Stochastic signaling network mediates the probabilistic induction of long-term depression

INFORMATION ON THE MODEL

Figure 1-3, Table 1-3

Table of Contents

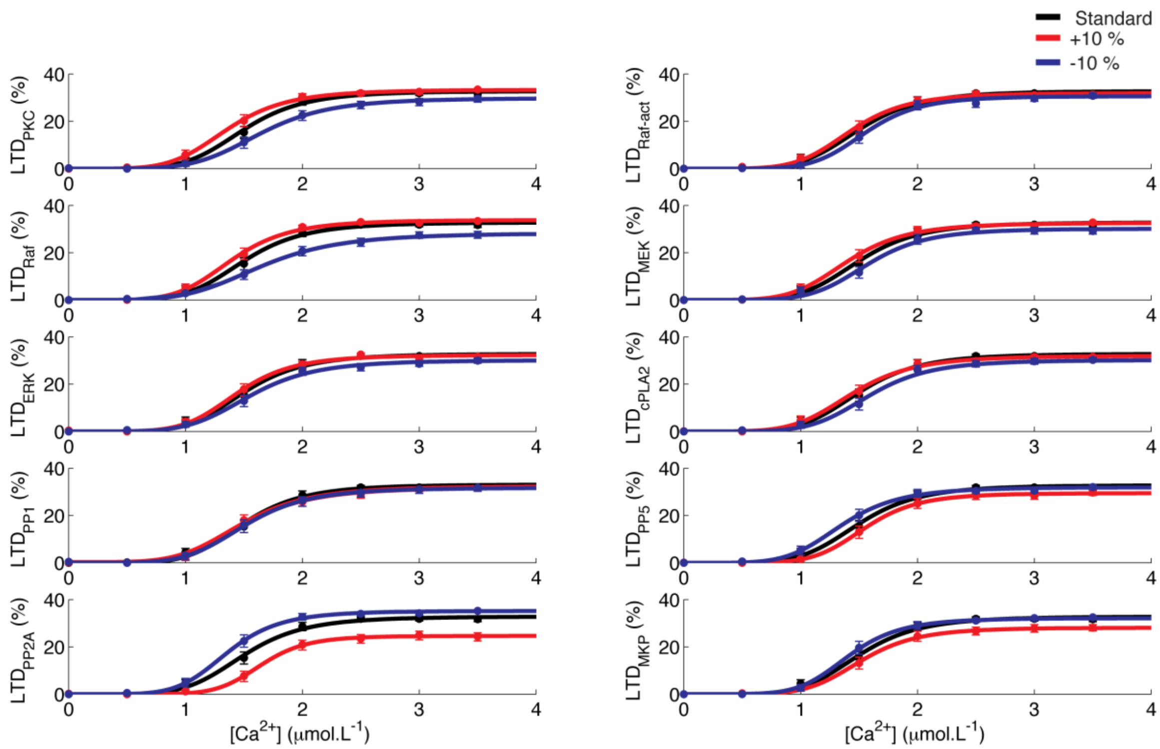

Figure 1 Sensitivity analysis of the population size of the different components of the positive feedback loop. The curve obtained with the standard model (Standard) was used for comparison. Ca^{2+}-induced LTD (pulses of 4 s and 0.0-3.5 μmol.L^{-1}) was used to verify the role of small variations in the population size of each component of the feedback loop on the macroscopic behavior of the model. Data are plotted as means ± SEM.

