Supporting Information to
Integrative Model of the Immune Response to a Pulmonary Macrophage Infection: What Determines the Infection Duration?

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\textbf{S1. Complete model description}

This model describes the infection and immune dynamics induced by a pathogen targeting pulmonary macrophages in the lung. It focuses on the macrophage–virus interactions and highly details the innate immune response and cytokine regulations. The adaptive immune response is less detailed but includes the cellular, humoral and regulatory orientations and their main functions.

The model is characterised by 18 state variables: the free viral particles; five effectors of the innate response, consisting of four macrophage states (susceptible, phagocyting, infected and latent, infected and excreting the virus) and the natural killers; three effectors of the adaptive response, representing the cellular, humoral and regulatory responses; nine cytokines composed of the major pro-inflammatory (IL\textsubscript{1/2}, IL\textsubscript{8}), the innate antiviral (TNF\textsubscript{α}, IFN\textsubscript{α}) and the immuno-regulatory (IFN\textsubscript{γ}, IL\textsubscript{12}, IL\textsubscript{10}, TGF\textsubscript{β}) cytokines.

We chose a deterministic continuous-time dynamic framework. Our model is hence a set of 18 ordinary differential equations, which represent the evolution over time of the state variables. The main processes that drive their evolution over time and that are integrated in the model are: the phagocytosis of the viral particles by the macrophages; the macrophage infection by the virus; the excretion of free viral particles by the infected macrophages; the recruitment and decay/migration of the macrophages; the activation and decay/migration of the other effectors; the cytokine productions by the immune cells and their decay; the cytokine regulations.

The functional diagram of the system appears in Figure 1 (main text). Figure 2 (main text) gives a schematic representation of the model (without regulations). Parameter descriptions and values are synthesised in Table 1 (main text). The cytokine regulations and syntheses represented in our model as well as the related literature references are summarised in Table S1 and Table S2 respectively.

We first present how the cytokine regulations are formalised in the model and then describe the dynamics of the various state variables: macrophages, free viral particles, natural killers, effectors of the adaptive response and cytokines.

\textbf{Cytokine regulations}

Cytokines regulate the cellular functions through their recognition by specific receptors, inducing cascaded reactions within the cells. The higher the cytokine concentration, the stronger the effect. However, there is a limited number of cytokine receptors on the cell surface, so the effect saturates above a given cytokine concentration. We formalised the cytokine effects by a Michaelis–Menten function ($\kappa$) of the cytokine concentration ($C_i$) as follows:

$$\kappa(C_i) = \frac{K C_i}{C_i + k}$$
where $K$ represents the saturation factor and $k$ the half-saturation cytokine concentration [1–3].

Considering a flow ($R$), which can either be an inflow (e.g. recruitment) or an outflow (e.g. decay), a cytokine can have three possible effects listed below.

- **Activation:** $R \kappa(C_i)$. The flow is only possible in the presence of the cytokine and it increases with the cytokine concentration.
- **Amplification:** $R \left[1 + \kappa(C_i) \right]$. The flow increases with the cytokine concentration.
- **Inhibition:** $R/\left[1 + \kappa(C_i) \right]$. The flow decreases with the cytokine concentration.

Regulations often involve several cytokines ($C_i$ and $C_j$), which can act

- either independently:
  - co-activation: $R \left[\kappa(C_i) + \kappa(C_j) \right]$,
  - co-amplification: $R \left[1 + \kappa(C_i) \right] \left[1 + \kappa(C_j) \right]$,
  - co-inhibition: $R/\left[\left[1 + \kappa(C_i) \right] \left[1 + \kappa(C_j) \right] \right]$;

- or in synergy:
  - co-activation: $R \kappa(C_i, C_j) = R \kappa(C_i) \kappa(C_j)$,
  - co-amplification: $R \left[1 + \kappa(C_i, C_j) \right] = R \left[1 + \kappa(C_i) \kappa(C_j) \right]$,
  - co-inhibition: $R/\left[1 + \kappa(C_i, C_j) \right] = R/\left[1 + \kappa(C_i) \kappa(C_j) \right]$.

As very few studies estimate the regulation parameters ($k$ and $K$) in the literature [3], we used the same parameter values for all cytokine regulations.

