Modelling of immune response to a respiratory virus targeting pulmonary macrophages : exploration of the host susceptibility and viral virulence.

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Modelling of Immune Response to a Respiratory Virus Targeting Pulmonary Macrophages: Exploration of the Susceptibility and Virulence

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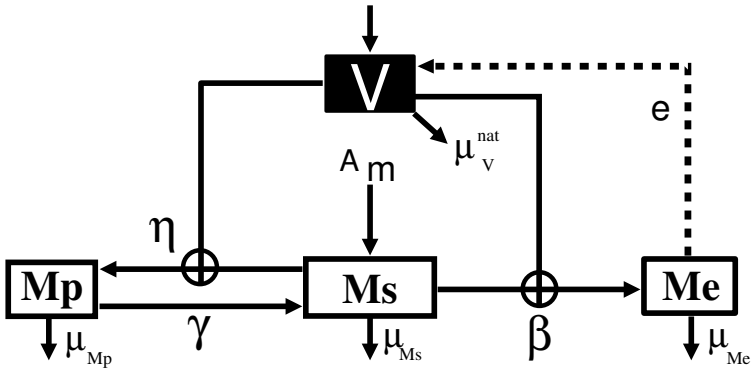
INTRODUCTION

- **Background**: control of respiratory infections
- **Needs:** better understanding of immune dynamics
- Focus: virus targeting pulmonary macrophages
  - ⋆ phagocyting *vs* infected status
  - ⋆ alteration of the immune dynamics
- **Hypothesis:** macrophage – virus interactions are determining for the infection outcome.
- **Application:** PRRSV = porcine virus targetting pulomary macrophages

⇒ MODELLING APPROACH to explore the immune response to PRRSV and its variability

STEPS

Basic model



Model development

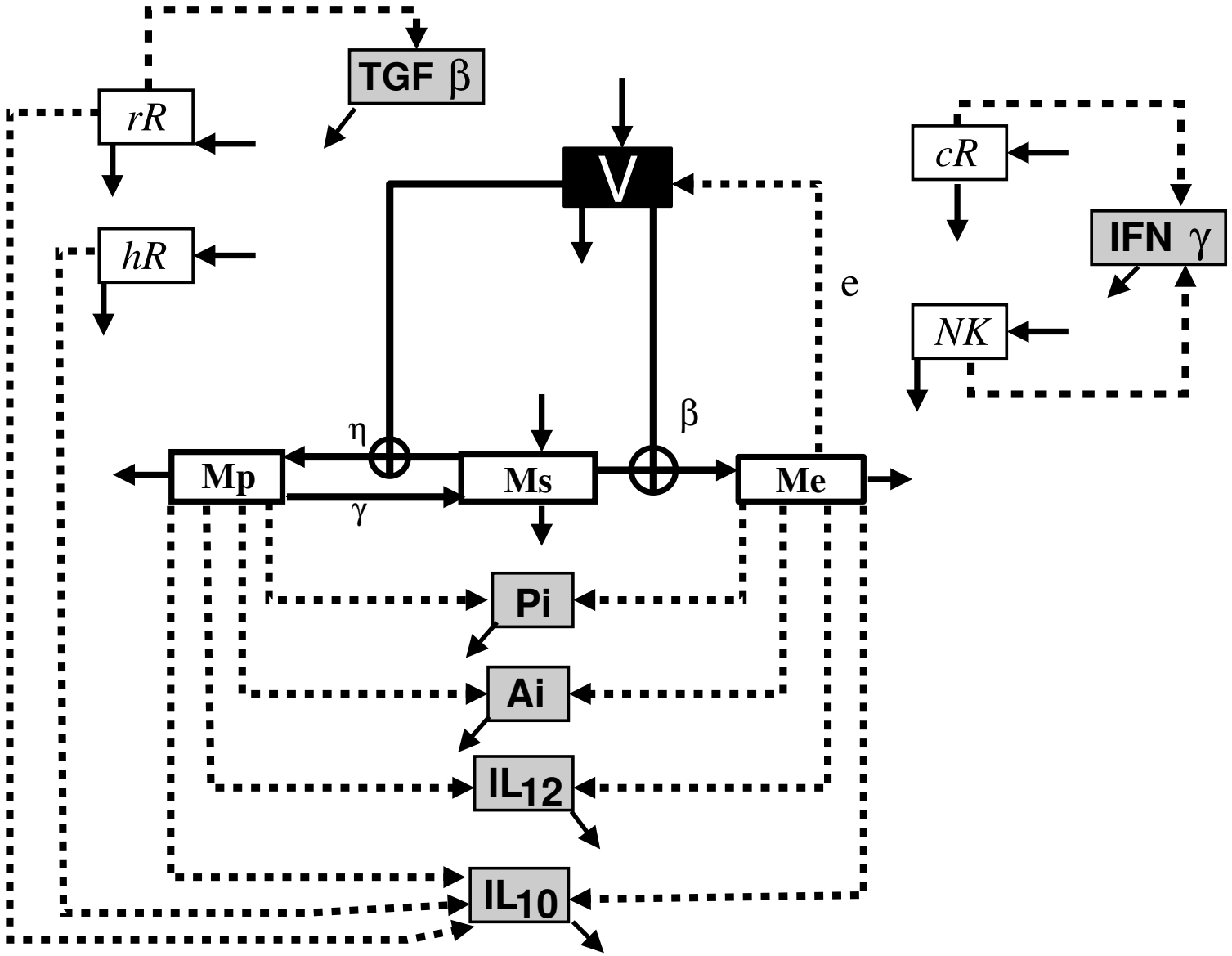
- Cytokine syntheses and regulations
- Adaptive response

