Exploration of the macrophage – virus interactions during a PRRSV infection by a modelling approach

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EXPLORATION OF THE MACROPHAGE – VIRUS INTERACTIONS DURING PRRSV INFECTION BY A MODELLING APPROACH

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Introduction

The Porcine Respiratory and Reproductive Syndrome Virus (PRRSV) **responsible for reproductive failures and production losses** is a major concern for swine industry. To improve the efficiency of control measures, one challenge is the identification of the immune mechanisms allowing to reduce the infection severity and duration. Several studies **discuss the influence** of the immune functions of the target cells (macrophages), the role of the cytotoxic cells involving a key anti-viral cytokine (IFN_γ) and the humoral response involving a key immuno-modulatory cytokine (IL_{10}). The high between-host variability and the heterogeneity of viral strains in the field increase the uncertainties. To unravel these limits, we proposed here a modelling approach.

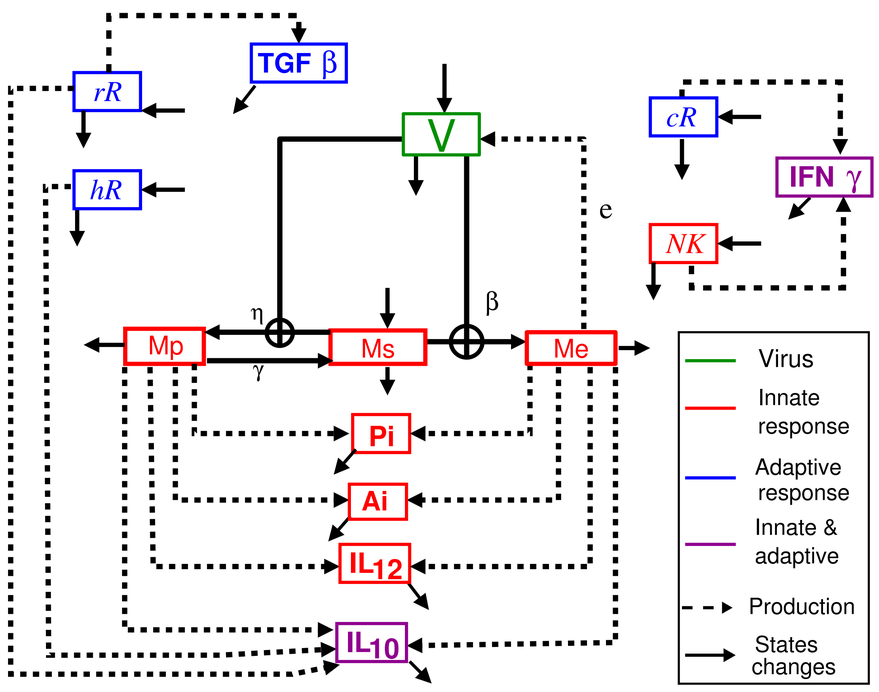
Aims : **(i)** Provide a detailed representation of the immune and infection dynamics in the infection place, the lung.

(ii) Estimate the model parameters resulting in simulations covering the response variability.

(iii) Identify the immune mechanisms determining the infection duration in various scenarios of virulence and susceptibility.

Modelling Approach

Summary **Deterministic ODE model, 14 state variables, 28 parameters, complex and non-linear interactions ⇒ difficult to calibrate. Detailed representation of the macrophage – virus interactions and its regulations involving cytokines and adaptive cells.**



MODEL DIAGRAM

Cells

Macrophages : susceptible macrophages M_s activation by virus $V \Rightarrow$ phagocytosis M_p or infection M_e.

Natural killers : NK destroy the infected cells.

Adaptive cells : the cellular cR destroy infected cells, the humoral hR neutralize free viral particles and the regulatory rR inhibit all immune mechanisms.

Cytokines

Inflammatory : P_i = $IL_{1\beta}$ + IL_6 + IL_8 amplify the recruitment of M_s and NK.

