Mathematical model of IL6 signal transduction pathway

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This document updates the mathematical model of the IL6 signal transduction pathway presented by Singh *et al*., 2006. A MATLAB program for the updated IL6 model is also included in this work.

The model presented by Singh *et al*., 2006, is based upon the model structure proposed by Heinrich *et al*., 2003, where the dynamic model of Jak-STAT signaling is adopted from Yamada *et al*., 2003, and parts of the detailed kinetic model of Erk-C/EBPβ signaling proposed by Schoeberl *et al*. 2002, are also used.

In the model presented by Singh *et al*., 2006, SOCS3 can bind to the receptor complex that may have STAT3 or SHP2 bound to it. The reason for including these mechanisms is that Singh *et al*.'s Jak-STAT model is based upon a dynamic model of the Jak-STAT pathway stimulated by IFN-γ (Yamada *et al*., 2003). However, the binding sites of the IL-6 receptor complex have different characteristics than the one for the IFN-γ complex as SOCS3 and SHP2 compete for the same binding site and SOCS3 also inhibits activation of STAT3 (Fischer and Hilfiker-Kleiner, 2008). As a result of this Eq. (1) ~ (4) from Singh *et al*., 2006's model are replaced with the reaction shown in Eq. (5) in this work.

$$\text{STAT3C} + (\text{IL6-gp80-gp130-JAK})^*_2\text{-SOCS3} \rightleftharpoons (\text{IL6-gp80-gp130-JAK})^*_2\text{-STAT3C-SOCS3} \quad (1)$$

$$\text{SHP2} + (\text{IL6-gp80-gp130-JAK})^*_2\text{-STAT3C-SOCS3} \rightleftharpoons (\text{IL6-gp80-gp130-JAK})^*_2\text{-STAT3C-SOCS3-SHP2} \quad (2)$$

$$(\text{IL6-gp80-gp130-JAK})^*_2\text{-STAT3C-SOCS3-SHP2} \longrightarrow (\text{IL6-gp80-gp130-JAK})^*_2 + \text{STAT3C} + \text{SOCS3} + \text{SHP2} \quad (3)$$

$$(\text{IL6-gp80-gp130-JAK})^*_2\text{-STAT3C-SOCS3-SHP2} \longrightarrow (\text{IL6-gp80-gp130-JAK})^*_2\text{-STAT3C-SHP2} + \text{SOCS3} \quad (4)$$

$$(\text{IL6-gp80-gp130-JAK})^*_2\text{-SOCS3} \longrightarrow (\text{IL6-gp80-gp130-JAK})^*_2 + \text{SOCS3} \quad (5)$$

This document is structured as follows: Section 1 presents the updated structure of the IL6 signal transduction pathway. Section 2 contains an ordinary differential equation (ODE) model for the updated IL6 signaling. Based upon this ODE model, a MATLAB program is developed and briefly described in Section 3.

1. IL-6 signal transduction pathway

1) $\text{gp80} + \text{IL6} \underset{kr1}{\overset{kf1}{\rightleftharpoons}} \text{IL6-gp80}$
2) $\text{gp130} + \text{JAK} \underset{kr2}{\overset{kf2}{\rightleftharpoons}} \text{gp130-JAK}$
3) $\text{IL6-gp80} + \text{gp130-JAK} \underset{kr3}{\overset{kf3}{\rightleftharpoons}} \text{IL6-gp80-gp130-JAK}$
4) $\text{IL6-gp80-gp130-JAK} + \text{IL6-gp80-gp130-JAK} \underset{kr4}{\overset{kf4}{\rightleftharpoons}} (\text{IL6-gp80-gp130-JAK})_2$
5) $(\text{IL6-gp80-gp130-JAK})_2 \overset{k5}{\rightarrow} (\text{IL6-gp80-gp130-JAK})^*_2$
6) $(\text{IL6-gp80-gp130-JAK})^*_2 + \text{STAT3C} \underset{kr6}{\overset{kf6}{\rightleftharpoons}} (\text{IL6-gp80-gp130-JAK})^*_2 \text{ - STAT3C}$
7) $(\text{IL6-gp80-gp130-JAK})^*_2 \text{ - STAT3C} \overset{k7}{\rightarrow} (\text{IL6-gp80-gp130-JAK})^*_2 + \text{STAT3C*}$
8) $(\text{IL6-gp80-gp130-JAK})^*_2 + \text{STAT3C*} \underset{kr8}{\overset{kf8}{\rightleftharpoons}} (\text{IL6-gp80-gp130-JAK})^*_2 \text{ - STAT3C*}$
9) $\text{STAT3C*} + \text{STAT3C*} \underset{kr9}{\overset{kf9}{\rightleftharpoons}} \text{STAT3C*-STAT3C*}$
10) $(\text{IL6-gp80-gp130-JAK})^*_2 + \text{SHP2} \underset{kr10}{\overset{kf10}{\rightleftharpoons}} (\text{IL6-gp80-gp130-JAK})^*_2\text{-SHP2}$
11) $(\text{IL6-gp80-gp130-JAK})^*_2\text{-SHP2} \overset{k11}{\rightarrow} (\text{IL6-gp80-gp130-JAK})_2 + \text{SHP2}$

