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Supplementary Materials for

Fault Diagnosis Engineering of Digital Circuits Can Identify Vulnerable Molecules in Complex Cellular Pathways

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Supplementary Materials

Supplementary Methods

Vulnerability assessment algorithm

Here we summarize our molecular vulnerability assessment algorithm, through which the vulnerability of a cellular signaling network to the dysfunction of its components can be calculated. The details of each step are explained in the Method Section.

1. Specify the inputs nodes (such as ligands, receptors, secondary messengers, etc.) and the output nodes (such as different transcription factors relevant to the input signal), as well as the intermediate molecules that allow the input signals to propagate from the inputs to the outputs. Then specify the type of the interactions among the molecules (stimulatory or inhibitory), using the existing literature.
2. Use Rule #1 and Rule #2, to derive a binary logic equation for every intermediate molecule and the output molecules, using the interactions specified in Step 1.
3. Construct the digital circuit of the network from the binary logic equations of Step 2, using the AND, OR, NOT and BUFFER digital circuit elements.
4. Identify the feedback paths of the digital circuit of Step 3, using the depth-first search (DFS) algorithm. If there is no feedback path, proceed directly to the next step.
5. Finally, apply the EPP algorithm to the circuit obtained in the previous step, to calculate the vulnerability levels of all the input and intermediate nodes (the vulnerability of the output node is always 1, since if the output node is dysfunctional, the network will not operate efficiently anyway).

Deriving the logic equations

The logic equation of each molecule is a symbolic Boolean expression that shows how the activity of the molecule is regulated by its inputs. Using Rule #1 and Rule #2, a binary logic equation for each intermediate molecule and the output molecule were obtained, in terms of the input stimulators and inhibitors. These two rules are devised based on the known physiological mechanisms that different regulators employ to control the activity of signaling molecules. Rule #1 applies the Boolean OR of activating inputs to a signaling network. Rule #2 applies the Boolean AND of inverted inhibitory inputs to the network. In the derived equations for the networks, ', + and × stand for the binary logic operations NOT, OR and AND, respectively.

Constructing the digital circuits

To obtain the digital circuit schematic of a set of logic equations for a particular network, the ', + and × operations were represented in the circuit by NOT, OR and AND circuit components, respectively. Equations of the form $X = Y$, where X and Y are two different molecules and X is activated by Y, were implemented using the BUFFER circuit component.

Table S1. Logic equations of the caspase3-FKHR network. Each logic equation specifies the input signals to a molecule using the logic operations ', + and ×, which represent NOT, OR and AND, respectively. These equations are used to generate the digital electronic caspase3-FKHR circuit (Fig. 2B).

Molecule	Logic equation
AKT	AKT=EGFR+Insulin
Caspase3	Caspase3=AKT'×(Caspase8+JNK1+MK2)
Caspase8	Caspase8=$cFLIP_L$'×(ComplexII+ERK)
$cFLIP_L$	$cFLIP_L$=NFκB
ComplexI	ComplexI=TNF
ComplexII	ComplexII=TNF+ComplexI
EGFR	EGFR=EGF
ERK	ERK=MEK
FKHR	FKHR=AKT
IKK	IKK=ComplexI
IRS1	IRS1=Insulin
JNK1	JNK1=MKK7
MEK	MEK=EGFR+IRS1
MEKK1ASK1	MEKK1ASK1=ComplexI
MK2	MK2=p38
MKK3	MKK3=MEKK1ASK1
MKK7	MKK7=MEKK1ASK1
NFκB	NFκB=IKK
P38	p38=MKK3

