

Table S1-I. Model Species

<i>Abbreviation</i>	<i>Model Index</i>	<i>Description</i>
E	1	Epidermal Growth Factor Ligand
H	2	Heregulin Growth Factor Ligand
E ₁	3	ErbB1 Free Receptor
E ₂	4	ErbB2 Free Receptor
E ₃	5	ErbB3 Free Receptor
E ₄	6	ErbB4 Free Receptor
E-E ₁	7	ErbB1 bound to EGF
H-E ₃	8	ErbB3 bound to HRG
H-E ₄	9	ErbB4 bound to HRG
E ₁₁	10	EGF-ErbB1 dimers
E ₁₂	11	EGF-ErbB1 ErbB2 dimers
E ₂₃	12	HRG-ErbB3 ErbB2 dimers
E ₃₄	13	HRG-ErbB3 HRG-ErbB4 dimers
E ₂₄	14	ErbB2 HRG-ErbB4 dimers
E ₄₄	15	HRG-ErbB4 dimers
E ₁₁ P	16	Phosphorylated E ₁₁
E ₁₂ P	17	Phosphorylated E ₁₂
E ₂₃ P	18	Phosphorylated E ₂₃
E ₃₄ P	19	Phosphorylated E ₃₄
E ₂₄ P	20	Phosphorylated E ₂₄
E ₄₄ P	21	Phosphorylated E ₄₄
G	22	Free Grb2
S	23	Free Shc
I	24	Free PI-3K

R	25	Free RasGAP
O	26	Free SOS
A	27	Free Gab1
E ₁₁ G	28	1-1 dimer bound to Grb2
E ₁₁ S	29	1-1 dimer bound to Shc
E ₁₁ R	30	1-1 dimer bound to RasGAP
E ₁₂ G	31	1-2 dimer bound to Grb2
E ₁₂ S	32	1-2 dimer bound to Shc
E ₁₂ R	33	1-2 dimer bound to RasGAP
E ₂₃ G	34	2-3 dimer bound to Grb2
E ₂₃ S	35	2-3 dimer bound to Shc
E ₂₃ I	36	2-3 dimer bound to PI-3K
E ₂₃ R	37	2-3 dimer bound to RasGAP
E ₃₄ G	38	3-4 dimer bound to Grb2
E ₃₄ S	39	3-4 dimer bound to Shc
E ₃₄ I	40	3-4 dimer bound to PI-3K
E ₃₄ R	41	3-4 dimer bound to RasGAP
E ₂₄ G	42	2-4 dimer bound to Grb2
E ₂₄ S	43	2-4 dimer bound to Shc
E ₂₄ I	44	2-4 dimer bound to PI-3K
E ₂₄ R	45	2-4 dimer bound to RasGAP
E ₄₄ G	46	4-4 dimer bound to Grb2
E ₄₄ S	47	4-4 dimer bound to Shc
E ₄₄ I	48	4-4 dimer bound to PI-3K
E ₄₄ R	49	4-4 dimer bound to RasGAP
ΣG	50	Membrane localized Grb2

ΣS	51	Membrane localized Shc
ΣI	52	Membrane localized PI-3K
ΣR	53	Membrane localized RasGAP
ΣA	55	Membrane localized Gab1
ΣSP	56	Phosphorylated membrane localized Shc
ΣAP	57	Phosphorylated membrane localized Gab1
$\Sigma G-O$	58	SOS bound to membrane bound Grb2
$\Sigma G-A$	59	Gab1 bound to membrane bound Grb2
$\Sigma SP-G$	60	Grb2 bound to membrane localized, phosphorylated Shc
$\Sigma AP-S$	61	Shc bound to membrane localized, phosphorylated Gab1
$\Sigma AP-I$	62	PI-3K bound to membrane localized, phosphorylated Gab1
$\Sigma AP-R$	63	RasGAP bound to membrane localized, phosphorylated Gab1
P_3-A	64	Gab1 bound to PIP_3
P_2	65	Free PIP_2
P_3	66	Free PIP_3
Akt	67	Free, inactive Akt
Akt*	68	Free, active Akt
RsD	69	Ras-GDP
RsT	70	Ras-GTP
ΣRP	71	Membrane localized, phosphorylated RasGAP
Raf	72	Free, inactive Raf
Raf*	73	Free, active Raf
MEK	74	Free, inactive MEK
MEK*	75	Free, active MEK
ERK	76	Free, inactive ERK
ERK*	77	Free, active ERK

