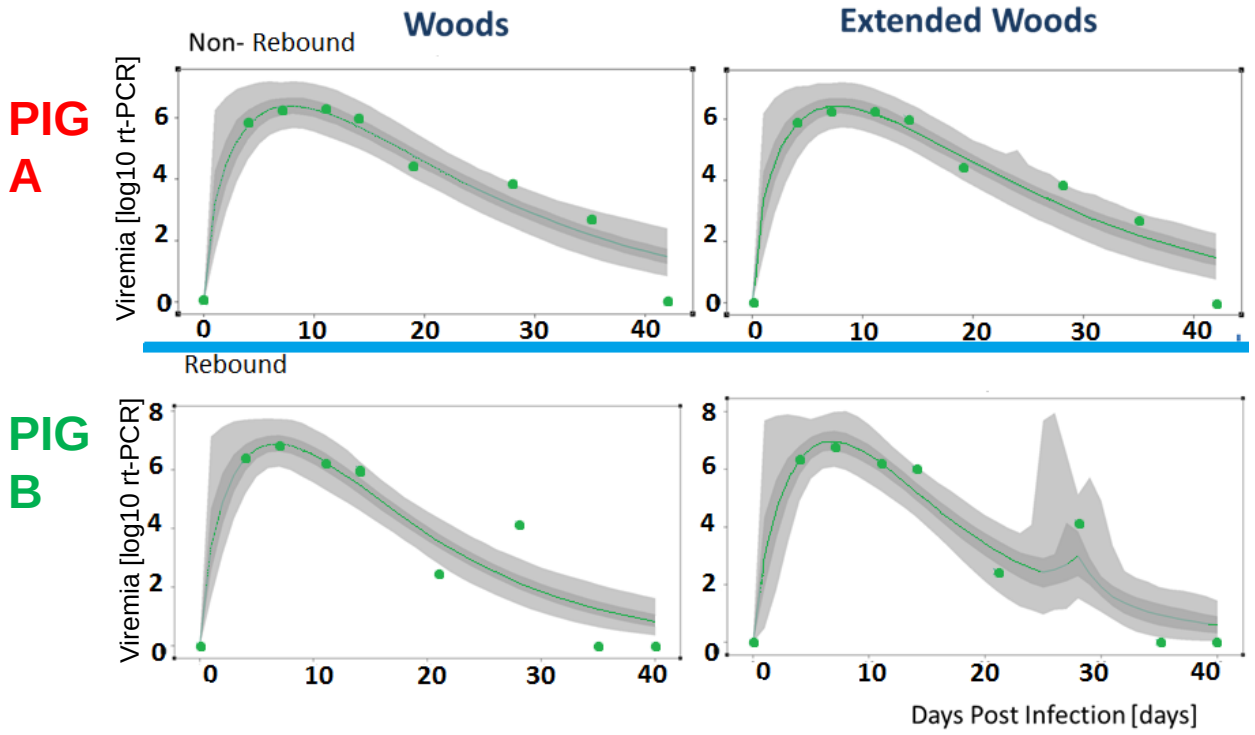
Islam et al., PLoS ONE 2012

Steps of the empirical (statistical) modelling approach

1. Examine the viraemia data and find a mathematical function that describes the virus load profiles
2. Explore the function
3. Fit the function to the data (see inference lectures)
4. **Use the function to gain new insights into infection characteristics**

Is viraemia rebound a genuine phenomenon?

Approach: Fit both, the uni-modal and bi-modal Woods model to viraemia data of each individual pig to obtain a statistical classification of pigs into rebounders / non-rebounders based on goodness of model fit



Number of individuals assigned to each class:	
Class 1: Non-Rebound	**Class 2: Rebound**
683 (78%)	191(22%)

Statistical analysis implies that rebound is a genuine phenomenon rather than an artefact of the data

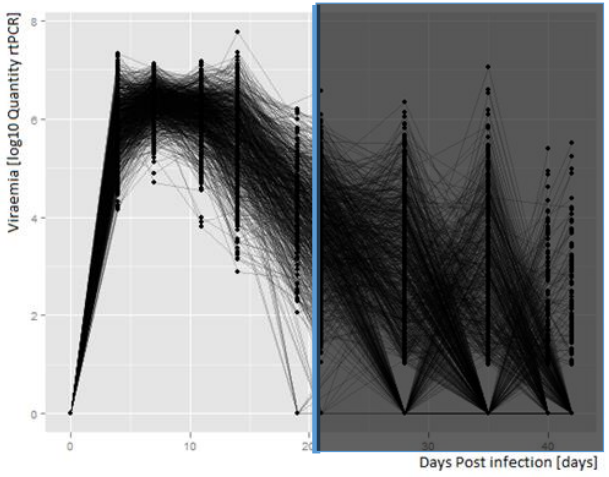
Islam et al., PLoS ONE 2012

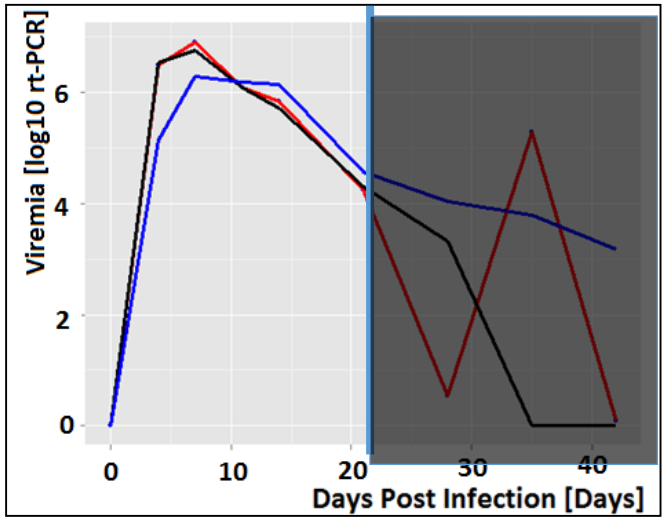
To what extent is the shape of the viraemia profile determined by the genetics of the pig?

- The model fitting process provides for every pig new descriptors for its viremia profile characteristics (e.g. uni-/bimodal, peak viraemia, …)
- These can be used as response variables in statistical models for estimating genetic effects
  - See e.g. Hess et al. (GSE 2016); Quantitative genetic analysis revealed that viraemia rebound is not heritable, i.e. the pig's genetic makeup does not determine whether or not it will experience viraemia rebound when infected with PRRSV

➢ What other factors could determine whether rebound will happen?

Can we predict whether rebound will occur?





Process:

- Chop all data off at 21 days post infection
- Fit the Woods function to the truncated profile
- Compare the Woods function parameters between profiles from different viremia classes (e.g. ANOVA)
- Compare resulting mean profiles

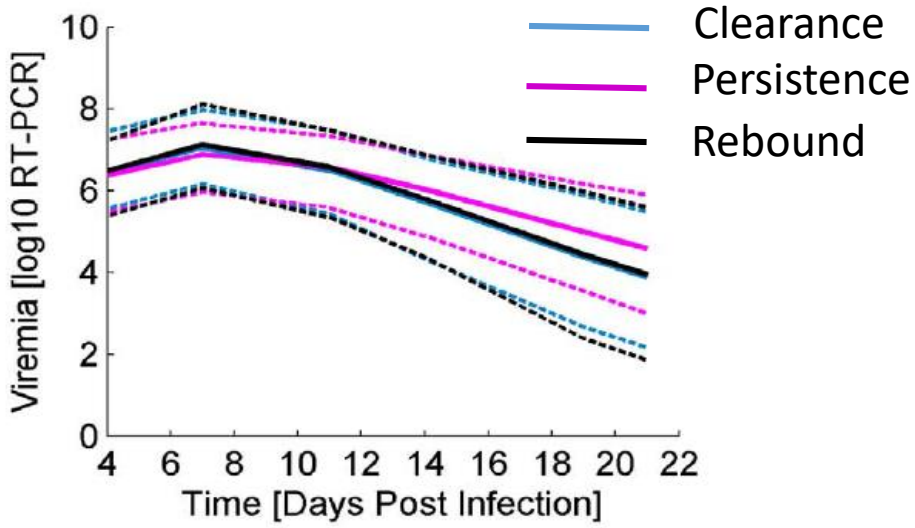
Compare Woods parameter estimates

Woods parameter estimates derived from the primary phase (0-21dpi)

Group	**A1 (se)**	**B1 (se)**	**C1 (se)**
Non-Rebound	3.99 (0.034)	0.627 (0.009)	0.0903 (0.001)
Rebound	3.89 (0.070)	0.676 (0.019)	0.0986 (0.003)
Significantly Different?	No P=0.2146	**Yes** P=0.0181	**Yes** P=0.005

Estimates for parameters b_1 and c_1 are significantly different between rebounders and non-rebounders

Compare predicted viraemia profiles



Mean Woods model predictions with 95% confidence intervals for viraemia profiles of pigs from the 3 different viraemia classes 'Clearance, Persistence, Rebound'

- Average virus load profiles for pigs that clear the infection and experience rebound are very similar (impossible to distinguish within first 3 weeks)
- 'Persistent' profiles are however distinguishable
- We cannot exclude that 'persistent' pigs don't experience rebound

Combining empirical & mechanistic models: The systems biology pipeline

Data

- Biological observations
- "noisy"

Empirical model

- Data driven
- Remove noise, retain & describe characteristic features
- New insights, e.g. about Rebound

Hypothesis

- Whether rebound occurs or not depends on the relative strength of different interacting immune processes

Mechanistic model

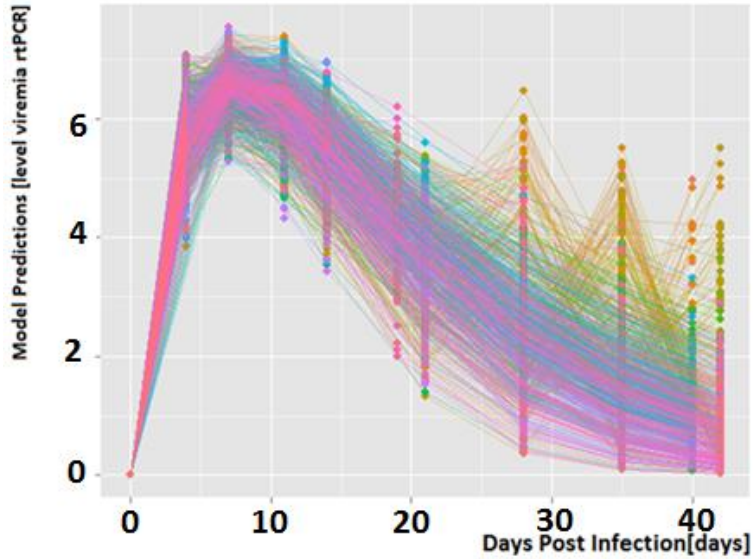
- Hypothesis driven
- Explore how different biological mechanisms interact over time & affect viraemia profiles

Recap: Recipe for building mechanistic models

1. Define phenomena of interest / formulate questions & hypotheses
2. Identify key biological processes to be included in a model
   - Apply principle of Ockham's razor: start simple & gradually build up complexity
3. Abstract them into a mathematical model
   - Determine variables and parameters
   - Determine mathematical equations
4. Analyse the model behaviour
5. Validate model with data (if available)

1. PRRS phenomena of interest

- What causes the observed diversity in PRRS viraemia profiles?
- Which biological processes are responsible for fast clearance or for viraemia rebound?



