Supplementary Table 1. Computational model details: biochemical reactions, kinetics, parameters and references.

Supplementary Table 2. Initial concentrations of the signaling molecules.

Supplementary Fig. 1. NGFR model simulated PI3K (top panel), Akt (middle panel) and Raf (bottom panel) inhibition. (A and D) Akt phosphorylation; (B and E) Raf phosphorylation; (C, F and G) Erk phosphorylation.

Supplementary Fig. 2. Effect of Akt expression on Erk phosphorylation. (A) EGFR model, (B) NGFR model; Original Akt concentrations is 10nM and increased to ten, hundred times.

Supplementary Table 1. Computational model details: biochemical reactions, kinetics, parameters and references

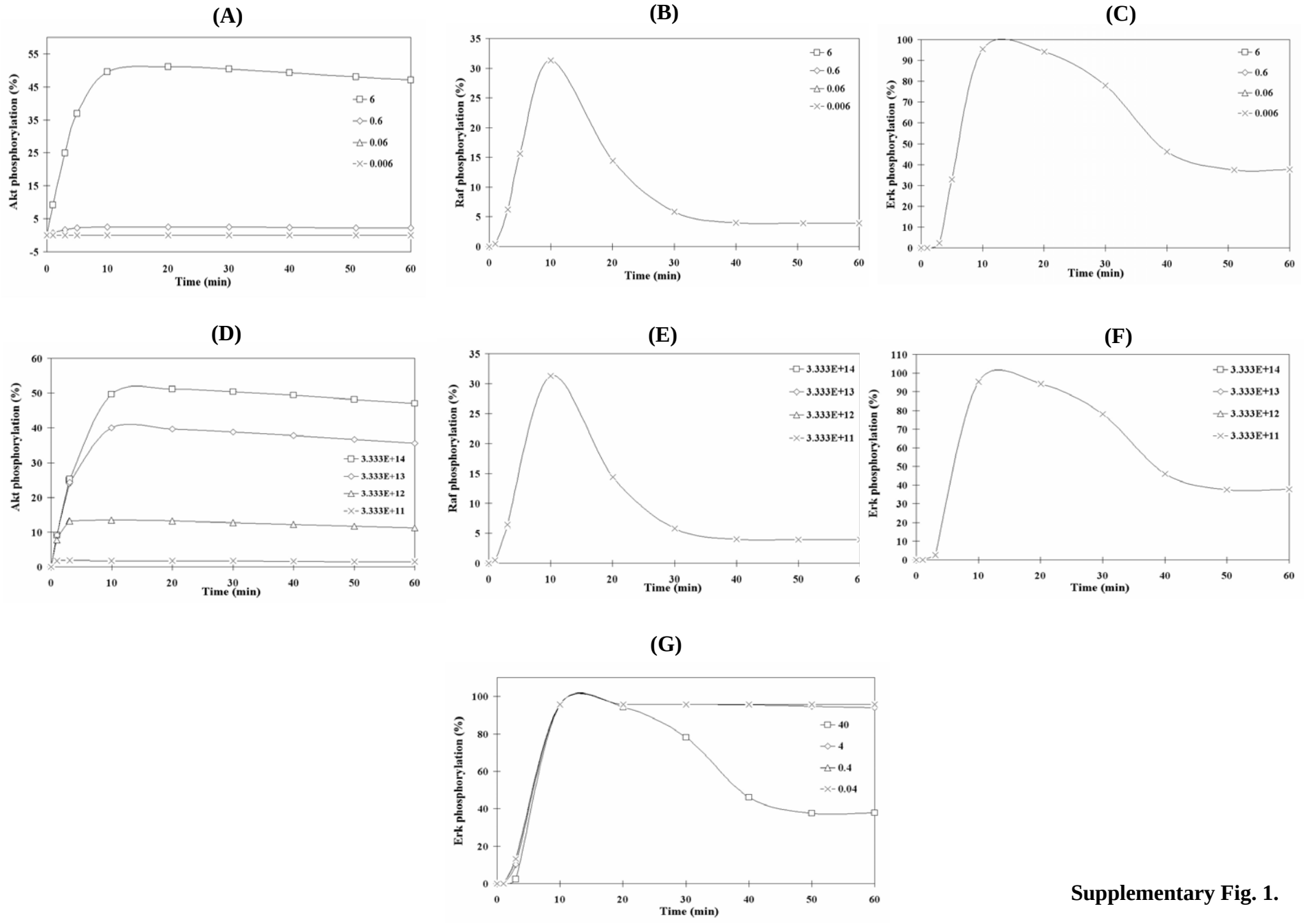
Reaction no.	Biochemical reactions	Kinetic type	Kinetic values	Reference
1	EGFR + EGF = EGF-EGFR	Mass action	k_f = 3.84E+08, k_r = 0.73	13
2	EGF-EGFR → EGFR-I + EGF	Mass action	k = 0.7, f = 0.2, E = 0.12, ΔT = 6.5	13
3	EGFR-I = EGFR	Mass action with time delay	k_f = 0.048, k_r = 0.7, f = 0.2, E = 0.12, ΔT = 6.5	13
4	EGF-EGFR + EGF-EGFR = EGFR-D	Mass action	k_f = 0.00138	13
5	EGFR-D → EGFR-IDS	Mass action with time delay	k_f = 0.35, f = 0.2, E = 0.12, ΔT = 6.5	13
6	EGFR-D + CPP = EGFR-CPP	Mass action	k_f = 1, k_r = 0.00347, f = 0.2	13
7	EGFR-CPP → EGFR-IDS	Mass action with time delay	k_f = 0.35, E = 0.12, ΔT = 6.5	13
8	EGFR-IDS → EGFR-I + EGFR-I + EGF + EGF	Mass action with time delay	k_f = 0.35, E = 0.12, ΔT = 6.5	13
9	Rs→ Ractivated	Mass action	k = 1.3E-002	14, 15
10	Ractivated →	Mass action	k = 1.5E-002	14, 15
11	→ Rs	Mass action	k = 277	14, 15
12	Rs →	Mass action	k = 6.9E-03	14, 15
13	Shc → ShcP	Michaelis-Menten	k_{cat} = 12, K_M = 6000,Enzymes=$_{EGFR\text{-}D,EGFR\text{-}CPP,EGFR\text{-}IDS}$	13
14	ShcP → Shc	Henri-Michaelis-Menten	K_M = 6000, V = 300000,	13
15	ShcP + Sos = ShcS	Mass action	k_f = 0.002, k_r = 3.81	13
16	ShcS → ShcP + SosP	Michaelis-Menten	k_{cat} = 1.6, K_M = 60000, Enzyme = ERKPP	13
17	SosP → Sos	Henri-Michaelis-Menten	K_M = 20000, V = 75	13
18	RasGDP + ShcS = Ras-ShcS	Mass action	k_f = 0.0163, k_r = 10	13
19	Ras-ShcS → RasGTP + ShcS	Mass action	k = 15	13
20	RasGTP + GAP = Ras-GAP	Mass action	k_f = 0.005, k_r = 60	13

