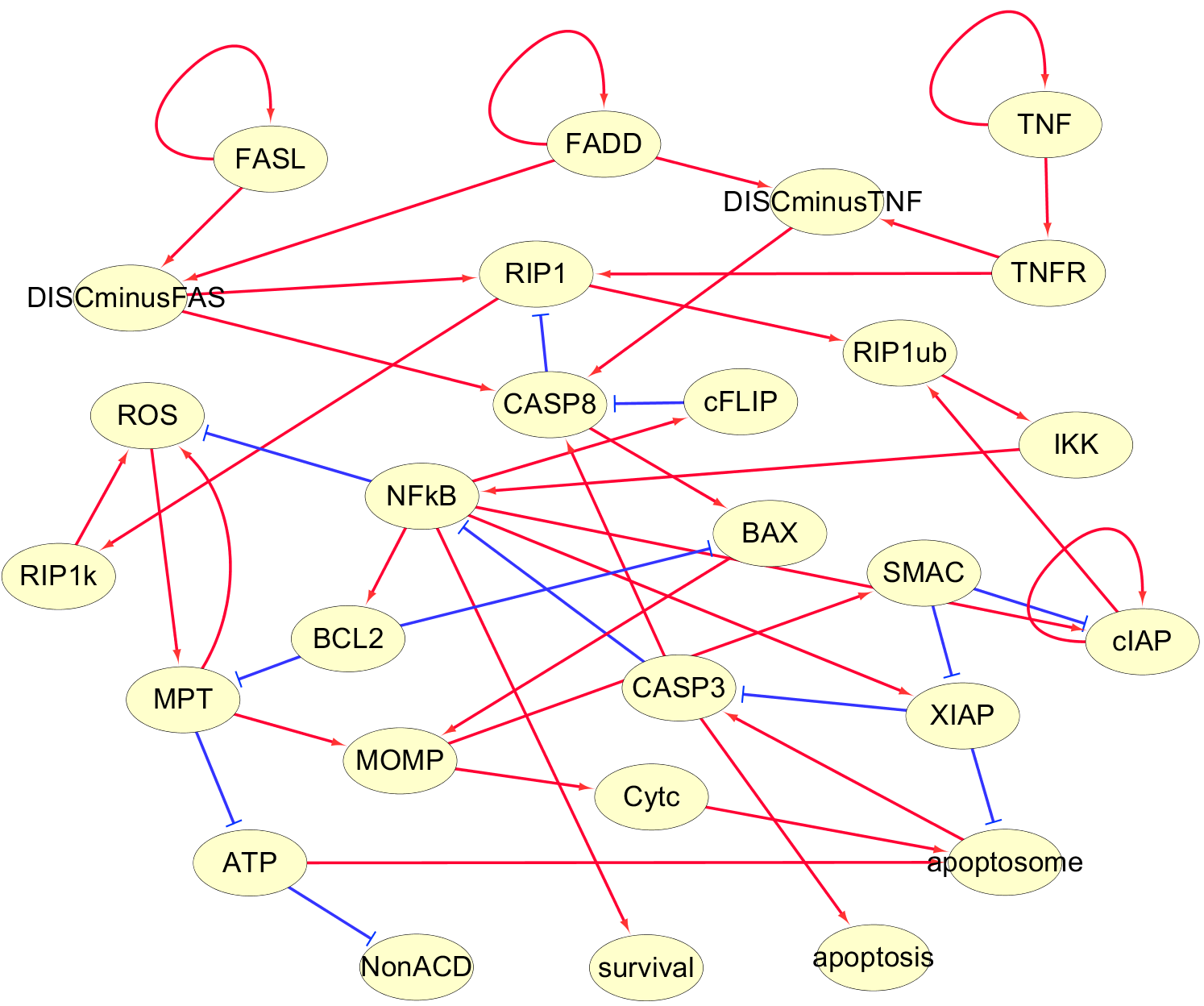
**Table S1.** Detailed experimental results on attractor-transition control of random complex BNs.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Point to point** | | | | | | | | |
| **Number of elements in control inputs** | | | | | | | | |
| Network size | Average | | | | 95% confidence interval | | | |
| Proposed  algorithm | One-step control | Stable motif control | FVS control | Proposed  algorithm | One-step control | Stable motif control | FVS control |
| node\_010 | 1.63 | 1.3 | 2.64 | 4.64 | 0.148311 | 0.095639 | 0.204385 | 0.183901 |
| node\_020 | 1.86 | 1.285714 | 2.602041 | 6.091837 | 0.195433 | 0.103798 | 0.214931 | 0.225004 |
| node\_030 | 2.11 | 1.463918 | 3.051546 | 7.463918 | 0.197205 | 0.120161 | 0.19158 | 0.265125 |
| node\_040 | 2.08 | 1.5 | 3.5 | 8.5 | 0.212325 | 0.135794 | 0.741952 | 0.453008 |
| node\_050 | 2.22 | 1.54717 | N/A | 9.733333 | 0.226639 | 0.183839 | N/A | 0.476751 |
| **Computational time (secs)** | | | | | | | | |
| Network size | Average | | | | 95% confidence interval | | | |