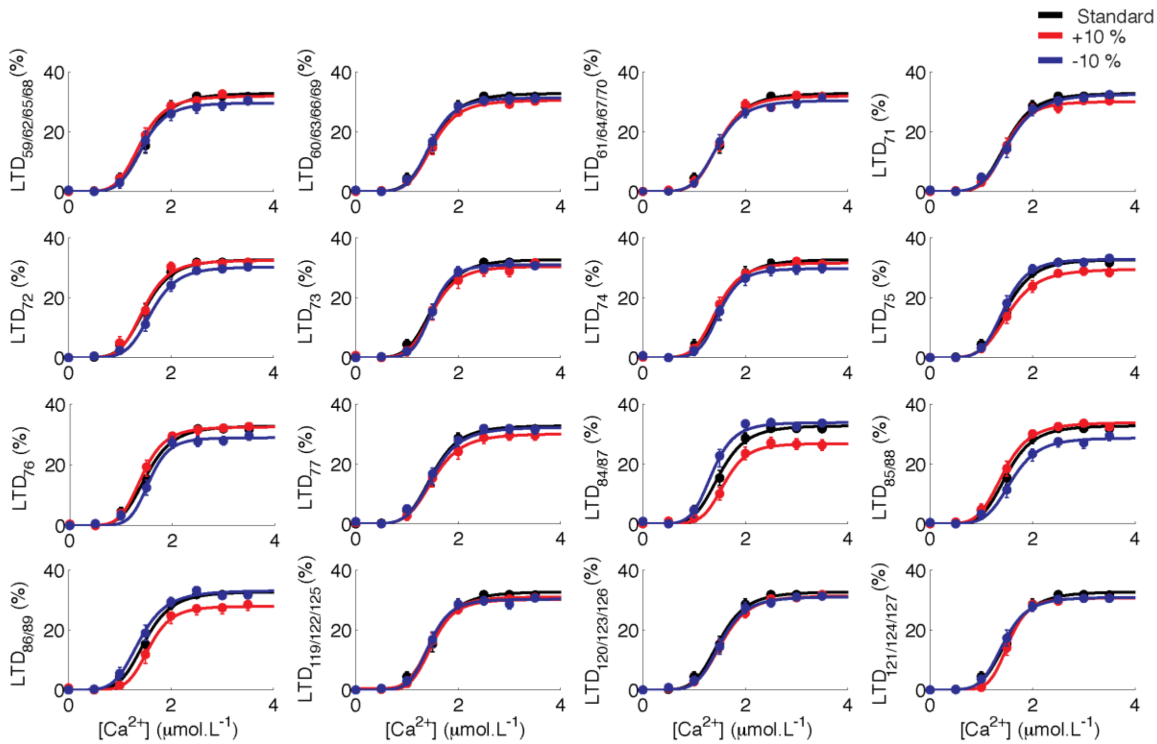

Figure 2 Sensitivity analysis of the rate constants of the positive feedback loop. The number indicated in the y-axis corresponds to the identity of the rate constant of the reactions (reac) shown in Supplementary Table I. Ca^{2+}-induced LTD (pulses of 4 s and 0.0-3.5 μmol.L^{-1}) was used to verify the role of variation in the rate constants on the macroscopic behavior of the model. The standard model was included for comparison. Data are plotted as means ± SEM.

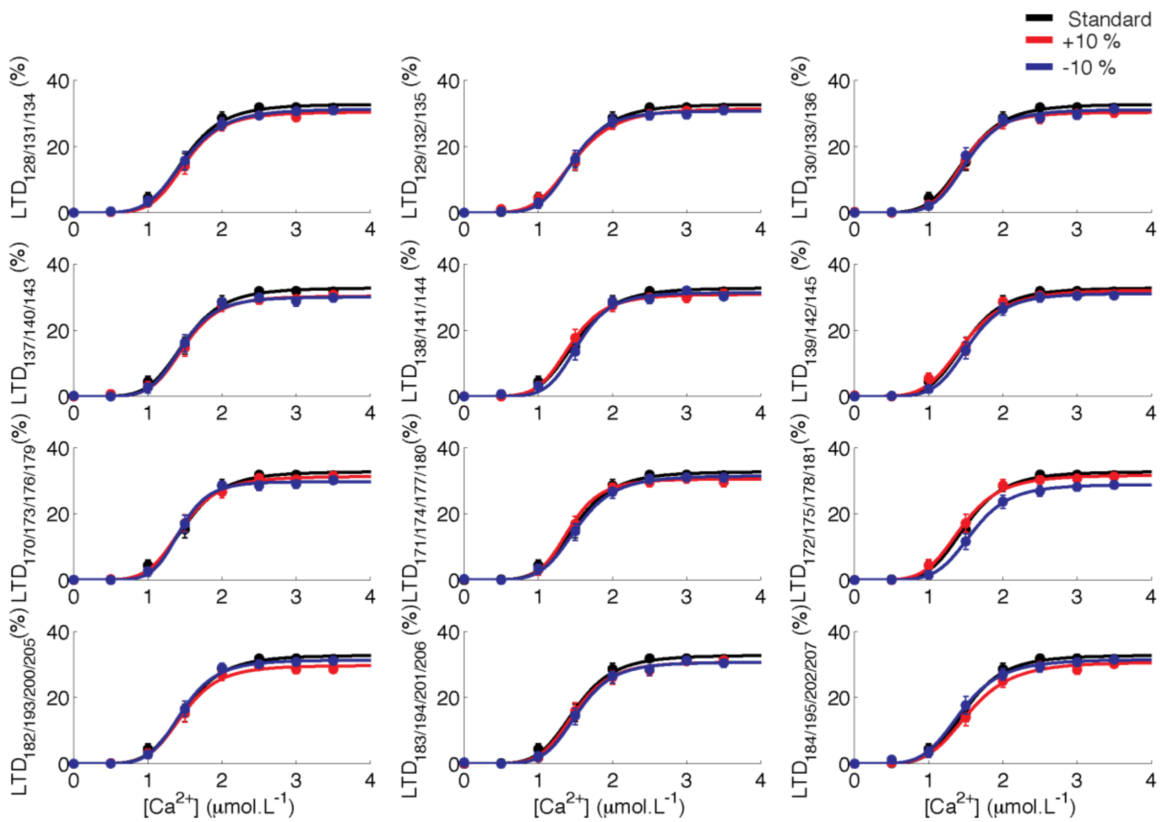

Figure 3 Continuation of the sensitivity analysis of the rate constants of the positive feedback loop. The number indicated in the y-axis corresponds to the identity of the rate constant of the reactions (reac) shown in Supplementary Table I. The figures show results of Ca^{2+}-induced LTD (pulses of 4 s and 0.0-3.5 μmol.L^{-1}). Data are plotted as means ± SEM.

Table 1 Parameters used in the model of cerebellar LTD

Parameter identity	Parameters of the model: chemical reactions, rate constants, population and geometric dimensions	References
1	Spine volume: 0.08 μm^3	(Harris and Stevens, 1988)
2	SER volume: 0.017 μm^3	(Harris and Stevens, 1988)
3	PSD area: 0.15 μm^2	(Harris and Stevens, 1988)
4	Basal $[Ca^{2+}]$ = 45 $nmol.L^{-1}$ [a]	(Schmidt et al., 2003)
5	PMA = 10 molecules	(Doi et al., 2005)
6	NCX = 3 molecules	(Doi et al., 2005)
7	SERCA = 100 molecules	(Doi et al., 2005)
8	[PV] = 40 $\mu mol.L^{-1}$	(Schmidt et al., 2003)
9	[CB] = 40 $\mu mol.L^{-1}$	(Schmidt et al., 2003)
10	PKC = 48 molecules	(Cheng et al., 2006)
11	[Raf_act] = 0.5 $\mu mol.L^{-1}$	This paper
12	[Raf] = 0.1 $\mu mol.L^{-1}$	(Huang and Ferrell, 1996; Pearson et al., 2001)
13	[MEK] = 1.5 $\mu mol.L^{-1}$	(Huang and Ferrell, 1996; Pearson et al., 2001; Fujioka et al., 2006)
14	[PP5] = 1.0 $\mu mol.L^{-1}$	(Bahl et al., 2001; Rossie et al., 2006)
15	[PP2A] = 1.5 $\mu mol.L^{-1}$	(Cheng et al., 2006)