21	Ras-GAP $\rightarrow$ RasGDP + GAP	Mass action	k = 720	13
22	RasGTP + Raf = Ras-Raf	Mass action	k_f = 0.0012, k_r = 3	13
23	Ras-Raf $\rightarrow$ RasGTP + Raf*	Mass action	k = 27	13
24	Raf* $\rightarrow$ Raf	Michaelis-Menten	k_{cat} = 40, K_M = 4.86E+15, Enzymes = Akt-PI-PP, E	13
25	MEK $\rightarrow$ MEKP	Michaelis-Menten	k_{cat} = 50, K_M = 9000, Enzyme = Raf*	13
26	MEKP $\rightarrow$ MEK	Henri-Michaelis-Menten	K_M = 600000, V = 92000	13
27	MEKP $\rightarrow$ MEKPP	Michaelis-Menten	k_{cat} = 50, K_M = 9000, Enzyme = Raf*	13
28	MEKPP $\rightarrow$ MEKP	Henri-Michaelis-Menten	K_M = 600000, V = 92000	13
29	ERK $\rightarrow$ ERKP	Michaelis-Menten	k_{cat} = 8.3, K_M = 90000, Enzyme = MEKP & MEKPP	13
30	ERKP $\rightarrow$ ERK	Henri-Michaelis-Menten	K_M = 600000, V = 200000	13
31	ERKP $\rightarrow$ ERKPP	Michaelis-Menten	k_{cat} = 8.3, K_M = 90000, Enzyme = MEKP & MEKPP	13
32	ERKPP $\rightarrow$ ERKP	Henri-Michaelis-Menten	K_M = 600000, V = 400000	13
33	PI3K $\rightarrow$ PI3KP	Michaelis-Menten	k_{cat}=6,K_M =1.2E+07,Enzymes=$_{EGFR-D,EGFR-CPP,EGFR-IDS}$	44
34	PI3KP $\rightarrow$ PI3K	Henri-Michaelis-Menten	K_M = 2.216E+018, V = 9.46E+019	44
35	PtdIns(4,5)P_2 $\rightarrow$ PtdInsP_3	Michaelis-Menten	k_{cat} = 1014, K_M = 2346, Enzyme = PI3KP	44
36	PtdInsP_3 $\rightarrow$ PtdIns(4,5)P_2	Henri-Michaelis-Menten	K_M = 5.43E+15, V = 6.11E+20	44
37	Akt + PIP3 = Akt-PIP3	Mass action	k_f = 2.e-003, k_r = 3.81	44
38	Akt-PIP3 $\rightarrow$ Akt-PI-P	Michaelis-Menten	k_{cat} = 3.33E+14, K_M = 1333.3, Enzyme = PI3KP	44
39	Akt-PI-P $\rightarrow$ Akt-PIP3	Michaelis-Menten	k_{cat} = 2E+17, K_M = 4.818E+19, Enzyme = PP2A	44
40	Akt-PI-P $\rightarrow$ Akt-PI-PP	Michaelis-Menten	k_{cat} = 3.33E+14, K_M = 1333.3, Enzyme = PI3KP	44
41	Akt-PI-PP $\rightarrow$ Akt-PI-P	Michaelis-Menten	k_{cat} = 2E+17, K_M = 4.818E+19, Enzyme = PP2A	44