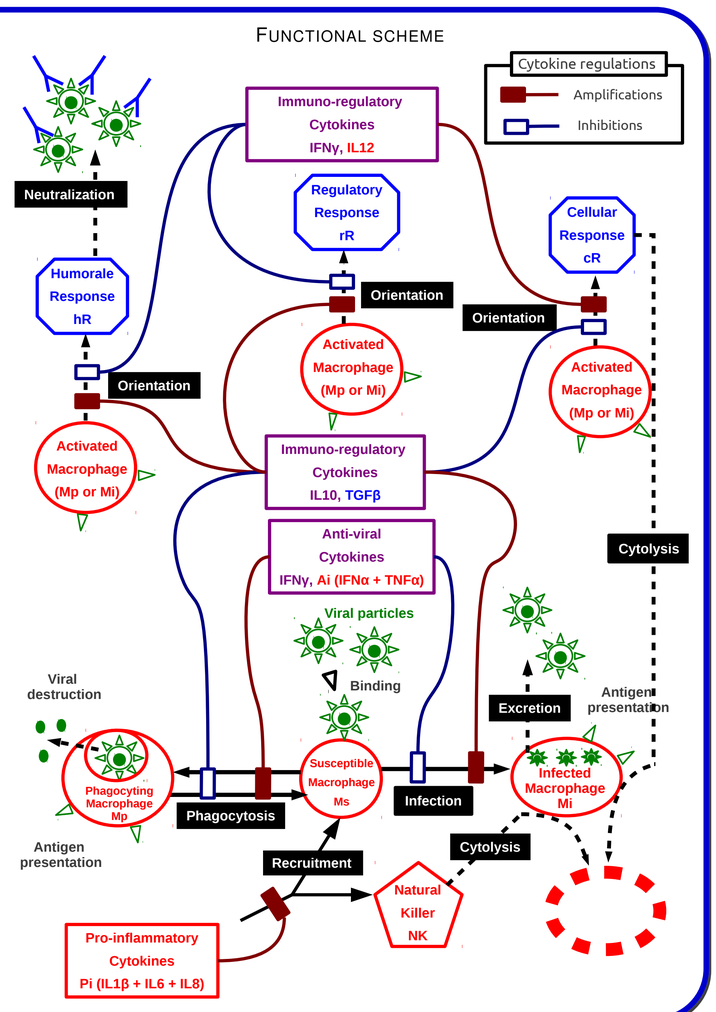
Anti-viral : IFN_γ and A_i = TNF_α + IFN_α promote phagocytosis, inhibit viral replication, orientate towards the cR response.

Immuno-regulatory : IL_{12} has a similar effect than IFN_γ, IL_{10} and $TGF\beta$ have a nearly opposit effect.

$$\begin{aligned}\dot{M}_s = {} & A_m\,(1+\frac{V_m\,P_i}{k_m\,+\,P_i})\\ & -\eta\,M_s\,V\,\frac{k_m}{k_m\,+\,IL_{10}\,+\,TGF_\beta}\,(1+\frac{V_m\,(\,A_i\,+\,IFN_\gamma\,)}{k_m\,+\,A_i\,+\,IFN_\gamma})\\ & +\gamma\,M_p\,\frac{k_m}{k_m\,+\,IL_{10}}\,(1\,+\frac{V_m(A_i\,+\,IFN_\gamma)}{k_m\,+\,A_i\,+\,IFN_\gamma})\\ & -\beta\,M_s\,V\,\frac{k_m}{k_m+\,A_i\,+\,IFN_\gamma\,+TGF_\beta}\,(1\,+\frac{V_m\,IL_{10}}{k_m\,+\,IL_{10}})\\ & -M_s\,(\,\mu_M^{nat}\,+\,\mu_M^{inf}\,\frac{A_i}{k_m\,+\,A_i}\,)\end{aligned}$$

EQUATION of the dynamic of susceptible macrophages

FUNCTIONAL SCHEME



Parameter Range Estimation

Method Few experimental data, high variability and uncertainty ⇒ ad hoc method :

(i) Simulations from large parameter range (10 000, LHS design) – FIG. a

(ii) Definition of quantitative criteria for realistic dynamics based on experimental data – FIG. b, grey area