16	[ERK] = 1.0 μmol.L^{-1}	(Huang and Ferrell, 1996; Pearson et al., 2001; Cheng et al., 2006; Fujioka et al., 2006)
17	[MKP] = 0.26 μmol.L^{-1}	(Huang and Ferrell, 1996)
18	[cPLA$_2$] = 0.4 μmol.L^{-1}	(Tanaka et al., 2007)
19	PP1 = 30 molecules	(Cheng et al., 2006)
20	Synaptic AMPAR ~ 120-130 molecules	(Momiyama et al., 2003; Masugi-Tokita et al., 2007)
21	GRIP = 141 molecules	This paper
Reac1	$PMCA + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})PMCA$, [b] k_f = 25000.0 μmol^{-1}.L.s^{-1}	(Doi et al., 2005)
Reac2	$(Ca^{2+})PMCA \xrightarrow{k_b} PMCA + Ca^{2+}$, k_b = 2000.0 s^{-1}	(Doi et al., 2005)
Reac3	$(Ca^{2+})PMCA \xrightarrow{k_{cat}} PMCA$, k_{cat} = 500.0 s^{-1}	(Doi et al., 2005)
Reac4	$NCX + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})NCX$, k_f = 93.827 μmol^{-1}.L.s^{-1}	(Doi et al., 2005)
Reac5	$(Ca^{2+})NCX \xrightarrow{k_b} NCX + Ca^{2+}$, k_b = 612.6 s^{-1}	(Doi et al., 2005)
Reac6	$(Ca^{2+})NCX + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2NCX$, k_f = 93.827 μmol^{-1}.L.s^{-1}	(Doi et al., 2005)
Reac7	$(Ca^{2+})_2NCX \xrightarrow{k_b} (Ca^{2+})NCX + Ca^{2+}$, k_b = 612.6 s^{-1}	(Doi et al., 2005)
Reac8	$(Ca^{2+})_2NCX \xrightarrow{k_{cat}} NCX$, k_{cat} = 1000.0 s^{-1}, non-conservative reaction	(Doi et al., 2005)
Reac9	$SERCA + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})SERCA$, k_f = 17147.0 μmol^{-1}.L.s^{-1}	(Doi et al., 2005)

Reac10	$(Ca^{2+})SERCA \xrightarrow{k_b} SERCA + Ca^{2+}$, k_b = 8426.3 s^{-1}	(Doi et al., 2005)
Reac11	$(Ca^{2+})SERCA + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2 SERCA$, k_f = 17147.0 $\mu mol^{-1}.L.s^{-1}$	(Doi et al., 2005)
Reac12	$(Ca^{2+})_2 SERCA \xrightarrow{k_b} (Ca^{2+})SERCA + Ca^{2+}$, k_b = 8426.3 s^{-1}	(Doi et al., 2005)
Reac13	$(Ca^{2+})_2 SERCA \xrightarrow{k_{cat}} SERCA + 2Ca^{2+}_{SER}$, k_{cat} = 250.0 s^{-1}	(Doi et al., 2005)
Reac14	$\xrightarrow{k_{leak}} Ca^{2+}$, k_{leak} = 1900.0 $\mu mol.L^{-1}.s^{-1}$	This paper
Reac15	$PV + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})PV$, k_f = 107.0 $\mu mol^{-1}.L.s^{-1}$	(Schmidt et al., 2003)
Reac16	$(Ca^{2+})PV \xrightarrow{k_b} PV + Ca^{2+}$, k_b = 0.95 s^{-1}	(Schmidt et al., 2003)
Reac17	$(Ca^{2+})PV + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2 PV$, k_f = 107.0 $\mu mol^{-1}.L.s^{-1}$	(Schmidt et al., 2003)
Reac18	$(Ca^{2+})_2 PV \xrightarrow{k_b} (Ca^{2+})PV + Ca^{2+}$, k_b = 0.95 s^{-1}	(Schmidt et al., 2003)
Reac19	$PV \xrightarrow{[Mg^{2+}]k_f} (Mg^{2+})PV$, k_f = 472.0 s^{-1}	(Schmidt et al., 2003)
Reac20	$(Mg^{2+})PV \xrightarrow{k_b} PV$, k_b = 25.0 s^{-1}	(Schmidt et al., 2003)
Reac21	$(Mg^{2+})PV \xrightarrow{[Mg^{2+}]k_f} (Mg^{2+})_2 PV$, k_f = 472.0 s^{-1}	(Schmidt et al., 2003)
Reac22	$(Mg^{2+})_2 PV \xrightarrow{k_b} (Mg^{2+})PV$, k_b = 25.0 s^{-1}	(Schmidt et al., 2003)
Reac23	$CB + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})CB$, k_f = 5.5 $\mu mol^{-1}.L.s^{-1}$, high affinity site	(Schmidt et al., 2003)
Reac24	$(Ca^{2+})CB \xrightarrow{k_b} CB + Ca^{2+}$, k_b = 2.6 s^{-1}, high affinity site	(Schmidt et al., 2003)
Reac25	$(Ca^{2+})CB + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2 CB$, k_f = 5.5 $\mu mol^{-1}.L.s^{-1}$, high affinity site	(Schmidt et al., 2003)
Reac26	$(Ca^{2+})_2 CB \xrightarrow{k_b} (Ca^{2+})CB + Ca^{2+}$, k_b = 2.6 s^{-1}, high affinity site	(Schmidt et al., 2003)