Abl to Dok, Abl to p53[43,83,104], Abl to Vav, AC2 to cAMP, AC5 to cAMP, AKT to CASPASE9, AKT to p53[50,90,119,121,125,166], APS to Vav, Ca^{2+} to AC5, Ca^{2+} to PKC, cAMP to PKA, CASPASE3 to PIP5K, CASPASE3 to PP2A[72,117], CASPASE3 to PTEN[26,147], CASPASE8 to CASPASE3[18,38,84,130], CASPASE9 to CASPASE3[78,103,128], Cdc42 to PAK, DAG to PKC, Dok to RasGAP, Gab1 to PI3K, Grb10 to PI3K, Grb2 to Gab1, Grb2 to Vav, ILK to AKT, Insulin to IR, IP3 to IP3R, IP3R to Ca^{2+} [139], IR to Grb10, IR to IRS1, IR to IRS2, IRS1 to Grb2, IRS1 to NCK, IRS1 to PI3K, IRS2 to PI3K, JIP to JNK, JNK to IRS1, JNK to JIP, JNK to p53, NCK to Abl, NCK to PAK, PAK to Abl, PDGF to PDGFR, PDGFR to APS, PDGFR to PLCγ, PDGFR to SHP2, PDK1 to AKT, PDK1 to PKC, PI3K to PIP3, PIP2 to AKT, PIP2 to CASPASE3, PIP2 to CASPASE8[94,112], PIP2 to CASPASE9, PIP2 to PMCA, PIP2 to RyR, PIP3 to AKT, PIP3 to ILK, PIP3 to PDK1, PIP3 to PKC, PIP3 to Vav, PIP3K to PIP2, PIP5K to PIP2, PKA to IP3R, PKA to p53, PKA to PLCβ, PKA to PLCγ, PKA to PMCA, PKC to Abl, PKC to AC2, PKC to AC5, PKC to IRS1, PKC to PLCβ, PKC to PMCA, PKC to SHP2, PLCβ to DAG, PLCβ to IP3, PLCβ to PIP2, PLCγ to DAG, PLCγ to IP3, PLCγ to PIP2, PMCA to Ca^{2+} [105], PP2A to AKT[11,98,151], PTEN to PIP3[77,110], Rac to PAK, RasGAP to AKT, Rho to PIP5K, Rho to ROCK, Rock to JIP, RyR to Ca^{2+} [59], SHP2 to Gab1, SHP2 to Grb2, SHP2 to PI3K, Vav to Cdc42, Vav to Rac, Vav to Rho

Fig. S1. Intermolecular interactions of the p53 network. This network (Fig. 3A) includes the above 94 interactions, listed alphabetically, according to the name of *"source"* molecules. At least one representative reference from the national library of medicine (Pub Med) is listed for each individual interaction. These references are listed at the end of the Supplementary Materials.

Table S2. **Logic equations of the p53 network.** Each logic equation specifies the input signals to a molecule using the logic operations ', + and ×, which represent NOT, OR and AND, respectively. These equations are used to generate the digital p53 circuit (Fig. S2).

Molecule	Logic equation
Abl	Abl=NCK+PKC+PAK
AC2	AC2=PKC
AC5	AC5=(Ca^{2+})'×PKC
APS	APS=PDGFR
Ca^{2+}	Ca^{2+}=PMCA'×(IP3R+RyR)
cAMP	cAMP=AC2+AC5
CASPASE3	CASPASE3=PIP2'×(CASPASE8+CASPASE9)

CASPASE8	CASPASE8=PIP2’
CASPASE9	CASPASE9=PIP2’×AKT’
Cdc42	Cdc42=Vav
DAG	DAG=PLCβ+PLCγ
Dok	Dok=Abl
Gab1	Gab1=SHP2’×Grb2
Grb2	Grb2=IRS1+SHP2
Grb10	Grb10=IR
ILK	ILK=PIP3
IP3	IP3=PLCβ+PLCγ
IP3R	IP3R=PKA’×IP3
IR	IR=Insulin
IRS1	IRS1=JNK’×PKC’×IR
IRS2	IRS2=IR
JIP	JIP=ROCK+JNK
JNK	JNK=JIP’
NCK	NCK=IRS1
p53	p53=AKT’×(Abl+PKA+JNK)
PAK	PAK=Cdc42+NCK+Rac
PDK1	PDK1=PIP3
PDGFR	PDGFR=PDGF
PI3K	PI3K=Gab1+Grb10+IRS1+IRS2+SHP2
PIP2	PIP2=PI3K’×PLCβ’×PLCγ’×PIP5K
PIP3	PIP3=PTEN’×PI3K
PIP5K	PIP5K=CASPASE3’×Rho
PKA	PKA=cAMP
AKT	AKT=PP2A’×(ILK+PDK1+PIP2+PIP3+RasGAP)
PKC	PKC=PDK1+PIP3+DAG+Ca^{2+}
PLCβ	PLCβ=PKA’×PKC’
PLCγ	PLCγ=PKA’×PDGFR
PMCA	PMCA=PKA’×PKC’×PIP2
PP2A	PP2A=CASPASE3’
PTEN	PTEN=CASPASE3’
Rac	Rac=Vav
RasGAP	RasGAP=Dok
Rho	Rho=Vav
ROCK	ROCK=Rho
RyR	RyR=PIP2
SHP2	SHP2=PDGFR+PKC
Vav	Vav=Abl+APS+Grb2+PIP3

