Supplementary Materials

1 Integration of multiple STAT pathways (Fig 1A main text)

This section provides more details regarding the interactions between multiple STAT pathways, schematically represented in Fig 1A in the main text. Several STATs, for example STAT3 and STAT5 (1, 2), lead to the production of IFN-γ and IL-10. The molecular mechanism of IFN-γ and IL-10 production via STAT3 and STAT5 is as follows.

Extracellular IL-2, IL-6 and IL-21 bind to their complementary receptors. The receptors remain in complex with JAKs. Binding of the interleukins to their receptors induces the autophosphorylation of the receptors and the bound JAKs (3). The phosphorylated receptor-JAK complexes can be dephosphorylated by SHP-1 (4). Phosphorylation of STAT3 is performed by JAK in IL-2R:JAK and IL-6R:JAK complexes, while STAT5 is phosphorylated by IL-2R:JAK and IL-21R:JAK (5-7). STAT3 and STAT5 are dephosphorylated by SHP-1 and SHP-2 phosphatases respectively (8, 9). The phosphorylated STAT3 and STAT5 then can form either homo- or hetero- dimers (5, 6). The dimers translocate into the cell nucleus and promote transcription of genes responsible for IFN-γ and IL-10 production. Both IFN-γ and IL-10 are degraded by various factors of dissociation such as the cytokine-receptor binding, diffusion and cleavage by metalloproteases (10), which, in our model, we denote as Mp1 and Mp2 for IFN-γ and IL-10, respectively.

Other STAT pathways, in addition to STAT3 and STAT5, can also lead to the induction of IFN-γ and IL-10 production. The production of IFN-γ is induced by the following interleukins: IL-12, IL-21, IL-2 and IL-35 (11-14). Interleukins IL-12 and IL-35 activate STAT4 through the JAK-STAT pathway (6) while IL-21 and IL-2 activate STAT5 (15, 16). The production of anti-inflammatory IL-10 is up-regulated by STAT1, STAT3 and STAT6 (2, 17, 18). In particular, STAT1 is activated by IL-6 and IL-35; STAT3 by IL-2 and IL-6; STAT6 by IL-3 and IL-4 (6, 7, 19, 20).

2 Mathematical model

In this section, mathematical details of the model for STAT-STAT interactions are provided. We derived the equations employed in the STAT3-STAT5 (Fig 1B), STAT3-STAT4 (Fig 1C) and the combined STAT3-STAT4-STAT5 (Fig 5A) circuits. Table S1 shows the short names and abbreviations used in our model.

Table S1. Abbreviations used in the STAT phosphorylation model.

Abbreviation	Meaning
I2	IL-2
RJ2	IL-2 Receptor complex with JAK
I2RJ2	IL-2 Receptor:JAK complex with bound IL-2
RpJ2	Phosphorylated IL-2 Receptor:JAK complex
P2	SHP-1 phosphatase
RpJ2P2	Phosphorylated IL-2 Receptor:JAK complex with SHP-1
I6	IL-6
RJ6	IL-6 Receptor:JAK complex
I6RJ6	IL-6 Receptor:JAK complex with bound IL-6
RpJ6	Phosphorylated IL-6 Receptor:JAK complex
P6	SHP-2 phosphatase
RpJ6P6	Phosphorylated IL-6 Receptor:JAK complex with SHP-2
I12	IL-12
RJ12	IL-12 Receptor:JAK complex
I12RJ12	IL-12 Receptor:JAK complex with bound IL-12
RpJ12	Phosphorylated IL-12 Receptor:JAK complex
P12	JAK phosphatase
RpJ12P12	Phosphorylated IL-12 Receptor:JAK complex with P12 phosphatase
I35	IL-35
RJ35	IL-35 Receptor:JAK complex
I35RJ35	IL-35 Receptor:JAK complex with bound IL-35
RpJ35	Phosphorylated IL-35 Receptor:JAK complex
P35	JAK phosphatase
RpJ35P35	Phosphorylated IL-35 Receptor:JAK complex with P35 phosphatase
I21	IL-21

RJ21	IL-21 Receptor:JAK complex
I21RJ21	IL-21 Receptor:JAK complex with bound IL-21
RpJ21	Phosphorylated IL-21 Receptor:JAK complex
P21	JAK phosphatase
RpJ21P21	Phosphorylated IL-21 Receptor:JAK complex with P21 phosphatase
S3	STAT3
RpJ2S3	Phosphorylated IL-2 Receptor:JAK complex with STAT3
RpJ6S3	Phosphorylated IL-6 Receptor:JAK complex with STAT3
S3p	Phosphorylated STAT3
P3	SHP-1 phosphatase
P3S3p	Phosphorylated STAT3 complex with SHP-1
S4	STAT4
S4p	Phosphorylated STAT4
RpJ12S4	Phosphorylated IL-12 Receptor:JAK complex with STAT4
RpJ35S4	Phosphorylated IL-35 Receptor:JAK complex with STAT4
P4	PTP phosphatase
P4S4p	Phosphorylated STAT4 complex with PTP phosphatase
S5	STAT5
S5p	Phosphorylated STAT5
RpJ2S5	Phosphorylated IL-2 Receptor:JAK complex with STAT5
RpJ21S5	Phosphorylated IL-21 Receptor:JAK complex with STAT5
P5	SHP-2 phosphatase
P5S5p	Phosphorylated STAT5 complex with SHP-2 phosphatase
S33	STAT3:STAT3 homodimer
S34	STAT3:STAT4 heterodimer
S44	STAT4:STAT4 homodimer
S35	STAT3:STAT5 heterodimer
S55	STAT5:STAT5 homodimer
Gg	Gene responsible for IFN-γ production
S44Gg	IFN-γ gene complex with STAT4:STAT4 homodimer
S55Gg	IFN-γ gene complex with STAT5:STAT5 homodimer
S44S55Gg	IFN-γ gene complex with STAT4:STAT4 and

	STAT5:STAT5
Ig	IFN-γ
Mp1	Metalloprotease that cleaves IFN-γ
IgMp1	Metalloprotease complex with IFN-γ gene
Ign	Non-active IFN-γ
G10	IL-10 gene
S33G10	IL-10 gene complex with STAT3:STAT3 homodimer
Sp1	SP1 transcription factor
Sp1a	SP1 transcription factor in active form
S33Sp1aG10	IL-10 gene complex with STAT3:STAT3 and Sp1a
Sp1aG10	Complex of Sp1a with IL-10 gene
Mp2	Metalloprotease that cleaves IL-10
I10Mp2	Metalloprotease complex with IL-10 gene
I10n	Non-active IL-10

2.1 Model for the STAT3-STAT5 circuit

The biochemical reactions involved in the STAT3-STAT5 circuit (Fig 1B) are given by:

$$\mathrm{I2} + \mathrm{RJ2} \underset{f_3}{\overset{f_1}{\rightleftarrows}} \mathrm{I2RJ2} \xrightarrow{f_2} \mathrm{RpJ2}$$

$$\mathrm{RpJ2} + \mathrm{P2} \underset{f_6}{\overset{f_4}{\rightleftarrows}} \mathrm{RpJ2P2} \xrightarrow{f_5} \mathrm{RJ2} + \mathrm{P2}$$

$$\mathrm{I6} + \mathrm{RJ6} \underset{f_9}{\overset{f_7}{\rightleftarrows}} \mathrm{I6RJ6} \xrightarrow{f_8} \mathrm{RpJ6}$$

$$\mathrm{RpJ6} + \mathrm{P6} \underset{f_{12}}{\overset{f_{10}}{\rightleftarrows}} \mathrm{RpJ6P6} \xrightarrow{f_{11}} \mathrm{RJ6} + \mathrm{P6}$$

$$\mathrm{I21} + \mathrm{RJ21} \underset{f_{15}}{\overset{f_{13}}{\rightleftarrows}} \mathrm{I21RJ21} \xrightarrow{f_{14}} \mathrm{RpJ21}$$

$$\mathrm{RpJ21} + \mathrm{P21} \underset{f_{18}}{\overset{f_{16}}{\rightleftarrows}} \mathrm{RpJ21P21} \xrightarrow{f_{17}} \mathrm{RJ21} + \mathrm{P21}$$

$$\mathrm{RpJ2} + \mathrm{S3} \underset{a_3}{\overset{a_1}{\rightleftarrows}} \mathrm{RpJ2S3} \xrightarrow{a_2} \mathrm{RpJ2} + \mathrm{S3p}$$

$$\mathrm{RpJ6} + \mathrm{S3} \underset{a_6}{\overset{a_4}{\rightleftarrows}} \mathrm{RpJ6S3} \xrightarrow{a_5} \mathrm{RpJ6} + \mathrm{S3p}$$

$$\mathrm{P3} + \mathrm{S3p} \underset{a_9}{\overset{a_7}{\rightleftarrows}} \mathrm{P3S3p} \xrightarrow{a_8} \mathrm{P3} + \mathrm{S3}$$

$$\mathrm{RpJ2} + \mathrm{S5} \underset{a_{12}}{\overset{a_{10}}{\rightleftarrows}} \mathrm{RpJ2S5} \xrightarrow{a_{11}} \mathrm{RpJ2} + \mathrm{S5p}$$

$$\mathrm{RpJ21} + \mathrm{S5} \underset{a_{15}}{\overset{a_{13}}{\rightleftarrows}} \mathrm{RpJ21S5} \xrightarrow{a_{14}} \mathrm{RpJ21} + \mathrm{S5p}$$

$$\mathrm{P5} + \mathrm{S5p} \underset{a_{18}}{\overset{a_{16}}{\rightleftarrows}} \mathrm{P5S5p} \xrightarrow{a_{17}} \mathrm{P5} + \mathrm{S5} \qquad \text{(S1)}$$

$$\mathrm{S3p} + \mathrm{S3p} \underset{a_{20}}{\overset{a_{19}}{\rightleftarrows}} \mathrm{S33}$$

$$\mathrm{S3p} + \mathrm{S5p} \underset{a_{22}}{\overset{a_{21}}{\rightleftarrows}} \mathrm{S35}$$

$$\mathrm{S5p} + \mathrm{S5p} \underset{a_{24}}{\overset{a_{23}}{\rightleftarrows}} \mathrm{S55}$$

$$\mathrm{I2} + \mathrm{Sp1} \underset{l_2}{\overset{l_1}{\rightleftarrows}} \mathrm{I2Sp1}$$

$$\mathrm{I2Sp1} + \mathrm{CD46} \underset{l_4}{\overset{l_3}{\rightleftarrows}} \mathrm{Sp1a}$$

$$\mathrm{CD46} + \mathrm{Sp1} \underset{l_4}{\overset{l_3}{\rightleftarrows}} \mathrm{CD46Sp1}$$

$$\mathrm{CD46Sp1} + \mathrm{I2} \underset{l_2}{\overset{l_1}{\rightleftarrows}} \mathrm{Sp1a}$$

$$\mathrm{S55} + \mathrm{Gg} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{S55Gg}$$

$$\mathrm{S55Gg} \xrightarrow{l_5} \mathrm{Ig}$$

$$\mathrm{Ig} + \mathrm{Mp1} \underset{k_5}{\overset{k_3}{\rightleftarrows}} \mathrm{IgMp1} \xrightarrow{k_4} \mathrm{Ign} + \mathrm{Mp1}$$

$$\mathrm{S33} + \mathrm{G10} \underset{k_7}{\overset{k_6}{\rightleftarrows}} \mathrm{S33G10}$$

$$\mathrm{S33G10} + \mathrm{Sp1a} \underset{k_9}{\overset{k_8}{\rightleftarrows}} \mathrm{S33Sp1aG10}$$

$$\mathrm{Sp1a} + \mathrm{G10} \underset{k_9}{\overset{k_8}{\rightleftarrows}} \mathrm{Sp1aG10}$$

$$\mathrm{Sp1aG10} + \mathrm{S33} \underset{k_7}{\overset{k_6}{\rightleftarrows}} \mathrm{S33Sp1aG10}$$

$$\mathrm{S33G10} \xrightarrow{l_6} \mathrm{I10}$$

$$\mathrm{Sp1aG10} \xrightarrow{l_6} \mathrm{I10}$$

$$\mathrm{S33Sp1aG10} \xrightarrow{l_6} \mathrm{I10}$$

$$\mathrm{I10} + \mathrm{Mp2} \underset{k_{12}}{\overset{k_{10}}{\rightleftarrows}} \mathrm{I10Mp2} \xrightarrow{k_{11}} \mathrm{I10n} + \mathrm{Mp2}$$

The system of reactions (S1) can be divided into three major subsystems of interactions: i) Cytokine-receptor interactions, ii) STAT phosphorylation and dimerization, iii) Cytokine production.

2.1.1 Cytokine-receptor interactions

In the most general case the reactions can be written as follows:

$$\begin{aligned} &\mathrm{C} + \mathrm{RJ} \underset{q_3}{\overset{q_1}{\rightleftarrows}} \mathrm{CRJ} \xrightarrow{q_2} \mathrm{RpJ}, \\ &\mathrm{RpJ} + \mathrm{P} \underset{q_6}{\overset{q_4}{\rightleftarrows}} \mathrm{RpJP} \xrightarrow{q_5} \mathrm{RJ} + \mathrm{P}, \end{aligned} \tag{S2}$$

where C is cytokine, RJ is Receptor:JAK complex, P is phosphatase and small p denotes phosphorylated state.

The ODEs for the system (S2):

$$\begin{aligned}
&\frac{d}{dt}[CRJ] = q_1[C][RJ] - (q_2 + q_3)[CRJ],\\
&\frac{d}{dt}[RpJ] = q_2[CRJ] - q_4[RpJ][P] + q_6[RpJP],\\
&\frac{d}{dt}[RpJP] = q_4[RpJ][P] - (q_5 + q_6)[RpJP].
\end{aligned} \tag{S3}$$

Corresponding conservation equations:

$$\begin{aligned}
&R_T = [RJ] + [CRJ] + [RpJ] + [RpJP],\\
&P_T = [P] + [RpJP],
\end{aligned} \tag{S4}$$

where R_T and P_T are the total amounts of receptors and phosphatase, respectively. Here we neglected STAT-receptor interactions since STAT proteins do not have a significant impact on receptor dephosphorylation.

Equations (S4) can be written as follows:

$$\begin{aligned}
&R_T = \alpha + \beta + \gamma + \omega,\\
&P_T = p + \omega,
\end{aligned} \tag{S5}$$

where $\alpha = [RJ], \beta = [CRJ], \gamma = [RpJ], \omega = [RpJP], p = [P], c = [C].$

The ODEs (S3) can be rewritten in the following way:

$$\begin{aligned}
&\frac{d}{dt}\beta = q_1 c\alpha - (q_2 + q_3)\beta,\\
&\frac{d}{dt}\gamma = q_2\beta - q_4\gamma p + q_6\omega,\\
&\frac{d}{dt}\omega = q_4\gamma p - (q_5 + q_6)\omega.
\end{aligned} \tag{S6}$$

We need to find steady-state solutions of Equations (S6):

$$\begin{aligned}
&0 = q_1 c\alpha - (q_2 + q_3)\beta,\\
&0 = q_2\beta - q_4\gamma p + q_6\omega,\\
&0 = q_4\gamma p - (q_5 + q_6)\omega,\\
&R_T = \alpha + \beta + \gamma + \omega,\\
&P_T = p + \omega.
\end{aligned} \tag{S7}$$

We found the concentrations of the complexes:

$$\omega = P_T \frac{\gamma}{\frac{q_5+q_6}{q_4}+\gamma} = \frac{P_T\gamma}{Q_2+\gamma},$$

$$\beta = \frac{q_5}{q_2}\omega = \frac{q_5}{q_2}\frac{P_T\gamma}{Q_2+\gamma} = \frac{P_T\gamma}{Q_3(Q_2+\gamma)}, \quad \text{(S8)}$$

$$\alpha = \frac{q_2+q_3}{q_1}\frac{\beta}{c} = \frac{Q_1 P_T\gamma}{cQ_3(Q_2+\gamma)},$$

where $Q_1 = \frac{q_2+q_3}{q_1}$ and $Q_2 = \frac{q_5+q_6}{q_4}$ are the Michaelis constants for phosphorylation and dephosphorylation, respectively, and $Q_3 = \frac{q_2}{q_5}$.

We can write the following equation using the conservation Equation for the receptor (S5):

$$R_T = \gamma + \frac{P_T\gamma}{Q_2+\gamma}\left(\frac{Q_1}{cQ_3}+\frac{1}{Q_3}+1\right). \quad \text{(S9)}$$

As a result, we obtained a quadratic equation:

$$0 = \gamma^2 + \gamma\chi - \delta, \quad \text{(S10)}$$

where $\chi = Q_2 - R_T + P_T\left(\frac{Q_1}{cQ_3}+\frac{1}{Q_3}+1\right)$, $\delta = R_T Q_2$.

The solution of Equation (S10) is:

$$\gamma = -\frac{\chi}{2} + \frac{\sqrt{\chi^2+4\delta}}{2} \quad \text{(S11)}$$

Equation (S11) can be rewritten as follows:

$$\gamma = \frac{1}{2}\left(\sqrt{\left(\lambda+\frac{\rho}{c}\right)^2+4\delta} - \lambda - \frac{\rho}{c}\right), \quad \text{(S12)}$$

where $\lambda = Q_2 - R_T + P_T\left(\frac{1}{Q_3}+1\right)$ and $\rho = \frac{P_T Q_1}{Q_3}$.