### Macrophage dynamics

Macrophages phagocyte and destroy the virus, but they are also target cells for the virus. Activated macrophages (either phagocytizing or infected) present the viral antigen and activate the adaptive response. The macrophage activation also induces the synthesis of innate cytokines: pro-inflammatory (IL\(_1\beta\), IL\(_6\), IL\(_8\)), antiviral (IFN\(_\alpha\), TNF\(_\alpha\)) and immuno-regulatory (IL\(_{12}\), IL\(_{10}\), TGF\(_\beta\)) cytokines [4].

**States** In the model, macrophages can either be susceptible ($M_S$), phagocyting ($M_P$), or infected; in this latter case, they are either latent ($M_L$) or excreting the virus ($M_E$). We represented the evolution over time of the macrophage concentrations for these four states.

**Decay** All macrophage states are submitted to natural death or/and migration (rate $\mu^{nat}_{M}$), as well as apoptosis induced by TNF\(_\alpha\) (rate $\mu^{ap}_{M}$) [5]. The natural death rate is considered higher for infected macrophages than for susceptible and phagocytating macrophages (multiplicative factor $\delta_{M}$). Moreover, infected macrophages can be destroyed by natural killers (rate $\mu^{inn}_{M}$) and cells from the cellular response (rate $\mu^{ad}_{M}$).

**Recruitment** Susceptible macrophages are recruited from the bloodstream (rate $A_m$). Cytokines IL\(_6\) and IL\(_{12}\) co-amplify the macrophage recruitment [6–8] in synergy and IL\(_8\) attracts the macrophages in the infection place [8]. In the absence of virus, the cytokine concentrations are supposed to be negligible and the resulting concentration of susceptible macrophages in the lung is constant: $M_S = M^0_S = \frac{A_m}{\mu^{nat}_{M}}$. 
**Phagocytosis and infection** When susceptible macrophages encounter free viral particles ($V$), they can either phagocyte the virus (rate $\eta$) or become infected (rate $\beta$). We assume that phagocytizing macrophages revert to the susceptible state after viral destruction (rate $\gamma$), whereas infected macrophages remain infected (i.e., they cannot eliminate the virus). We also assume that the infected and phagocytizing states are exclusive and that once phagocytizing or infected, macrophages cannot phagocyte or be infected by other viral particles [9].

The phagocytosis is amplified by the antiviral cytokines (IFN$_{\alpha}$, TNF$_{\alpha}$, IFN$_{\gamma}$) and inhibited by the immuno-modulatory cytokines (IL$_{10}$, TGF$_{\beta}$) – . The phagocytosis ending is amplified by the antiviral cytokines and inhibited by IL$_{10}$. The macrophage infection is amplified by IL$_{10}$ and inhibited by innate antiviral cytokines (IFN$_{\alpha}$, TNF$_{\alpha}$) and TGF$_{\beta}$.

**Viral excretion** Infected macrophages are first latent (mean duration $1/\lambda$) before they start excreting. The transition between the latent and excreting states (rate $\lambda$) is inhibited by the antiviral cytokines. Excretion is supposed to be transitory and excreting macrophages may revert to the latent state in the presence of antiviral cytokines.

