Table 1. Boolean functions of the CFL1 model. Depicted are the Boolean functions of the analyzed model. Interactions are described by logical connectives AND (∧), OR (∨), and NOT (¬). Linear interactions have been simplified by time delays ((-2) or (-3)).

Node; t + 1	Boolean Function, t	References
TCF7L2	¬PRKD1	PRKD1 inhibits TCF7L2 expression [11].
AURKA	PAK1	PAK1 phosphorylates AURKA [47–49].
Phosphorylated-CFL1	CD44 ∨ TCF7L2 ∨ (CFL1 ∧ LIMK ∧ ¬SSH1L)	TCF7L2 activates CFL1 expression [11]. CD44 induces CFL1 expression [50,51]. LIMK inhibits CFL1 [52–57]. If both, SSH1L and LIMK are active, CFL1 stays unphosphorylated [58–60].
CFL1	(SSH1L ∧ Phosphorylated-CFL1) ∨ (SSH1L ∧ LIMK ∧ Phosphorylated-CFL1)	SSH1L dephosphorylates CFL1 [12,52–54,56–58,61]. LIMK phosphorylates CFL1 [12,52,53,56,58]. If SSH1L and LIMK are present, LIMK may restore phosphorylation, but the dephosphorylation of SSH1L is more pronounced [58–60].
CD44	TWIST1	TWIST1 upregulates CD44 [62,63].
TWIST1	AURKA	AURKA inhibits degradation of TWIST1 [63].
LIMK	(RHOA ∨ PAK1 ∨ PAK4) ∧ ¬SSH1L	LIMK is activated by dephosphorylation of PAK1, PAK4 and ROCK (downstream of RHOA) [48,53,55,59,61,64–66]. LIMK and SSH1L can build a complex that effectively dephosphorylates both [59,60].
SSH1L	((F-actin$_{new}$ ∨ F-actin$_{old}$) ∧ ¬PRKD1) ∨ (PI3K ∧ AURKA) ∨ (LIMK ∧ SSH1L)	F-actin enhances SSH1L activity [52,57,59,61]. PRKD1 phosphorylates SSH1L [52,53,61]. In the presence of PI3K, AURKA induces SSH1L expression [54,56,57]. LIMK and SSH1L can build a complex that effectively dephosphorylates both [59,60].
F-actin$_{new}$	(CFL1 ∧ ARP2/3) ∨ (RHOA(-3) ∧ ¬CFL1)	CFL1 and ARP2/3 work in synergy to create new branched actin fibres [58,67–72]. RHOA/ROCK/DIA pathway polymerizes F-actin (here RHOA delay) [64,73–75].
F-actin$_{old}$	(F-actin$_{old}$ ∧ ¬CFL1) ∨ F-actin$_{new}$	CFL1 severs F-actin [52,65,67] preferring old ADP-F-actin [58,68,76,77]. Newly formed actin fibres are built, prolonged and thus converted into old ones.
ARP2/3	RAC1(-2)	Downstream of RAC1, ARP2/3 is activated by WAVE or WASP (here by a RAC1 delay) [58,64,69].
KRAS	1	Activating KRAS mutations are present in more than 90% of PDAC patients [3,46,78,79]. For this reason, the protein KRAS is assumed to be always active. Therefore, we modeled it as active (1).
PI3K	KRAS ∨ CD44	The PI3K-pathway is one of the main effector pathways downstream of RAS [80]. CD44 receptor binding activates PI3K/AKT pathway [62,81,82].
PRKD1	RHOA	RHOA activates PRKD1 [11,52,53,65].
RHOA	¬PAK4	PAK4 inhibits RHOA [83].
RAC1	PI3K ∨ Phorsphorylated-CFL1(-3)	RAC1 is activated by PI3K [54,80,84]. Phosphorylated CFL1 activates RAC1 via PLD1 and DOCK (here with delay) [85].

