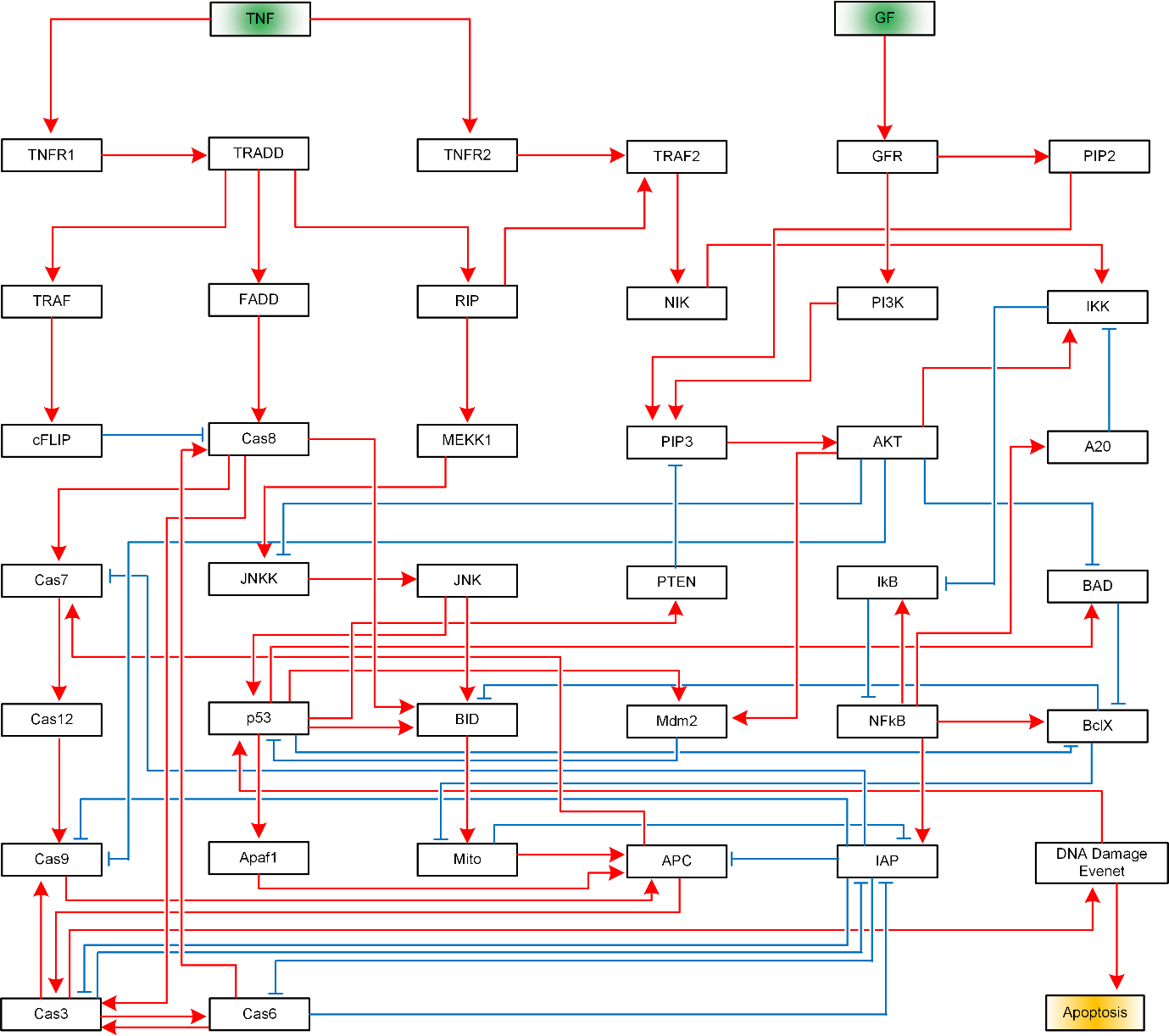
**Table S1.** Detailed experimental results on output stabilization of complex random BNs.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Number of elements in control inputs** | | | | | | |
| Network size | Average (±95% confidence interval) | | | | | |
| Proposed algorithm | Logical DOI | Phenotype CK | Stable motifs | FVS | BN simple reduction |
| node 20 | 1.64 (±0.1246) | 1.55 (±0.1106) | 1.32 (±0.093) | 1.86 (±0.1596) | 4.19 (±0.2047) | 2.27 (±0.1434) |
| node 30 | 1.65 (±0.1421) | 1.38 (±0.1047) | N/A | 1.86 (±0.1621) | 5.31 (±0.302) | 2.4 (±0.1595) |
| node 40 | 1.58 (±0.1415) | 1.27 (±0.1011) | N/A | 1.96 (±0.1804) | 5.82 (±0.347) | 2.61 (±0.2032) |
| node 50 | 1.6 (±0.1261) | 1.33 (±0.0979) | N/A | N/A | N/A | 2.7 (±0.2043) |
| node 60 | 1.68 (±0.1407) | 1.35 (±0.1069) | N/A | N/A | N/A | 2.89 (±0.1869) |
| node 70 | 1.77 (±0.1257) | 1.33 (±0.0938) | N/A | N/A | N/A | 2.76 (±0.1808) |
| node 80 | 1.75 (±0.1529) | 1.33 (±0.1019) | N/A | N/A | N/A | 3.06 (±0.178) |
| node 90 | 1.75 (±0.1364) | 1.34 (±0.1063) | N/A | N/A | N/A | 3.09 (±0.1915) |
| node 100 | 1.73 (±0.1488) | 1.34 (±0.1063) | N/A | N/A | N/A | 3.05 (±0.2263) |
| **Computational time (secs)** | | | | | | |
| Network size | Average (±95% confidence interval) | | | | | |
| Proposed algorithm | Logical DOI | Phenotype CK | Stable motifs | FVS | BN simple reduction |
| node 20 | 1.2319 (±0.2075) | 1.1848 (±0.1409) | 3.1946 (±1.2713) | 1.6656 (±1.0566) | 0.0785 (±0.0292) | 0.0426 (±0.0031) |
| node 30 | 3.2925 (±0.7892) | 3.1853 (±0.4449) | N/A | 15.9457 (±13.12) | 5.2242 (±2.613) | 0.14 (±0.0658) |
| node 40 | 4.2041 (±0.643) | 6.4332 (±1.0065) | N/A | 331.2181 (±432.584) | 146.6484 (±159.2632) | 0.2454 (±0.0764) |
| node 50 | 5.8572 (±1.0755) | 11.845 (±1.78) | N/A | N/A | N/A | 1.5443 (±1.0675) |
| node 60 | 6.7569 (±1.1522) | 18.8316 (±2.9274) | N/A | N/A | N/A | 13.4116 (±20.3484) |
| node 70 | 9.3353 (±1.3953) | 26.9846 (±4.5457) | N/A | N/A | N/A | 2.7217 (±0.9547) |
| node 80 | 12.6747 (±1.9207) | 34.3801 (±5.5428) | N/A | N/A | N/A | 147.5445 (±182.1626) |
| node 90 | 12.7573 (±1.9496) | 48.1833 (±6.941) | N/A | N/A | N/A | 403.3321 (±411.5167) |
| node 100 | 15.6761 (±2.7037) | 65.764 (±10.2845) | N/A | N/A | N/A | 309.3599 (±424.7023) |