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12) PP1 + STAT3C* $\underset{kr12}{\overset{kf12}{\rightleftarrows}}$ PP1-STAT3C*

13) PP1-STAT3C* $\overset{k13}{\longrightarrow}$ PP1 + STAT3C

14) PP1 + STAT3C*-STAT3C* $\underset{kr14}{\overset{kf14}{\rightleftarrows}}$ PP1-STAT3C*-STAT3C*

15) PP1-STAT3C*-STAT3C* $\overset{k15}{\longrightarrow}$ PP1 + STAT3C-STAT3C*

16) STAT3C + STAT3C* $\underset{kr16}{\overset{kf16}{\rightleftarrows}}$ STAT3C-STAT3C*

17) STAT3C*-STAT3C* $\overset{k17}{\longrightarrow}$ STAT3N*-STAT3N*

18) STAT3N*-STAT3N* $\underset{kr18}{\overset{kf18}{\rightleftarrows}}$ STAT3N* + STAT3N*

19) PP2 + STAT3N* $\underset{kr19}{\overset{kf19}{\rightleftarrows}}$ PP2-STAT3N*

20) PP2-STAT3N* $\overset{k20}{\longrightarrow}$ PP2 + STAT3N

21) PP2 + STAT3N*-STAT3N* $\underset{kr21}{\overset{kf21}{\rightleftarrows}}$ PP2-STAT3N*-STAT3N*

22) PP2-STAT3N*-STAT3N* $\overset{k22}{\longrightarrow}$ PP2 + STAT3N-STAT3N*

23) STAT3N-STAT3N* $\underset{kr23}{\overset{kf23}{\rightleftarrows}}$ STAT3N + STAT3N*

24) STAT3N $\overset{k24}{\longrightarrow}$ STAT3C

25) STAT3N*-STAT3N* $\xrightarrow{Michaelis\ Menten,k25a,k25b}$ mRNA-SOCS3N

26) mRNA-SOCS3N $\overset{k26}{\longrightarrow}$ mRNA-SOCS3C

27) mRNA-SOCS3C $\overset{mass}{\longrightarrow}$ SOCS3

28) SOCS3 + (IL6-gp80- gp130-JAK)*$_2$ $\underset{kr28}{\overset{kf28}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$ -SOCS3

29) mRNA-SOCS3C $\overset{mass}{\longrightarrow}$ mRNA-SOCS3C

30) SOCS3 $\overset{mass}{\longrightarrow}$ SOCS3

31) (IL6-gp80- gp130-JAK)*$_2$-SOCS3 $\overset{k31}{\longrightarrow}$ SOCS3 + (IL6-gp80- gp130-JAK)$_2$

32) (IL6-gp80- gp130-JAK)*$_2$-SHP2 $\underset{kr32}{\overset{kf32}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*

33) (IL6-gp80- gp130-JAK)*2-SHP2* + Grb2 $\underset{kr33}{\overset{kf33}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2

34) (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2 + SOS $\underset{kr34}{\overset{kf34}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS

35) (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS + Ras-GDP $\underset{kr35}{\overset{kf35}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS-Ra-GDP

36) (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS-Ra-GDP $\underset{kr36}{\overset{kf36}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS + Ras-GTP

37) Raf + Ras-GTP $\underset{kr37}{\overset{kf37}{\rightleftarrows}}$ Raf-Ras-GTP

38) Raf + Ras-GTP $\underset{kr38}{\overset{kf38}{\rightleftarrows}}$ Raf* + Ras-GTP*

39) Ras-GTP* + (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS $\underset{kr39}{\overset{kf39}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS-Ras-GTP

40) (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS-Ras-GTP $\underset{kr40}{\overset{kf40}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS + Ras-GDP

41) (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS $\underset{kr41}{\overset{kf41}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$ + SHP2*-Grb2-SOS

42) SHP2*-Grb2-SOS $\underset{kr42}{\overset{kf42}{\rightleftarrows}}$ Grb2-SOS + SHP2*

43) Grb2-SOS $\underset{kr43}{\overset{kf43}{\rightleftarrows}}$ Grb2 + SOS

44) SHP2* $\xrightarrow{Michaelis\ Menten,Vm,Km}$ SHP2

45) (IL6-gp80- gp130-JAK)*$_2$-SHP2* $\underset{kr45}{\overset{kf45}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$ + SHP2*