\[
\begin{align*}
\dot{M}_S &= A_m \left[ 1 + \kappa(\text{IL}_{12}, \text{IL}_6) \right] \left[ 1 + \kappa(\text{IL}_8) \right] \\
&\quad - \eta M_S V \frac{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right]}{\left[ 1 + \kappa(\text{IL}_{10}) \right] \left[ 1 + \kappa(\text{TGF}_\beta) \right]} \\
&\quad + \gamma M_P \frac{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right]}{1 + \kappa(\text{IL}_{10})} \\
&\quad - \beta M_S V \frac{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right]}{1 + \kappa(\text{IL}_{10})} \\
&\quad - M_S \left( \mu^\text{nat}_M + \mu^\text{inf}_M \text{TNF}_\alpha \right) \quad \leftarrow \text{recruitment} \\
&\quad \quad \leftarrow \text{phagocytosis} \\
&\quad \quad \leftarrow \text{phagocytosis ending} \\
&\quad \quad \leftarrow \text{infection} \\
&\quad \quad \leftarrow \text{decay} \\
\dot{M}_P &= \eta M_S V \frac{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right]}{\left[ 1 + \kappa(\text{IL}_{10}) \right] \left[ 1 + \kappa(\text{TGF}_\beta) \right]} \\
&\quad - \gamma M_P \frac{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right]}{1 + \kappa(\text{IL}_{10})} \\
&\quad - M_P \left( \mu^\text{nat}_M + \mu^\text{ap}_M \text{TNF}_\alpha \right) \quad \leftarrow \text{phagocytosis} \\
&\quad \quad \leftarrow \text{phagocytosis ending} \\
&\quad \quad \leftarrow \text{decay} \\
\dot{M}_L &= \beta M_S V \frac{1 + \kappa(\text{IL}_{10})}{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{TGF}_\beta) \right]} \\
&\quad - \lambda M_L \frac{1}{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right]} \\
&\quad + \nu M_E \left[ \kappa(\text{TNF}_\alpha) + \kappa(\text{IFN}_\gamma) + \kappa(\text{IFN}_\alpha) \right] \\
&\quad - M_L \left( \mu^\text{nat}_M \delta_\mu + \mu^\text{ap}_M \text{TNF}_\alpha + \mu^\text{inn}_M \text{NK} + \mu^\text{ad}_M R_c \right) \quad \leftarrow \text{infection} \\
&\quad \quad \leftarrow \text{excretion} \\
&\quad \quad \leftarrow \text{excretion ending} \\
&\quad \quad \leftarrow \text{decay} \\
\dot{M}_E &= \lambda M_L \frac{1}{\left[ 1 + \kappa(\text{TNF}_\alpha) \right] \left[ 1 + \kappa(\text{IFN}_\gamma) \right] \left[ 1 + \kappa(\text{IFN}_\alpha) \right]} \\
&\quad - \nu M_E \left[ \kappa(\text{TNF}_\alpha) + \kappa(\text{IFN}_\gamma) + \kappa(\text{IFN}_\alpha) \right] \\
&\quad - M_E \left( \mu^\text{nat}_M \delta_\mu + \mu^\text{ap}_M \text{TNF}_\alpha + \mu^\text{inn}_M \text{NK} + \mu^\text{ad}_M R_c \right) \quad \leftarrow \text{excretion} \\
&\quad \quad \leftarrow \text{excretion ending} \\
&\quad \quad \leftarrow \text{decay} 
\end{align*}
\]
Viral dynamics

The virus enters the body through the mucosal surfaces of the respiratory tract and replicates in the pulmonary macrophages.

We represented the evolution over time of the free viral particles ($V$). When they encounter susceptible macrophages ($M_S$), they can either be phagocyted by the macrophages (rate $\eta$), resulting in viral destruction, or they can infect the macrophages (rate $\beta$), resulting in virus replication. Free viral particles are released in the lung by excreting macrophages (rate $e$). They can be neutralised by antibodies represented by the humoral response $R_h$ (rate $\mu_{ad}$). They are also submitted to natural death and migration outside the lung (rate $\mu_{V}^{\text{nat}}$).

\[
\dot{V} = e M_E - \eta M_S V \frac{[1 + \kappa TNF_{\alpha}] [1 + \kappa IFN_{\alpha}] [1 + \kappa IFN_{\gamma}]}{[1 + \kappa IL_{10}] [1 + \kappa TGF_{\beta}]} - \beta M_S V \frac{1 + \kappa IL_{10}}{[1 + \kappa TNF_{\alpha}] [1 + \kappa IFN_{\alpha}] [1 + \kappa TGF_{\beta}]} - V (\mu_V^{\text{nat}} + \mu_V^{ad} R_h)
\]

Natural killer dynamics

Natural killers are effectors of the innate response. Their main immune functions are the destruction of infected cells and IFN$_\gamma$ synthesis [4, 8, 10, 11]. These cytotoxic cells are recruited on the infection by pro-inflammatory cytokines. Their proliferation and immune functions are activated by several cytokines (IFN$_\gamma$, IL$_{12}$, IL$_{15}$, IL$_{18}$, IL$_{21}$, IFN$_{\alpha \beta}$), whereas IL$_{10}$ inhibits the natural killer differentiation and their immune functions [10].

