Using mathematical models to solve mysteries of host-pathogen interaction in mammals: Insights from a viral disease in pigs

Andrea Doeschl-Wilson & Lucina Galina-Pantoja

Outline

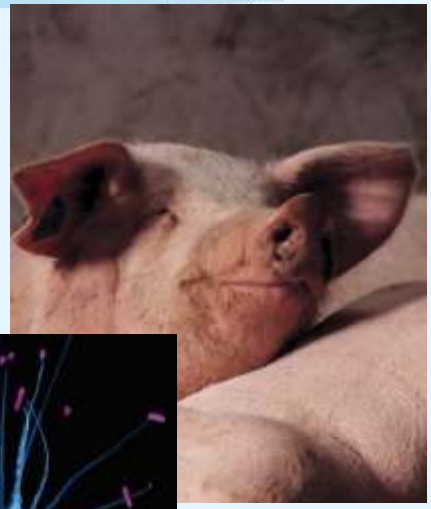
- The role of mathematical models in understanding host-pathogen interactions
- The porcine reproductive and respiratory syndrome (PRRS) and its mysteries
- Using mathematical models to unravel some mysteries of PRRS virus dynamics
- Conclusions and implications

The role of mathematical models for disease research

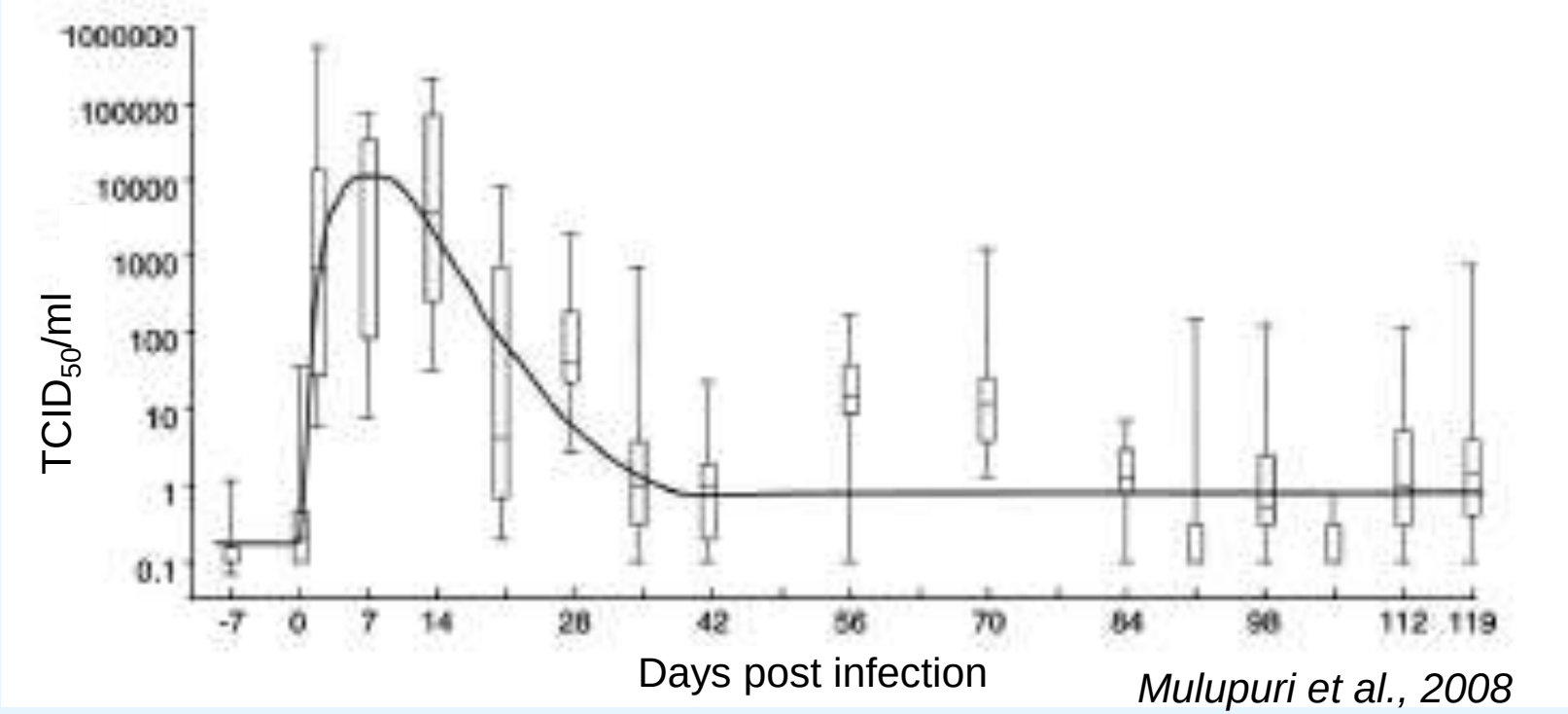
- Host-pathogen interactions mostly studied by microbiologists, veterinarians & immunologists
- Molecular techniques provide relevant insight of cellular pathways
- But limited understanding of the system as a whole
- Mathematical models integrate existing knowledge into a comprehensive theoretical framework
- Huge contribution of mathematical models to human diseases but few applications to livestock

Porcine reproductive and respiratory syndrome (PRRS)

- Endemic viral disease, causes dramatic losses to pig industry
- Symptoms:
  - Reproductive failure in mature pigs
  - Respiratory problems, fever, weight loss, death in growing pigs
- Target cells: subpopulation of macrophages in lung and other tissues
- Vast amount of research, but no efficient control measures



Atypical viremia profile



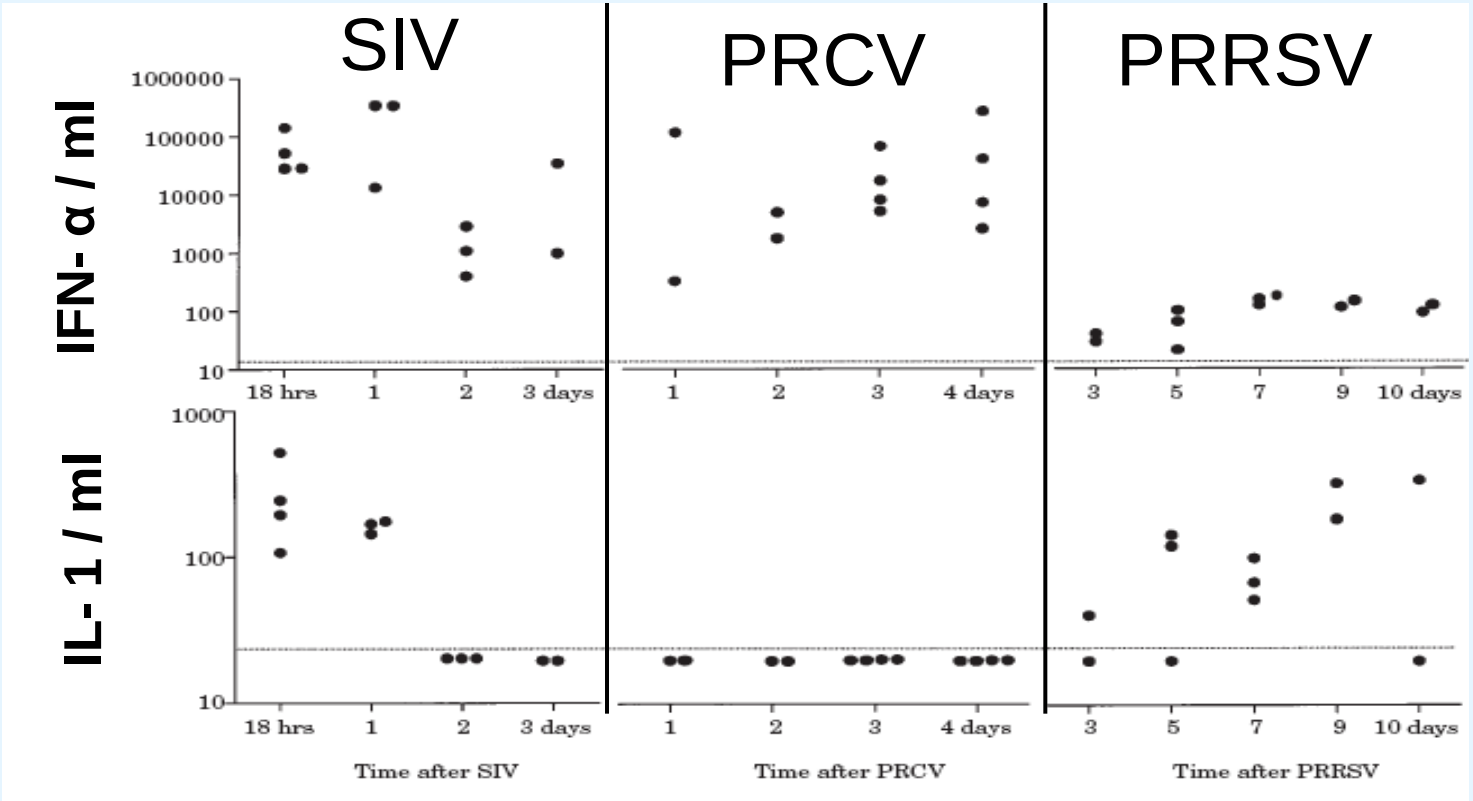
Mulupuri et al., 2008

- peak levels at 7-14 days post infection
- acute phase lasts approx. 4 weeks
- long-term persistence at low levels
- large variation between hosts

} Atypical profile for virus infections!