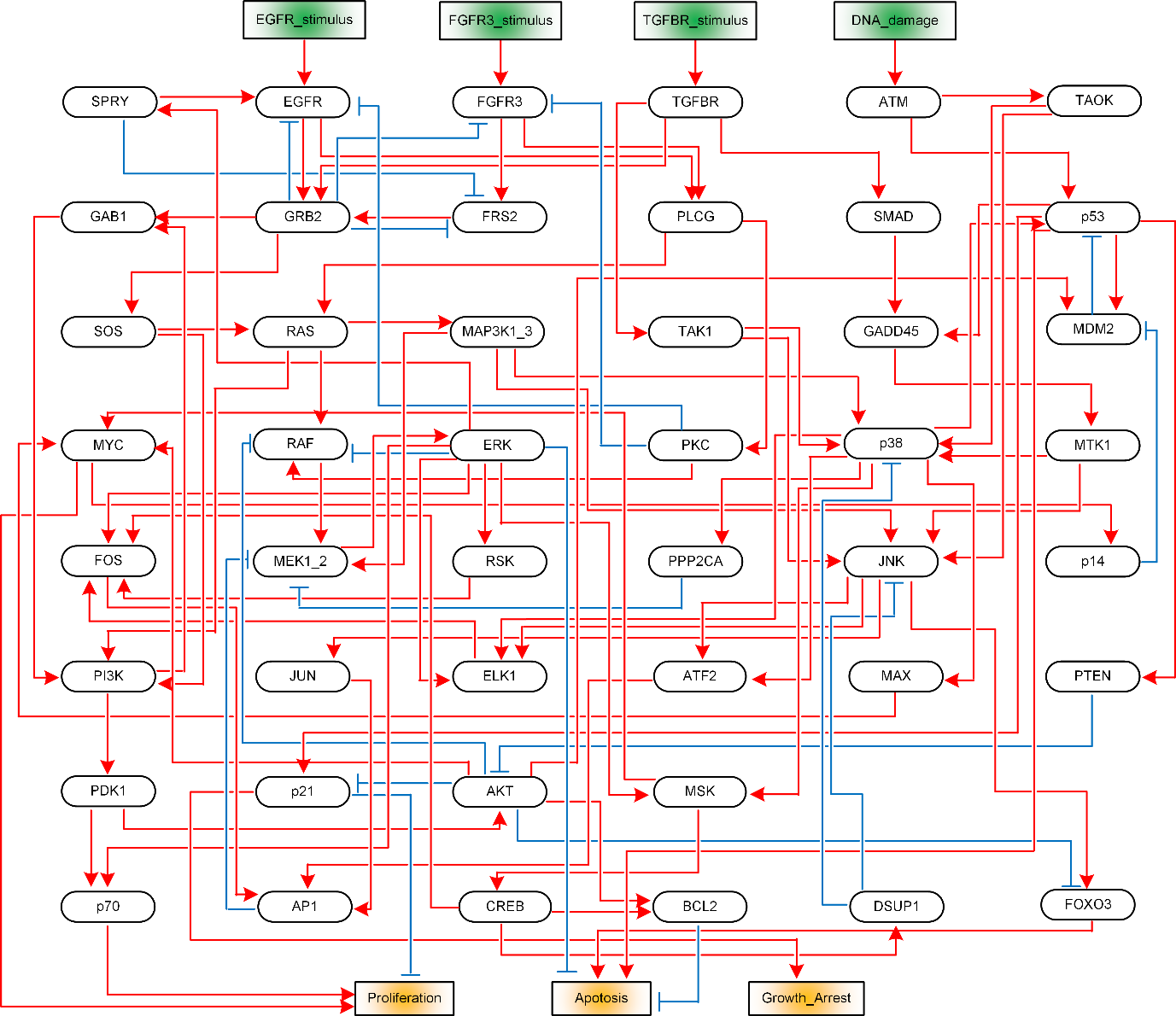
**Fig. S1.** Connectivity graph of the cellular apoptosis network [33], where red edges with arrows represent activation and blue ones with bars inhibition.