We represented the dynamics of activated natural killers (NK) and only included the regulations by the most influential cytokines. The recruitment of natural killers from the bloodstream (rate $\alpha_N$) requires pro-inflammatory cytokines: IL$_{12}$ and IL$_{6}$ co-activate the recruitment, whereas IL$_{8}$ acts independently. Natural killers are then activated by IFN$_\gamma$ and IL$_{12}$, whereas IL$_{10}$ inhibits the activation. They are submitted to natural death or/and migration (rate $\mu_R$).

\[
\dot{NK} = \alpha_N \frac{[\kappa(\text{IL}_{12}, \text{IL}_6) + \kappa(\text{IL}_8)] [\kappa(\text{IFN}_\gamma) + \kappa(\text{IL}_{12})]}{[1 + \kappa(\text{IL}_{10})]} - \mu_R NK
\]

Adaptive effector dynamics

The adaptive response activation begins with the naive CD$^+$ T cell differentiation by antigen presenting cells (dendritic cells or macrophages) within the lymphoid tissues. Depending on the cytokine profiles in the lymph nodes, CD$^+$ T cells differentiate in one of three main CD$^+$ effector types, which each have specific immune functions: type 1 T helpers ($T_{h1}$, belonging to the cellular response), type 2 T helpers ($T_{h2}$, belonging to the humoral response) and regulatory T lymphocytes ($T_{reg}$, belonging to the regulatory response) [4, 12–19]. The differentiation towards $T_{h1}$ is induced by IL$_{12}$ and amplified by IFN$_\gamma$. The differentiation towards $T_{h2}$ is induced by IL$_6$ and amplified by IL$_4$. The differentiation towards $T_{reg}$ is induced by TGF$_\beta$ and amplified by IL$_{10}$. The cytokines responsible for the differentiation towards a CD$^+$ effector type simultaneously inhibit the differentiation towards the two other types. After the differentiation step, the CD$^+$ effectors express their specific immune functions and proliferate. $T_{h1}$ synthesise the IL$_2$ and IFN$_\gamma$ cytokines. In addition, they are responsible for the differentiation of the CD$^+$ T cells in cytotoxic lymphocytes (CTL). CTL synthesise IFN$_\gamma$ and TNF$_\alpha$, and destroy the infected
macrophages. \( T_{h2} \) synthesise IL4 and IL10. In addition, they are the main activator of the B lymphocytes (through IL4 and IL10), which produce the neutralising antibodies. \( T_{reg} \) synthesise the TGF\( \beta \) and IL10 immuno-modulatory cytokines. In summary:

- The cellular response: (i) includes the \( T_{h1} \) and CTL; (ii) is activated by IL12 and IFN\( \gamma \) and inhibited by IL6, IL10 and TGF\( \beta \); and (iii) is responsible for the synthesis of IL2, IFN\( \gamma \) and TNF\( \alpha \).
- The humoral response: (i) includes the \( T_{h2} \), B lymphocytes and antibodies; (ii) is activated by IL6, IL4 and IL10 and inhibited by IL12, IFN\( \gamma \) and TGF\( \beta \); and (iii) is responsible for the synthesis of IL4 and IL10 and for the viral particle neutralisation.
- The regulatory response: (i) only includes the \( T_{reg} \); (ii) is activated by TGF\( \beta \) and IL10 and inhibited by IL6, IL12 and IFN\( \gamma \); and (iii) is responsible for the immune response inhibition through its synthesis of the TGF\( \beta \) and IL10 immuno-modulatory cytokines.

In our model, we represented the adaptive response by three effectors corresponding to the three main orientations: cellular \( (R_c) \), humoral \( (R_h) \) and regulatory \( (R_r) \) responses. As for the NK cells, we only represented the dynamics of the activated effectors.

Based on the model proposed by Yates et al. for the regulation of T helper cell populations [19], we synthesised the dynamics of each adaptive effector by three steps: activation by activated macrophages (rate \( \alpha_R \)), proliferation (rate \( p_R \)) and decay. We represented the regulations of the activation and proliferation steps by the most influential cytokines: IFN\( \gamma \), IL12, IL10 and TGF\( \beta \).

The decay includes the natural decay (rate \( \mu_R \)) and the Activation Induced Cell Death (AICD) induced by the interaction with a \( T_{h1} \) from the \( R_c \) compartment (rate \( \delta_{R_c} \)) [19].

