Exploration of the immune response to the Porcine Respiratory and Reproductive Syndrome Virus PRRSV by a modelling approach: conditions for viral clearance

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Exploration of the Immune Response to the PRRSv 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. Our poor understanding of the immune response to PRRSV is a limitation for the development of efficient control measures. The immune response is characterized by (i) a no-standard innate response, (ii) a low and delayed synthesis of the anti-viral cytokine IFN_γ and neutralizing antibodies resulting in a prolonged viremia. However the relative influence of immune mechanisms on the infection resolution is unknown. The high between- host variability and the heterogeneity of viral strains in the field increase the uncertainty. As the virus replicates mainly in pulmonary macrophages which have key immune functions, we developed an original model of the immune response centered on the macrophage – virus interactions.

Aims : **(i)** Simulate the immune response during a PRRSV infection by a detailed mathematical model.
(ii) Test biological hypothesis and explore the conditions for the infection control.

Model Description

Summary : Deterministic model, 18 Ordinary Differential Equations (virus, 4 cell types and 9 cytokines), 30 parameters, complex and non-linear interactions regulated by immune cells and cytokines
⇒ Simulation of immune and infection dynamics in the lung. Few data to calibrate the model.

Infection start

A unique input of viral particles (V_0) at the beginning of the simulation ⇒ first interaction between virus (V) and its target cell (M_s).

Cells

Macrophages. Macrophage activation by virus ⇒ phagocytosis (M_p) or infection (M_i) and then viral replication (M_e).
Natural killers (NK) destroy the infected cells.
Adaptive cells. Induced by activated macrophages. Three orientations of the adaptive response : the cellular (cR) destroy infected cells, the humoral (hR) neutralize free viral particles through antibodies and the regulatory (rR) inhibit all immune mechanisms.

Cytokines

Inflammatory : $IL_{1\beta}$, IL_6, IL_8, IL_{12} . Synthesized by activated macrophages. Amplify the recruitment of M_s and NK.
Anti-viral : TNF_α, IFN_α, IFN_γ. Synthesized by activated macrophages, cR cells and NK. Promote phagocytosis, inhibit macrophage permissiveness and viral replication, orientate towards the cR response.
Immuno-modulatory : IL_{10}. Synthesized by activated macrophages, hR and rR cells. Inhibit phagocytosis, inflammatory and anti-viral cytokine synthesis, amplify macrophage permissiveness and orientate towards the hR response.
Immuno-suppressive : $TGF\beta$. Synthesized by rR cells. Inhibit IFN_γ synthesis, phagocytosis and macrophage permissiveness and promote IL_{10} synthesis.

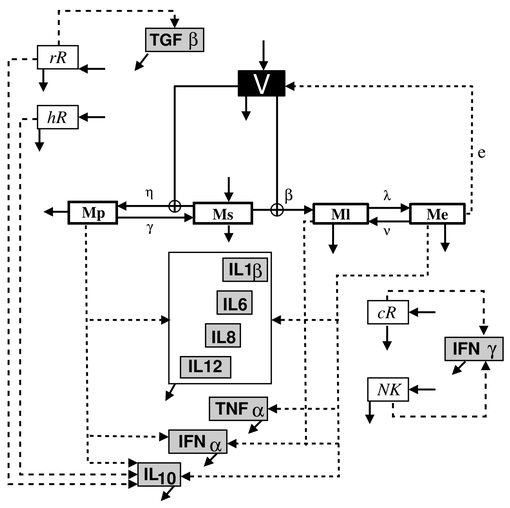


Diagram of the simplified conceptual model. We represented (i) the state variables : macrophages states (Mp, Ms, Mi, Me), virus (dark box), cytokines (grey boxes), other immune cells (italic), (ii) the interactions between variables (solid arrows) and (iii) the virus and cytokine productions (dotted arrows).