| Proposed  algorithm | One-step control | Stable motif control | FVS control | Proposed  algorithm | One-step control | Stable motif control | FVS control |
| node\_010 | 0.029199 | 0.08825 | 7.228399 | 0.010599 | 0.001333 | 0.002844 | 2.399274 | 0.000727 |
| node\_020 | 0.052899 | 0.488541 | 28.55952 | 0.356635 | 0.005025 | 0.088113 | 16.43326 | 0.102527 |
| node\_030 | 0.213739 | 99.73753 | 2084.96 | 39.13659 | 0.203003 | 181.8864 | 1295.758 | 17.51666 |
| node\_040 | 0.427908 | 382.2998 | 5652.155 | 2024.485 | 0.336508 | 166.4318 | 9307.556 | 1065.48 |
| node\_050 | 2.558455 | 6820.283 | N/A | 23094.53 | 3.416093 | 2976.547 | N/A | 7406.768 |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Point to cycle** | | | | | | | | |
| **Number of elements in control inputs** | | | | | | | | |
| Network size | Average | | | | 95% confidence interval | | | |
| Proposed  algorithm | One-step control | Stable motif control | FVS control | Proposed  algorithm | One-step control | Stable motif control | FVS control |
| node\_010 | 1.31 | 1.360825 | 2 | N/A | 0.108111 | 0.105633 | 0.181228 | N/A |
| node\_020 | 1.75 | 1.488889 | 2.241379 | N/A | 0.160469 | 0.141268 | 0.232031 | N/A |