$\Rightarrow$ Complex model with 18 state variables and 300 parameters

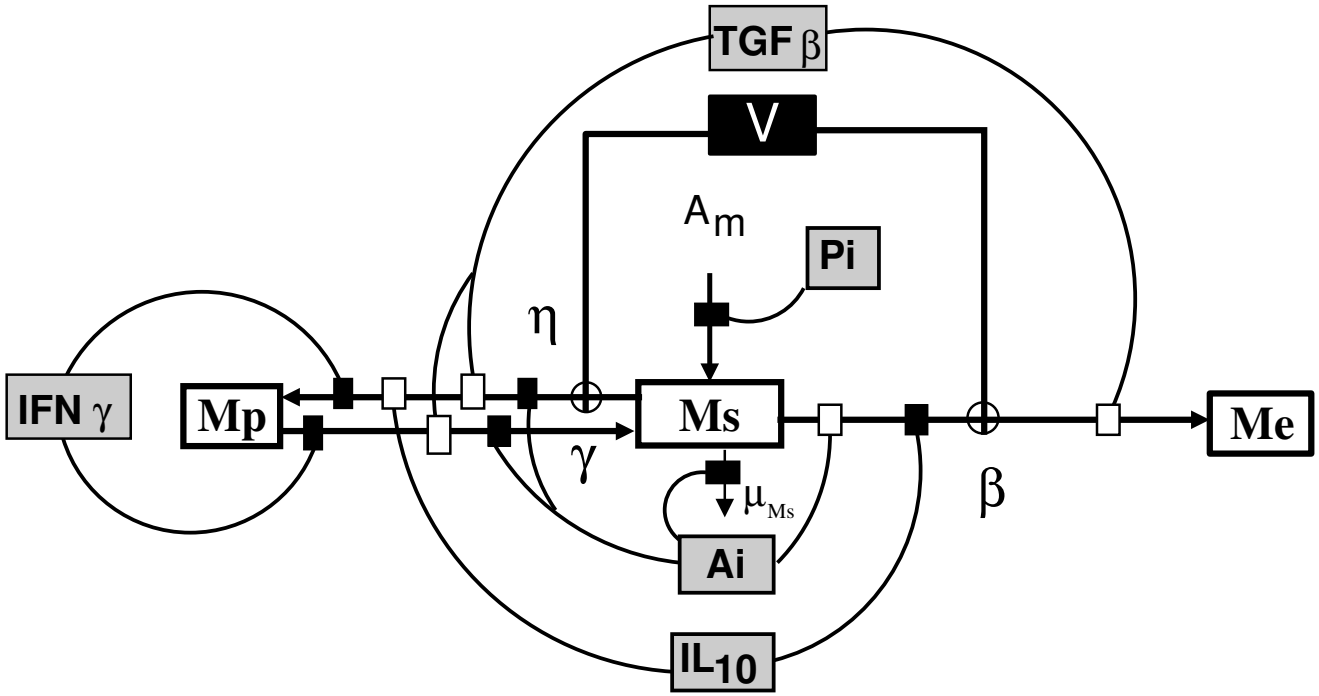
Limits: lack of data $\rightarrow$ model calibration very difficult

