

# Supplementary Information

## Boolean Update Rules for All Pathways in the BBCN118 Network

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## S1. Cell Cycle Pathway

Internal nodes (in order):

$$\{\text{CDKN2A}, \text{CCND1}, \text{E2F1}, \text{CDKN1A}, \text{RB1}, \text{TEAD1}\}.$$

Table 1: Boolean update rules for the Cell Cycle pathway (context-dependent externals  $e$ ).

Node	Update rule $x_i(t+1)$
CDKN2A	$\text{CDKN2A}' = \neg(\text{MYC} \vee \text{SRC}) \wedge \text{CASP3}.$
CCND1	$\text{CCND1}' = (\text{TCF7L2} \vee \text{TEAD1} \vee \text{MYC}) \wedge \neg(\text{GSK3B} \vee \text{CDKN2A} \vee \text{CDKN1A}).$
E2F1	$\text{E2F1}' = \neg(\text{RB1}).$
CDKN1A	$\text{CDKN1A}' = \neg(\text{MAPK1} \vee \text{AKT1} \vee \text{MYC}).$
RB1	$\text{RB1}' = \neg(\text{CCND1}).$
TEAD1	$\text{TEAD1}' = \text{YAP1}.$

## S2. Wnt Pathway

Internal nodes:

$$\{\text{APC}, \text{AXIN1}, \text{CTNNB1}, \text{DC}, \text{DVL1}, \text{FZD3}, \text{NOTCH1}, \text{RND1}, \text{TCF7L2}, \text{WNT1}\}.$$

Table 2: Boolean rules for the Wnt pathway.

Node	Update rule
APC	$\text{APC}' = \text{AXIN1}.$
AXIN1	$\text{AXIN1}' = \neg(\text{DVL1}) \wedge \text{GSK3B}.$
CTNNB1	$\text{CTNNB1}' = \neg(\text{DC}) \wedge (\text{WNT1} \vee \text{SRC} \vee \text{YAP1}).$
DC	$\text{DC}' = \text{APC} \wedge \text{GSK3B}.$
DVL1	$\text{DVL1}' = \text{FZD3} \vee \text{NF1}.$
FZD3	$\text{FZD3}' = \text{WNT1} \vee \text{CREB1}.$
NOTCH1	$\text{NOTCH1}' = \text{DLL1} \vee \text{CTNNB1} \vee \text{LCK} \vee \text{MDM2}.$
RND1	$\text{RND1}' = \text{GRB7} \vee \text{DVL1}.$
TCF7L2	$\text{TCF7L2}' = \text{CTNNB1} \vee \text{JUN}.$
WNT1	$\text{WNT1}' = \text{WNT1}.$

### S3. Apoptosis – Extrinsic Pathway

Nodes:

{FAS, FASLG, FADD, TRADD, CASP8, BID, CASP3, CASP9}.

Table 3: Boolean rules for the extrinsic apoptosis pathway.

Node	Update rule
FAS	$FAS' = FASLG.$
FASLG	$FASLG' = JUN \vee RELA \vee TP53.$
FADD	$FADD' = FAS \vee TRADD.$
TRADD	$TRADD' = FAS.$
CASP8	$CASP8' = FADD \wedge \neg(CFLAR).$
BID	$BID' = CASP8.$
CASP3	$CASP3' = (CASP8 \vee CASP9) \wedge \neg(XIAP).$
CASP9	$CASP9' = CYCS \wedge APAF1.$

### S4. Apoptosis – Intrinsic Pathway

Nodes:

{BAD, BAK1, BAX, BCL2, BCL2L1, BIM, CYCS, APAF1}.

Table 4: Boolean rules for the intrinsic apoptosis pathway.

Node	Update rule
BAD	$BAD' = \neg(PAK1 \vee AKT1 \vee MAPK1 \vee PIM).$
BAK1	$BAK1' = (BIM \vee TP53 \vee BCL2) \wedge \neg(MCL1 \vee BCL2 \vee BCL2L1).$
BAX	$BAX' = (BIM \vee TP53 \vee BCL2) \wedge \neg(MCL1 \vee BCL2 \vee BCL2L1).$
BCL2	$BCL2' = \neg(BAD \vee BIM) \wedge (CREB1 \vee MAPK1).$
BCL2L1	$BCL2L1' = \neg(BAD \vee BIM) \wedge CREB1.$
BIM	$BIM' = FOXO3 \vee FOXO1.$
CYCS	$CYCS' = BAK1 \vee BAX.$
APAF1	$APAF1' = TP53 \vee FOXO1 \vee FOXO3.$

### S5. Apoptosis – Regulatory Module

Nodes:

{MCL1, PAK1, PRKACA, SRC}.