Little innate immune response

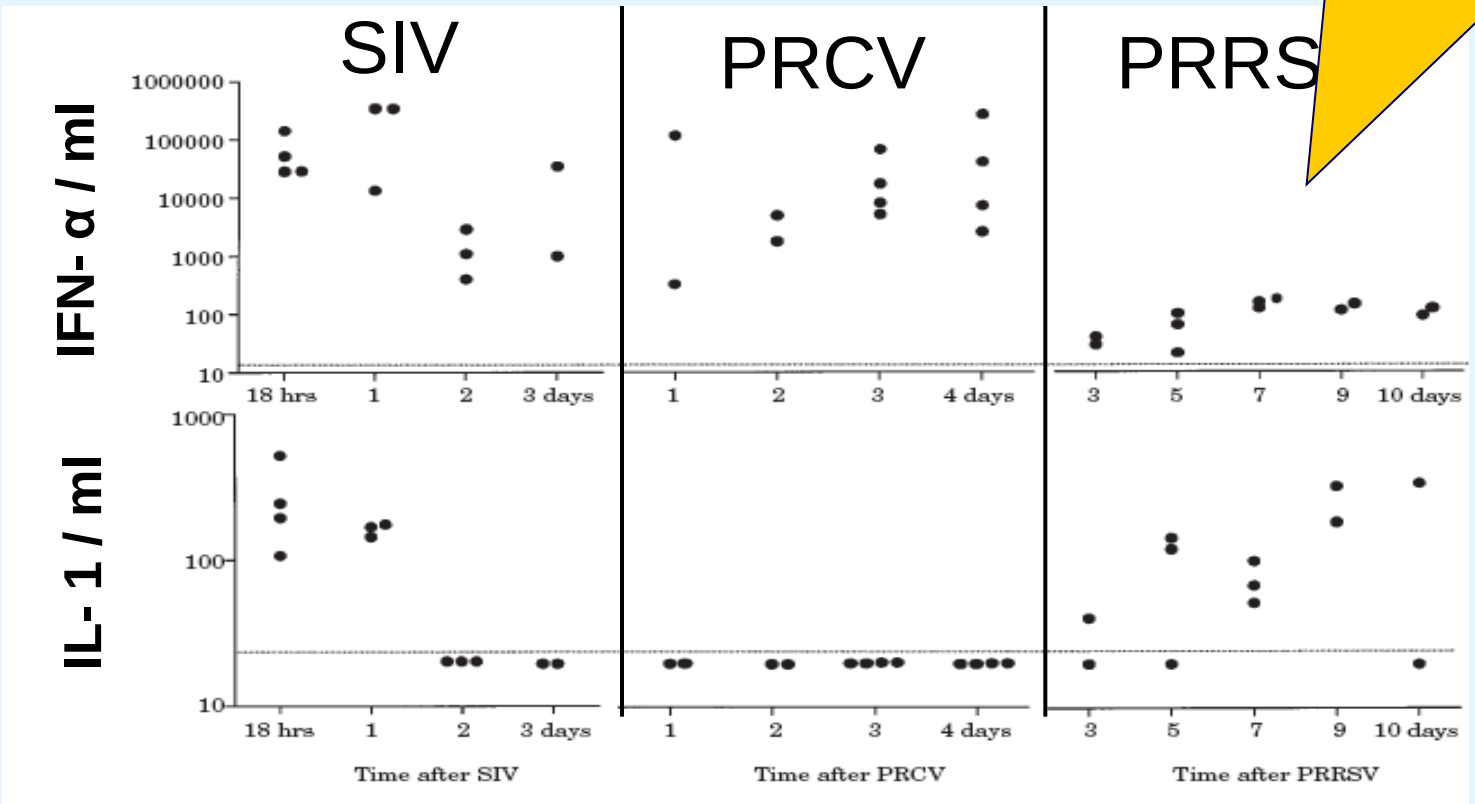
- Lack of typical cytokine expressions
- Virus seems to manipulate innate response to its favour



