Table S1. Reactions and Kinetic Parameters for Bradykinin Receptor Activation, Related to Figure 3

Name	**Reaction**	**Reaction Type**	**Kinetic parameters**	**References and Notes**
Bradykinin receptor binds ligand and GRK near simultaneously	B_2R+ Bradykinin + GRK ⇔ B_2R_p	Binding	K_{on}=10 $\mu M^{-1}.s^{-1}$ K_{off}=0.033 s^{-1}	The binding affinity of B_2R to bradykinin is ~ 3nM (Gera et al., 2011). Varying k_{on} and k_{off} such that the ratio was maintained did not change the results.
Arrestin binds B_2R_p	B_2R_p + arrestin ⇔ Arrestin bound receptor	Binding	K_{on}=0.45 $\mu M^{-1}.s^{-1}$ K_{off}=1.0 s^{-1}	We used the same values as arrestin binding βAR (Vayttaden et al., 2010).

These reactions were taken from (Gera et al., 2011) and (Vayttaden et al., 2010).

Table S2. Initial Concentrations and Diffusivities for Bradykinin Receptor Signaling, Related to Figure 3

Initial concentrations for bradykinin receptor signaling (Figure 3)		
Name	**Initial concentration**	**Compartment**
GRK	0.2 μM	Cytoplasm
Arrestin	1 μM	Cytoplasm
Bradykinin	1.0 μM	Extracellular space
B_2R_p	0 molecules/μm^2	Plasma membrane
Arrestin bound receptor	0 molecules/μm^2	Plasma membrane
B2R	100 molecules/μm^2	Plasma membrane
Diffusion coefficients for B_2R signaling (Related to Figure 3)		
Name	**Diffusivity ($\mu m^2.s^{-1}$)**	**References/Notes**
B_2R	0.2	(Philip et al., 2007)
B_2R_p	0.2	(Philip et al., 2007)
Arrestin bound receptor	0.002	(Philip et al., 2007; Slepak and Hurley, 2007)
GRK	1	assumed
Arrestin	1	assumed

Table S3. Reactions and Kinetic Parameters for EGF Signaling, Related to Figure 4

Name	**Reaction**	**Reaction Type**	**Kinetic parameters**
EGF binds receptor	EGF + EGFR ⇔ EGF-EGFR	Binding	K_{on}=1 $\mu M^{-1}.s^{-1}$ K_{off}=0.0001s^{-1}
EGFR dimerization	2 EGF-EGFR ⇔ EGFR_active	Binding	K_{on}=1 $\mu M^{-1}.s^{-1}$ K_{off}=0.1s^{-1}
SHC phosphorylation	SHC + EGFR_active ⇔ SHC-p	Enzymatic	K_m=1 μM K_{cat} =0.05 s^{-1}
SHC inactivation	SHC-p ⇔ SHC	Inactivation	K_{on}=0.001 s^{-1}
Sos-Grb2 binding	Sos + Grb2 ⇔ Sos-Grb2	Binding	K_{on}=0.25 $\mu M^{-1}.s^{-1}$ K_{off}=0.0168 s^{-1}
Shc-p binds PDGFR	EGF-EGFR + Shc-p ⇔ EGF-EGFR-Shcp	Binding	K_{on}=6.0 $\mu M^{-1}.s^{-1}$ K_{off}=0.3 s^{-1}
SHC binding Sos-Grb2	Sos-Grb2 + EGF-EGFR-SHC-p ⇔ EGF-EGFR-Sos-Grb2-Shc-p	Binding	K_{on}=0.5 $\mu M^{-1}.s^{-1}$ K_{off}=0.1 s^{-1}
Ras activation	Ras-GDP + **EGF-EGFR-Sos-Grb2-Shc-p** ⇔ Ras-GTP	Enzymatic	K_m = 0.5 μM K_{cat} =0.05 s^{-1}
Ras inactivation	Ras-GTP ⇔ Ras-GDP	Inactivation	K_{on} = 0.002 s^{-1}
Raf activation	Raf + **Ras-GTP** ⇔ Raf*	Enzymatic	K_m=0.5 μM K_{cat}=1 s^{-1}
Raf inactivation	Raf* + **PP2A** ⇔ Raf	Enzymatic	K_m=15.7 μM K_{cat}=5 s^{-1}
MEK activation	MEK + **Raf*** ⇔ MEK*	Enzymatic	K_m=0.1591 μM K_{cat}=0.105 s^{-1}
MEK inactivation	MEK* + **PP2A** ⇔ MEK	Enzymatic	K_m=15.7 μM K_{cat}=5 s^{-1}
MAPK activation	MAPK + **MEK*** ⇔ MAPK*	Enzymatic	K_m=0.1591 μM K_{cat}=0.105 s^{-1}
MAPK inactivation	MAPK* + **PTP** ⇔ MAPK	Enzymatic	K_m=0.46 μM K_{cat}=1.02 s^{-1}
Ras-GAP	Ras-GTP + **Ras-GAP** ⇔ Ras-GDP	Enzymatic	K_m=1.0 μM K_{cat}=0.01 s^{-1}
MAPK nuclear translocation	MAPK* ⇔ MAPK_nucleus	First order	K_f=1.0 s^{-1} K_b=0.1 s^{-1}