**Cellular response** [16–18, 20–23] \( R_c \) represents the type 1 T helper cells and the cytotoxic lymphocytes. Activation is amplified by IFN\( \gamma \) and IL12 and inhibited by IL10. Proliferation is activated by IFN\( \gamma \) and IL12 and inhibited by IL10 and TGF\( \beta \). \( R_c \) synthesises IFN\( \gamma \) and is responsible for the destruction of infected cells.

\[
\dot{R}_c = \alpha_R (M_P + M_L + M_E) \left[ \frac{1 + \kappa(\text{IFN}_\gamma)}{1 + \kappa(\text{IL})} \right] \left[ \frac{1 + \kappa(\text{IL}12)}{1 + \kappa(\text{IL})} \right] \quad \leftarrow \text{activation} \\
+ p_R R_c \left[ \frac{\kappa(I\text{F}N_\gamma) + \kappa(\text{IL}12)}{1 + \kappa(\text{IFN}_\gamma) + \kappa(\text{IL}12)} \right] \left[ \frac{1 + \kappa(\text{IL}10)}{1 + \kappa(\text{IFN}_\gamma) + \kappa(\text{IL}12)} \right] \left[ \frac{1 + \kappa(\text{TGF}_{\beta})}{1 + \kappa(\text{IL}10)} \right] \quad \leftarrow \text{proliferation} \\
- \mu_R R_c - \delta_{R_c} R_c^2 \quad \leftarrow \text{decay}
\]

**Humoral response** [16–18, 24] \( R_h \) represents the type 2 T helper cells, the B lymphocytes and the antibodies. Activation is amplified by IL10 and inhibited by IFN\( \gamma \) and IL12. Proliferation is activated by IL10 and inhibited by IFN\( \gamma \), IL12 and TGF\( \beta \). \( R_h \) synthesises IL10 and is responsible for the neutralisation of free viral particles through antibodies.

\[
\dot{R}_h = \alpha_R (M_P + M_L + M_E) \left[ \frac{1 + \kappa(\text{IL}10)}{1 + \kappa(\text{IFN}_\gamma) + \kappa(\text{IL}12)} \right] \left[ \frac{1 + \kappa(\text{IL}10)}{1 + \kappa(\text{IFN}_\gamma) + \kappa(\text{IL}12)} \right] \left[ \frac{\kappa(\text{IL}10)}{1 + \kappa(\text{IFN}_\gamma) + \kappa(\text{IL}12)} \right] \quad \leftarrow \text{activation} \\
+ p_R R_h \left[ \frac{\kappa(\text{IFN}_\gamma)}{1 + \kappa(\text{IL}12)} \right] \left[ \frac{1 + \kappa(\text{IL}10)}{1 + \kappa(\text{IFN}_\gamma) + \kappa(\text{IL}12)} \right] \left[ \frac{1 + \kappa(\text{TGF}_{\beta})}{1 + \kappa(\text{IL}10)} \right] \quad \leftarrow \text{proliferation} \\
- \mu_R R_h - \delta_{R_c} R_c R_h \quad \leftarrow \text{decay}
\]
**Regulatory response** [16–18, 25]  
$R_r$ represents the regulatory T cells. Activation is amplified by IL$_{10}$ and TGF$_{β}$ and inhibited by IFN$_{γ}$ and IL$_{12}$. Proliferation is activated by TGF$_{β}$ and inhibited by IL$_{10}$, IFN$_{γ}$ and IL$_{12}$. $R_r$ synthesises IL$_{10}$ and TGF$_{β}$.

\[
\begin{align*}
\dot{R}_r &= \alpha_R \frac{(M_P + M_L + M_E)}{[1 + \kappa(\text{IL}_{10})] [1 + \kappa(\text{TGF}_{β})]} \quad \leftarrow \text{activation} \\
&+ p_R \frac{R_r [1 + \kappa(\text{IL}_{10})][1 + \kappa(\text{IFN}_{γ})][1 + \kappa(\text{IL}_{12})]}{[1 + \kappa(\text{TGF}_{β})]} \quad \leftarrow \text{proliferation} \\
&- \mu_R R_r - \delta_{R_c} R_c R_r \quad \leftarrow \text{decay}
\end{align*}
\]

**Cytokines dynamics**

Cytokines are small proteins that play a key role in cell-signalling. They are produced by activated immune cells and affect the behaviour of other cells, sometimes the releasing cell itself. They act through specific membranous receptors inducing cascaded reactions within the target cell. They have various functions. In particular, cytokines modulate the balance between the humoral and cellular responses. Some cytokines enhance or inhibit the action of other cytokines in complex ways.