46) SHP2* + Grb2 $\underset{kr46}{\overset{kf46}{\rightleftarrows}}$ SHP2*-Grb2

47) (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2 $\underset{kr47}{\overset{kf47}{\rightleftarrows}}$ SHP2*-Grb2 + (IL6-gp80- gp130-JAK)*$_2$

48) SHP2*-Grb2 + SOS $\underset{kr48}{\overset{kf48}{\rightleftarrows}}$ SHP2*-Grb2-SOS

49) (IL6-gp80- gp130-JAK)*$_2$-SHP2* + Grb2-SOS $\underset{kr49}{\overset{kf49}{\rightleftarrows}}$ (IL6-gp80- gp130-JAK)*$_2$-SHP2*-Grb2-SOS

50) Raf* + Phosp1 $\underset{kr50}{\overset{kf50}{\rightleftarrows}}$ Raf*-Phosp1

51) Raf*-Phosp1 $\overset{k51}{\longrightarrow}$ Raf + Phosp1

52) MEK + Raf* $\underset{kr52}{\overset{kf52}{\rightleftarrows}}$ MEK-Raf*

53) MEK-Raf* $\overset{k53}{\longrightarrow}$ MEK-P + Raf*

54) MEK-P + Raf* $\underset{kr54}{\overset{kf54}{\rightleftarrows}}$ MEK-P-Raf*

55) MEK-P-Raf* $\overset{k55}{\longrightarrow}$ MEK-PP + Raf*

56) MEK-PP + Phosp2 $\underset{kr56}{\overset{kf56}{\rightleftarrows}}$ MEK-PP-Phosp2

57) MEK-PP-Phosp2 $\overset{k57}{\longrightarrow}$ MEK-P + Phosp2

58) MEK-P + Phosp2 $\underset{kr58}{\overset{kf58}{\rightleftarrows}}$ MEK-P-Phosp2

59) MEK-P-Phosp2 $\overset{k59}{\longrightarrow}$ MEK + Phosp2

60) ERK + MEK-PP $\underset{kr60}{\overset{kf60}{\rightleftarrows}}$ ERK-MEK-PP

61) ERK-MEK-PP $\overset{k61}{\longrightarrow}$ ERK-P + MEK-PP

62) ERK-P + MEK-PP $\underset{kr62}{\overset{kf62}{\rightleftarrows}}$ ERK-P-MEK-PP

63) ERK-P-MEK-PP $\overset{k63}{\longrightarrow}$ ERK-PP + MEK-PP

64) ERK-PP + Phosp3 $\underset{kr64}{\overset{kf64}{\rightleftarrows}}$ ERK-PP-Phosp3

65) ERK-PP-Phosp3 $\overset{k65}{\longrightarrow}$ ERK-PP + Phosp3

66) ERK-PP + Phosp3 $\underset{kr66}{\overset{kf66}{\rightleftarrows}}$ ERK-P-Phosp3

