Supplemental Information
for

Protein-protein interactions generate hidden feedback and feed-forward loops to trigger bistable switches, oscillations and biphasic dose-responses

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In this supplementary information (SI), we present in detail the reactions, parameter values, and ordinary differential equations of the various models presented and discussed in the main text. In all the following tables, the concentrations and the Michaelis-Menten constants (K_ms) are given in nM. First- and second-order rate constants are expressed in s^{-1} and nM^{-1} s^{-1}. Maximum rates Vs of the enzymes catalysed reactions are expressed in nM s^{-1}. In addition, the supplementary figures are shown in section 4.

S1. Single isolated PPI event

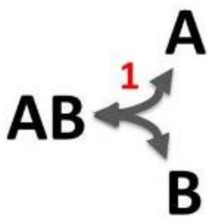


Table S1. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	A + B ←→ AB	$v_1 = k_{1f}.[A][B] - k_{1r}.[AB]$	k_{1f}= 0.00001, k_{1r}= 0.0005

Table S1. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S1.

Left-hand Sides	Right-hand Sides	Initial Concentrations (nM)
d[A]/dt	$-v_1$	150
d[B]/dt	$-v_1$	0
d[AB]/dt	v_1	150

S2. Single PPI network exhibiting bistability

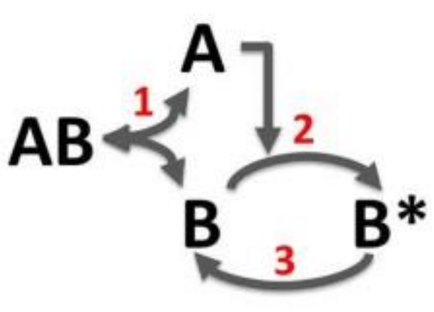


Table S2. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	A + B ←→ AB	$v_1 = k_{1f}.[A][B] - k_{1r}.[AB]$	k_{1f}= 0.444116, k_{1r}= 0.0138931
2	B → B*	$v_2 = \frac{kc_2.[A].[B]}{Km_2 + [B]}$	kc_2= 2.17889, Km_2= 48.8039
3	B* → B	$v_3 = \frac{V_3.[B*]}{Km_3 + [B*]}$	V_3= 0.0149644, Km_3= 3.09516

Table S2. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S2.

Left-hand Sides	Right-hand Sides	Initial Concentrations (nM)
d[A]/dt	$-v_1$	15
d[B]/dt	$v_3 - v_1 - v_2$	100
d[AB]/dt	v_1	0
d[B*]/dt	$v_2 - v_3$	0

S3. Single PPI network exhibiting Sustained Oscillation

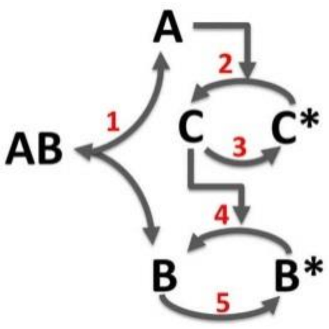


Table S3. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	A + B ←→ AB	$v_1 = k_{1f}.[A][B] - k_{1r}.[AB]$	k_{1f}= 0.00143087, k_{1r}= 0.000653442
2	C* → C	$v_2 = \frac{kc_2.[A].[C*]}{Km_2 + [C*]}$	kc_2= 24.0512, Km_2= 151.308
3	C → C*	$v_3 = \frac{V_3.[C]}{Km_3 + [C]}$	V_3= 2.69421, Km_3= 1.93629
4	B* → B	$v_4 = \frac{kc_4.[C].[B*]}{Km_4 + [B*]}$	kc_4= 0.723006, Km_4= 48.6098
5	B → B*	$v_5 = \frac{V_5.[B]}{Km_5 + [B]}$	V_5= 11.8224, Km_5= 2.2509

Table S3. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S3.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[A]/dt	$-v_1$	39
d[B]/dt	$v_4 - v_1 - v_5$	455
d[AB]/dt	v_1	0
d[B*]/dt	$v_5 - v_4$	0
d[C]/dt	$v_2 - v_3$	122

d[C*]/dt	$v_3 - v_2$	0

S4. Single PPI network exhibiting Damped Oscillation

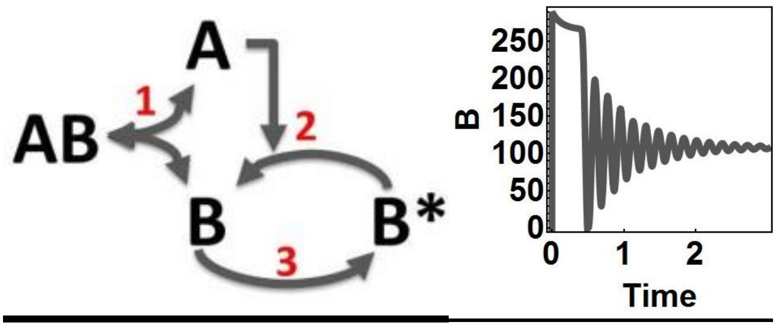


Table S4. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	A + B ↔ AB	$v_1 = k_{1f}.[A][B] - k_{1r}.[AB]$	k_{1f}=0.000021458, k_{1r}= 0.000227335
2	B* → B	$v_2 = \frac{kc_2.[A].[B*]}{Km_2 + [B*]}$	kc_2=6.63297, Km_2= 0.0555913
3	B → B*	$v_3 = \frac{V_3.[B]}{Km_3 + [B]}$	V_3=13.9797, Km_3= 0.0102194