Using Equation (S12) we can now write for $[RpJ2]$,$[RpJ6]$ and $[RpJ21]$ in non-dimensional form respectively:

$$[w2] = -\frac{M_2 - r2_t + p2_t\left(\frac{M_1}{n_1[i2]} + \frac{1}{n_1} + 1\right)}{2} + \frac{\sqrt{\left(M_2 - r2_t + p2_t\left(\frac{M_1}{n_1[i2]} + \frac{1}{n_1} + 1\right)\right)^2 + 4r2_t M_2}}{2},$$

$$[w6] = -\frac{M_4 - r6_t + p6_t\left(\frac{M_3}{n_2[i6]} + \frac{1}{n_2} + 1\right)}{2} + \frac{\sqrt{\left(M_4 - r6_t + p6_t\left(\frac{M_3}{n_2[i6]} + \frac{1}{n_2} + 1\right)\right)^2 + 4r6_t M_4}}{2},$$

$$[w21] = -\frac{M_6 - r21_t + p21_t\left(\frac{M_5}{n_3[i21]} + \frac{1}{n_3} + 1\right)}{2} + \frac{\sqrt{\left(M_6 - r21_t + p21_t\left(\frac{M_5}{n_3[i21]} + \frac{1}{n_3} + 1\right)\right)^2 + 4r21_t M_6}}{2}, \quad \text{(S13)}$$

where

$$[i2] = \frac{[I2]}{S3_T}, [w2] = \frac{[RpJ2]}{S3_T}, r2_t = \frac{R2_T}{S3_T}, p2_t = \frac{P2_T}{S3_T}, M_1 = \frac{f_2 + f_3}{f_1 S3_T}, M_2 = \frac{f_5 + f_6}{f_4 S3_T}, n_1 = \frac{f_2}{f_5}, [i6] = \frac{[I6]}{S3_T},$$

$$[w6] = \frac{[RpJ6]}{S3_T}, r6_t = \frac{R6_T}{S3_T}, p6_t = \frac{P6_T}{S3_T}, M_3 = \frac{f_8 + f_9}{f_7 S3_T}, M_4 = \frac{f_{11} + f_{12}}{f_{10} S3_T}, n_2 = \frac{f_8}{f_{11}}, [i21] = \frac{[I21]}{S3_T},$$

$$[w21] = \frac{[RpJ21]}{S3_T}, r21_t = \frac{R21_T}{S3_T}, p21_t = \frac{P21_T}{S3_T}, M_5 = \frac{f_{14} + f_{15}}{f_{13} S3_T}, M_6 = \frac{f_{17} + f_{18}}{f_{16} S3_T}, n_3 = \frac{f_{14}}{f_{17}}.$$

2.1.2 STAT phosphorylation and dimerization

The ODEs describing biochemical reactions in the STAT subsystem:

$$
\begin{aligned}
&\frac{d}{dt}[RpJ2S3] = a_1[RpJ2][S3] - (a_2 + a_3)[RpJ2S3],\\
&\frac{d}{dt}[RpJ6S3] = a_4[RpJ6][S3] - (a_5 + a_6)[RpJ6S3],\\
&\frac{d}{dt}[S3p] = a_2[RpJ2S3] + a_5[RpJ6S3] - a_7[P3][S3p] + a_9[P3S3p] -\\
&\qquad -2a_{19}[S3p]^2 + 2a_{20}[S33] - a_{21}[S3p][S5p] + a_{22}[S35],\\
&\frac{d}{dt}[P3S3p] = a_7[P3][S3p] - (a_8 + a_9)[P3S3p],\\
&\frac{d}{dt}[RpJ2S5] = a_{10}[RpJ2][S5] - (a_{11} + a_{12})[RpJ2S5],\\
&\frac{d}{dt}[RpJ21S5] = a_{13}[RpJ21][S5] - (a_{14} + a_{15})[RpJ21S5],\\
&\frac{d}{dt}[S5p] = a_{11}[RpJ2S5] + a_{14}[RpJ21S5] - a_{16}[P5][S5p] + a_{18}[P5S5p] -\\
&\qquad -a_{21}[S3p][S5p] + a_{22}[S35] - 2a_{23}[S5p]^2 + 2a_{24}[S55],\\
&\frac{d}{dt}[P5S5p] = a_{16}[P5][S5p] - (a_{17} + a_{18})[P5S5p],\\
&\frac{d}{dt}[S33] = a_{19}[S3p]^2 - a_{20}[S33],\\
&\frac{d}{dt}[S35] = a_{21}[S3p][S5p] - a_{22}[S35],\\
&\frac{d}{dt}[S55] = a_{23}[S5p]^2 - a_{24}[S55].
\end{aligned}
\tag{S14}
$$

Conservation equations are given by:

$$
\begin{aligned}
S3_T &= [S3] + [S3p] + 2[S33] + [S35] + [RpJ2S3] + [RpJ6S3] + [P3S3p],\\
S5_T &= [S5] + [S5p] + 2[S55] + [S35] + [RpJ2S5] + [RpJ21S5] + [P5S5p],\\
P3_T &= [P3] + [P3S3p],\\
P5_T &= [P5] + [P5S5p].
\end{aligned}
\tag{S15}
$$

Then we can normalize Equations (S15) to $S3_T$:

$$
\begin{aligned}
1 &= [s3] + [s3p] + 2[s33] + [s35] + [w2s3] + [w6s3] + [p3s3p],\\
s5_t &= [s5] + [s5p] + 2[s55] + [s35] + [w2s5] + [w21s5] + [p5s5p],\\
p3_t &= [p3] + [p3s3p],\\
p5_t &= [p5] + [p5s5p],
\end{aligned}
\tag{S16}
$$

where

$$[s3]=\frac{[S3]}{S3_T},[s3p]=\frac{[S3p]}{S3_T},[w2s3]=\frac{[RpJ2S3]}{S3_T},[w6s3]=\frac{[RpJ6S3]}{S3_T},[p3s3p]=\frac{[P3S3p]}{S3_T},s5_t=\frac{S5_T}{S3_T},$$
$$[s5]=\frac{[S5]}{S3_T},[s5p]=\frac{[S5p]}{S3_T},[w2s5]=\frac{[RpJ2S5]}{S3_T},[w21s5]=\frac{[RpJ21S5]}{S3_T},[p5s5p]=\frac{[P5S5p]}{S3_T},$$
$$[s33]=\frac{[S33]}{S3_T},[s35]=\frac{[S35]}{S3_T},[s55]=\frac{[S55]}{S3_T},[p3]=\frac{[P3]}{S3_T},[p5]=\frac{[P5]}{S3_T},\ p3_t=\frac{P3_T}{S3_T},p5_t=\frac{P5_T}{S3_T}.$$

The ODEs (S14) can be written in non-dimensional form as follows:

$$\begin{aligned}
&\frac{d}{d\tau}[w2s3]=m_1[w2][s3]-[w2s3],\\
&\frac{d}{d\tau}[w6s3]=m_3[w6][s3]-(m_4+m_5)[w6s3],\\
&\frac{d}{d\tau}[s3p]=m_2[w2s3]+m_4[w6s3]-m_6[p3][s3p]+m_8[p3s3p]-\\
&\qquad -2m_{18}[s3p]^2+2m_{19}[s33]-m_{20}[s3p][s5p]+m_{21}[s35],\\
&\frac{d}{d\tau}[p3s3p]=m_6[p3][s3p]-(m_7+m_8)[p3s3p],\\
&\frac{d}{d\tau}[w2s5]=m_9[w2][s5]-(m_{10}+m_{11})[w2s5],\\
&\frac{d}{d\tau}[w21s5]=m_{12}[w21][s5]-(m_{13}+m_{14})[w21s5],\\
&\frac{d}{d\tau}[s5p]=m_{10}[w2s5]+m_{13}[w21s5]-m_{15}[p5][s5p]+m_{17}[p5s5p]-\\
&\qquad -m_{20}[s3p][s5p]+m_{21}[s35]-2m_{22}[s5p]^2+2m_{23}[s55],\\
&\frac{d}{d\tau}[p5s5p]=m_{15}[p5][s5p]-(m_{16}+m_{17})[p5s5p],\\
&\frac{d}{d\tau}[s33]=m_{18}[s3p]^2-m_{19}[s33],\\
&\frac{d}{d\tau}[s35]=m_{20}[s3p][s5p]-m_{21}[s35],\\
&\frac{d}{d\tau}[s55]=m_{22}[s5p]^2-m_{23}[s55],
\end{aligned}\tag{S17}$$

where

$$\tau=t(a_2+a_3),m_1=\frac{a_1}{a_2+a_3}S3_T,m_2=\frac{a_2}{a_2+a_3},m_3=\frac{a_4}{a_2+a_3}S3_T,m_4=\frac{a_5}{a_2+a_3},m_5=\frac{a_6}{a_2+a_3},$$
$$m_6=\frac{a_7}{a_2+a_3}S3_T,m_7=\frac{a_8}{a_2+a_3},m_8=\frac{a_9}{a_2+a_3},\ m_9=\frac{a_{10}}{a_2+a_3}S3_T,m_{10}=\frac{a_{11}}{a_2+a_3},m_{11}=\frac{a_{12}}{a_2+a_3},$$
$$m_{12}=\frac{a_{13}}{a_2+a_3}S3_T,m_{13}=\frac{a_{14}}{a_2+a_3},m_{14}=\frac{a_{15}}{a_2+a_3},\ m_{15}=\frac{a_{16}}{a_2+a_3}S3_T,m_{16}=\frac{a_{17}}{a_2+a_3},m_{17}=\frac{a_{18}}{a_2+a_3},$$
$$m_{18}=\frac{a_{19}}{a_2+a_3}S3_T,m_{19}=\frac{a_{20}}{a_2+a_3},m_{20}=\frac{a_{21}}{a_2+a_3}S3_T,m_{21}=\frac{a_{22}}{a_2+a_3},m_{22}=\frac{a_{23}}{a_2+a_3}S3_T,m_{23}=\frac{a_{24}}{a_2+a_3}.$$

We need to find steady-state solutions of Equations (S17):

$$
\begin{aligned}
0 &= m_1[w2][s3]-[w2s3],\\
0 &= m_3[w6][s3]-(m_4+m_5)[w6s3],\\
\frac{d}{d\tau}[s3p] &= m_2[w2s3]+m_4[w6s3]-m_6[p3][s3p]+m_8[p3s3p]-\\
&\quad -2m_{18}[s3p]^2+2m_{19}[s33]-m_{20}[s3p][s5p]+m_{21}[s35],\\
0 &= m_6[p3][s3p]-(m_7+m_8)[p3s3p],\\
0 &= m_9[w2][s5]-(m_{10}+m_{11})[w2s5],\\
0 &= m_{12}[w21][s5]-(m_{13}+m_{14})[w21s5],\\
\frac{d}{d\tau}[s5p] &= m_{10}[w2s5]+m_{13}[w21s5]-m_{15}[p5][s5p]+m_{17}[p5s5p]-\\
&\quad -m_{20}[s3p][s5p]+m_{21}[s35]-2m_{22}[s5p]^2+2m_{23}[s55],\\
0 &= m_{15}[p5][s5p]-(m_{16}+m_{17})[p5s5p],\\
0 &= m_{18}[s3p]^2-m_{19}[s33],\\
0 &= m_{20}[s3p][s5p]-m_{21}[s35],\\
0 &= m_{22}[s5p]^2-m_{23}[s55].
\end{aligned}
\tag{S18}
$$

Equations (S18) can be simplified as follows:

$$
\begin{aligned}
0 &= m_1[w2][s3]-[w2s3],\\
0 &= m_3[w6][s3]-(m_4+m_5)[w6s3],\\
\frac{d}{d\tau}[s3p] &= m_2[w2s3]+m_4[w6s3]-m_7[p3s3p],\\
0 &= m_6[p3][s3p]-(m_7+m_8)[p3s3p],\\
0 &= m_9[w2][s5]-(m_{10}+m_{11})[w2s5],\\
0 &= m_{12}[w21][s5]-(m_{13}+m_{14})[w21s5],\\
\frac{d}{d\tau}[s5p] &= m_{10}[w2s5]+m_{13}[w21s5]-m_{16}[p5s5p],\\
0 &= m_{15}[p5][s5p]-(m_{16}+m_{17})[p5s5p],\\
0 &= m_{18}[s3p]^2-m_{19}[s33],\\
0 &= m_{20}[s3p][s5p]-m_{21}[s35],\\
0 &= m_{22}[s5p]^2-m_{23}[s55].
\end{aligned}
\tag{S19}
$$

Then using conservation Equations (S16) and System (S19) we obtained:

$$
\begin{aligned}
\frac{d}{d\tau}[s3p] &= m_2[w2s3]+m_4[w6s3]-m_7[p3s3p],\\
\frac{d}{d\tau}[s5p] &= m_{10}[w2s5]+m_{13}[w21s5]-m_{16}[p5s5p],
\end{aligned}
\tag{S20}
$$

where

$$[p3s3p] = p3_t \frac{[s3p]}{\frac{m_7 + m_8}{m_6} + [s3p]},$$

$$[p5s5p] = p5_t \frac{[s5p]}{\frac{m_{16} + m_{17}}{m_{15}} + [s5p]},$$

$$[s33] = \frac{m_{18}}{m_{19}}[s3p]^2,$$

$$[s35] = \frac{m_{20}}{m_{21}}[s3p][s5p],$$

$$[s55] = \frac{m_{22}}{m_{23}}[s5p]^2,$$

$$[w2s3] = m_1[w2][s3],$$

$$[w6s3] = \frac{m_3}{m_4 + m_5}[w6][s3],$$

$$[w2s5] = \frac{m_9}{m_{10} + m_{11}}[w2][s5],$$

$$[w21s5] = \frac{m_{12}}{m_{13} + m_{14}}[w21][s5],$$

$$[s3] = \frac{1 - [s3p] - 2[s33] - [s35] - [p3s3p]}{1 + m_1[w2] + \frac{m_3}{m_4 + m_5}[w6]}, \quad \text{(S21)}$$

$$[s5] = \frac{s5_t - [s5p] - 2[s55] - [s35] - [p5s5p]}{1 + \frac{m_9}{m_{10} + m_{11}}[w2] + \frac{m_{12}}{m_{13} + m_{14}}[w21]}.$$

We can rewrite Equations (S21):

$$
\begin{aligned}
[p3s3p] &= p3_t \frac{[s3p]}{M_9 + [s3p]},\\
[p5s5p] &= p5_t \frac{[s5p]}{M_{12} + [s5p]},\\
[s33] &= \frac{[s3p]^2}{M_{13}},\\
[s35] &= \frac{[s3p][s5p]}{M_{14}},\\
[s55] &= \frac{[s5p]^2}{M_{15}},\\
[w2s3] &= \frac{[w2][s3]}{M_7},\\
[w6s3] &= \frac{[w6][s3]}{M_8},\\
[w2s5] &= \frac{[w2][s5]}{M_{10}},\\
[w21s5] &= \frac{[w21][s5]}{M_{11}},\\
[s3] &= \frac{1-[s3p]-2[s33]-[s35]-[p3s3p]}{1+\frac{[w2]}{M_7}+\frac{[w6]}{M_8}},\\
[s5] &= \frac{s5_t-[s5p]-2[s55]-[s35]-[p5s5p]}{1+\frac{[w2]}{M_{10}}+\frac{[w21]}{M_{11}}},
\end{aligned}
\tag{S22}
$$

where we denoted the Michaelis constants

$$
M_7 = \frac{a_2 + a_3}{a_1 S3_T}, M_8 = \frac{a_5 + a_6}{a_4 S3_T}, M_9 = \frac{a_8 + a_9}{a_7 S3_T}, M_{10} = \frac{a_{11} + a_{12}}{a_{10} S3_T}, M_{11} = \frac{a_{14} + a_{15}}{a_{13} S3_T}, M_{12} = \frac{a_{17} + a_{18}}{a_{16} S3_T},
$$

$$
M_{13} = \frac{a_{20}}{a_{19} S3_T}, M_{14} = \frac{a_{22}}{a_{21} S3_T}, M_{15} = \frac{a_{24}}{a_{23} S3_T}.
$$

We look for steady-state solutions of System (S20):

$$
\begin{aligned}
0 &= m_2[w2s3] + m_4[w6s3] - m_7[p3s3p],\\
0 &= m_{10}[w2s5] + m_{13}[w21s5] - m_{16}[p5s5p].
\end{aligned}
\tag{S23}
$$

We can rewrite Equations (S23) as follows:

$$
\begin{aligned}
0 &= n_4[w2s3] + n_5[w6s3] - [p3s3p],\\
0 &= n_6[w2s5] + n_7[w21s5] - [p5s5p],
\end{aligned}
\tag{S24}
$$

where $n_4 = \frac{a_2}{a_8}, n_5 = \frac{a_5}{a_8}, n_6 = \frac{a_{11}}{a_{17}}, n_7 = \frac{a_{14}}{a_{17}}$.

System (S24) can be rewritten after substituting solutions from Equation (S22):

$$\begin{aligned}
0 &= [s3p] + 2\frac{[s3p]^2}{M_{13}} + \frac{[s3p][s5p]}{M_{14}} + \\
&\quad + p3_t \frac{[s3p]}{M_9 + [s3p]}\left(1 + \frac{M_7 M_8 + M_8[w2] + M_7[w6]}{n_4 M_8[w2] + n_5 M_7[w6]}\right) - 1, \\
0 &= [s5p] + 2\frac{[s5p]^2}{M_{15}} + \frac{[s3p][s5p]}{M_{14}} + \\
&\quad + p5_t \frac{[s5p]}{M_{12} + [s5p]}\left(1 + \frac{M_{10} M_{11} + M_{11}[w2] + M_{10}[w21]}{n_6 M_{11}[w2] + n_7 M_{10}[w21]}\right) - s5_t,
\end{aligned} \tag{S25}$$

We solved System (S25) for $[s3p]$ and $[s5p]$ numerically.

2.1.3 Cytokine production

In general case, transcription factor T can activate gene G by forming a complex with the gene TG:

$$\mathrm{T} + \mathrm{G} \underset{h_2}{\overset{h_1}{\rightleftarrows}} \mathrm{TG} \tag{S26}$$

The ODEs for Equation (S26):

$$\begin{aligned}
\frac{d}{dt}[G] &= -h_1[T][G] + h_2[TG], \\
\frac{d}{dt}[TG] &= h_1[T][G] - h_2[TG].
\end{aligned} \tag{S27}$$

Conservation equation that follows from Equations (S27):

$$G_T = [G] + [TG], \tag{S28}$$

where G_T is the total concentration of the gene.

Equation (S28) can be written as follows:

$$G_T = \lambda + \theta, \tag{S29}$$

where $\lambda = [G], \theta = [TG]$.

The ODEs (S27) can be rewritten in the following way:

$$\begin{aligned}\frac{d}{dt}\lambda &= -h_1 T\lambda + h_2\theta,\\ \frac{d}{dt}\theta &= h_1 T\lambda - h_2\theta,\end{aligned} \tag{S30}$$

where $T = [T]$.

We need to find steady-state solutions of Equation (S30):

$$\begin{aligned}0 &= h_1 T\lambda - h_2\theta,\\ G_T &= \lambda + \theta.\end{aligned} \tag{S31}$$

We can find θ from Equations (S31):

$$\theta = G_T \frac{T}{Qh + T}, \tag{S32}$$

where $Qh = \frac{h_2}{h_1}$ is the Michaelis constant.

In the most general case the reactions of the activation of a gene G by two transcription factors T1 and T2 are:

$$\begin{aligned}&\mathrm{T1} + \mathrm{G} \underset{b_2}{\overset{b_1}{\rightleftarrows}} \mathrm{T1G}\\ &\mathrm{T1G} + \mathrm{T2} \underset{b_4}{\overset{b_3}{\rightleftarrows}} \mathrm{T1T2G}\\ &\mathrm{T2} + \mathrm{G} \underset{b_4}{\overset{b_3}{\rightleftarrows}} \mathrm{T2G}\\ &\mathrm{T2G} + \mathrm{T1} \underset{b_2}{\overset{b_1}{\rightleftarrows}} \mathrm{T1T2G}\end{aligned} \tag{S33}$$

The ODEs for System (S33):

$$\begin{aligned}\frac{d}{dt}[G] &= -b_1[T1][G] + b_2[T1G] - b_3[T2][G] + b_4[T2G],\\ \frac{d}{dt}[T1G] &= b_1[T1][G] - b_2[T1G] - b_3[T1G][T2] + b_4[T1T2G],\\ \frac{d}{dt}[T2G] &= b_3[T2][G] - b_4[T2G] - b_1[T2G][T1] + b_2[T1T2G],\\ \frac{d}{dt}[T1T2G] &= b_3[T1G][T2] - b_4[T1T2G] + b_1[T2G][T1] - b_2[T1T2G].\end{aligned} \tag{S34}$$

Conservation equation that follows from Equations (S34):

$$G_T = [G] + [T1G] + [T2G] + [T1T2G], \tag{S35}$$

where G_T is the total amount of the gene.