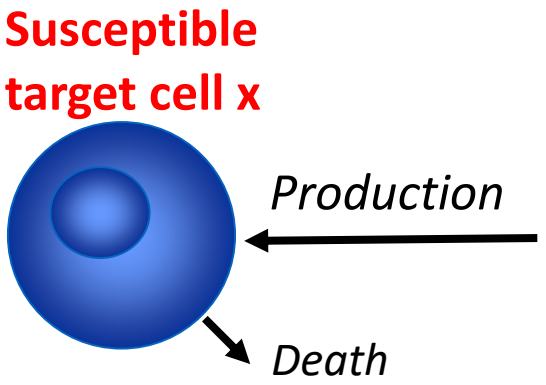
2. Identify key processes to be included in the model

Applying principle of Ockham's razor:

Start with the simplest possible model with minimum number of components:

- Model the infection process at the target site of infection, i.e. the lung
  - Ignore flow of virus / cells between blood and organs
- Start with modelling the interactions between virus and target cells
  - Target cells are a subset of alveolar macrophages
  - Assume that the virus is a homogeneous entity
- Gradually introduce immune response
- Ignore everything else

2. Identify key processes to be included in the model



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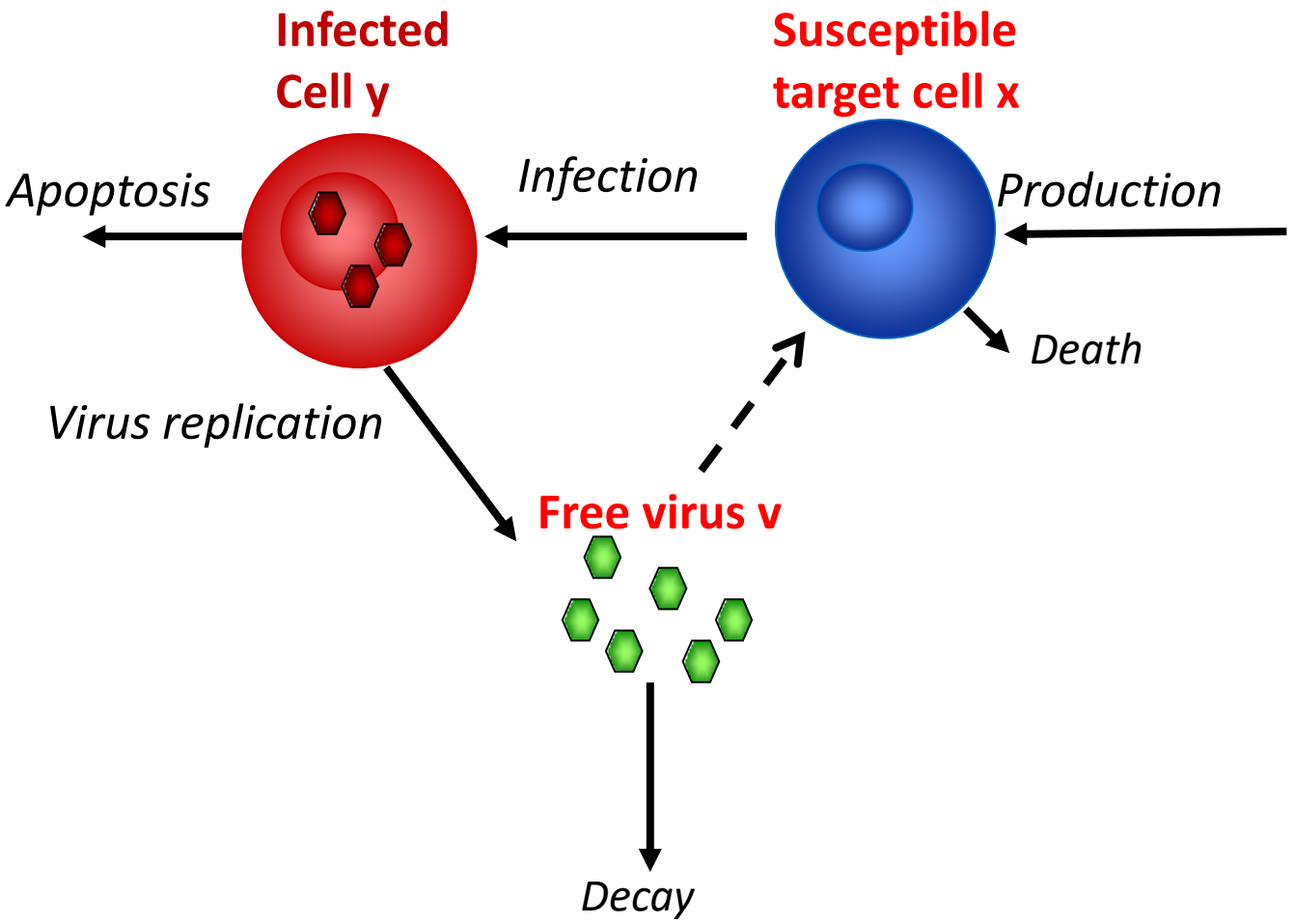

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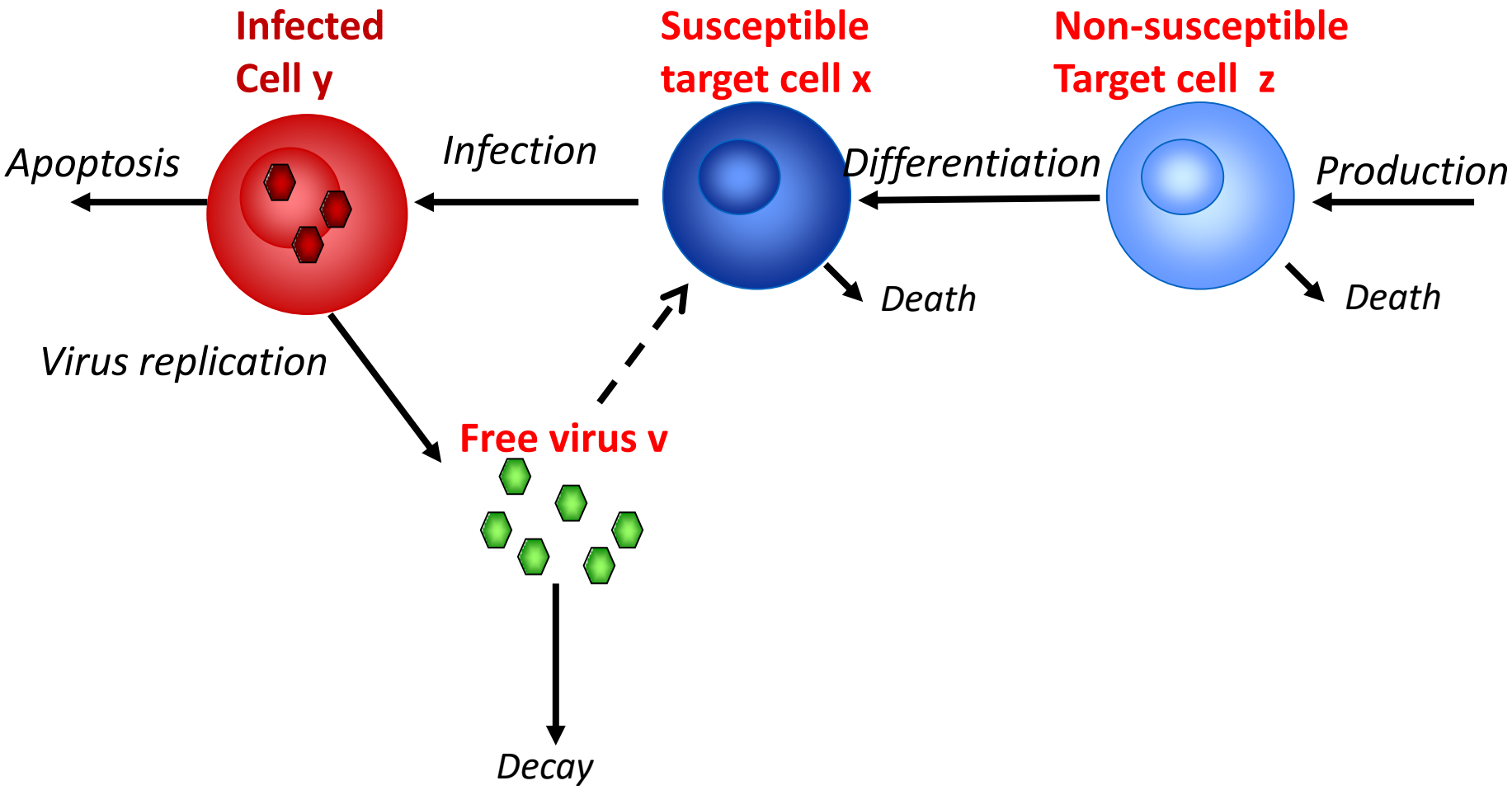
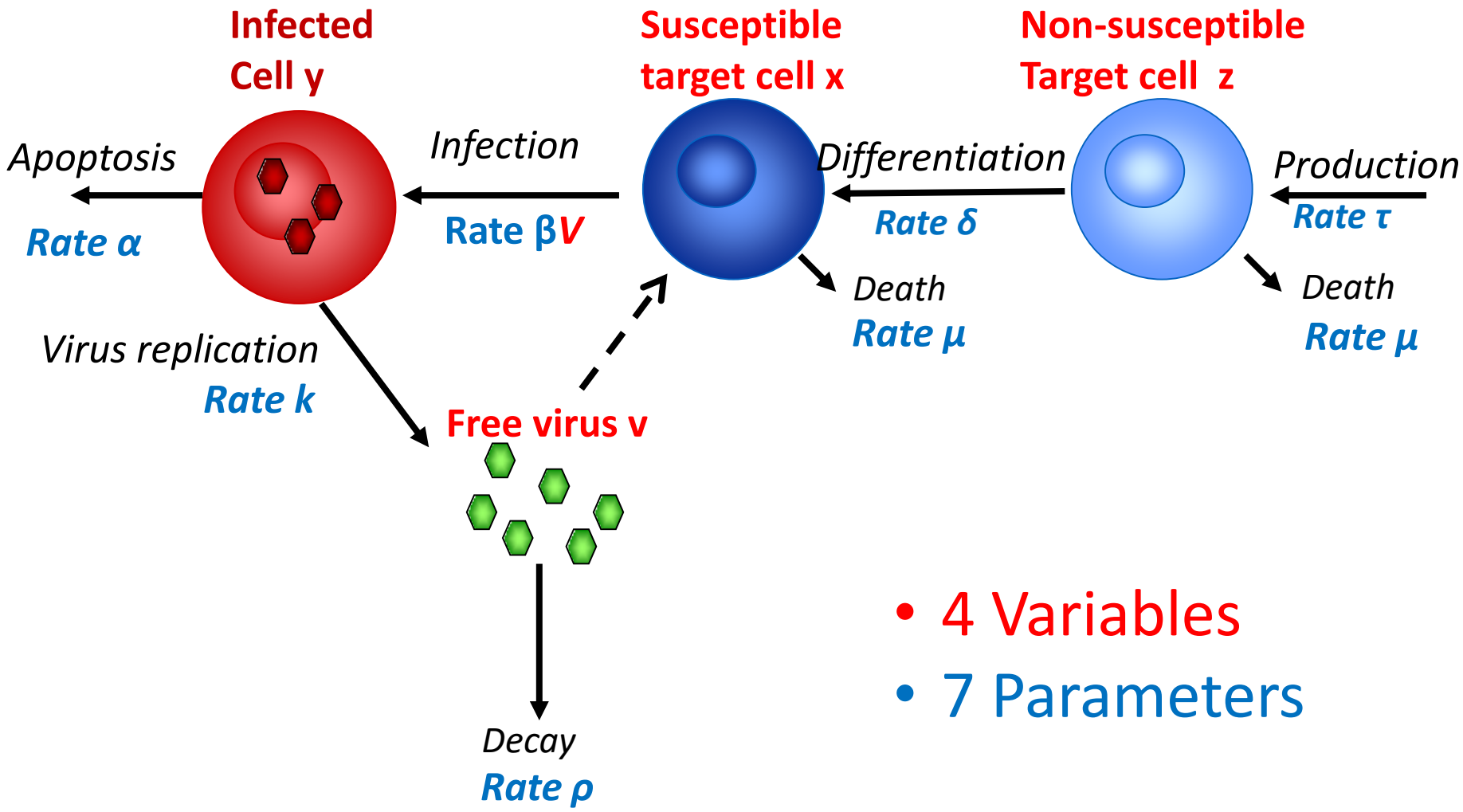
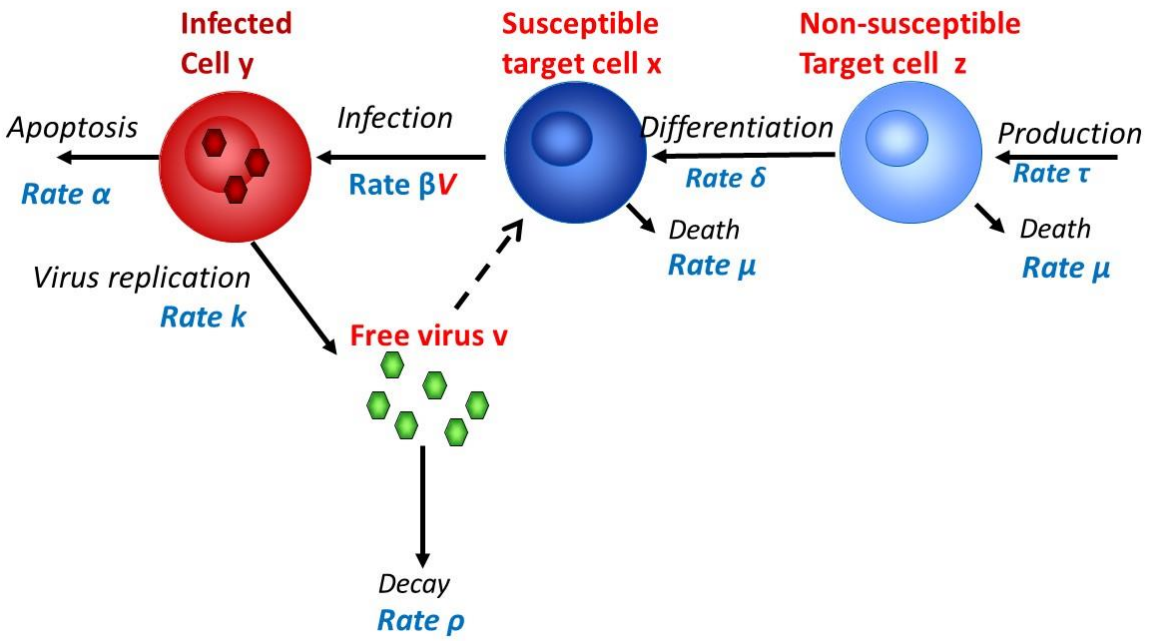


3. Towards a mathematical formulation: define model variables and parameters



- 4 Variables
- 7 Parameters

3. Mathematical formulation



What assumptions are entailed in the model?
Can you see the similarity to the predator-prey model?