OP	78	Inactive, phosphorylated SOS
AP	79	Inactive, phosphorylated Gab1
A- Σ G-O	82	Membrane bound Grb2 bound to Gab1 and SOS
Σ A-G	83	Gab1 bound to PIP ₃ and Grb2
Σ A-G-O	84	Gab1 bound to PIP ₃ and Grb2-SOS
Σ O	85	Membrane localized SOS
E ₁₃	86	ErbB1-ErbB3 dimers
E ₁₄	87	ErbB1-ErbB4 dimers
E ₁₃ P	88	Phosphorylated ErbB1-ErbB3 dimers
E ₁₄ P	89	Phosphorylated ErbB1-ErbB4 dimers
E ₁₃ G	90	Grb2 bound to ErbB1-ErbB3 dimers
E ₁₃ S	91	Shc bound to ErbB1-ErbB3 dimers
E ₁₃ I	92	PI-3K bound to ErbB1-ErbB3 dimers
E ₁₃ R	93	RasGAP bound to ErbB1-ErbB3 dimers
E ₁₄ G	94	Grb2 bound to ErbB1-ErbB3 dimers
E ₁₄ S	95	Shc bound to ErbB1-ErbB3 dimers
E ₁₄ I	96	PI-3K bound to ErbB1-ErbB3 dimers
E ₁₄ R	97	RasGAP bound to ErbB1-ErbB3 dimers
f _{int}	98	Empirical PI-3K fractional multiplier
T	99	Free PTP-1B
E ₁₁ T	100	PTP-1B bound to ErbB1 dimers
E ₁₂ T	101	PTP-1B bound to ErbB1-ErbB2 dimers
E ₂₃ T	102	PTP-1B bound to ErbB2-ErbB3 dimers
E ₃₄ T	103	PTP-1B bound to ErbB3-ErbB4 dimers
E ₂₄ T	104	PTP-1B bound to ErbB2-ErbB4 dimers
E ₄₄ T	105	PTP-1B bound to ErbB4 dimers

$E_{13}T$	106	PTP-1B bound to ErbB1-ErbB3 dimers
$E_{14}T$	107	PTP-1B bound to ErbB1-ErbB4 dimers
$\Sigma AP-T$	108	PTP-1B bound to membrane-localized Gab1
ΣT	109	Membrane localized PTP-1B
E_1-PT	110	Threonine Phosphorylated ErbB1
E_2-PT	111	Threonine Phosphorylated ErbB2
E_4-PT	112	Threonine Phosphorylated ErbB4
$E-E_1-PT$	113	Threonine Phosphorylated ErbB1 bound to EGF
$H-E_4-PT$	114	Threonine Phosphorylated ErbB4 bound to HRG
pERK	115	Monophosphorylated ERK
ERK-MEK*	116	Unphosphorylated ERK bound to active MEK
pERK-MEK*	117	Monophosphorylated ERK bound to active MEK
ERKppase	118	ERK phosphatase
ERK*-ERKppase	119	Active ERK bound to ERK phosphatase
pERK-ERKppase	120	Monophosphorylated ERK bound to ERK phosphatase

Table S1-II. Reactions

Parameter values can be found in the Supplementary file Estimation.xls. VeVc is taken to be 33.3 [Kholodenko et al., 1999]. All units are in terms of s and nM: Concentration (nM), V_{\max} (nM/s), k_{cat} (1/s), k_{on} (1/s/nM), k_{off} (1/s), K_m (nM), K_d (nM), k_f (1/s), k_r (1/s), k_{PTP} (1/s), k_{deg} (1/s).