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**Table S2.** Boolean logic rules of the cellular apoptosis network.

TNFR1 = TNF  
Cas8 = (Cas6 & ~cFLIP) | (FADD & ~cFLIP)  
cFLIP = TRAF  
Cas3 = (APC & ~IAP) | (Cas6 & ~IAP) | (Cas8 & ~IAP)  
PTEN = p53  
Cas6 = Cas3 & ~IAP  
NFkB = ~IkB  
TRAF2 = RIP | TNFR2  
BclX = NFkB & ~BAD & ~p53  
RIP = TRADD  
A20 = NFkB  
PI3K = GFR  
JNKK = MEKK1 & ~AKT  
AKT = PIP3  
DNADamageEvent = Cas3  
Cas9 = (Cas12 & ~AKT & ~IAP) | (Cas3 & ~AKT & ~IAP)  
TNFR2 = TNF  
PIP2 = GFR  
TRAF = TRADD  
BID = (Cas8 & p53 & ~BclX) | (JNK & p53 & ~BclX)  
APC = Apaf1 & Cas9 & Mito & ~IAP  
TRADD = TNFR1  
MEKK1 = RIP  
Mdm2 = AKT | p53  
Apaf1 = p53  
JNK = JNKK  
IKK = (AKT & ~A20) | (NIK & ~A20)  
BAD = p53 & ~AKT  
Cas12 = Cas7  
GFR = GF  
IAP = (NFkB & ~Cas3 & ~Mito) | (NFkB & ~Cas6 & ~Mito)  
Cas7 = (APC & ~IAP) | (Cas8 & ~IAP)  
NIK = TRAF2  
FADD = TRADD  
Mito = BID & ~BclX  
p53 = (DNADamageEvent & ~Mdm2) | (JNK & ~Mdm2)  
Apoptosis = DNADamageEvent  
PIP3 = PI3K & PIP2 & ~PTEN  
IkB = NFkB & ~IKK