67) ERK-P-Phosp3 $\overset{k67}{\longrightarrow}$ ERK + Phosp3

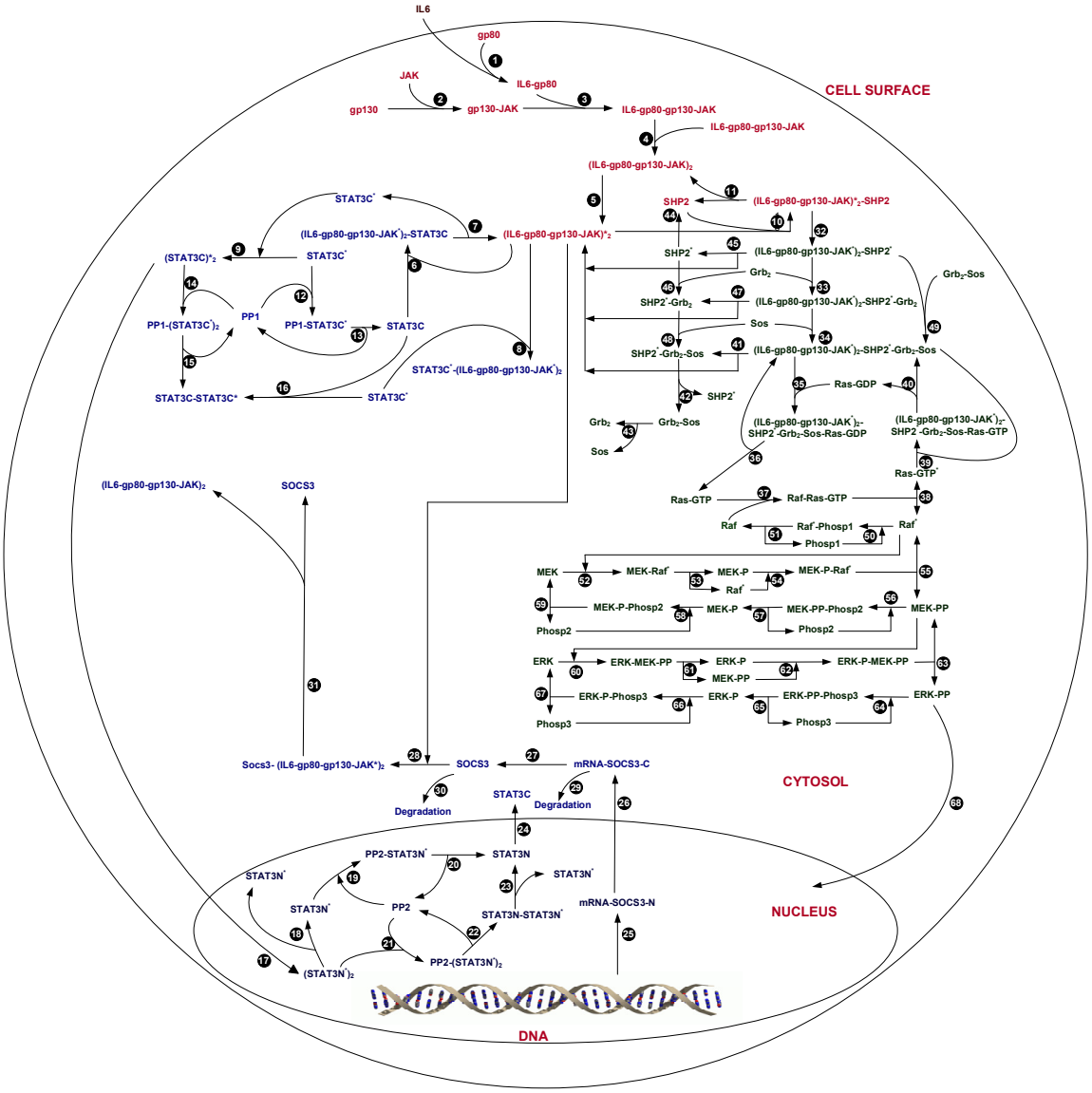

Figure 1, Schematic diagram of IL-6 signal transduction pathway

2. Ordinary differential equation (ODE) model of IL-6 signaling

$$
\begin{aligned}
dx_1/dt &= 0 \\
dx_2/dt &= k_{f1}x_1u - k_{r1}x_2 - k_{f3}x_2x_5 + k_{r3}x_6 \\
dx_3/dt &= 0 \\
dx_4/dt &= -k_{f2}x_3x_4 + k_{r2}x_5 \\
dx_5/dt &= k_{f2}x_3x_4 - k_{r2}x_5 - k_{f3}x_2x_5 + k_{r3}x_6 \\
dx_6/dt &= k_{f3}x_2x_5 - k_{r3}x_6 - 2k_{f4}x_6x_6 + 2k_{r4}x_7 \\
dx_7/dt &= k_{f4}x_6x_6 - k_{r4}x_7 - k_5x_7 + k_{11}x_{15} + k_{31}x_{30} \\
dx_8/dt &= k_5x_7 - k_{f6}x_8x_9 + k_{r6}x_{10} + k_7x_{10} - k_{f8}x_8x_{11} + k_{r8}x_{12} - k_{f10}x_8x_{14} + k_{r10}x_{15} - k_{f28}x_{29}x_8 + k_{r28}x_{30} + k_{f41}x_{35} \\
&\quad -k_{r41}x_8x_{44} + k_{f45}x_{31} - k_{r45}x_8x_{46} + k_{f47}x_{33} - k_{r47}x_{47}x_8 \\
dx_9/dt &= -k_{f6}x_8x_9 + k_{r6}x_{10} + k_{13}x_{17} - k_{f16}x_9x_{11} + k_{r16}x_{19} + k_{24}x_{24} \\
dx_{10}/dt &= k_{f6}x_8x_9 - k_{r6}x_{10} - k_7x_{10} \\
dx_{11}/dt &= k_7x_{10} - k_{f8}x_8x_{11} + k_{r8}x_{12} - 2k_{f9}x_{11}x_{11} + 2k_{r9}x_{13} - k_{f12}x_{16}x_{11} + k_{r12}x_{17} - k_{f16}x_9x_{11} + k_{r16}x_{19}
\end{aligned}
$$