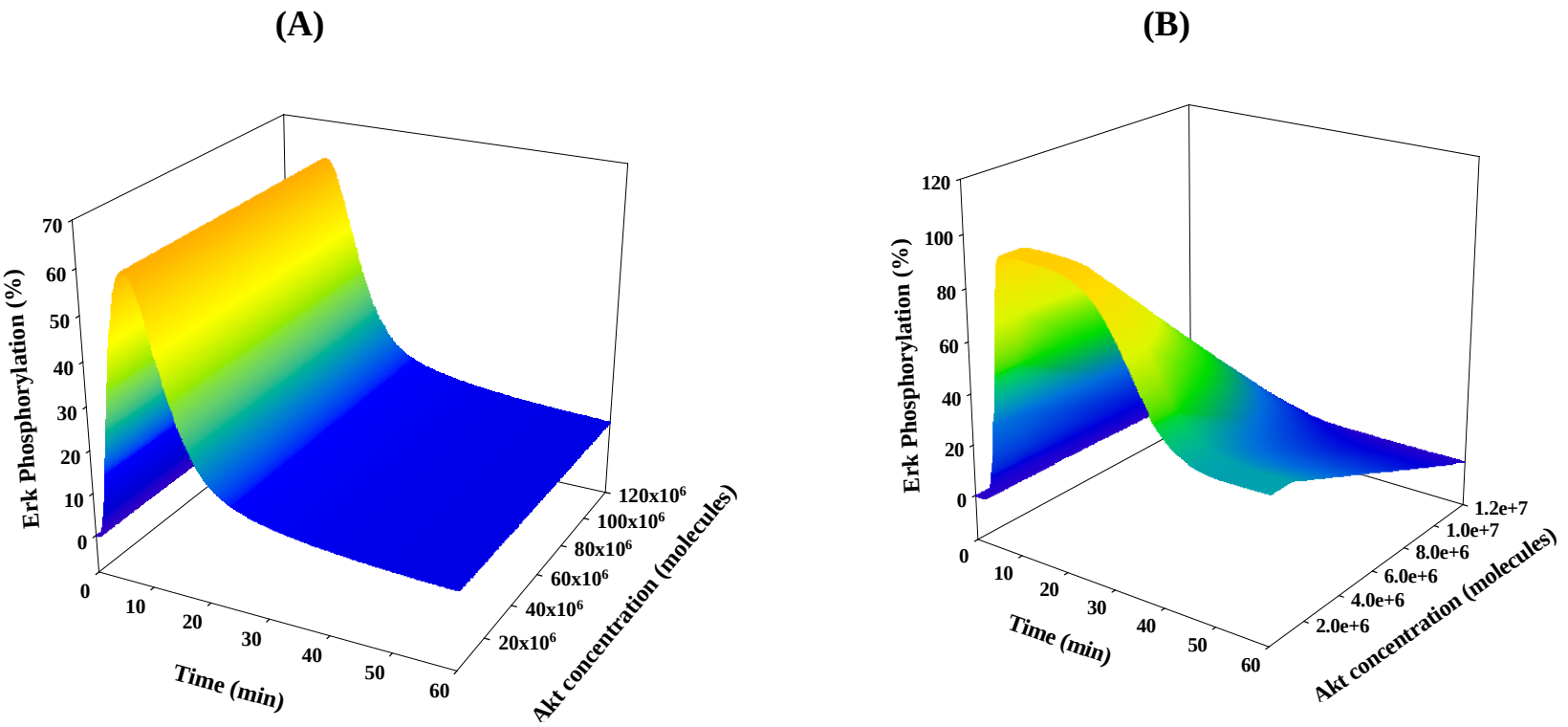
Supplementary Table 2. Initial concentrations of the signaling molecules

Proteins	Concentration (molecules/cell)
EGF and NGF	100*
EGFR	1.11×10^{4}
EGFR-I	4.0×10^{3}
Shc	3.0×10^{4}
Sos	2.0×10^{4}
GAP	1.5×10^{4}
Ras	2.0×10^{4}
Raf	1.0×10^{4}
MEK	3.6×10^{5}
ERK	7.5×10^{5}
PI3K	6.02×10^{15}
$PtdIns(4,5)P_2$	4.80×10^{17}
Akt	1.20×10^{5}
PP2A	6.86×10^{15}
E	4.21×10^{15}

*nM



Supplementary Fig. 1.



Supplementary Fig. 2.