**Fig. S2.** Connectivity graph of the MAPK signaling network [34], where red edges with arrows represent activation and blue ones with bars inhibition. This illustration is taken from [29].



**Table S3.** Boolean logic rules of the MAPK signaling network.

AKT = PDK1 & ~PTEN  
AP1 = JUN & (FOS | ATF2)  
Apoptosis = ~BCL2 & ~ERK & FOXO3 & p53  
ATF2 = JNK | p38  
ATM = DNA\_damage  
BCL2 = CREB & AKT  
CREB = MSK  
DNA\_damage = DNA\_damage  
DUSP1 = CREB  
EGFR = (EGFR\_stimulus | SPRY) & ~(PKC | GRB2)  
EGFR\_stimulus = EGFR\_stimulus  
ELK1 = ERK | JNK | p38  
ERK = MEK1\_2  
FGFR3 = FGFR3\_stimulus & ~(GRB2 | PKC)  
FGFR3\_stimulus = FGFR3\_stimulus  
FOS = ERK & RSK & (ELK1 | CREB)  
FOXO3 = JNK & ~AKT  
FRS2 = FGFR3 & ~SPRY & ~GRB2  
GAB1 = GRB2 | PI3K  
GADD45 = SMAD | p53  
GRB2 = EGFR | FRS2 | TGFBR  
Growth\_Arrest = p21  
JNK = (TAOK & MAP3K1\_3) | (MAP3K1\_3 & MTK1) | (TAOK & MTK1) | (TAK1 & MTK1) | (TAK1 & MAP3K1\_3) | (TAK1 & TAOK) | ((TAOK | MTK1 | MAP3K1\_3 | TAK1) & ~DUSP1)  
JUN = JNK  
MAP3K1\_3 = RAS  
MAX = p38  
MDM2 = (p53 | AKT) & ~p14  
MEK1\_2 = (RAF | MAP3K1\_3) & ~(PPP2CA | AP1)  
MSK = ERK | p38  
MTK1 = GADD45  
MYC = (MSK & MAX) | (MSK & AKT)  
p14 = MYC  
p21 = ~AKT & p53  
p38 = (TAOK & MAP3K1\_3) | (MAP3K1\_3 & MTK1) | (TAOK & MTK1) | (TAK1 & MTK1) | (TAK1 & MAP3K1\_3) | (TAK1 & TAOK) | ((TAOK | MTK1 | MAP3K1\_3 | TAK1) & ~DUSP1)  
p53 = (ATM & p38) | ((ATM | p38) & ~MDM2)  
p70 = PDK1 & ERK  
PDK1 = PI3K  
PI3K = GAB1 | (RAS & SOS)  
PKC = PLCG  
PLCG = EGFR | FGFR3  
PPP2CA = p38  
Proliferation = p70 & MYC & ~p21  
PTEN = p53  
RAF = (RAS | PKC) & ~(ERK | AKT)  
RAS = SOS | PLCG  
RSK = ERK  
SMAD = TGFBR  
SOS = GRB2 & ~RSK  
SPRY = ERK  
TAK1 = TGFBR  
TAOK = ATM  
TGFBR = TGFBR\_stimulus  
TGFBR\_stimulus = TGFBR\_stimulus

**Table S4.** Control input sets provided by the Logical DOI method for output stabilization of the cellular apoptosis network.