$$
\begin{aligned}
dx_{12}/dt &= k_{f8}x_8x_{11} - k_{r8}x_{12}\\
dx_{13}/dt &= k_{f9}x_{11}x_{11} - k_{r9}x_{13} - k_{f14}x_{16}x_{13} + k_{r14}x_{18} - k_{17}x_{13}\\
dx_{14}/dt &= -k_{f10}x_8x_{14} + k_{r10}x_{15} + k_{11}x_{15} + v_m x_{46}/(k_m + x_{46})\\
dx_{15}/dt &= k_{f10}x_8x_{14} - k_{r10}x_{15} - k_{11}x_{15} - k_{f32}x_{15} + k_{r32}x_{31}\\
dx_{16}/dt &= -k_{f12}x_{16}x_{11} + k_{r12}x_{17} + k_{13}x_{17} - k_{f14}x_{16}x_{13} + k_{r14}x_{18} + k_{15}x_{18}\\
dx_{17}/dt &= k_{f12}x_{16}x_{11} - k_{r12}x_{17} - k_{13}x_{17}\\
dx_{18}/dt &= k_{f14}x_{16}x_{13} - k_{r14}x_{18} - k_{15}x_{18}\\
dx_{19}/dt &= k_{15}x_{18} + k_{f16}x_9x_{11} - k_{r16}x_{19}\\
dx_{20}/dt &= k_{17}x_{13} - k_{f18}x_{20} + k_{r18}x_{21}x_{21} - k_{f21}x_{22}x_{20} + k_{r21}x_{25}\\
dx_{21}/dt &= 2k_{f18}x_{20} - 2k_{r18}x_{21}x_{21} - k_{f19}x_{22}x_{21} + k_{r19}x_{23} + k_{r23}x_{26} - k_{f23}x_{24}x_{21}\\
dx_{22}/dt &= -k_{f19}x_{22}x_{21} + k_{r19}x_{23} + k_{20}x_{23} - k_{f21}x_{22}x_{20} + k_{r21}x_{25} + k_{22}x_{25}\\
dx_{23}/dt &= k_{f19}x_{22}x_{21} - k_{r19}x_{23} - k_{20}x_{23}\\
dx_{24}/dt &= k_{20}x_{23} + k_{r23}x_{26} - k_{f23}x_{24}x_{21} - k_{24}x_{24}\\
dx_{25}/dt &= k_{f21}x_{22}x_{20} - k_{r21}x_{25} - k_{22}x_{25}\\
dx_{26}/dt &= k_{22}x_{25} - k_{r23}x_{26} + k_{f23}x_{24}x_{21}\\
dx_{27}/dt &= k_{25a}x_{20}/(k_{25b} + x_{20}) - k_{26}x_{27}\\
dx_{28}/dt &= k_{26}x_{27} - k_{29}x_{28}\\
dx_{29}/dt &= k_{27}x_{28} - k_{f28}x_{29}x_8 + k_{r28}x_{30} - k_{30}x_{29} + k_{31}x_{30}\\
dx_{30}/dt &= k_{f28}x_{29}x_8 - k_{r28}x_{30} - k_{31}x_{30}\\
dx_{31}/dt &= k_{f32}x_{15} - k_{r32}x_{31} - k_{f33}x_{31}x_{32} + k_{r33}x_{33} - k_{f45}x_{31} + k_{r45}x_8x_{46} - k_{f49}x_{31}x_{45} + k_{r49}x_{35}\\
dx_{32}/dt &= -k_{f33}x_{31}x_{32} + k_{r33}x_{33} + k_{f43}x_{45} - k_{r43}x_{32}x_{34} - k_{f46}x_{46}x_{32} + k_{r46}x_{47}\\
dx_{33}/dt &= k_{f33}x_{31}x_{32} - k_{r33}x_{33} - k_{f34}x_{33}x_{34} + k_{r34}x_{35} - k_{f47}x_{33} + k_{r47}x_{47}x_8\\
dx_{34}/dt &= -k_{f34}x_{33}x_{34} + k_{r34}x_{35} + k_{f43}x_{45} - k_{r43}x_{32}x_{34} - k_{f48}x_{47}x_{34} + k_{r48}x_{44}\\
dx_{35}/dt &= k_{f34}x_{33}x_{34} - k_{r34}x_{35} - k_{f35}x_{35}x_{36} + k_{r35}x_{37} + k_{f36}x_{37} - k_{r36}x_{37}x_{38} - k_{f39}x_{42}x_{35} + k_{r39}x_{43} + k_{f40}x_{43} - k_{r40}x_{35}x_{36} -\\
&\quad k_{f41}x_{35} + k_{r41}x_8x_{44} + k_{f49}x_{31}x_{45} - k_{r49}x_{35}\\
dx_{36}/dt &= -k_{f35}x_{35}x_{36} + k_{r35}x_{37} + k_{f40}x_{43} - k_{r40}x_{35}x_{36}\\
dx_{37}/dt &= k_{f35}x_{35}x_{36} - k_{r35}x_{37} - k_{f36}x_{37} + k_{r36}x_{35}x_{38}\\
dx_{38}/dt &= k_{f36}x_{37} - k_{r36}x_{35}x_{38} - k_{f37}x_{39}x_{38} + k_{r36}x_{40}\\