Table S4. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S4.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[A]/dt	$- v_1$	25
d[B]/dt	$v_2 - v_1 - v_3$	0
d[AB]/dt	v_1	0
d[B*]/dt	$v_3 - v_2$	290

S5. Single PPI network exhibiting Biphasic Response

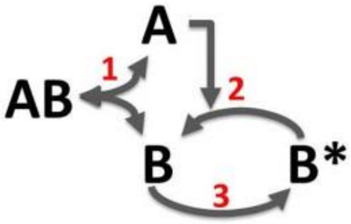


Table S5. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	A + B ↔ AB	$v_1 = k_{1f}.[A][B] - k_{1r}.[AB]$	k_{1f}=0.000662316, k_{1r}= 0.000701878
2	B* → B	$v_2 = \frac{kc_2.[A].[B*]}{Km_2 + [B*]}$	kc_2=2.98182, Km_2= 11.0657
3	B → B*	$v_3 = \frac{V_3.[B]}{Km_3 + [B]}$	V_3=53.6473, Km_3= 1880.36

Table S5. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S5.

Left-hand Sides	Right-hand Sides	Initial Concentrations (nM)
d[A]/dt	$-v_1$	50
d[B]/dt	$v_2 - v_1 - v_3$	0
d[AB]/dt	v_1	0
d[B*]/dt	$v_3 - v_2$	134

S6. Single PPI network exhibiting Coherent Feedforward Regulation

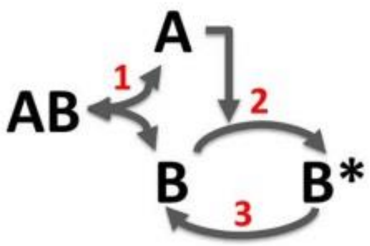


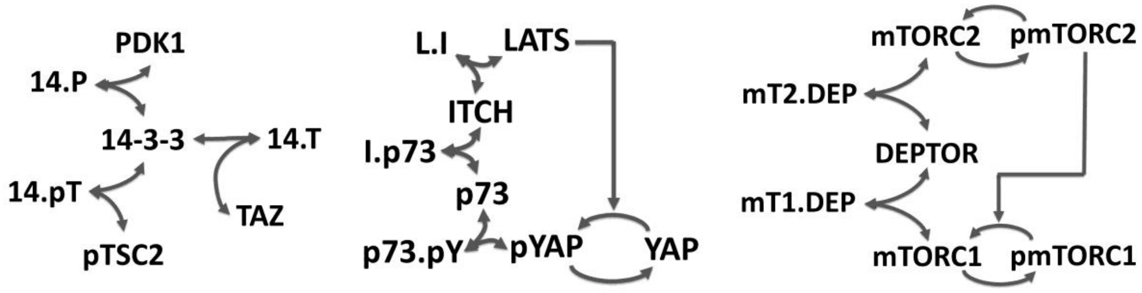
Table S6. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	A + B ←→ AB	$v_1 = k_{1f}.[A][B] - k_{1r}.[AB]$	k_{1f}= 0.00907778, k_{1r}= 0.0295832
2	B → B*	$v_2 = \frac{kc_2.[A].[B]}{Km_2 + [B]}$	kc_2= 0.0208362, Km_2= 79.0018
3	B* → B	$v_3 = \frac{V_3.[B*]}{Km_3 + [B*]}$	V_3= 2.37913, Km_3= 24.4436

Table S6. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S6.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[A]/dt	$- v_1$	200
d[B]/dt	$v_3 - v_1 - v_2$	40
d[AB]/dt	v_1	0
d[B*]/dt	$v_2 - v_3$	0

S7. *In vivo* PPI examples



S8. Coupled isolated PPI event

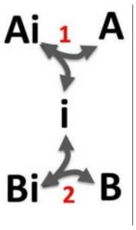


Table S8. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	A + i ←→ Ai	$v_1 = k_{1f}.[A][i] - k_{1r}.[Ai]$	k_{1f}= 0.00005, k_{1r}= 0.002
2	B + i ←→ Bi	$v_2 = k_{2f}.[B][i] - k_{2r}.[Bi]$	k_{2f}= 0.00005, k_{2r}= 0.002

Table S8. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S8.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[A]/dt	$-v_1$	200
d[i]/dt	$-v_1 - v_2$	300
d[B]/dt	$-v_2$	200
d[Ai]/dt	v_1	0
d[Bi]/dt	v_2	0

S9. Coupled PPI network exhibiting Sustained Oscillation

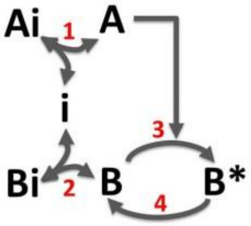


Table S9. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	A + i ←→ Ai	$v_1 = k_{1f}.[A][i] - k_{1r}.[Ai]$	k_{1f}= 0.000156153, k_{1r}= 0.0000766173
2	B + i ←→ Bi	$v_2 = k_{2f}.[B][i] - k_{2r}.[Bi]$	k_{2f}= 0.000125176, k_{2r}= 0.00208669
3	B → B*	$v_3 = \frac{kc_3.[A].[B]}{Km_3 + [B]}$	kc_3= 4.95119, Km_3= 0.103278
4	B* → B	$v_4 = \frac{V_4.[B*]}{Km_4 + [B*]}$	V_4= 8.30799, Km_4= 21.4724