<i>Index</i>	<i>Description</i>	<i>Rate Equation</i>
1	EGF binding to ErbB1	$k_{on1}[E][E_1]/VeVc - k_{off1}[E - E_1]/VeVc$
2	HRG binding to ErbB3	$k_{on2}[H][E_3]/VeVc - k_{off2}[H - E_3]/VeVc$
3	HRG binding to ErbB4	$k_{on3}[H][E_4]/VeVc - k_{off3}[H - E_4]/VeVc$
4	ErbB1 homodimerization	$k_{on4}[E - E_1]^2 - k_{off4}[E_{11}]$
5	ErbB1/ErbB2 dimerization	$k_{on5}[E - E_1][E_2] - k_{off5}[E_{12}]$
6	ErbB2/ErbB3 dimerization	$k_{on6}[H - E_3][E_2] - k_{off6}[E_{23}]$
7	ErbB3/ErbB4 dimerization	$k_{on7}[H - E_3][H - E_4] - k_{off7}[E_{34}]$
8	ErbB2/ErbB4 dimerization	$k_{on8}[E_2][H - E_4] - k_{off8}[E_{24}]$
9	ErbB4 homodimerization	$k_{on9}[H - E_4]^2 - k_{off9}[E_{44}]$
10	1-1 phosphorylation	$k_{f10}[E_{11}] - \frac{V_{max10}[E_{11}P]}{K_{m10} + [E_{11}P]} - k_{PTP10}[\Sigma T][E_{11}P] - k_{deg}[E_{11}P]$
11	1-2 phosphorylation	$k_{f11}[E_{12}] - \frac{V_{max11}[E_{12}P]}{K_{m11} + [E_{12}P]} - k_{PTP11}[\Sigma T][E_{12}P]$

12	2-3 phosphorylation	$\frac{k_{f12} [E_{23}] - \frac{V_{max12} [E_{23} P]}{K_{m12} + [E_{23} P]} - k_{PTP12} [\Sigma T] [E_{23} P]}$
13	3-4 phosphorylation	$\frac{k_{f13} [E_{34}] - \frac{V_{max13} [E_{34} P]}{K_{m13} + [E_{34} P]} - k_{PTP13} [\Sigma T] [E_{34} P]}$
14	2-4 phosphorylation	$\frac{k_{f14} [E_{24}] - \frac{V_{max14} [E_{24} P]}{K_{m14} + [E_{24} P]} - k_{PTP14} [\Sigma T] [E_{24} P]}$
15	4-4 phosphorylation	$\frac{k_{f15} [E_{44}] - \frac{V_{max15} [E_{44} P]}{K_{m15} + [E_{44} P]} - k_{PTP15} [\Sigma T] [E_{44} P]}$
16	Grb2 binding to E ₁₁	$4 * k_{on16} [E_{11} P] [G] - k_{off16} [E_{11} G] f_{\Sigma G} - k_{deg} [E_{11} G]$
17	Shc binding to E ₁₁	$8 * k_{on17} [E_{11} P] [S] - k_{off17} [E_{11} S] f_{\Sigma S} - k_{deg} [E_{11} S]$
18	RasGAP binding to E ₁₁	$2 * k_{on18} [E_{11} P] [R] - k_{off18} [E_{11} R] f_{\Sigma R} - k_{deg} [E_{11} R]$
19	Grb2 binding to E ₁₂	$3 * k_{on19} [E_{12} P] [G] - k_{off19} [E_{12} G] f_{\Sigma G}$
20	Shc binding to E ₁₂	$6 * k_{on20} [E_{12} P] [S] - k_{off20} [E_{12} S] f_{\Sigma S}$
21	RasGAP binding to E ₁₂	$2 * k_{on21} [E_{12} P] [R] - k_{off21} [E_{12} R] f_{\Sigma R}$
22	Grb2 binding to E ₂₃	$3 * k_{on22} [E_{23} P] [G] - k_{off22} [E_{23} G] f_{\Sigma G}$
23	Shc binding to E ₂₃	$3 * k_{on23} [E_{23} P] [S] - k_{off23} [E_{23} S] f_{\Sigma S}$