dx_{39}/dt &= -k_{f37}x_{39}x_{38} + k_{r37}x_{40} + k_{51}x_{49}\\
dx_{40}/dt &= k_{f37}x_{39}x_{38} - k_{r37}x_{40} - k_{f38}x_{40} + k_{r38}x_{41}x_{42}\\
dx_{41}/dt &= k_{f38}x_{40} - k_{r38}x_{41}x_{42} - k_{f50}x_{41}x_{48} + k_{r50}x_{49} - k_{f52}x_{50}x_{41} + k_{r52}x_{51} + k_{53}x_{51} - k_{f54}x_{52}x_{41} + k_{r54}x_{53} + k_{55}x_{53}\\
dx_{42}/dt &= k_{f38}x_{40} - k_{r38}x_{41}x_{42} - k_{f39}x_{42}x_{35} + k_{r39}x_{43}\\
dx_{43}/dt &= k_{f39}x_{42}x_{35} - k_{r39}x_{43} - k_{f40}x_{43} + k_{r40}x_{35}x_{36}\\
dx_{44}/dt &= k_{f41}x_{35} - k_{r41}x_8x_{44} - k_{f42}x_{44} + k_{r42}x_{45}x_{46} + k_{f48}x_{47}x_{34} - k_{r48}x_{44}\\
dx_{45}/dt &= k_{f42}x_{44} - k_{r42}x_{45}x_{46} - k_{f43}x_{45} + k_{r43}x_{32}x_{34} - k_{f49}x_{31}x_{45} + k_{r49}x_{35}\\
dx_{46}/dt &= k_{f42}x_{44} - k_{r42}x_{45}x_{46} - v_m x_{46}/(k_m + x_{46}) + k_{f45}x_{31} - k_{r45}x_8x_{46} - k_{f46}x_{46}x_{32} + k_{r46}x_{47}\\
dx_{47}/dt &= k_{f46}x_{46}x_{32} - k_{r46}x_{47} + k_{f47}x_{33} - k_{r47}x_{47}x_8 - k_{f48}x_{47}x_{34} + k_{r48}x_{44}\\
dx_{48}/dt &= -k_{f50}x_{41}x_{48} + k_{r50}x_{49} + k_{51}x_{49}\\
dx_{49}/dt &= k_{f50}x_{41}x_{48} - k_{r50}x_{49} - k_{51}x_{49}\\
dx_{50}/dt &= -k_{f52}x_{50}x_{41} + k_{r52}x_{51} + k_{59}x_{57}\\
dx_{51}/dt &= k_{f52}x_{50}x_{41} - k_{r52}x_{51} - k_{53}x_{51}\\
dx_{52}/dt &= k_{53}x_{51} - k_{f54}x_{52}x_{41} + k_{r54}x_{53} + k_{57}x_{56} - k_{f58}x_{52}x_{55} + k_{r58}x_{57}\\
dx_{53}/dt &= k_{f54}x_{52}x_{41} - k_{r54}x_{53} - k_{55}x_{53}\\
dx_{54}/dt &= k_{55}x_{53} - k_{f56}x_{54}x_{55} + k_{r56}x_{56} - k_{f60}x_{58}x_{54} + k_{r60}x_{59} + k_{61}x_{59} - k_{f62}x_{60}x_{54} + k_{r62}x_{61} + k_{63}x_{61}\\
dx_{55}/dt &= -k_{f56}x_{54}x_{55} + k_{r56}x_{56} + k_{57}x_{56} - k_{f58}x_{52}x_{55} + k_{r58}x_{57} + k_{59}x_{57}\\
dx_{56}/dt &= k_{f56}x_{54}x_{55} - k_{r56}x_{56} - k_{57}x_{56}\\
dx_{57}/dt &= k_{f58}x_{52}x_{55} - k_{r58}x_{57} - k_{59}x_{57}\\
dx_{58}/dt &= -k_{f60}x_{58}x_{54} + k_{r60}x_{59} + k_{67}x_{65}\\
dx_{59}/dt &= k_{f60}x_{58}x_{54} - k_{r60}x_{59} - k_{61}x_{59}\\
dx_{60}/dt &= k_{61}x_{59} - k_{f62}x_{60}x_{54} + k_{r62}x_{61} + k_{65}x_{64} - k_{f66}x_{60}x_{63} + k_{r66}x_{65}\\
dx_{61}/dt &= k_{f62}x_{60}x_{54} - k_{r62}x_{61} - k_{63}x_{61}\\
dx_{62}/dt &= k_{63}x_{61} - k_{f64}x_{62}x_{63} + k_{r64}x_{64}\\
dx_{63}/dt &= -k_{f64}x_{62}x_{63} + k_{r64}x_{64} + k_{65}x_{64} - k_{f66}x_{60}x_{63} + k_{r66}x_{65} + k_{67}x_{65}\\
dx_{64}/dt &= k_{f64}x_{62}x_{63} - k_{r64}x_{64} - k_{65}x_{64}\\
dx_{65}/dt &= k_{f66}x_{60}x_{63} - k_{r66}x_{65} - k_{67}x_{65}
\end{aligned}
$$

