Supporting Figures

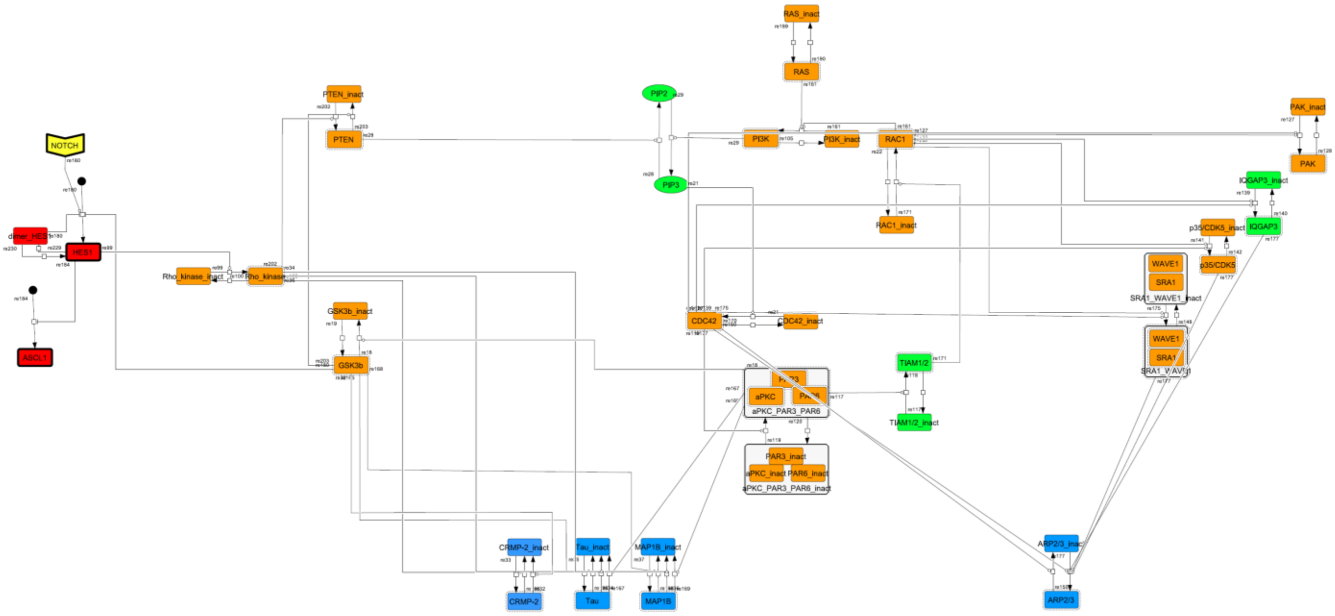


Figure S1: Cascade-contracted network. To find a feedback loop motif, the whole signaling network was contracted by cascade contraction.

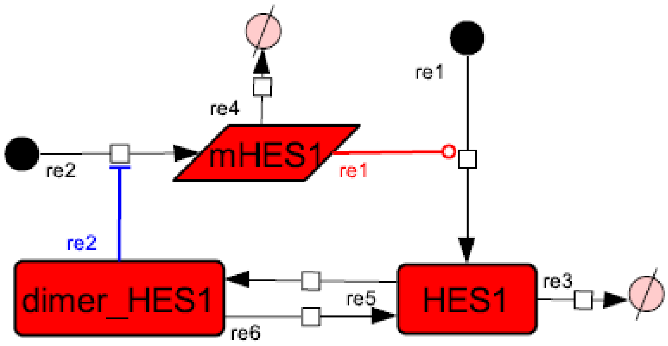


Figure S2: Diagram of the HES1 self-loop model without delay. The model consisting of HES1 self-loop by three nodes without delay. Red edge represents positive regulation. Blue edge represents negative regulation.