Table S9. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S9.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[A]/dt	$-v_1$	25
d[i]/dt	$-v_1 - v_2$	74
d[B]/dt	$v_4 - v_3 - v_2$	672
d[Ai]/dt	v_1	0
d[Bi]/dt	v_2	0
d[B*]/dt	$v_3 - v_4$	0

S10. Coupled PPI network exhibiting Biphasic Response

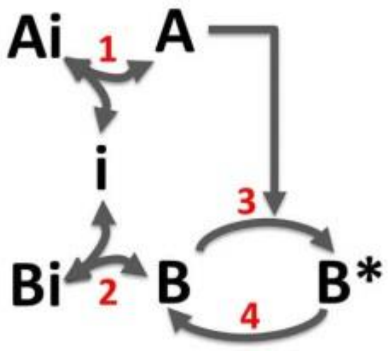


Table S10. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	A + i ←→ Ai	$v_1 = k_{1f}.[A][i] - k_{1r}.[Ai]$	k_{1f}= 0.0147496, k_{1r}= 0.000192892
2	B + i ←→ Bi	$v_2 = k_{2f}.[B][i] - k_{2r}.[Bi]$	k_{2f}= 0.175098, k_{2r}= 0.127203
3	B → B*	$v_3 = \frac{kc_3.[A].[B]}{Km_3 + [B]}$	kc_3= 0.136761, Km_3= 10.9548
4	B* → B	$v_4 = \frac{V_4.[B*]}{Km_4 + [B*]}$	V_4= 5.2157, Km_4= 195.135

Table S10. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S10.

Left-hand Sides	Right-hand Sides	Initial Concentrations (nM)
d[A]/dt	$- v_1$	100
d[i]/dt	$- v_1 - v_2$	100
d[B]/dt	$v_4 - v_3 - v_2$	100
d[Ai]/dt	v_1	0
d[Bi]/dt	v_2	0
d[B*]/dt	$v_3 - v_4$	0

S11. Coupled PPI network exhibiting Bistability

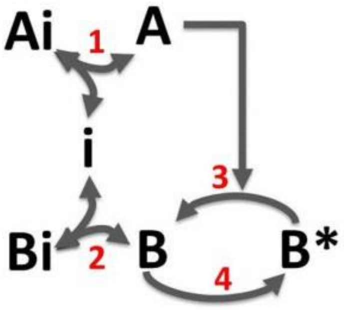


Table S11. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	A + i ←→ Ai	$v_1 = k_{1f}.[A][i] - k_{1r}.[Ai]$	k_{1f}= 1.30884, k_{1r}= 1.22917
2	B + i ←→ Bi	$v_2 = k_{2f}.[B][i] - k_{2r}.[Bi]$	k_{2f}= 0.0154033, k_{2r}= 0.0533712
3	B* → B	$v_3 = \frac{kc_3.[A].[B*]}{Km_3 + [B*]}$	kc_3= 0.0103728, Km_3= 1.42502
4	B → B*	$v_4 = \frac{V_4.[B]}{Km_4 + [B]}$	V_4= 0.120356, Km_4= 3.22874

Table S11. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S11.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[A]/dt	$-v_1$	70
d[i]/dt	$-v_1 - v_2$	100
d[B]/dt	$v_3 - v_4 - v_2$	100
d[Ai]/dt	v_1	0
d[Bi]/dt	v_2	0
d[B*]/dt	$v_4 - v_3$	0