$$
\begin{aligned}
\dot{M}_s = {} & A_m\,[1+\kappa_1(\mathbf{IL_{12}},\mathbf{IL_6})]\,[1+\kappa_1(\mathbf{IL_8})] \\
& - \eta\, M_s\, V\, \frac{[1+\kappa_1(\mathbf{TNF_\alpha})]\,[1+\kappa_1(\mathbf{IFN_\gamma})]\,[1+\kappa_1(\mathbf{IFN_\alpha})]}{[1+\kappa_1(\mathbf{IL_{10}})]\,[1+\kappa_1(\mathbf{TGF\beta})]} \\
& + \gamma\, M_p\, \frac{[1+\kappa_1(\mathbf{TNF_\alpha})]\,[1+\kappa_1(\mathbf{IFN_\gamma})]\,[1+\kappa_1(\mathbf{IFN_\alpha})]}{1+\kappa_1(\mathbf{IL_{10}})} \\
& - \beta\, M_i\, V\, \frac{1+\kappa_1(\mathbf{IL_{10}})}{[1+\kappa_1(\mathbf{TNF_\alpha})]\,[1+\kappa_1(\mathbf{IFN_\alpha})]\,[1+\kappa_1(\mathbf{TGF\beta})]} \\
& - M_s\,[\mu_M^{\mathrm{nat}} + \mu_M^{\mathrm{inf}}\ \mathbf{TNF_\alpha}]
\end{aligned}
$$

Equation of the dynamic of susceptible macrophages. Cytokines in bold, macrophage statuses in blue and viral particles in red.

Sensitivity Analysis

Aims. (i) Explore the model behaviour in a large range of parameter values.
(ii) Identify key parameters which highly influence the dynamic of the state variables.
(iii) Identify the parameter values resulting in realistic infection and immune dynamic.
Method. Model simulations with 2187 combinations of parameter values ⇒ Quantification of the variance of the state variables between simulations by a multivariate method (*Multisensi*).
Results. Key parameters linked to macrophage – virus interactions.

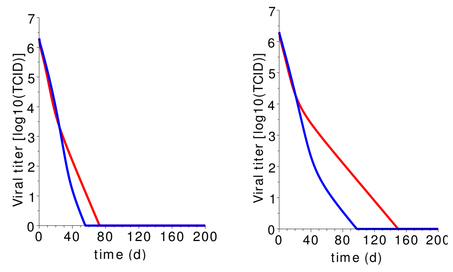
Positive (++) and negative (–) correlations :	V, M_i & M_e	M_p
inoculation rate V_0		
infection rate β	++	–
excretion rate e		
phagocytosis rate η	–	++

Model Exploration

Aim. Explore the influence of host susceptibility and viral virulence on the infection outcome.
Method. Two levels of host susceptibility and viral virulence tested. High susceptibility simulated with low rate of anti-viral cytokine synthesis and high rate of immuno- modulatory and suppressive cytokine synthesis. High virulence simulated with low phagocytosis rate and high excretion rate.
Results.

Infection dynamic.
> Higher virulence ⇒ longer infection regardless of the susceptibility.
> Lower susceptibility ⇒ faster resolution.
> The difference in infection duration depending on the susceptibility is higher in condition of high virulence.
Immune dynamic.
> Higher virulence ⇒ lower concentration of M_p & higher adaptive response.
> Lower susceptibility ⇒ higher concentration of anti-viral cytokines & lower concentration of all immune cells.

Dynamic of viral titer depending on the virulence strain of high and low susceptible pig.



Low virulent **High virulent**

Conclusion

Model.
Original model taking into account all macrophage – virus interactions, interactions between innate and adaptive cells, and regulations by innate and adaptive cytokines
⇒ Powerful tool to simulate the immune and infection dynamics and to test hypothesis on each immune mechanism by varying the parameter values.
Influence of macrophage – virus interactions.
- The key parameters are linked to the macrophage – virus interactions ⇒ the first immune steps seem determinant for the infection resolution.
- The viral capacity to replicate in the macrophages and the cell capacities to synthesize cytokines involved in regulation of the macrophages – virus interactions have a strong influence for the infection resolution.
- The viral capacity to replicate in the macrophages has a higher impact on the infection resolution than the cell capacity to synthesize anti-viral cytokines. The cell capacity to synthesize cytokines is more influent in condition of infection by a highly virulent strain.
- The phagocytosis and anti-viral cytokines seem more efficient to reduce the infection duration than the immune cells.
Control measures.
- The promotion of the macrophage immune functions seem be an efficient way to reduce the infection severity.
- We can expect that the selection of resistant pigs and the optimization of breeding condition to reduce stress could help to prevent severe PRRSV infection.
- The promoting of anti-viral cytokine synthesis by vaccine adjuvant could be involved in the limitation of infection duration.
Perspectives.
We will extend our model to represent the dynamics not only in the lung but in whole pig.

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