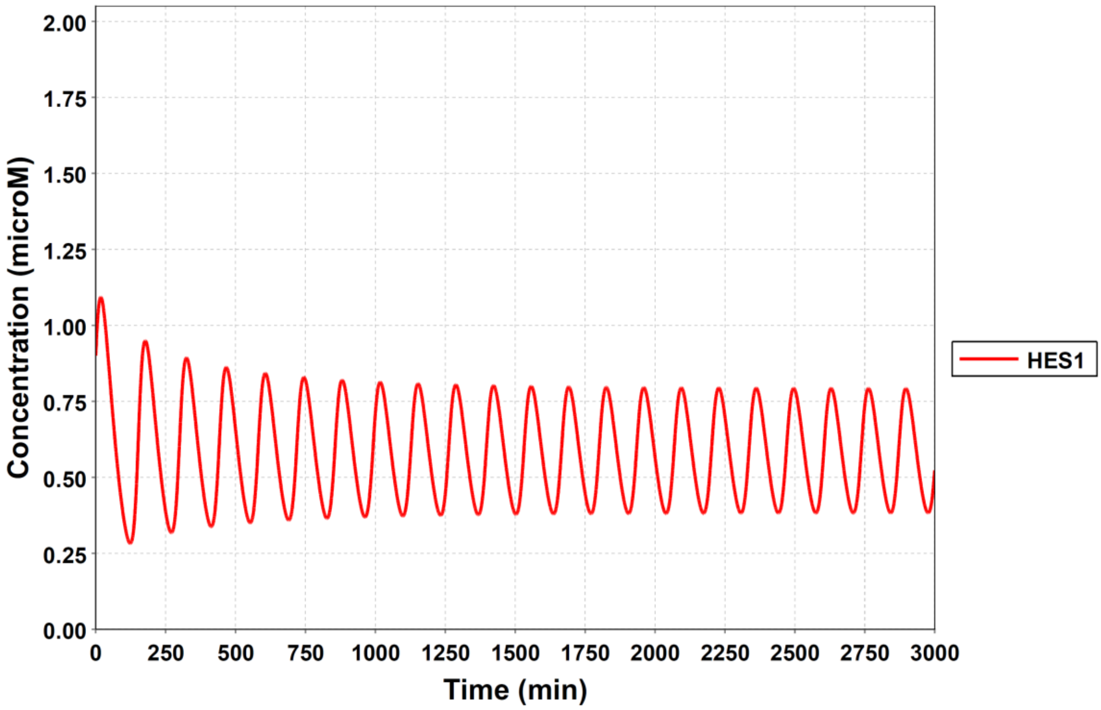
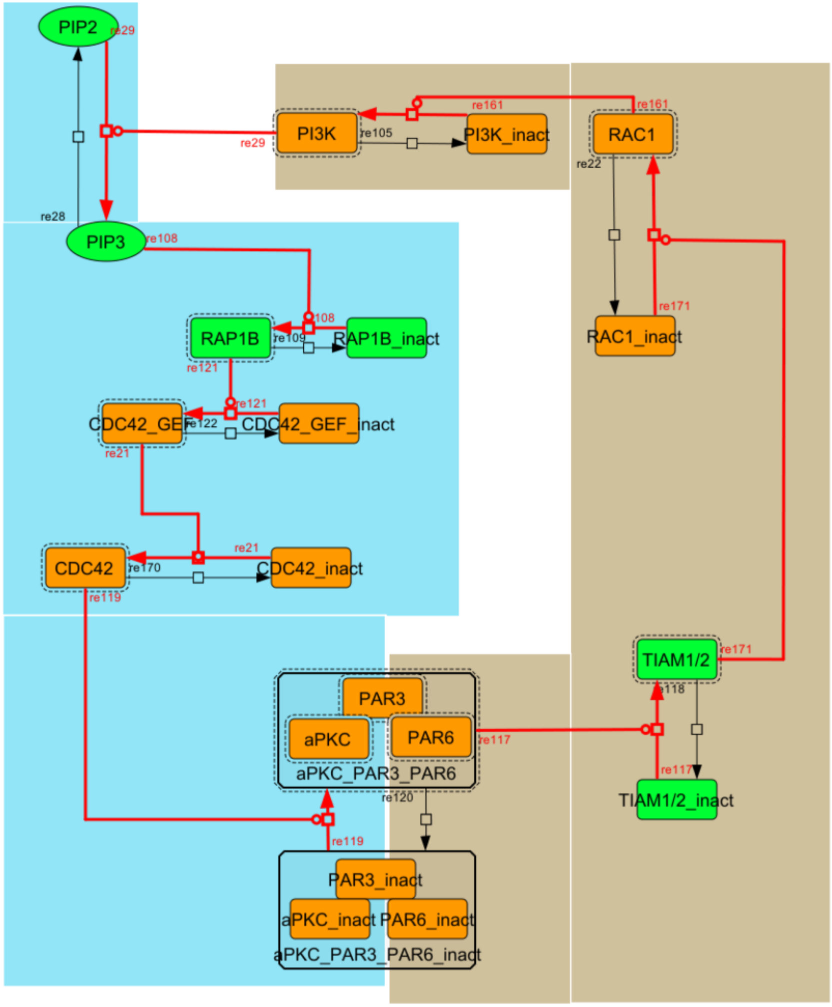