Van Reeth et al., 1999

Little innate immune response

Down-regulation of IFN-α facilitates virus replication



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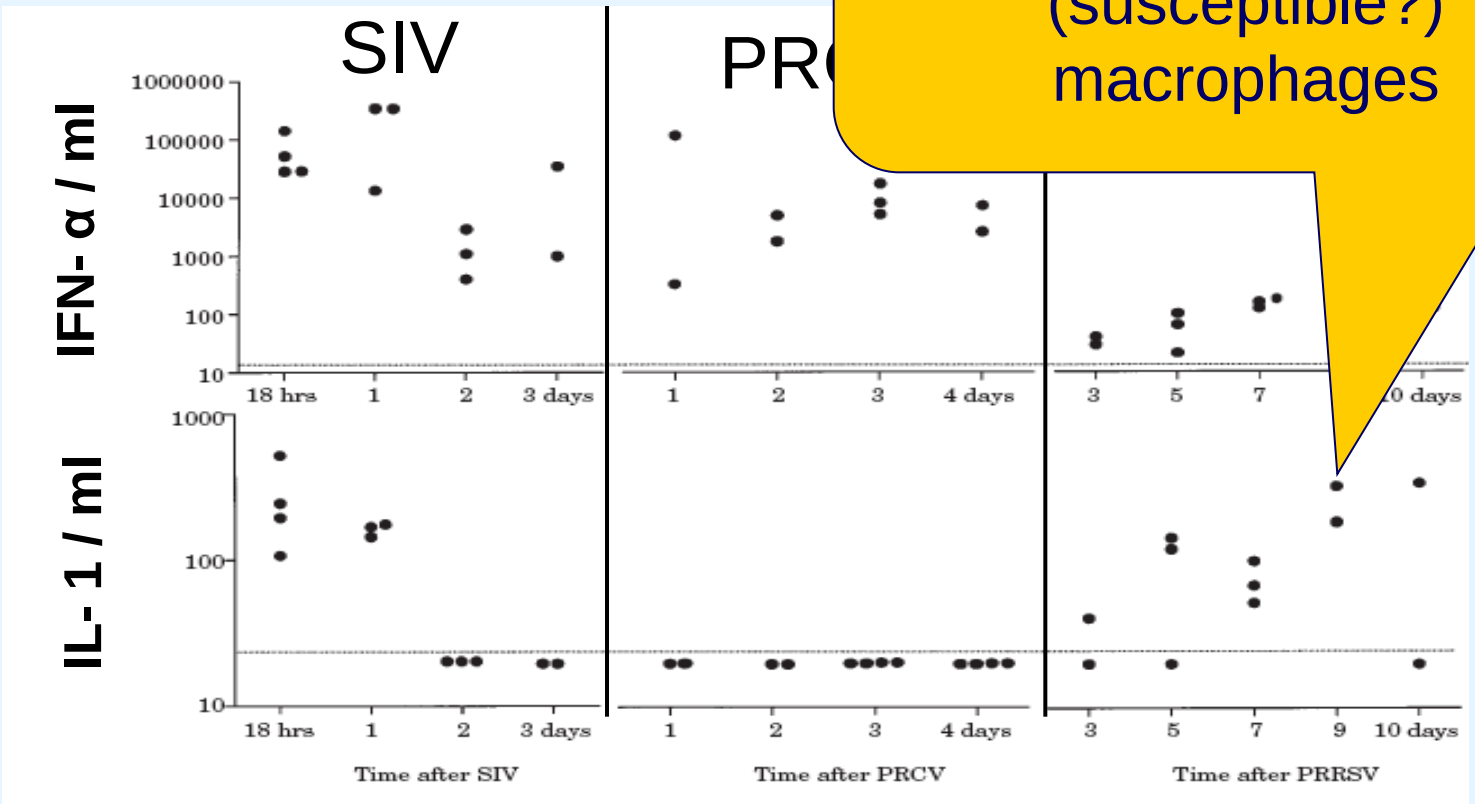
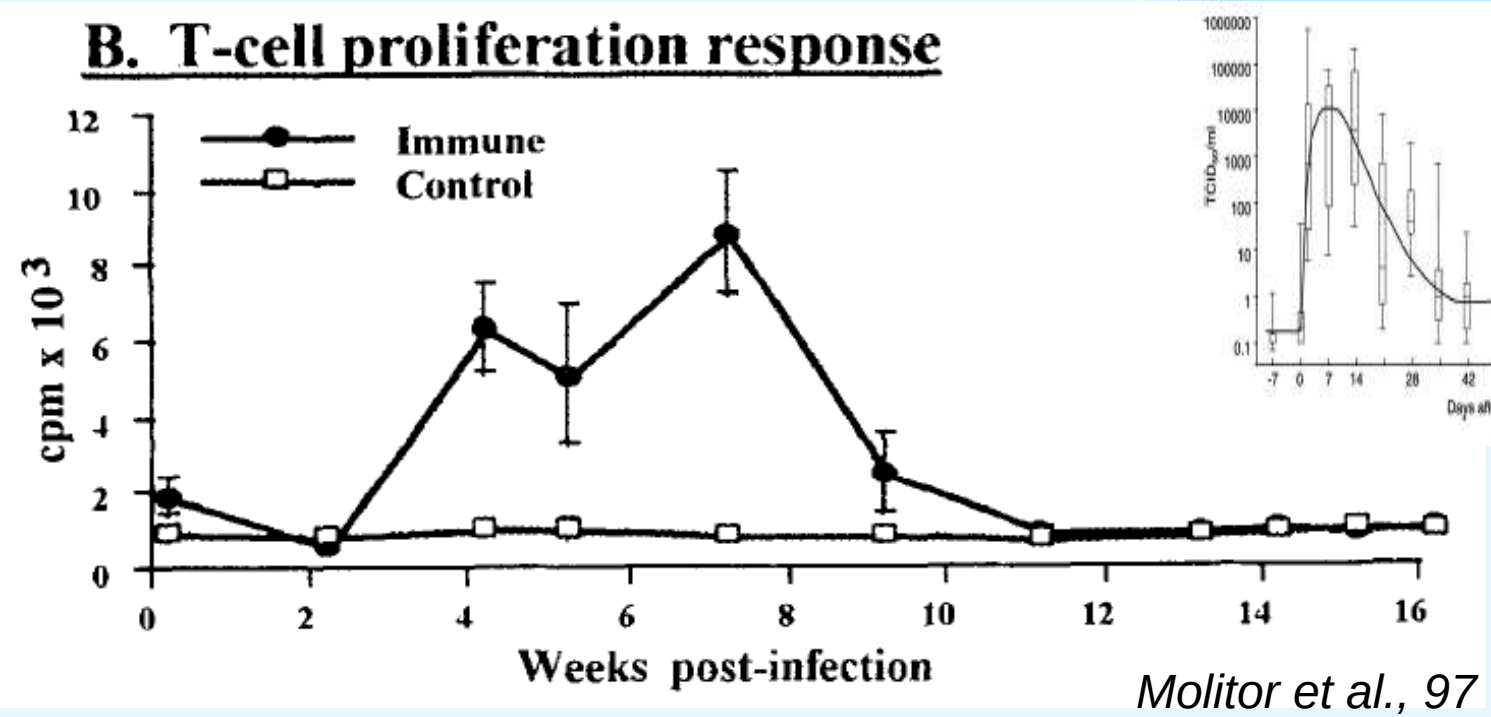
Little innate immune response

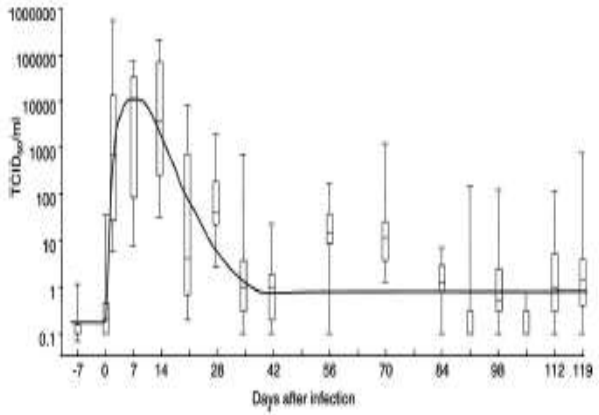
Up-regulation of IL-1 stimulates influx of new (susceptible?) macrophages



Van Reeth et al., 1999

Weak and delayed adaptive immune response



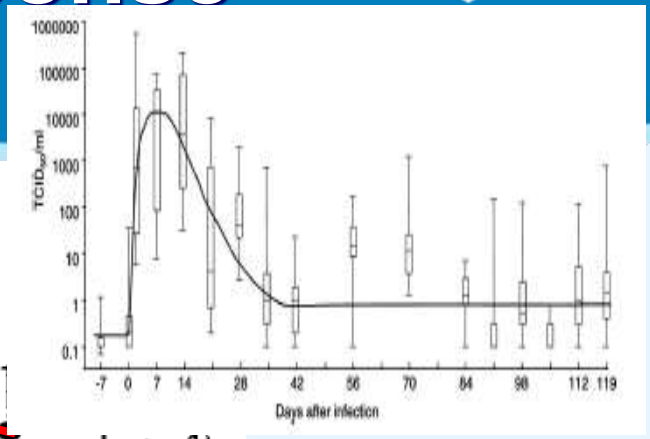


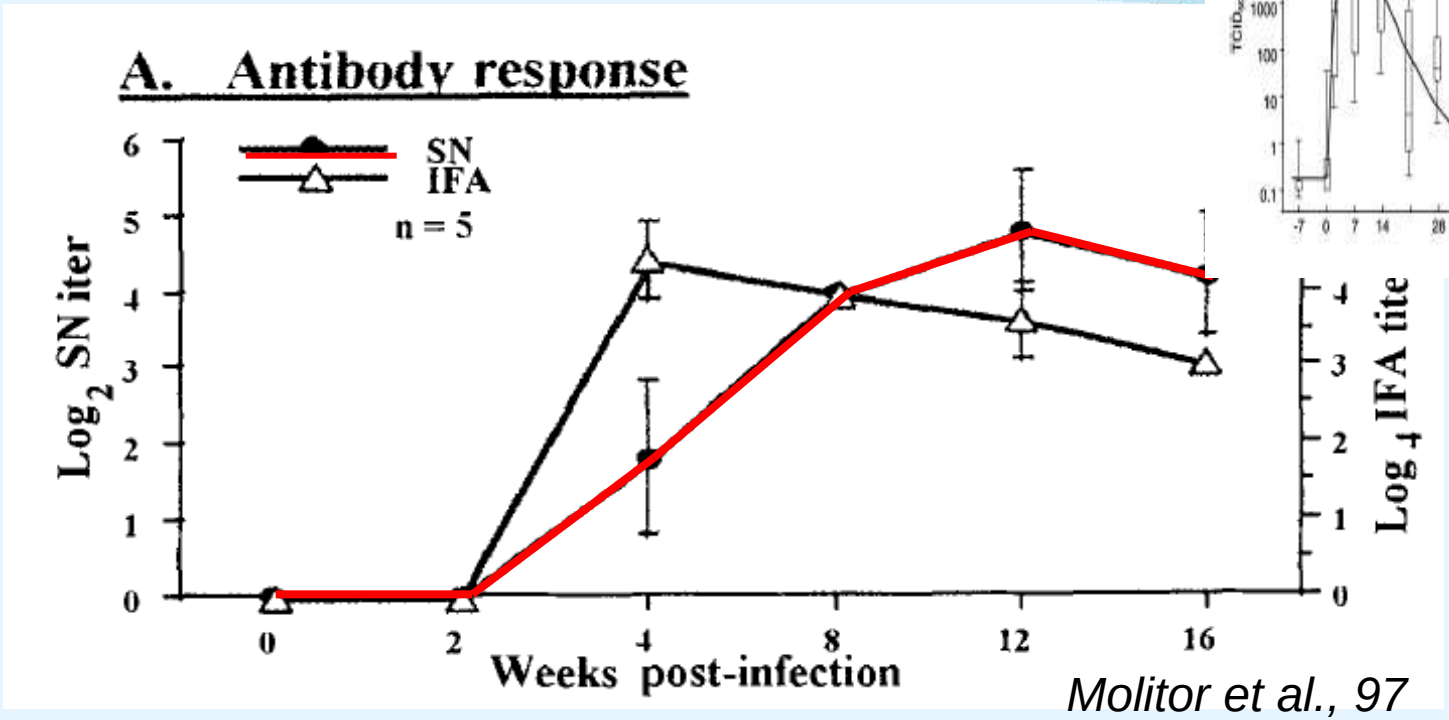
Molitor et al., 97

- T cell response delayed & weak
- out of synch with virus load
- Large variation between hosts

What role do T cells play in clearing the infection?