| node\_030 | 1.78 | 1.549451 | 2.270588 | N/A | 0.190403 | 0.128993 | 0.206212 | N/A |
| node\_040 | 1.7 | 1.428571 | 2.603175 | N/A | 0.165652 | 0.131706 | 0.24997 | N/A |
| node\_050 | 1.62 | 1.5 | N/A | N/A | 0.151298 | 0.135513 | N/A | N/A |
| **Computational time (secs)** | | | | | | | | |
| Network size | Average | | | | 95% confidence interval | | | |
| Proposed  algorithm | One-step control | Stable motif control | FVS control | Proposed  algorithm | One-step control | Stable motif control | FVS control |
| node\_010 | 0.016675 | 0.060598 | 5.813827 | N/A | 0.000981 | 0.008787 | 2.192466 | N/A |
| node\_020 | 0.027392 | 0.645689 | 24.56716 | N/A | 0.001705 | 0.14492 | 17.08657 | N/A |
| node\_030 | 0.036949 | 24.96004 | 913.2133 | N/A | 0.001905 | 13.56912 | 769.3241 | N/A |
| node\_040 | 0.046575 | 652.4675 | 2882.806 | N/A | 0.002492 | 374.5864 | 2520.818 | N/A |
| node\_050 | 0.059757 | 13842 | N/A | N/A | 0.003025 | 5643.747 | N/A | N/A |

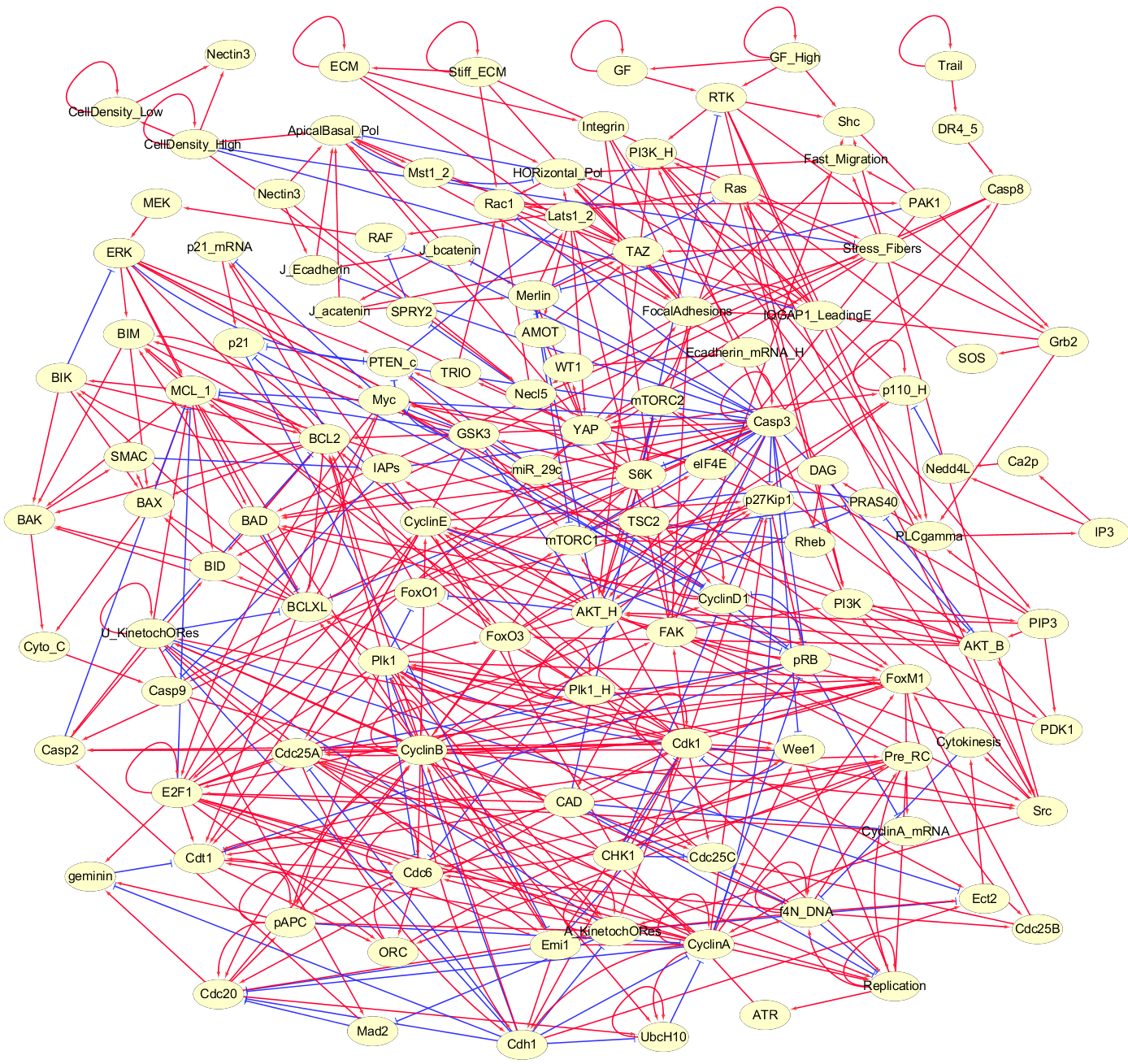
**Fig. S1.** Connectivity graph of the death receptor signaling network [38], where red edges with arrows represent activation and blue ones with bars inhibition.