Model simplifications

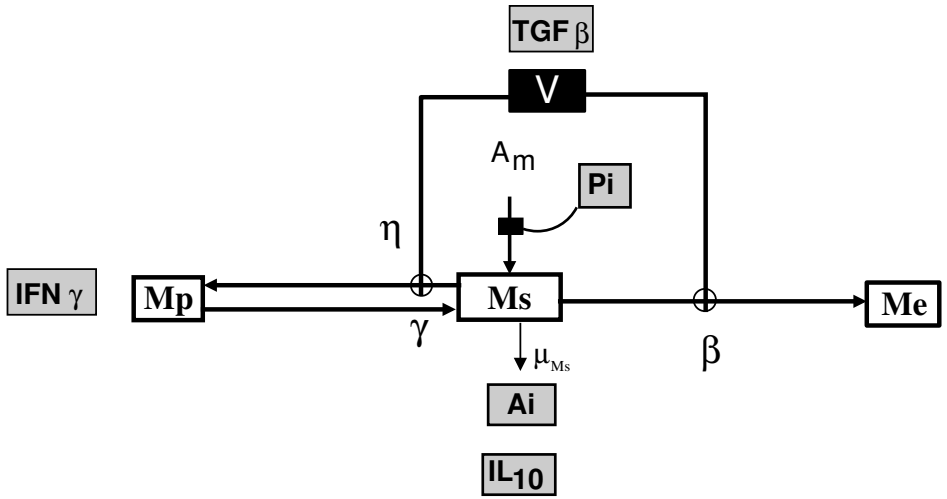
CONCEPTUAL MODEL



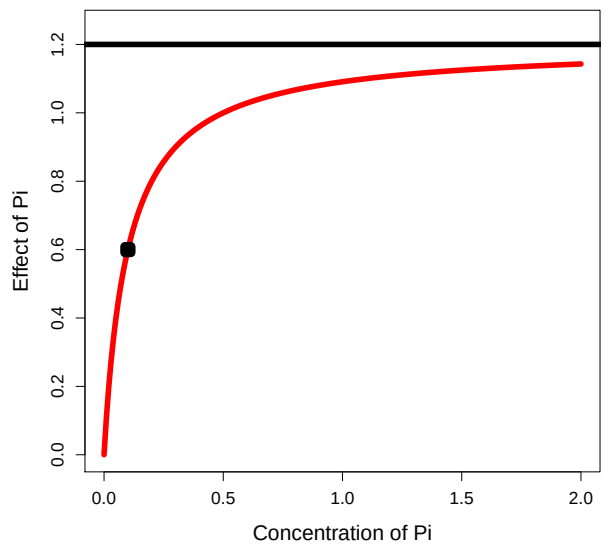
MODEL FORMALISATION



MODEL FORMALISATION



$$\dot{M}_s = A_m \left(1 + \frac{v_m P_i}{k_m + P_i}\right)$$



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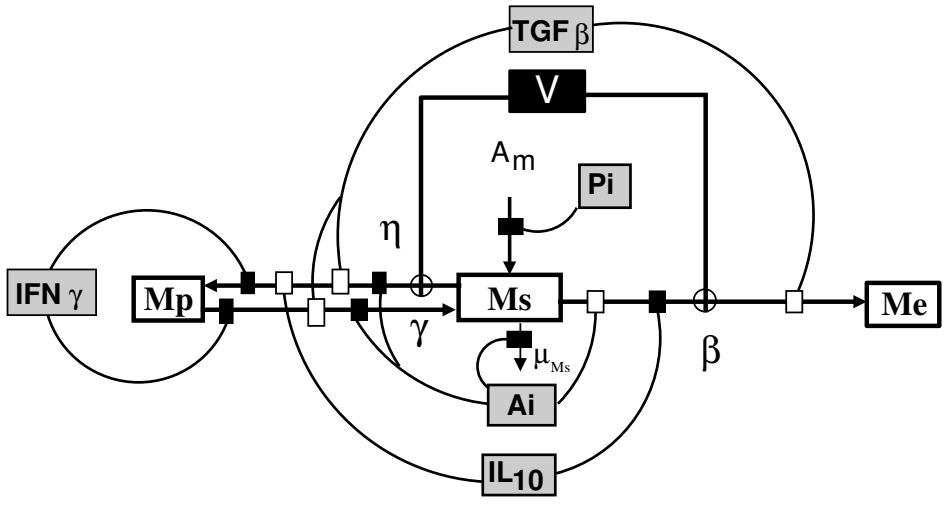
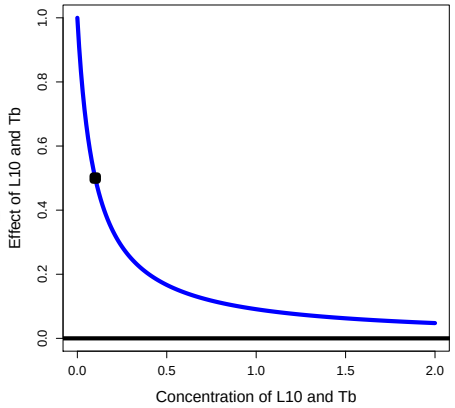
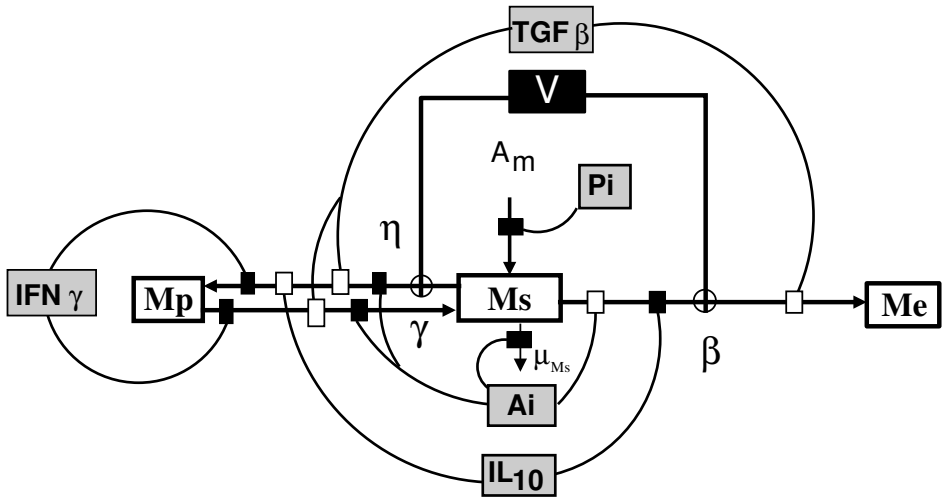