Table 1. *Cont.*

Node; t + 1	Boolean Function, t	References
PAK1	RAC1	PAK1 is activated by RAC1 [47,48,55,86,87].
PAK4	RAC1	PAK4 is activated by RAC1 [47,48,55].
CDH1	¬TWIST1	TWIST1 inhibits CDH1 expression [63,88–91].
CTNNB1	PAK1 ∧ ¬PRKD1 ∧ ¬CDH1	PAK1 stabilizes CTNNB1 [48,55,86,87]. CDH1 blocks CTNNB1 entering the nucleus [91–94]. PRKD1 inhibits CTNNB1 expression [11].
GSK3B	¬AKT	AKT inactivates GSK3B [56,80,95–97].
MYC	(¬GSK3B ∧ STAT3) ∨ (CTNNB1 ∧ ¬GSK3B)	STAT3 induces MYC expression [56,98–102]. GSK3B ubiquitinates MYC [103]. GSK3B blocks expression of MYC by CTNNB1 [55,94,104,105].
CCND1	(¬GSK3B ∧ MYC ∧ AKT)	GSK3B destabilizes CCND1 [96,97]. AKT supports the assembly of CCND1 with CDK4/6 [97,106–110]. MYC induces CCND1 expression [95,110–112].
RB	¬CCND1	CCND1 inhibits RB [95,96,113].
E2F	¬RB	RB inhibits E2F [95,96,113].
CCNE1	E2F	E2F induces the expression of CCNE1 [95,96].
S-phase	E2F ∧ CCNE1	The synergy of CCNE1 and E2F is responsible for S-phase transition [95,96,103].
AKT	PI3K ∧ STAT3	PI3K activates AKT [54,96,106,110,114]. STAT3 induces expression and activation of AKT [98,115–117].
STAT3	(Phosphorylated-CFL1 ∨ CFL1) ∧ CD44	CFL1 regulates amount of STAT3 [45]. CD44 activates STAT3 [56,118].
Anti-apoptotic proteins	STAT3	STAT3 induces expression of BCL2L1 or MCL1 [99–102,119].
Pro-apoptotic proteins	¬AKT	AKT phosphorylates BAD [119–121].
CYCS	Pro-apoptotic proteins ∧ ¬Anti-apoptotic proteins ∧ CFL1	Imbalance between pro- and anti-apoptotic proteins induce release of CYCS by activating BAX. Unphosphorylated CFL1 translocates to the mitochondrion after induction of apoptosis [122–125] and acts as a carrier for BAX [126].
Caspases	CYCS ∧ ¬AKT	Released CYCS forms an apoptosome further activating caspases signalling [119,120,122,124,127–129]. AKT phosphorylates caspase-9 [119–121].

Abbreviations: ∧ = and; ∨ = or; ¬ = not; (-2) = time delay of two time steps; (-3) = time delay of three time steps; ADP = Adenosine diphosphate; AKT = protein kinase B; ARP2/3 = actin-related protein-2/3 complex; AURKA = aurora kinase A; Anti-apoptotic proteins = [pooled BAD (=Bcl2-antagonist of cell death), BAX (=Bcl-2-associated X protein), BAK (=Bcl2-anatgonist/killer)]; APAF-1 = apoptotic peptidase activating factor 1; Caspases = pooled caspase-3 and caspase-9 with their corresponding pro-caspases; CCND1 = Cyclin D1; CCNE1 = Cyclin E1; CDH1 = E-cadherin; CD44 = CD44 antigen; CDK4/6 = cyclin dependent kinase 4/6; CFL1 = cofilin-1; CTNNB1 = β-catenin; CYCS = Cytochrome C; DIA = diaphanous related formin; DOCK = dedictor of cytokinesis; E2F = E2F transcription factor; GSK3B = glycogen synthase kinase 3β; KRAS = Kirsten rat sarcoma oncogene; LIMK = LIM domain kinase; MYC = MYC proto-oncogene; PAK1 = p21 activated kinase 1; PAK4 = p21 activated kinase 4; RAC1 = ras-related botulinum toxin substrate 1; RB = retinoblastoma protein; RHOA = ras homolog family member A; PI3K = phosphoinositide-3-kinase; PLD1 = phospholipase D1; PRDK1 = protein kinase D1; Pro-apoptotic proteins = [BCL2L1 (=Bcl2-like 1), MCL1 (=myeloid leukemia cell differentiation protein)]; RAS = rat sarcoma; ROCK = Rho-associated protein kinase; SSH1L = slingshot protein phosphatase 1; STAT3 = signal transducer and activator of transcription 3; TCF7L2 = transcription factor 7-like 2; TWIST1 = twist family BHLH transcription factor 1, WASP = Wiskott-Adrich syndrome protein; WAVE = Verpolin-homologous protein.