Equation (S35) can be written as follows:

$$G_T = \psi + \xi + \varphi + \nu, \tag{S36}$$

where $\psi = [G], \xi = [T1G], \varphi = [T2G], \nu = [T1T2G]$.

The ODEs (S34) can be rewritten in the following way:

$$\begin{aligned}
\frac{d}{dt}\psi &= -b_1 T1\psi + b_2\xi - b_3 T2\psi + b_4\varphi, \\
\frac{d}{dt}\xi &= b_1 T1\psi - b_2\xi - b_3\xi T2 + b_4\nu, \\
\frac{d}{dt}\varphi &= b_3 T2\psi - b_4\varphi - b_1\varphi T1 + b_2\nu, \\
\frac{d}{dt}\nu &= b_3\xi T2 - b_4\nu + b_1\varphi T1 - b_2\nu,
\end{aligned} \tag{S37}$$

where $T1 = [T1], T2 = [T2]$.

We found steady-state solutions of Equations (S37):

$$\begin{aligned}
0 &= b_1 T1\psi - b_2\xi - b_3\xi T2 + b_4\nu, \\
0 &= b_3 T2\psi - b_4\varphi - b_1\varphi T1 + b_2\nu, \\
0 &= b_3\xi T2 - b_4\nu + b_1\varphi T1 - b_2\nu, \\
G_T &= \psi + \xi + \varphi + \nu.
\end{aligned} \tag{S38}$$

Next, we found concentrations of the complexes:

$$\xi = G_T \frac{\frac{b_4}{b_3} T1}{\left(\frac{b_2}{b_1} + T1\right)\left(\frac{b_4}{b_3} + T2\right)} = G_T \frac{Qb_2 T1}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)},$$

$$\varphi = G_T \frac{\frac{b_2}{b_1} T2}{\left(\frac{b_2}{b_1} + T1\right)\left(\frac{b_4}{b_3} + T2\right)} = G_T \frac{Qb_1 T2}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)}, \quad \text{(S39)}$$

$$\nu = G_T \frac{T1T2}{\left(\frac{b_2}{b_1} + T1\right)\left(\frac{b_4}{b_3} + T2\right)} = G_T \frac{T1T2}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)},$$

where $Qb_1 = \frac{b_2}{b_1}, Qb_2 = \frac{b_4}{b_3}$ are the Michaelis constants.

If a protein is activated by the first and the second transcription factors at the same time, then its concentration is proportional to the concentration ν only:

$$\nu = G_T \frac{T1}{Qb_1 + T1} \cdot \frac{T2}{Qb_2 + T2}, \quad \text{(S40)}$$

which is a probability of the two transcription factors to be bound to the same gene.

If a protein is activated by the first or the second transcription factors, then it is proportional to the sum of concentrations $\xi + \varphi + \nu$:

$$\xi + \varphi + \nu = G_T \frac{Qb_2 T1 + Qb_1 T2 + T1T2}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)},$$

$$\xi + \varphi + \nu = G_T \frac{Qb_2 T1 + Qb_1 T2 + T1T2 + T1T2 - T1T2}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)},$$

$$\xi + \varphi + \nu = G_T \frac{T1\left(Qb_2 + T2\right) + T2\left(Qb_1 + T1\right) - T1T2}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)}, \quad \text{(S41)}$$

$$\xi + \varphi + \nu = G_T \left(\frac{T1}{Qb_1 + T1} + \frac{T2}{Qb_2 + T2} - \frac{T1T2}{\left(Qb_1 + T1\right)\left(Qb_2 + T2\right)} \right),$$

$$\xi + \varphi + \nu = G_T \left(\frac{T1}{Qb_1 + T1} + \frac{T2}{Qb_2 + T2} - \frac{T1}{Qb_1 + T1} \frac{T2}{Qb_2 + T2} \right),$$

which is a probability of either of the two transcription factors to be bound to the same gene.

CD46

The full mechanism of how CD46 enhances IL-10 production is still not clear. We assumed here that the mechanism of reactions is similar to the one described in Equation (S33). Thus it can be written for the concentration of SP1 in non-dimensional form according to Equation (S40):

$$\left[sp1a\right] = sp1_t \frac{\left[i2\right]}{M_{16} + \left[i2\right]} \cdot \frac{\left[cd46\right]}{M_{17} + \left[cd46\right]}, \tag{S42}$$

where $\left[sp1a\right] = \frac{\left[SP1a\right]}{S3_T}$, $sp1_t = \frac{SP1_T}{S3_T}$, $\left[cd46\right] = \frac{\left[CD46\right]}{S3_T}$, $M_{16} = \frac{l_2}{l_1 S3_T}$, and $M_{17} = \frac{l_4}{l_3 S3_T}$.

We assumed here that the gene interaction with the transcription factor and its subsequent expression lead to the mRNA translation and certain cytokine secretion. The produced cytokine then can be degraded by a metalloprotease. In this case the biochemical reactions can be written as follows:

$$\begin{aligned} &\mathrm{TG} \xrightarrow{KP} \mathrm{C}, \\ &\mathrm{C} + \mathrm{Mp} \underset{u_3}{\overset{u_1}{\rightleftarrows}} \mathrm{CMp} \xrightarrow{u_2} \mathrm{Cn} + \mathrm{Mp}, \end{aligned} \tag{S43}$$

where TG is the transcription factor complex with gene, C is the active cytokine, Mp is the metalloprotease, CMp is cytokine-metalloprotease complex and Cn is a non-active cytokine.

The ODEs for the reactions in System (S43):

$$\begin{aligned} \frac{d}{dt}\left[C\right] &= KP\left[TG\right] - u_1\left[C\right]\left[Mp\right] + u_3\left[CMp\right], \\ \frac{d}{dt}\left[CMp\right] &= u_1\left[C\right]\left[Mp\right] - \left(u_2 + u_3\right)\left[CMp\right], \\ \frac{d}{dt}\left[Mp\right] &= -u_1\left[C\right]\left[Mp\right] + \left(u_2 + u_3\right)\left[CMp\right]. \end{aligned} \tag{S44}$$

Conservation equation that follows from Equations (S44):

$$Mp_T = \left[Mp\right] + \left[CMp\right] \tag{S45}$$

We found steady-state solutions of System (S44):

$$\begin{aligned} 0 &= KP[TG] - u_1[C][Mp] + u_3[CMp], \\ 0 &= u_1[C][Mp] - (u_2 + u_3)[CMp]. \end{aligned} \tag{S46}$$

Thus, we obtain a system of equations:

$$\begin{aligned} 0 &= KP\vartheta - u_2\sigma, \\ 0 &= u_1 C\zeta - (u_2 + u_3)\sigma, \\ Mp_T &= \zeta + \sigma, \end{aligned} \tag{S47}$$

where $\vartheta = [TG], C = [C], \zeta = [Mp], \sigma = [CMp]$.

We can find σ from this system of Equations (S47):

$$\sigma = Mp_T \frac{C}{Qu + C}, \tag{S48}$$

where $Qu = \frac{u_2 + u_3}{u_1}$ is the Michaelis constant.

We next substituted σ from equation (S48) to the first equation in System (S47):

$$\begin{aligned} 0 &= KP\vartheta - u_2 Mp_T \frac{C}{Qu + C}, \\ C &= \frac{KP\vartheta Qu}{u_2 Mp_T - KP\vartheta}, \\ C &= \frac{Qu}{\frac{u_2 Mp_T}{KP\vartheta} - 1}. \end{aligned} \tag{S49}$$

Since *C* should be positive and the maximum value for $\frac{Mp_T}{\vartheta}$ is 1, $KP < u_2$, which implies that the rate of the cytokine production should be less than its maximum rate of the degradation by metalloprotease.

Equation (S49) can be written as follows:

$$C = \frac{Qu}{\frac{Mp_T}{Qp\vartheta} - 1}, \tag{S50}$$

where $Qp = \frac{KP}{u_2},\ Qp < 1.$

When the cytokine production is up-regulated by one transcription factor only, $\vartheta = \theta$ from Equation (S32) and thus it can be written:

$$C = \frac{Qu}{\frac{Mp_T}{QpG_T \frac{T}{Qh + T}} - 1}. \tag{S51}$$

If the cytokine production is up-regulated by two transcription factors at the same time, $\vartheta = \nu$ as shown in Equation (S40), it can be written:

$$C = \frac{Qu}{\frac{Mp_T}{QpG_T \frac{T1}{Qb_1 + T1} \frac{T2}{Qb_2 + T2}} - 1}. \tag{S52}$$

If the cytokine production is up-regulated by either of the two transcription factors, $\vartheta = \xi + \varphi + \nu$ as shown in Equation (S41), and thus it can be written:

$$C = \frac{Qu}{\frac{Mp_T}{QpG_T \left(\frac{T1}{Qb_1 + T1} + \frac{T2}{Qb_2 + T2} - \frac{T1}{Qb_1 + T1} \frac{T2}{Qb_2 + T2} \right)} - 1}. \tag{S53}$$

IFN-γ and IL-10 production

Since IFN-γ is activated by STAT55 only (Fig 1B) we can write using Equation (S51):

$$[ig] = \frac{M_{18}}{\frac{mp1_t}{n_8 gg_t \frac{[s55]}{M_{19} + [s55]}} - 1}, \tag{S54}$$

where $[ig] = \frac{[Ig]}{S3_T}, mp1_t = \frac{Mp1_T}{S3_T}, gg_t = \frac{Gg_T}{S3_T}, M_{18} = \frac{k_4 + k_5}{k_3 S3_T}, M_{19} = \frac{k_2}{k_1 S3_T}, n_8 = \frac{l_5}{k_4}, n_8 < 1.$

IL-10 gene can be activated by either STAT33 or CD46. Thus, it can be written according to Equation (S53):

$$[i10]=\frac{M_{20}}{\dfrac{mp2_t}{n_9 g10_t\left(\dfrac{[s33]}{M_{21}+[s33]}+\dfrac{[sp1a]}{M_{22}+[sp1a]}-\dfrac{[s33]}{M_{21}+[s33]}\dfrac{[sp1a]}{M_{22}+[sp1a]}\right)}-1}, \qquad \text{(S55)}$$

where $mp2_t=\frac{Mp2_t}{S3_T}, g10_t=\frac{G10_t}{S3_T}, M_{20}=\frac{k_{11}+k_{12}}{k_{10}S3_T}, M_{21}=\frac{k_7}{k_6 S3_T}, M_{22}=\frac{k_9}{k_8 S3_T}, n_9=\frac{l_6}{k_{11}}, n_9<1.$

2.2 Model for the STAT3-STAT4 circuit

The biochemical reactions involved in the STAT3-STAT4 circuit (Fig 1C) are as follows:

$$\mathrm{I2}+\mathrm{RJ2}\underset{f_3}{\overset{f_1}{\rightleftarrows}}\mathrm{I2RJ2}\xrightarrow{f_2}\mathrm{RpJ2}$$

$$\mathrm{RpJ2}+\mathrm{P2}\underset{f_6}{\overset{f_4}{\rightleftarrows}}\mathrm{RpJ2P2}\xrightarrow{f_5}\mathrm{RJ2}+\mathrm{P2}$$

$$\mathrm{I6}+\mathrm{RJ6}\underset{f_9}{\overset{f_7}{\rightleftarrows}}\mathrm{I6RJ6}\xrightarrow{f_8}\mathrm{RpJ6}$$

$$\mathrm{RpJ6}+\mathrm{P6}\underset{f_{12}}{\overset{f_{10}}{\rightleftarrows}}\mathrm{RpJ6P6}\xrightarrow{f_{11}}\mathrm{RJ6}+\mathrm{P6}$$

$$\mathrm{I12}+\mathrm{RJ12}\underset{f_{15}}{\overset{f_{13}}{\rightleftarrows}}\mathrm{I12RJ12}\xrightarrow{f_{14}}\mathrm{RpJ12}$$

$$\mathrm{RpJ12}+\mathrm{P12}\underset{f_{18}}{\overset{f_{16}}{\rightleftarrows}}\mathrm{RpJ12P12}\xrightarrow{f_{17}}\mathrm{RJ12}+\mathrm{P12}$$

$$\mathrm{I35}+\mathrm{RJ35}\underset{f_{21}}{\overset{f_{19}}{\rightleftarrows}}\mathrm{I35RJ35}\xrightarrow{f_{20}}\mathrm{RpJ35}$$

$$\mathrm{RpJ35 + P35 \underset{f_{24}}{\overset{f_{22}}{\rightleftarrows}} RpJ35P35 \xrightarrow{f_{23}} RJ35 + P35}$$

$$\mathrm{RpJ2 + S3 \underset{a_3}{\overset{a_1}{\rightleftarrows}} RpJ2S3 \xrightarrow{a_2} RpJ2 + S3p}$$

$$\mathrm{RpJ6 + S3 \underset{a_6}{\overset{a_4}{\rightleftarrows}} RpJ6S3 \xrightarrow{a_5} RpJ6 + S3p}$$

$$\mathrm{P3 + S3p \underset{a_9}{\overset{a_7}{\rightleftarrows}} P3S3p \xrightarrow{a_8} P3 + S3}$$

$$\mathrm{RpJ12 + S4 \underset{a_{12}}{\overset{a_{10}}{\rightleftarrows}} RpJ12S4 \xrightarrow{a_{11}} RpJ12 + S4p}$$

$$\mathrm{RpJ35 + S4 \underset{a_{15}}{\overset{a_{13}}{\rightleftarrows}} RpJ35S4 \xrightarrow{a_{14}} RpJ35 + S4p}$$

$$\mathrm{P4 + S4p \underset{a_{18}}{\overset{a_{16}}{\rightleftarrows}} P4S4p \xrightarrow{a_{17}} P4 + S4}$$

$$\mathrm{S3p + S3p \underset{a_{20}}{\overset{a_{19}}{\rightleftarrows}} S33}$$

$$\mathrm{S3p + S4p \underset{a_{22}}{\overset{a_{21}}{\rightleftarrows}} S34}$$

$$\mathrm{S4p + S4p \underset{a_{24}}{\overset{a_{23}}{\rightleftarrows}} S44}$$

$$\mathrm{I2 + Sp1 \underset{l_2}{\overset{l_1}{\rightleftarrows}} I2Sp1}$$

$$\mathrm{I2Sp1 + CD46 \underset{l_4}{\overset{l_3}{\rightleftarrows}} Sp1a}$$

$$\mathrm{CD46 + Sp1 \underset{l_4}{\overset{l_3}{\rightleftarrows}} CD46Sp1}$$

$$\mathrm{CD46Sp1 + I2 \underset{l_2}{\overset{l_1}{\rightleftarrows}} Sp1a}$$

$$\mathrm{S44 + Gg \underset{k_2}{\overset{k_1}{\rightleftarrows}} S44Gg}$$

$$\mathrm{S44Gg \xrightarrow{l_5} Ig}$$

$$\mathrm{Ig + Mp1 \underset{k_5}{\overset{k_3}{\rightleftarrows}} IgMp1 \xrightarrow{k_4} Ign + Mp1}$$

$$\mathrm{S33 + G10 \underset{k_7}{\overset{k_6}{\rightleftarrows}} S33G10} \qquad \text{(S56)}$$

$$\mathrm{S33G10} + \mathrm{Sp1a} \underset{k_9}{\overset{k_8}{\rightleftarrows}} \mathrm{S33Sp1aG10}$$

$$\mathrm{Sp1a} + \mathrm{G10} \underset{k_9}{\overset{k_8}{\rightleftarrows}} \mathrm{Sp1aG10}$$

$$\mathrm{Sp1aG10} + \mathrm{S33} \underset{k_7}{\overset{k_6}{\rightleftarrows}} \mathrm{S33Sp1aG10}$$

$$\mathrm{S33G10} \xrightarrow{l_6} \mathrm{I10}$$

$$\mathrm{Sp1aG10} \xrightarrow{l_6} \mathrm{I10}$$

$$\mathrm{S33Sp1aG10} \xrightarrow{l_6} \mathrm{I10}$$

$$\mathrm{I10} + \mathrm{Mp2} \underset{k_{12}}{\overset{k_{10}}{\rightleftarrows}} \mathrm{I10Mp2} \xrightarrow{k_{11}} \mathrm{I10n} + \mathrm{Mp2}$$

2.2.1 Cytokine-receptor interactions

According to Equations (1.12) we can write for $\left[RpJ2\right]$, $\left[RpJ6\right]$, $\left[RpJ12\right]$ and $\left[RpJ35\right]$ in non-dimensional form respectively:

$$\left[w2\right] = -\frac{M_2 - r2_t + p2_t\left(\frac{M_1}{n_1\left[i2\right]} + \frac{1}{n_1} + 1\right)}{2} + \\ + \frac{\sqrt{\left(M_2 - r2_t + p2_t\left(\frac{M_1}{n_1\left[i2\right]} + \frac{1}{n_1} + 1\right)\right)^2 + 4r2_t M_2}}{2},$$

$$\left[w6\right] = -\frac{M_4 - r6_t + p6_t\left(\frac{M_3}{n_2\left[i6\right]} + \frac{1}{n_2} + 1\right)}{2} + \\ + \frac{\sqrt{\left(M_4 - r6_t + p6_t\left(\frac{M_3}{n_2\left[i6\right]} + \frac{1}{n_2} + 1\right)\right)^2 + 4r6_t M_4}}{2},$$

$$[w12] = -\frac{M_6 - r12_t + p12_t\left(\frac{M_5}{n_3[i12]} + \frac{1}{n_3} + 1\right)}{2} + \frac{\sqrt{\left(M_6 - r12_t + p12_t\left(\frac{M_5}{n_3[i12]} + \frac{1}{n_3} + 1\right)\right)^2 + 4r12_t M_6}}{2},$$

$$[w35] = -\frac{M_8 - r35_t + p35_t\left(\frac{M_7}{n_4[i35]} + \frac{1}{n_4} + 1\right)}{2} + \frac{\sqrt{\left(M_8 - r35_t + p35_t\left(\frac{M_7}{n_4[i35]} + \frac{1}{n_4} + 1\right)\right)^2 + 4r35_t M_8}}{2}, \quad \text{(S57)}$$

$$[i2] = \frac{[I2]}{S3_t}, [w2] = \frac{[RpJ2]}{S3_T}, r2_t = \frac{R2_T}{S3_T}, p2_t = \frac{P2_T}{S3_T}, M_1 = \frac{f_2 + f_3}{f_1 S3_T}, M_2 = \frac{f_5 + f_6}{f_4 S3_T}, n_1 = \frac{f_2}{f_5}, [i6] = \frac{[I6]}{S3_T},$$

where $[w6] = \frac{[RpJ6]}{S3_T}, r6_t = \frac{R6_T}{S3_T}, p6_t = \frac{P6_T}{S3_T}, M_3 = \frac{f_8 + f_9}{f_7 S3_T}, M_4 = \frac{f_{11} + f_{12}}{f_{10} S3_T}, n_2 = \frac{f_8}{f_{11}}, [i12] = \frac{[I12]}{S3_T},$

$$[w12] = \frac{[RpJ12]}{S3_T}, r12_t = \frac{R12_T}{S3_T}, p12_t = \frac{P12_T}{S3_T}, M_5 = \frac{f_{14} + f_{15}}{f_{13} S3_T}, M_6 = \frac{f_{17} + f_{18}}{f_{16} S3_T}, n_3 = \frac{f_{14}}{f_{17}},$$

$$[i35] = \frac{[I35]}{S3_T}, [w35] = \frac{[RpJ35]}{S3_T}, r35_t = \frac{R35_T}{S3_T}, p35_t = \frac{P35_T}{S3_T}, M_7 = \frac{f_{20} + f_{21}}{f_{19} S3_T}, M_8 = \frac{f_{23} + f_{24}}{f_{22} S3_T}, n_4 = \frac{f_{20}}{f_{23}}.$$