S12. The MST2-Raf-1 signaling network

a. Facilitates Sustained Oscillation

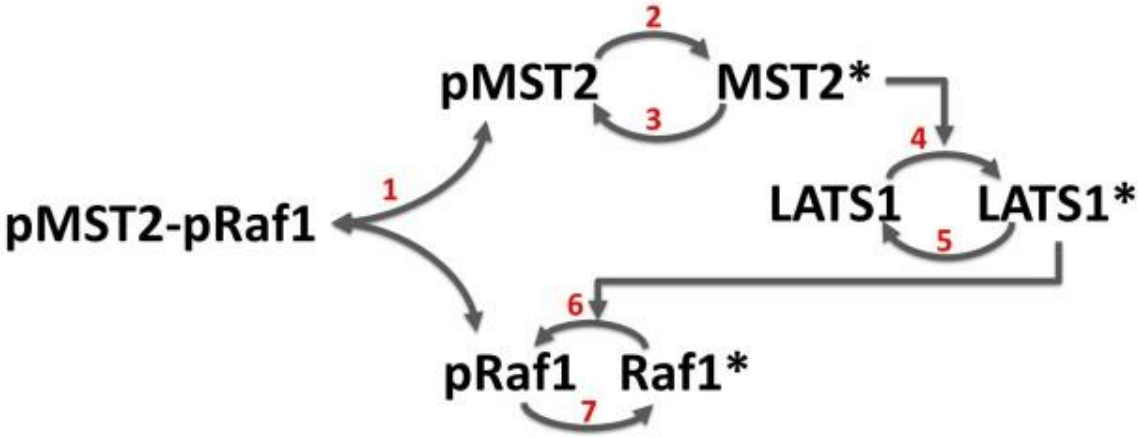


Table S12.a. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	pMST2 + pRaf1 ←→ pMST2-pRaf1	$v_1 = k_{1f}.[pMST2][pRaf1] - k_{1r}.[pMST2.pRaf1]$	k_{1f}=0.185164, k_{1r}=0.0985695
2	pMST2 → MST2*	$v_2 = \frac{V_2.[MST2]}{Km_2 + [MST2*]}$	V_2=0.0454014, Km_2=330.376
3	MST2* → pMST2	$v_3 = \frac{V_3.[MST2*]}{Km_3 + [pMST2]}$	V_3=0.0525323, Km_3=99.4278
4	LATS1 → LATS1*	$v_4 = \frac{kc_4.[MST2*].[LATS1]}{Km_4 + [LATS1]}$	kc_4=1.367, Km_4=41.4402
5	LATS1* → LATS1	$v_5 = \frac{V_5.[LATS1*]}{Km_5 + [LATS1*]}$	V_5=0.757472, Km_5=0.581622
6	Raf1* → pRaf1	$v_6 = \frac{kc_6.[LATS1*].[Raf1*]}{Km_6 + [Raf1*]}$	kc_6=0.00229352, Km_6=0.151116
7	pRaf1 → Raf1*	$v_7 = \frac{V_7.[pRaf1]}{Km_7 + [pRaf1]}$	V_7=0.0387405, Km_7=0.670203

Table S12.a. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S12.a. .

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[pMST2]/dt	$v_3 - v_2 - v_1$	0
d[pRaf1]/dt	$v_6 - v_7 - v_1$	0
d[pMST2-pRaf1]/dt	v_1	0
d[MST2]/dt	$v_2 - v_3$	12
d[LATS1]/dt	$v_5 - v_4$	250
d[LATS1*]/dt	$v_4 - v_5$	0
d[Raf1*]/dt	$v_7 - v_6$	37

b. Facilitates Biphasic Response

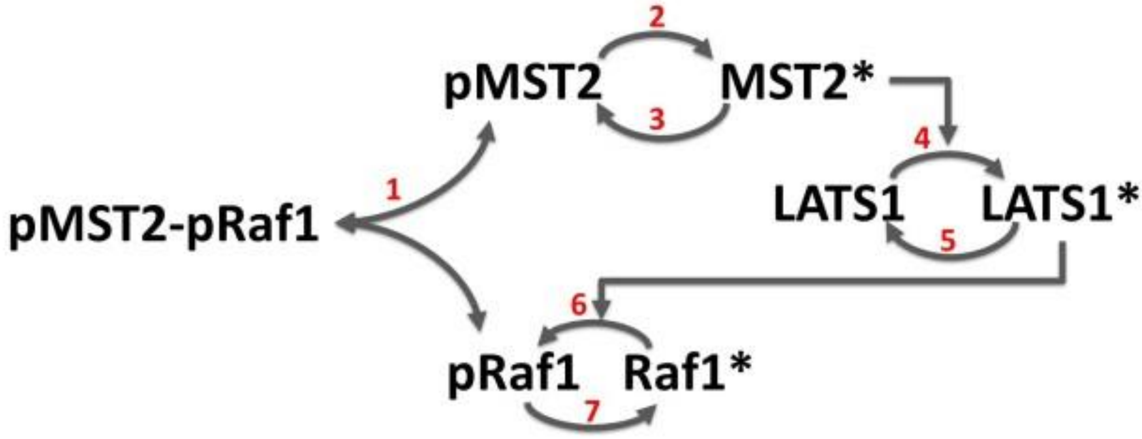


Table S12.b. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	pMST2 + pRaf1 ←→ pMST2-pRaf1	$v_1 = k_{1f}.[pMST2][pRaf1] - k_{1r}.[pMST2.pRaf1]$	k_{1f}= 0.0119962, k_{1r}= 0.111344
2	pMST2 → MST2*	$v_2 = \frac{V_2.[MST2]}{Km_2 + [MST2*]}$	V_2= 0.0363027, Km_2= 6.98519
3	MST2* → pMST2	$v_3 = \frac{V_3.[MST2*]}{Km_3 + [pMST2]}$	V_3= 0.147123, Km_3= 31.0557
4	LATS1 → LATS1*	$v_4 = \frac{kc_4.[MST2*].[LATS1]}{Km_4 + [LATS1]}$	kc_4= 0.307658, Km_4= 2.56876
5	LATS1* → LATS1	$v_5 = \frac{V_5.[LATS1*]}{Km_5 + [LATS1*]}$	V_5= 3.20068, Km_5= 0.0641184
6	Raf1* → pRaf1	$v_6 = \frac{kc_6.[LATS1*].[Raf1*]}{Km_6 + [Raf1*]}$	kc_6= 0.00963654, Km_6= 0.0688294
7	pRaf1 → Raf1*	$v_7 = \frac{V_7.[pRaf1]}{Km_7 + [pRaf1]}$	V_7= 0.207988, Km_7= 62.1023

Table S12.b. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S12.b. .

