

Supplementary material 1. Fuzzy logic propositions.

Modeling of the effect of environmental cytokines, nutrient conditions and hypoxia on CD4+ cell differentiation.

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$$WTCR = \text{Antigen} * (1 - \text{CTLA4DIM})$$

$$WCD28 = \text{CD8086} * (1 - \text{CTLA4DIM})$$

$$WAP1 = \text{RASGTPR} * (1 - \text{PRED})$$

$$WCD25 = \text{IL2G} * (1 - \text{CTLA4DIM})$$

$$WIL2G = \text{NFAT} * \text{AP1} * (1 - \text{NDRG1})$$

$$WIL2E = \text{IL2G}$$

$$WMTOR = (\text{CD25} + \text{AKT}) - (\text{CD25} * \text{AKT})$$

$$WZAP70 = (\text{TCR} * \text{LCK}) * (1 - \text{CTLA4DIM}) * (1 - \text{PRED})$$

$$WSTAT5 = \text{CD25} * (1 - \text{CTLA4DIM})$$

$$WNFAT = (\text{CA}) * (1 - \text{CS})$$

$$WNFKB = \text{PKC} * (1 - \text{PRED})$$

$$WAKT = (((\text{CD28}) * (1 - \text{CTLA4DIM})) + (\text{PDK1})) - (((\text{CD28}) * (1 - \text{CTLA4DIM})) * (\text{PDK1}))$$

$$WCTLA4 = \text{IL2G} * \text{ZAP70}$$

$$WCTLA4DIM = ((\text{CTLA4} * \text{CD8086}) + (\text{FOXP3} * \text{TGFB})) - ((\text{CTLA4} * \text{CD8086}) * (\text{FOXP3} * \text{TGFB}))$$

$$WBCL2 = \text{AKT}$$

$$WNDRG1 = \text{NFAT} * (1 - \text{AKT})$$

$$WDAG = \text{PLC} * \text{PIP2}$$

$$WSOS = \text{CD28}$$

$$WRASGTPR = ((\text{LAT} * \text{SOS} * \text{DAG}) + (\text{CD25} * \text{DAG})) - ((\text{LAT} * \text{SOS} * \text{DAG}) * (\text{CD25} * \text{DAG}))$$

$$WLCK = \text{TCR} * (1 - \text{CTLA4DIM})$$

$$WPK1 = (\text{CD25} + \text{CD28} + \text{PIP3}) - (\text{CD25} * \text{CD28} * \text{PIP3})$$

$$WLAT = \text{ZAP70}$$

$$WPLC = (\text{ZAP70} + \text{CD25}) - (\text{ZAP70} * \text{CD25})$$

$$WPI3K = (\text{ZAP70} + \text{CD25}) - (\text{ZAP70} * \text{CD25})$$

$$WPIP2 = (\text{PI3K} + \text{PLC}) - (\text{PI3K} * \text{PLC})$$

WPIP3 = PIP2

WIP3 = PIP2 * PLC

WCA = IP3

WPKC = DAG

WTBET = (IL33E * IL18E * IL12E * IL2E * IFNGE * MTORC1 * NFKB * NFAT * AP1 * TRP * AKG) * (1 - IL4) * (1 - IL10) * (1 - GATA3)

WIFNG = (TBET * AP1 * NFAT) * (1 - GATA3)

WGATA3 = (IL33E * IL4E * IL2E * MTORC2 * STAT5 * NFAT) * (1 - TBET) * (1 - TGFB) * (1 - IFNG) * (1 - BCL6)

WIL4 = (GATA3) * (1 - TBET) * (1 - IFNG)

WFOXP3 = (((TGFB * IL10E * NFAT * STAT5 * AP1 * IL2E) + (TGFB * IL10E * IL10 * CTLA4) + (TGFB * TGFB)) - ((TGFB * IL10E * NFAT * STAT5 * AP1 * IL2E) * (TGFB * IL10E * IL10 * CTLA4) * (TGFB * TGFB))) * (1 - IFNG) * (1 - HIF1A) * (1 - IL6E)

WIL10 = TGFB * FOXP3

WTGFB = FOXP3

WRORGT = (((IL6E * IL21E * TGFB * AP1 * MTORC1 * TRP) + (IL21E * TGFB * AP1 * MTORC1 * AKG) + (HIF1A)) - ((IL21E * TGFB * AP1 * MTORC1 * TRP) * (IL6E * IL21E * TGFB * AP1 * MTORC1 * AKG) * (HIF1A))) * (1 - TBET) * (1 - FOXP3) * (1 - GATA3)

WIL21 = (((IL21E * RORGT) + (IL6E * BCL6)) - ((IL21E * RORGT) * (IL6E * BCL6))) * (1 - IFNG) * (1 - IL4) * (1 - IL10)

WIL17 = RORGT

WBCL6 = (IL6E * IL21E * AP1 * MTORC1) * (1 - RORGT) * (1 - TBET) * (1 - GATA3)

WIL9 = BCL6

WCD40L = BCL6

WMTORC1 = (((MTOR * AKT) + (MTOR * AKG)) - ((MTOR * AKT) * (MTOR * AKG))) * (1 - AMPK) * (1 - RAPA)

WMTORC2 = ((MTOR * AMPK) + (MTOR * IL4E)) - ((MTOR * AMPK) * (MTOR * IL4E))

WLKB1 = (AKT * AMPATPratio)

WAMPK = ((LKB1 * (1 - MTORC1)) + (CA * AMPATPratio * (1 - MTORC1)) + (AKT * AMPATPratio * (1 - MTORC1)) + (FOXP3) + (BCL6) + (METF)) - ((LKB1 * (1 - MTORC1)) * (CA * AMPATPratio * (1 - MTORC1)) * (AKT * AMPATPratio * (1 - MTORC1)) * (FOXP3) * (BCL6) * (METF))

WGlycolysis = (((MTORC1 * GLC) + (HIF1A * GLC)) - ((MTORC1 * GLC) * (HIF1A * GLC))) * (1 - AMPATPratio) * (1 - BCL6)

WGLUTAMINOLISIS = GLN

WAKG = GLUTAMINOLISIS

WOXPPOS = AMPK * FA

$WAMPATPratio = Glycolysis * (1 - OXPHOS)$

$WHIF1A = Hypoxia * AKT$