Reac27	$CB + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})CB$, k_f = 43.5 μmol^{-1}.L.s^{-1}, medium affinity site	(Schmidt et al., 2003)
Reac28	$(Ca^{2+})CB \xrightarrow{k_b} CB + Ca^{2+}$, k_b = 35.8 s^{-1}, medium affinity site	(Schmidt et al., 2003)
Reac29	$(Ca^{2+})CB + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2CB$, k_f = 43.5 μmol^{-1}.L.s^{-1}, medium affinity site	(Schmidt et al., 2003)
Reac30	$(Ca^{2+})_2CB \xrightarrow{k_b} (Ca^{2+})CB + Ca^{2+}$, k_b = 35.8 s^{-1}, medium affinity site	(Schmidt et al., 2003)
Reac31	$PKC + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})PKC$, k_f = 13.3 μmol^{-1}.L.s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac32	$(Ca^{2+})PKC \xrightarrow{k_b} PKC + Ca^{2+}$, k_b = 12.0 s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac33	$(Ca^{2+})PKC + 2Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_3PKC$, k_f = 1.0 μmol^{-2}.L.s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac34	$(Ca^{2+})_3PKC \xrightarrow{k_b} (Ca^{2+})PKC + 2Ca^{2+}$, k_b = 12.0 s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac35	$(Ca^{2+})_3PKC \xrightarrow{k_f} (Ca^{2+})_3PKC*$, [c] k_f = 11.3 s^{-1}	(Bittova et al., 2001; Newton, 2001, 2009)

Reac36	$(Ca^{2+})_3PKC^* \xrightarrow{k_b} (Ca^{2+})_3PKC$, k_b = 0.23 s^{-1}	(Bittova et al., 2001; Newton, 2001, 2009)
Reac37	$PKC + AA \xrightarrow{k_f} (AA)PKC$, k_f = 1.0 $\mu mol^{-1}.L.s^{-1}$	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac38	$(AA)PKC \xrightarrow{k_b} PKC + AA$, k_b = 10.0 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac39	$(AA)PKC \xrightarrow{k_f} (AA)PKC^*$, k_f = 0.017 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac40	$(AA)PKC^* \xrightarrow{k_b} (AA)PKC$, k_b = 0.0055 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac41	$(Ca^{2+})PKC + AA \xrightarrow{k_f} (AA)(Ca^{2+})PKC$, k_f = 1.0 $\mu mol^{-1}.L.s^{-1}$,	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac42	$(AA)(Ca^{2+})PKC \xrightarrow{k_b} (Ca^{2+})PKC + AA$, k_b = 10.0 s^{-1}	(Shinomura et al., 1991;

		Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac43	$(AA)(Ca^{2+})PKC \xrightarrow{k_f} (AA)(Ca^{2+})PKC^*$, k_f = 0.017 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac44	$(AA)(Ca^{2+})PKC^* \xrightarrow{k_b} (AA)(Ca^{2+})PKC$, k_b = 0.0055 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac45	$(AA)(Ca^{2+})PKC^* + 2Ca^{2+} \xrightarrow{k_f} (AA)(Ca^{2+})_3 PKC^*$, k_f = 1.0 $\mu mol^{-2}.L.s^{-1}$	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac46	$(AA)(Ca^{2+})_3 PKC^* \xrightarrow{k_b} (AA)(Ca^{2+})PKC^* + 2Ca^{2+}$, k_b = 12.0 s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac47	$(AA)PKC + Ca^{2+} \xrightarrow{k_f} (AA)(Ca^{2+})PKC$, k_f = 13.3 $\mu mol^{-1}.L.s^{-1}$	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)

Reac48	$(AA)(Ca^{2+})PKC \xrightarrow{k_b} (AA)PKC + Ca^{2+}$, k_b = 12.0 s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac49	$(AA)(Ca^{2+})PKC + 2Ca^{2+} \xrightarrow{k_f} (AA)(Ca^{2+})_3 PKC$, k_f = 1.0 $\mu mol^{-2}.L.s^{-1}$	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac50	$(AA)(Ca^{2+})_3 PKC \xrightarrow{k_b} (AA)(Ca^{2+})PKC + 2Ca^{2+}$, k_b = 12.0 s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac51	$(AA)(Ca^{2+})_3 PKC \xrightarrow{k_f} (AA)(Ca^{2+})_3 PKC^*$, k_f = 11.3 s^{-1}	(Bittova et al., 2001; Newton, 2001, 2009)
Reac52	$(AA)(Ca^{2+})_3 PKC^* \xrightarrow{k_b} (AA)(Ca^{2+})_3 PKC$, k_b = 0.23 s^{-1}	(Bittova et al., 2001; Newton, 2001, 2009)
Reac53	$(Ca^{2+})_3 PKC + AA \xrightarrow{k_f} (AA)(Ca^{2+})_3 PKC$, k_f = 1.0 $\mu mol^{-1}.L.s^{-1}$,	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac54	$(AA)(Ca^{2+})_3 PKC \xrightarrow{k_b} (Ca^{2+})_3 PKC + AA$, k_b = 10.0 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993;