2.2.2 STAT phosphorylation and subsequent dimerization

ODEs for the STAT phosphorylation and dimerization module are given by:

$$
\begin{aligned}
&\frac{d}{dt}[RpJ2S3] = a_1[RpJ2][S3] - (a_2 + a_3)[RpJ2S3],\\
&\frac{d}{dt}[RpJ6S3] = a_4[RpJ6][S3] - (a_5 + a_6)[RpJ6S3],\\
&\frac{d}{dt}[S3p] = a_2[RpJ2S3] + a_5[RpJ6S3] - a_7[P3][S3p] + a_9[P3S3p] -\\
&\qquad -2a_{19}[S3p]^2 + 2a_{20}[S33] - a_{21}[S3p][S5p] + a_{22}[S35],\\
&\frac{d}{dt}[P3S3p] = a_7[P3][S3p] - (a_8 + a_9)[P3S3p],\\
&\frac{d}{dt}[RpJ12S4] = a_{10}[RpJ12][S4] - (a_{11} + a_{12})[RpJ12S4],\\
&\frac{d}{dt}[RpJ35S4] = a_{13}[RpJ35][S4] - (a_{14} + a_{15})[RpJ35S4],\\
&\frac{d}{dt}[S4p] = a_{11}[RpJ12S4] + a_{14}[RpJ35S4] - a_{16}[P4][S4p] + a_{18}[P4S4p] -\\
&\qquad -a_{21}[S3p][S4p] + a_{22}[S34] - 2a_{23}[S4p]^2 + 2a_{24}[S44],\\
&\frac{d}{dt}[P4S4p] = a_{16}[P4][S4p] - (a_{17} + a_{18})[P4S4p],\\
&\frac{d}{dt}[S33] = a_{19}[S3p]^2 - a_{20}[S33],\\
&\frac{d}{dt}[S34] = a_{21}[S3p][S4p] - a_{22}[S34],\\
&\frac{d}{dt}[S44] = a_{23}[S4p]^2 - a_{24}[S44].
\end{aligned}
\tag{S58}
$$

Conservation equations:

$$
\begin{aligned}
&S3_T = [S3] + [S3p] + 2[S33] + [S34] + [RpJ2S3] + [RpJ6S3] + [P3S3p],\\
&S4_T = [S4] + [S4p] + 2[S44] + [S34] + [RpJ12S4] + [RpJ35S4] + [P4S4p],\\
&P3_T = [P3] + [P3S3p],\\
&P4_T = [P4] + [P4S4p].
\end{aligned}
\tag{S59}
$$

Conservation Equations (S59) in non-dimensional form:

$$
\begin{aligned}
&1 = [s3] + [s3p] + 2[s33] + [s34] + [w2s3] + [w6s3] + [p3s3p],\\
&s4_t = [s4] + [s4p] + 2[s44] + [s34] + [w12s4] + [w35s4] + [p4s4p],\\
&p3_t = [p3] + [p3s3p],\\
&p4_t = [p4] + [p4s4p],
\end{aligned}
\tag{S60}
$$

where

$$[s3]=\frac{[S3]}{S3_T},[s3p]=\frac{[S3p]}{S3_T},[w2s3]=\frac{[RpJ2S3]}{S3_T},[w6s3]=\frac{[RpJ6S3]}{S3_T},[p3s3p]=\frac{[P3S3p]}{S3_T},s4_t=\frac{S4_T}{S3_T},$$
$$[s4]=\frac{[S4]}{S3_T},[s4p]=\frac{[S4p]}{S3_T},[w12s4]=\frac{[RpJ12S4]}{S3_T},[w35s4]=\frac{[RpJ35S4]}{S3_T},[p4s4p]=\frac{[P4S4p]}{S3_T},$$
$$[s33]=\frac{[S33]}{S3_T},[s34]=\frac{[S34]}{S3_T},[s44]=\frac{[S44]}{S3_T},[p3]=\frac{[P3]}{S3_T},[p4]=\frac{[P4]}{S3_T},p3_t=\frac{P3_T}{S3_T},p4_t=\frac{P4_T}{S3_T}.$$

ODEs (S58) in non-dimensional form can be written as follows:

$$\begin{aligned}
&\frac{d}{d\tau}[w2s3]=m_1[w2][s3]-[w2s3]\\
&\frac{d}{d\tau}[w6s3]=m_3[w6][s3]-(m_4+m_5)[w6s3]\\
&\frac{d}{d\tau}[s3p]=m_2[w2s3]+m_4[w6s3]-m_6[p3][s3p]+m_8[p3s3p]-\\
&\qquad -2m_{18}[s3p]^2+2m_{19}[s33]-m_{20}[s3p][s4p]+m_{21}[s34]\\
&\frac{d}{d\tau}[p3s3p]=m_6[p3][s3p]-(m_7+m_8)[p3s3p]\\
&\frac{d}{d\tau}[w12s4]=m_9[w12][s4]-(m_{10}+m_{11})[w12s4]\\
&\frac{d}{d\tau}[w35s4]=m_{12}[w35][s4]-(m_{13}+m_{14})[w35s4]\\
&\frac{d}{d\tau}[s4p]=m_{10}[w12s4]+m_{13}[w35s4]-m_{15}[p4][s4p]+m_{17}[p4s4p]-\\
&\qquad -m_{20}[s3p][s4p]+m_{21}[s34]-2m_{22}[s4p]^2+2m_{23}[s44]\\
&\frac{d}{d\tau}[p4s4p]=m_{15}[p4][s4p]-(m_{16}+m_{17})[p4s4p]\\
&\frac{d}{d\tau}[s33]=m_{18}[s3p]^2-m_{19}[s33]\\
&\frac{d}{d\tau}[s34]=m_{20}[s3p][s4p]-m_{21}[s34]\\
&\frac{d}{d\tau}[s44]=m_{22}[s4p]^2-m_{23}[s44]
\end{aligned}\qquad \text{(S61)}$$

where

$$\tau=t(a_2+a_3),m_1=\frac{a_1}{a_2+a_3}S3_T,m_2=\frac{a_2}{a_2+a_3},m_3=\frac{a_4}{a_2+a_3}S3_T,m_4=\frac{a_5}{a_2+a_3},m_5=\frac{a_6}{a_2+a_3},$$
$$m_6=\frac{a_7}{a_2+a_3}S3_T,m_7=\frac{a_8}{a_2+a_3},m_8=\frac{a_9}{a_2+a_3},\ m_9=\frac{a_{10}}{a_2+a_3}S3_T,m_{10}=\frac{a_{11}}{a_2+a_3},m_{11}=\frac{a_{12}}{a_2+a_3},$$
$$m_{12}=\frac{a_{13}}{a_2+a_3}S3_T,m_{13}=\frac{a_{14}}{a_2+a_3},m_{14}=\frac{a_{15}}{a_2+a_3},\ m_{15}=\frac{a_{16}}{a_2+a_3}S3_T,m_{16}=\frac{a_{17}}{a_2+a_3},m_{17}=\frac{a_{18}}{a_2+a_3},$$
$$m_{18}=\frac{a_{19}}{a_2+a_3}S3_T,m_{19}=\frac{a_{20}}{a_2+a_3},m_{20}=\frac{a_{21}}{a_2+a_3}S3_T,m_{21}=\frac{a_{22}}{a_2+a_3},m_{22}=\frac{a_{23}}{a_2+a_3}S3_T,m_{23}=\frac{a_{24}}{a_2+a_3}.$$

We need to find steady-state solution of System (S61):

$$
\begin{aligned}
0 &= m_1[w2][s3]-[w2s3]\\
0 &= m_3[w6][s3]-(m_4+m_5)[w6s3]\\
\frac{d}{d\tau}[s3p] &= m_2[w2s3]+m_4[w6s3]-m_6[p3][s3p]+m_8[p3s3p]-\\
&\quad -2m_{18}[s3p]^2+2m_{19}[s33]-m_{20}[s3p][s4p]+m_{21}[s34]\\
0 &= m_6[p3][s3p]-(m_7+m_8)[p3s3p]\\
0 &= m_9[w12][s4]-(m_{10}+m_{11})[w12s4]\\
0 &= m_{12}[w35][s4]-(m_{13}+m_{14})[w35s4]\\
\frac{d}{d\tau}[s4p] &= m_{10}[w12s4]+m_{13}[w35s4]-m_{15}[p4][s4p]+m_{17}[p4s4p]-\\
&\quad -m_{20}[s3p][s4p]+m_{21}[s34]-2m_{22}[s4p]^2+2m_{23}[s44]\\
0 &= m_{15}[p4][s4p]-(m_{16}+m_{17})[p4s4p]\\
0 &= m_{18}[s3p]^2-m_{19}[s33]\\
0 &= m_{20}[s3p][s4p]-m_{21}[s34]\\
0 &= m_{22}[s4p]^2-m_{23}[s44]
\end{aligned}
\qquad \text{(S62)}
$$

We can simplify System (S62):

$$
\begin{aligned}
0 &= m_1[w2][s3]-[w2s3]\\
0 &= m_3[w6][s3]-(m_4+m_5)[w6s3]\\
\frac{d}{d\tau}[s3p] &= m_2[w2s3]+m_4[w6s3]-m_7[p3s3p]\\
0 &= m_6[p3][s3p]-(m_7+m_8)[p3s3p]\\
0 &= m_9[w12][s4]-(m_{10}+m_{11})[w12s4]\\
0 &= m_{12}[w35][s4]-(m_{13}+m_{14})[w35s4]\\
\frac{d}{d\tau}[s4p] &= m_{10}[w12s4]+m_{13}[w35s4]-m_{16}[p4s4p]\\
0 &= m_{15}[p4][s4p]-(m_{16}+m_{17})[p4s4p]\\
0 &= m_{18}[s3p]^2-m_{19}[s33]\\
0 &= m_{20}[s3p][s4p]-m_{21}[s34]\\
0 &= m_{22}[s4p]^2-m_{23}[s44]
\end{aligned}
\qquad \text{(S63)}
$$

Then using conservation Equations (S60) and System (S63) we obtained:

$$
\begin{aligned}
\frac{d}{d\tau}[s3p] &= m_2[w2s3]+m_4[w6s3]-m_7[p3s3p],\\
\frac{d}{d\tau}[s4p] &= m_{10}[w12s4]+m_{13}[w35s4]-m_{16}[p4s4p],
\end{aligned}
\qquad \text{(S64)}
$$

where

$$[p3s3p] = p3_t \frac{[s3p]}{\frac{m_7 + m_8}{m_6} + [s3p]}$$

$$[p4s4p] = p4_t \frac{[s4p]}{\frac{m_{16} + m_{17}}{m_{15}} + [s4p]}$$

$$[s33] = \frac{m_{18}}{m_{19}}[s3p]^2$$

$$[s34] = \frac{m_{20}}{m_{21}}[s3p][s4p]$$

$$[s44] = \frac{m_{22}}{m_{23}}[s4p]^2$$

$$[w2s3] = m_1[w2][s3]$$

$$[w6s3] = \frac{m_3}{m_4 + m_5}[w6][s3]$$

$$[w12s4] = \frac{m_9}{m_{10} + m_{11}}[w12][s4]$$

$$[w35s4] = \frac{m_{12}}{m_{13} + m_{14}}[w35][s4]$$

$$[s3] = \frac{1 - [s3p] - 2[s33] - [s34] - [p3s3p]}{1 + m_1[w2] + \frac{m_3}{m_4 + m_5}[w6]}$$

$$[s4] = \frac{s4_t - [s4p] - 2[s44] - [s34] - [p4s4p]}{1 + \frac{m_9}{m_{10} + m_{11}}[w12] + \frac{m_{12}}{m_{13} + m_{14}}[w35]}$$

Or we can rewrite it as follows:

$$
\begin{aligned}
[p3s3p] &= p3_t \frac{[s3p]}{M_{11}+[s3p]} \\
[p4s4p] &= p4_t \frac{[s4p]}{M_{14}+[s4p]} \\
[s33] &= \frac{[s3p]^2}{M_{15}} \\
[s34] &= \frac{[s3p][s4p]}{M_{16}} \\
[s44] &= \frac{[s4p]^2}{M_{17}} \\
[w2s3] &= \frac{[w2][s3]}{M_9} \\
[w6s3] &= \frac{[w6][s3]}{M_{10}} \\
[w12s4] &= \frac{[w12][s4]}{M_{12}} \\
[w35s4] &= \frac{[w35][s4]}{M_{13}} \\
[s3] &= \frac{1-[s3p]-2[s33]-[s34]-[p3s3p]}{1+\frac{[w2]}{M_9}+\frac{[w6]}{M_{10}}} \\
[s4] &= \frac{s4_t-[s4p]-2[s44]-[s34]-[p4s4p]}{1+\frac{[w12]}{M_{12}}+\frac{[w35]}{M_{13}}}
\end{aligned}
\tag{S65}
$$

where we denote the Michaelis constants

$$
M_9 = \frac{a_2+a_3}{a_1 S3_T}, M_{10} = \frac{a_5+a_6}{a_4 S3_T}, M_{11} = \frac{a_8+a_9}{a_7 S3_T}, M_{12} = \frac{a_{11}+a_{12}}{a_{10} S3_T}, M_{13} = \frac{a_{14}+a_{15}}{a_{13} S3_T},
$$

$$
M_{14} = \frac{a_{17}+a_{18}}{a_{16} S3_T}, M_{15} = \frac{a_{20}}{a_{19} S3_T}, M_{16} = \frac{a_{22}}{a_{21} S3_T}, M_{17} = \frac{a_{24}}{a_{23} S3_T}.
$$

When considering steady-state solutions of System (S64) we can write:

$$
\begin{aligned}
0 &= m_2[w2s3] + m_4[w6s3] - m_7[p3s3p], \\
0 &= m_{10}[w12s4] + m_{13}[w35s4] - m_{16}[p4s4p].
\end{aligned}
\tag{S66}
$$

Or we can rewrite Equations (S66) as follows:

$$
\begin{aligned}
0 &= n_5[w2s3] + n_6[w6s3] - [p3s3p], \\
0 &= n_7[w12s4] + n_8[w35s4] - [p4s4p],
\end{aligned}
\tag{S67}
$$

where $n_5 = \frac{a_2}{a_8}, n_6 = \frac{a_5}{a_8}, n_7 = \frac{a_{11}}{a_{17}}, n_8 = \frac{a_{14}}{a_{17}}$.

We can rewrite System (S67) substituting Equations (S65):

$$\begin{aligned} 0 &= [s3p] + 2\frac{[s3p]^2}{M_{15}} + \frac{[s3p][s4p]}{M_{16}} + \\ &+ p3_t \frac{[s3p]}{M_{11} + [s3p]}\left(1 + \frac{M_9 M_{10} + M_{10}[w2] + M_9[w6]}{n_5 M_{10}[w2] + n_6 M_9[w6]}\right) - 1, \\ 0 &= [s4p] + 2\frac{[s4p]^2}{M_{17}} + \frac{[s3p][s4p]}{M_{16}} + \\ &+ p4_t \frac{[s4p]}{M_{14} + [s4p]}\left(1 + \frac{M_{12} M_{13} + M_{13}[w12] + M_{12}[w35]}{n_7 M_{13}[w12] + n_8 M_{12}[w35]}\right) - s4_t, \end{aligned} \quad \text{(S68)}$$

We find $[s3p]$ and $[s4p]$ in System (S68) numerically.

CD46

It can be written for SP1 in non-dimensional form according to Equation (S40):

$$[sp1a] = sp1_t \frac{[i2]}{M_{18} + [i2]} \frac{[cd46]}{M_{19} + [cd46]}, \quad \text{(S69)}$$

where $[sp1a] = \frac{[SP1a]}{S3_T}$, $sp1_t = \frac{SP1_T}{S3_T}$, $[cd46] = \frac{[CD46]}{S3_T}$, $M_{18} = \frac{l_2}{l_1 S3_T}$, and $M_{19} = \frac{l_4}{l_3 S3_t}$.

2.2.3 IFN-γ and IL-10 production

Since IFN-γ is activated in this module by STAT44 only (Fig 1C) we can write using Equation (S51):

$$[ig] = \frac{M_{20}}{\frac{mp1_t}{n_9 gg_t \frac{[s44]}{M_{21} + [s44]}} - 1}, \quad \text{(S70)}$$

where $[ig] = \frac{[Ig]}{S3_T}, mp1_t = \frac{Mp1_T}{S3_T}, gg_t = \frac{Gg_T}{S3_T}, M_{20} = \frac{k_4 + k_5}{k_3 S3_T}, M_{21} = \frac{k_2}{k_1 S3_T}, n_9 = \frac{l_5}{k_4}, n_9 < 1$.