Atypical antibody response





Molitor et al., 97

- Neutralizing antibodies appear late
- Antibody levels remain high
- Large variation between hosts

What role do neutralizing antibodies play in clearing the virus?

Questions addressed in this modelling study

1. What causes the virus decline during the acute phase of infection (before adaptive response kicks in)?

2. What role does the adaptive immune response play?

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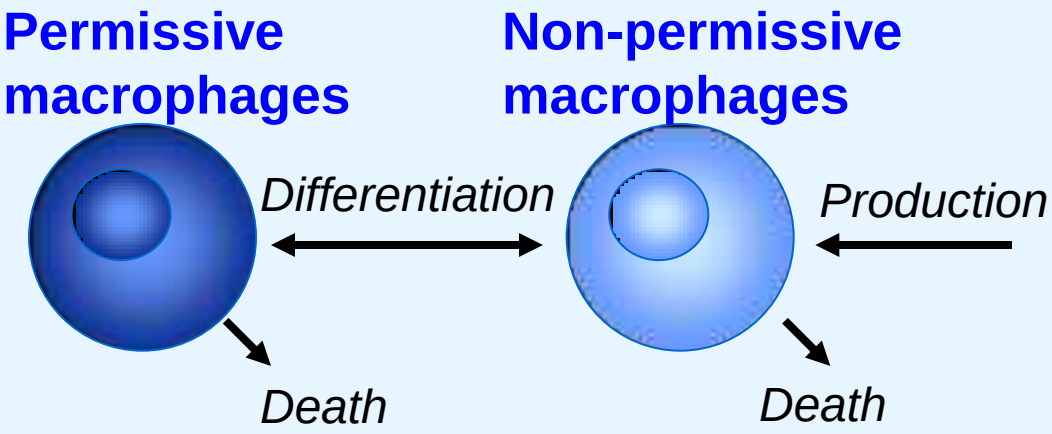
Basic model of PRRSV dynamics – no immune response



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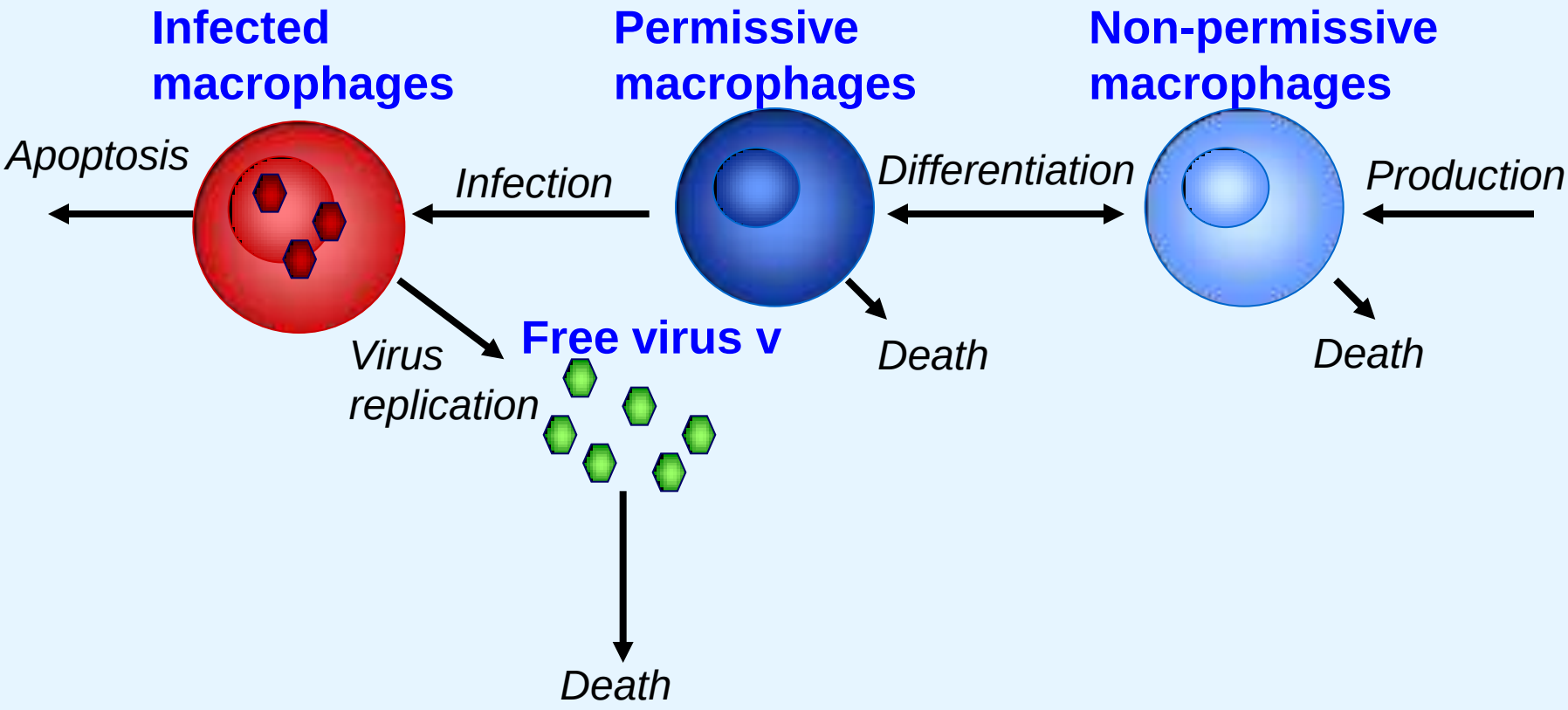

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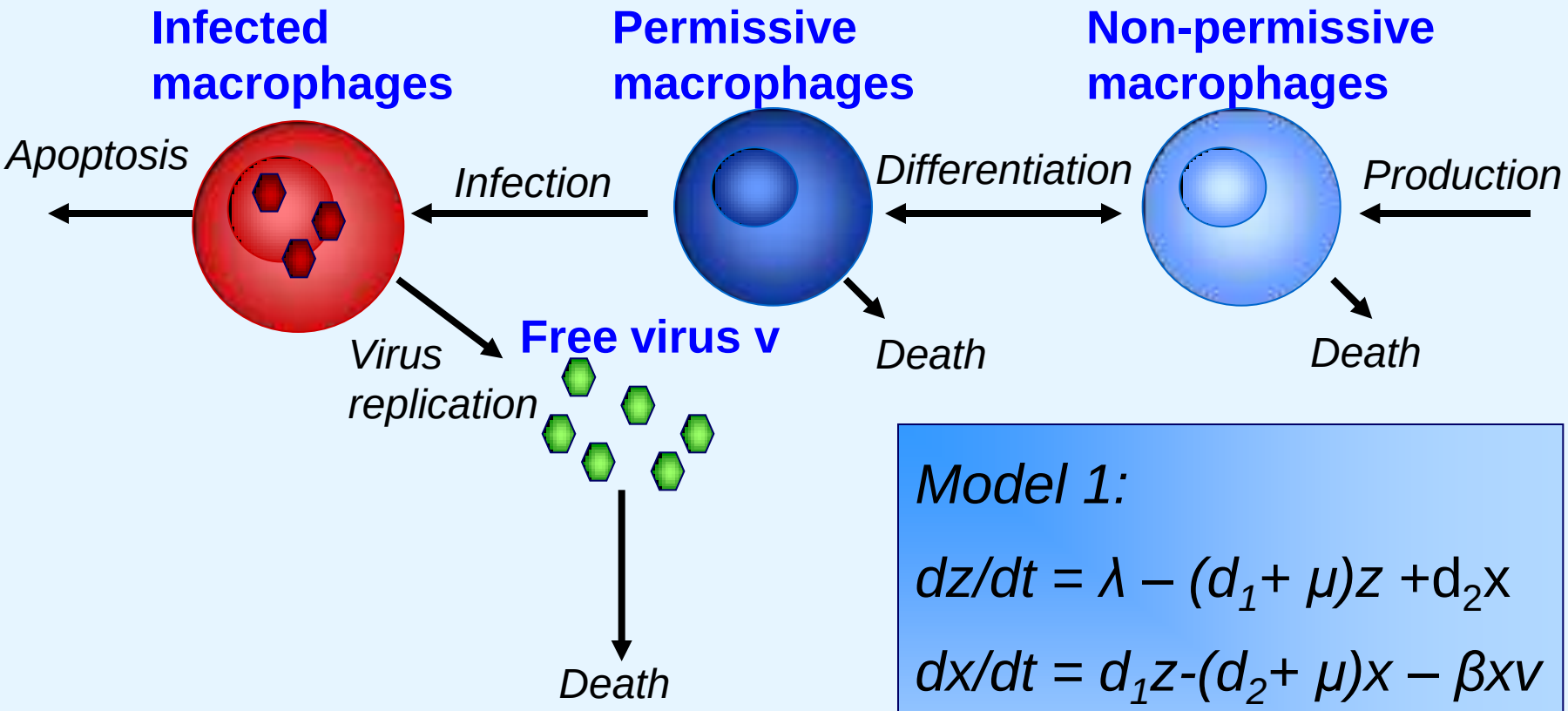