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[pMST2]/dt	$v_3 - v_2 - v_1$	0
d[pRaf1]/dt	$v_6 - v_7 - v_1$	0
d[pMST2-pRaf1]/dt	v_1	0
d[MST2]/dt	$v_2 - v_3$	100
d[LATS1]/dt	$v_5 - v_4$	85
d[LATS1*]/dt	$v_4 - v_5$	0
d[Raf1*]/dt	$v_7 - v_6$	38

S13.A. Raf- MEK-ERK signaling network facilitates oscillation

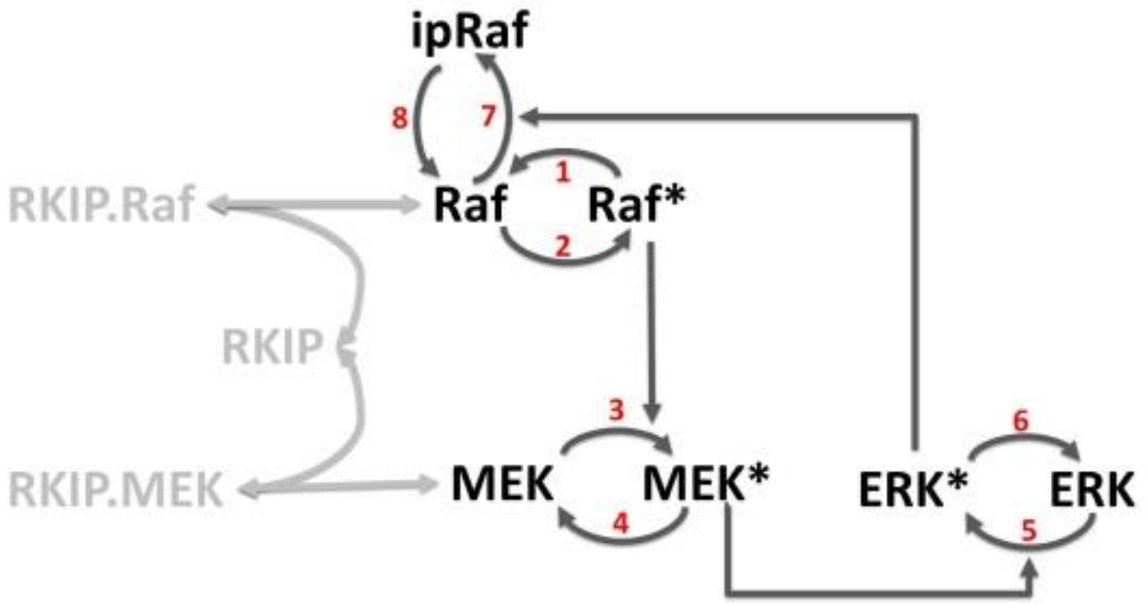


Table S13.A. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	Raf → Raf*	$v_1 = \frac{V_1.[Raf]}{Km_1 + [Raf]}$	V_3=1.227, Km_1=1218
2	Raf* → Raf	$v_2 = \frac{V_2.[Raf *]}{Km_2 + [Raf *]}$	V_2=1.034, Km_2=254
3	MEK → MEK*	$v_3 = \frac{kc_3.[Raf *].[MEK]}{Km_3 + [MEK]}$	kc_3=0.006, Km_3=387
4	MEK* → MEK	$v_4 = \frac{V_4.[MEK *]}{Km_4 + [MEK *]}$	V_4=0.186, Km_4=90
5	ERK → ERK*	$v_5 = \frac{kc_5.[MEK *].[ERK]}{Km_5 + [ERK]}$	kc_5=0.05, Km_5=2
6	ERK* → ERK	$v_6 = \frac{V_6.[ERK *]}{Km_6 + [ERK *]}$	V_6=3.305, Km_6=1458
7	Raf → ipRaf	$v_7 = \frac{kc_7.[ERK *].[Raf]}{Km_7 + [Raf]}$	kc_7=0.006, Km_7=1
8	ipRaf → Raf	$v_8 = \frac{V_8.[ipRaf]}{Km_8 + [ipRaf]}$	V_8=0.404, Km_8=3

Table S13.A. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S13.A.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[Raf]/dt	$v_1+v_8 - v_2 - v_7$	100
d[Raf*]/dt	$v_2 - v_1$	0
d[ipRaf]/dt	$v_7 - v_8$	0
d[MEK]/dt	$v_4 - v_3$	100
d[MEK*]/dt	$v_3 - v_4$	0
d[ERK]/dt	$v_6 - v_5$	100
d[ERK*]/dt	$v_5 - v_6$	0