24	PI-3K binding to E ₂₃	$3 * k_{on24} [E_{23} P][I] - k_{off24} [E_{23} I]$
25	RasGAP binding to E ₂₃	$2 * k_{on25} [E_{23} P][R] - k_{off25} [E_{23} R] f_{\Sigma R}$
26	Grb2 binding to E ₃₄	$4 * k_{on26} [E_{34} P][G] - k_{off26} [E_{34} G] f_{\Sigma G}$
27	Shc binding to E ₃₄	$3 * k_{on27} [E_{34} P][S] - k_{off27} [E_{34} S] f_{\Sigma S}$
28	PI-3K binding to E ₃₄	$4 * k_{on28} [E_{34} P][I] - k_{off28} [E_{34} I]$
29	RasGAP binding to E ₃₄	$2 * k_{on29} [E_{34} P][R] - k_{off29} [E_{34} R] f_{\Sigma R}$
30	Grb2 binding to E ₂₄	$3 * k_{on30} [E_{24} P][G] - k_{off30} [E_{24} G] f_{\Sigma G}$
31	Shc binding to E ₂₄	$4 * k_{on31} [E_{24} P][S] - k_{off31} [E_{24} S] f_{\Sigma S}$
32	PI-3K binding to E ₂₄	$1 * k_{on32} [E_{24} P][I] - k_{off32} [E_{24} I]$
33	RasGAP binding to E ₂₄	$2 * k_{on33} [E_{24} P][R] - k_{off33} [E_{24} R] f_{\Sigma R}$
34	Grb2 binding to E ₄₄	$4 * k_{on34} [E_{44} P][G] - k_{off34} [E_{44} G] f_{\Sigma G}$
35	Shc binding to E ₄₄	$4 * k_{on35} [E_{44} P][S] - k_{off35} [E_{44} S] f_{\Sigma S}$
36	PI-3K binding to E ₄₄	$2 * k_{on36} [E_{44} P][I] - k_{off36} [E_{44} I]$
37	RasGAP binding to E ₄₄	$2 * k_{on37} [E_{44} P][R] - k_{off37} [E_{44} R] f_{\Sigma R}$

38	Membrane localized Shc phosphorylation	$k_{j38} [\Sigma S][\Sigma EP] - \frac{V_{max38} [\Sigma SP]}{K_{m38} + [\Sigma S P]} - k_{PTP38} [\Sigma T][\Sigma SP]$ $[\Sigma EP] = [E_{11} P] + [E_{12} P] + [E_{23} P] + [E_{24} P] + [E_{34} P] + [E_{44} P] + [E_{13} P] + [E_{14} P]$
39	Membrane localized Gab1 phosphorylation	$k_{j39} [\Sigma A][\Sigma EP] - \frac{V_{max39} [\Sigma AP]}{K_{m39} + [\Sigma A P]} - k_{PTP39} [\Sigma T][\Sigma AP]$ $[\Sigma EP] = [E_{11} P] + [E_{12} P] + [E_{23} P] + [E_{24} P] + [E_{34} P] + [E_{44} P] + [E_{13} P] + [E_{14} P]$
40	SOS binding to membrane localized Grb2	$k_{on40} [\Sigma G][O] - k_{off40} [\Sigma G - O]$
41	Gab1 binding to membrane localized Grb2	$k_{on41} [\Sigma G][A] - k_{off41} [\Sigma G - A] f_{\Sigma A}$
42	Grb2 binding to membrane localized Shc-P	$k_{on42} [\Sigma SP][G] - k_{off42} [\Sigma SP - G] f_{\Sigma G}$
43	Shc binding to membrane localized Gab1-P	$3 * k_{on43} [\Sigma AP][S] - k_{off43} [\Sigma AP - S] f_{\Sigma S}$
44	PI-3K binding to membrane localized Gab1-P	$3 * k_{on44} [\Sigma AP][I] - k_{off44} [\Sigma AP - I]$
45	RasGAP binding to membrane localized Gab1-P	$2 * k_{on45} [\Sigma AP][R] - k_{off45} [\Sigma AP - R] f_{\Sigma R}$
46	Gab1 binding to PIP ₃	$k_{on46} [A][P_3] - k_{off46} [P_3 - A] f_{\Sigma A}$