Model 1:

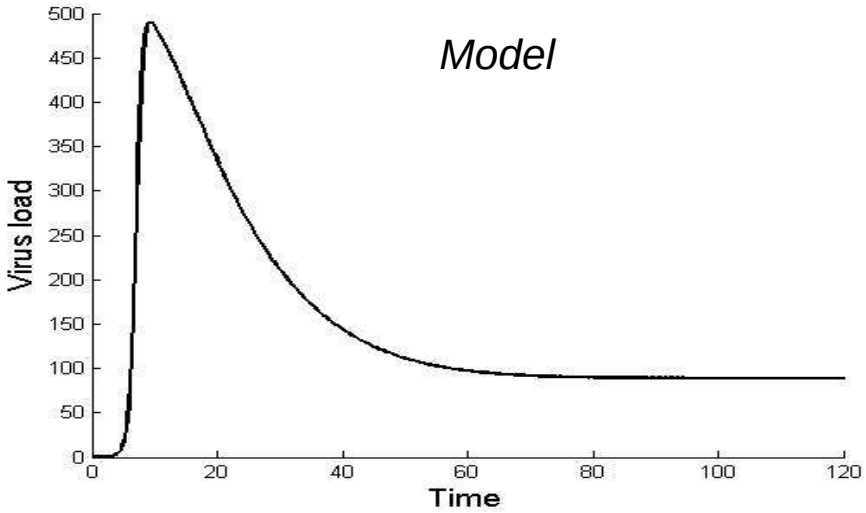
$dz/dt = \lambda - (d_1 + \mu)z + d_2 x$

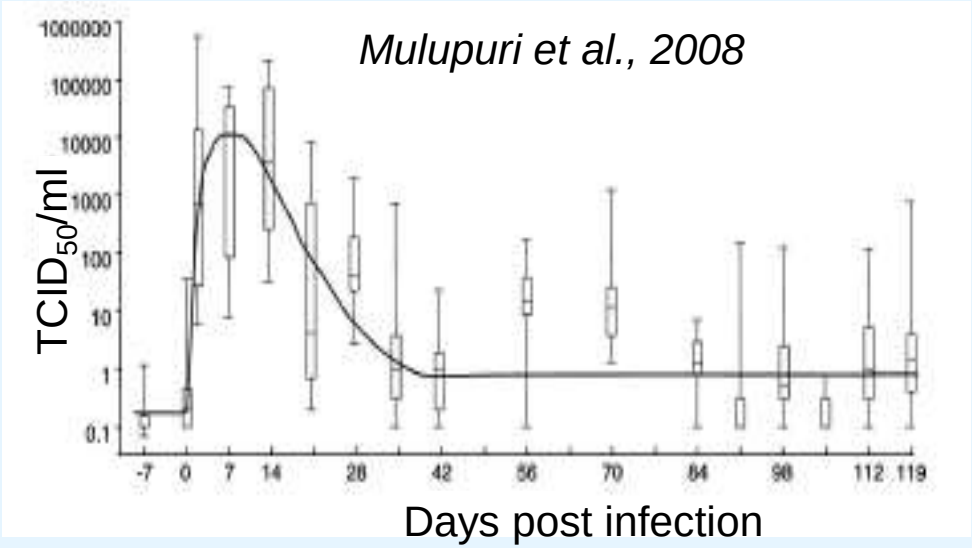
$dx/dt = d_1 z - (d_2 + \mu)x - \beta xv$