S13.B. Raf- RKIP-MEK signaling network facilitates oscillation

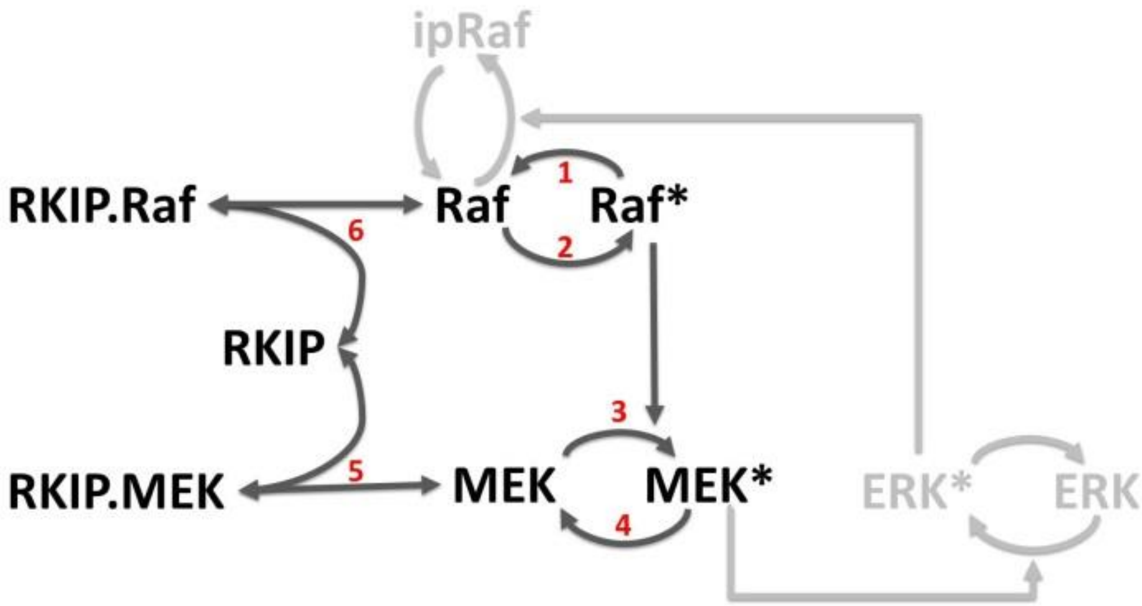


Table S13.B. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	Raf ⟶ Raf*	$v_1 = \frac{V_1.[Raf]}{Km_1 + [Raf]}$	V_3=0.107, Km_1=130
2	Raf* ⟶ Raf	$v_2 = \frac{V_2.[Raf *]}{Km_2 + [Raf *]}$	V_2=0.198, Km_2=111
3	MEK ⟶ MEK*	$v_3 = \frac{kc_3.[Raf *].[MEK]}{Km_3 + [MEK]}$	kc_3=0.616, Km_3=0.1
4	MEK* ⟶ MEK	$v_4 = \frac{V_4.[MEK *]}{Km_4 + [MEK *]}$	V_4=4.572, Km_4=0.1
5	RKIP + MEK ←→ RKIP.MEK	$v_5 = k_{5f}.[RKIP][MEK] - k_{5r}.[RKIP.MEK]$	k_{5f}=0.005, k_{5r}=0.001
6	RKIP + Raf ←→ RKIP.Raf	$v_6 = k_{6f}.[RKIP][Raf] - k_{6r}.[RKIP.Raf]$	k_{6f}=0.005, k_{6r}=0.00009

Table S13.B. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S13.B.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[Raf]/dt	$v_1 - v_2 - v_6$	100
d[Raf*]/dt	$v_2 - v_1$	0
d[MEK]/dt	$v_4 - v_3 - v_5$	100
d[MEK*]/dt	$v_3 - v_4$	0
d[RKIP.Raf]/dt	v_6	0
d[RKIP.MEK]/dt	v_5	0
d[RKIP]/dt	$- v_6 - v_5$	100

S13.C. Raf- RKIP-MEK-ERK signaling network facilitates oscillation

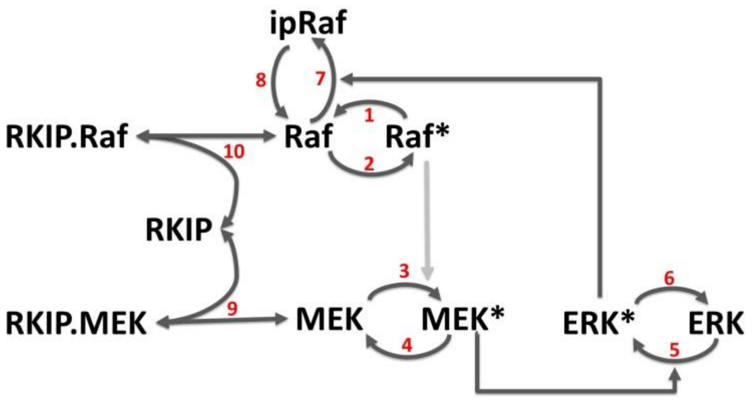


Table S13.C. Reactions and rates of the kinetic model.