47	Akt to Akt*	$\frac{k_{f47} [P_3][Akt]}{K_{mf47} + [Akt]} - \frac{V_{maxr47} [Akt^*]}{K_{mr47} + [Akt^*]}$
48	PIP ₂ to PIP ₃	$\frac{k_{f48}(1 - f_{int} * f_{11})[\Sigma I][P_2]}{\frac{K_{mf48} + [P_2]}{3 * [PTEN][P_3]}} - \frac{K_{mr48} + [P_3]}{f_{11} = \frac{[E_{11} P]}{[\Sigma EP]}}$ $\frac{d f_{int}}{dt} = a_{98} * (-f_{int} + b_{98})$
49	RasGDP to RasGTP	$\frac{k_{f49} [\Sigma O][RsD]}{K_{mf49} + [RsD]} - \frac{k_{r49} [\Sigma R][RsT]}{K_{mr49} + [RsT]} - \frac{k_{r49b} [\Sigma R P][RsT]}{K_{mr49b} + [RsT]} - k_{con49} [RsT]$
50	Membrane localized RasGAP phosphorylation	$\frac{k_{j50} [\Sigma R][\Sigma EP] - V_{max50} [\Sigma R P]}{K_{m50} + [\Sigma R P]} - k_{PTP50} [\Sigma T][\Sigma R P]$ $[\Sigma EP] = [E_{11} P] + [E_{12} P] + [E_{23} P] + [E_{24} P] + [E_{34} P] + [E_{44} P] + [E_{13} P] + [E_{14} P]$
51	Raf to Raf*	$\frac{k_{j51} [RsT][Raf]}{K_{mf51} + [Raf]} - \frac{V_{maxr51} [Raf^*]}{K_{mr51} + [Raf^*]}$
52	MEK to MEK*	$\frac{k_{j52} [Raf^*][MEK]}{K_{mf52} + [MEK]} - \frac{V_{maxr52} [MEK^*]}{K_{mr52} + [MEK^*]}$
53	No reaction	

54	SOS to phosphorylated, inactive SOS	$\frac{k_{f54}[ERK^*][O]}{\frac{K_{mf54}+[O]}{\frac{V_{maxr54}[OP]}{K_{mr54}+[OP]}}}$
55	Gab1 to phosphorylated, inactive Gab1	$\frac{k_{f55}[ERK^*][A]}{\frac{K_{mf55}+[A]}{\frac{V_{maxr55}[AP]}{K_{mr55}+[AP]}}}$
56	No reaction	
57	Grb2 binding to Gab1 bound to PIP ₃	$\frac{k_{on57}[\Sigma A][G]-k_{off57}[\Sigma A-G]}{}$
58	SOS binding to PIP ₃ -Gab1-Grb2 complex	$\frac{k_{on58}[\Sigma A-G][O]-k_{off58}[\Sigma A-G-O]}{}$
59	Gab1 binding to membrane localized Grb2-SOS complex	$\frac{k_{on59}[\Sigma G-O][A]-k_{off59}[A-\Sigma G-O]f_{\Sigma A}}{}$
60	SOS binding to membrane localized Grb2-Gab1 complex	$\frac{k_{on60}[\Sigma G-A][O]-k_{off60}[A-\Sigma G-O]}{}$
61	ErbB1/ErbB3 dimerization	$\frac{k_{on61}[H-E_3][E-E_1]-k_{off61}[E_{13}]}{}$
62	ErbB1/ErbB4 dimerization	$\frac{k_{on62}[E-E_1][H-E_4]-k_{off62}[E_{14}]}{}$
63	1-3 phosphorylation	$\frac{k_{f63}[E_{13}]-\frac{V_{max63}[E_{13}P]}{K_{m63}+[E_{13}P]}-k_{PTP63}[\Sigma T][E_{13}]}{}$
64	1-4 phosphorylation	$\frac{k_{f64}[E_{14}]-\frac{V_{max64}[E_{14}P]}{K_{m64}+[E_{14}P]}-k_{PTP64}[\Sigma T][E_{14}]}{}$
65	Grb2 binding to E ₁₃	$\frac{4*k_{on65}[E_{13}P][G]-k_{off65}[E_{13}G]f_{\Sigma G}}{}$
66	Shc binding to E ₁₃	$\frac{5*k_{on66}[E_{13}P][S]-k_{off66}[E_{13}S]f_{\Sigma S}}{}$