$dy/dt = \beta xv - \alpha y$

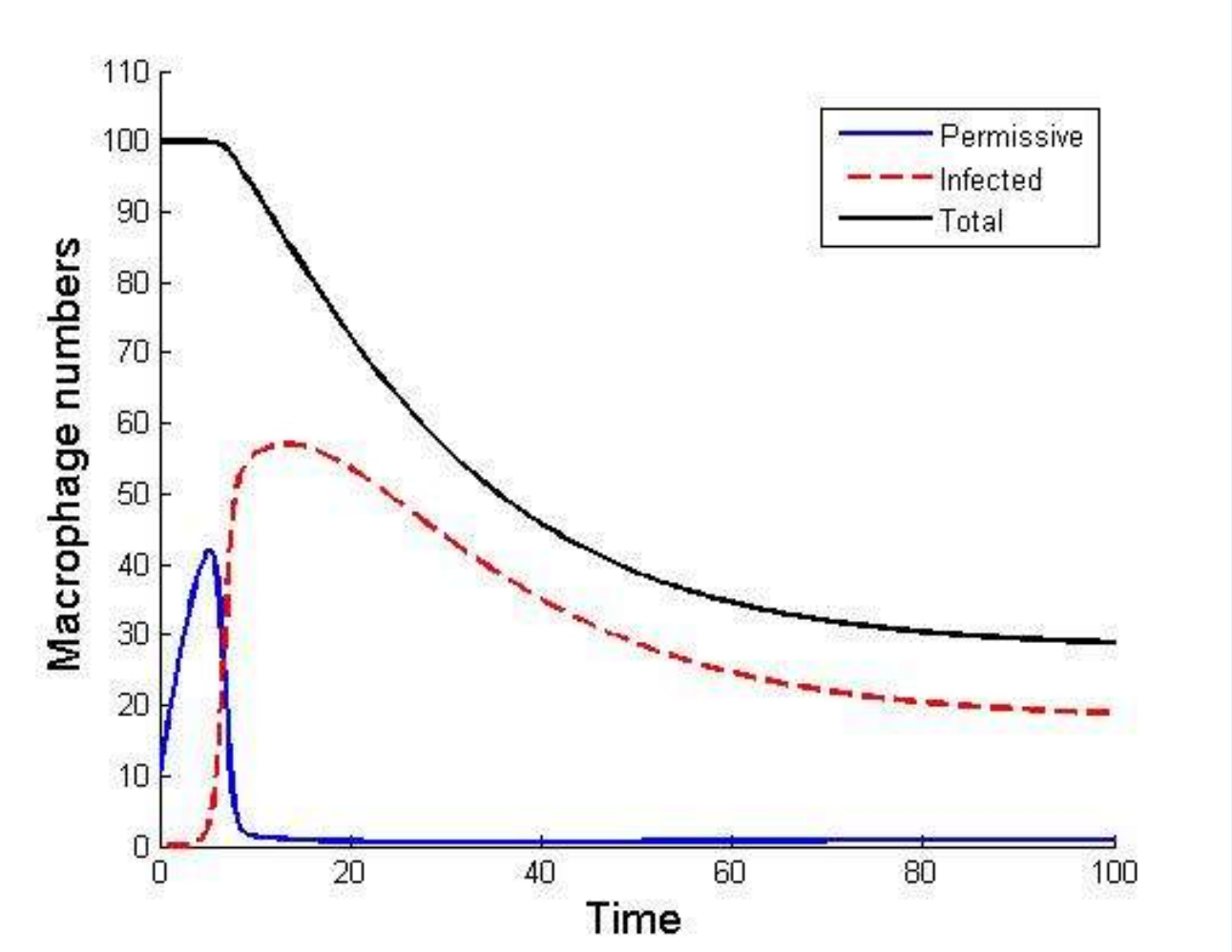
$dv/dt = ky - \varphi v$

Time trend for virus load





Time trend for macrophages



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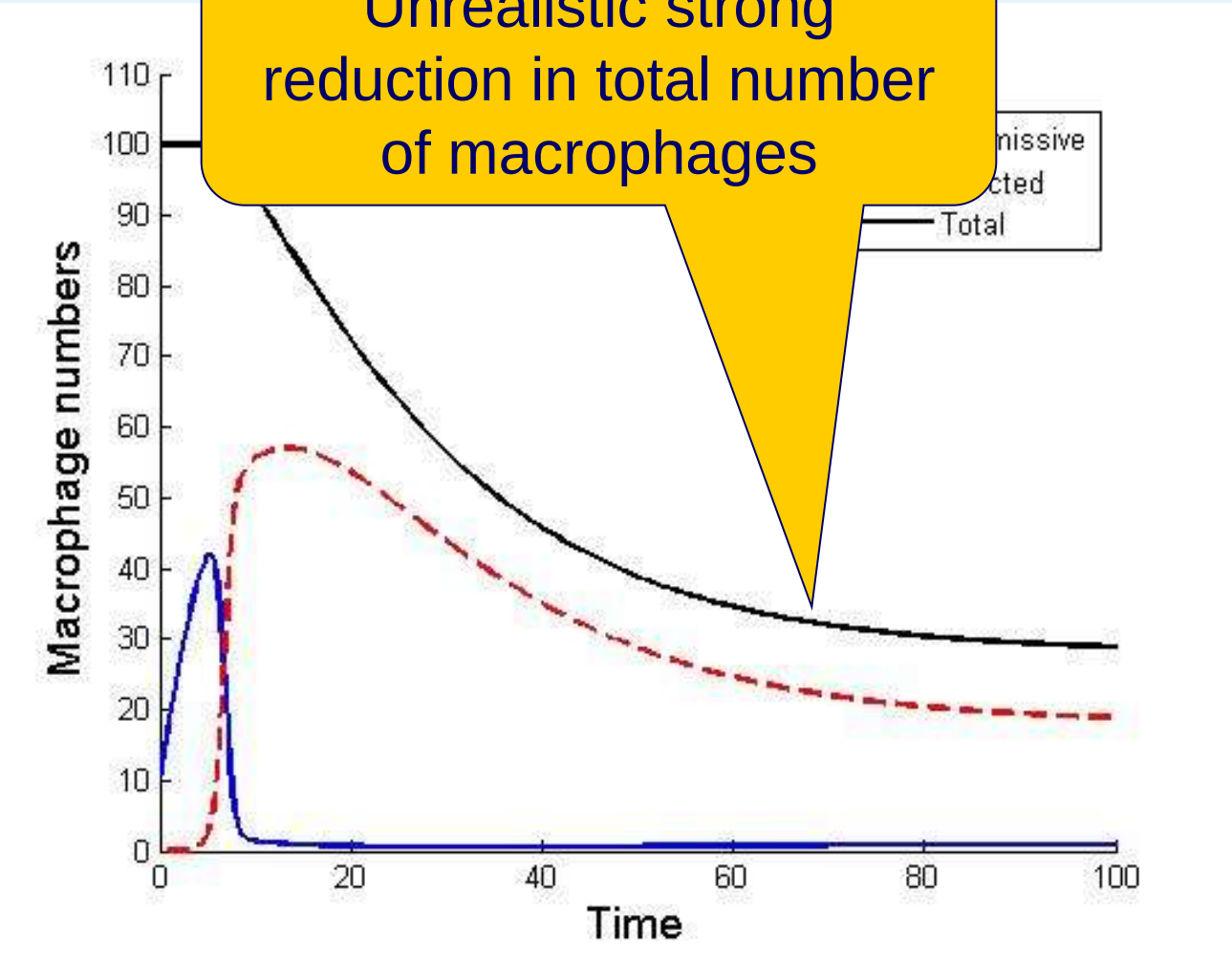
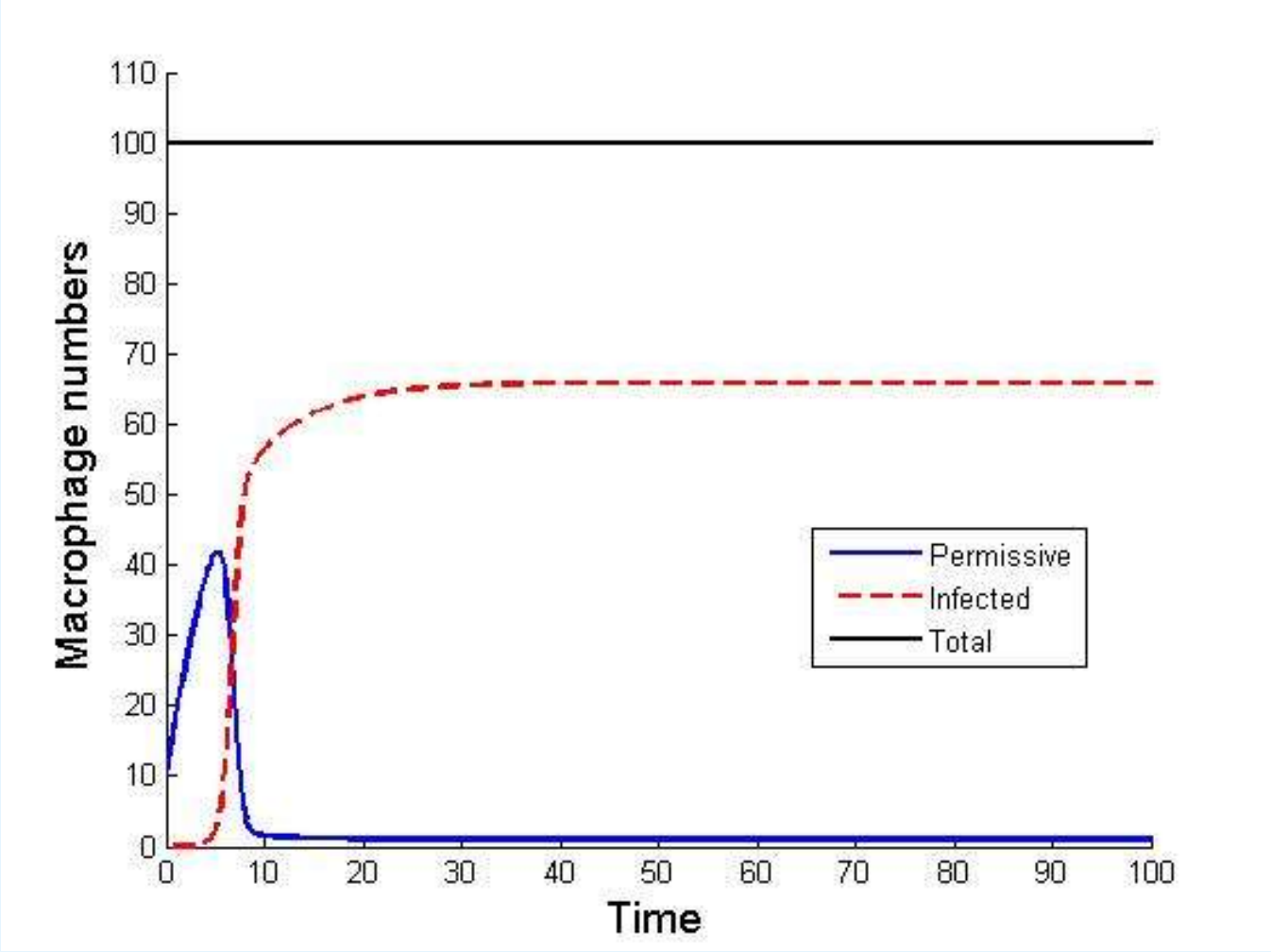


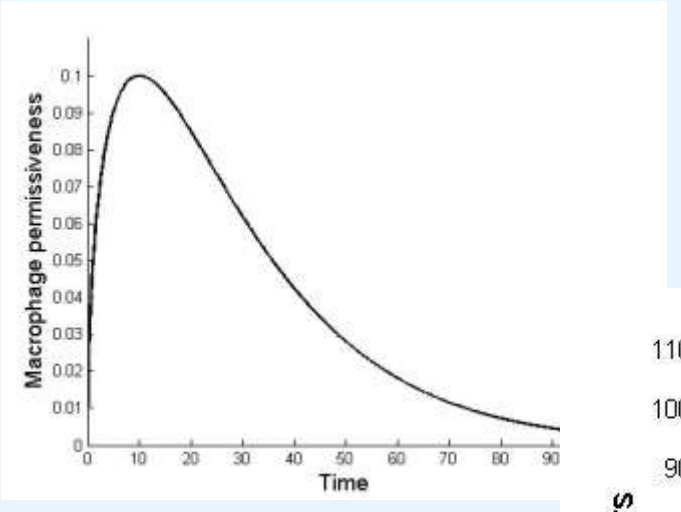
No decline in virus load under constant influx of macrophages