Model equations:

$$\frac{dZ}{dt} = \tau - \delta Z - \mu Z$$

$$\frac{dX}{dt} = \delta Z - \mu X - \beta V X$$

$$\frac{dY}{dt} = \beta V X - \alpha Y$$

$$\frac{dV}{dt} = \varepsilon Y - \rho V$$

4. Analyse the ODE model

To analyse the model, it helps to distinguish between 3 phases:

1. Initial phase: prior to infection ($t \leq 0$)
2. Acute phase: dynamic phase $0 < t \ll \infty$
3. Long-term outcome: steady state (equilibrium) ($t \to \infty$)

Initial state, prior to infection

Assumptions:

- No virus, no infected cells
- Uninfected cells are at equilibrium

$$\frac{dZ}{dt} = \tau - \delta Z - \mu Z$$
$$\frac{dX}{dt} = \delta Z - \mu X - \beta V X$$
$$\frac{dY}{dt} = \beta V X - \alpha Y$$
$$\frac{dV}{dt} = kY - \rho V$$

$$\frac{dZ}{dt} = 0$$
$$\frac{dX}{dt} = 0$$

$$Y = 0$$
$$V = 0$$

Initial state, prior to infection

Assumptions:

- No virus, no infected cells
- Uninfected cells are at equilibrium

$$\frac{dZ}{dt} = \tau - \delta Z - \mu Z$$
$$\frac{dX}{dt} = \delta Z - \mu X - \beta V X$$
$$\frac{dY}{dt} = \beta V X - \alpha Y$$
$$\frac{dV}{dt} = kY - \rho V$$

$$\frac{dZ}{dt} = 0$$
$$\frac{dX}{dt} = 0$$

Solve equations to get:

$$Z = \frac{\tau}{\delta + \mu}$$
$$X = \frac{\tau\delta}{\mu(\delta + \mu)}$$
$$Y = 0$$
$$V = 0$$

Steady state ($t \rightarrow \infty$)

$$\frac{dZ}{dt} = \tau - \delta Z - \mu Z$$
$$\frac{dX}{dt} = \delta Z - \mu X - \beta V X$$
$$\frac{dY}{dt} = \beta V X - \alpha Y$$
$$\frac{dV}{dt} = kY - \rho V$$

Steady state conditions:

$$\frac{dZ}{dt} = \frac{dX}{dt} = \frac{dY}{dt} = \frac{dV}{dt} = 0$$

2 possible outcomes:

(a) Virus clearance – reversion to initial state

$$Z_1 = \frac{\tau}{\delta + \mu} \qquad X_1 = \frac{\delta\tau}{\mu(\delta + \mu)}$$

$$Y_1 = 0 \qquad V_1 = 0$$

(b) Persistent infection:

$$Z_2 = \frac{\tau}{\delta + \mu} \qquad X_2 = \frac{\alpha\rho}{\beta\kappa}$$

$$Y_2 = \frac{\delta\tau}{(\delta+\mu)\alpha} - \frac{\rho\mu}{\beta\kappa} \qquad V_2 = \frac{\kappa\delta\tau}{(\delta+\mu)\alpha\rho} - \frac{\mu}{\beta}$$

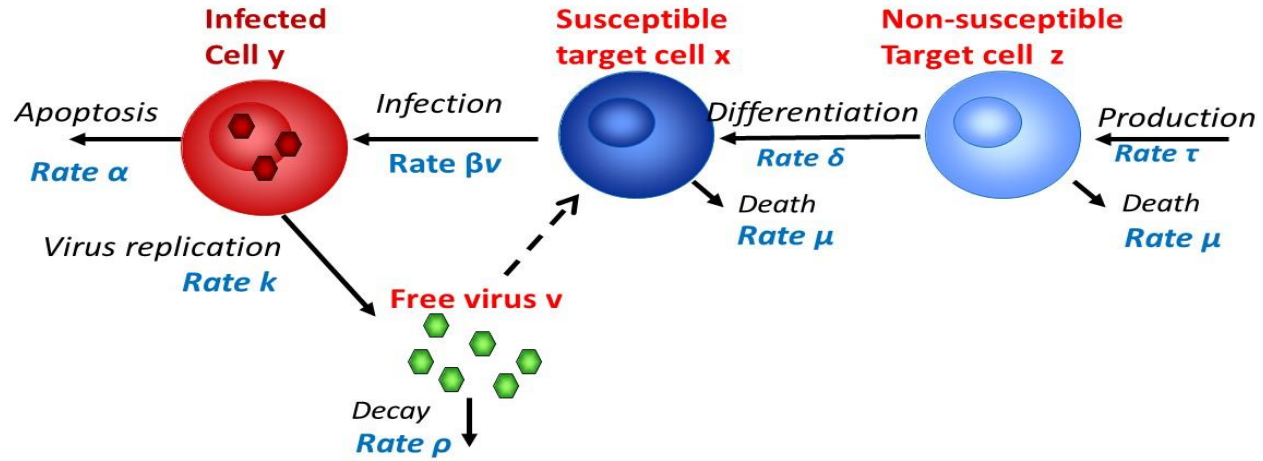
Which outcome will occur?

The answer lies in the basic reproductive ratio R_0

Definition: Basic reproductive ratio R_0
The average number of newly infected cells that arise from one infected cells when all other cells are non-infected

- $R_0 = 1$ is a threshold between productive / non-productive infection
- $R_0 > 1$: Infection can invade
- $R_0 < 1$: Infection will die out

Calculating R_0



1. An infected cell lives on average $\frac{1}{\alpha}$ seconds
2. An infected cell produces on average *k* free virus particles per second, each persisting for $\frac{1}{\rho}$ seconds.
3. Each virus particle infects βX cells
4. Prior to infection: $\mathrm{X} = \frac{\tau\delta}{\mu(\delta+\mu)}$

Multiplying all 4 components gives

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

Steady state ($t \to \infty$)

Previously shown: There are 2 possible outcomes:

(a) Virus clearance

$$Z_1 = \frac{\tau}{\delta + \mu} \qquad X_1 = \frac{\delta\tau}{\mu(\delta + \mu)}$$

$$Y_1 = 0 \qquad V_1 = 0$$

(b) Persistent infection:

$$Z_2 = \frac{\tau}{\delta + \mu} \qquad X_2 = \frac{\alpha\rho}{\beta\kappa}$$

$$Y_2 = \frac{\delta\tau}{(\delta+\mu)\alpha} - \frac{\rho\mu}{\beta\kappa} \qquad \boxed{V_2 = \frac{\kappa\delta\tau}{(\delta+\mu)\alpha\rho} - \frac{\mu}{\beta}}$$

Which outcome will occur?

- One can show that $R_0 > 1$ is equivalent to $V_2 > 0$
- In other words, the model predicts that if infection can invade, it will persist

➢ **This model is clearly not an adequate representation of PRRS infection dynamics**

Acute phase dynamics

$$\frac{dZ}{dt} = \tau - \delta Z - \mu Z$$
$$\frac{dX}{dt} = \delta Z - \mu X - \beta V X$$
$$\frac{dY}{dt} = \beta V X - \alpha Y$$
$$\frac{dV}{dt} = kY - \rho V$$

- We need to solve these equations to determine how values for the model variables Z, X, Y and V change over time t
- No analytical solutions can be derived
- Requires computer program to obtain numerical solutions (see tutorial)

e.g. $Z(0) = z_0$, $X(0) = x_0$, $Y(0)=0$, $V(0) = v_0$

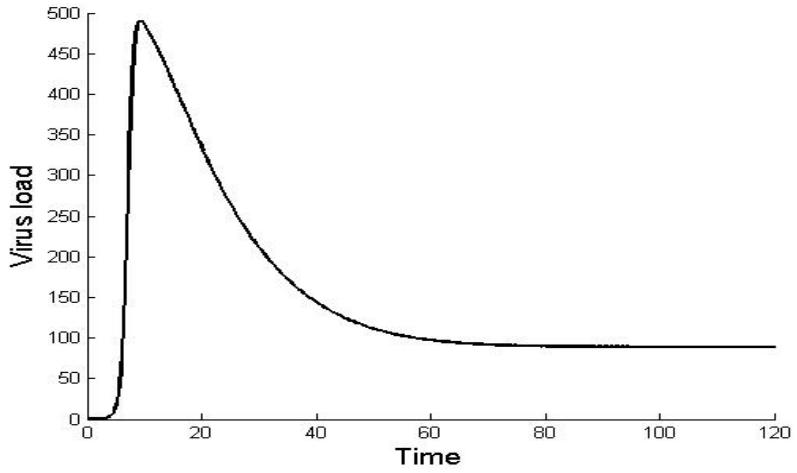
Assessing the acute phase dynamics

Recap (Lecture 4) – adopted approach (see tutorial)

1. Choose arbitrary values for the model parameters
2. Define initial conditions $Z(0) = z_0$, $X(0) = x_0$, $Y(0)=0$, $V(0) = v_0$
3. Code the differential equations
4. Call a numerical solver (e.g. 'lsoda' in R) to generate predictions for the model variables Z, X, Y and V at different time points
5. Plot & examine the corresponding profiles
6. Interpret the results

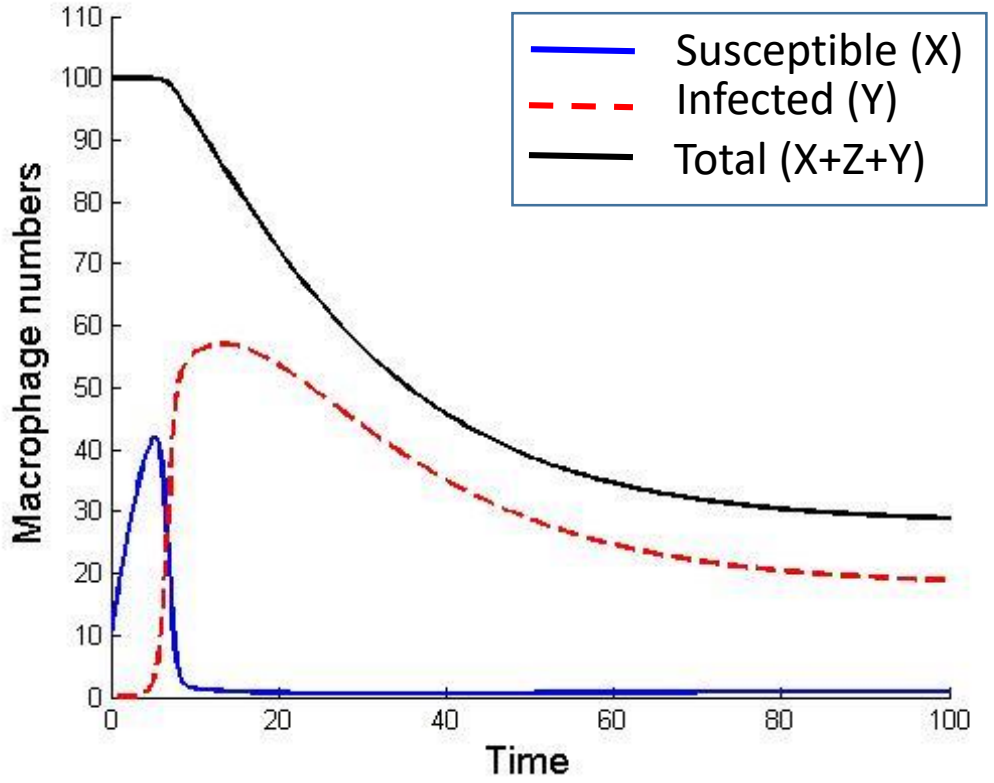
Virus load profile generated by the model

- The model can generate virus load profiles of similar shape as those observed in the experimental data



What causes the virus load decline in the model?