$$\dot{M}_s = A_m \left(1 + \frac{v_m P_i}{k_m + P_i}\right) - \eta M_s V \frac{k_m}{k_m + L_{10} + T_\beta} \left(1 + \frac{v_m (A_i + I_\gamma)}{k_m + A_i + I_\gamma}\right)$$



MODEL FORMALISATION



$$\dot{M}_s = A_m \left(1 + \frac{v_m\, P_i}{k_m + P_i}\right)$$
$$- \eta\, M_s\, V \frac{k_m}{k_m + L_{10} + T_\beta} \left(1 + \frac{v_m\,(A_i + I_\gamma)}{k_m + A_i + I_\gamma}\right)$$
$$+ \gamma\, M_p \frac{k_m}{k_m + L_{10}} \left(1 + \frac{v_m(A_i + I_\gamma)}{k_m + A_i + I_\gamma}\right)$$
$$- \beta\, M_s\, V \frac{k_m}{k_m + A_i + I_\gamma + T_\beta} \left(1 + \frac{v_m\, L_{10}}{k_m + L_{10}}\right)$$
$$- M_s \left(\mu_M^{\text{nat}} + \mu_M^{\text{inf}} \frac{A_i}{k_m + A_i}\right)$$

Model

- Deterministic mathematical model of 14 ODE and 30 parameters
- Highly complex and non-linear

Data

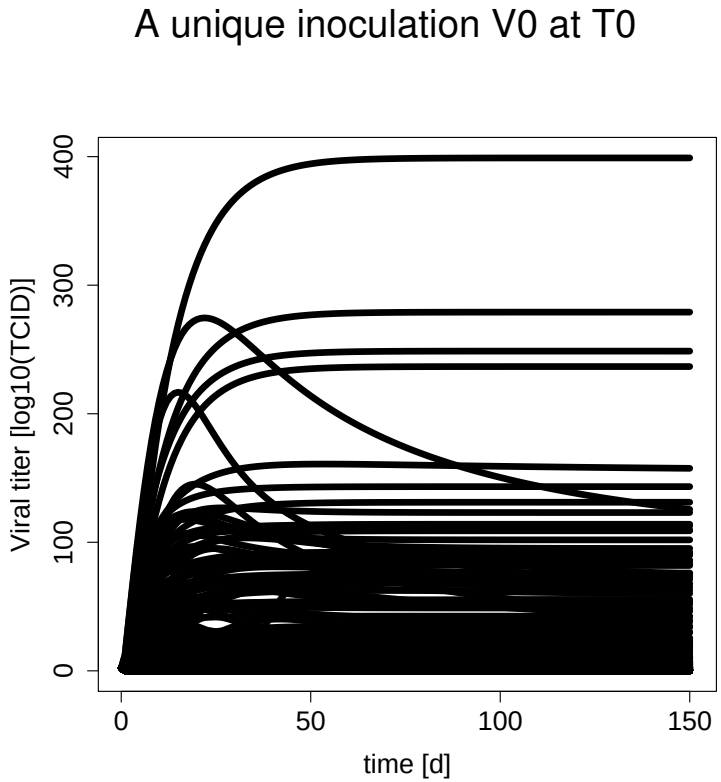
- **Experimental studies on PRRSV:**
  - ⋆ Viral dynamic in the blood and lung
  - ⋆ Immune dynamic in the lung: insufficient data

  $\Rightarrow$ Calibration on viral dynamic output, consideration of the variability and uncertainty.
- **Modelling studies**
  - ⋆ 1 conceptual model of PRRSV infection
  - ⋆ Many models of Influenza and Tuberculosis infection

  $\Rightarrow$ Setting of large variation range of parameters which need to be refine

METHOD

- **Exploration of the large range**
  - ⋆ Definition of a **fractional factorial design** (PLANOR library of R)
    $\rightarrow$ 4096 parameter value combinations
  - ⋆ Model simulations $\rightarrow$ many viral dynamics



METHOD

- **Exploration of the large range**
- **Selection of parameter values**

Inventory of published data $\longrightarrow$ Synthesis and summary in 5 aggregated variables