Reaction number	**Reactions**	**Reaction rates**	**Parameter values**
1	Raf → Raf*	$v_1 = \frac{V_1.[Raf]}{Km_1 + [Raf]}$	V_3=0.368, Km_1=0.1
2	Raf* → Raf	$v_2 = \frac{V_2.[Raf*]}{Km_2 + [Raf*]}$	V_2=61.37, Km_2=3
3	MEK → MEK*	$v_3 = \frac{V_3.[MEK]}{Km_3 + [MEK]}$	V_3=0.152, Km_3=5494
4	MEK* → MEK	$v_4 = \frac{V_4.[MEK*]}{Km_4 + [MEK*]}$	V_4=8.48, Km_4=25485
5	ERK → ERK*	$v_5 = \frac{kc_5.[MEK*].[ERK]}{Km_5 + [ERK]}$	kc_5=0.977, Km_5=2
6	ERK* → ERK	$v_6 = \frac{V_6.[ERK*]}{Km_6 + [ERK*]}$	V_6=0.432, Km_6=0.02
7	Raf → ipRaf	$v_7 = \frac{kc_7.[ERK*].[Raf]}{Km_7 + [Raf]}$	kc_7=1.6, Km_7=530
8	ipRaf → Raf	$v_8 = \frac{V_8.[ipRaf]}{Km_8 + [ipRaf]}$	V_8=0.678, Km_8=1
9	RKIP + MEK ←→ RKIP.MEK	$v_9 = k_{9f}.[RKIP][MEK] - k_{9r}.[RKIP.MEK]$	k_{9f}=0.0007, k_{9r}=0.00004
10	RKIP + Raf ←→ RKIP.Raf	$v_{10} = k_{10f}.[RKIP][Raf] - k_{10r}.[RKIP.Raf]$	k_{10f}= 0.001, k_{10r}=0.002

Table S13.C. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S13.C.

Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[Raf]/dt	$v_1 + v_8 - v_2 - v_7 - v_{10}$	100
d[Raf*]/dt	$v_2 - v_1$	0
d[ipRaf]/dt	$v_7 - v_8$	0
d[MEK]/dt	$v_4 - v_3 - v_9$	100
d[MEK*]/dt	$v_3 - v_4$	0
d[ERK]/dt	$v_6 - v_5$	100
d[ERK*]/dt	$v_5 - v_6$	0
d[RKIP.Raf]/dt	v_{10}	0
d[RKIP.MEK]/dt	v_9	0
d[RKIP]/dt	$- v_9 - v_{10}$	100

S14. Akt-YAP-14.3.3 signaling network facilitates Bistability

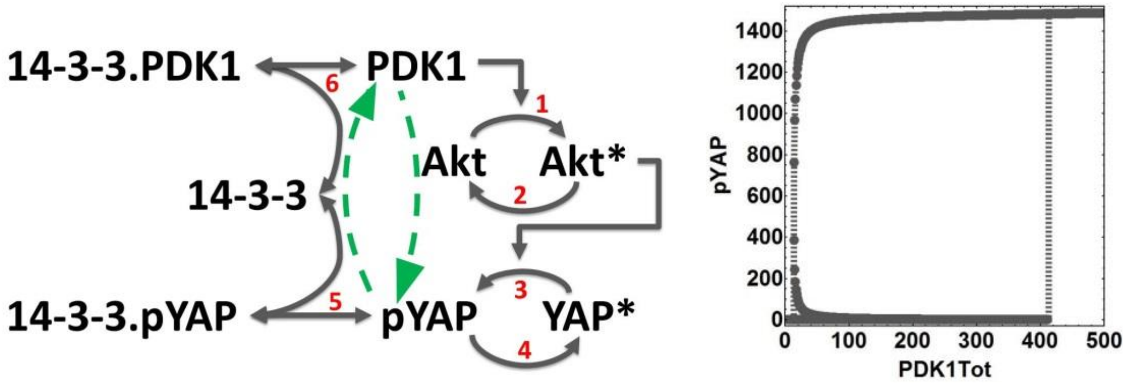


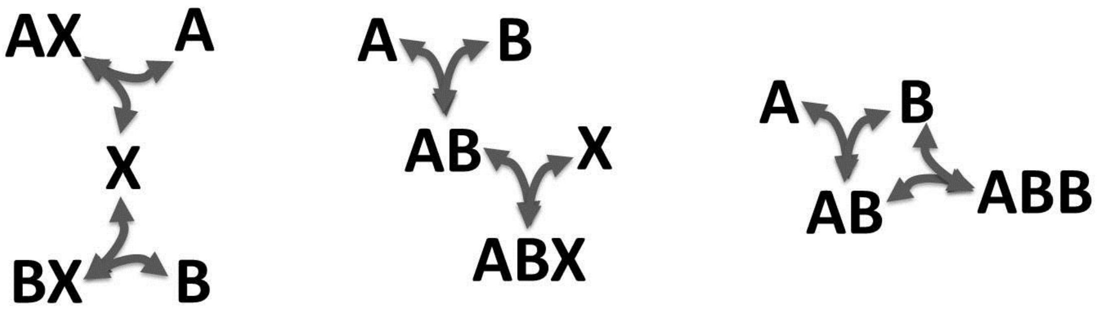
Table S14. Reactions and rates of the kinetic model.

Reaction number	Reactions	Reaction rates	Parameter values
1	Akt → Akt*	$v_1 = \frac{kc_1.[PDK1].[Akt]}{Km_1 + [Akt]}$	kc_1= 0.02, Km_1= 3259
2	Akt* → Akt	$v_2 = \frac{V_2.[B]}{Km_2 + [B]}$	V_2= 14.79, Km_2= 806
3	YAP* → pYAP	$v_3 = \frac{kc_3.[Akt *].[YAP *]}{Km_3 + [YAP *]}$	kc_3=7.39, Km_3= 203
4	pYAP → YAP*	$v_4 = \frac{V_4.[pYAP]}{Km_4 + [pYAP]}$	V_4=0.257, Km_4= 0.6
5	14-3-3 + pYAP ←→ 14-3-3.pYAP	$v_5 = k_{5f}.[14.3.3][pYAP] - k_{5r}.[14.3.3 - pYAP]$	k_{5f}=0.094, k_{5r}=0.014
6	14-3-3 + PDK1 ←→ 14-3-3.PDK1	$v_6 = k_{6f}.[14.3.3][PDK1] - k_{6r}.[14.3.3 - PDK1]$	k_{6f}=0.019, k_{6r}=0.059

Table S14. Ordinary differential equations of the kinetic model. The reaction rates are given in Table S14.