****

**Table S2.** Boolean logic rules provided in the .bnet file format for the death receptor signaling network.

|  |
| --- |
| FADD = FADD  FASL = FASL  TNF = TNF  ATP = ~MPT  BAX = ~BCL2 & CASP8  BCL2 = NFkB  CASP3 = ~XIAP & apoptosome  CASP8 = DISCminusTNF & ~cFLIP | DISCminusFAS & ~cFLIP | CASP3 & ~cFLIP  Cytc = MOMP  DISCminusFAS = FADD & FASL  DISCminusTNF = FADD & TNFR  IKK = RIP1ub  MOMP = MPT | BAX  MPT = ~BCL2 & ROS  NFkB = ~CASP3 & IKK  RIP1 = ~CASP8 & TNFR | ~CASP8 & DISCminusFAS  RIP1k = RIP1  RIP1ub = RIP1 & cIAP  ROS = ~NFkB & RIP1k | MPT & ~NFkB  SMAC = MOMP  TNFR = TNF  XIAP = NFkB & ~SMAC  apoptosome = ATP & Cytc & ~XIAP  cFLIP = NFkB  cIAP = ~SMAC & cIAP | NFkB & ~SMAC  NonACD = ~ATP  apoptosis = CASP3  survival = NFkB |

**Fig. S2.** Connectivity graph of the cell cycle/apoptosis network [39], where red edges with arrows represent activation and blue ones with bars inhibition.



**Table S3.** Boolean logic rules provided in the .bnet file format for the cell cycle/apoptosis network.

|  |
| --- |
| CellDensity\_High = CellDensity\_High  CellDensity\_Low = CellDensity\_Low | CellDensity\_High  Stiff\_ECM = Stiff\_ECM  ECM = ECM | Stiff\_ECM  GF\_High = GF\_High  GF = GF | GF\_High  RTK = ~CAD & (GF\_High | GF)  Shc = RTK & GF\_High & (FAK | Src)  Grb2 = Shc & RTK  SOS = Grb2  Ras = Grb2 & SOS & Src & (IQGAP1\_LeadingE | (~Merlin) )  RAF = ~Casp3 & Ras & (~SPRY2)  MEK = RAF  ERK = MEK & ~BIK  mTORC2 = PIP3 | ~S6K  PI3K = (FAK | Src) & (Ras | RTK)  PIP3 = PI3K\_H | PI3K  PDK1 = PI3K & PIP3  AKT\_B = ~Casp3 & PIP3 & (PDK1 | mTORC2)  p110\_H = YAP & ((FoxO3 & ~Nedd4L) | (p110\_H & (FoxO3 | ~Nedd4L) ) )  PI3K\_H = (~PTEN\_c) & p110\_H & RTK & PI3K & Ras  AKT\_H = AKT\_B & p110\_H & PI3K\_H & PIP3 & PDK1 & mTORC2 & (Ras | PAK1)  FoxO3 = ~(AKT\_B | AKT\_H | ERK) | ( ~(AKT\_H & (Plk1 | Plk1\_H | AKT\_B | ERK) ) & ~(Plk1 & Plk1\_H & ERK) )  PLCgamma = RTK & Grb2 & p110\_H & PI3K\_H & PIP3  IP3 = PLCgamma  Ca2p = IP3  Nedd4L = Ca2p & IP3  FoxO1 = ~Plk1 & ~AKT\_H  p21\_mRNA = (FoxO1 & FoxO3) | (~Myc & (FoxO1 | FoxO3) )  TSC2 = ~AKT\_H | ~(AKT\_B | ERK)  PRAS40 = ~AKT\_H & (~mTORC1 | ~AKT\_B)  DAG = PLCgamma  Rheb = ~TSC2 & DAG  mTORC1 = ~Casp3 & ( (Rheb & ~PRAS40 & ~Merlin) | E2F1 | (CyclinB & Cdk1 & GSK3) )  S6K = ~Casp3 & mTORC1  eIF4E = ~Casp3 & mTORC1  GSK3 = ~AKT\_H & ~(S6K & ERK)  Integrin = ECM  FAK = ~Casp3 & ~(Cdk1 & CyclinB) & Integrin  Src = (Integrin & (RTK | FAK) ) | (Cdk1 & CyclinB)  