(iii) Identification of realistic parameter sets (17) – FIG. a in grey

(iv) Selection of representative parameter sets (2) – FIG. b

(v) Robustness : parameters ± 5% (2 sets x 10 000 simulations, LHS designs) – FIG. b

Results

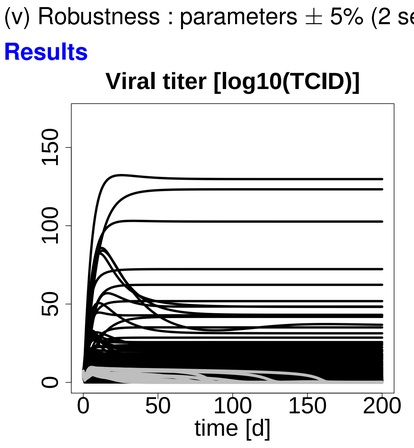
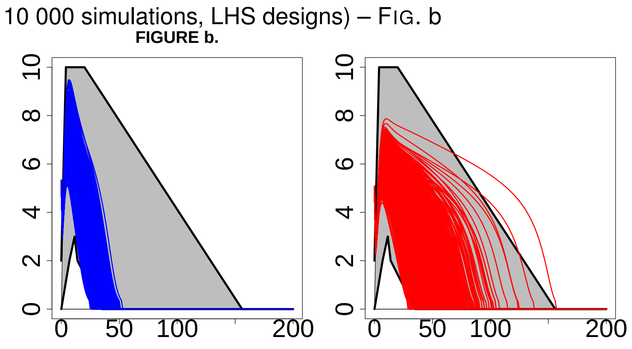


FIGURE a.

FIGURE b.



Conclusions **2 parameter ranges generating contrasted viral dynamics (short duration & high peak vs long duration & low peak) associated with realistic immune dynamics (results not shown).**

Infection Duration

Method Comparison of scenarios. Reference scenario **S0** . Low **S1** vs high **S2** infection capacity. Low **SA** vs high **SB** anti-viral capacity. High **S2A** vs low **S1B** virulence and susceptibility – See **Viral titer**

Results Immune mechanisms determining the infection duration :

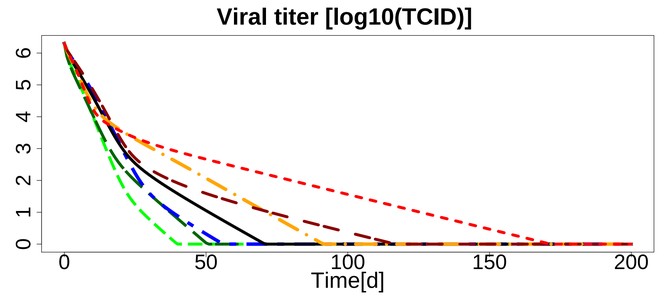


TABLE. Correlations with the infection duration ($R^2 \geq 0.7$).

Groups	% IFN_γ	% IL_{10}	% TGF_β	M_p	M_i	P_i	A_i
S1, S2	+	-	- -	- -	+	+	+ +
SA, SB	- -	+ +	+ +	+ +	+ + +	+ +	- -
S1B, S2A	-	+	+		+ +	+ + +	-

– **SA** & **S2A** ⇒ long duration, % $IL_{10} \geq$ 90, strong hR and rR.

– **SB** & **S1B** ⇒ short duration, % IFN_γ $\geq$ 80, strong cR.

– **S2** (high rate of viral replication – e) ⇒ long duration, high IFN_γ and cR.

– **S1** (low e) ⇒ short duration, high IL_{10} and hR.

Conclusions **Various mechanisms can determine the infection duration ⇒ Take into account the variability between hosts and strains to improve the control measures.**

Perspectives

Model extension to represent the dynamics not only in the lung but in whole pig ⇒ integration of dendritic cells and more detailed representation of the adaptive response.

Use of the model to :

(i) Test the efficiency of **individual control measures** such as vaccination and propose directions to better control the infection

(iii) Identify the key immune mechanisms that drive the infection resolution, to integrate them in an **immuno-epidemiological model at the population scale**.

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