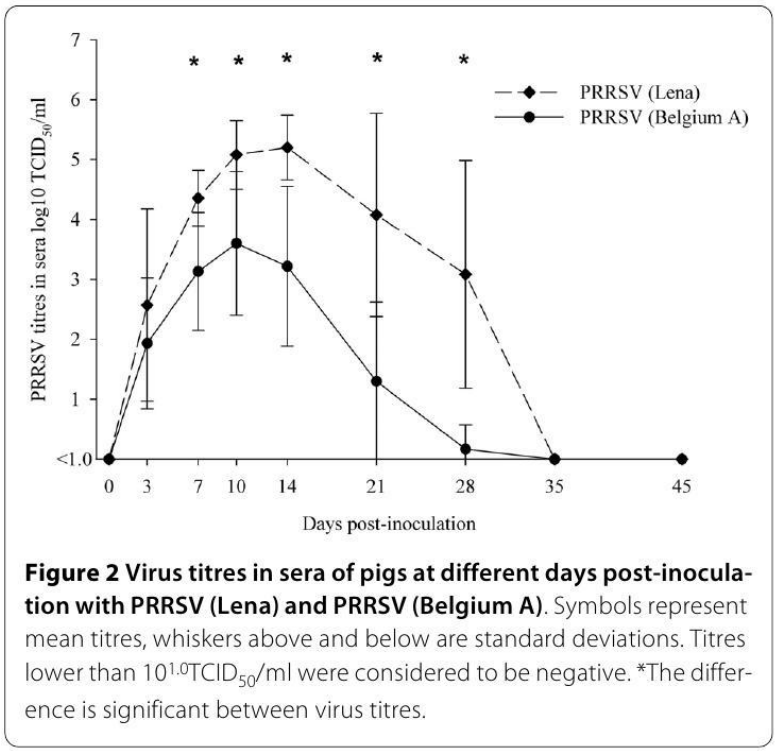
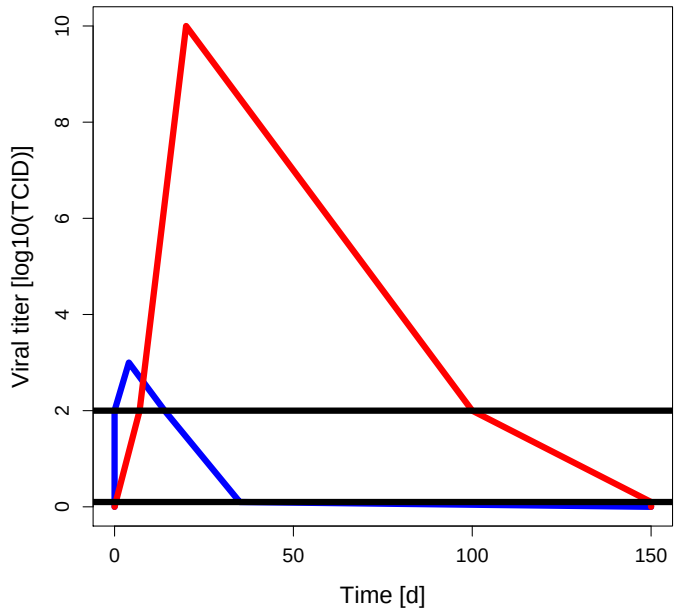


Figure 2 Virus titres in sera of pigs at different days post-inoculation with PRRSV (Lena) and PRRSV (Belgium A). Symbols represent mean titres, whiskers above and below are standard deviations. Titres lower than $10^{1.0}$TCID$_{50}$/ml were considered to be negative. *The difference is significant between virus titres.