67	PI-3K binding to E ₁₃	$3 * k_{on67}[E_{13}P][I] - k_{off67}[E_{13}I]$
68	RasGAP binding to E ₁₃	$2 * k_{on68}[E_{13}P][R] - k_{off68}[E_{13}R]f_{\Sigma R}$
69	Grb2 binding to E ₁₄	$4 * k_{on69}[E_{14}P][G] - k_{off69}[E_{14}G]f_{\Sigma G}$
70	Shc binding to E ₁₄	$6 * k_{on70}[E_{14}P][S] - k_{off70}[E_{14}S]f_{\Sigma S}$
71	PI-3K binding to E ₁₄	$1 * k_{on71}[E_{14}P][I] - k_{off71}[E_{14}I]$
72	RasGAP binding to E ₁₄	$2 * k_{on72}[E_{14}P][R] - k_{off72}[E_{14}R]f_{\Sigma R}$
73	PTP-1B binding to E ₁₁	$4 * k_{on73}[E_{11}P][T] - k_{off73}[E_{11}T] - k_{deg}[E_{11}T]$
74	PTP-1B binding to E ₁₂	$3 * k_{on74}[E_{12}P][T] - k_{off74}[E_{12}T]$
75	PTP-1B binding to E ₂₃	$2 * k_{on75}[E_{23}P][T] - k_{off75}[E_{23}T]$
76	PTP-1B binding to E ₃₄	$2 * k_{on76}[E_{34}P][T] - k_{off76}[E_{34}T]$
77	PTP-1B binding to E ₂₄	$2 * k_{on77}[E_{24}P][T] - k_{off77}[E_{24}T]$
78	PTP-1B binding to E ₄₄	$2 * k_{on78}[E_{44}P][T] - k_{off78}[E_{44}T]$
79	PTP-1B binding to E ₁₃	$3 * k_{on79}[E_{13}P][T] - k_{off79}[E_{13}T]$
80	PTP-1B binding to E ₁₄	$3 * k_{on80}[E_{14}P][T] - k_{off80}[E_{14}T]$

81	ErbB1 phosphorylated, inactive ErbB1	$\frac{k_{f81} [ERK^*][E_1]}{K_{mf81} + [E_1]} - \frac{V_{maxr81} [E_1 - PT]}{K_{mr81} + [E_1 - PT]}$
82	ErbB2 to phosphorylated, inactive ErbB2	$\frac{k_{f82} [ERK^*][E_2]}{K_{mf82} + [E_2]} - \frac{V_{maxr82} [E_2 - PT]}{K_{mr82} + [E_2 - PT]}$
83	ErbB4 to phosphorylated, inactive ErbB4	$\frac{k_{f83} [ERK^*][E_4]}{K_{mf83} + [E_4]} - \frac{V_{maxr83} [E_4 - PT]}{K_{mr83} + [E_4 - PT]}$
84	E-ErbB1 to phosphorylated, inactive E-ErbB1	$\frac{k_{f84} [ERK^*][E - E_1]}{K_{mf84} + [E - E_1]} - \frac{V_{maxr84} [E - E_1 - PT]}{K_{mr84} + [E - E_1 - PT]}$
85	H-ErbB4 to phosphorylated, inactive H-ErbB4	$\frac{k_{f85} [ERK^*][H - E_4]}{K_{mf85} + [H - E_4]} - \frac{V_{maxr85} [H - E_4 - PT]}{K_{mr85} + [H - E_4 - PT]}$
86	EGF binding to ErbB1-PT	$k_{on86} [E][E_1 - PT] / VeVc - k_{off86} [E - E_1 - PT] / VeVc$
87	HRG binding to ErbB4-PT	$k_{on87} [H][E_4] / VeVc - k_{off87} [H - E_4] / VeVc$
88	PTP-1B binding to membrane localized Gab1-P	$2 * k_{on88} [\Sigma AP][T] - k_{off88} [\Sigma AP - T]$
89	ERK binding to MEK*	$k_{on89} [ERK][MEK^*] - k_{off89} [ERK - MEK^*]$
90	ERK phosphorylation	$k_{cat90} [ERK - MEK^*]$
91	pERK binding to MEK*	$k_{on91} [pERK][MEK^*] - k_{off91} [pERK - MEK^*]$

92	pERK phosphorylation	$k_{cat92} [pERK - MEK^*]$
93	ERK* binding to ERK Phosphatase	$k_{on93} [ERK^*][ERKPPase] - k_{off89} [ERK^* - ERKPPase]$
94	Dephosphorylation of ERK*	$k_{cat94} [ERK^* - ERKPPase]$
95	pERK binding to ERK Phosphatase	$k_{on95} [pERK][ERKPPase] - k_{off95} [pERK - ERKPPase]$
96	Dephosphorylation of pERK	$k_{cat96} [pERK - ERKPPase]$

Table S1-III. Observable Definitions

When comparing experimental data to the model, what is measured (observable) does not usually have a direct correspondence to a single model variable. For example, the phospho-ErbB1 measurement corresponds to all ErbB1 states that are phosphorylated and unbound and are bound to adaptor proteins. Below we define observables in terms of model variable indices, with C representing concentration.