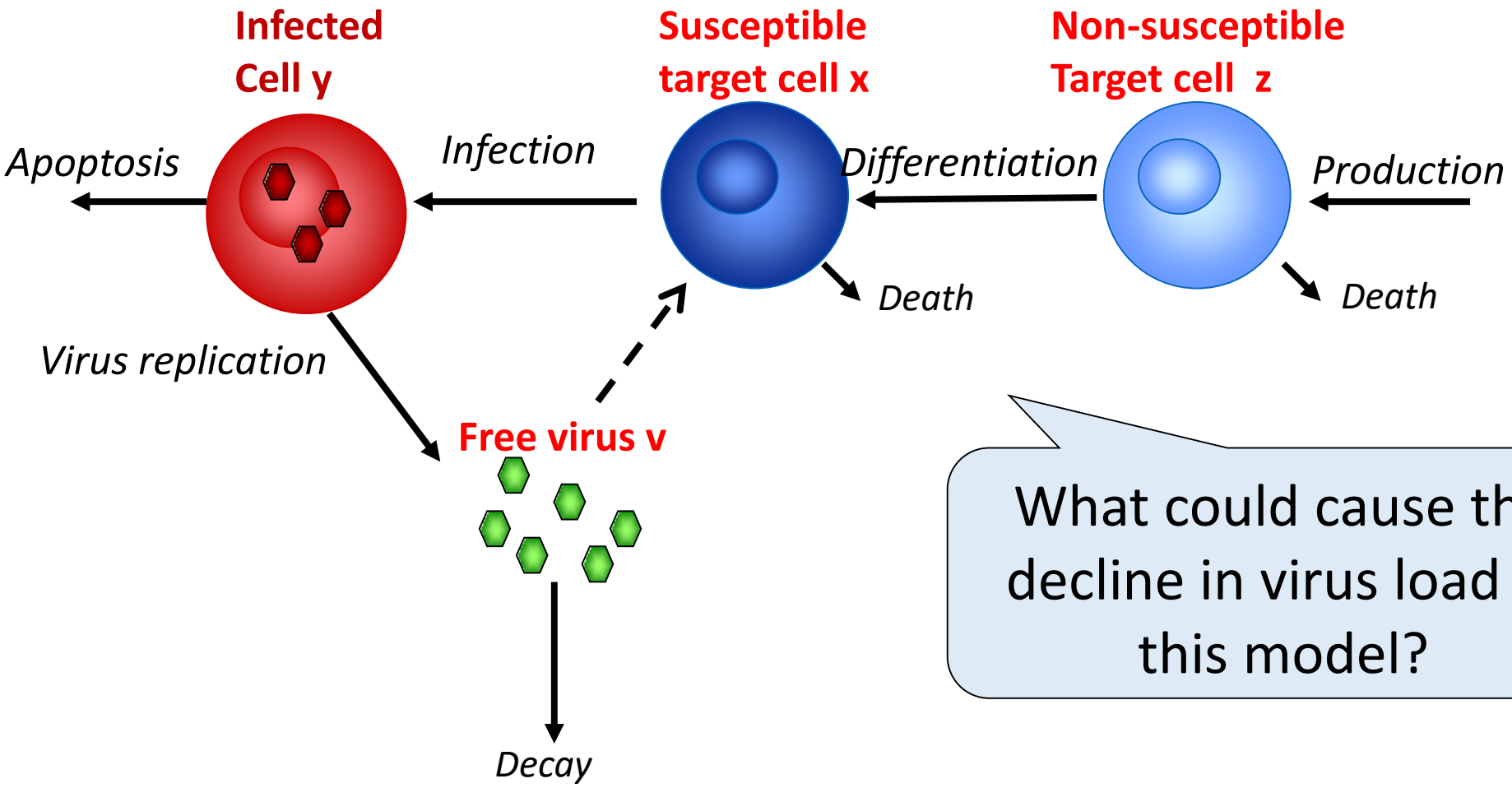
Time profiles for cell numbers



- Reduction in virus load can only be achieved when the pool of susceptible target cells (X) gets depleted.
- This can only occur if the total number of host cells (Z+X+Y) decreases
- Contradicts experimental findings

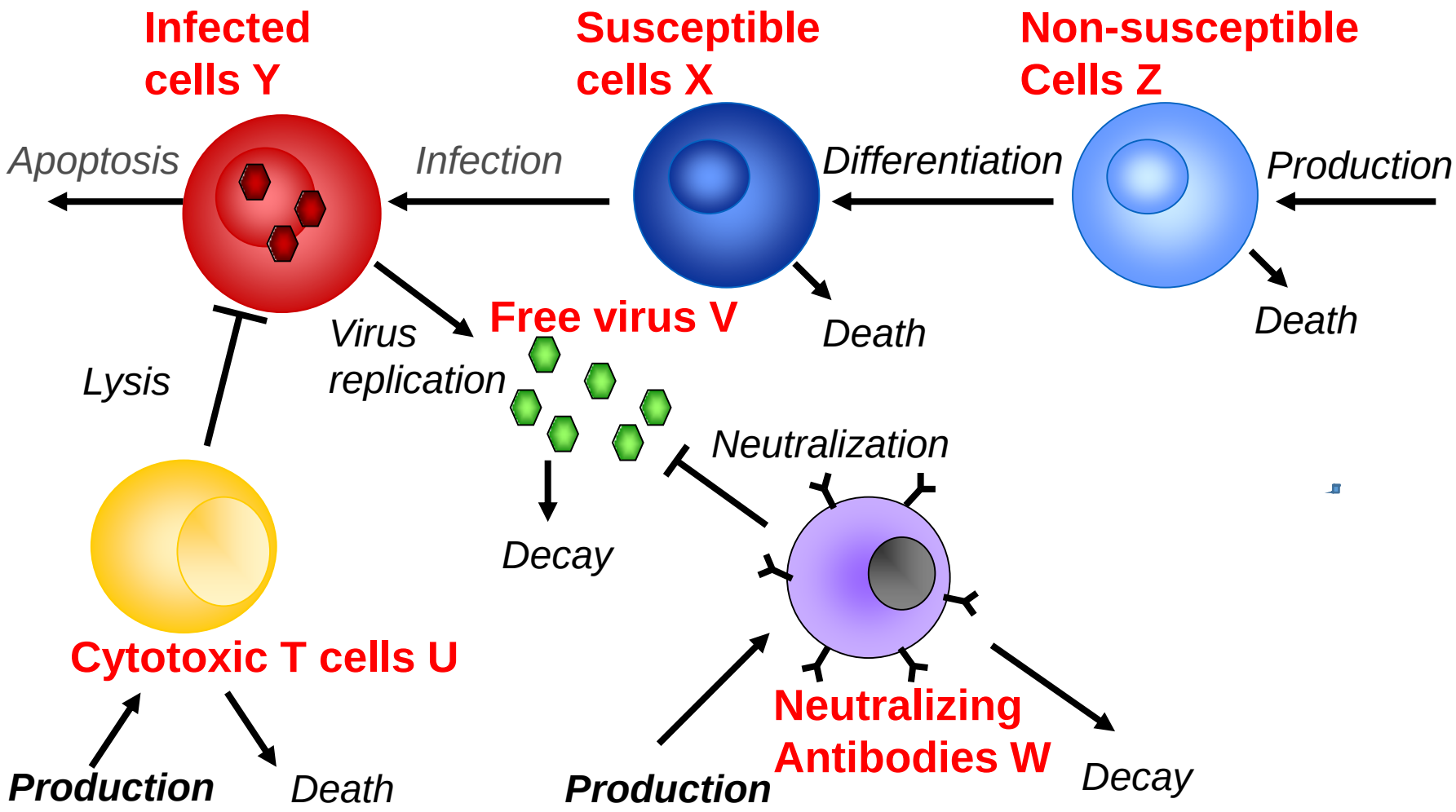
➢ **The Model is clearly not an adequate representation of PRRS infection dynamics**

Back to the drawing board

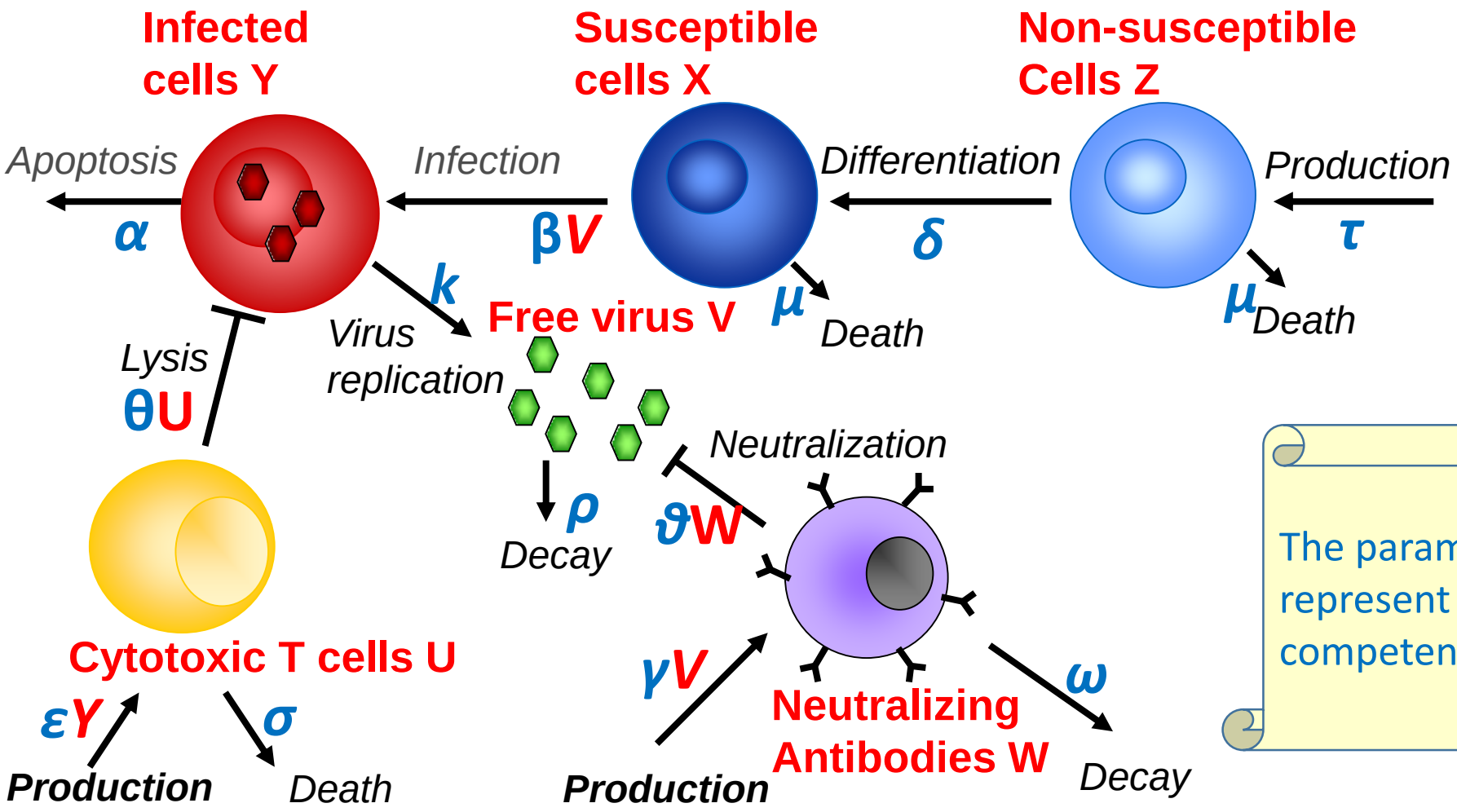


What could cause the decline in virus load in this model?

Increase model complexity: add immune response



The host-pathogen interaction model with parameters



The parameters ε & γ represent the immuno-competence of a host

Model equations and assumptions

Assume constant replenishment of target cells, so that Z(t) + X(t) + Y(t) = constant M

Model equations:

$$\frac{dX}{dt} = \delta(M - X - Y) - \mu X - \beta VX$$

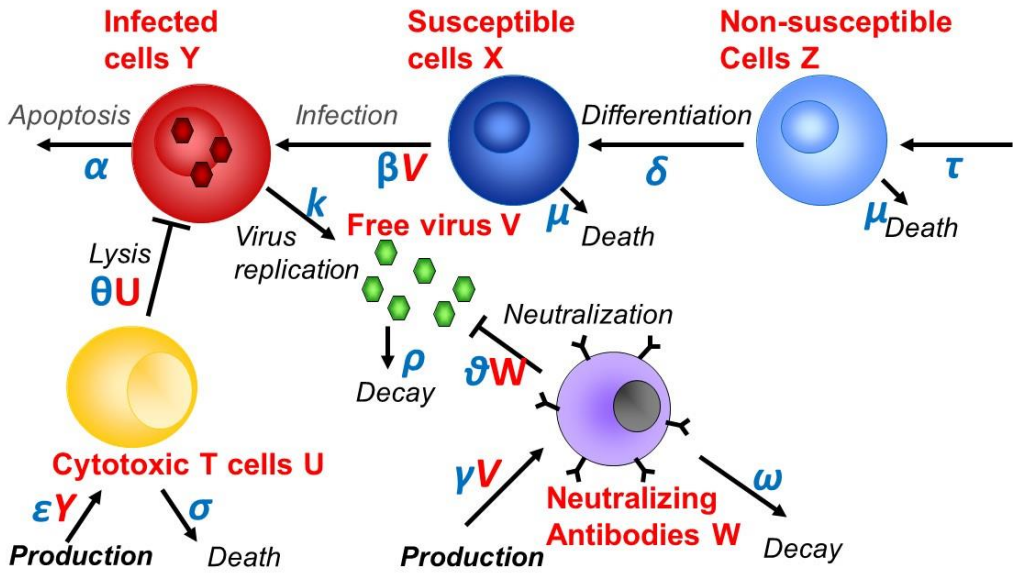
$$\frac{dY}{dt} = \beta VX - \alpha Y - \theta UY$$