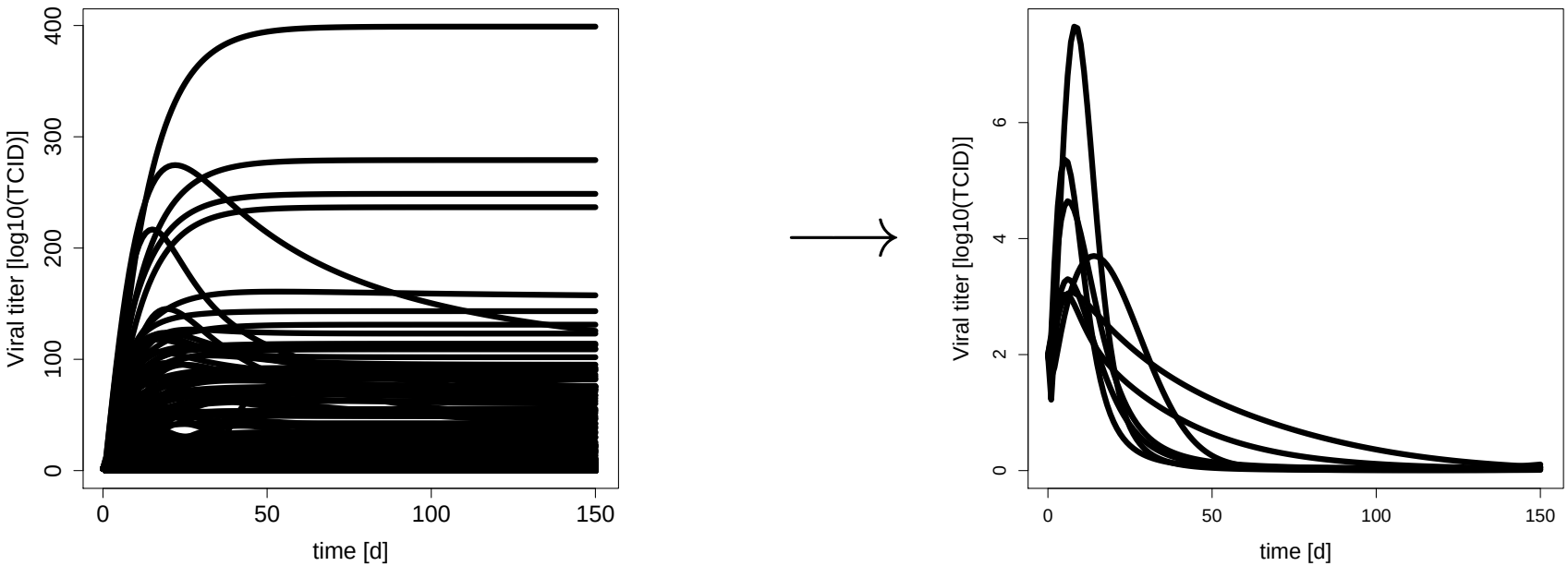
Karniychuk *et al.* BMC Veterinary Research 2010, 6:30



Peak begining, Peak date, Viral titer at peak, Peak ending, Resolution Date

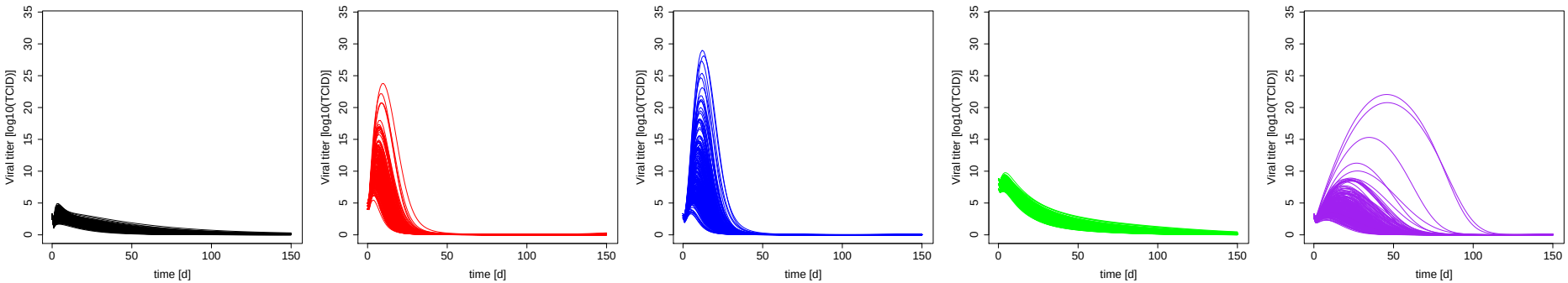
METHOD

- **Exploration of the large range**
- **Selection of parameter values**
  - ⋆ Definition of the variation range for each criterion representing the variability & uncertainties
  - ⋆ Identification of the parameter combinations resulting in simulations which comply each criterion