Table 5: Boolean rules for apoptosis-regulatory nodes.

Node	Update rule
MCL1	$MCL1' = \neg(GSK3B) \wedge MAPK1.$
PAK1	$PAK1' = TCF7L2.$
PRKACA	$PRKACA' = AKT1 \vee WNT1.$
SRC	$SRC' = PRKACA \vee ABL1.$

## S6. MAPK Pathway

Nodes:

{HRAS, MAP2K1, RAF1, KRAS, SOS1, NF1, MAPK8, MAPK1, DUSP1}.

Table 6: Boolean rules for MAPK signaling.

Node	Update rule
HRAS	$HRAS' = SOS1 \wedge \neg(NF1).$
MAP2K1	$MAP2K1' = RAF1.$
RAF1	$RAF1' = HRAS \vee KRAS.$
KRAS	$KRAS' = SOS1.$
SOS1	$SOS1' = GRB2.$
NF1	$NF1' = (TP53 \vee FOXO3) \wedge \neg(MAPK1 \vee AKT1).$
MAPK8	$MAPK8' = (FAS \vee TRADD) \wedge \neg(AKT1 \vee MAPK1).$
MAPK1	$MAPK1' = MAP2K1 \wedge \neg(DUSP1).$
DUSP1	$DUSP1' = MAPK1 \vee MAPK8 \vee JUN.$

## S7. RTK Pathway

Nodes:

{EGF, EGFR, GRB2, GRB7, ERBB2, ERBB3, INS, INSR, IRS1, PI3K\_C, ABL1}.

## S8. Transcription Factor (TF) Module

Nodes:

{CEBPB, CREB1, EIF4E, GATA3, IL8, LATS1, MYC, NF2}.

Table 7: Boolean rules for RTK signaling.

Node	Update rule
EGF	$EGF' = EGF.$
EGFR	$EGFR' = (EGF \vee (ERBB2 \wedge ERBB3)) \wedge \neg(MAP2K1).$
GRB2	$GRB2' = IRS1 \vee (LATS1 \vee (EGFR \vee SRC)).$
GRB7	$GRB7' = INSR \wedge \neg(PRKACA).$
ERBB2	$ERBB2' = ERBB3 \vee EGF.$
ERBB3	$ERBB3' = NRG1 \vee ERBB2.$
INS	$INS' = INS.$
INSR	$INSR' = INS \vee FOXO3.$
IRS1	$IRS1' = \neg(S6K1) \wedge (INSR \vee IGF1R).$
PI3K_C	$PI3K_C' = GRB2 \vee IRS1.$
ABL1	$ABL1' = GRB2 \vee EGFR \vee ERBB2 \vee INSR.$

Table 8: Boolean rules for the TF module.

Node	Update rule
CEBPB	$CEBPB' = ABL2 \vee CREB1.$
CREB1	$CREB1' = AKT1 \wedge \neg(PTEN).$
EIF4E	$EIF4E' = \neg(EIF4EBP1).$
GATA3	$GATA3' = \neg(STAT1).$
IL8	$IL8' = \neg(GATA3).$
LATS1	$LATS1' = NF2 \vee LCK.$
MYC	$MYC' = (CTNNB1 \vee PIM \vee MAPK1 \vee STAT3 \vee ESR1) \wedge \neg(GSK3B).$
NF2	$NF2' = NEDD4L.$

## S9. PI3K Pathway

Nodes:

$$\{PIP3, PTEN, PDPK1, RAC1, NOS3\}.$$

## S10. AKT Pathway

Nodes:

$$\{AKT1, FOXO1, SGK1, NEDD4L, MDM2, TP53, FOXO3, JUN, GSK3B, XIAP, CFLAR\}.$$

Table 9: Boolean rules for PI3K signaling.