In the model, we only integrated the regulations by the nine most influential cytokines. We grouped them into three classes depending on their main function: pro-inflammatory (IL$_{1,β}$, IL$_6$, IL$_8$), antiviral (TNF$_{α}$, IFN$_{α}$, IFN$_{γ}$) and immuno-regulatory (IL$_{12}$, IL$_{10}$, TGF$_{β}$) cytokines. TNF$_{α}$ is generally considered as a pro-inflammatory cytokine, but we were here more interested in its antiviral function.

We assumed that the cytokines are efficient enough in order to neglect their consumption when they interact with a cell. So the cytokine dynamics results from their synthesis by immune cells (rates $\rho_x$, where $x$ depends on the cytokine considered) and their natural death (rate $\mu_C$).

The main cytokine regulations are summarised in Table S1 and the cytokine syntheses in Table S2.

**Pro-inflammatory cytokines** [4,6–8,31,35]  
Pro-inflammatory cytokines IL$_{1,β}$, IL$_6$ and IL$_8$ amplify the recruitment of macrophages and activated natural killers. They are synthesised by the activated macrophages. As we had no information on their respective production rate, we used the same synthesis rate ($\rho_P$) for the three cytokines. The synthesis of IL$_{1,β}$ is inhibited by IL$_{10}$, whereas the synthesis of IL$_6$ and IL$_8$ is co-activated by IL$_{1,β}$ and TNF$_{α}$.

\[
\begin{align*}
\dot{\text{IL}}_{1,β} &= \rho_P \frac{(M_P + M_L + M_E)}{1 + \kappa(\text{IL}_{10})} \quad \leftarrow \text{synthesis} \\
&- \mu_C \text{IL}_{1,β} \quad \leftarrow \text{decay} \\

\dot{\text{IL}}_{6} &= \rho_P \frac{(M_P + M_L + M_E)}{\kappa(\text{IL}_{1,β}, \text{TNF}_{α})} \quad \leftarrow \text{synthesis} \\
&- \mu_C \text{IL}_{6} \quad \leftarrow \text{decay} \\

\dot{\text{IL}}_{8} &= \rho_P \frac{(M_P + M_L + M_E)}{\kappa(\text{IL}_{1,β}, \text{TNF}_{α})} \quad \leftarrow \text{synthesis} \\
&- \mu_C \text{IL}_{8} \quad \leftarrow \text{decay}
\end{align*}
\]

**Antiviral cytokines**  
Antiviral cytokines promote the phagocytosis and reduce the infection by inhibiting the macrophage permissiveness and/or the viral replication. The innate antiviral cytokines TNF$_{α}$ and IFN$_{α}$ are synthesised by activated macrophages [5,6,20,21,26–29,31]. IL$_{10}$ inhibits the synthesis of TNF$_{α}$.
Table S1. Cytokine regulations.

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>pro-inf. $P_t$</th>
<th>innate antiviral</th>
<th>immuno-regulatory</th>
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<tbody>
<tr>
<td><strong>Innate response</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Macrophage recruitment</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>NK recruitment &amp; activation</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<td>Macrophage apoptosis</td>
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<tr>
<td>Phagocytosis</td>
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<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Macrophage permissiveness</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Viral replication</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Adaptive response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular response</td>
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<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Humoral response</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Regulatory response</td>
<td>–</td>
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Cytokine syntheses

<table>
<thead>
<tr>
<th>Pro-inflammatory IL$_{1,3}$</th>
<th>IL$_6$, IL$_8$</th>
<th>Innate antiviral TNF$_a$</th>
<th>Adaptive antiviral IFN$_\gamma$</th>
<th>Immuno-regulatory IL$_{12}$</th>
<th>IL$_{10}$</th>
<th>TGF$_\beta$</th>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
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</tr>
</tbody>
</table>

Specific references: [7, 8, 23] [5, 20, 21, 26–29] [20–23] [24] [7, 30–35] [25]

Common references: [6, 31] [16–18]

Global references: [4, 12–15, 36–38]

Main positive (+) and negative (–) regulations included in the model for various immune mechanisms.

* Pro-inflammatory cytokines $P_t = \text{IL}_{1,3},\text{IL}_6,\text{IL}_8$

Table S2. Cytokine syntheses.