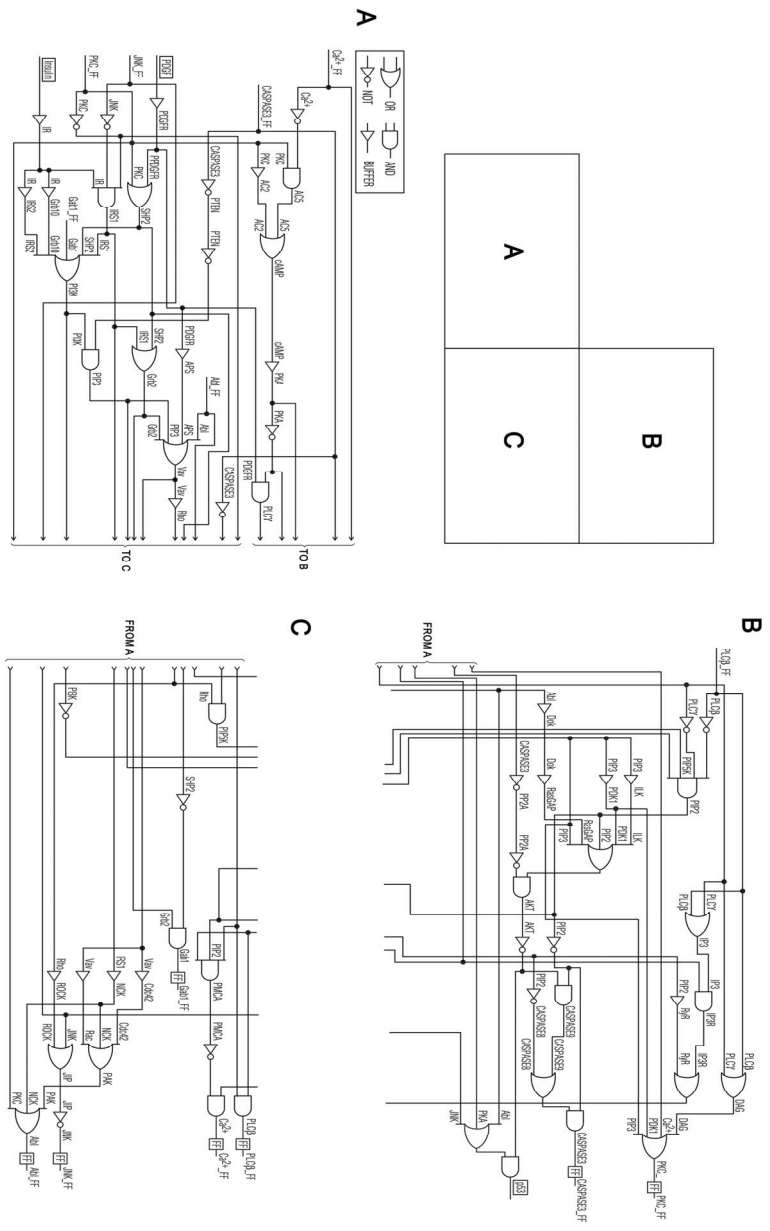

Fig. S2. The digital electronic p53 circuit. There are seven feedback paths in this circuit, initiated from the following nodes: Ca^{2+}, JNK, caspase3, Gab1, PLCβ, Abl, and PKC. These feedbacks are identified using the DFS algorithm, and then one flip-flop (FF) is inserted in each path (FF is a one-bit digital logic memory unit). For example, there is an FF at the upper right corner of the circuit, with PKC and PKC_FF as its input and output, respectively. The name PKC_FF appears again at the lower left corner of the circuit, which means that PKC is "fed back" from the right side of the circuit to the left side. The feedback wire itself is not shown, to make the circuit diagram easier to read.

5-HT1AR to Galphas, 5-HT1AR to Galphaz, 5-HT1AR to Gbetagamma, 5-HT2AR to Gbetagamma, 5-HT4R to Galphas, 5-HT4R to Gbetagamma, A1R to Galphai, A1R to Gbetagamma, A2AR to Galphas, A2AR to Galphas, A2AR to Gbetagamma, AC1 to cAMP, AC2 to cAMP, AC5 to cAMP, Ach to M1R, Ach to M2R, Ach to M4R, Adenosine to A1R, Adenosine to A2AR, AKT to GSK3, Ca^{2+} to AC5, Ca^{2+} to Calmodulin, Ca^{2+} to PKC, Calmodulin to AC1, Calmodulin to CaMKII, Calmodulin to CaMKIV, Calmodulin to CaMKK, Calmodulin to $mGluR_7$, Calmodulin to NMDAR, Calmodulin to PLCβ, Calmodulin to PP2B, CaMKI to CREB, CaMKII to CREB, CaMKII to N-type CaCh, CaMKII to PP2A, CaMKIV to CREB, CaMKIV to CREM, CaMKK to AKT, CaMKK to CaMKI, CaMKK to CaMKIV, cAMP to PKA, CBP to cJun, cJun to CREB, CREM to CREB, D1R to Galphai, D1R to Galphas, D1R to Gbetagamma, D2R to Galphai, D2R to Galphaz, D2R to Gbetagamma, D3R to Galphai, D3R to