Node	Update rule
PIP3	$PIP3' = PI3K\_C \wedge \neg(PTEN)$ .
PTEN	$PTEN' = \neg(SRC)$ .
PDPK1	$PDPK1' = PIP3 \vee IGF1R$ .
RAC1	$RAC1' = (PI3K\_C \vee DVL1) \wedge \neg(AKT1)$ .
NOS3	$NOS3' = HSP90AA1 \vee AKT1$ .

Table 10: Boolean rules for AKT pathway nodes.

Node	Update rule
AKT1	$AKT1' = MTORC2\_C \wedge PDPK1 \wedge PIP3$ .
FOXO1	$FOXO1' = \neg(SGK1 \vee AKT1)$ .
SGK1	$SGK1' = MTORC2\_C \vee MTORC1\_C \vee PDPK1$ .
NEDD4L	$NEDD4L' = \neg(SGK1 \vee PRKACA)$ .
MDM2	$MDM2' = TP53 \vee AKT1$ .
TP53	$TP53' = \neg(MDM2)$ .
FOXO3	$FOXO3' = \neg(AKT1)$ .
JUN	$JUN' = (MAPK8 \vee MAPK1 \vee RELA) \wedge \neg(PPARG \vee DUSP1)$ .
GSK3B	$GSK3B' = \neg(AKT1 \vee MAPK1)$ .
XIAP	$XIAP' = AKT1 \vee JUN$ .
CFLAR	$CFLAR' = (AKT1 \vee RELA \vee CREB1) \wedge \neg(TP53)$ .

## S11. mTOR Pathway

Nodes:

{RHEB, MTORC1, MTORC2, TSC2, TWIST1}.

Table 11: Boolean rules for mTOR signaling.

Node	Update rule
RHEB	$RHEB' = \neg(TSC2)$ .
MTORC1	$MTORC1' = RHEB$ .
MTORC2	$MTORC2' = PIP3$ .
TSC2	$TSC2' = \neg(AKT1 \vee MAPK1) \wedge (PRKAA2 \vee GSK3B)$ .
TWIST1	$TWIST1' = MAPK1 \vee AKT1 \vee MAPK8$ .

## S12. JAK–STAT Pathway

Nodes:

{JAK2, STAT3, STAT1, SOCS3}.

Table 12: Boolean rules for JAK–STAT signaling.

Node	Update rule
JAK2	$JAK2' = IL6 \wedge IL6R.$
STAT3	$STAT3' = JAK2.$
STAT1	$STAT1' = JAK2 \wedge \neg(AKT1).$
SOCS3	$SOCS3' = STAT3 \vee STAT1.$

## S13. Others / Stemness / Notch-Related Module

Nodes:

{ABL2, DLLI, HES1, HEY1, EIF4EBP1, MYOD1, MYOG, NCID}.

Table 13: Boolean rules for the “Others” module.

Node	Update rule
ABL2	$ABL2' = ABL1.$
DLLI	$DLLI' = DLLI.$
HES1	$HES1' = NCID.$
HEY1	$HEY1' = NCID.$
EIF4EBP1	$EIF4EBP1' = \neg(MTORC1).$
MYOD1	$MYOD1' = \neg(HES1 \vee ABL1).$
MYOG	$MYOG' = \neg(HEY1) \wedge MYOD1.$
NCID	$NCID' = NOTCH1.$

## S14. Hormone Pathway

Nodes:

{ES, ESR1, KMT2D, PG, PGR}.

Table 14: Boolean rules for hormone signaling.

Node	Update rule
ES	$ES' = ES.$
ESR1	$ESR1' = AKT1 \vee FOXO3 \vee (ES \vee KMT2D \vee PGR).$
KMT2D	$KMT2D' = PAX7.$
PG	$PG' = PG.$
PGR	$PGR' = PG \wedge \neg(MAPK1 \vee ESR1).$

## S15. NF $\kappa$ B Pathway

Nodes:

$$\{IKBKB, NFKBIA, RELA\}.$$

Table 15: Boolean rules for NF $\kappa$ B signaling.

Node	Update rule
IKBKB	$IKBKB' = TNF \vee IL1 \vee TLR \vee AKT1.$
NFKBIA	$NFKBIA' = \neg(IKBKB).$
RELA	$RELA' = IKBKB \wedge \neg(NFKBIA).$