		O'Flaherty et al., 2001)
Reac55	$(AA)PKC^* + Ca^{2+} \xrightarrow{k_f} (AA)(Ca^{2+})PKC^*$, k_f = 13.3 μmol^{-1}.L.s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac56	$(AA)(Ca^{2+})PKC^* \xrightarrow{k_b} (AA)PKC^* + Ca^{2+}$, k_b = 12.0 s^{-1}	(Keranen and Newton, 1997; Kohout et al., 2002; Torrecillas et al., 2004)
Reac57	$(Ca^{2+})_3PKC^* + AA \xrightarrow{k_f} (AA)(Ca^{2+})_3PKC^*$, k_f = 1.0 μmol^{-1}.L.s^{-1},	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac58	$(AA)(Ca^{2+})_3PKC^* \xrightarrow{k_b} (Ca^{2+})_3PKC^* + AA$, k_b = 10.0 s^{-1}	(Shinomura et al., 1991; Schaechter and Benowitz, 1993; O'Flaherty et al., 2001)
Reac59	$(Ca^{2+})_3PKC^* + Raf\_act \xrightarrow{k_f} ((Ca^{2+})_3PKC^*)Raf\_act$, k_f = 5.8 μmol^{-1} l s^{-1}	(Woodgett et al., 1986)
Reac60	$((Ca^{2+})_3PKC^*)Raf\_act \xrightarrow{k_b} (Ca^{2+})_3PKC^* + Raf\_act$, k_b = 3.608 s^{-1}	(Woodgett et al., 1986)
Reac61	$((Ca^{2+})_3PKC^*)Raf\_act \xrightarrow{k_{cat}} (Ca^{2+})_3PKC^* + Raf\_act^*$, k_{cat} = 4.7 s^{-1}	(Woodgett et al., 1986)
Reac62	$(AA)PKC^* + Raf\_act \xrightarrow{k_f} (AA)(PKC^*)Raf\_act$, k_f = 5.8 μmol^{-1} l s^{-1}	(Woodgett et al., 1986)

Reac63	$((AA)PKC^*)Raf\_act \xrightarrow{k_b} (AA)PKC^* + Raf\_act$, $k_b = 3.608\ s^{-1}$	(Woodgett et al., 1986)
Reac64	$(AA)(PKC^*)Raf\_act \xrightarrow{k_{cat}} (AA)PKC^* + Raf\_act^*$, $k_{cat} = 4.7\ s^{-1}$	(Woodgett et al., 1986)
Reac65	$(AA)(Ca^{2+})PKC^* + Raf\_act \xrightarrow{k_f} ((AA)(Ca^{2+})PKC^*)Raf\_act$, $k_f = 5.8\ \mu mol^{-1}\ l\ s^{-1}$	(Woodgett et al., 1986)
Reac66	$((AA)(Ca^{2+})PKC^*)Raf\_act \xrightarrow{k_b} (AA)(Ca^{2+})PKC^* + Raf\_act$, $k_b = 3.608\ s^{-1}$	(Woodgett et al., 1986)
Reac67	$((AA)(Ca^{2+})PKC^*)Raf\_act \xrightarrow{k_{cat}} (AA)(Ca^{2+})PKC^* + Raf\_act^*$, $k_{cat} = 4.7\ s^{-1}$	(Woodgett et al., 1986)
Reac68	$(AA)(Ca^{2+})_3PKC^* + Raf\_act \xrightarrow{k_f} ((AA)(Ca^{2+})_3PKC^*)Raf\_act$, $k_f = 5.8\ \mu mol^{-1}\ l\ s^{-1}$	(Woodgett et al., 1986)
Reac69	$((AA)(Ca^{2+})_3PKC^*)Raf\_act \xrightarrow{k_b} (AA)(Ca^{2+})_3PKC^* + Raf\_act$, $k_b = 3.608\ s^{-1}$	(Woodgett et al., 1986)
Reac70	$((AA)(Ca^{2+})_3PKC^*)Raf\_act \xrightarrow{k_{cat}} (AA)(Ca^{2+})_3PKC^* + Raf\_act^*$, $k_{cat} = 4.7\ s^{-1}$	(Woodgett et al., 1986)
Reac71	$Raf\_act^* \xrightarrow{k_f} Raf\_act$, $k_b = 1.0\ s^{-1}$	(Lenzen et al., 1998; Brinkmann et al., 2002)
Reac72	$Raf\_act^* + Raf \xrightarrow{k_f} (Raf\_act^*)Raf$, $k_f = 1.0\ \mu mol^{-1}.L.s^{-1}$	(Aksan and Kurnaz, 2003; Kiyatkin et al., 2006)
Reac73	$(Raf\_act^*)Raf \xrightarrow{k_b} Raf\_act^* + Raf$, $k_b = 2.0\ s^{-1}$	(Aksan and Kurnaz, 2003; Kiyatkin et al., 2006)
Reac74	$(Raf\_act^*)Raf \xrightarrow{k_{cat}} Raf\_act^* + Raf^*$, $k_{cat} = 1.5\ s^{-1}$	(Aksan and Kurnaz, 2003; Kiyatkin et al., 2006)
Reac75	$PP5 + Raf^* \xrightarrow{k_f} (PP5)Raf^*$, $k_f = 0.55\ \mu mol^{-1}.L.s^{-1}$	(Aksan and Kurnaz, 2003; Kiyatkin et