Gbetagamma, D3R to Grb2, DAG to PKC, Dopamine to D1R, Dopamine to D2R, Dopamine to D3R, DOR to Galphai, DOR to Gbetagamma, Enkephalin to DOR, Enkephalin to KOR, Enkephalin to MOR, Enkephalin to NOR, GABA to GABABR, GABABR to Gbetagamma, Galphai to AC2, Galphai to AC5, Galphas to AC1, Galphas to AC2, Galphas to AC5, Galphaz to AC1, Galphaz to AC5, Gbetagamma to AC1, Gbetagamma to AC2, Gbetagamma to N-type CaCh, Gbetagamma to P/Q-type CaCh, Gbetagamma to PI3K, Gbetagamma to PLCβ, Gbetagamma to RasGAP, Glutamate to $mGluR_1$, Glutamate to $mGluR_7$, Glutamate to NMDAR, Grb2 to SAM68, GSK3 to cJun, GSK3 to CREB, ILK to AKT, ILK to GSK3, KOR to Gbetagamma, M1R to Gbetagamma, M2R to Galphai, M2R to Gbetagamma, M4R to Galphai, M4R to Gbetagamma, $mGluR_1$ to Gbetagamma, $mGluR_7$ to Galphai, $mGluR_7$ to Gbetagamma, MOR to Gbetagamma, NMDAR to Ca^{2+} [86], NMDAR to CaMKII, NMDAR to PLCγ, NOR to Gbetagamma, N-type CaCh to Ca^{2+} [157], P/Q-type CaCh to Ca^{2+} [53], PDK1 to AKT, PDK1 to PKC, PDK1 to RSK, PI3K to PIP2, PI3K to PIP3, PIP2 to AKT, PIP3 to AKT, PIP3 to ILK, PIP3 to PDK1, PIP3 to PKC, PKA to CaMKK, PKA to CBP, PKA to CREB, PKA to D1R, PKA to $mGluR_7$, PKA to NMDAR, PKA to P/Q-type CaCh, PKA to PLCβ, PKA to PLCγ, PKC to AC2, PKC to AC5, PKC to GSK3, PKC to $mGluR_1$, PKC to $mGluR_7$, PKC to NMDAR, PKC to N-type CaCh, PKC to PLCβ, PLCβ to DAG, PLCβ to PIP2, PLCγ to DAG, PLCγ to PIP2, PP2A to AKT, PP2A to CaMKI, PP2A to CaMKIV, PP2A to CREB, PP2A to GSK3, PP2A to NMDAR, PP2B to CaMKIV, PP2B to CREB, PP2B to NMDAR, RasGAP to AKT, RSK to CREB, SAM68 to CBP, Serotonin to 5-HT1AR, Serotonin to 5-HT2AR, Serotonin to 5-HT4R

