This file includes the mathematical model according to the simplified network and additional Table S1 list the initial values of all components in the model.

(A) The built mathematical model according to the simplified network (Figure 3 in the main text)

\[
\begin{align*}
\frac{dx_1}{dt} &= \frac{k_1 x_1}{(0.5 + x_1)(1 + a_1 x_4)(1 + a_2 x_7)} - d_1 x_1 \\
\frac{dx_2}{dt} &= \frac{k_2 x_1}{(1 + a_3 x_4)(1 + a_4 x_5)} - d_2 x_2 \\
\frac{dx_3}{dt} &= k_3 x_3 + k_3_{-2} x_2 + k_3_{-15} x_{15} + k_3_{-47} x_{47} - d_3 x_3 \\
\frac{dx_4}{dt} &= k_4_{-2} x_2 + k_4_{-7} x_7 + k_4_{-15} x_{15} - d_4 x_4 \\
\frac{dx_5}{dt} &= k_5_{-2} x_2 + k_5_{-6} x_6 + \frac{k_5_{-14}}{1 + a_5 x_{14}} - d_5 x_5 \\
\frac{dx_6}{dt} &= k_6 x_6 + k_6_{-4} x_4 + k_6_{-5} x_5 + k_6_{-17} x_{17} + k_6_{-19} x_{19} - d_6 x_6 \\
\frac{dx_7}{dt} &= k_7 x_7 + k_7_{-14} x_{14} + k_7_{-47} x_{47} - d_7 x_7 \\
\frac{dx_8}{dt} &= k_8_{-48} x_{48} - d_8 x_8 \\
\frac{dx_9}{dt} &= k_9_{-46} x_{46} - d_9 x_9 \\
\frac{dx_{10}}{dt} &= k_{10_{-6}} x_6 - d_{10} x_{10} \\
\frac{dx_{11}}{dt} &= k_{11_1} x_{11} + k_{11_{-2}} x_2 + k_{11_{-47}} x_{47} + k_{11_{-48}} x_{48} - d_{11} x_{11} \\
\frac{dx_{12}}{dt} &= k_{12_{-2}} x_2 + k_{12_{-48}} x_{48} - d_{12} x_{12} \\
\frac{dx_{13}}{dt} &= k_{13_{-15}} x_{15} + k_{13_{-47}} x_{47} - d_{13} x_{13} \\
\frac{dx_{14}}{dt} &= k_{14_{-5}} x_5 - d_{14} x_{14} \\
\frac{dx_{15}}{dt} &= k_{15} x_{15} + k_{15_{-2}} x_2 + k_{15_{-4}} x_4 + k_{15_{-13}} x_{13} + k_{15_{-19}} x_{19} - d_{15} x_{15} \\
\frac{dx_{16}}{dt} &= k_{16_{-2}} x_2 + k_{16_{-11}} x_{11} + k_{16_{-48}} x_{48} - d_{16} x_{16} \\
\frac{dx_{17}}{dt} &= k_{17_{-2}} x_2 - d_{17} x_{17} \\
\frac{dx_{18}}{dt} &= k_{18} x_{18} - d_{18} x_{18}
\end{align*}
\]
\[
\begin{align*}
\frac{dx_{19}}{dt} &= k_{19,2}x_{2} + k_{19,6}x_{6} - d_{19}x_{19} \\
\frac{dx_{20}}{dt} &= k_{20,2}x_{2} + k_{20,18}x_{18} + k_{20,47}x_{47} + k_{20,48}x_{48} - d_{20}x_{20} \\
\frac{dx_{21}}{dt} &= k_{21,14}x_{14} - d_{21}x_{21} \\
\frac{dx_{22}}{dt} &= k_{22,22} + k_{22,3}x_{3} + k_{22,25}x_{25} + k_{22,26}x_{26} + k_{22,43}x_{43} - d_{22}x_{22} \\
\frac{dx_{23}}{dt} &= k_{23,2}x_{2} + k_{23,22}x_{22} - d_{23}x_{23} \\
\frac{dx_{24}}{dt} &= k_{24,2}x_{2} + k_{24,25}x_{25} - d_{24}x_{24} \\
\frac{dx_{25}}{dt} &= k_{25}x_{25} - d_{25}x_{25} \\
\frac{dx_{26}}{dt} &= k_{26}x_{26} + k_{26,2}x_{2} + k_{26,23}x_{23} - d_{26}x_{26} \\
\frac{dx_{27}}{dt} &= k_{27,2}x_{2} + k_{27,22}x_{22} - d_{27}x_{27} \\
\frac{dx_{28}}{dt} &= k_{28}x_{28} + k_{28,2}x_{2} + k_{28,9}x_{9} + k_{28,29}x_{29} + k_{28,30}x_{30} + k_{28,34}x_{34} + k_{28,35}x_{35} + k_{28,36}x_{36} + k_{28,37}x_{37} + k_{28,39}x_{39} + k_{28,46}x_{46} - d_{28}x_{28} \\
\frac{dx_{29}}{dt} &= k_{29,2}x_{2} - d_{29}x_{29} \\
\frac{dx_{30}}{dt} &= k_{30,2}x_{2} - d_{30}x_{30} \\
\frac{dx_{31}}{dt} &= k_{31,2}x_{2} + k_{31,28}x_{28} + \frac{k_{31,40}}{1 + a_0x_{40}} - d_{31}x_{31} \\
\frac{dx_{32}}{dt} &= k_{32}x_{32} + k_{32,2}x_{2} + k_{32,28}x_{28} - d_{32}x_{32} \\
\frac{dx_{33}}{dt} &= k_{33,28}x_{28} - d_{33}x_{33} \\
\frac{dx_{34}}{dt} &= k_{34,2}x_{2} + k_{34,28}x_{28} + k_{34,32}x_{32} - d_{34}x_{34} \\
\frac{dx_{35}}{dt} &= k_{35,2}x_{2} + k_{35,28}x_{28} + k_{35,30}x_{30} + k_{35,32}x_{32} + k_{35,36}x_{36} + k_{35,37}x_{37} + k_{35,39}x_{39} - d_{35}x_{35} \\
\frac{dx_{36}}{dt} &= k_{36,2}x_{2} + k_{36,28}x_{28} + k_{36,30}x_{30} + k_{36,32}x_{32} + k_{36,35}x_{35} + k_{36,37}x_{37} + k_{36,39}x_{39} - d_{35}x_{36} \\
\frac{dx_{37}}{dt} &= k_{37,2}x_{2} + k_{37,28}x_{28} - d_{37}x_{37} \\
\frac{dx_{38}}{dt} &= k_{38,2}x_{2} + k_{38,36}x_{36} - d_{38}x_{38} 
\end{align*}
\]
We gave the following explanations for the above equations.