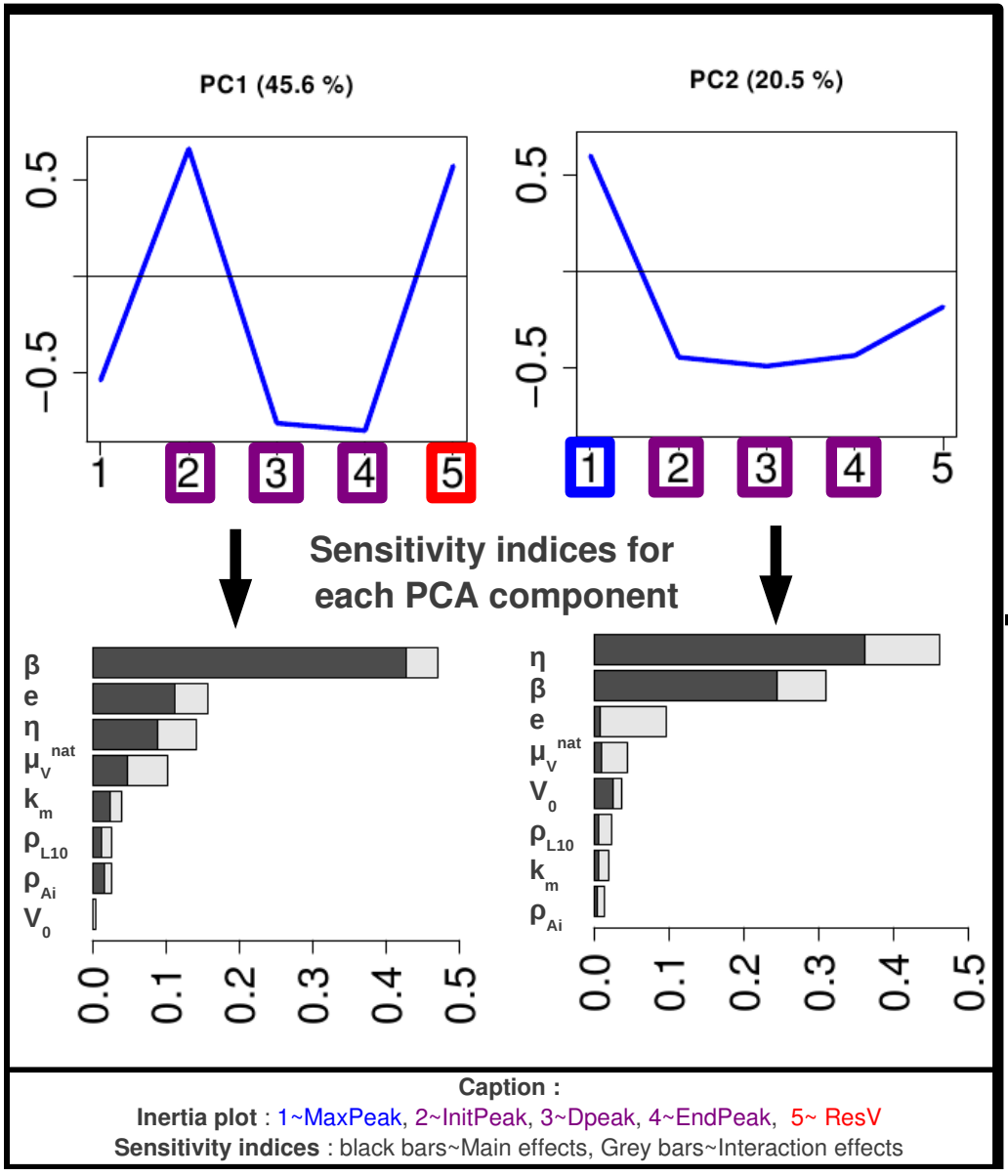
METHOD

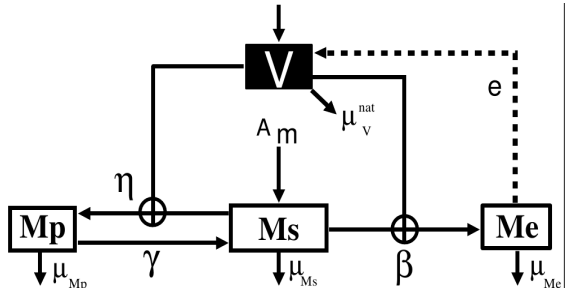
- **Exploration of the large value range**
- **Selection of parameter values**
- **Model robustness** (first approach)
  - ⋆ Selection of 5 combinations corresponding to contrasted dynamics
  - ⋆ Definition of 5 designs with a 10% variation
  - ⋆ Model simulations (5 x 2187 = 10935)

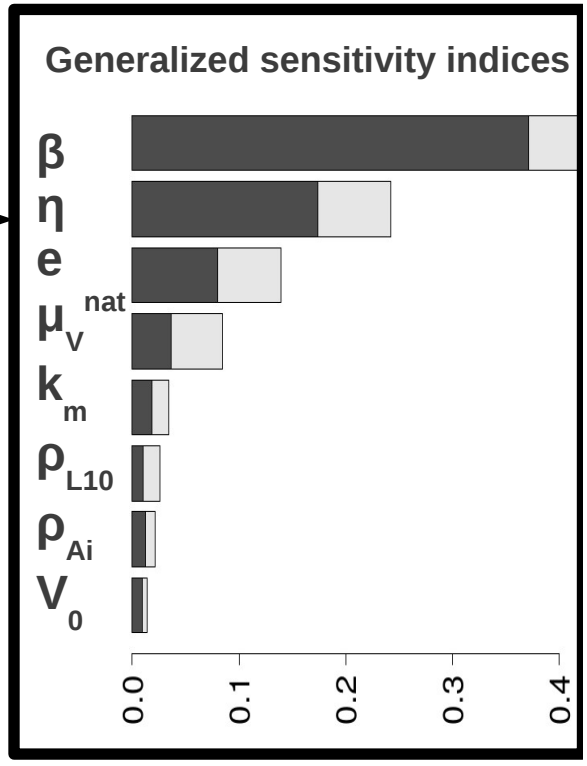


  - ⋆ Multivariate sensitivity analysis of the parameter influence on criteria variance