$$\frac{dV}{dt} = kY - \rho V - \vartheta VW$$

$$\frac{dU}{dt} = \epsilon YU - \sigma U$$

$$\frac{dW}{dt} = \gamma VW - \omega W$$

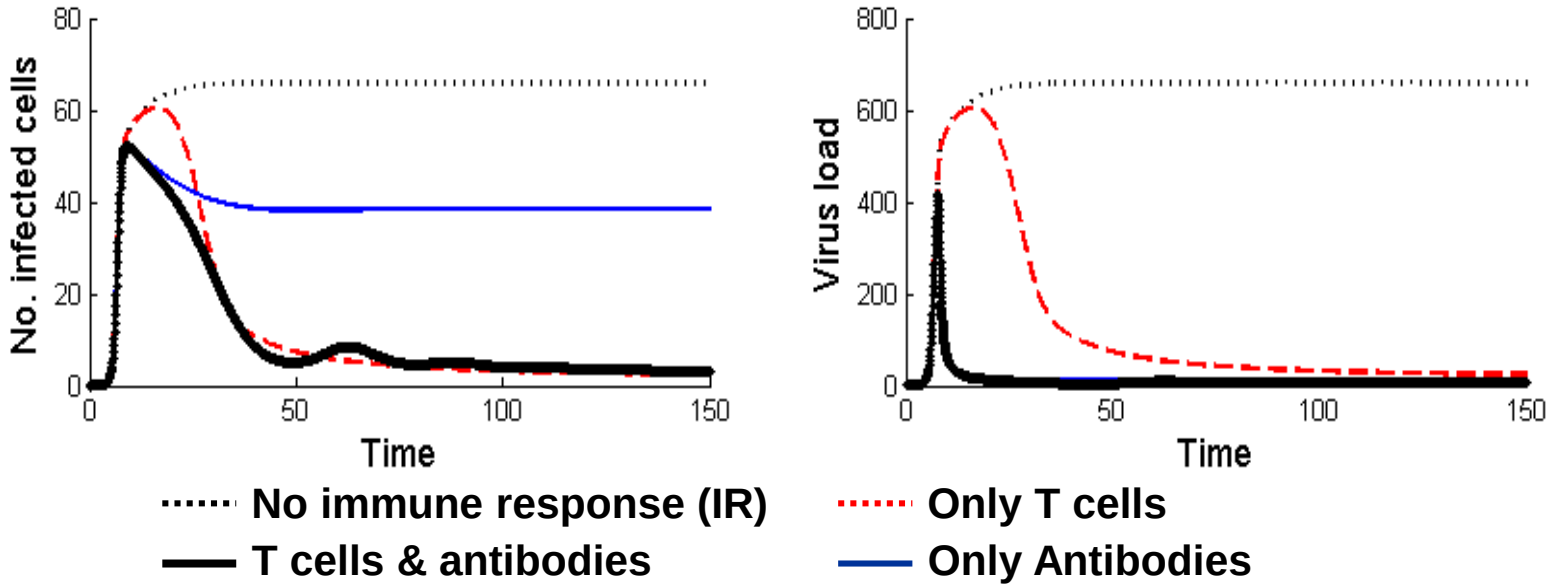
The assumption of constant cell numbers allows reduction from 6 to 5 model variables



How does the model represent interactions between cells, virus and immune response?

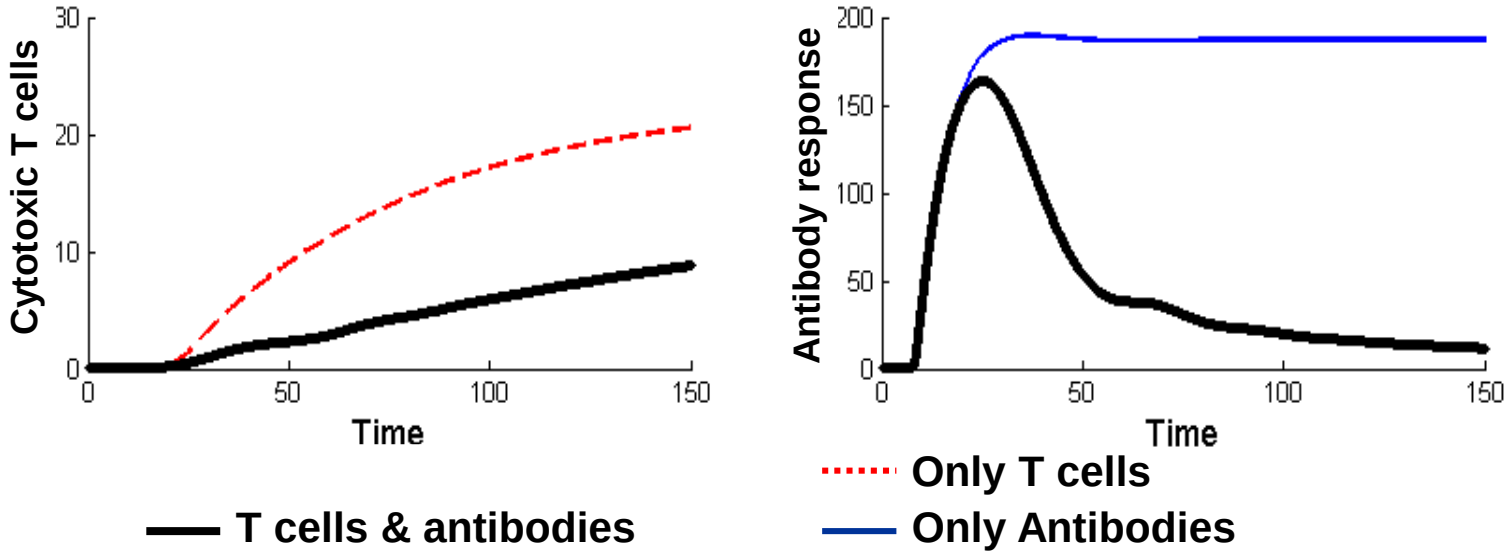
Model predictions for the acute phase of infection: Infection profiles

- To investigate the role of each immune component, include one component at a time (by setting parameter values to zero)
- Assuming constant replenishment of susceptible cells produces the following profiles:



- Both types of adaptive responses drastically reduce the virus load
- Antibodies alone cannot clear the infection – T cells are crucial for clearing infection

Model predictions for the acute phase of infection: Interactions between cellular and humoral immune response



- Both types of immune responses compete with each other
- We can show that the relative strength of immune responses determines the outcome of infection

5 possible long-term outcomes (equilibria)

- By setting all differential equations to zero we can get expressions for the variables Z, X, Y, V, U & W at the equilibrium
- These represent 5 possible outcomes:
  1. Infection & Immune response clear (E1)

     virus load (V) = 0, nr. Infected cells (Y) = 0, Nr. nABs (W) = 0, nr. T-cells (U) = 0
  2. Persistent infection, virus outcompetes immune response (E2)

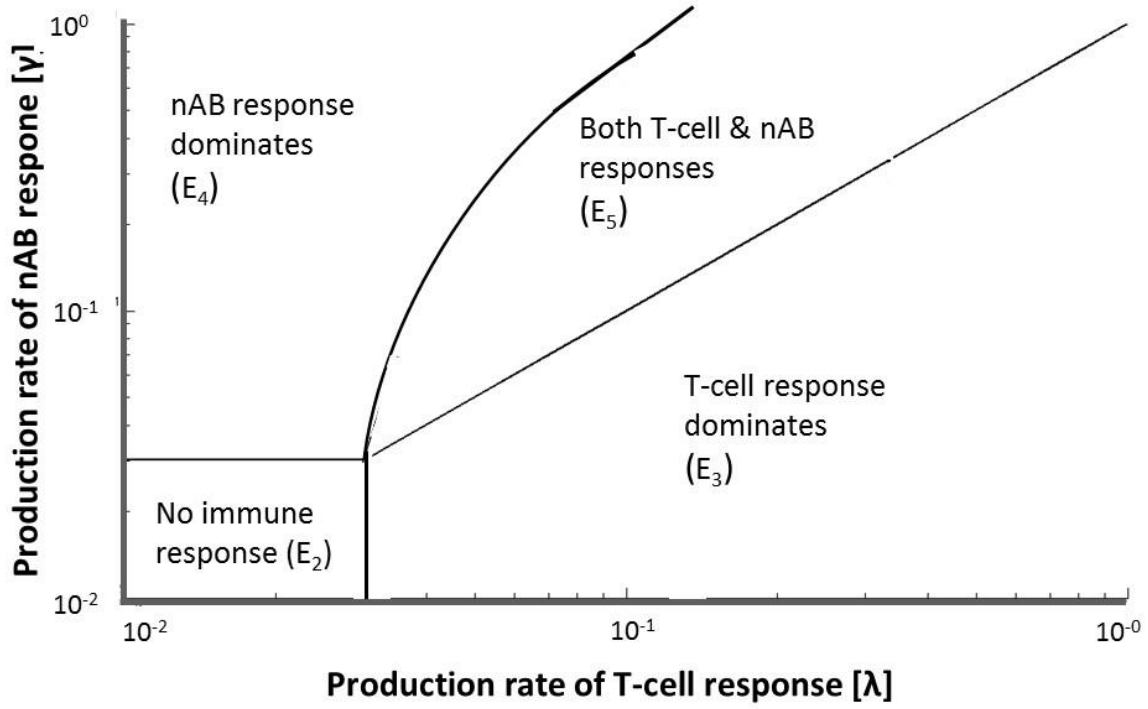
     $V > 0, Y > 0, W = U = 0$
  3. Persistent infection, T-cell response dominates (E3)

     $V > 0, Y > 0, W = 0, U > 0$
  4. Persistent infection, nAB response dominates (E4)

     $V > 0, Y > 0, W > 0, U = 0$
  5. Persistent infection, both types of immune responses prevail (E5)

     $V > 0, Y > 0, W > 0, U > 0$

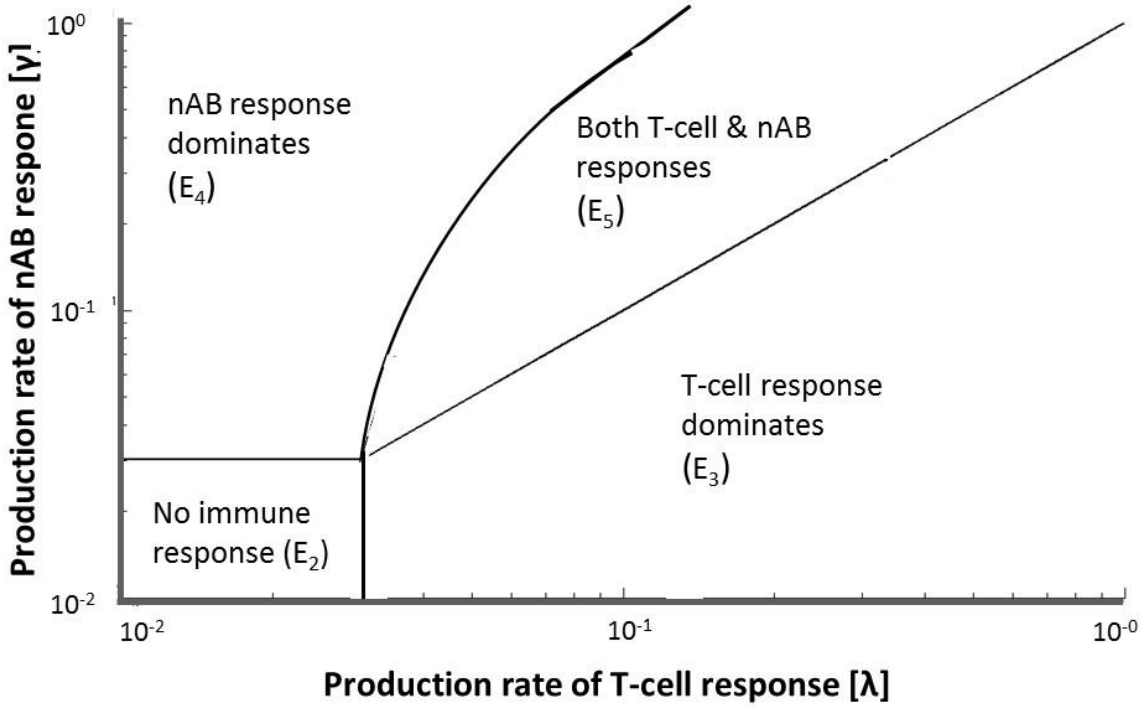
The outcome depends on the relative strengths of both arms of immunity



The regions corresponding to the different outcomes were obtained by stability analysis (not shown in this course)

Doeschl-Wilson and Galina-Pantoja (2010)

The outcome depends on the relative strengths of both arms of immunity

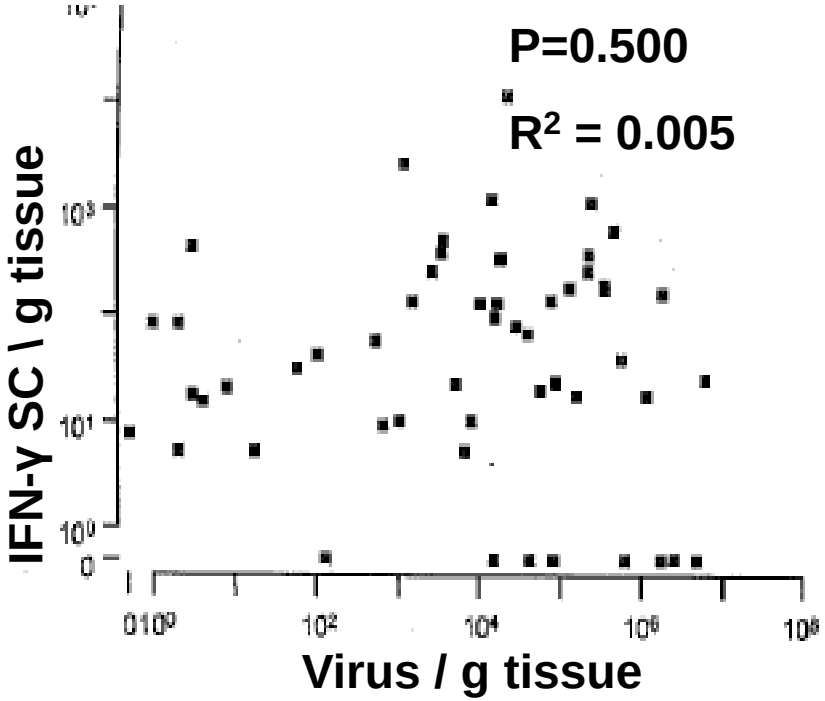


- Slight differences in individuals' immuno-competence can lead to different infection outcomes
- ➢ Possible explanation for large variation in PRRS infection profiles?
- One can show mathematically that the system always converges to the outcome corresponding to minimum virus load
- ➢ Is the (real) immune system optimised for minimising virus load?