		al., 2006)
Reac76	$(PP5)Raf^* \xrightarrow{k_b} PP5 + Raf^*$, k_b = 2.0 s^{-1}	(Aksan and Kurnaz, 2003; Kiyatkin et al., 2006)
Reac77	$(PP5)Raf^* \xrightarrow{k_{cat}} PP5 + Raf$, k_{cat} = 0.5 s^{-1}	(Aksan and Kurnaz, 2003; Kiyatkin et al., 2006)
Reac78	$Raf^* + MEK \xrightarrow{k_f} (Raf^*)MEK$, k_f = 0.65 $\mu mol^{-1}.L.s^{-1}$	(Fujioka et al., 2006)
Reac79	$(Raf^*)MEK \xrightarrow{k_b} Raf^* + MEK$, k_b = 0.065 s^{-1}	(Fujioka et al., 2006)
Reac80	$(Raf^*)MEK \xrightarrow{k_{cat}} Raf^* + MEK^P$, [d] k_{cat} = 1.0 s^{-1}	(Fujioka et al., 2006)
Reac81	$Raf^* + MEK^P \xrightarrow{k_f} (Raf^*)MEK^P$, k_f = 0.65 $\mu mol^{-1}.L.s^{-1}$	(Fujioka et al., 2006)
Reac82	$(Raf^*)MEK^P \xrightarrow{k_b} Raf^* + MEK^P$, k_b = 0.065 s^{-1}	(Fujioka et al., 2006)
Reac83	$(Raf^*)MEK^P \xrightarrow{k_{cat}} Raf^* + MEK^*$, k_{cat} = 1.0 s^{-1}	(Fujioka et al., 2006)
Reac84	$PP2A + MEK^* \xrightarrow{k_f} (PP2A)MEK^*$, k_f = 0.75 $\mu mol^{-1}.L.s^{-1}$	(Huang and Ferrell, 1996; Fujioka et al., 2006; Kiyatkin et al., 2006)
Reac85	$(PP2A)MEK^* \xrightarrow{k_b} PP2A + MEK^*$, k_b = 2.0 s^{-1}	(Huang and Ferrell, 1996; Fujioka et al., 2006; Kiyatkin et al., 2006)
Reac86	$(PP2A)MEK^* \xrightarrow{k_{cat}} PP2A + MEK^P$, k_{cat} = 0.5 s^{-1}	(Huang and Ferrell, 1996; Fujioka et

		al., 2006; Kiyatkin et al., 2006)
Reac87	$PP2A + MEK^P \xrightarrow{k_f} (PP2A)MEK^P$, k_f = 0.75 μmol^{-1}.L.s^{-1}	(Huang and Ferrell, 1996; Fujioka et al., 2006; Kiyatkin et al., 2006)
Reac88	$(PP2A)MEK^P \xrightarrow{k_b} PP2A + MEK^P$, k_b = 2.0 s^{-1}	(Huang and Ferrell, 1996; Fujioka et al., 2006; Kiyatkin et al., 2006)
Reac89	$(PP2A)MEK^P \xrightarrow{k_{cat}} PP2A + MEK$, k_{cat} = 0.5 s^{-1}	(Huang and Ferrell, 1996; Fujioka et al., 2006; Kiyatkin et al., 2006)
Reac90	$MEK* + ERK \xrightarrow{k_f} (MEK*)ERK$, k_f = 16.2 μmol^{-1}.L.s^{-1}	(Fujioka et al., 2006)
Reac91	$(MEK*)ERK \xrightarrow{k_b} MEK* + ERK$, k_b = 0.6 s^{-1}	(Fujioka et al., 2006)
Reac92	$(MEK*)ERK \xrightarrow{k_{cat}} MEK* + ERK^P$, k_{cat} = 0.15 s^{-1}	(Fujioka et al., 2006)
Reac93	$MEK* + ERK^P \xrightarrow{k_f} (MEK*)ERK^P$, k_f = 16.2 μmol^{-1}.L.s^{-1}	(Fujioka et al., 2006)
Reac94	$(MEK*)ERK^P \xrightarrow{k_b} MEK* + ERK^P$, k_b = 0.6 s^{-1}	(Fujioka et al., 2006)
Reac95	$(MEK*)ERK^P \xrightarrow{k_{cat}} MEK* + ERK*$, k_{cat} = 0.3 s^{-1}	(Markevich et al., 2004; Fujioka et al., 2006)
Reac96	$MKP + ERK* \xrightarrow{k_f} (MKP)ERK*$, k_f = 28.0 μmol^{-1}.L.s^{-1}	(Zhao and Zhang, 2001; Zhou et al., 2002)

Reac97	$(MKP)ERK^* \xrightarrow{k_b} MKP + ERK^*$, k_b = 0.56 s^{-1}	(Zhao and Zhang, 2001; Zhou et al., 2002)
Reac98	$(MKP)ERK^* \xrightarrow{k_{cat}} MKP + ERK^P$, k_{cat} = 0.14 s^{-1}	(Zhao and Zhang, 2001; Zhou et al., 2002)
Reac99	$MKP + ERK^P \xrightarrow{k_f} (MKP)ERK^P$, k_f = 13.0 μmol^{-1}.L.s^{-1}	(Zhao and Zhang, 2001; Zhou et al., 2002)
Reac100	$(MKP)ERK^P \xrightarrow{k_b} MKP + ERK^P$, k_b = 0.396 s^{-1}	(Zhao and Zhang, 2001; Zhou et al., 2002)
Reac101	$(MKP)ERK^P \xrightarrow{k_{cat}} MKP + ERK$, k_{cat} = 0.099 s^{-1}	(Zhao and Zhang, 2001; Zhou et al., 2002)
Reac102	$cPLA_2 + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})cPLA_2$, k_f = 1.93 μmol^{-1}.L.s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac103	$(Ca^{2+})cPLA_2 \xrightarrow{k_b} cPLA_2 + Ca^{2+}$, k_b = 108.0 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac104	$(Ca^{2+})cPLA_2 + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2cPLA_2$, k_f = 10.8 μmol^{-1}.L.s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke,

		2002)
Reac105	$(Ca^{2+})_2cPLA_2 \xrightarrow{k_b} (Ca^{2+})cPLA_2 + Ca^{2+}$, k_b = 108.0 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac106	$(Ca^{2+})_2cPLA_2 \xrightarrow{k_f} (Ca^{2+})_2cPLA_2*$, k_f = 300.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Stahelin et al., 2007)
Reac107	$(Ca^{2+})_2cPLA_2* \xrightarrow{k_b} (Ca^{2+})_2cPLA_2$, k_b = 15.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Stahelin et al., 2007)
Reac108	$(Ca^{2+})cPLA_2 \xrightarrow{k_f} (Ca^{2+})cPLA_2memb$, [e] k_f = 30.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Stahelin et al., 2007)
Reac109	$(Ca^{2+})cPLA_2memb \xrightarrow{k_b} (Ca^{2+})cPLA_2$, k_b = 15.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Stahelin et al., 2007)
Reac110	$cPLA_2 \xrightarrow{k_f} cPLA_2memb$, k_f = 3.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002;