Fig. S3. Intermolecular interactions of the CREB network. This network (Fig. 4A) includes 152 interactions, listed alphabetically according to the name of *"source"* molecules. At least one representative reference from the national library of medicine (Pub Med) is listed for each individual interaction. These references are listed at the end of the Supplementary Materials.

Table S3. Logic equations of the CREB network. Each logic equation specifies the input signals to a molecule using the logic operations ', + and ×, which represent NOT, OR and AND, respectively. These equations are used to generate the digital electronic CREB circuit (Fig. S4).

Molecule	Logic equation
A1R	A1R=Adenosine
A2AR	A2AR=Adenosine
AC1	AC1=Gbetagamma'×Galphaz'×(Galphas+Calmodulin)
AC2	AC2=Galphai'×(Gbetagamma+Galphas+PKC)
AC5	AC5=Galphai'×Galphaz'×(Ca^{2+})'×(PKC+Galphas)
PP2B	PP2B=Calmodulin
Ca^{2+}	Ca^{2+}=NMDAR+N-typeCaCh+P/QtypeCaCh
Calmodulin	Calmodulin=Ca^{2+}
CaMKI	CaMKI=PP2A'×CaMKK
CaMKII	CaMKII=Calmodulin+NMDAR
CaMKIV	CaMKIV=PP2A'×PP2B'×(Calmodulin+CaMKK)
CaMKK	CaMKK=PKA'×Calmodulin
cAMP	cAMP=AC1+AC2+AC5
CBP	CBP=SAM68'×PKA
cJun	cJun=GSK3'×CBP
CREB	CREB=PP2A'×PP2B'×CREM'×(GSK3+PKA+cJun+RSK+CaMKII +CaMKIV+CaMKI)
CREM	CREM=CaMKIV
D1R	D1R=PKA'×Dopamine
D2R	D2R=Dopamine
D3R	D3R=Dopamine
DAG	DAG=PLCβ+PLCγ
DOR	DOR=Enkephalin
5-HT1AR	5-HT1AR=Serotonin
5-HT2AR	5-HT2AR=Serotonin
5-HT4R	5-HT4R=Serotonin
GABABR	GABABR=GABA'
Galphai	Galphai=A1R+D1R+D2R+D3R+M4R+M2R+$mGluR_7$+DOR+KOR +MOR+NOR+5-HT1AR
Galphas	Galphas=A2AR+D1R+5-HT1AR+5-HT4R
Galphaz	Galphaz=D2R+5-HT1AR
Gbetagamma	Gbetagamma=A1R+A2AR+M1R+M4R+M2R+D1R+D2R+D3R +GABABR+$mGluR_1$+$mGluR_7$+DOR+KOR+MOR+NOR +5-HT1AR+5-HT2AR+5-HT4R
Grb2	Grb2=D3R
GSK3	GSK3=ILK'×AKT'×PKC'×PP2A
ILK	ILK=PIP3
KOR	KOR=Enkephalin
M1R	M1R=Ach