According to Equation (S53) we can write:

$$[i10]=\frac{\dfrac{M_{22}}{mp2_t}}{n_{10}g10_t\left(\dfrac{[s33]}{M_{23}+[s33]}+\dfrac{[sp1a]}{M_{24}+[sp1a]}-\dfrac{[s33]}{M_{23}+[s33]}\dfrac{[sp1a]}{M_{24}+[sp1a]}\right)}-1, \qquad \text{(S71)}$$

where

$$mp2_t=\frac{Mp2_T}{S3_T}, g10_t=\frac{G10_T}{S3_T}, M_{22}=\frac{k_{11}+k_{12}}{k_{10}S3_T}, M_{23}=\frac{k_7}{k_6S3_T}, M_{24}=\frac{k_9}{k_8S3_T}, n_{10}=\frac{l_6}{k_{11}}, n_{10}<1.$$

2.3 Combined STAT3-STAT4-STAT5 model

The reactions involved in STAT3-STAT4-STAT5 circuit (Fig 5A):

$$\mathrm{I2}+\mathrm{RJ2}\underset{f_3}{\overset{f_1}{\rightleftarrows}}\mathrm{I2RJ2}\xrightarrow{f_2}\mathrm{RpJ2}$$

$$\mathrm{RpJ2}+\mathrm{P2}\underset{f_6}{\overset{f_4}{\rightleftarrows}}\mathrm{RpJ2P2}\xrightarrow{f_5}\mathrm{RJ2}+\mathrm{P2}$$

$$\mathrm{I6}+\mathrm{RJ6}\underset{f_9}{\overset{f_7}{\rightleftarrows}}\mathrm{I6RJ6}\xrightarrow{f_8}\mathrm{RpJ6}$$

$$\mathrm{RpJ6}+\mathrm{P6}\underset{f_{12}}{\overset{f_{10}}{\rightleftarrows}}\mathrm{RpJ6P6}\xrightarrow{f_{11}}\mathrm{RJ6}+\mathrm{P6}$$

$$\mathrm{I12}+\mathrm{RJ12}\underset{f_{15}}{\overset{f_{13}}{\rightleftarrows}}\mathrm{I12RJ12}\xrightarrow{f_{14}}\mathrm{RpJ12}$$

$$\mathrm{RpJ12} + \mathrm{P12} \underset{f_{18}}{\overset{f_{16}}{\rightleftarrows}} \mathrm{RpJ12P12} \xrightarrow{f_{17}} \mathrm{RJ12} + \mathrm{P12}$$

$$\mathrm{I35} + \mathrm{RJ35} \underset{f_{21}}{\overset{f_{19}}{\rightleftarrows}} \mathrm{I35RJ35} \xrightarrow{f_{20}} \mathrm{RpJ35}$$

$$\mathrm{RpJ35} + \mathrm{P35} \underset{f_{24}}{\overset{f_{22}}{\rightleftarrows}} \mathrm{RpJ35P35} \xrightarrow{f_{23}} \mathrm{RJ35} + \mathrm{P35}$$

$$\mathrm{I21} + \mathrm{RJ21} \underset{f_{27}}{\overset{f_{25}}{\rightleftarrows}} \mathrm{I21RJ21} \xrightarrow{f_{26}} \mathrm{RpJ21}$$

$$\mathrm{RpJ21} + \mathrm{P21} \underset{f_{30}}{\overset{f_{28}}{\rightleftarrows}} \mathrm{RpJ21P21} \xrightarrow{f_{29}} \mathrm{RJ21} + \mathrm{P21}$$

$$\mathrm{RpJ2} + \mathrm{S3} \underset{a_3}{\overset{a_1}{\rightleftarrows}} \mathrm{RpJ2S3} \xrightarrow{a_2} \mathrm{RpJ2} + \mathrm{S3p}$$

$$\mathrm{RpJ6} + \mathrm{S3} \underset{a_6}{\overset{a_4}{\rightleftarrows}} \mathrm{RpJ6S3} \xrightarrow{a_5} \mathrm{RpJ6} + \mathrm{S3p}$$

$$\mathrm{P3} + \mathrm{S3p} \underset{a_9}{\overset{a_7}{\rightleftarrows}} \mathrm{P3S3p} \xrightarrow{a_8} \mathrm{P3} + \mathrm{S3}$$

$$\mathrm{RpJ12} + \mathrm{S4} \underset{a_{12}}{\overset{a_{10}}{\rightleftarrows}} \mathrm{RpJ12S4} \xrightarrow{a_{11}} \mathrm{RpJ12} + \mathrm{S4p}$$

$$\mathrm{RpJ35} + \mathrm{S4} \underset{a_{15}}{\overset{a_{13}}{\rightleftarrows}} \mathrm{RpJ35S4} \xrightarrow{a_{14}} \mathrm{RpJ35} + \mathrm{S4p}$$

$$\mathrm{P4} + \mathrm{S4p} \underset{a_{18}}{\overset{a_{16}}{\rightleftarrows}} \mathrm{P4S4p} \xrightarrow{a_{17}} \mathrm{P4} + \mathrm{S4}$$

$$\mathrm{RpJ2} + \mathrm{S5} \underset{a_{21}}{\overset{a_{19}}{\rightleftarrows}} \mathrm{RpJ2S5} \xrightarrow{a_{20}} \mathrm{RpJ2} + \mathrm{S5p} \qquad \text{(S72)}$$

$$\mathrm{RpJ21} + \mathrm{S5} \underset{a_{24}}{\overset{a_{22}}{\rightleftarrows}} \mathrm{RpJ21S5} \xrightarrow{a_{23}} \mathrm{RpJ21} + \mathrm{S5p}$$

$$\mathrm{P5} + \mathrm{S5p} \underset{a_{27}}{\overset{a_{25}}{\rightleftarrows}} \mathrm{P5S5p} \xrightarrow{a_{26}} \mathrm{P5} + \mathrm{S5}$$

$$\mathrm{S3p} + \mathrm{S3p} \underset{a_{29}}{\overset{a_{28}}{\rightleftarrows}} \mathrm{S33}$$

$$\mathrm{S3p} + \mathrm{S4p} \underset{a_{31}}{\overset{a_{30}}{\rightleftarrows}} \mathrm{S34}$$

$$S4p + S4p \underset{a_{33}}{\overset{a_{32}}{\rightleftarrows}} S44$$

$$S3p + S5p \underset{a_{35}}{\overset{a_{34}}{\rightleftarrows}} S35$$

$$S5p + S5p \underset{a_{37}}{\overset{a_{36}}{\rightleftarrows}} S55$$

$$S44 + Gg \underset{k_2}{\overset{k_1}{\rightleftarrows}} S44Gg$$

$$S44Gg + S55 \underset{k_4}{\overset{k_3}{\rightleftarrows}} S44S55Gg$$

$$S55 + Gg \underset{k_4}{\overset{k_3}{\rightleftarrows}} S55Gg$$

$$S55Gg + S44 \underset{k_2}{\overset{k_1}{\rightleftarrows}} S44S55Gg$$

$$S44Gg \xrightarrow{l_1} Ig$$

$$S55Gg \xrightarrow{l_1} Ig$$

$$S44S55Gg \xrightarrow{l_1} Ig$$

$$Ig + Mp1 \underset{k_7}{\overset{k_5}{\rightleftarrows}} IgMp1 \xrightarrow{k_6} Ign + Mp1$$

$$I2 + Sp1 \underset{l_3}{\overset{l_2}{\rightleftarrows}} I2Sp1$$

$$I2Sp1 + CD46 \underset{l_5}{\overset{l_4}{\rightleftarrows}} Sp1a$$

$$CD46 + Sp1 \underset{l_5}{\overset{l_4}{\rightleftarrows}} CD46Sp1$$

$$CD46Sp1 + I2 \underset{l_3}{\overset{l_2}{\rightleftarrows}} Sp1a$$

$$S33 + G10 \underset{k_9}{\overset{k_8}{\rightleftarrows}} S33G10$$

$$S33G10 + Sp1a \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} S33Sp1aG10$$

$$Sp1a + G10 \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} Sp1aG10$$

$$Sp1aG10 + S33 \underset{k_9}{\overset{k_8}{\rightleftarrows}} S33Sp1aG10$$

$$S33G10 \xrightarrow{l_6} I10$$

$$Sp1aG10 \xrightarrow{l_6} I10$$

$$S33Sp1aG10 \xrightarrow{l_6} I10$$

$$I10 + Mp2 \underset{k_{14}}{\overset{k_{12}}{\rightleftarrows}} I10Mp2 \xrightarrow{k_{13}} I10n + Mp2$$

2.3.1 Cytokine-receptor interactions

According to Equation (S12) we can write for $[RpJ2]$, $[RpJ6]$, $[RpJ12]$, $[RpJ35]$ and $[RpJ21]$ in non-dimensional form respectively:

$$[w2] = -\frac{M_2 - r2_t + p2_t\left(\frac{M_1}{n_1[i2]} + \frac{1}{n_1} + 1\right)}{2} + \frac{\sqrt{\left(M_2 - r2_t + p2_t\left(\frac{M_1}{n_1[i2]} + \frac{1}{n_1} + 1\right)\right)^2 + 4r2_t M_2}}{2},$$

$$[w6] = -\frac{M_4 - r6_t + p6_t\left(\frac{M_3}{n_2[i6]} + \frac{1}{n_2} + 1\right)}{2} + \frac{\sqrt{\left(M_4 - r6_t + p6_t\left(\frac{M_3}{n_2[i6]} + \frac{1}{n_2} + 1\right)\right)^2 + 4r6_t M_4}}{2},$$

$$[w12] = -\frac{M_6 - r12_t + p12_t\left(\frac{M_5}{n_3[i12]} + \frac{1}{n_3} + 1\right)}{2} + \frac{\sqrt{\left(M_6 - r12_t + p12_t\left(\frac{M_5}{n_3[i12]} + \frac{1}{n_3} + 1\right)\right)^2 + 4r12_t M_6}}{2},$$

$$[w35] = -\frac{M_8 - r35_t + p35_t\left(\frac{M_7}{n_4[i35]} + \frac{1}{n_4} + 1\right)}{2} + \frac{\sqrt{\left(M_8 - r35_t + p35_t\left(\frac{M_7}{n_4[i35]} + \frac{1}{n_4} + 1\right)\right)^2 + 4r35_t M_8}}{2},$$

$$[w21] = -\frac{M_{10} - r21_t + p21_t\left(\frac{M_9}{n_5[i21]} + \frac{1}{n_5} + 1\right)}{2} + \frac{\sqrt{\left(M_{10} - r21_t + p21_t\left(\frac{M_9}{n_5[i21]} + \frac{1}{n_5} + 1\right)\right)^2 + 4r21_t M_{10}}}{2}, \quad \text{(S73)}$$

$$[i2]=\frac{[I2]}{S3_T},[w2]=\frac{[RpJ2]}{S3_T},r2_t=\frac{R2_T}{S3_T},p2_t=\frac{P2_T}{S3_T},\ M_1=\frac{f_2+f_3}{f_1S3_T},M_2=\frac{f_5+f_6}{f_4S3_T},n_1=\frac{f_2}{f_5},[i6]=\frac{[I6]}{S3_T},$$

$$[w6]=\frac{[RpJ6]}{S3_T},r6_t=\frac{R6_T}{S3_T},p6_t=\frac{P6_T}{S3_T},\ M_3=\frac{f_8+f_9}{f_7S3_T},M_4=\frac{f_{11}+f_{12}}{f_{10}S3_T},n_2=\frac{f_8}{f_{11}},[i12]=\frac{[I12]}{S3_T},$$

where

$$[w12]=\frac{[RpJ12]}{S3_T},r12_t=\frac{R12_T}{S3_T},p12_t=\frac{P12_T}{S3_T},\ M_5=\frac{f_{14}+f_{15}}{f_{13}S3_T},M_6=\frac{f_{17}+f_{18}}{f_{16}S3_T},n_3=\frac{f_{14}}{f_{17}},[i35]=\frac{[I35]}{S3_T},$$

$$[w35]=\frac{[RpJ35]}{S3_T},r35_t=\frac{R35_T}{S3_T},p35_t=\frac{P35_T}{S3_T},\ M_7=\frac{f_{20}+f_{21}}{f_{19}S3_T},M_8=\frac{f_{23}+f_{24}}{f_{22}S3_T},n_4=\frac{f_{20}}{f_{23}},$$

$$[i21]=\frac{[I21]}{S3_T},[w21]=\frac{[RpJ21]}{S3_T},r21_t=\frac{R21_T}{S3_T},p21_t=\frac{P21_T}{S3_T},\ M_9=\frac{f_{26}+f_{27}}{f_{25}S3_T},M_{10}=\frac{f_{29}+f_{30}}{f_{28}S3_T},n_5=\frac{f_{26}}{f_{29}}.$$

2.3.2 STAT phosphorylation and dimerization

ODEs for the STAT module are given by:

$$\frac{d}{dt}[RpJ2S3]=a_1[RpJ2][S3]-(a_2+a_3)[RpJ2S3],$$

$$\frac{d}{dt}[RpJ6S3]=a_4[RpJ6][S3]-(a_5+a_6)[RpJ6S3],$$

$$\begin{aligned}\frac{d}{dt}[S3p]=&\,a_2[RpJ2S3]+a_5[RpJ6S3]-a_7[P3][S3p]+a_9[P3S3p]-\\&-2a_{28}[S3p]^2+2a_{29}[S33]-a_{30}[S3p][S4p]+a_{31}[S34]-\\&-a_{34}[S3p][S5p]+a_{35}[S35],\end{aligned}$$

$$\frac{d}{dt}[P3S3p]=a_7[P3][S3p]-(a_8+a_9)[P3S3p],$$

$$
\begin{aligned}
&\frac{d}{dt}[RpJ12S4] = a_{10}[RpJ12][S4] - (a_{11} + a_{12})[RpJ12S4],\\
&\frac{d}{dt}[RpJ35S4] = a_{13}[RpJ35][S4] - (a_{14} + a_{15})[RpJ35S4],\\
&\frac{d}{dt}[S4p] = a_{11}[RpJ12S4] + a_{14}[RpJ35S4] - a_{16}[P4][S4p] + a_{18}[P4S4p] -\\
&\qquad -a_{30}[S3p][S4p] + a_{31}[S34] - 2a_{32}[S4p]^2 + 2a_{33}[S44],\\
&\frac{d}{dt}[P4S4p] = a_{16}[P4][S4p] - (a_{17} + a_{18})[P4S4p],\\
&\frac{d}{dt}[RpJ2S5] = a_{19}[RpJ2][S5] - (a_{20} + a_{21})[RpJ2S5],\\
&\frac{d}{dt}[RpJ21S5] = a_{22}[RpJ21][S5] - (a_{23} + a_{24})[RpJ21S5],\\
&\frac{d}{dt}[S5p] = a_{20}[RpJ2S5] + a_{23}[RpJ21S5] - a_{25}[P5][S5p] + a_{27}[P5S5p] -\\
&\qquad -a_{34}[S3p][S5p] + a_{35}[S35] - 2a_{36}[S5p]^2 + 2a_{37}[S55],\\
&\frac{d}{dt}[P5S5p] = a_{25}[P5][S5p] - (a_{26} + a_{27})[P5S5p],\\
&\frac{d}{dt}[S33] = a_{28}[S3p]^2 - a_{29}[S33],\\
&\frac{d}{dt}[S34] = a_{30}[S3p][S4p] - a_{31}[S34],\\
&\frac{d}{dt}[S44] = a_{32}[S4p]^2 - a_{33}[S44],\\
&\frac{d}{dt}[S35] = a_{34}[S3p][S5p] - a_{35}[S35],\\
&\frac{d}{dt}[S55] = a_{36}[S5p]^2 - a_{37}[S55].
\end{aligned}
\tag{S74}
$$

Conservation equations:

$$
\begin{aligned}
S3_T &= [S3] + [S3p] + 2[S33] + [S34] + [S35] + [RpJ2S3] + [RpJ6S3] + [P3S3p],\\
S4_T &= [S4] + [S4p] + 2[S44] + [S34] + [RpJ12S4] + [RpJ35S4] + [P4S4p],\\
S5_T &= [S5] + [S5p] + 2[S55] + [S35] + [RpJ2S5] + [RpJ21S5] + [P5S5p],\\
P3_T &= [P3] + [P3S3p],\\
P4_T &= [P4] + [P4S4p],\\
P5_T &= [P5] + [P5S5p].
\end{aligned}
\tag{S75}
$$

Conservation Equations (S75) in non-dimensional form:

$$
\begin{aligned}
1 &= [s3] + [s3p] + 2[s33] + [s34] + [s35] + [w2s3] + [w6s3] + [p3s3p], \\
s4_t &= [s4] + [s4p] + 2[s44] + [s34] + [w12s4] + [w35s4] + [p4s4p], \\
s5_t &= [s5] + [s5p] + 2[s55] + [s35] + [w2s5] + [w21s5] + [p5s5p], \\
p3_t &= [p3] + [p3s3p], \\
p4_t &= [p4] + [p4s4p], \\
p5_t &= [p5] + [p5s5p],
\end{aligned}
\tag{S76}
$$

where

$$
[s3] = \frac{[S3]}{S3_T}, [s3p] = \frac{[S3p]}{S3_T}, [w2s3] = \frac{[RpJ2S3]}{S3_T}, [w6s3] = \frac{[RpJ6S3]}{S3_T}, [p3s3p] = \frac{[P3S3p]}{S3_T}, s4_t = \frac{S4_t}{S3_T},
$$

$$
[s4] = \frac{[S4]}{S3_T}, [s4p] = \frac{[S4p]}{S3_T}, [w12s4] = \frac{[RpJ12S4]}{S3_T}, [w35s4] = \frac{[RpJ35S4]}{S3_T}, [p4s4p] = \frac{[P4S4p]}{S3_T},
$$

$$
s5_t = \frac{S5_T}{S3_T}, [s5] = \frac{[S5]}{S3_T}, [s5p] = \frac{[S5p]}{S3_T}, [w2s5] = \frac{[RpJ2S5]}{S3_T}, [w21s5] = \frac{[RpJ21S5]}{S3_T}, [p5s5p] = \frac{[P5S5p]}{S3_T},
$$

$$
[s33] = \frac{[S33]}{S3_T}, [s34] = \frac{[S34]}{S3_T}, [s44] = \frac{[S44]}{S3_T}, [s35] = \frac{[S35]}{S3_T}, [s55] = \frac{[S55]}{S3_T}, [p3] = \frac{[P3]}{S3_T}, [p4] = \frac{[P4]}{S3_T},
$$

$$
[p5] = \frac{[P5]}{S3_T}, p3_t = \frac{P3_T}{S3_T}, p4_t = \frac{P4_T}{S3_T}, p5_t = \frac{P5_T}{S3_T}.
$$