		Frazier et al., 2002; Stahelin et al., 2007)
Reac111	$cPLA_2memb \xrightarrow{k_b} cPLA_2$, k_b = 15.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Stahelin et al., 2007)
Reac112	$cPLA_2memb + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})cPLA_2memb$, k_f = 1.93 $\mu mol^{-1}.L.s^{-1}$	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac113	$(Ca^{2+})cPLA_2memb \xrightarrow{k_b} cPLA_2memb + Ca^{2+}$, k_b = 0.41 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac114	$(Ca^{2+})cPLA_2memb + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2cPLA_2*$, k_f = 10.8 $\mu mol^{-1}.L.s^{-1}$	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac115	$(Ca^{2+})_2cPLA_2* \xrightarrow{k_b} (Ca^{2+})cPLA_2memb + Ca^{2+}$, k_b = 2.5 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski

		and Falke, 2002)
Reac116	$(Ca^{2+})_2cPLA_2{*}\xrightarrow{k_f}((Ca^{2+})_2cPLA_2{*})APC$, k_f = 43.0 s^{-1}, pseudo-first order reaction of interaction between $cPLA_2$ and its substrate (*APC*)	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac117	$((Ca^{2+})_2cPLA_2{*})APC\xrightarrow{k_b}(Ca^{2+})_2cPLA_2{*}$, k_b = 600.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac118	$((Ca^{2+})_2cPLA_2{*})APC\xrightarrow{k_{cat}}(Ca^{2+})_2cPLA_2{*}+AA$, k_{cat} = 450.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac119	$ERK{*}+cPLA_2\xrightarrow{k_f}(ERK{*})cPLA_2$, k_f = 4.0 $\mu mol^{-1}.L.s^{-1}$	(Waas and Dalby, 2002; Waas et al., 2003)
Reac120	$(ERK{*})cPLA_2\xrightarrow{k_b}ERK{*}+cPLA_2$, k_b = 1.0 s^{-1}	(Waas and Dalby, 2002; Waas et al., 2003)
Reac121	$(ERK{*})cPLA_2\xrightarrow{k_{cat}}ERK{*}+cPLA_2{}^P$, k_{cat} = 14.0 s^{-1}	(Waas and Dalby, 2002; Waas et al., 2003)
Reac122	$ERK{*}+(Ca^{2+})cPLA_2\xrightarrow{k_f}(ERK{*})(Ca^{2+})cPLA_2$, k_f = 4.0 $\mu mol^{-1}.L.s^{-1}$	(Waas and Dalby, 2002; Waas et al., 2003)
Reac123	$(ERK{*})(Ca^{2+})cPLA_2\xrightarrow{k_b}ERK{*}+(Ca^{2+})cPLA_2$, k_b = 1.0 s^{-1}	(Waas and Dalby, 2002; Waas et al., 2003)
Reac124	$(ERK{*})(Ca^{2+})cPLA_2\xrightarrow{k_{cat}}ERK{*}+(Ca^{2+})cPLA_2{}^P$, k_{cat} = 14.0 s^{-1}	(Waas and Dalby, 2002; Waas et al., 2003)
Reac125	$ERK{*}+(Ca^{2+})_2cPLA_2\xrightarrow{k_f}(ERK{*})(Ca^{2+})_2cPLA_2$,	(Waas and Dalby,

	k_f = 4.0 μmol^{-1}.L.s^{-1}	2002; Waas et al., 2003)
Reac126	$(ERK^*)(Ca^{2+})_2cPLA_2 \xrightarrow{k_b} ERK^* + (Ca^{2+})_2cPLA_2$, k_b = 1.0 s^{-1}	(Waas and Dalby, 2002; Waas et al., 2003)
Reac127	$(ERK^*)(Ca^{2+})_2cPLA_2 \xrightarrow{k_{cat}} ERK^* + (Ca^{2+})_2cPLA_2{}^P$, k_{cat} = 14.0 s^{-1}	(Waas and Dalby, 2002; Waas et al., 2003)
Reac128	$PP2A + cPLA_2{}^P \xrightarrow{k_f} (PP2A)cPLA_2{}^P$, k_f = 1.4 μmol^{-1}.L.s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac129	$(PP2A)cPLA_2{}^P \xrightarrow{k_b} PP2A + cPLA_2{}^P$, k_b = 1.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac130	$(PP2A)cPLA_2{}^P \xrightarrow{k_{cat}} PP2A + cPLA_2$, k_{cat} = 2.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac131	$PP2A + (Ca^{2+})cPLA_2{}^P \xrightarrow{k_f} (PP2A)(Ca^{2+})cPLA_2{}^P$, k_f = 1.4 μmol^{-1}.L.s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac132	$(PP2A)(Ca^{2+})cPLA_2{}^P \xrightarrow{k_b} PP2A + (Ca^{2+})cPLA_2{}^P$, k_b = 1.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac133	$(PP2A)(Ca^{2+})cPLA_2{}^P \xrightarrow{k_{cat}} PP2A + (Ca^{2+})cPLA_2$, k_{cat} = 2.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)