M2R	M2R=Ach
M4R	M4R=Ach
$mGluR_1$	$mGluR_1$=PKC+Glutamate
$mGluR_7$	$mGluR_7$=Calmodulin'×(PKC+PKA+Glutamate)
MOR	MOR=Enkephalin
NMDAR	NMDAR=PKC'×PP2A'×Calmodulin'×PP2B'×(PKA+Glutamate)
NOR	NOR=Enkephalin
N-type CaCh	N-typeCaCh=Gbetagamma'×(PKC+CaMKII)
PDK1	PDK1=PIP3
PI3K	PI3K=Gbetagamma
PIP2	PIP2=PI3K'×PLCβ'×PLCγ'
PIP3	PIP3=PI3K
PKA	PKA=cAMP
AKT	AKT=PP2A'×(RasGAP+ILK+PIP3+PDK1+PIP2+CaMKK)
PKC	PKC=PDK1+PIP3+DAG+Ca^{2+}
PLCβ	PLCβ=PKA'×PKC'×(Gbetagamma+Calmodulin)
PLCγ	PLCγ=PKA'×NMDAR
PP2A	PP2A=CaMKII'
P/Q type CaCh	P/QtypeCaCh=PKA'×Gbetagamma
RasGAP	RasGAP=Gbetagamma
RSK	RSK=PDK1
SAM68	SAM68=Grb2