Nectin3 = CellDensity\_Low | CellDensity\_High  Necl5 = FocalAdhesions | ~(Nectin3 & CellDensity\_High)  SPRY2 = ~Necl5  J\_Ecadherin = ~Casp3 & Nectin3  J\_bcatenin = ~Casp3 & J\_Ecadherin  J\_acatenin = J\_bcatenin  FocalAdhesions = Integrin & FAK & ECM & (Stiff\_ECM | (YAP & Rac1 & IQGAP1\_LeadingE))  Stress\_Fibers = ~CellDensity\_High & Stiff\_ECM & FocalAdhesions  YAP = FocalAdhesions & Stress\_Fibers & ~(ApicalBasal\_Pol & J\_acatenin & AMOT & Merlin & Lats1\_2)  TRIO = YAP  WT1 = YAP  TAZ = Stress\_Fibers & ~(ApicalBasal\_Pol & J\_acatenin & AMOT & Merlin & Lats1\_2)  Ecadherin\_mRNA\_H = ~(YAP & WT1)  ApicalBasal\_Pol = CellDensity\_High & Nectin3 & J\_Ecadherin & J\_bcatenin & J\_acatenin & (Ecadherin\_mRNA\_H | ~HORizontal\_Pol)  Mst1\_2 = ApicalBasal\_Pol  Lats1\_2 = Mst1\_2 & Merlin  AMOT = Lats1\_2 & Merlin  Merlin = J\_bcatenin & J\_acatenin & (~PAK1) & (~AKT\_H)  IQGAP1\_LeadingE = ~CellDensity\_High & FocalAdhesions & (HORizontal\_Pol | Rac1 | Grb2)  HORizontal\_Pol = ~ApicalBasal\_Pol & ECM & IQGAP1\_LeadingE & FocalAdhesions & TAZ & FAK  Rac1 = ~Casp3 & Stiff\_ECM & FocalAdhesions & Necl5 & HORizontal\_Pol & TRIO  PAK1 = Rac1  Fast\_Migration = HORizontal\_Pol & Stress\_Fibers & FocalAdhesions & PAK1  miR\_29c = YAP  PTEN\_c = ~miR\_29c & ( (S6K & ~(ERK & GSK3) ) | (~ERK & ~GSK3) )  p21 = p21\_mRNA & ~Casp3 & ~CyclinE  pRB = ~Casp3 & ~CyclinD1 & ~CyclinA & (p27Kip1 | ~CyclinE)  p27Kip1 = ~Casp3 & ~CyclinD1 & ~(Cdk1 & CyclinB) & ( (~(CyclinA & Necl5 & CyclinE) & (FoxO3 & FoxO1) ) | ( (~CyclinA | ~(Necl5 | CyclinE)) & (FoxO3 | FoxO1) ) | (~CyclinA & ~(Necl5 & CyclinE) ) )  Myc = ( ERK & YAP ) | ( (ERK | YAP) & (eIF4E & ~GSK3) ) | ( E2F1 & (~pRB) & (eIF4E | ERK | ~GSK3) )  CyclinD1 = ~CHK1 & ( ( ~p21 & ( (~GSK3 & YAP & (Myc | E2F1) ) | (CyclinD1 & YAP & (Myc | E2F1 ) | (Myc & E2F1) ) ) ) | ( ~pRB & E2F1 & ( (Myc & CyclinD1) | (Myc & ~GSK3) | (YAP & CyclinD1 & ~GSK3) ) ) )  E2F1 = ~(CAD | CyclinA | pRB) & ( (YAP & (E2F1 | Myc)) | (E2F1 & Myc) )  CyclinE = E2F1 & Cdc6 & Pre\_RC & ~(pRB | p27Kip1 | CHK1 | Casp3)  ORC = E2F1 | (Pre\_RC & Cdt1 & Cdc6)  Cdc6 = ~Casp3 & ~(f4N\_DNA & CyclinA) & ( (E2F1 & ORC & ~Plk1) | (Pre\_RC & ORC & Cdc6 & Cdt1) )  Cdt1 = ~geminin & ORC & Cdc6 & ~(CyclinE & CyclinA & Cdc25A) & ( (Pre\_RC & (E2F1 | Myc) ) | (E2F1 & (Myc | ~pRB) ) )  Pre\_RC = ORC & Cdc6 & Cdt1 & ~(Replication & f4N\_DNA)  geminin = E2F1 & ~Cdh1 & ~(pAPC & Cdc20)  CyclinA\_mRNA = ~CAD & ( (E2F1 & ~pRB) | FoxM1 )  Emi1 = (E2F1 | ~pRB | ~p21) & ~(Plk1 & CyclinB & Cdk1 & (U\_KinetochORes | A\_KinetochORes) )  FoxM1 = ((Myc | YAP) & CyclinE) | (CyclinA & Cdc25A & Cdc25B) | (Plk1 & CyclinB & Cdk1)  Cdc25A = ( (FoxM1 & E2F1 & ~pRB) | (~Cdh1 & (FoxM1 | (E2F1 & ~pRB) ) ) ) & (~(GSK3 | CHK1) | CyclinE | CyclinA | (CyclinB & Cdk1) )  CyclinA = CyclinA\_mRNA & ~pAPC & ( (Cdc25A & (~Cdh1 | Emi1) ) | (CyclinA & ( (~Cdh1 & (Emi1 | ~UbcH10) ) | (Emi1 & ~UbcH10) ) ) )  Wee1 = ~Casp3 & ~(Cdk1 & CyclinB) & (Replication | CHK1) & (CHK1 | ~(Cdk1 & CyclinA & Plk1) )  UbcH10 = ~Cdh1 | (UbcH10 & (Cdc20 | CyclinA | CyclinB) )  CyclinB = (FoxM1 | (FoxO3 & CyclinB) ) & ~(Cdh1 | (pAPC & Cdc20) )  Cdc25B = FoxM1 & f4N\_DNA  Plk1 = ~Cdh1 & (FoxM1 | Plk1\_H) & ( (CyclinB & Cdk1) | (CyclinA & ~Wee1 & Cdc25A) )  Cdc25C = f4N\_DNA & Plk1 & ( (Cdc25B & ~CHK1) | (CyclinB & Cdk1) )  Cdk1 = CyclinB & Cdc25C & ( ~CHK1 | (~Wee1 & Cdk1) )  pAPC = (CyclinB & Cdk1 & Plk1) | (CyclinB & Cdk1 & pAPC) | (pAPC & Cdc20)  Cdc20 = pAPC & ~Emi1 & ~Cdh1 & ( ~Mad2 | ( ~CyclinA & ~(CyclinB & Cdk1) ) )  Cdh1 = ~(CyclinB & Cdk1) & ~( CyclinA & (Emi1 | Cdc25A) )  Replication = ~CAD & Pre\_RC & ( (E2F1 & CyclinE & Cdc25A) | (Replication & CyclinA & Cdc25A & (E2F1 | ~f4N\_DNA) ) )  ATR = Replication  CHK1 = ATR  f4N\_DNA = ~CAD & ( (Replication & ( (Pre\_RC & CyclinA) | f4N\_DNA) ) | (f4N\_DNA & ~Cytokinesis) )  U\_KinetochORes = f4N\_DNA & ~Cdh1 & ~A\_KinetochORes & ( (CyclinB & Cdk1) | U\_KinetochORes )  Mad2 = U\_KinetochORes & ~A\_KinetochORes  A\_KinetochORes = f4N\_DNA & ~Cdh1 & ~(pAPC & Cdc20) & ( A\_KinetochORes | (U\_KinetochORes & Src & Plk1 & CyclinB & Cdk1) )  Plk1\_H = Plk1 & FoxM1 & (Plk1\_H | FoxO3 | FoxO1)  Ect2 = f4N\_DNA & Plk1\_H & Cdh1 & ~U\_KinetochORes & ~A\_KinetochORes  Cytokinesis = Ect2 & FAK & Src  Trail = Trail  DR4\_5 = Trail  Casp8 = DR4\_5 | Casp3  Casp2 = Casp3 | (U\_KinetochORes & Mad2 & ~(CyclinB & Cdk1) )  MCL\_1 = ~Casp3 & ~Casp2 & (~GSK3 | (AKT\_B & (ERK | ~E2F1) ) ) & (~(Cdk1 & CyclinB & U\_KinetochORes) )  BCLXL = ~Casp3 & (BCL2 | ~BAD) & ( ~U\_KinetochORes | ( Plk1 & ( ~(CyclinB & Cdk1) | (BCL2 & MCL\_1) ) ) | ( (BCL2 & MCL\_1) & ~(CyclinB & Cdk1) ) )  BCL2 = ~(Casp3 | BAD | BIM | BIK) & ( ~U\_KinetochORes | (MCL\_1 & BCLXL) | (Plk1 & (BCLXL | MCL\_1 | ~(Cdk1 & CyclinB) ) ) )  BAD = Casp3 | ~(AKT\_H | AKT\_B | ERK | S6K) | ( Casp8 & (~(AKT\_B & ERK & S6K) & ~(AKT\_H & (AKT\_B | ERK) ) ) )  BIK = ~(MCL\_1 | BCLXL | BCL2)  BIM = FoxO3 & GSK3 & ~(ERK | MCL\_1 | BCLXL | BCL2)  BID = Casp8 | ( Casp2 & ~(BCL2 | BCLXL | MCL\_1) )  BAK = (BID & (BIM | BIK | ~(BCL2 & BCLXL & MCL\_1) ) ) | ( (BIM | BIK) & ~(BCLXL | MCL\_1) )  BAX = (BIM & ( (BID | BIK) | ~(BCL2 & BCLXL & MCL\_1) ) ) | ( (BID | BIK) & ~(BCL2 | BCLXL) )  Cyto\_C = BAX | BAK  SMAC = BAX | BAK  IAPs = ~SMAC | AKT\_H  Casp9 = Casp3 | (~IAPs & Cyto\_C)  Casp3 = (Casp9 & Casp8) | ( Casp3 & (Casp9 | Casp8) ) | ( ~IAPs & (Casp9 | Casp8 | Casp3) )  CAD = Casp3 & Casp9 |

**Table S4.** Control input sets provided by all the applied methods for attractor-transition control of the death receptor signaling network and the cell cycle/apoptosis network.

|  |  |
| --- | --- |
| **Control input sets for the death receptor signaling network** | |
| **Proposed algorithm** | '!MPT&CASP8', 'CASP8&!ROS', '!MPT&!IKK', '!IKK&!ROS', '!MPT&!NFkB', '!MPT&!RIP1', '!MPT&!RIP1ub', '!MPT&!cFLIP', '!NFkB&!ROS', '!RIP1&!ROS', '!RIP1ub&!ROS', '!cFLIP&!ROS' |
| **One-step control** | '!RIP1k&!cFLIP', 'MOMP&!RIP1k', '!NFkB&!RIP1k', 'CASP8&!RIP1k', '!RIP1k&SMAC', 'BAX&!RIP1k', '!RIP1k&!RIP1ub', 'CASP3&!RIP1k', '!RIP1&!RIP1k', '!RIP1k&!cIAP', '!IKK&!RIP1k' |
| **Stable motif control** | 'FADD&FASL&!MPT&!TNF&!cIAP', 'FADD&FASL&!ROS&!TNF&!cIAP',  'FADD&FASL&!IKK&!MPT&!TNF',  'FADD&FASL&!IKK&!ROS&!TNF',  'FADD&FASL&!MPT&!RIP1ub&!TNF',  'FADD&FASL&!RIP1ub&!ROS&!TNF',  'FADD&FASL&!MPT&!NFkB&!TNF',  'FADD&FASL&!NFkB&!ROS&!TNF',  'FADD&FASL&!MPT&!RIP1&!TNF',  'FADD&FASL&!RIP1&!ROS&!TNF',  'FADD&FASL&!MPT&!TNF&!cFLIP',  'FADD&FASL&!ROS&!TNF&!cFLIP',  'CASP8&FADD&FASL&!MPT&!TNF',  'CASP8&FADD&FASL&!ROS&!TNF',  'BAX&FADD&FASL&!MPT&!TNF',  'CASP3&FADD&FASL&!MPT&!TNF',  'FADD&FASL&MOMP&!MPT&!TNF',  'BAX&FADD&FASL&!ROS&!TNF',  'CASP3&FADD&FASL&!ROS&!TNF',  'FADD&FASL&MOMP&!ROS&!TNF' |
| **FVS control** | 'BAX&FADD&FASL&!MPT&!NFkB&!TNF&!cIAP', 'BAX&FADD&FASL&!NFkB&!ROS&!TNF&!cIAP', 'CASP3&CASP8&FADD&FASL&!MPT&!TNF&!cIAP', 'CASP3&CASP8&FADD&FASL&!ROS&!TNF&!cIAP', 'CASP3&FADD&FASL&!IKK&!MPT&!TNF&!cIAP', 'CASP3&FADD&FASL&!IKK&!ROS&!TNF&!cIAP', 'CASP3&FADD&FASL&!MPT&!NFkB&!TNF&!cIAP', 'CASP3&FADD&FASL&!MPT&!RIP1&!TNF&!cIAP', 'CASP3&FADD&FASL&!MPT&!RIP1ub&!TNF&!cIAP', 'CASP3&FADD&FASL&!MPT&!TNF&!cFLIP&!cIAP', 'CASP3&FADD&FASL&!NFkB&!ROS&!TNF&!cIAP', 'CASP3&FADD&FASL&!RIP1&!ROS&!TNF&!cIAP', 'CASP3&FADD&FASL&!RIP1ub&!ROS&!TNF&!cIAP', 'CASP3&FADD&FASL&!ROS&!TNF&!cFLIP&!cIAP', 'CASP8&FADD&FASL&!MPT&!NFkB&!TNF&!cIAP', 'CASP8&FADD&FASL&!NFkB&!ROS&!TNF&!cIAP', 'FADD&FASL&MOMP&!MPT&!NFkB&!TNF&!cIAP', 'FADD&FASL&MOMP&!NFkB&!ROS&!TNF&!cIAP' |