ODEs (S74) in non-dimensional form are given by:

$$\frac{d}{d\tau}[w2s3] = m_1[w2][s3] - [w2s3]$$

$$\frac{d}{d\tau}[w6s3] = m_3[w6][s3] - (m_4 + m_5)[w6s3]$$

$$\frac{d}{d\tau}[s3p] = m_2[w2s3] + m_4[w6s3] - m_6[p3][s3p] + m_8[p3s3p] -$$
$$-2m_{27}[s3p]^2 + 2m_{28}[s33] - m_{29}[s3p][s4p] + m_{30}[s34] -$$
$$-m_{33}[s3p][s5p] + m_{34}[s35]$$

$$\frac{d}{d\tau}[p3s3p] = m_6[p3][s3p] - (m_7 + m_8)[p3s3p]$$

$$\frac{d}{d\tau}[w12s4] = m_9[w12][s4] - (m_{10} + m_{11})[w12s4]$$

$$\frac{d}{d\tau}[w35s4] = m_{12}[w35][s4] - (m_{13} + m_{14})[w35s4]$$

$$\frac{d}{d\tau}[s4p] = m_{10}[w12s4] + m_{13}[w35s4] - m_{15}[p4][s4p] +$$
$$+m_{17}[p4s4p] - m_{29}[s3p][s4p] +$$
$$+m_{30}[s34] - 2m_{31}[s4p]^2 + 2m_{32}[s44]$$

$$\frac{d}{d\tau}[p4s4p] = m_{15}[p4][s4p] - (m_{16} + m_{17})[p4s4p]$$

$$\frac{d}{d\tau}[w2s5] = m_{18}[w2][s5] - (m_{19} + m_{20})[w2s5]$$

$$\frac{d}{d\tau}[w21s5] = m_{21}[w21][s5] - (m_{22} + m_{23})[w21s5]$$

$$\frac{d}{d\tau}[s5p] = m_{19}[w2s5] + m_{22}[w21s5] - m_{24}[p5][s5p] + m_{26}[p5s5p] -$$
$$-m_{33}[s3p][s5p] + m_{34}[s35] - 2m_{35}[s5p]^2 + 2m_{36}[s55]$$

$$\frac{d}{d\tau}[p5s5p] = m_{24}[p5][s5p] - (m_{25} + m_{26})[p5s5p]$$

$$\frac{d}{d\tau}[s33] = m_{27}[s3p]^2 - m_{28}[s33]$$

$$\frac{d}{d\tau}[s34] = m_{29}[s3p][s4p] - m_{30}[s34]$$

$$\frac{d}{d\tau}[s44] = m_{31}[s4p]^2 - m_{32}[s44] \qquad \text{(S77)}$$

$$\frac{d}{d\tau}[s35] = m_{33}[s3p][s5p] - m_{34}[s35]$$

$$\frac{d}{d\tau}[s55] = m_{35}[s5p]^2 - m_{36}[s55]$$

where

$$\tau = t\left(a_2 + a_3\right), m_1 = \frac{a_1}{a_2 + a_3} S3_t, m_2 = \frac{a_2}{a_2 + a_3}, m_3 = \frac{a_4}{a_2 + a_3} S3_t, m_4 = \frac{a_5}{a_2 + a_3}, m_5 = \frac{a_6}{a_2 + a_3}, m_6 = \frac{a_7}{a_2 + a_3} S3_t,$$

$$m_7 = \frac{a_8}{a_2 + a_3}, m_8 = \frac{a_9}{a_2 + a_3},\ m_9 = \frac{a_{10}}{a_2 + a_3} S3_t, m_{10} = \frac{a_{11}}{a_2 + a_3}, m_{11} = \frac{a_{12}}{a_2 + a_3}, m_{12} = \frac{a_{13}}{a_2 + a_3} S3_t, m_{13} = \frac{a_{14}}{a_2 + a_3},$$

$$m_{14} = \frac{a_{15}}{a_2 + a_3},\ m_{15} = \frac{a_{16}}{a_2 + a_3} S3_t, m_{16} = \frac{a_{17}}{a_2 + a_3}, m_{17} = \frac{a_{18}}{a_2 + a_3}, m_{18} = \frac{a_{19}}{a_2 + a_3} S3_t, m_{19} = \frac{a_{20}}{a_2 + a_3}, m_{20} = \frac{a_{21}}{a_2 + a_3},$$

$$m_{21} = \frac{a_{22}}{a_2 + a_3} S3_t, m_{22} = \frac{a_{23}}{a_2 + a_3}, m_{23} = \frac{a_{24}}{a_2 + a_3}, m_{24} = \frac{a_{25}}{a_2 + a_3} S3_t, m_{25} = \frac{a_{26}}{a_2 + a_3}, m_{26} = \frac{a_{27}}{a_2 + a_3},$$

$$m_{27} = \frac{a_{28}}{a_2 + a_3} S3_t, m_{28} = \frac{a_{29}}{a_2 + a_3}, m_{29} = \frac{a_{30}}{a_2 + a_3} S3_t, m_{30} = \frac{a_{31}}{a_2 + a_3}, m_{31} = \frac{a_{32}}{a_2 + a_3} S3_t, m_{32} = \frac{a_{33}}{a_2 + a_3},$$

$$m_{33} = \frac{a_{34}}{a_2 + a_3} S3_t, m_{34} = \frac{a_{35}}{a_2 + a_3}, m_{35} = \frac{a_{36}}{a_2 + a_3} S3_t, m_{36} = \frac{a_{37}}{a_2 + a_3}.$$

We need to find a steady-state solution of System (S77):

$$\begin{aligned}
0 &= m_1[w2][s3] - [w2s3] \\
0 &= m_3[w6][s3] - (m_4 + m_5)[w6s3] \\
\frac{d}{d\tau}[s3p] &= m_2[w2s3] + m_4[w6s3] - m_6[p3][s3p] + m_8[p3s3p] - 2m_{27}[s3p]^2 + \\
&\quad + 2m_{28}[s33] - m_{29}[s3p][s4p] + m_{30}[s34] - \\
&\quad - m_{33}[s3p][s5p] + m_{34}[s35] \\
0 &= m_6[p3][s3p] - (m_7 + m_8)[p3s3p] \\
0 &= m_9[w12][s4] - (m_{10} + m_{11})[w12s4] \\
0 &= m_{12}[w35][s4] - (m_{13} + m_{14})[w35s4] \\
\frac{d}{d\tau}[s4p] &= m_{10}[w12s4] + m_{13}[w35s4] - m_{15}[p4][s4p] + m_{17}[p4s4p] - m_{29}[s3p][s4p] + \\
&\quad + m_{30}[s34] - 2m_{31}[s4p]^2 + 2m_{32}[s44] \\
0 &= m_{15}[p4][s4p] - (m_{16} + m_{17})[p4s4p] \\
0 &= m_{18}[w2][s5] - (m_{19} + m_{20})[w2s5] \\
0 &= m_{21}[w21][s5] - (m_{22} + m_{23})[w21s5] \\
\frac{d}{d\tau}[s5p] &= m_{19}[w2s5] + m_{22}[w21s5] - m_{24}[p5][s5p] + m_{26}[p5s5p] - \\
&\quad - m_{33}[s3p][s5p] + m_{34}[s35] - 2m_{35}[s5p]^2 + 2m_{36}[s55] \\
0 &= m_{24}[p5][s5p] - (m_{25} + m_{26})[p5s5p] \\
0 &= m_{27}[s3p]^2 - m_{28}[s33] \\
0 &= m_{29}[s3p][s4p] - m_{30}[s34] \\
0 &= m_{31}[s4p]^2 - m_{32}[s44] \\
0 &= m_{33}[s3p][s5p] - m_{34}[s35] \\
0 &= m_{35}[s5p]^2 - m_{36}[s55]
\end{aligned} \tag{S78}$$

We can simplify System (S78):

$$
\begin{aligned}
0 &= m_1[w2][s3] - [w2s3] \\
0 &= m_3[w6][s3] - (m_4 + m_5)[w6s3] \\
\frac{d}{d\tau}[s3p] &= m_2[w2s3] + m_4[w6s3] - m_7[p3s3p] \\
0 &= m_6[p3][s3p] - (m_7 + m_8)[p3s3p] \\
0 &= m_9[w12][s4] - (m_{10} + m_{11})[w12s4] \\
0 &= m_{12}[w35][s4] - (m_{13} + m_{14})[w35s4] \\
\frac{d}{d\tau}[s4p] &= m_{10}[w12s4] + m_{13}[w35s4] - m_{16}[p4s4p] \\
0 &= m_{15}[p4][s4p] - (m_{16} + m_{17})[p4s4p] \\
0 &= m_{18}[w2][s5] - (m_{19} + m_{20})[w2s5] \\
0 &= m_{21}[w21][s5] - (m_{22} + m_{23})[w21s5] \\
\frac{d}{d\tau}[s5p] &= m_{19}[w2s5] + m_{22}[w21s5] - m_{25}[p5s5p] \\
0 &= m_{24}[p5][s5p] - (m_{25} + m_{26})[p5s5p] \\
0 &= m_{27}[s3p]^2 - m_{28}[s33] \\
0 &= m_{29}[s3p][s4p] - m_{30}[s34] \\
0 &= m_{31}[s4p]^2 - m_{32}[s44] \\
0 &= m_{33}[s3p][s5p] - m_{34}[s35] \\
0 &= m_{35}[s5p]^2 - m_{36}[s55]
\end{aligned}
\tag{S79}
$$

Then using conservation Equations (S76) and System (S79) we obtained:

$$
\begin{aligned}
\frac{d}{d\tau}[s3p] &= m_2[w2s3] + m_4[w6s3] - m_7[p3s3p] \\
\frac{d}{d\tau}[s4p] &= m_{10}[w12s4] + m_{13}[w35s4] - m_{16}[p4s4p] \\
\frac{d}{d\tau}[s5p] &= m_{19}[w2s5] + m_{22}[w21s5] - m_{25}[p5s5p]
\end{aligned}
\tag{S80}
$$

where

$$[p3s3p] = p3_t \frac{[s3p]}{\frac{m_7 + m_8}{m_6} + [s3p]}$$

$$[p4s4p] = p4_t \frac{[s4p]}{\frac{m_{16} + m_{17}}{m_{15}} + [s4p]}$$

$$[p5s5p] = p5_t \frac{[s5p]}{\frac{m_{25} + m_{26}}{m_{24}} + [s5p]}$$

$$[s33] = \frac{m_{27}}{m_{28}}[s3p]^2$$

$$[s34] = \frac{m_{29}}{m_{30}}[s3p][s4p]$$

$$[s44] = \frac{m_{31}}{m_{32}}[s4p]^2$$

$$[s35] = \frac{m_{33}}{m_{34}}[s3p][s5p]$$

$$[s55] = \frac{m_{35}}{m_{36}}[s5p]^2$$

$$[w2s3] = m_1[w2][s3]$$

$$[w6s3] = \frac{m_3}{m_4 + m_5}[w6][s3]$$

$$[w12s4] = \frac{m_9}{m_{10} + m_{11}}[w12][s4]$$

$$[w35s4] = \frac{m_{12}}{m_{13} + m_{14}}[w35][s4]$$

$$[w2s5] = \frac{m_{18}}{m_{19} + m_{20}}[w2][s5]$$

$$[w21s5] = \frac{m_{21}}{m_{22} + m_{23}}[w21][s5]$$

$$[s3] = \frac{1 - [s3p] - 2[s33] - [s34] - [s35] - [p3s3p]}{1 + m_1[w2] + \frac{m_3}{m_4 + m_5}[w6]}$$

$$[s4] = \frac{s4_t - [s4p] - 2[s44] - [s34] - [p4s4p]}{1 + \frac{m_9}{m_{10} + m_{11}}[w12] + \frac{m_{12}}{m_{13} + m_{14}}[w35]}$$

$$[s5] = \frac{s5_t - [s5p] - 2[s55] - [s35] - [p5s5p]}{1 + \frac{m_{18}}{m_{19} + m_{20}}[w2] + \frac{m_{21}}{m_{22} + m_{23}}[w21]}$$

Or we can rewrite it in the following way:

$$[p3s3p] = p3_t \frac{[s3p]}{M_{13} + [s3p]}$$

$$[p4s4p] = p4_t \frac{[s4p]}{M_{16} + [s4p]}$$

$$[p5s5p] = p5_t \frac{[s5p]}{M_{19} + [s5p]}$$

$$[s33] = \frac{[s3p]^2}{M_{20}}$$

$$[s34] = \frac{[s3p][s4p]}{M_{21}}$$

$$[s44] = \frac{[s4p]^2}{M_{22}}$$

$$[s35] = \frac{[s3p][s5p]}{M_{23}}$$

$$[s55] = \frac{[s5p]^2}{M_{24}}$$

$$[w2s3] = \frac{[w2][s3]}{M_{11}}$$

$$[w6s3] = \frac{[w6][s3]}{M_{12}}$$

$$[w12s4] = \frac{[w12][s4]}{M_{14}}$$

$$[w35s4] = \frac{[w35][s4]}{M_{15}}$$

$$[w2s5] = \frac{[w2][s5]}{M_{17}}$$

$$[w21s5] = \frac{[w21][s5]}{M_{18}}$$

$$[s3] = \frac{1 - [s3p] - 2[s33] - [s34] - [s35] - [p3s3p]}{1 + \frac{[w2]}{M_{11}} + \frac{[w6]}{M_{12}}}$$

$$[s4] = \frac{s4_t - [s4p] - 2[s44] - [s34] - [p4s4p]}{1 + \frac{[w12]}{M_{14}} + \frac{[w35]}{M_{15}}} \qquad \text{(S81)}$$

$$[s5] = \frac{s5_t - [s5p] - 2[s55] - [s35] - [p5s5p]}{1 + \frac{[w2]}{M_{17}} + \frac{[w21]}{M_{18}}}$$

where we denoted the Michaelis constants

$$M_{11}=\frac{a_2+a_3}{a_1S3_T}, M_{12}=\frac{a_5+a_6}{a_4S3_T}, M_{13}=\frac{a_8+a_9}{a_7S3_T}, M_{14}=\frac{a_{11}+a_{12}}{a_{10}S3_T}, M_{15}=\frac{a_{14}+a_{15}}{a_{13}S3_T}, M_{16}=\frac{a_{17}+a_{18}}{a_{16}S3_T},$$
$$M_{17}=\frac{a_{20}+a_{21}}{a_{19}S3_T}, M_{18}=\frac{a_{23}+a_{24}}{a_{22}S3_T}, M_{19}=\frac{a_{26}+a_{27}}{a_{25}S3_T}, M_{20}=\frac{a_{29}}{a_{28}S3_T}, M_{21}=\frac{a_{31}}{a_{30}S3_T}, M_{22}=\frac{a_{33}}{a_{32}S3_T},$$
$$M_{23}=\frac{a_{35}}{a_{34}S3_T}, M_{24}=\frac{a_{37}}{a_{36}S3_T}.$$

We looked for steady-state solutions of System (S80):

$$\begin{aligned}0&=m_2[w2s3]+m_4[w6s3]-m_7[p3s3p],\\0&=m_{10}[w12s4]+m_{13}[w35s4]-m_{16}[p4s4p],\\0&=m_{19}[w2s5]+m_{22}[w21s5]-m_{25}[p5s5p].\end{aligned} \tag{S82}$$

We can rewrite Equations (S82) as follows:

$$\begin{aligned}0&=n_6[w2s3]+n_7[w6s3]-[p3s3p],\\0&=n_8[w12s4]+n_9[w35s4]-[p4s4p],\\0&=n_{10}[w2s5]+n_{11}[w21s5]-[p5s5p].\end{aligned} \tag{S83}$$

where $n_6=\frac{a_2}{a_8}, n_7=\frac{a_5}{a_8}, n_8=\frac{a_{11}}{a_{17}}, n_9=\frac{a_{14}}{a_{17}}, n_{10}=\frac{a_{20}}{a_{26}}, n_{11}=\frac{a_{23}}{a_{26}}$.

We can rewrite System (S83) substituting Equations (S81):

$$\begin{cases}0=[s3p]+2\dfrac{[s3p]^2}{M_{20}}+\dfrac{[s3p][s4p]}{M_{21}}+\dfrac{[s3p][s5p]}{M_{23}}+\\ \qquad +p3_t\dfrac{[s3p]}{M_{13}+[s3p]}\left(1+\dfrac{M_{11}M_{12}+M_{12}[w2]+M_{11}[w6]}{n_6M_{12}[w2]+n_7M_{11}[w6]}\right)-1,\\ 0=[s4p]+2\dfrac{[s4p]^2}{M_{22}}+\dfrac{[s3p][s4p]}{M_{21}}+\\ \qquad +p4_t\dfrac{[s4p]}{M_{16}+[s4p]}\left(1+\dfrac{M_{14}M_{15}+M_{15}[w12]+M_{14}[w35]}{n_8M_{15}[w12]+n_9M_{14}[w35]}\right)-s4_t,\\ 0=[s5p]+2\dfrac{[s5p]^2}{M_{24}}+\dfrac{[s3p][s5p]}{M_{23}}+\\ \qquad +p5_t\dfrac{[s5p]}{M_{19}+[s5p]}\left(1+\dfrac{M_{17}M_{18}+M_{18}[w2]+M_{17}[w21]}{n_{10}M_{18}[w2]+n_{11}M_{17}[w21]}\right)-s5_t,\end{cases} \tag{S84}$$

We found $[s3p]$, $[s4p]$ and $[s5p]$ in System (S84) numerically.

CD46

It can be written for SP1 in non-dimensional form according to Equation (S40):

$$[sp1a] = sp1_t \frac{[i2]}{M_{25} + [i2]} \frac{[cd46]}{M_{26} + [cd46]}, \tag{S85}$$

where $[sp1a] = \frac{[SP1a]}{S3_T}$, $sp1_t = \frac{SP1_T}{S3_T}$, $[cd46] = \frac{[CD46]}{S3_T}$, $M_{25} = \frac{l_3}{l_2 S3_T}$, and $M_{26} = \frac{l_5}{l_4 S3_T}$.

2.3.3 IFN-γ and IL-10 production

Since IFN-γ gene is activated by either STAT44 or STAT55, it can be written according to Equation (S53):

$$[ig] = \frac{M_{27}}{\frac{mp1_t}{n_{12} gg_t \left(\frac{[s44]}{M_{28} + [s44]} + \frac{[s55]}{M_{29} + [s55]} - \frac{[s44]}{M_{28} + [s44]} \frac{[s55]}{M_{29} + [s55]} \right)} - 1}, \tag{S86}$$

where

$$[ig] = \frac{[Ig]}{S3_T}, mp1_t = \frac{Mp1_T}{S3_T}, gg_t = \frac{Gg_T}{S3_T}, M_{27} = \frac{k_6 + k_7}{k_5 S3_T}, M_{28} = \frac{k_2}{k_1 S3_T}, KM_{29} = \frac{k_4}{k_3 S3_T}, n_{12} = \frac{l_1}{k_6}, \text{ and}$$

$n_{12} < 1$.

The production of IL-10 can be activated by either STAT33 or SP1 through CD46. Thus, according to Equation (S53), it can be written:

$$[i10] = \frac{M_{30}}{\frac{mp2_t}{n_{13} g10_t \left(\frac{[s33]}{M_{31} + [s33]} + \frac{[sp1a]}{M_{32} + [sp1a]} - \frac{[s33]}{M_{31} + [s33]} \frac{[sp1a]}{M_{32} + [sp1a]} \right)} - 1}, \tag{S87}$$

where $mp2_t = \frac{Mp2_T}{S3_T}, g10_t = \frac{G10_T}{S3_T}, M_{30} = \frac{k_{13} + k_{14}}{k_{12} S3_T}, M_{31} = \frac{k_9}{k_8 S3_T}, M_{32} = \frac{k_{11}}{k_{10} S3_T}, n_{13} = \frac{l_6}{k_{13}}$,

where $n_{13} < 1$.

3 Model parameters

3.1 Parameter fitting

For the parameter fitting in the STAT3-STAT5 model, we used the Genetic Algorithm (GA) tool integrated to MATLAB. As the criterion for fitting we chose the squared error, which can be described as $SM = \sum_{i=1}^{N} \left(E_i - M_i \right)^2$, where E_i is experimental data for cytokine concentration (IFN-γ or IL-10) corresponding to the *i*-th value of IL-2 concentration, M is the model predictions for cytokine concentration corresponding to the same IL-2 concentration, i is the number of experimental data point, $N = 4$ is the total number of experimental data points. The GA tool allows minimizing the squared error using the integrated algorithms for the optima search.

We selected a "nominal" set of parameters "by hand", which qualitatively demonstrates the switching between IFN-γ and IL-10. This set of parameters is represented as "Nom" in Table S2. The sets of the optimized parameters and corresponding squared errors are also shown in Table S2. We performed 15 optimization tests setting the allowable ranges for the parameters ten-fold either side of the nominal values of parameters and chose the best fitting (set "O3" in Table S2) with the smallest squared error $SM = 7.34 \cdot 10^{-7}$. Fig S1 shows the distribution of five parameter sets with the closest minimum squared errors SM, namely sets "O2", "O3", "O9", "O10" and "O12".