The concentration of component $X_i$ that changes over time can be described by an ordinary differential equation (ODE)

$$\frac{dX_i}{dt} = V_{i, \text{production}} - V_{i, \text{degradation}}$$

where $V_{i, \text{production}}$ and $V_{i, \text{degradation}}$ represent the production rate and the degradation rate of reactant $X_i$, respectively. In general, based on the law of mass action, we assume that the production rates and the degradation rates of these components are linearly proportional to their concentrations. But several special processes (S1-S7) are different based on the available experimental data and network topology.

1. The regulations of the positive and negative feedbacks are described using Hill functions.

   (1) In Eq.S1, we used the term $\frac{k_i x_i}{0.5 + x_i}$ to represent the replication of $x_1$ (influenza A virus, IAV),
which is equivalent to the positive feedback, the terms \( \frac{1}{1 + a_i x_i} \) and \( \frac{1}{1 + a_j x_j} \) to represent the negative feedbacks of \( x_4 \) (IL27) and \( x_7 \) (IFN-alpha) to \( x_1 \) (IAV), respectively.

\[
\frac{dx_1}{dt} = \frac{k_{1,x_1}}{(0.5 + x_1)(1 + a_i x_i)(1 + a_j x_j)} - d_1 x_1 \quad (S1)
\]

(2) In Eq.S2, \( x_4 \) (IL27) and \( x_5 \) (IL32) have also a negative feedback to \( x_2 \) (COX-2), respectively.

\[
\frac{dx_2}{dt} = \frac{k_{2,x_1}}{(1 + a_i x_4)(1 + a_j x_j)} - d_2 x_2 \quad (S2)
\]

(3) In Eqs.S3, \( x_{14} \) (NOS2) has a negative feedback to \( x_5 \) (IL32)

\[
\frac{dx_5}{dt} = k_{5,x_2} x_2 + k_{5,x_6} x_6 + \frac{k_{5,x_{14}}}{1 + a_j x_{14}} - d_5 x_5 \quad (S3)
\]

(5) In Eqs.S4, \( x_{40} \) (IL16) has a negative feedback to \( x_{31} \) (CXCR3)

\[
\frac{dx_{31}}{dt} = k_{31,x_2} x_2 + k_{31,x_{28}} x_{28} + \frac{k_{31,x_{40}}}{1 + a_j x_{40}} - d_{31} x_{31} \quad (S4)
\]

2. Coordinate interactions are represented by multiplying together. In Eq.S1, because \( x_1 \) (IAV) is coordinately regulated by interlinked positive and negative feedbacks, we use the multiply \( \frac{k_{1,x_1}}{0.5 + x_1} \cdot \frac{1}{1 + a_i x_i} \cdot \frac{1}{1 + a_j x_j} \). Similarly, in Eq.S2, we use \( \frac{k_{2,x_1}}{(1 + a_i x_4)(1 + a_j x_j)} \) to represent that the \( x_2 \) (COX-2) is regulated by two negative feedbacks altogether.

3. Binding interactions are formulated by linear product. In Eqs. S5-S7, both \( x_{44} \) (IL22RA1) and \( x_{45} \) (IL22RA2) are the receptor factors of \( x_{43} \) (IL22) (See the additional file 2) and they altogether can bind to the \( x_{43} \) (IL22). Therefore, these terms are formulated by linear product.

(B) Table S1 The initial values of all components.

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<th>Chemical species</th>
<th>Initial value</th>
<th>Chemical species</th>
<th>Initial value</th>
<th>Chemical species</th>
<th>Initial value</th>
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Abbreviations are as follows: 