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>pro-inf. $P_t^*$</th>
<th>innate antiviral</th>
<th>immuno-regulatory</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><strong>Innate cells</strong></td>
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<td></td>
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</tr>
<tr>
<td>Activated macrophages</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>[8, 39]†</td>
</tr>
<tr>
<td>Activated natural killers</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>[8, 11]†</td>
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<td><strong>Adaptive cells</strong></td>
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<td>†</td>
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</tbody>
</table>

Production of cytokines included (✓) in the model by innate or adaptive immune cells.

* Pro-inflammatory cytokines $P_t = \text{IL}_{1,3},\text{IL}_6,\text{IL}_8$

† Global references: [4, 12–15, 17, 36, 40, 41]
The adaptive antiviral cytokine IFN\(_\gamma\) is synthesised by cells of the cellular response (R\(_c\)) and natural killers (NK). This synthesis is auto-amplified. It is also amplified by IFN\(_\alpha\) and TNF\(_\alpha\), in synergy with IL\(_{12}\), and inhibited by IL\(_{10}\) and TGF\(_\beta\). IFN\(_\gamma\) is also an immuno-regulatory cytokine and it orients the adaptive response towards the cellular response [16–18,20–23].

\[
\dot{\text{IFN}}_{\gamma} = \rho_{\text{IFN}_{\gamma}} (R_c + NK) \left[ \frac{1 + \kappa(\text{IFN}_{\gamma}) [1 + \kappa(\text{IL}_{12}, \text{TNF}_{\alpha})] [1 + \kappa(\text{IL}_{12}, \text{IFN}_{\alpha})]}{[1 + \kappa(\text{IL}_{10})] [1 + \kappa(\text{TGF}_{\beta})]} \right] \leftarrow \text{synthesis} \\
- \mu_C \text{IFN}_{\gamma} \leftarrow \text{decay}
\]

**Immuno-regulatory cytokines [12–18]** The immuno-regulatory cytokines IL\(_{12}\), IFN\(_\gamma\) (see above), IL\(_{10}\) and TGF\(_\beta\) have various functions, in particular the regulation of the adaptive immune response. They also regulate the recruitment of macrophages and natural killers, the phagocytosis and infection, as well as the cytokine syntheses. They are produced by cells of the innate and adaptive response.

IL\(_{12}\) co-amplifies the recruitment of macrophages, activates the natural killers and orients the adaptive response towards the cellular response. It is synthesised by activated macrophages. Its synthesis is inhibited by IL\(_{10}\).

\[
\dot{\text{IL}}_{12} = \rho_{\text{IL}_{12}} (M_P + M_L + M_E) \left( \frac{1}{1 + \kappa(\text{IL}_{10})} \right) \leftarrow \text{synthesis} \\
- \mu_C \text{IL}_{12} \leftarrow \text{decay}
\]

IL\(_{10}\) and TGF\(_\beta\) are both immuno-modulatory cytokines. IL\(_{10}\) inhibits the natural killer activation and the phagocytosis, it amplifies the macrophage permissiveness and it orients the adaptive response towards the humoral and regulatory responses. IL\(_{10}\) is synthesised by activated macrophages and cells of the regulatory (R\(_r\)) and humoral (R\(_h\)) responses. Its synthesis by macrophages and R\(_r\) is amplified by TGF\(_\beta\), whereas its synthesis by R\(_h\) is auto-amplified and inhibited by TGF\(_\beta\).

\[
\dot{\text{IL}}_{10} = \rho_{\text{IL}_{10}} \left( (M_P + M_L + M_E + R_r) [1 + \kappa(\text{TGF}_{\beta})] + R_h \frac{1 + \kappa(\text{IL}_{10})}{1 + \kappa(\text{TGF}_{\beta})} \right) \leftarrow \text{synthesis} \\
- \mu_C \text{IL}_{10} \leftarrow \text{decay}
\]

TGF\(_\beta\) inhibits the phagocytosis and macrophage permissiveness and orients the adaptive response towards the regulatory response. In the model, we neglected the synthesis of TGF\(_\beta\) by activated macrophages, so it is only synthesised by cells of the regulatory response.

\[
\dot{\text{TGF}}_{\beta} = \rho_{\text{TGF}_{\beta}} R_r \leftarrow \text{synthesis} \\
- \mu_C \text{TGF}_{\beta} \leftarrow \text{decay}
\]
References