Table S2. Nominal, optimized parameters and squared error SM.

Par	Nom	O1	O2	O3	O4	O5	O6	O7	O8	O9	O10	O11	O12	O13	O14	O15
$r2_t$	0.003	0.003509	0.002832	0.0027	0.000642	0.019794	0.00045	0.019193	0.007935	0.001365	0.0004	0.027443	0.017109	0.004116	0.001955	0.000483
$p2_t$	0.003	0.027889	0.005466	0.0027	0.003567	0.003013	0.00236	0.000391	0.001873	0.003381	0.000954	0.018632	0.006114	0.002781	0.001408	0.00091
M_1	0.1	0.025534	0.47271	0.1333	0.040663	0.3277	0.026149	0.40489	0.20611	0.033704	0.015943	0.72946	0.056363	0.13378	0.021674	0.019028
M_2	4.00E-05	0.000204	0.000161	4.25E-05	0.000197	7.32E-05	0.000283	1.62E-05	0.000343	3.83E-05	0.000223	7.22E-05	5.12E-05	6.21E-05	3.20E-05	9.20E-05
n_1	120	134.51	644.3	118.42	72.739	103.68	560.59	820.37	200.61	862.9	283.75	105.73	274.74	34.881	230.86	14.268
$s5_t$	0.025	0.024774	0.1077	0.0247	0.002822	0.023708	0.013273	0.018098	0.11675	0.00651	0.004803	0.23769	0.12053	0.023753	0.015575	0.010874
$p3_t$	2.6	0.89728	1.2949	2.5924	24.163	22.171	7.4742	10.399	5.6766	10.873	4.9583	21.681	19.95	20.225	16.902	7.6764
$p5_t$	0.001	0.001858	0.000861	0.0012	0.000221	0.006268	0.000882	0.00265	0.009407	0.001797	0.000474	0.000497	0.009068	0.000475	0.001185	0.006386
M_7	4.00E-04	0.001728	4.57E-05	3.63E-04	0.001127	0.000878	4.59E-05	0.001467	0.001375	0.000268	0.001358	0.000201	0.002265	0.000388	8.25E-05	0.000542
M_9	48	9.6863	44.177	47.714	6.8966	69.877	16.866	6.4433	13.955	20.904	5.4463	8.2154	13.764	10.142	8.9364	6.9836
M_{13}	19	43.297	12.157	19.154	26.49	64.47	11.366	3.0619	6.861	29.894	4.2357	58.53	2.3561	28.926	2.0914	54.439
n_4	0.2	0.2107	1.2957	0.1987	0.83912	1.0389	0.27776	0.65197	0.13579	0.31198	1.6554	0.99071	1.015	0.46062	0.3713	0.94161
n_5	1.6	9.207	7.6231	1.5589	11.252	0.79439	0.60074	0.68472	1.4609	0.34328	0.43991	3.5845	10.667	1.1144	0.41878	0.22359
M_{14}	0.1	0.052263	0.94864	0.1002	0.14521	0.42794	0.74908	0.68789	0.045914	0.23346	0.64129	0.026867	0.19001	0.71674	0.87757	0.22681
M_{10}	0.005	0.007492	0.001309	0.0047	0.040772	0.005439	0.006246	0.007474	0.001363	0.002274	0.019538	0.002244	0.00649	0.000814	0.01832	0.001643
M_{12}	2.00E+03	3354	558.06	1.96E+03	2941.2	7507.6	643.49	542.99	712.59	1185.3	1028.3	1391.6	248.85	257.14	17278	4567.5
M_{15}	0.5	1.3545	1.3625	0.3787	0.073671	0.62091	1.3246	0.04003	0.1918	2.5022	0.36109	1.2976	0.29186	0.50924	0.51241	1.027
n_6	5.5	2.7485	1.1754	5.5056	33.297	2.4937	1.0916	1.3194	20.942	1.999	1.5219	55	17.825	13.946	0.63868	25.109
n_7	0.03	0.14378	0.17183	0.0322	0.14479	0.060788	0.007304	0.022957	0.19581	0.031909	0.033886	0.025282	0.13774	0.006371	0.004357	0.019089
Q_6	0.001	0.000604	0.000987	0.0014	0.001767	0.000368	0.002322	0.001199	0.009353	0.000293	0.001671	0.001688	0.002172	0.001201	0.00045	0.000147
Q_{21}	3.40E-11	1.82E-11	3.29E-11	3.42E-11	8.30E-11	6.91E-12	9.33E-11	2.18E-11	2.57E-11	2.05E-11	1.36E-10	9.48E-12	6.35E-11	9.55E-12	4.26E-11	1.97E-11
gg_t	0.9	0.15956	0.28281	0.8949	5.7607	6.1621	5.1155	0.76901	0.12177	6.8237	5.0325	5.1714	0.71957	0.11343	0.5014	8.0729
$mp1_t$	0.003	0.000362	0.011831	0.0034	0.002017	0.00276	0.000491	0.010081	0.000543	0.001536	0.023098	0.002676	0.01239	0.003733	0.00066	0.019531
M_{18}	10	49.794	12.051	9.913	17.075	12.601	2.0105	16.569	1.2898	3.2815	57.245	1.3748	4.9301	27.867	11.032	46.883
M_{19}	5	1.0175	1.6903	4.354	7.0324	29.257	1.8676	24.928	4.1342	3.3328	11.128	23.95	1.5233	1.3154	22.729	19.486
n_8	0.01	0.001766	0.007209	0.0101	0.00607	0.005921	0.003473	0.024054	0.003863	0.053508	0.057119	0.001551	0.001237	0.006047	0.023173	0.031357
$g10_t$	7	6.9815	8.8946	7.2184	63.392	14.123	42.777	11.788	1.5184	2.3453	1.1908	10.022	0.89799	25.713	13.946	13.284
$mp2_t$	0.6	1.2895	0.26955	0.5933	4.5548	3.0464	0.78732	0.29224	0.57425	0.060594	0.20987	0.26053	0.36536	1.293	0.67941	4.3577
M_{20}	0.015	0.018369	0.019073	0.0149	0.020308	0.030563	0.003852	0.007404	0.020735	0.019924	0.020195	0.014823	0.055386	0.054662	0.02151	0.074155
M_{21}	0.01	0.024239	0.032193	0.0138	0.024077	0.022656	0.003987	0.00449	0.006201	0.002048	0.001389	0.095423	0.03017	0.001637	0.001683	0.019085
M_{22}	0.2	0.21423	1.2631	0.1885	0.044434	1.0261	0.035059	0.13186	0.10364	0.051725	0.3348	0.1968	0.5264	0.055339	0.18746	0.20254
n_9	0.02	0.035162	0.006445	0.0191	0.014896	0.031773	0.00877	0.009492	0.06544	0.005009	0.033464	0.00655	0.030446	0.003868	0.007794	0.021937
cd46	0.7	0.073077	0.1249	0.6826	0.17389	0.23045	0.1164	1.9959	0.98331	2.6895	0.60932	0.14905	0.5349	2.0231	3.279	0.12424
$sp1_t$	33	89.836	37.294	33.142	9.0941	18.309	249.25	22.863	16.009	5.3526	14.461	131.19	204.26	16.788	115.79	14.167
M_{16}	9.00E-06	6.77E-05	8.85E-06	8.96E-06	5.10E-06	4.47E-06	7.37E-05	1.21E-05	7.99E-06	1.28E-05	6.40E-06	2.10E-05	1.55E-05	2.26E-05	6.83E-05	9.60E-07
M_{17}	0.1	0.017299	0.013423	0.1071	0.93739	0.059451	0.16776	0.11441	0.014937	0.070503	0.027861	0.076081	0.37638	0.29741	0.031363	0.9858
SM	1.19E-06	1.15E-06	9.18E-07	7.34E-07	1.81E-06	1.56E-06	2.13E-06	1.21E-06	2.11E-06	7.96E-07	7.92E-07	2.22E-06	8.70E-07	1.13E-06	1.54E-06	1.31E-06

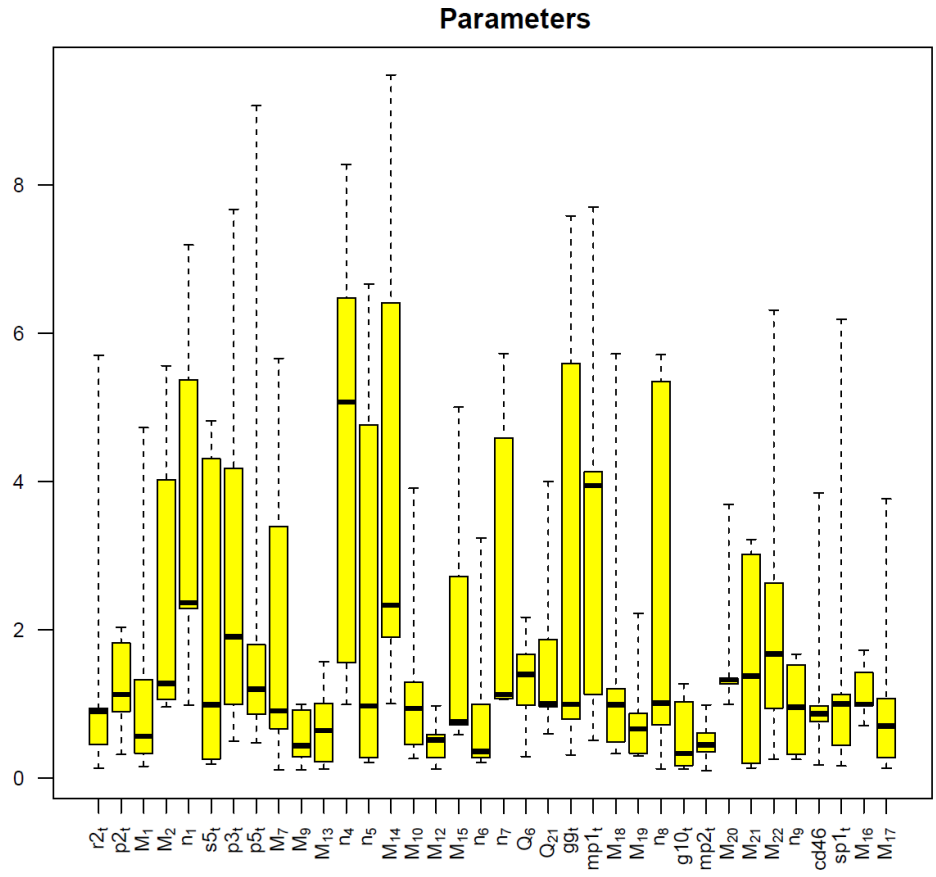

Fig S1. The distribution of the optimized parameters. The parameter sets with the closest minimum squared errors SM , namely "O2", "O3", "O9", "O10" and "O12".

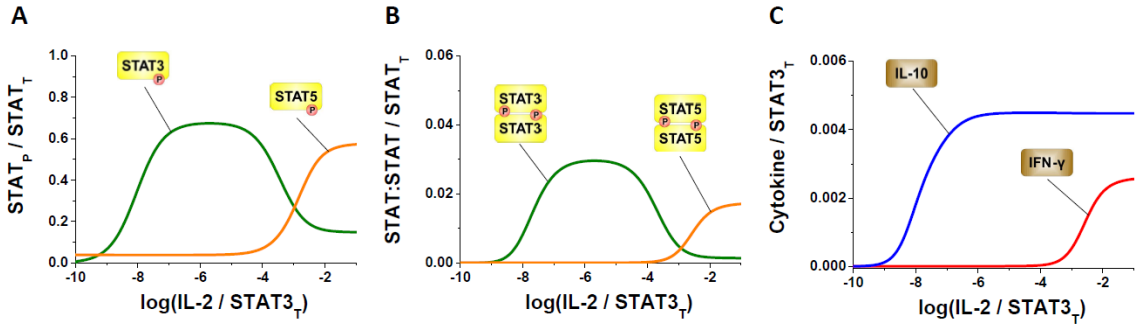

Fig S2. Model predictions for the swapped parameters. A. STAT monomers. B. STAT homodimers. C. Produced cytokines.

Table S3. The effects of the parametric changes on the concentration of produced IFN-γ and IL-10 shown in Fig 3.

Fig	Parameters	Perturbation		
		↓	thin line (optimized)	↑
3A	n_9	$163\cdot10^{-4}$	$191\cdot10^{-4}$	$220\cdot10^{-4}$
	M_{20}	$119\cdot10^{-4}$	$149\cdot10^{-4}$	$179\cdot10^{-4}$
3B	$s5_t$	$198\cdot10^{-4}$	$247\cdot10^{-4}$	$297\cdot10^{-4}$
	M_{18}	7.93	9.913	11.896
	n_8	$81\cdot10^{-4}$	$101\cdot10^{-4}$	$121\cdot10^{-4}$
	M_{14}	0.068	0.1	0.145
	M_9	69.185	47.714	32.445
3C	$r2_t$	$2.7\cdot10^{-4}$	$27\cdot10^{-4}$	$268\cdot10^{-4}$
	n_1	11.842	118.42	1184.2
3D	M_7	$3.63\cdot10^{-2}$	$3.63\cdot10^{-4}$	$3.63\cdot10^{-6}$
3E	M_{10}	470	$47\cdot10^{-4}$	$47\cdot10^{-9}$
3F, G	Q_6	$1\cdot10^{-4}$	$14\cdot10^{-4}$	$209\cdot10^{-4}$

Table S4. Parameters in the STAT3-STAT4 subsystem and their correspondence to the parameters in the STAT3-STAT5 subsystem.

Parameters in STAT3-STAT5	Parameters in STAT3-STAT4	Values
$r2_t$	$r2_t$	0.0027
$p2_t$	$p2_t$	0.0027
M_1	M_1	0.1333
M_2	M_2	4.25E-05
n_1	n_1	118.42
$s5_t$	$s4_t$	0.0247
$p3_t$	$p3_t$	2.5924
$p5_t$	$p4_t$	0.0012
M_7	M_9	3.63E-04
M_9	M_{11}	47.714
M_{13}	M_{15}	19.154
n_4	n_5	0.1987
n_5	n_6	1.5589
M_{14}	M_{16}	0.1002
M_{12}	M_{14}	1.96E+03
M_{15}	M_{17}	0.3787
n_6	n_7	5.5056
n_7	n_8	0.0322
Q_6	Q_6, Q_{12}	0.0014
Q_{21}	Q_{35}	3.42E-11
gg_t	gg_t	0.8949
$mp1_t$	$mp1_t$	0.0034
M_{18}	M_{20}	9.913
M_{19}	M_{21}	4.354
n_8	n_9	0.0101
$g10_t$	$g10_t$	7.2184
$mp2_t$	$mp2_t$	0.5933
M_{20}	M_{22}	0.0149
M_{21}	M_{23}	0.0138
M_{22}	M_{24}	0.1885
n_9	n_{10}	0.0191
cd46	cd46	0.6826
$sp1_t$	$sp1_t$	33.142
M_{16}	M_{18}	8.96E-06
M_{17}	M_{19}	0.1071

3.2 Parameter sensitivity analysis

In the main text, we suggested that IFN-γ to IL-10 switching (Fig 2) is due to the competition between STAT3 and STAT5 proteins. These model predictions are not obvious from the model structure due to the following. The structure of our model presented in Fig 1 is symmetrical in relation to the varied IL-2, i.e. IL-2 activates both STAT3 and STAT5. The model predictions for the phosphorylated states of STAT3, STAT5 and their homodimers could be swapped in Fig 2 if the parameters for STAT3 and STAT5 are swapped (Fig S2). However, in this case there would be no cytokine switching (Fig S2C). Thus the model predictions depend on the assumed structure of our model as well as on the chosen set of parameters. In this section, we performed parameter sensitivity analysis (SA) (21, 22) to identify the parameter conditions for the conclusions to hold.

First, we tested if the IFN-γ to IL-10 and STAT5 to STAT3 switchings are still present when we vary the parameters compared to their optimal values (set "O3" in Table S3). Quantitatively, we defined the switching of either IFN-γ to IL-10 or STAT5 to STAT3 as follows. We assumed that the switching occurs when the 2-fold changes take place, which is typically considered as significant change in Biology (23, 24). Thus, the changes should include at least 2-fold increase in IL-10 and STAT3 as well as decrease of the peak of IFN-γ and STAT5 concentrations within the range of the tested IL-2 concentrations.

We varied the parameters up to 10-fold either side of their values in the optimized set. We used the Latin Hypercube Sampling (LHS), which is considered as one of the most effective strategies for sampling the parameters (22, 25). We performed the LHS sampling and checked the assumed condition for switching for 1000 samples of the optimized parameters. Fig S3 illustrates the probability of the cases, in percent, where the switching of both cytokine and STAT (C+S+), cytokine but not STAT (C+S-), not cytokine but STAT (C-S+), neither cytokine nor STAT (C-S-) occurs for 1-10 fold change of the optimized parameters. The obvious result that follows from Fig S3 is that when the parameters are not perturbed, which corresponds to the 1-fold change, the probability of the presence of both cytokine and STAT switching is 100%. However, with an increase of the fold change up to ten, the probability for switching of both cytokine and STAT decreases down to 2.1% (data shown in Table S5). The probability of either of the cases (cytokine or STAT switching) is almost equal with an increase of the fold change as it can be seen from Fig S3. Thus, we can conclude that the model with the optimized parameters demonstrates both IFN-γ to IL-10 and STAT5 to STAT3 switching with higher probability (more than 50%) when the parameters are perturbed within 2-fold, with modest probability (between 10% and 50%) when the parameters are perturbed within 3-6-fold and

with low probability (less than 10%) when the parameters are perturbed within 7-fold and higher.

Next, we identified the most sensitive parameters that have the greatest impact on the steady-state concentrations of IFN-γ, IL-10, STAT5 and STAT3 for the three concentrations of IL-2: 10^{-10}, 10^{-6} and 10^{-1}, which correspond to the three assumed T cell phenotypes shown in Fig 1A: Th1, Th1/Tr1 and Tr1 respectively. We performed the SA using the eFast method (26), because it was reported as one of the most reliable methods of parameter sensitivity analysis (25). As a tool for the eFast sensitivity analysis, we used the SBToolbox software (27). We performed the SA over one order of magnitude of perturbation for 10000 simulations.

Fig S4-Fig S6 illustrate the results of the sensitivity analysis for IFN-γ, IL-10, STAT5 and STAT3 by the SBToolbox for the non-dimensional IL-2 concentrations $[i2] = 10^{-10}$ (Fig S4), $[i2] = 10^{-6}$ (Fig S5) and $[i2] = 10^{-1}$ (Fig S6). The bars indicate the sensitivity indices for each of the parameters of our model. Here we classified the parameters as sensitive if the corresponding sensitivity index is more than 0.5.