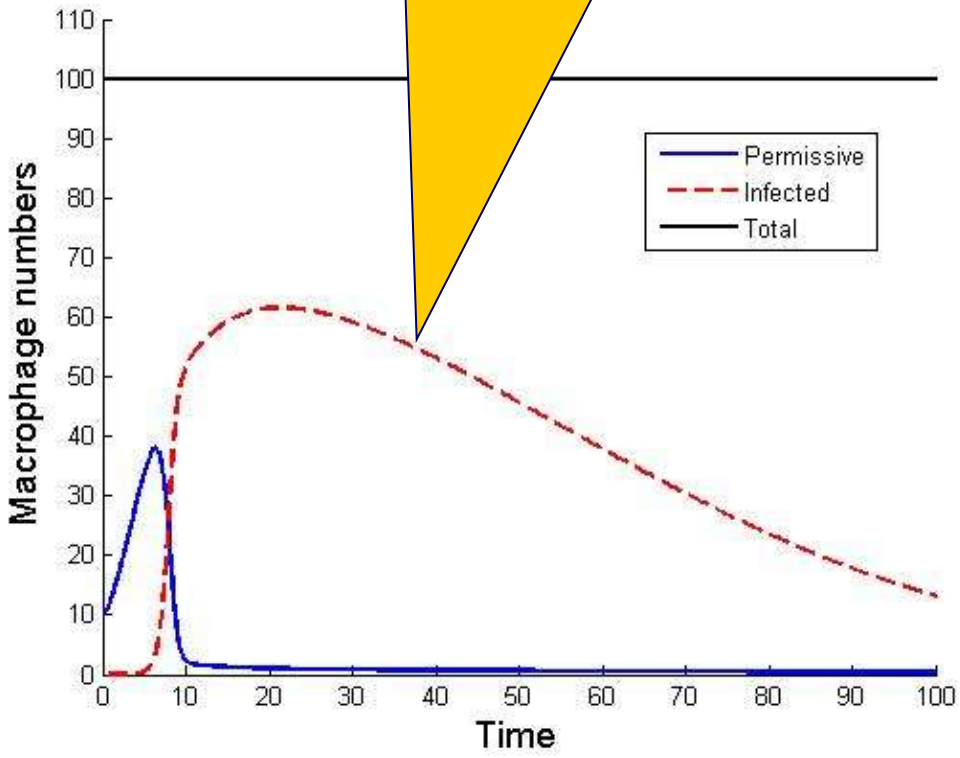
Potential factors contributing to the decline of virus load

- Reduction of virus replication rate over time
  - Contrary evidence (van Reeth, 1999): Down-regulation of IFN-α facilitates virus replication
- Change in permissiveness of macrophages
  - In vitro studies (Duan et al., 97; Gaudrealt et al. 09): macrophage permissiveness increases over the first 120 hours post infection (virus load also increases)
  - No studies covering longer time periods

Assume change in macrophage permissiveness over time



Virus load declines even if macrophage numbers are constant



What causes the virus decline during the acute phase of infection?

Model suggests that

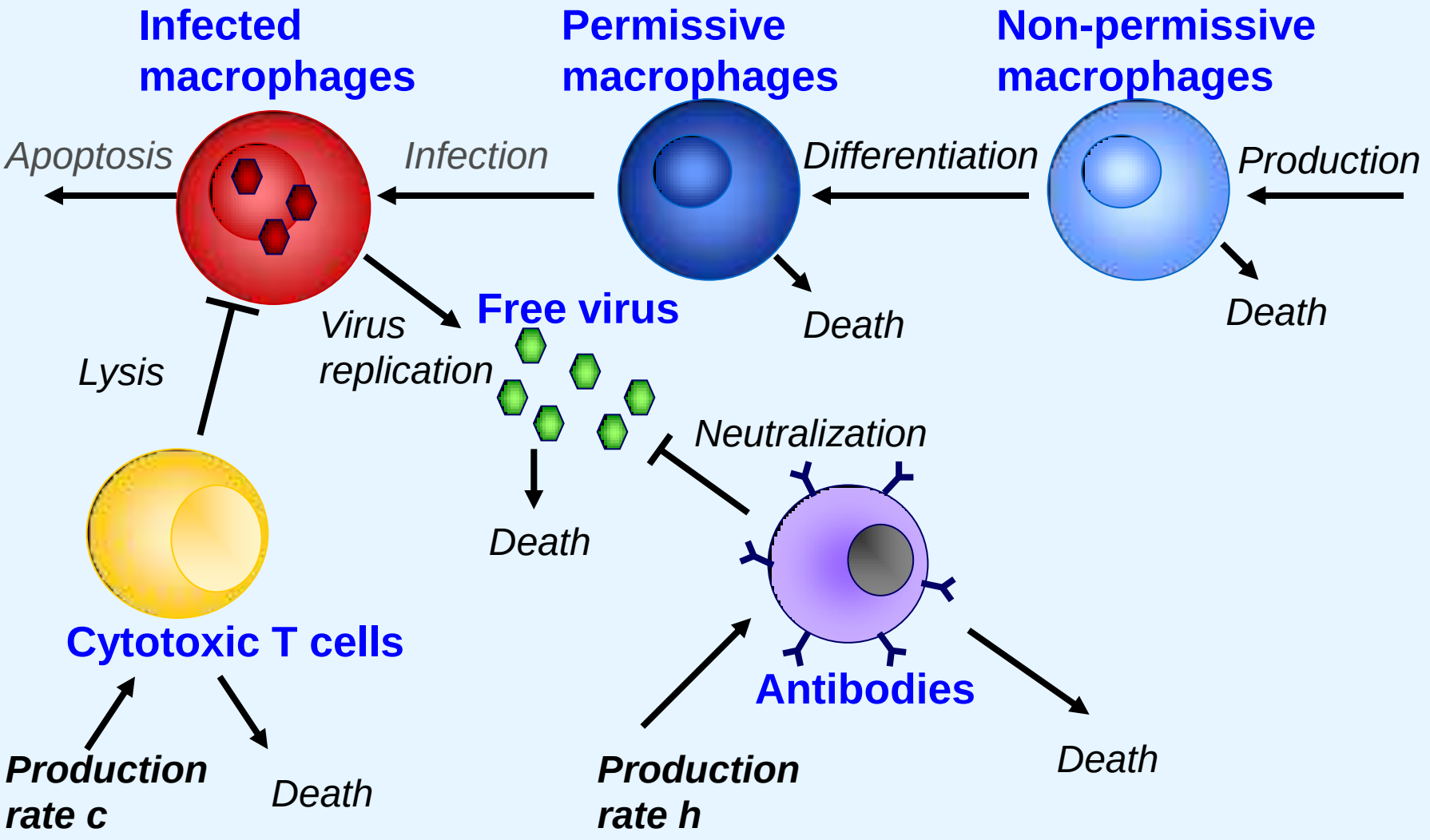
- Assuming no host immune response, reduction in virus load is impossible without reduction in macrophage numbers.
- Change in macrophage permissiveness would cause reduction in virus load without affecting macrophage numbers.
- Evidence for change in permissiveness only exists over short time period, but long-term study required to test model hypothesis.