Figure S3: Simulation result of the HES1-loop model. The model could simulate oscillatory state with a period of almost 2 hours. The following parameters were used: $k_3 = 0.00129$, $k_{3r} = 0.0232$, $kg_2 = 4.25$, $nm_{re1s9} = 5$, $kSm_{re1s9} = 0.00228$, $kg_1 = 3.24$, $k_{s3d} = 0.0258$, $k_{s2d} = 0.0355$.

A



B

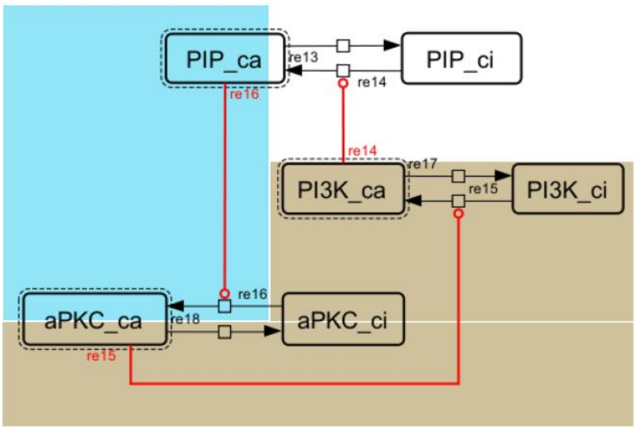
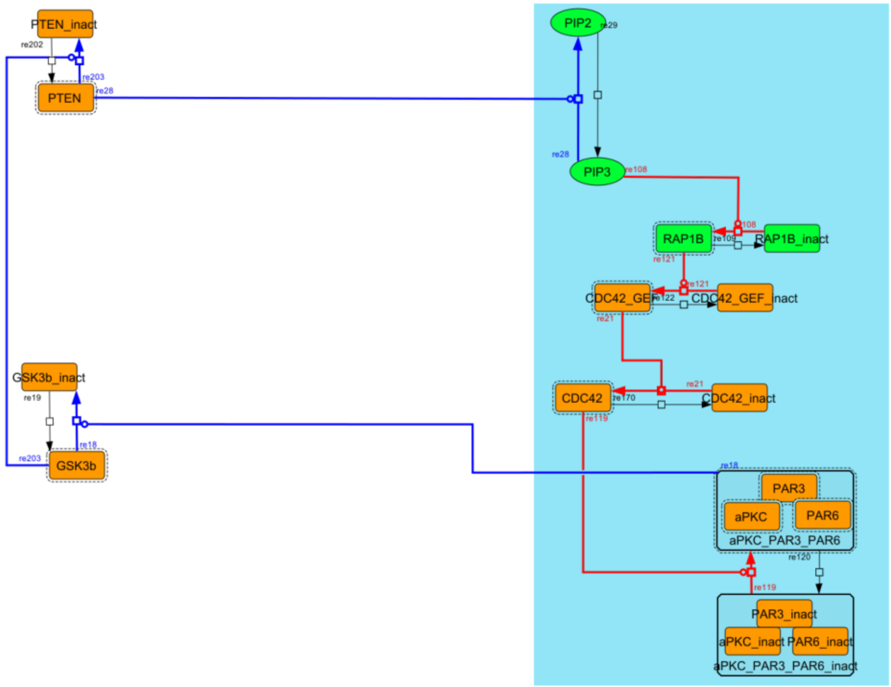


Figure S4: Diagram of the positive-feedback loop between PI3K and aPKC_PAR3_PAR6. (A) The positive-feedback loop in whole signaling network. (B) The contracted positive-feedback loop in toy model. Red edges represent positive regulations. Background colors show correspondence between before and after contraction.