Tabel 1, State variables of the model and their initial values

Name	Component	Initial value (nM)
u	IL6	3.83 (100 ng/ml)
x_1	gp80	8
x_2	IL6-gp80	0
x_3	gp130	0.8
x_4	JAK	12
x_5	gp130-JAK	0
x_6	IL6-gp80- gp130-JAK	0
x_7	(IL6-gp80- gp130-JAK)$_2$	0
x_8	(IL6-gp80- gp130-JAK)*$_2$	0
x_9	STAT3C	1000
x_{10}	(IL6-gp80- gp130-JAK)*$_2$ -STAT3C	0
x_{11}	STAT3C*	0
x_{12}	(IL6-gp80- gp130-JAK)*$_2$ -STAT3C*	0
x_{13}	STAT3C* -STAT3C*	0
x_{14}	SHP2	100
x_{15}	(IL6-gp80- gp130-JAK)*$_2$ –SHP2	0
x_{16}	PP1	50
x_{17}	PP1-STAT3C*	0
x_{18}	PP1-STAT3C*- STAT3C*	0
x_{19}	STAT3C -STAT3C*	0
x_{20}	STAT3N*- STAT3N*	0
x_{21}	STAT3N*	0
x_{22}	PP2	60
x_{23}	PP2-STAT3N*	0
x_{24}	STAT3N	0
x_{25}	PP2-STAT3N*- STAT3N*	0
x_{26}	STAT3N- STAT3N*	0
x_{27}	mRNA-SOCS3N	0
x_{28}	mRNA-SOCS3C	0
x_{29}	SOCS3	0
x_{30}	(IL6-gp80- gp130-JAK)*$_2$ –SOCS3	0
x_{31}	(IL6-gp80- gp130-JAK)*$_2$ –SHP2*	0
x_{32}	Grb2	85
x_{33}	(IL6-gp80- gp130-JAK)*$_2$ –SHP2*-Grb2	0
x_{34}	SOS	34
x_{35}	(IL6-gp80- gp130-JAK)*$_2$ –SHP2*-Grb2-SOS	0
x_{36}	Ras-GDP	19000
x_{37}	(IL6-gp80- gp130-JAK)*$_2$ –SHP2*-Grb2-SOS-Ras-GDP	0
x_{38}	Ras-GTP	0
x_{39}	Raf	67

x_{40}	Raf-Ras-GTP	0
x_{41}	Raf*	0
x_{42}	Ras-GTP*	0
x_{43}	(IL6-gp80- gp130-JAK)*$_2$ –SHP2*-Grb2-SOS-Ras-GTP	0
x_{44}	SHP2*-Grb2-SOS	0
x_{45}	Grb2- SOS	0
x_{46}	SHP2*	0
x_{47}	SHP2*-Grb2	0
x_{48}	Phosp1	67
x_{49}	Raf*- Phosp1	0
x_{50}	MEK	41667
x_{51}	MEK-Raf*	0
x_{52}	MEK-P	0
x_{53}	MEK-P-Raf*	0
x_{54}	MEK-PP	0
x_{55}	Phosp2	67
x_{56}	MEK-PP-Phosp2	0
x_{57}	MEK-P-Phosp2	0
x_{58}	ERK	35000
x_{59}	ERK- MEK-PP	0
x_{60}	ERK- P	0
x_{61}	ERK-P- MEK-PP	0
x_{62}	ERK- PP	0
x_{63}	Phosp3	16667
x_{64}	ERK-PP- Phosp3	0
x_{65}	ERK-P- Phosp3	0