Doeschl-Wilson and Galina-Pantoja (2010)

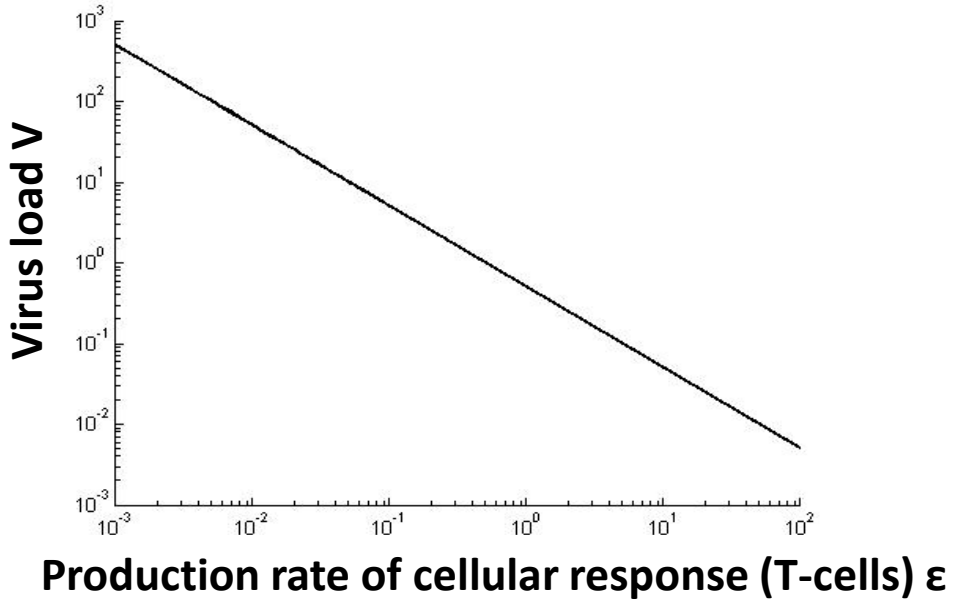
Model application: How important are T-cells for viral clearance?

- There are conflicting opinions about how important T-cells are for virus clearance
- Experimental findings report poor correlation between virus load and T cell response
- Does this imply that T-cells don't play a crucial role?



Model application: How important are T-cells for viral clearance?

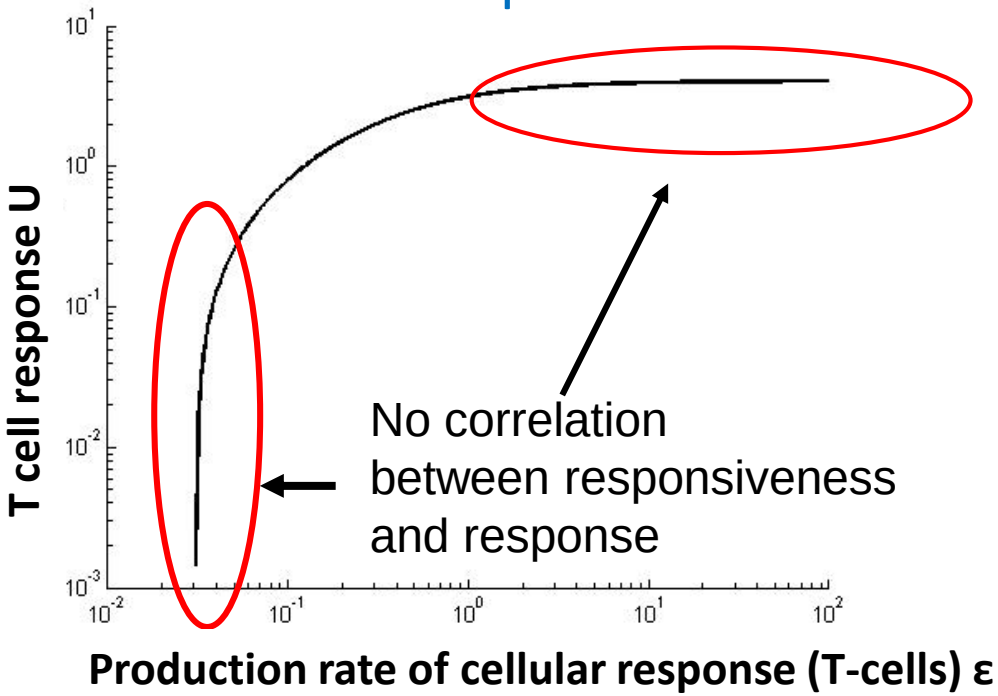
Model prediction



The model suggests that virus load is good indicator for host ability to launch a T-cell response

Model application: How important are T-cells for viral clearance?

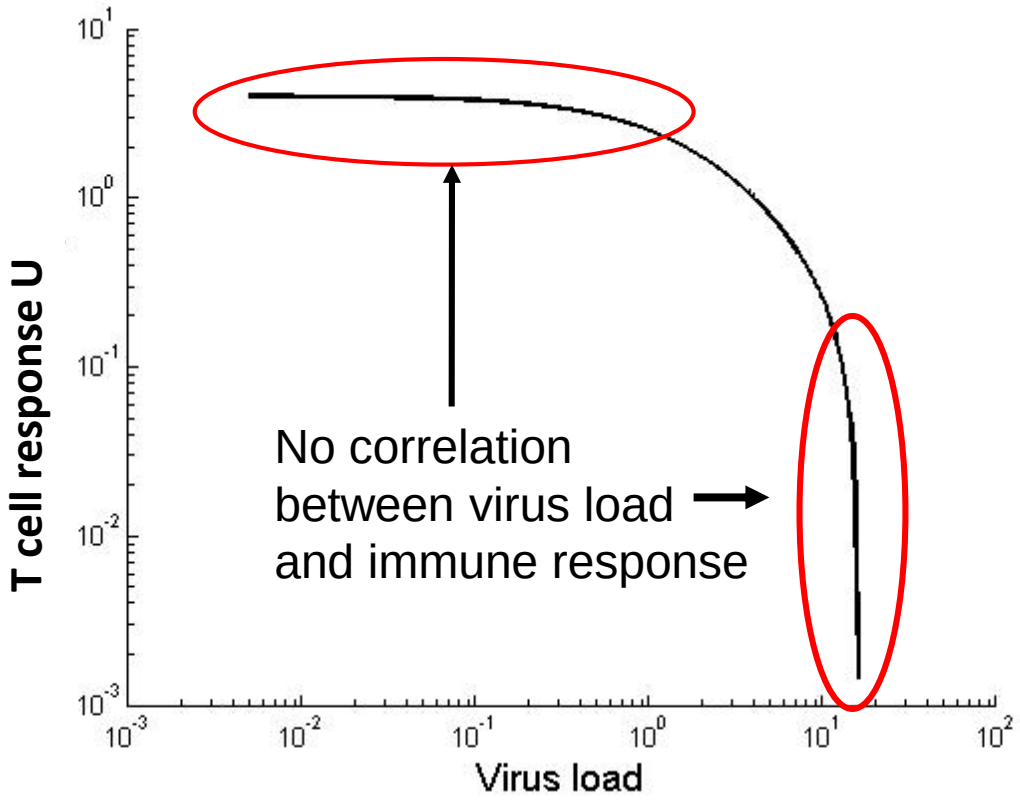
Model prediction



- However, the relationship between the host ability to launch T-cell response and the actual T-cell response is non-linear
- Relationship is only apparent if full range of values is expressed

Model application: How important are T-cells for viral clearance?

Model prediction

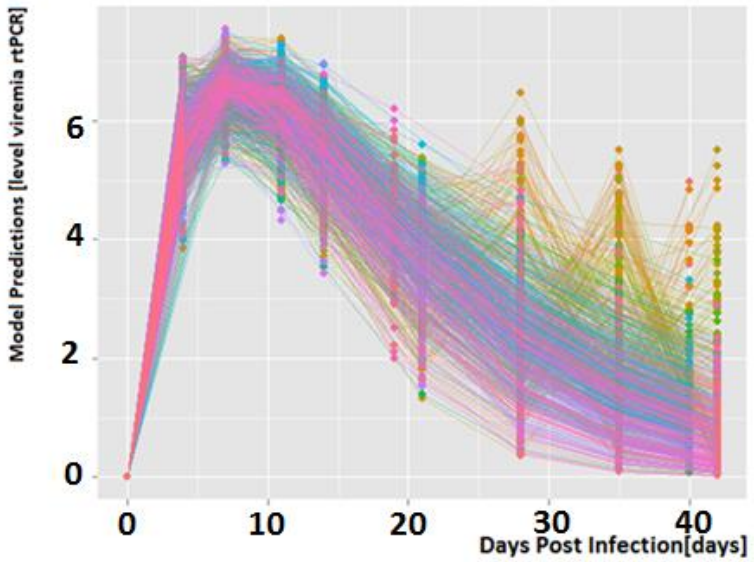


- Also, the relationship between virus load and T-cell response is non-linear and not apparent unless the full range of values is observed

➢ An observed weak correlation between virus load and immune response does not necessarily imply an inefficient immune response!

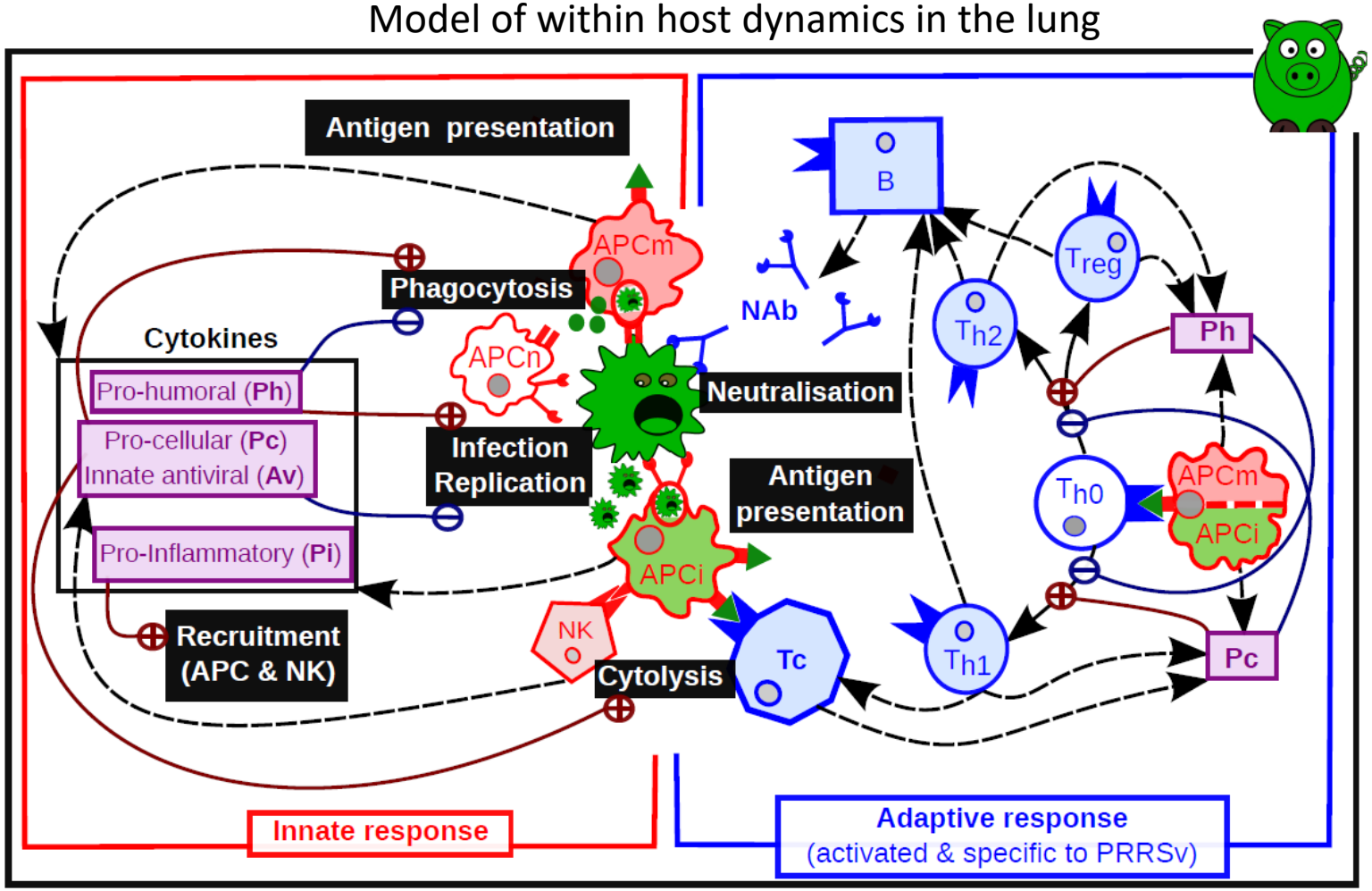
From a toy model towards a more realistic process based model of within host PRRS infection dynamics