| **Control input sets for the cell cycle/apoptosis network** | |
| **Proposed algorithm** | ('Casp3&!Cdc25C', 'Casp3&Cdh1', 'Casp3&!Cdk1', 'Casp3&!Plk1') |
| **One-step control** | N/A |
| **Stable motif control** | N/A |
| **FVS control** | N/A |

**Table S5.** Biological supporting evidences of the key control inputs identified by the proposed algorithm.

|  |  |
| --- | --- |
| **Complex biological networks** | **Biological supporting evidences** |
| **Death receptor signaling** | IKK inhibition leads to the repression of NFkB activity, which is a principal survival factor in this model. Moreover, constitutively activated CASP8 can lead to the suppression of NFkB activation.  In the model, ROS or MPT inhibition makes the escape of non-apoptotic cell death (called necrosis), because each inhibition can maintain a high level of ATP. A high level of ATP induces CASP3 activation, which is a key component for apoptosis (PMID: 16006727).  Thus, simultaneously perturbations of these combinatorial targets are effective to repress the survival phenotype, thereby inducing the apoptosis phenotype. |
| **Cell cycle/apoptosis** | Cdc25C plays a critical role in cell cycle progression, specifically during the G2 to M phase transition (PMID: 32518522).  Cdk1 (Cyclin-dependent kinase 1) is another key regulatory protein that forms complexes with different cyclin partners to control various cell cycle transitions (PMID: 32183020).  Plk1 is involved in multiple stages of the cell cycle and shows high activity during the G2 and M phases (PMID: 28953239). In the context of cancer treatment, inhibiting these molecules is effective to halt or interfere with cell cycle progression, which is often dysregulated in cancer cells.  In the same reason, Cdh1 corresponds to APC/Cdh1 (PMID: 31000600), and its activation can induce the same effect of Plk1 inhibition in this model.  Lastly, Casp3 is a key component of the caspase cascade, which is a crucial pathway for executing apoptosis (PMID: 23834359).  In summary, increasing levels of mitogenic stimulation (GFHigh) lead to cell cycle entry in cells. Under such constitutively activated input stimulus, our suggested targets (combinatorial targets with Casp3 activation) are effective in converging into an apoptosis phenotype, thereby escaping the cell cycle phenotype. |