A



B

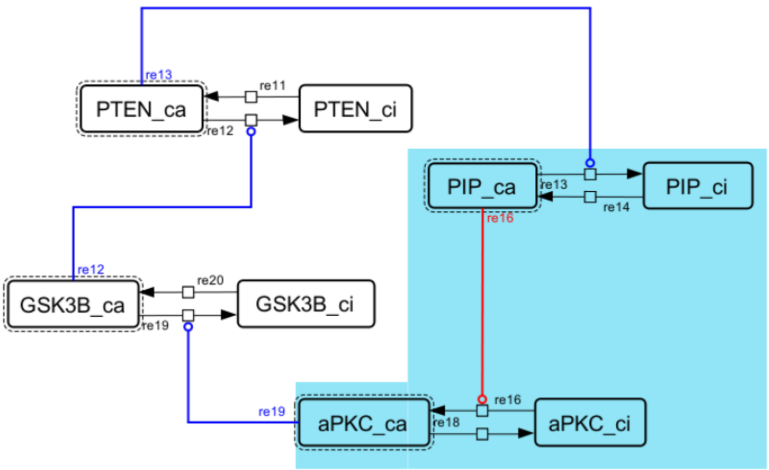
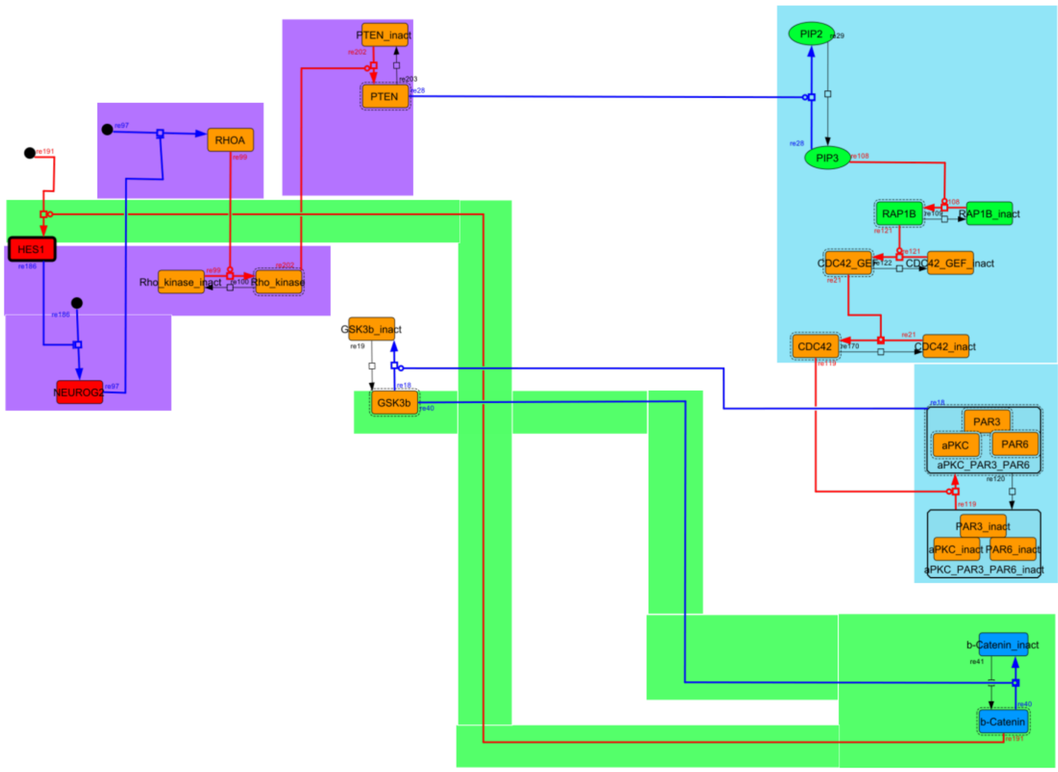


Figure S5: Diagram of the negative-feedback loop between PTEN and GSK3B. (A) The negative-feedback loop in whole signaling network. (B) The contracted negative-feedback loop in toy model. Red edges represent positive regulations. Blue edges represent negative regulations. Background color shows correspondence between before and after contraction.