- The simple host-pathogen interaction model provides an extremely crude & generic representation of the immune response
- It cannot produce virus load profiles that are a good match (in shape and scale) to the experimental data



A more realistic process based model of PRRSV infection dynamics

Model of within host dynamics in the lung



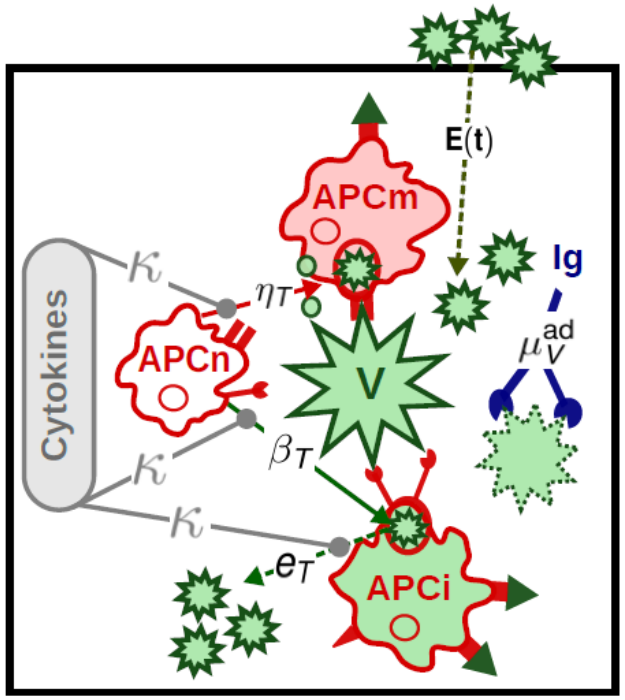
- The model synthesizes existing literature findings on immune response to PRRSV infection

APC = antigen presenting cell
(n=naïve, m = mature, i = infected)
NK = natural killer cell
Tc = cytotoxic T cells
Treg = regulatory T cells
Th = T helper cells
B = B-cell
NAb = neutralizing antibody

Go et al., PLoS ONE 2014

Model equations (example)

Viral dynamics:



$$\dot{V} = + \underbrace{E(t)}_{\text{exposure}}$$

$$- \underbrace{\eta_T \, V \, (APC_n + APC_m) \, \kappa^-(\bullet) \, [1 + \kappa^+(\bullet)]}_{\text{phagocytosis}}$$

$$- \underbrace{\beta_T \, V \, (APC_m + APC_n) \, \kappa^-(\bullet) \, [1 + \kappa^+(\bullet)]}_{\text{infection}}$$

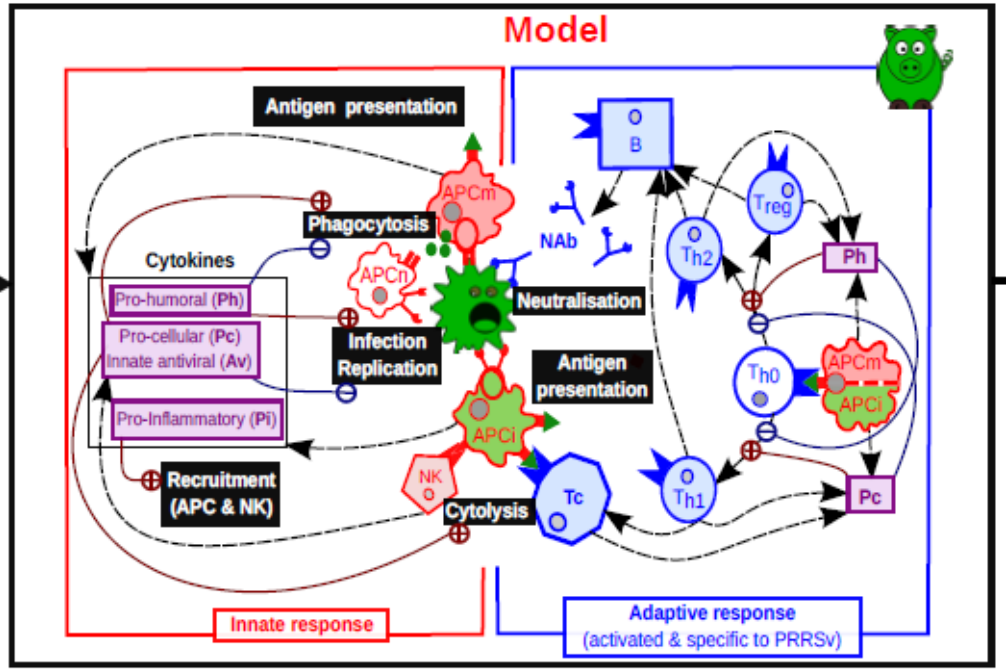
$$+ \underbrace{e_T \, APC_i \, \kappa^-(\bullet)}_{\text{excretion}}$$

$$- \underbrace{\mu_V^{ad} \, V \, I_g}_{\text{neutralisation}}$$

$$- \underbrace{\mu_V^{nat} \, V}_{\text{natural decay}}$$

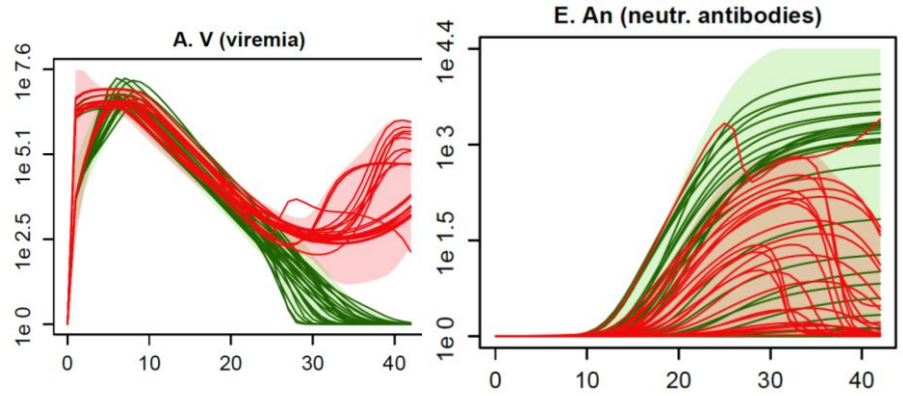
Model inputs and outputs:

Parameters [50]:
- APC-PRRSv interactions
- Adaptive response activation
- Adaptive response orientation
- Cytotoxic cell functions
- Antibody functions
- Cytokine synthesis
- Cytokine functions
- Other (decay, ...)
- Viral exposure



Dynamics of [19]
- PRRSv [1]
- Innate response [4]
  - APC [3]
  - NK [1]
- Adaptive response [6]
  - cellular [2]
  - humoral [3]
  - regulatory[1]
- Cytokines [8]
  - pro-Inf [1]
  - innate antiviral [2]
  - pro-cellular [2]
  - pro-humoral [3]

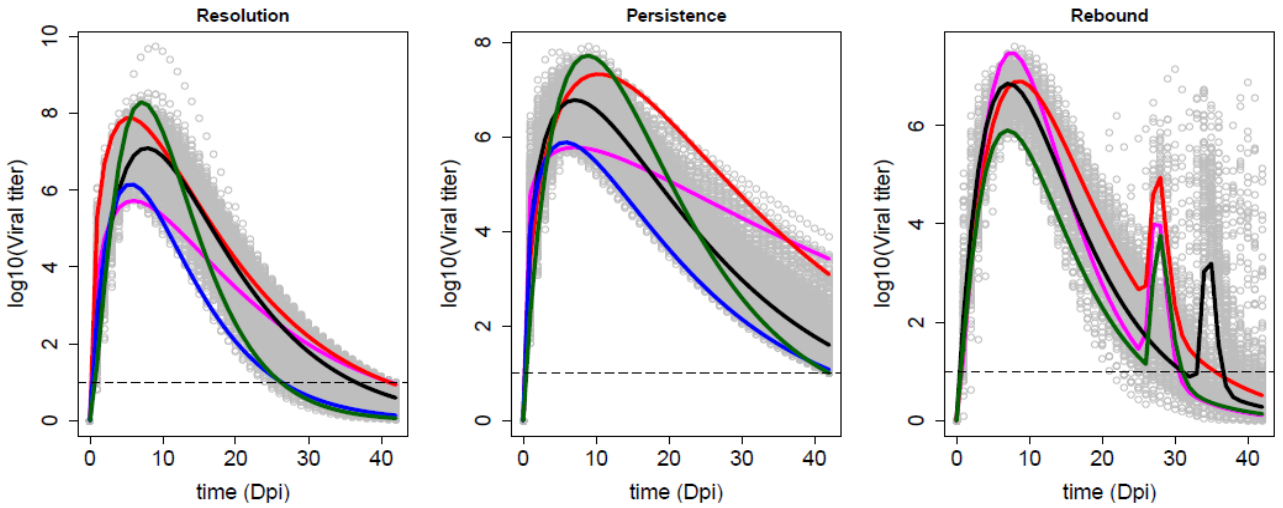
Pig	α	δ	ω	Φ
1	0.001	0.349	0.002	0.987
2	0..02	0.567	0.001	0/890
3	0.0004	0.345	0.002	0.987
4	0.0034	0.012	0.004	0.999
5	0.0023	0.675	0.007	0/.99

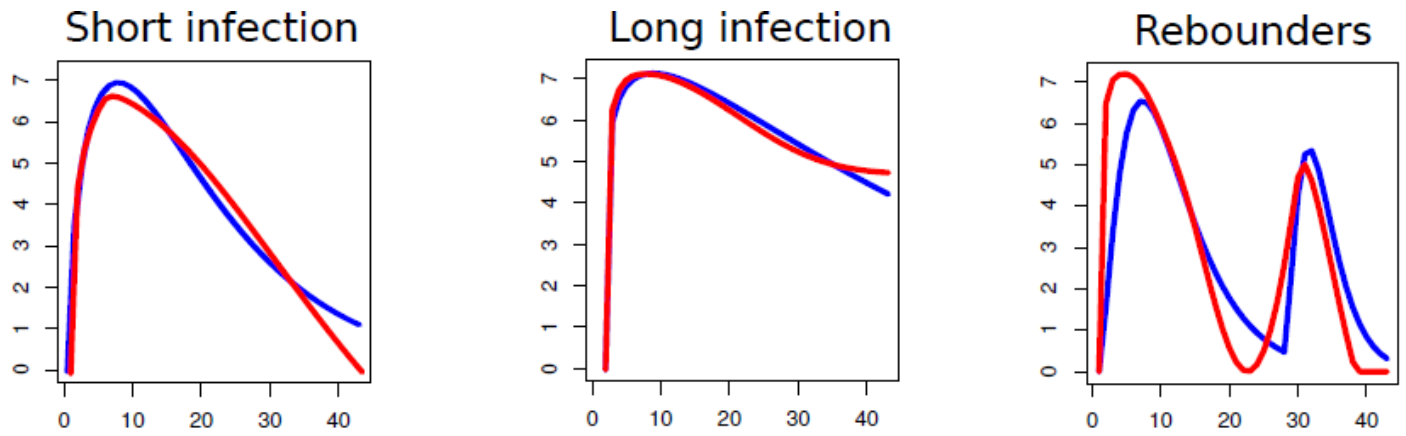


Modelling steps

1. Exploratory analysis
   - what types of viremia and immune response profiles can the model generate?
2. Fit model to experimental viremia data
   - Refine the data / specify criteria
   - Can the model reproduce the observed viremia profiles?
3. Identification of candidate mechanisms for rebound
   - Compare parameter estimates and immune response characteristics associated with either rebounders on non-rebounders
4. Validate candidate mechanisms
   - Perform an in-silico knock-out experiment

Exploratory analysis: Can this model reproduce the wide range of observed viraemia profiles?