These reactions were taken from (Bhalla et al., 2002).

Table S4. Initial Concentrations for EGF Signaling, Related to Figure 4

Name	**Initial concentration**	**Compartment**
Raf	0.2 μM	Cytoplasm
Raf*	0 μM	Cytoplasm
PP2A	0.1 μM	Cytoplasm
PTP	0.1 μM	Cytoplasm
MEK	0.18 μM	Cytoplasm
MEK*	0 μM	Cytoplasm
MAPK	0.36 μM	Cytoplasm
MAPK*	0 μM	Cytoplasm
Ras-GAP	0.002 μM	Cytoplasm
EGF	1.0 μM	Extracellular space
EGF-EGFR	0 molecules/μm^2	Plasma membrane
EGF-EGFR-Shcp	0 molecules/μm^2	Plasma membrane
Ras-GTP	0 molecules/μm^2	Plasma membrane
Shc-p	0 μM	Cytoplasm
Sos	0.1 μM	Cytoplasm
Grb2	1.0 μM	Cytoplasm
Sos-Grb2	1.0 μM	Cytoplasm
EGF-EGFR-Sos-Grb2-Shc-p	0 molecules/μm^2	Plasma membrane
Ras-GDP	500 molecules/μm^2	Plasma membrane
EGFR	250 molecules/μm^2	Plasma membrane
Shc	0.1 μM	Cytoplasm

These values were obtained from (Bhalla et al., 2002; Fujioka et al., 2006).

Table S5. Diffusion Constants for the Components in the EGFR Pathway, Related to Figure 4

Calculation of diffusion constants (Mayawala et al., 2006)			
Name	**Molecular weight (kDa)**	**Diffusivity ($\mu m^2.s^{-1}$)**	**Notes and References**
EGFR (dimer)	268	0.08	(Mayawala et al., 2006)
EGFR (monomer)	134	0.112	Calculated from Eqn. (S41)
EGFR-Shc	268+50	0.073	Calculated from Eqn. (S41)
EGFR-Shc-Sos-Grb2	268+50+150+28	0.058	Calculated from Eqn. (S41)
Shc	50	6.4	Calculated from Eqn. (S41)
Sos	150	3.7	Calculated from Eqn. (S41)
Grb2	28	8.5	Calculated from Eqn. (S41)
Ras-GAP	120	4.14	Calculated from Eqn. (S41)
Diffusivities of components in the EGF signaling pathway			
Name	**Diffusion coefficient**	**Compartment**	**Notes and References**
Raf	6.0 $\mu m^2/s$	Cytoplasm	(Storm et al., 1990)
Raf*	6.0 $\mu m^2/s$	Cytoplasm	(Storm et al., 1990)
PP2A	0 $\mu m^2/s$	Cytoplasm	PP2A is present uniformly in the cytoplasm
MEK	7.0 $\mu m^2/s$	Cytoplasm	(Fujioka et al., 2006; Seger et al., 1992),
MEK*	7.0 $\mu m^2/s$	Cytoplasm	(Bhalla et al., 2002; Fujioka et al., 2006; Seger et al., 1992),
MAPK	7.0 $\mu m^2/s$	Cytoplasm	(Bhalla et al., 2002; Sanghera et al., 1990)
MAPK*	7.0 $\mu m^2/s$	Cytoplasm	(Bhalla et al., 2002; Fujioka et al., 2006; Kholodenko et al., 1999; Sanghera et al., 1990)