A



B

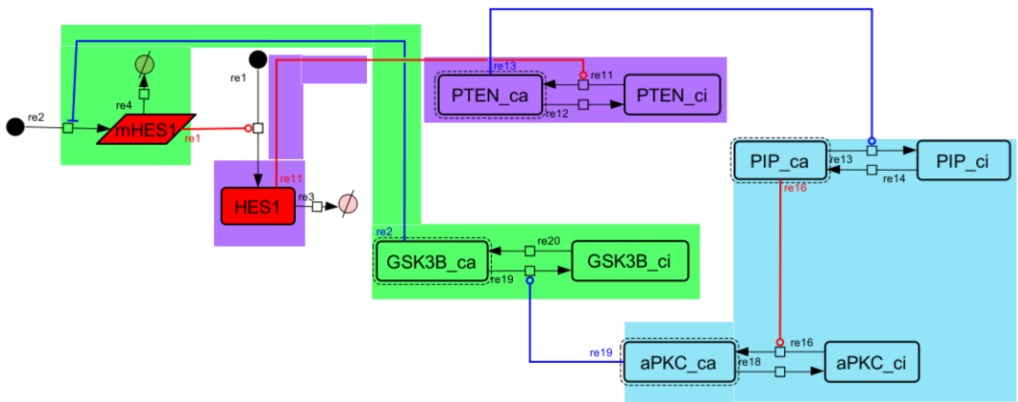


Figure S6: Diagram of negative-feedback loop between beta-catenin and HES1. (A) The negative-feedback loop in whole signaling network. (B) The contracted negative-feedback loop in toy model. Red edges represent positive regulations. Blue edges represent negative regulations. Background colors show correspondence between before and after contraction.