|  |
| --- |
| {'DNADamageEvent': True}  {'TNFR1': True, 'TRAF': False, 'NFkB': False}  {'Cas8': True, 'IkB': True}  {'APC': True, 'NFkB': False}  {'Cas3': True}  {'Cas8': True, 'NFkB': False}  {'TRADD': True, 'Mdm2': False, 'cFLIP': False, 'PIP3': False}  {'TRADD': True, 'cFLIP': False, 'NFkB': False}  {'TRADD': True, 'TRAF': False, 'NFkB': False}  {'TRADD': True, 'TRAF': False, 'IAP': False}  {'Cas7': True, 'Mito': True, 'p53': True}  {'Cas6': True, 'IAP': False}  {'APC': True, 'Mito': True}  {'p53': True, 'Cas6': True, 'cFLIP': False}  {'APC': True, 'IkB': True}  {'Cas8': True, 'IAP': False}  {'Mito': True, 'Cas6': True}  {'TNFR1': True, 'Cas9': True, 'p53': True, 'IkB': True}  {'JNK': True, 'Cas6': True, 'Mdm2': False}  {'BID': True, 'APC': True, 'BclX': False}  {'TNFR1': True, 'p53': True, 'TRAF': False}  {'Cas6': True, 'NFkB': False}  {'IkB': True, 'Cas6': True}  {'Cas8': True, 'p53': True}  {'TNF': True, 'TRAF': False, 'IAP': False}  {'APC': True, 'IAP': False}  {'Cas9': True, 'MEKK1': True, 'p53': True}  {'JNK': True, 'p53': True, 'Cas6': True}  {'TNFR1': True, 'IkB': True, 'cFLIP': False}  {'TNFR1': True, 'Mito': True, 'TRAF': False}  {'FADD': True, 'IkB': True, 'TRADD': False}  {'p53': True, 'TNF': True, 'Cas6': True}  {'Cas9': True, 'p53': True, 'TNF': True}  {'Mito': True, 'TNF': True, 'cFLIP': False}  {'BID': True, 'APC': True, 'BAD': True}  {'JNKK': True, 'TRADD': True, 'TRAF': False, 'Mdm2': False}  {'APC': True, 'TRADD': True, 'Mdm2': False, 'GFR': False}  {'Cas8': True, 'Mito': True}  {'FADD': True, 'TNF': False, 'NFkB': False}  {'MEKK1': True, 'p53': True, 'Cas6': True}  {'MEKK1': True, 'Cas12': True, 'p53': True}  {'FADD': True, 'IkB': True, 'TRAF': False}  {'FADD': True, 'cFLIP': False, 'NFkB': False}  {'p53': True, 'Cas6': True, 'TNF': False}  {'TRADD': True, 'p53': True, 'cFLIP': False}  {'BID': True, 'FADD': True, 'TRADD': False, 'BclX': False}  {'TRADD': True, 'Mito': True, 'TRAF': False}  {'TRADD': True, 'cFLIP': False, 'IAP': False}  {'Cas8': True, 'MEKK1': True, 'Mdm2': False, 'GF': False}  {'p53': True, 'Cas6': True, 'TRADD': False}  {'p53': True, 'Cas6': True, 'TNFR1': False}  {'FADD': True, 'TRAF': False, 'NFkB': False}  {'Cas9': True, 'TNF': True, 'PI3K': False, 'Mdm2': False}  {'IkB': True, 'TNF': True, 'TRAF': False}  {'TNFR1': True, 'Mito': True, 'cFLIP': False}  {'BID': True, 'Cas7': True, 'p53': True}  {'TNFR1': True, 'cFLIP': False, 'NFkB': False}  {'JNKK': True, 'Cas6': True, 'Mdm2': False}  {'MEKK1': True, 'Cas7': True, 'p53': True}  {'Cas8': True, 'MEKK1': True, 'Mdm2': False, 'GFR': False}  {'p53': True, 'TNF': True, 'TRAF': False}  {'Apaf1': True, 'Cas7': True, 'Mito': True, 'PIP2': False}  {'TRADD': True, 'p53': True, 'TRAF': False} |

**Table S5.** Control input sets provided by the Logical DOI method for output stabilization of the MAPK signaling network.