Ras-GAP	4.14 $\mu m^2/s$	Cytoplasm	See above part of Table
EGF	1.0 $\mu m^2/s$	Extracellular space	Assumed
EGF-EGFR	0.08 $\mu m^2/s$	Plasma membrane	See above part of Table
EGF-EGFR-Shcp	0.073 $\mu m^2/s$	Plasma membrane	See above part of Table
Ras-GTP	0.16 $\mu m^2/s$	Plasma membrane	(Bhalla et al., 2002; Kholodenko et al., 1999; Lommerse et al., 2006)We assume the diffusivity of GDP and GTP bound forms are similar.
Shc-p	6.4 $\mu m^2/s$	Cytoplasm	See above part of Table
Sos	3.7 $\mu m^2/s$	Cytoplasm	See above part of Table
Grb2	8.5 $\mu m^2/s$	Cytoplasm	See above part of Table
EGF-EGFR-Sos-Grb2-Shc-p	0.058 $\mu m^2/s$	Plasma membrane	See above part of Table
Ras-GDP	0.16 $\mu m^2/s$	Plasma membrane	(Kholodenko et al., 1999; Lommerse et al., 2006; Storm et al., 1990)
EGFR	0.112 $\mu m^2/s$	Plasma membrane	(Mayawala et al., 2006; Storm et al., 1990),
Shc	6.4 $\mu m^2/s$	Cytoplasm	See above part of Table

Table S6. Reactions, Kinetic Parameters, Initial Values, and Diffusivities for PDGF Signaling, Related to Figure 6

Name	**Reaction**	**Reaction Type**	**Kinetic parameters**
PDGF binds receptor	PDGF + PDGFR ⇔ PDGF-PDGFR	Binding	K_{on}=1 $\mu M^{-1}.s^{-1}$ K_{off}=0.01s^{-1}
Src phosphorylation	Src + PDGF-PDGFR ⇔ Src-p	Enzymatic	K_m=1 μM K_{cat} =0.1 s^{-1}
Src inactivation	Src-p +Csk_active ⇔ Src	Inactivation	K_m=1.5 μM K_{cat} =0.3 s^{-1}
Csk activation	Csk → Csk_active	Activation	k_f=0.001 s^{-1}
Initial concentrations for PDGF signaling (Figure 6)			
Name	**Initial concentration**	**Compartment**	**Notes and References**
PDGF	0 μM	Extracellular space	These values were based on the numbers used in the EGF signaling pathway.
PDGF	250 molecules.μm^{-2}	Receptor	
Src	0.1 μM	Cytoplasm	
Csk	0.1 μM	Cytoplasm	
Diffusivities of components in the PDGF signaling pathway			
Name	**Diffusion coefficient**	**Compartment**	
Csk_inactive	10.0 $\mu m^2/s$	Cytoplasm	Assumed to be in the same order of magnitude as MAPK.
Csk_active	10.0 $\mu m^2/s$	Cytoplasm	Assumed to be in the same order of magnitude as MAPK.
Src_active	1 $\mu m^2/s$	Cytoplasm	Active Src undergoes many chemical transformations including myristoylation and mechanical activation. We assumed that phosho-Src diffuses slowly compared to Src.
Src	10.0 $\mu m^2/s$	Cytoplasm	Assumed to be in the same order of magnitude as MAPK.
PDGF	1.0 $\mu m^2/s$	Cytoplasm	Assumed
PDGFR	0.041 $\mu m^2/s$	Cytoplasm	(Fujioka et al., 2006; Ljungquist-Hoddelius et al., 1991; Seger et al., 1992)
PDGF-PDGFR	0.041 $\mu m^2/s$	Cytoplasm	(Ljungquist-Hoddelius et al., 1991)