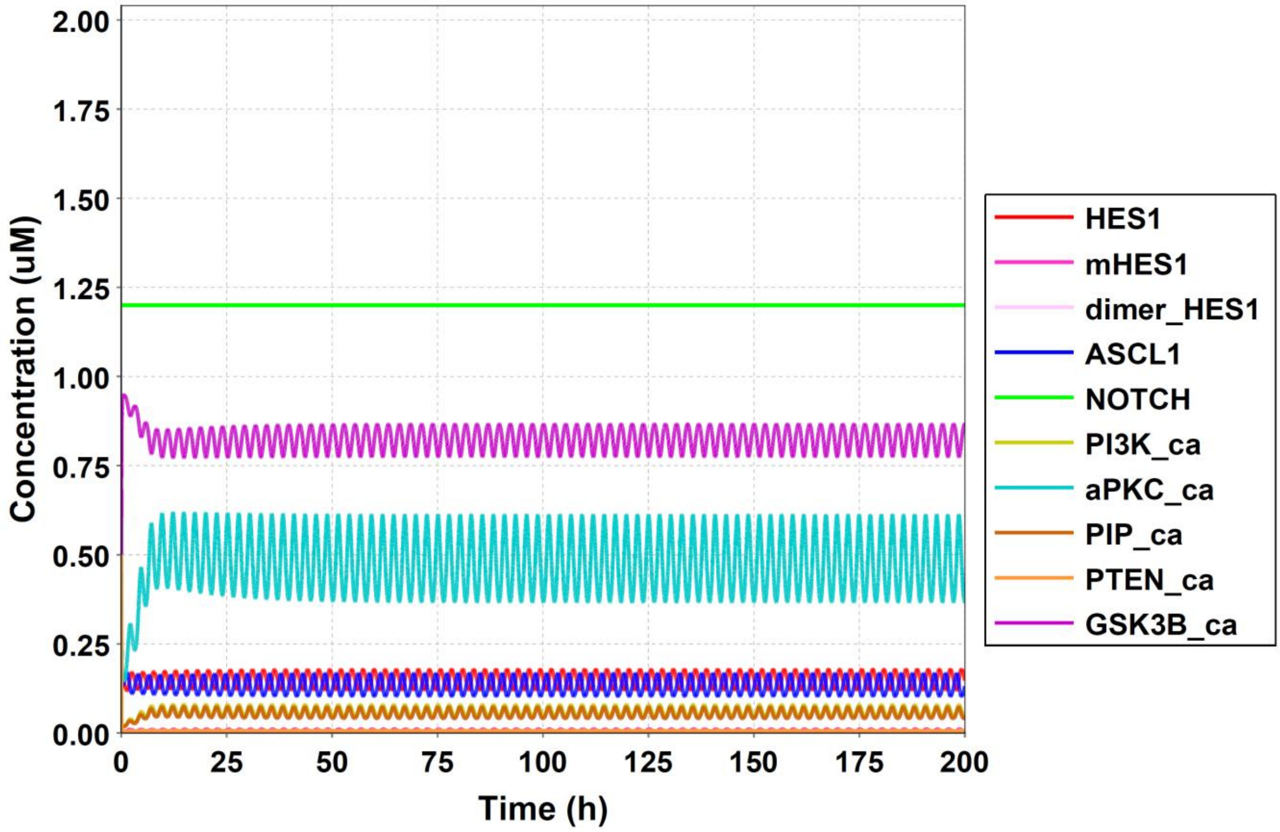


Figure S7: Simulation result of all species.

Table S1: Nodes removed by contraction.

Node name	Reason	Integrated to (identifier in the toy model)
NEUROG2	Cascade (whole signaling network)	Rho_kinase
MLC	Cascade (whole signaling network)	Rho_kinase
RhoA	Cascade (whole signaling network)	Rho_kinase
RAP1B	Cascade (whole signaling network)	PIP3
CDC42_GEF	Cascade (whole signaling network)	PIP3
Cofilin	Cascade (whole signaling network)	PAK
LIMK	Cascade (whole signaling network)	PAK
Stathmin	Cascade (whole signaling network)	PAK
N_WASP	Cascade (whole signaling network)	CDC42
MRCK	Cascade (whole signaling network)	CDC42
KLC	Cascade (whole signaling network)	GSK3B
APC	Cascade (whole signaling network)	GSK3B
b-catenin	Cascade (whole signaling network)	GSK3B
mTOR	Cascade (whole signaling network)	PIP3
RHEB	Cascade (whole signaling network)	PIP3
PDK1	Cascade (whole signaling network)	PIP3
ILK	Cascade (whole signaling network)	PIP3
AKT	Cascade (whole signaling network)	PIP3
L1	Cascade (whole signaling network)	RAS
CREB	Cascade (whole signaling network)	RAS
MAPKAP_K1	Cascade (whole signaling network)	RAS
MAPK	Cascade (whole signaling network)	RAS
MEK	Cascade (whole signaling network)	RAS
RAF	Cascade (whole signaling network)	RAS
MARK2	Cascade (whole signaling network)	aPKC_PAR3_PAR6
Arp2/3	Feedback loop extraction	-
IQGAP3	Feedback loop extraction	-
PAK	Feedback loop extraction	-
p35/CDK5	Feedback loop extraction	-
SRA1_WAVE1	Feedback loop extraction	-
MAP1B	Feedback loop extraction	-
Tau	Feedback loop extraction	-
CRMP-2	Feedback loop extraction	-
RAS	Parameterization	-
Rho_kinase	Cascade (core network)	PTEN_ca (s22)
TIAM1/2	Cascade (core network)	PI3K_ca (s20)
RAC1	Cascade (core network)	PI3K_ca (s20)
PIP3	Cascade (core network)	PIP_ca (s16)
GSK3B	Cascade (core network)	GSK3B_ca (s24)
PTEN	Cascade (core network)	PTEN_ca (s22)
aPKC_PAR3_PAR6	Cascade (core network)	aPKC_ca (s18)

Table S2: Differential equations of the HES1 self-loop model.

Equation No.	Differential equations
1	$\frac{\mathrm{d[HES1]}}{\mathrm{dt}} = kg_2 \cdot \mathrm{[mHES1]} - k_{s3_d} \cdot [HES1] - 2 \cdot k_3 \cdot [HES1]^2 + 2 \cdot k_{3r} \cdot [dimer_{HES1}]$
2	$\frac{d[mHES1]}{dt} = kg_1 \cdot \left(1 - \frac{[dimer_{HES1}]^{nm_{re1_{s9}}}}{[dimer_{HES1}]^{nm_{re1_{s9}}} + kSm_{re1_{s9}}^{nm_{re1_{s9}}}}\right) - k_{s2_d}[mHES1]$
3	$\frac{d[dimer_{HES1}]}{dt} = k_3 \cdot [HES1]^2 - k_{3r} \cdot [dimer_{HES1}]$