<i>Description</i>	<i>Definition</i>
pErbB1	$2 \cdot C(16) + C(17) + 2 \cdot C(28) + 2 \cdot C(29) + 2 \cdot C(30) + C(31) + C(32) + C(33) + C(88) + C(89) + C(90) + C(91) + C(92) + C(93) + C(94) + C(95) + C(96) + C(97) + 2 \cdot C(100) + C(101) + C(106) + C(107);$
pErbB2	$C(17) + C(18) + C(20) + C(31) + C(32) + C(33) + C(34) + C(35) + C(36) + C(37) + C(42) + C(43) + C(44) + C(45) + C(101) + C(102) + C(104)$
pShc	$C(56) + C(60)$
MEK*	$C(75) + C(116) + C(117)$
ERK*	$C(77) + C(120)$
Akt*	$C(68)$

Table S1-IV. Initial Conditions

All variables not shown in this table have zero initial conditions. Ligand (HRG and EGF) initial conditions are variable. The values of these initial conditions are derived from protein abundances, which were estimated along with the other model parameters as described in Sup_4.pdf. All units are nM.

<i>Species</i>	<i>Value</i>
ErbB1	274
ErbB2	158
ErbB3	294
ErbB4	399
Grb2	82.4
Shc	11.5
PI-3K	46.4
RasGAP	93.6
PTP-1B	500
SOS	82.3
Gab1	43.1
PIP ₂	197
Akt	444
Ras	95.7
Raf	743
MEK	772
ERK	750
ERK-Ppase	35

Table S1-V. On-Rate Multipliers for Virtual Phosphorylation Sites

These parameters were estimated as described in the manuscript and in Supplementary File Sup_5.xls. Their meaning is derived in Supplementary File Sup_6.pdf.

<i>Binding Partner</i>	<i>ErbB1</i>	<i>ErbB2</i>	<i>ErbB3</i>	<i>ErbB4</i>	<i>Gab1</i>
Grb2	2	1	2	2	0
Shc	4	2	1	2	3
PI-3K	0	0	3	1	3
RasGAP	1	1	1	1	2
PTP-1B	2	1	1	1	2

Table S1-VI. Moiety Conservation Equations for Adapter and Scaffold Proteins

<i>Protein</i>	<i>Conservation Equation</i>
Grb2	$G_{\text{tot}} = G + \Sigma G + A - \Sigma G + A - \Sigma G - O + \Sigma G - O$
Shc	$S_{\text{tot}} = S + \Sigma S + \Sigma SP + \Sigma SP - G$
RasGAP	$R_{\text{tot}} = R + \Sigma R + \Sigma RP$
PI-3K	$I_{\text{tot}} = I + \Sigma I$
PTP-1B	$T_{\text{tot}} = T + \Sigma T$
SOS	$O_{\text{tot}} = O + \Sigma O + OP$
Gab1	$A_{\text{tot}} = A + \Sigma A + \Sigma AP + \Sigma AP - S + \Sigma AP - I + \Sigma AP - R + \Sigma AP - T + AP$

Table S1-VII. Fraction Multipliers for Seeding Species Dissociation

<i>Name</i>	<i>Definition</i>	<i>Applicable Reactions</i>
$f_{\Sigma S}$	$\frac{[\Sigma S]}{[\Sigma S] + [\Sigma SP] + [\Sigma SP - G]}$	17, 20, 23, 27, 35, 31, 43
$f_{\Sigma G}$	$\frac{[\Sigma G]}{[\Sigma G] + [A - \Sigma G] + [\Sigma G - O] + [A - \Sigma G - O]}$	16, 19, 22, 26, 34, 30, 42
$f_{\Sigma A}$	$\frac{[\Sigma A]}{[\Sigma A] + [\Sigma AP] + [\Sigma AP - S] + [\Sigma AP - R] + [\Sigma AP - I] + [\Sigma AP - T]}$	46, 59, 41
$f_{\Sigma R}$	$\frac{[\Sigma R]}{[\Sigma R] + [\Sigma RP]}$	18, 21, 25, 29, 37, 33, 45

Additional Experimental Data

Figure S1-1. EGF-induced responses. For ErbB1 phosphorylation, data correspond to a single measurement, while all other data are the mean of two measurements. Error bars represent the range of two experiments.