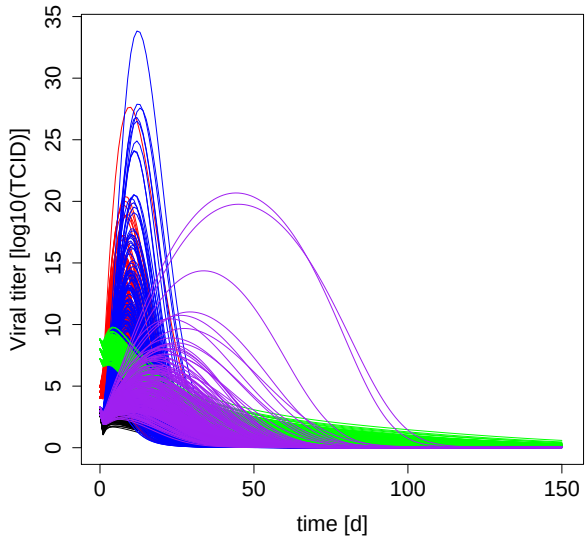
SENSITIVITY ANALYSIS

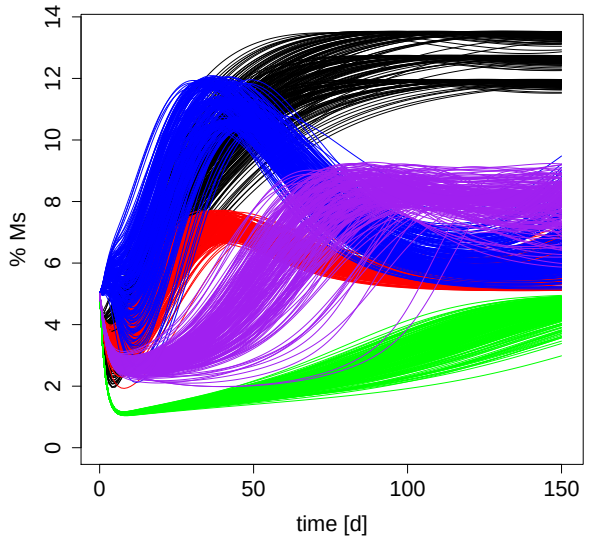


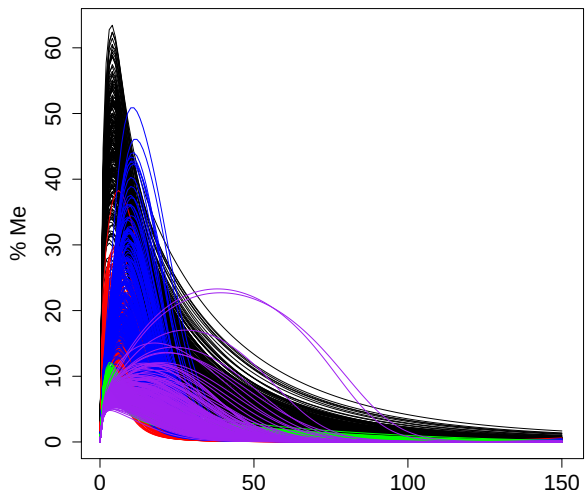


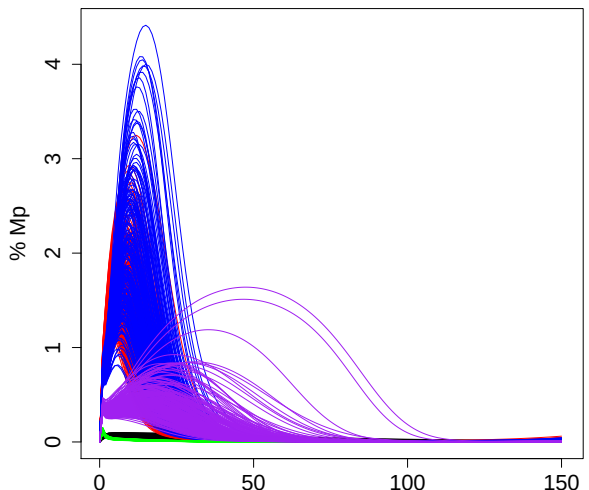


IMMUNE DYNAMICS









CONCLUSION

Model

- Original model centred on the macrophage – virus interactions
- Simplified representation able to reproduce realistic viral dynamic
- Framework to explore the innate mechanisms for respiratory infections

Calibration

- Method allowing to calibrate the model despite the lack of data
- Consideration of the uncertainties and variability
- **Improvements**: Better exploration of the parameter space & consideration of the immune dynamics

Perspective

- Model use to explore the innate response & test control measures
- Model extention to represent the infection dynamic for whole pig