It can be seen from Fig S4A, Fig S5A and Fig S6A that IFN-γ production is the most sensitive to the following parameters: M_{18}, gg_t, n_8, M_{19}, $mp1_t$ and $s5_t$, which demonstrated high sensitivity indices (more than 0.5) for all the three IL-2 concentrations. Parameters n_1, $r2_t$, n_6 and M_2 are sensitive for $[i2] = 10^{-10}$ (Fig S4A) and $[i2] = 10^{-6}$ (Fig S5A). Parameter M_{14} is sensitive only for $[i2] = 10^{-6}$ (Fig S5A) and $[i2] = 10^{-1}$ (Fig S6A). Another group of IFN-γ-sensitive parameters that includes $s5_t$ and n_6 is involved in the STAT5 pathway activation, which leads to the production of IFN-γ as shown in Fig 1B and Equations (6). There is also the third group of IFN-γ-sensitive parameters consisting of n_1, $r2_t$ and M_2 that are involved in

the upstream activation of IL-2 receptor described by Equation (1). Finally, IFN-γ is sensitive to the Michaelis constant of heterodimerization M_{14}.

The parameter sensitivity analysis revealed that the concentration of IL-10 is the most sensitive to $g10_t$ and n_9 for $[i2]=10^{-10}$ (Fig S4B), $[i2]=10^{-6}$ (Fig S5B) and $[i2]=10^{-1}$ (Fig S6B). Parameter M_9 is the most sensitive for the phosphorylated STAT3 for all the three IL-2 concentrations as it is shown in Fig S4C, Fig S5C and Fig S6C. Two parameters, namely, n_5 and Q_6, showed high sensitivity only for $[i2]=10^{-10}$ (Fig S4C) and $[i2]=10^{-6}$ (Fig S5C).

The concentration of phosphorylated STAT5 is the most sensitive to the total amount of STAT5, modeled by parameter $s5_t$, for all the three tested IL-2 concentrations as it is shown in Fig S4D, Fig S5D and Fig S6D. Parameter n_6 demonstrated high sensitivity indices for STAT5p for $[i2]=10^{-10}$ (Fig S4D) and $[i2]=10^{-6}$ (Fig S5D). This parameter is involved in the activation of STAT5 pathway as shown in Fig 1B and Equations (6). The concentration of STAT5p is sensitive to the Michaelis constant of heterodimerization M_{14} for $[i2]=10^{-6}$ (Fig S5D) and $[i2]=10^{-1}$ (Fig S6D). Three parameters, namely n_1, $r2_t$ and M_2, are sensitive for $[i2]=10^{-10}$ (Fig S4D) and $[i2]=10^{-6}$ (Fig S5D) involved in the activation of the IL-2 receptor and described by Equation (1).

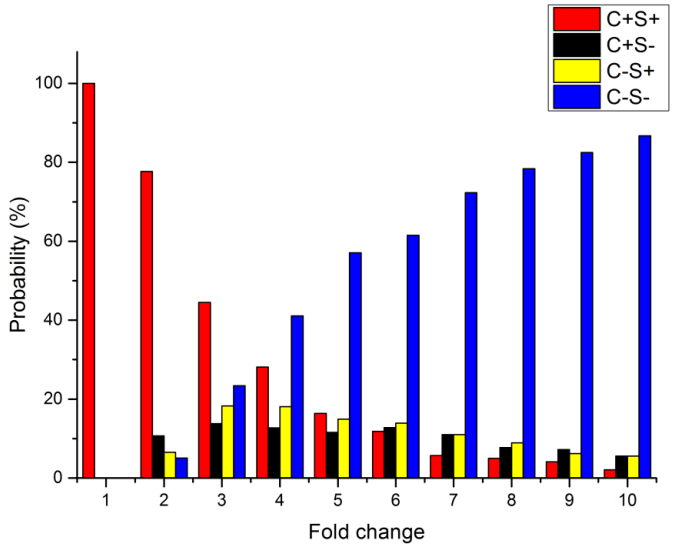

Fig S3. The probability of cases when the switching occurs. The percentage of cases when the switching of both cytokine and STAT (C+S+), cytokine but not STAT (C+S-), not cytokine but STAT (C-S+), neither cytokine nor STAT (C-S-) occurs for 1-10 fold change of the optimized parameters.

Table S5. The percentage of cases when the switching of both cytokine and STAT (C+S+), cytokine but not STAT (C+S-), not cytokine but STAT (C-S+), neither cytokine nor STAT (C-S-) occurs for 1-10 fold change of the optimized parameters.

FC	C+S+	C+S-	C-S+	C-S-
1	100	0	0	0
2	77.7	10.7	6.5	5.1
3	44.5	13.8	18.3	23.4
4	28.1	12.7	18.1	41.1
5	16.4	11.6	14.9	57.1
6	11.8	12.8	13.9	61.5
7	5.7	11	11	72.3
8	5	7.7	8.9	78.4
9	4.1	7.2	6.2	82.5
10	2.1	5.6	5.6	86.7

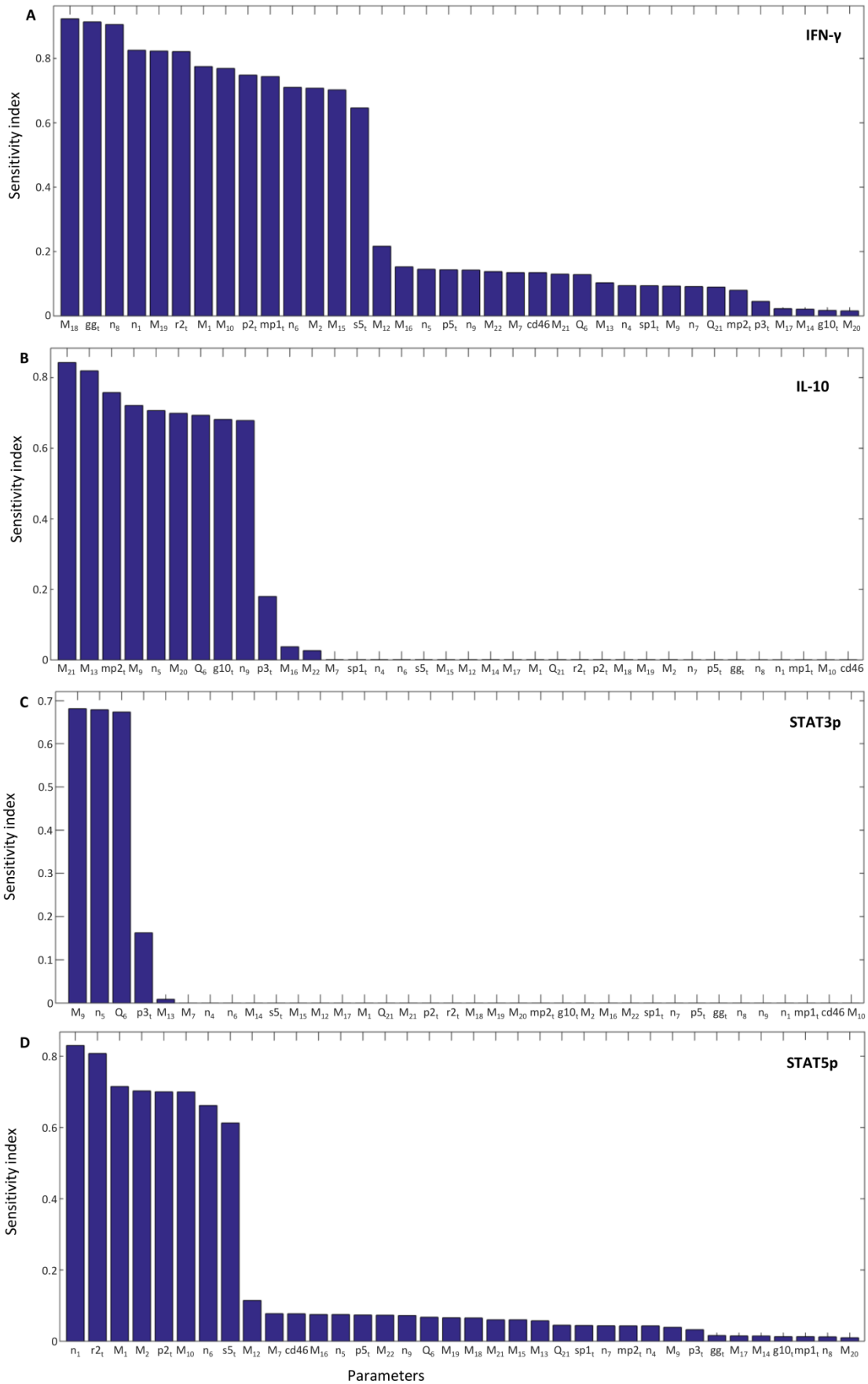

Fig S4. Parameter sensitivity analysis performed by eFAST for low concentrations of IL-2. Sensitivity indicators for the developed model for IFN-γ (A), IL-10 (B), STAT3 (C) and STAT5 (D) for non-dimensional IL-2 concentration $[i2] = 10^{-10}$.

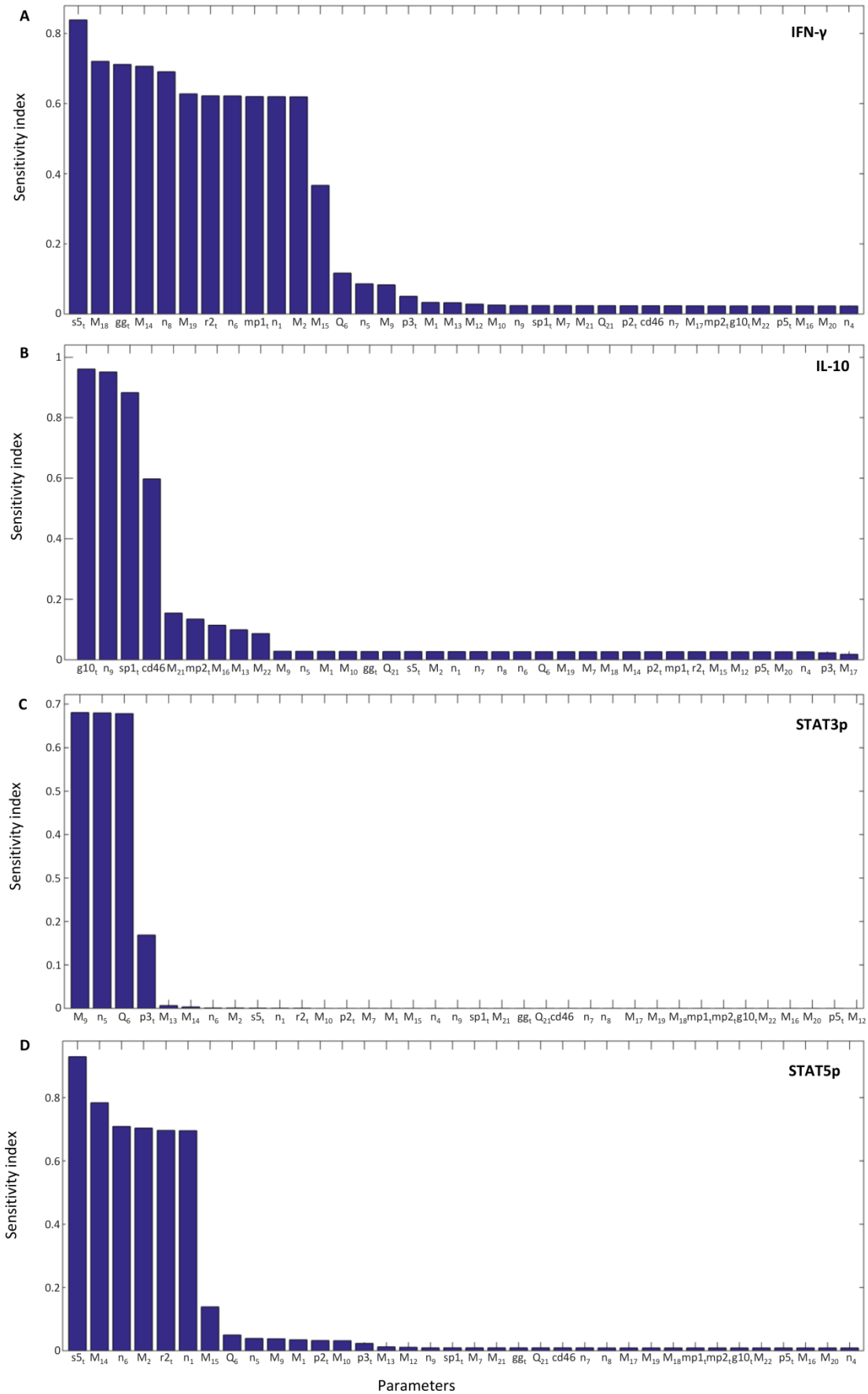

Fig S5. Parameter sensitivity analysis performed by eFAST for medium concentrations of IL-2. Sensitivity indicators for the developed model for IFN-γ (A), IL-10 (B), STAT3 (C) and STAT5 (D) for non-dimensional IL-2 concentration $[i2] = 10^{-6}$.

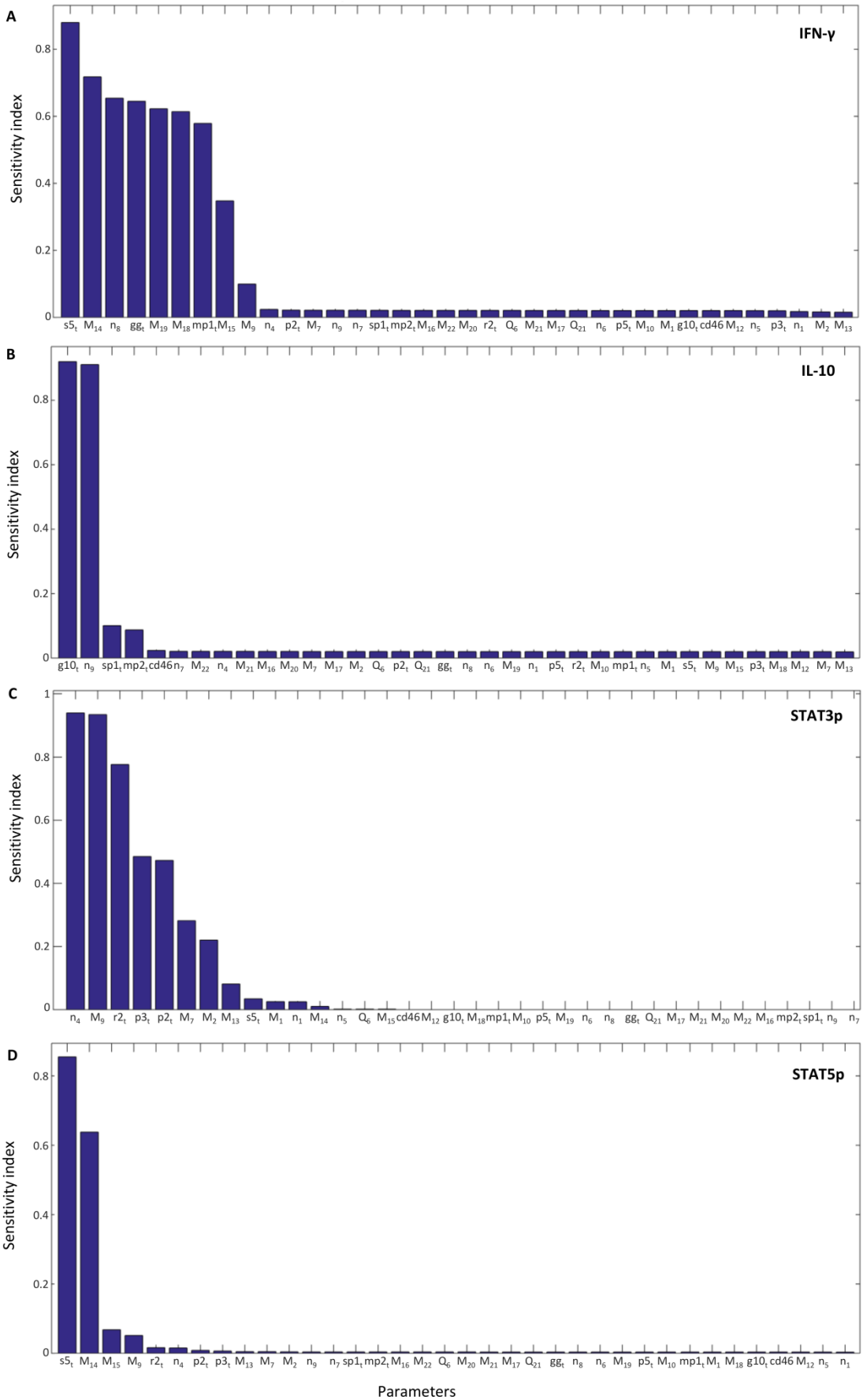

Fig S6. Parameter sensitivity analysis performed by eFAST for high concentrations of IL-2. Sensitivity indicators for the developed model for IFN-γ (A), IL-10 (B), STAT3 (C) and STAT5 (D) for non-dimensional IL-2 concentration $[i2] = 10^{-1}$.

4 FACS analysis

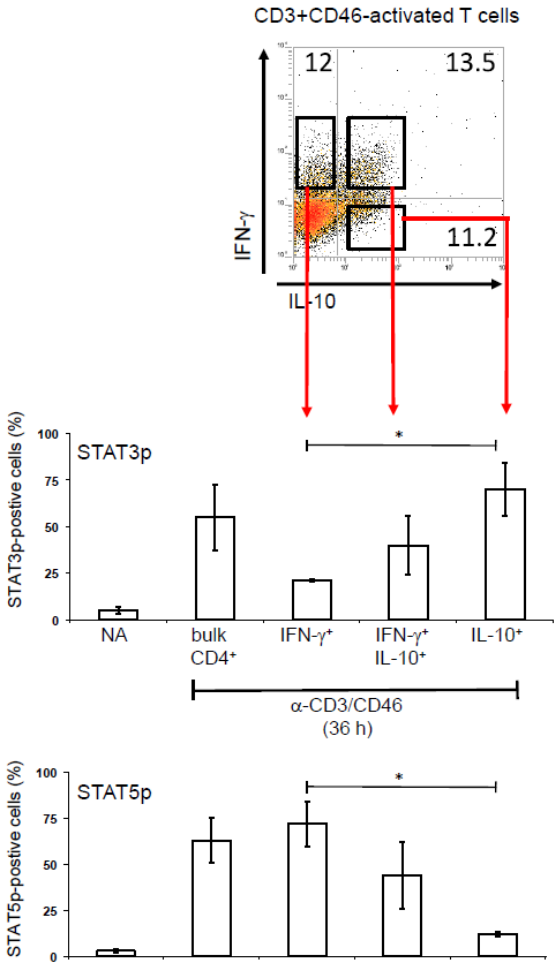

Fig S1. FACS analysis for STAT3p- and STAT5p-positive cells.
Purified human CD4+ T cells were activated with a-CD3/CD46 antibodies in the presence of 50U/ml rhIL-2 for 36 hours and percentage of STAT3p- and STAT5p-positive cells assessed by FACS analysis. Cells were analyzed either as bulk population (bulk CD4+) or after subsorting populations into the three IFN-γ +/- IL-10-secreting populations generated by CD3/CD46-activation. STAT3p and STAT5p values were normalized against respective non-phosphorylated STAT protein levels. NA, non-activated, n=3; shown are mean values ± SD of three independently performed experiments using a different donor each time.

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