Questions addressed in this modelling study

1. What causes the virus decline during the acute phase of infection (before adaptive response kicks in)?

2. What role does the adaptive immune response play?

Including adaptive immune response



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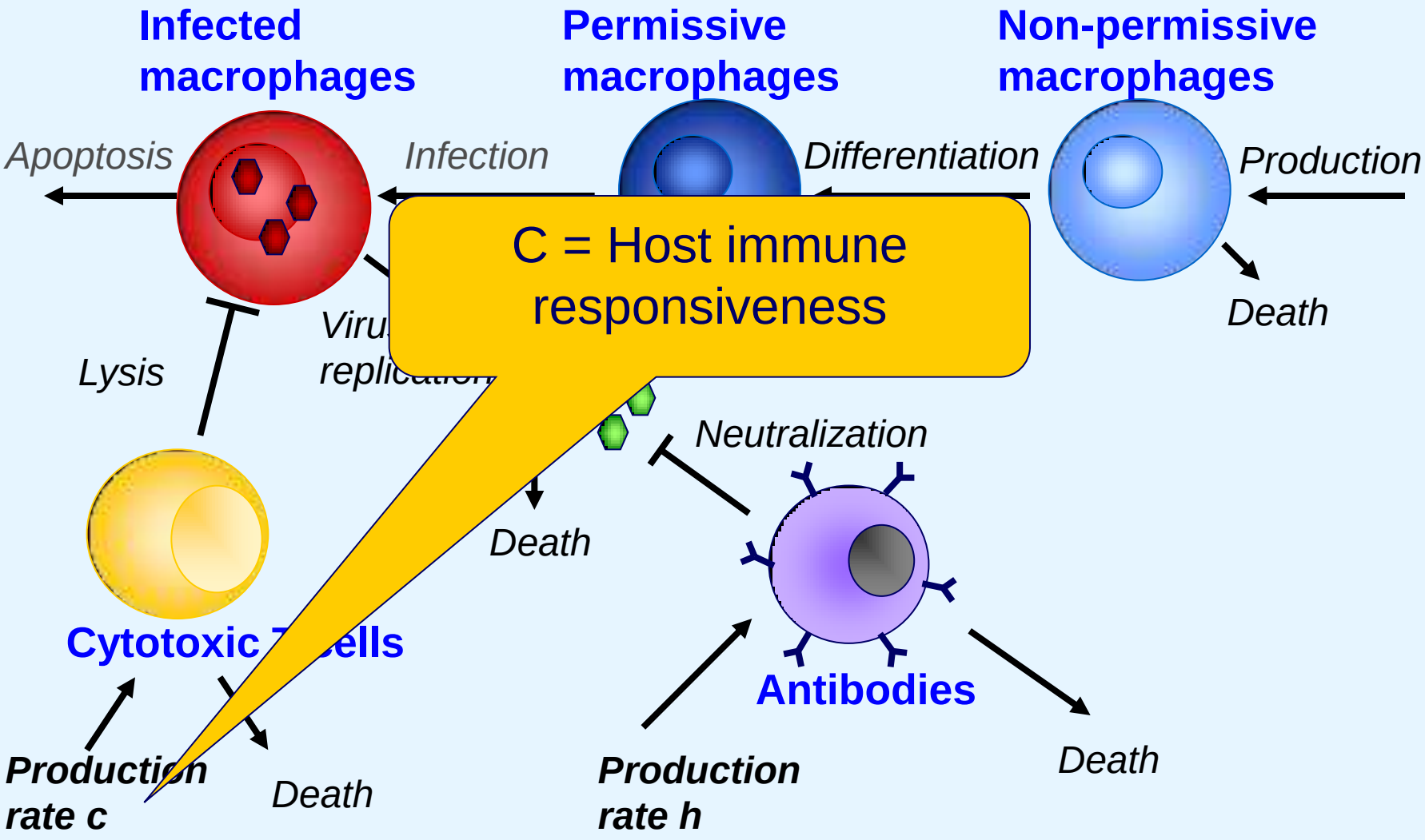
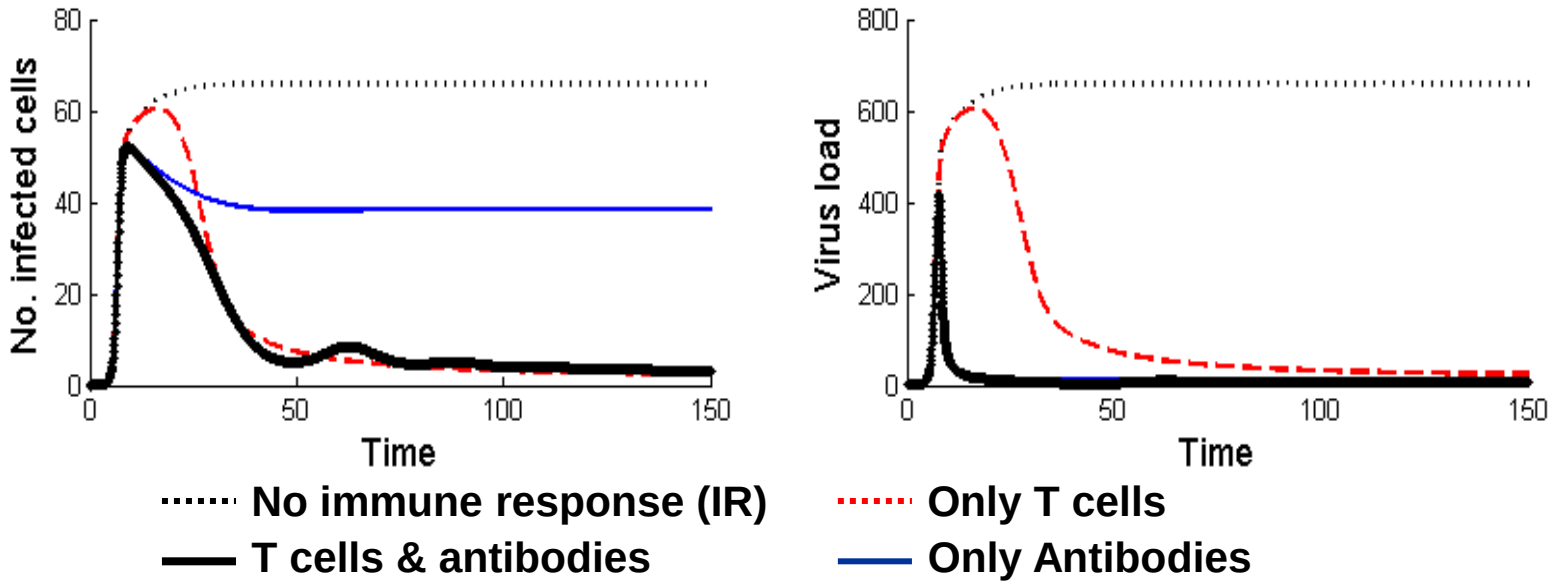
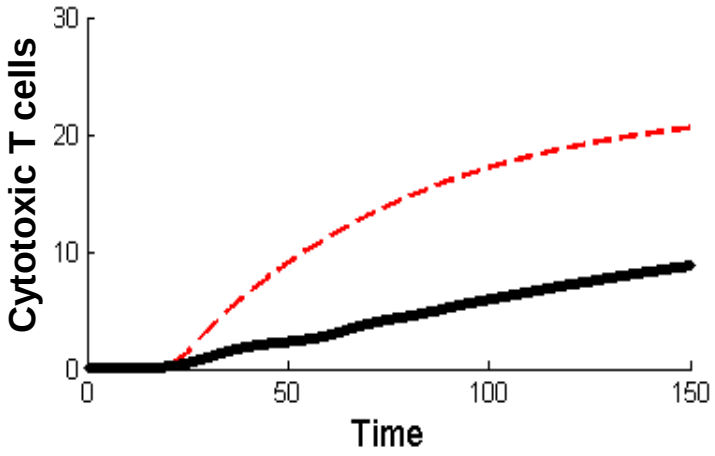


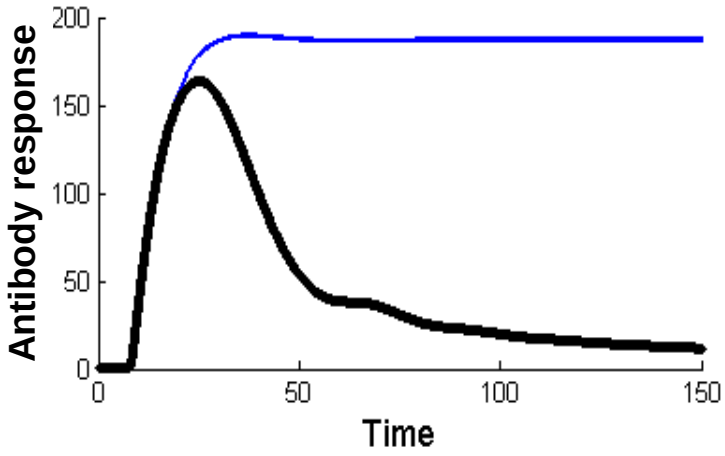
What is the role of the adaptive immune response in clearing the infection?



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

Acute stage – immune response





No immune response (IR)

T cells & antibodies

Only T cells

Only Antibodies

Both types of immune responses influence each other

- Possible explanation for observed delay in adaptive response?
- Possible explanation for observed large variation in host immune response?

Conclusions: What can we learn from mathematical models?

- Explanations for phenomena observed in empirical studies
  - E.g. large host variation in infection profile & immune response due to small differences in host immune responsiveness
- Suggestions for future empirical studies
  - E.g. investigate whether change in macrophage permissiveness causes virus load decline at the early stage of infection
- Prediction of impact of control strategies
  - E.g. use model to predict how selection for higher immune responsiveness affects infection dynamics

Acknowledgements

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- Dr Bob Rowland

THE ROYAL SOCIETY

SAC

Success through Knowledge