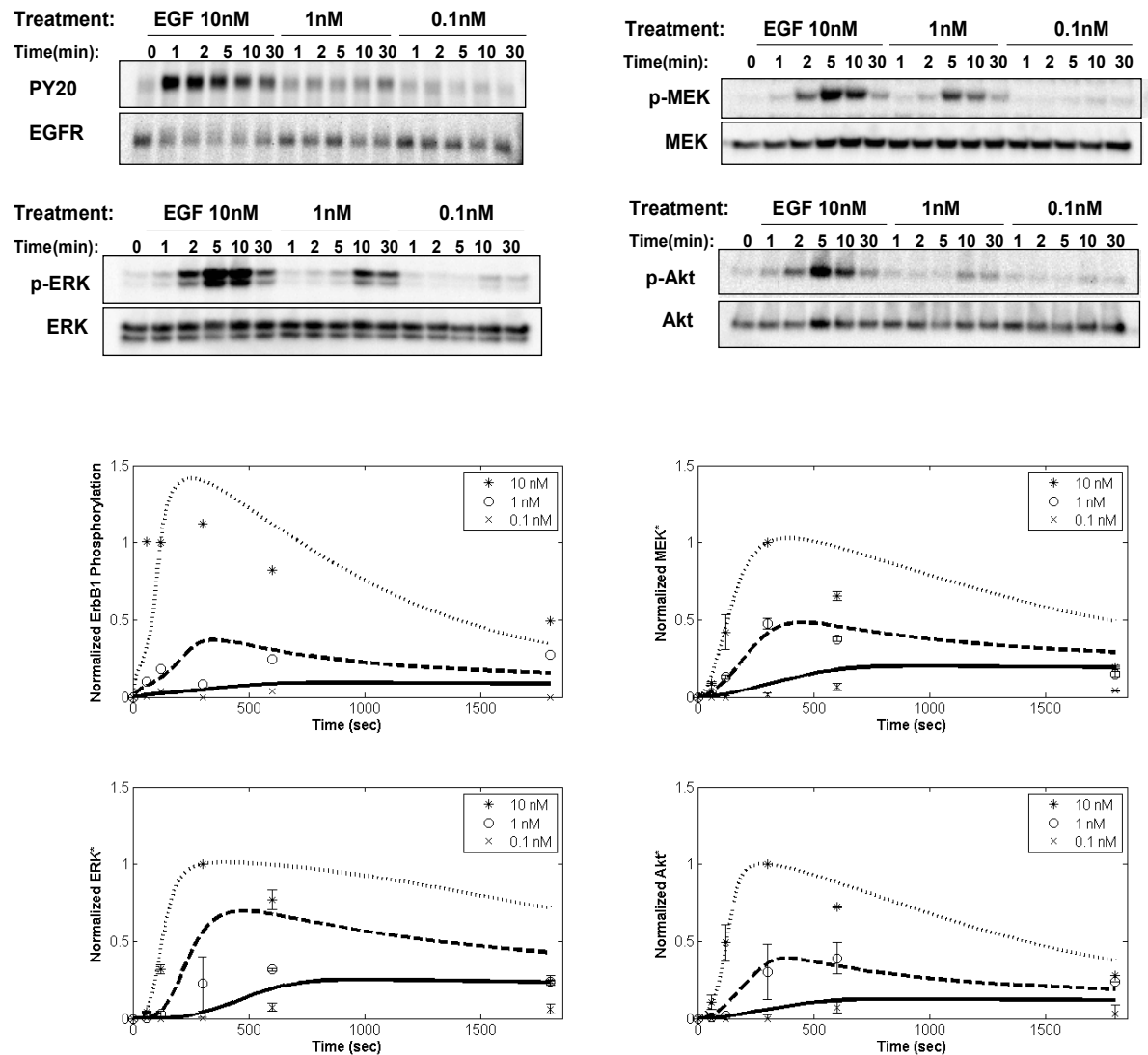


Figure S2-2. HRG-induced responses. For ErbB2 phosphorylation, data correspond to a single measurement, while all other data are the mean of two measurements. Error bars represent the range of two experiments.