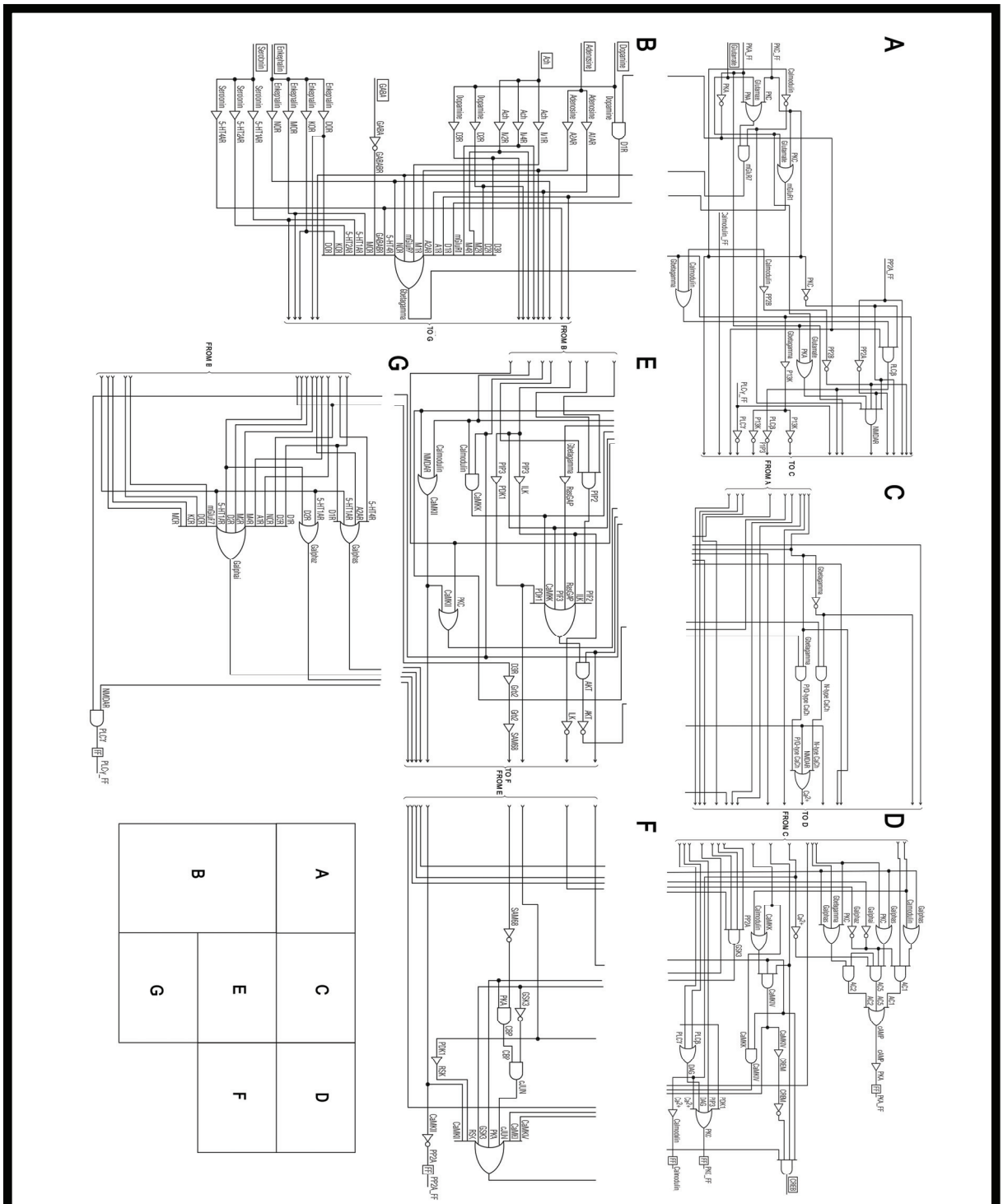

Fig. S4. The digital electronic CREB circuit. There are five feedback paths in this circuit, initiated from the following nodes: PLCγ, PP2A, calmodulin, PKA and PKC. These feedbacks are identified using the DFS algorithm, and then one flip-flop (FF) is inserted in each path. For example, there is an FF at the upper right corner of the circuit, with PKA and PKA_FF as its input and output, respectively. The name PKA_FF is appeared again at the upper left corner of the circuit, which means that PKA is "fed back" from the right side of the circuit to the left side. The feedback wire itself is not shown, to make the circuit diagram easier to read.

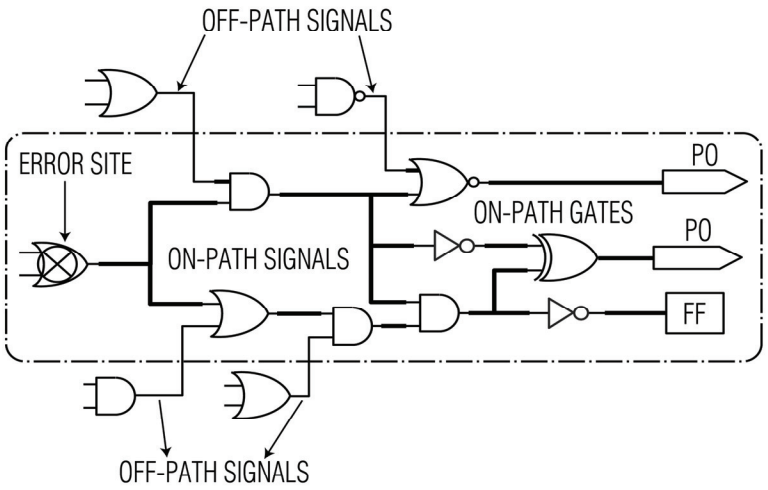

Fig. S5. A typical path between an erroneous node to primary outputs and flip-flops.

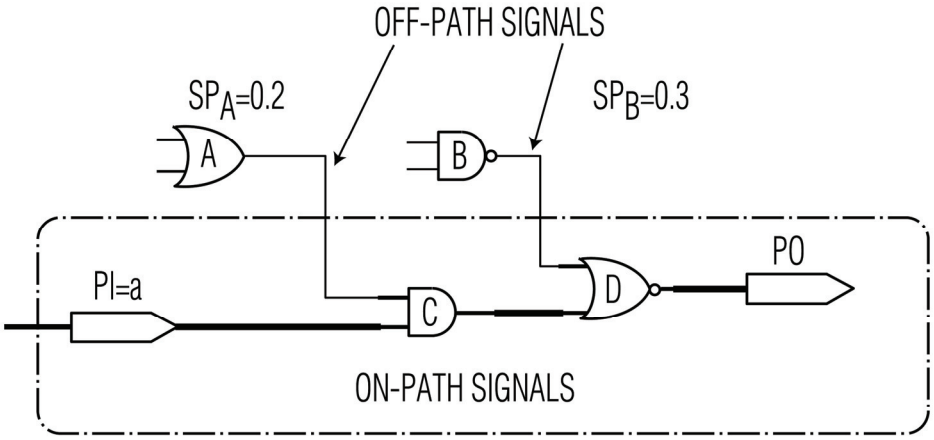

Fig. S6. A simple path between an erroneous input to a primary output.