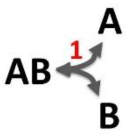
Left-hand Sides	**Right-hand Sides**	**Initial Concentrations (nM)**
d[PDK1]/dt	$– v_6$	300
d[Akt]/dt	$v_2 – v_1$	10
d[Akt*]/dt	$v_1 – v_2$	0
d[pYAP]/dt	$v_3 – v_4 – v_5$	0
d[YAP*]/dt	$v_4 – v_3$	2981
d[14-3-3]/dt	$– v_5 – v_6$	1512
d[14-3-3.pYAP]/dt	$– v_5$	0
d[14-3-3.PDK1]/dt	$– v_6$	0

S15. Alternate PPI coupling strategies



S16. Analytical Solution for PPI Dynamic Regulation Pattern

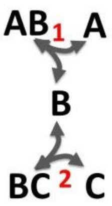
a. PPI event with no intermediates



$$\frac{d[B]}{dt} = -ka1.[A].[B] + kd1.[AB] \qquad \text{------}\!\!\longrightarrow ①$$

$$⇨ \ \frac{d[B]}{dt} \alpha - [A]$$

b. PPI event with one intermediate



$$\frac{d[C]}{dt} = -ka2.[B].[C] + kd2.[BC] \qquad \text{------}\!\!\longrightarrow ②$$

From ①,

$$[B] = \frac{1}{[A]}.\frac{1}{ka1}\left(kd1.[AB] - \frac{d[B]}{dt}\right)$$

Let $\frac{1}{ka1}\left(kd1.[AB] - \frac{d[B]}{dt}\right) = X$

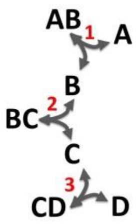
$$[B] = \frac{1}{[A]}.X \qquad \text{-----}\!\!\longrightarrow ③$$

Substituting ③ in ②,

$$\frac{d[C]}{dt} = -ka2.\frac{1}{[A]}.X.[C] + kd2.[BC] \qquad ----\rightarrow ④$$

$$\Rightarrow \frac{d[C]}{dt} \alpha - \frac{1}{[A]}$$

c. PPI event with two intermediates



$$\frac{d[D]}{dt} = -ka3.[C].[D] + kd3.[CD] \qquad -----\rightarrow ⑤$$

From ④,

$$[C] = [A].\frac{1}{X.ka2}\left(kd2.[BC] - \frac{d[C]}{dt}\right)$$

Let $\frac{1}{X.ka2}\left(kd2.[BC] - \frac{d[C]}{dt}\right) = Y$

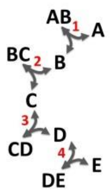
$$[C] = [A].Y \qquad ----\rightarrow ⑥$$

Substituting ⑥ in ⑤,

$$\frac{d[D]}{dt} = -ka3.[A].Y.[D] + kd3.[CD] \qquad ----\rightarrow ⑦$$

$$\Rightarrow \frac{d[D]}{dt} \alpha - [A]$$

d. PPI event with three intermediates



$$\frac{d[E]}{dt} = -ka4.[D].[E] + kd4.[DE] \qquad -----\rightarrow ⑧$$

From ⑦,

$$[D] = \frac{1}{[A]}.\frac{1}{Y.ka3}\left(kd3.[CD] - \frac{d[D]}{dt}\right)$$

Let $\frac{1}{Y.ka3}\left(kd3.[CD] - \frac{d[D]}{dt}\right) = Z$

$$[D] = \frac{1}{[A]}.Z \qquad ----\rightarrow ⑨$$

Substituting ⑨ in⑧,

$$\frac{d[E]}{dt} = -ka4.\frac{1}{[A]}.Z.[E] + kd4.[DE]$$

⇨ $\frac{d[E]}{dt} \alpha - \frac{1}{[A]}$

17. Protein Interaction Domains

Type	Motif	Example Proteins
Protein-Protein Interactions	SH2 Domain	PLCγ
		STAT
		PI3K
	PTB Domain	IRS
	14-3-3 Domain	
	SH3 Domain	Grb2
	PDZ Domain	PSD-95
		PSD-93
		SAP102
		SAP97
		GRIP1
	WW Domain	ITCH
	SAM Domain	Eph receptor
		STIM
	CH Domain	parvin
	FERM Domain	talin
		FAK
	ITAM	FcRγ
		TCR
		FCεRI
		Ig
	LIM Domain	LIN11
		ISL1
		MEC3
		Lasp-1
		PINCH
		paxillin
Protein-Lipid Interactions	BAR Domain	SNX family
	C2 Domain	PTEN
		PKC
		synaptotagmins
	ENTH Domain	Actin
	PH Domain	PLC
		PKB
		PLD
		Btk
		IRS
	PX Domain	SNX family
	FYVE Domain	EEA1
		PIKfyve