|  |
| --- |
| {'TGFBR\_stimulus': True}  {'TGFBR': True}  {'JNK': True, 'p14': True, 'p38': True}  {'FGFR3': True, 'ATM': True}  {'GRB2': True, 'DNA\_damage': True, 'RSK': False}  {'ATM': True, 'EGFR': True}  {'p53': True, 'EGFR': True}  {'DNA\_damage': True, 'MSK': False}  {'RAS': True, 'CREB': False}  {'TAK1': True, 'DUSP1': False}  {'MYC': True, 'ATM': True, 'MEK1\_2': False}  {'GADD45': True, 'DNA\_damage': True}  {'p53': True, 'PLCG': True}  {'p53': True, 'CREB': False}  {'JNK': True, 'p38': True}  {'FGFR3': True, 'p53': True}  {'GADD45': True, 'TAK1': True}  {'MTK1': True, 'TAK1': True}  {'p53': True, 'SOS': True}  {'p53': True, 'MSK': False}  {'SMAD': True, 'SOS': True}  {'ATM': True, 'DUSP1': False}  {'FOXO3': True, 'AP1': True, 'p53': True}  {'ATM': True, 'ERK': False, 'MSK': False}  {'JNK': True, 'p53': True}  {'TAK1': True, 'EGFR': True}  {'FRS2': True, 'p53': True, 'ERK': False}  {'FRS2': True, 'DNA\_damage': True, 'ERK': False}  {'MAP3K1\_3': True, 'DNA\_damage': True}  {'p53': True, 'ATM': True}  {'TAK1': True, 'CREB': False}  {'p53': True, 'TAK1': True}  {'GRB2': True, 'p38': True}  {'GADD45': True, 'p14': True, 'EGFR': True}  {'PLCG': True, 'CREB': False}  {'EGFR': True, 'CREB': False}  {'p38': True, 'PLCG': True}  {'p53': True, 'RAS': True}  {'p38': True, 'EGFR': True}  {'FOXO3': True, 'p38': True}  {'TAOK': True, 'EGFR': True, 'ERK': False}  {'TAK1': True, 'TAOK': True}  {'FGFR3': True, 'GADD45': True}  {'SMAD': True, 'DUSP1': False}  {'p53': True, 'TGFBR': True}  {'TGFBR\_stimulus': True, 'PDK1': False}  {'GRB2': True, 'JNK': True, 'CREB': False} |

**Table S6.** Control input sets provided by the FVS control algorithm for output stabilization of the MAPK signaling network.

|  |
| --- |
| {'p53': True, 'CREB': True, 'DNA\_damage': False, 'PKC': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'CREB': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'PI3K': True, 'CREB': True, 'DNA\_damage': False, 'PKC': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'PI3K': True, 'CREB': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'CREB': True, 'DNA\_damage': False, 'PKC': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'CREB': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'PI3K': True, 'CREB': True, 'DNA\_damage': False, 'PKC': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'PI3K': True, 'CREB': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'PKC': False, 'DNA\_damage': False, 'DUSP1': True, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'DNA\_damage': False, 'DUSP1': True, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'DUSP1': True, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'PI3K': True, 'DNA\_damage': False, 'DUSP1': True, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p53': True, 'PKC': False, 'DNA\_damage': False, 'DUSP1': True, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'DNA\_damage': False, 'DUSP1': True, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'DUSP1': True, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p53': True, 'PI3K': True, 'DNA\_damage': False, 'DUSP1': True, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': 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'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p38': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MDM2': False}  {'p38': True, 'PI3K': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MDM2': False}  {'p53': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MSK': True}  {'p53': True, 'PI3K': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MSK': True}  {'p38': True, 'p53': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p38': True, 'p53': True, 'PI3K': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'ERK': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True}  {'p38': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MDM2': False, 'MEK1\_2': False}  {'p38': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MDM2': False, 'MEK1\_2': False}  {'p53': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False, 'MSK': True}  {'p53': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False, 'MSK': True}  {'p38': True, 'p53': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p38': True, 'p53': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'GAB1': True, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p38': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MDM2': False, 'MEK1\_2': False}  {'p38': True, 'PI3K': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MDM2': False, 'MEK1\_2': False}  {'p53': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False, 'MSK': True}  {'p53': True, 'PI3K': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False, 'MSK': True}  {'p38': True, 'p53': True, 'PI3K': True, 'PKC': False, 'DNA\_damage': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False}  {'p38': True, 'p53': True, 'PI3K': True, 'DNA\_damage': False, 'PLCG': False, 'EGFR\_stimulus': False, 'FGFR3\_stimulus': False, 'TGFBR\_stimulus': True, 'GRB2': True, 'MEK1\_2': False} |

**Table S7.** Control input sets provided by the BN simple reduction control algorithm for output stabilization of the MAPK signaling network.

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