Table 2, Values of the parameters

Name	Value	Name	Value	Name	Value
k_{f1}	0.1	k_{r23}	0.2	k_{f45}	0.3
k_{r1}	0.05	k_{24}	0.05	k_{r45}	0.0009
k_{f2}	0.1	k_{25a}	0.01	k_{f46}	0.01
k_{r2}	0.05	k_{25b}	400	k_{r46}	0.55
k_{f3}	0.02	k_{26}	0.001	k_{f47}	0.3
k_{r3}	0.02	k_{27}	0.01	k_{r47}	0.0009
k_{f4}	0.04	k_{f28}	5	k_{f48}	0.03
k_{r4}	0.2	k_{r28}	0.1	k_{r48}	0.064
k_5	0.005	k_{29}	0.0005	k_{f49}	0.03
k_{f6}	0.008	k_{30}	0.0005	k_{r49}	0.0429
k_{r6}	0.8	k_{31}	0.003	k_{f50}	0.0717

k_7	0.4	k_{f32}	6	k_{r50}	0.2
k_{f8}	0.005	k_{r32}	0.06	k_{51}	1
k_{r8}	0.5	k_{f33}	0.01	k_{f52}	0.011
k_{f9}	0.02	k_{r33}	0.55	k_{r52}	0.001833
k_{r9}	0.1	k_{f34}	0.01	k_{53}	3.5
k_{f10}	0.001	k_{r34}	0.0214	k_{f54}	0.011
k_{r10}	0.2	k_{f35}	0.015	k_{r54}	0.001833
k_{11}	0.003	k_{r35}	1.3	k_{55}	2.9
k_{f12}	0.001	k_{f36}	0.5	k_{f56}	0.0143
k_{r12}	0.2	k_{r36}	0.0001	k_{r56}	0.8
k_{13}	0.003	k_{f37}	0.001	k_{57}	0.058
k_{f14}	0.001	k_{r37}	0.0053	k_{f58}	0.00025
k_{r14}	0.2	k_{f38}	1	k_{r58}	0.5
k_{15}	0.003	k_{r38}	0.0007	k_{59}	0.058
k_{f16}	0.0000002	k_{f39}	0.0079	k_{f60}	0.00011
k_{r16}	0.2	k_{r39}	0.4	k_{r60}	0.033
k_{17}	0.005	k_{f40}	0.023	k_{61}	16
k_{f18}	0.1	k_{r40}	0.00022	k_{f62}	0.00011
k_{r18}	0.02	k_{f41}	0.1	k_{r62}	0.033
k_{f19}	0.001	k_{r41}	0.000245	k_{63}	6.7
k_{r19}	0.2	k_{f42}	0.3	k_{f64}	0.014
k_{20}	0.005	k_{r42}	0.021	k_{r64}	0.6
k_{f21}	0.001	k_{f43}	0.0015	k_{65}	0.27
k_{r21}	0.2	k_{r43}	0.0045	k_{f66}	0.005
k_{22}	0.005	v_m	1.7	k_{r66}	0.5
k_{f23}	2E-7	k_m	340	k_{67}	0.3

Note: First order rate constants have units of 1/s and second order rate constants of [$nM^{-1}s^{-1}$].

3. MATLAB program for the model of IL6 signaling

The ODE model of IL6 signaling is contained in the document 'pathway_model.m', and the program 'Main.m' is used to run the program. Please follow the following procedures to run the program:

1) Place both programs, 'pathway_model.m' and 'Main.m', in the same folder;
2) Type Main in the command window to run the simulation.

Simulation results for nuclear STAT3 and SOCS3 for stimulation with 100 ng/ml IL6 are shown in Figure 2 and Figure 3, respectively.

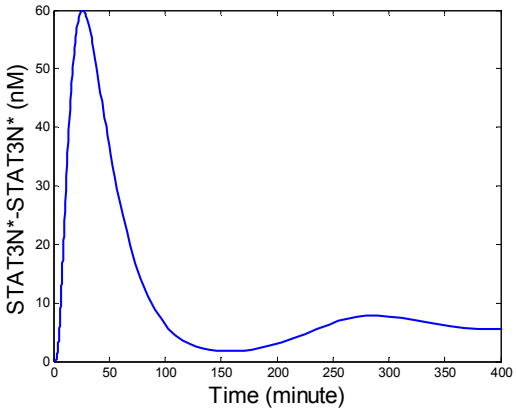

Figure 2, Simulation result for STAT3N*-STAT3N* with 100 ng/ml IL6 stimulation

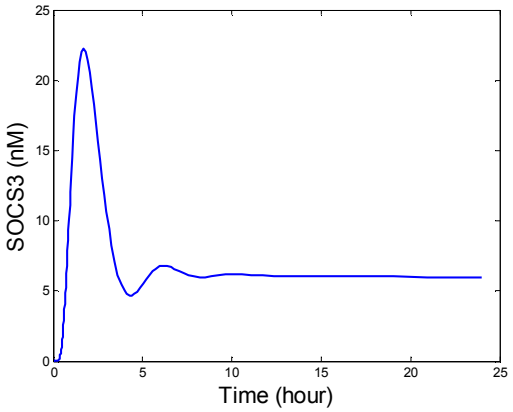

Figure 3, Simulation result for STAT3N*-STAT3N* with 100 ng/ml IL6 stimulation

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