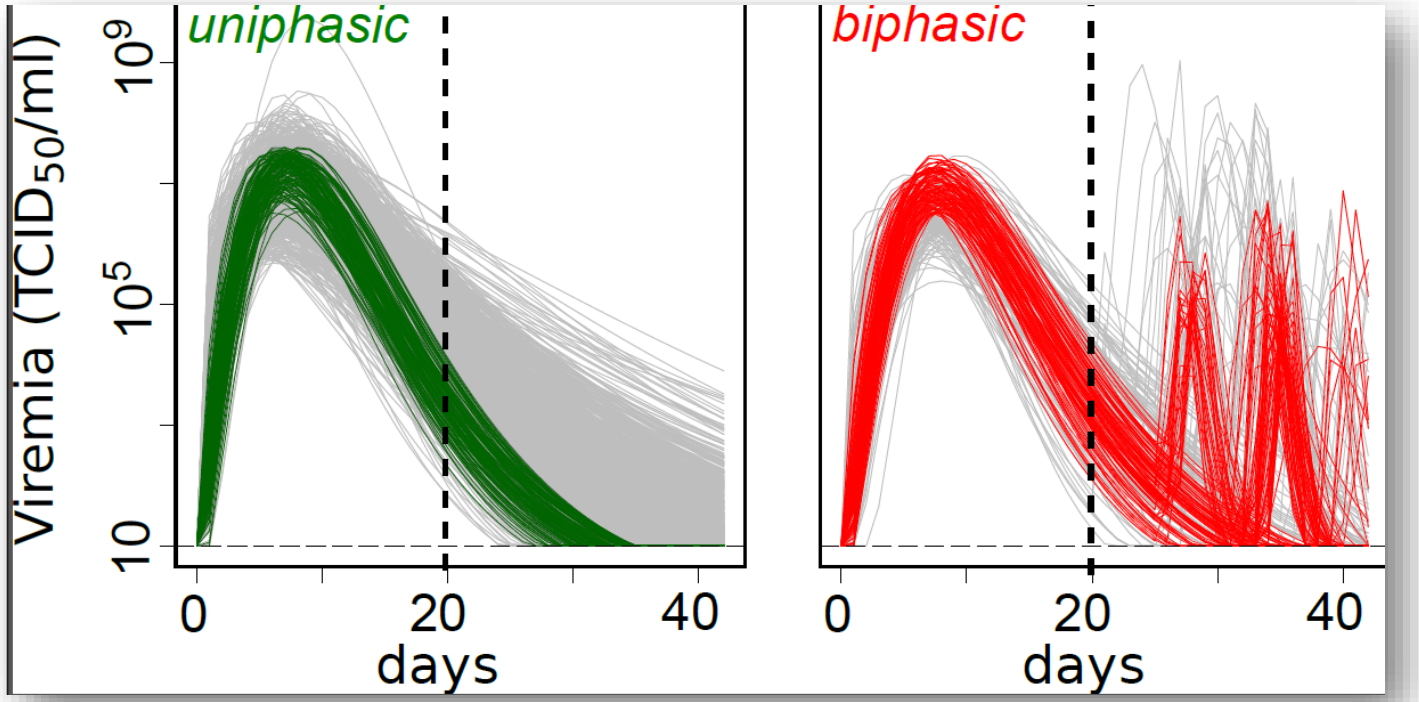


Fitting the process based ODE model to the data (smoothed by extended Woods function!) shows that the process based model is able to reproduce the full range of observed virus load profiles

Data
Model

Model fitting – data selection

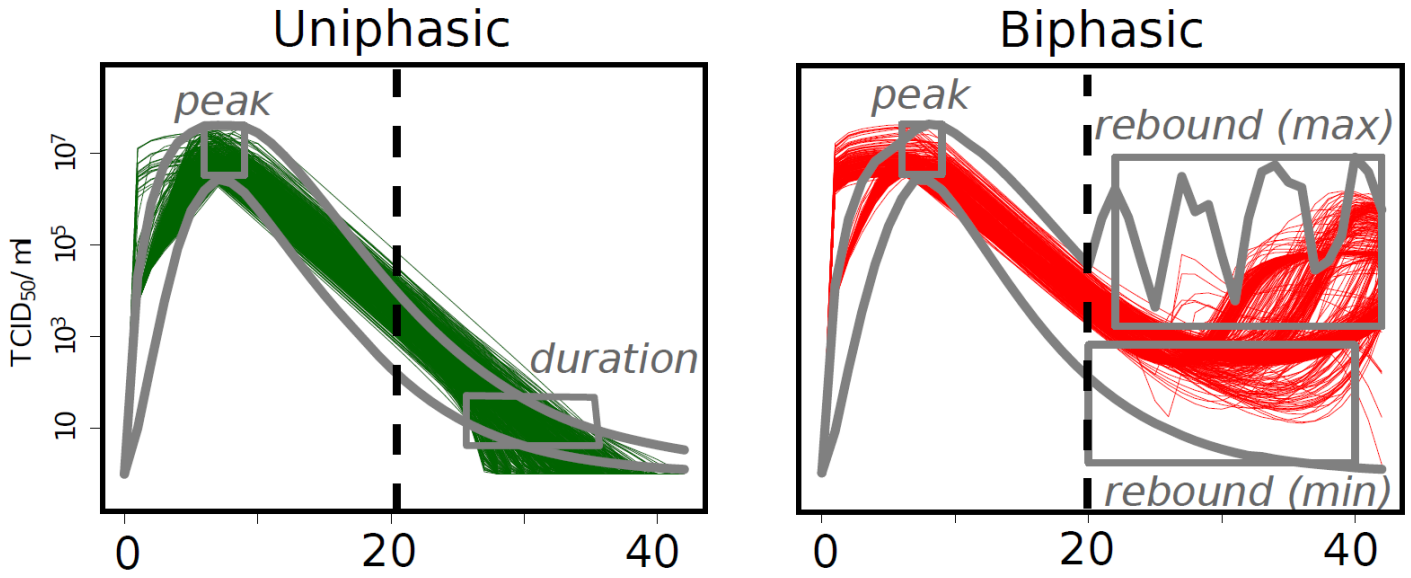
Woods viremia profiles from the PHGC nursery pigs



Avoid confounding by select subset of viremia profiles:

- Non-rebounders have cleared the virus from blood by day 35
- Rebounders and non-rebounders have similar characteristics within first 3 weeks post infection

Model fitting – defining goodness of fit



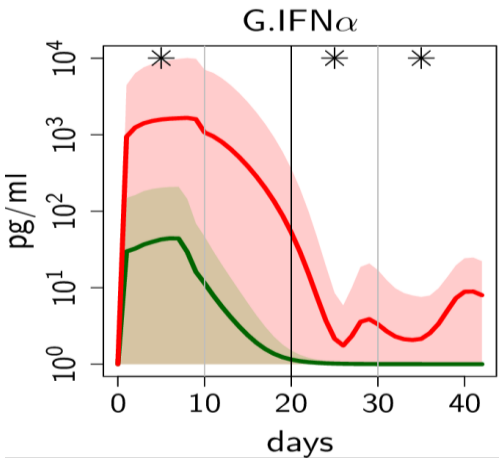
→ **Fitted viremia fully match & cover the whole data range**
(focus on viremia indicators)

All profiles within the grey data envelope are considered as acceptable

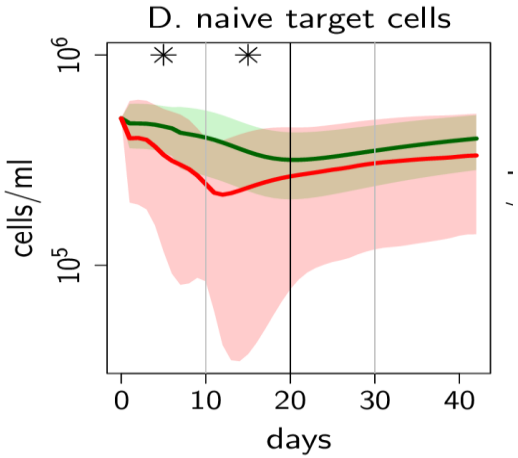
Parameter estimates obtained by an Adaptive Random Search algorithm applied to 625 randomly chosen initial parameter sets

Can this model help to determine which mechanisms are responsible for viremia rebound?

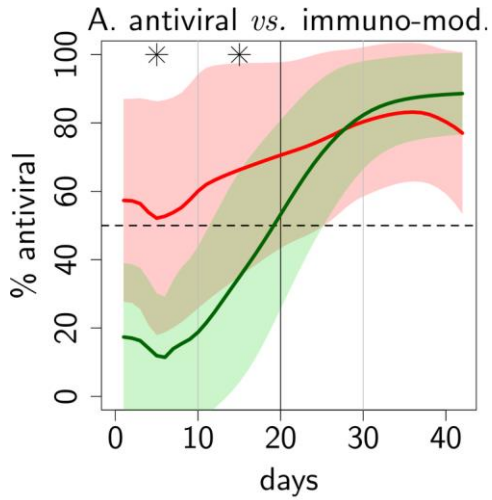
Rebounders are characterised by:



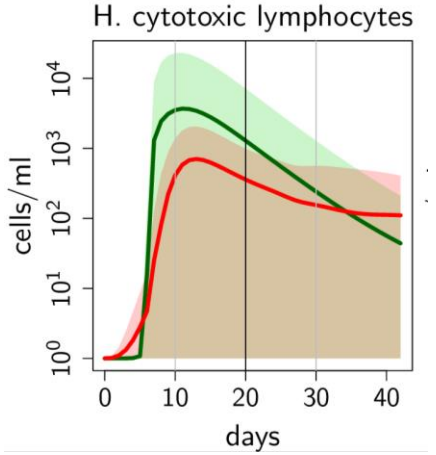
Stronger immune response activation



Faster depletion of target cells



Predominant orientation towards antiviral response



Lower CTL & nAB response

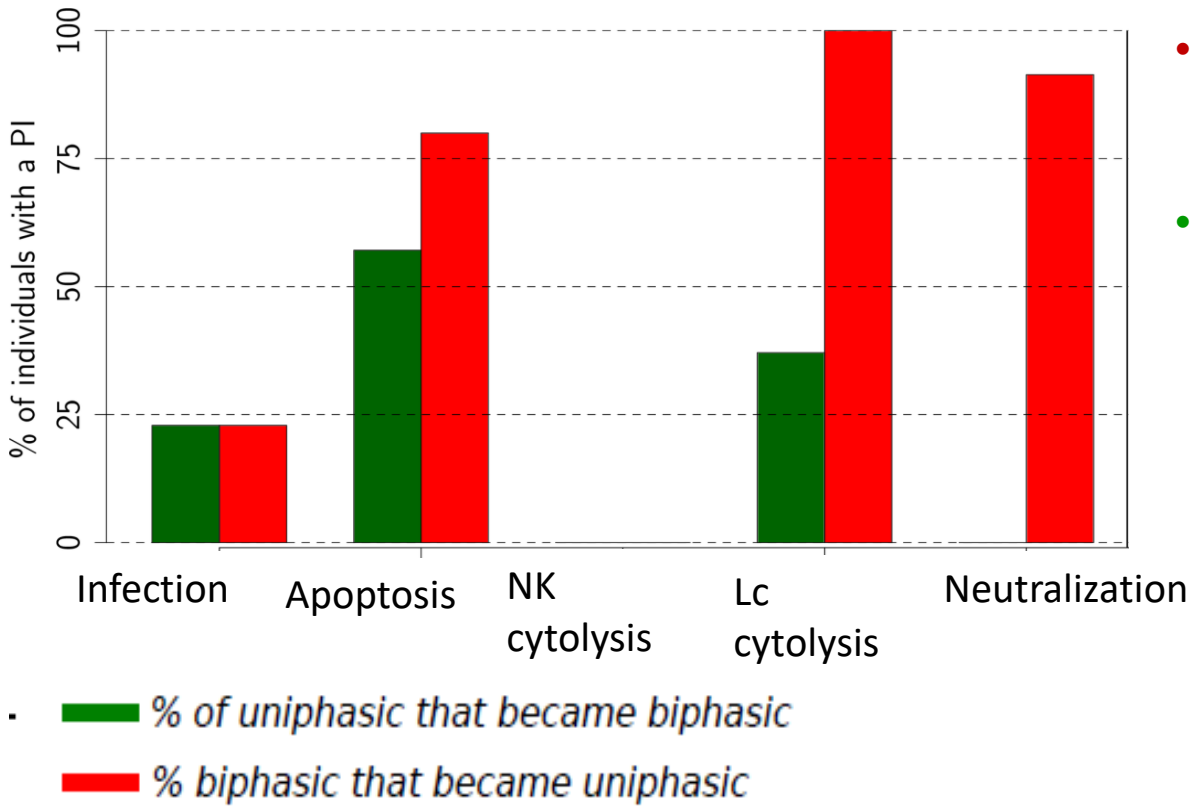
Non-rebound
Rebound

But which of these are causative?

Validation of candidate mechanisms for rebound

Simulated knock-out experiments:

- Can we **prevent rebound** by altering a specific mechanism?
- Can we **trigger rebound** by modulating the mechanism in the opposite direction?



- Boosting cytolysis or virus neutralization prevents rebound
- Weak virus neutralization alone does not cause rebound

Can we believe the model results?

- Modelling challenge: Many parameter combinations produce similar virus load profiles
  - This phenomenon is known as *Identifiability problem*
  - *Identifiability analysis*: group of statistical methods for estimating how well model parameters are determined by the amount and quality of experimental data

- But could this ambiguity in parameter estimates also reflect the real situation?
  - Many possible infection routes may lead to the same outcome
  - This may explain the apparent ambiguity in experimental results

- Only experimental validation can tell!

Summary

- Different types of mathematical models answer different types of questions
- Empirical & mechanistic models can be complementary
- Even very simple models can generate valuable insights
- There is a wealth of analytical tools available to rigorously examine differential equation models
- There is a trade-off between making the model sufficiently simple to gain relevant insights and sufficiently complex to be realistic
- Take home message: Start simple and gradually build up complexity

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