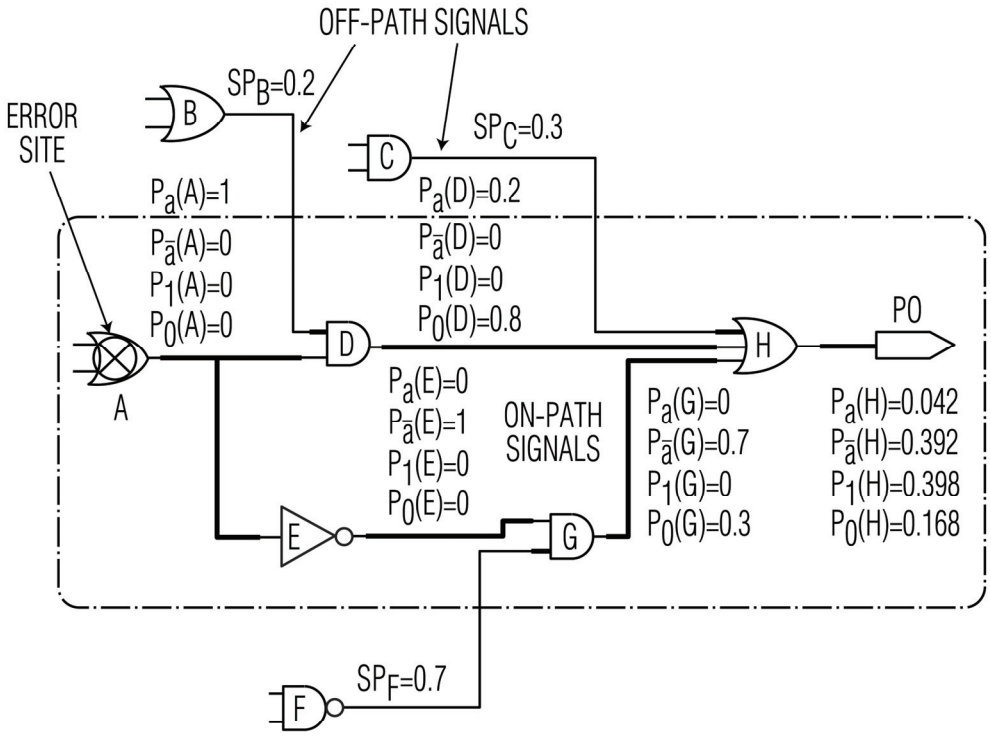

Fig. S7. Applying error propagation rules for a reconverging path.

Table S4. Computing probability at the output of a gate in terms of its inputs.

AND	$P_1(out) = \prod_{i=1}^{n} P_1(X_i)$ $P_a(out) = \prod_{i=1}^{n} [P_1(X_i) + P_a(X_i)] - P_1(out)$ $P_{\bar{a}}(out) = \prod_{i=1}^{n} [P_1(X_i) + P_{\bar{a}}(X_i)] - P_1(out)$ $P_0(out) = 1 - [P_1(out) + P_a(out) + P_{\bar{a}}(out)]$
OR	$P_0(out) = \prod_{i=1}^{n} P_0(X_i)$ $P_a(out) = \prod_{i=1}^{n} [P_0(X_i) + P_a(X_i)] - P_0(out)$ $P_{\bar{a}}(out) = \prod_{i=1}^{n} [P_0(X_i) + P_{\bar{a}}(X_i)] - P_0(out)$ $P_1(out) = 1 - [P_0(out) + P_a(out) + P_{\bar{a}}(out)]$
NOT	$P_0(out) = P_1(in)$, $P_1(out) = P_0(in)$ $P_a(out) = P_{\bar{a}}(in)$, $P_{\bar{a}}(out) = P_a(in)$

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