Reac134	$PP2A + (Ca^{2+})_2 cPLA_2{}^P \xrightarrow{k_f} (PP2A)(Ca^{2+})_2 cPLA_2{}^P$, k_f = 1.4 μmol^{-1}.L.s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac135	$(PP2A)(Ca^{2+})_2 cPLA_2{}^P \xrightarrow{k_b} PP2A + (Ca^{2+})_2 cPLA_2{}^P$, k_b = 1.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac136	$(PP2A)(Ca^{2+})_2 cPLA_2{}^P \xrightarrow{k_{cat}} PP2A + (Ca^{2+})_2 cPLA_2$, k_{cat} = 2.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac137	$PP1 + cPLA_2{}^P \xrightarrow{k_f} (PP1)cPLA_2{}^P$, k_f = 1.4 μmol^{-1}.L.s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac138	$(PP1)cPLA_2{}^P \xrightarrow{k_b} PP1 + cPLA_2{}^P$, k_b = 1.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac139	$(PP1)cPLA_2{}^P \xrightarrow{k_{cat}} PP1 + cPLA_2$, k_{cat} = 2.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac140	$PP1 + (Ca^{2+})cPLA_2{}^P \xrightarrow{k_f} (PP1)(Ca^{2+})cPLA_2{}^P$, k_f = 1.4 μmol^{-1}.L.s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac141	$(PP1)(Ca^{2+})cPLA_2{}^P \xrightarrow{k_b} PP1 + (Ca^{2+})cPLA_2{}^P$, k_b = 1.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992;

		Agostinis et al., 1996)
Reac142	$(PP1)(Ca^{2+})cPLA_2{}^P \xrightarrow{k_{cat}} PP1 + (Ca^{2+})cPLA_2$, k_{cat} = 2.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac143	$PP1 + (Ca^{2+})_2cPLA_2{}^P \xrightarrow{k_f} (PP1)(Ca^{2+})_2cPLA_2{}^P$, k_f = 1.4 $\mu mol^{-1}.L.s^{-1}$	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac144	$(PP1)(Ca^{2+})_2cPLA_2{}^P \xrightarrow{k_b} PP1 + (Ca^{2+})_2cPLA_2{}^P$, k_b = 1.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac145	$(PP1)(Ca^{2+})_2cPLA_2{}^P \xrightarrow{k_{cat}} PP1 + (Ca^{2+})_2cPLA_2{}^P$, k_{cat} = 2.5 s^{-1}	(Agostinis et al., 1987; Agostinis et al., 1992; Agostinis et al., 1996)
Reac146	$cPLA_2{}^P \xrightarrow{k_f} cPLA_2{}^{**}$, [c] k_f = 50.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Das et al., 2003; Stahelin et al., 2007)
Reac147	$cPLA_2{}^{**} \xrightarrow{k_b} cPLA_2{}^P$, k_b = 15.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Das et al., 2003; Stahelin et al., 2007)

Reac148	$cPLA_2{**}\xrightarrow{k_f}(cPLA_2{**})APC$, k_f = 43.0 s^{-1}, pseudo-first order reaction of interaction between $cPLA_2$ and its substrate	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac149	$(cPLA_2{**})APC\xrightarrow{k_b}cPLA_2{**}$, k_b = 600.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac150	$(cPLA_2{**})APC\xrightarrow{k_{cat}}cPLA_2{**}+AA$, k_{cat} = 3600.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac151	$(Ca^{2+})cPLA_2{}^P\xrightarrow{k_f}(Ca^{2+})cPLA_2{**}$, k_f = 50.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Das et al., 2003; Stahelin et al., 2007)
Reac152	$(Ca^{2+})cPLA_2{**}\xrightarrow{k_b}(Ca^{2+})cPLA_2{}^P$, k_b = 15.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Das et al., 2003; Stahelin et al., 2007)
Reac153	$(Ca^{2+})cPLA_2{**}\xrightarrow{k_f}((Ca^{2+})cPLA_2{**})APC$, k_f = 43.0 s^{-1}, pseudo-first order reaction of interaction between $cPLA_2$ and its substrate	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac154	$((Ca^{2+})cPLA_2{**})APC\xrightarrow{k_b}(Ca^{2+})cPLA_2{**}$,	(Bayburt and Gelb,

	k_b = 600.0 s^{-1}	1997; Berg et al., 2001; Tucker et al., 2009)
Reac155	$((Ca^{2+})cPLA_2{**})APC \xrightarrow{k_{cat}} (Ca^{2+})cPLA_2{**} + AA$, k_{cat} = 3600.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac156	$(Ca^{2+})_2cPLA_2{}^P \xrightarrow{k_f} (Ca^{2+})_2cPLA_2{**}$, k_f = 300.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Das et al., 2003; Stahelin et al., 2007)
Reac157	$(Ca^{2+})_2cPLA_2{**} \xrightarrow{k_b} (Ca^{2+})_2cPLA_2{}^P$, k_b = 15.0 s^{-1}	(Hixon et al., 1998; Das and Cho, 2002; Frazier et al., 2002; Das et al., 2003; Stahelin et al., 2007)
Reac158	$(Ca^{2+})_2cPLA_2{**} \xrightarrow{k_f} ((Ca^{2+})_2cPLA_2{**})APC$, k_f = 43.0 s^{-1}, pseudo-first order reaction of interaction between $cPLA_2$ and its substrate	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac159	$((Ca^{2+})_2cPLA_2{**})APC \xrightarrow{k_b} (Ca^{2+})_2cPLA_2{**}$, k_b = 600.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001; Tucker et al., 2009)
Reac160	$((Ca^{2+})_2cPLA_2{**})APC \xrightarrow{k_{cat}} (Ca^{2+})_2cPLA_2{**} + AA$, k_{cat} = 3600.0 s^{-1}	(Bayburt and Gelb, 1997; Berg et al., 2001;

		Tucker et al., 2009)
Reac161	$cPLA_2{}^P + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})cPLA_2{}^P$, k_f = 1.93 μmol^{-1}.L.s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac162	$(Ca^{2+})cPLA_2{}^P \xrightarrow{k_b} cPLA_2{}^P + Ca^{2+}$, k_b = 108 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac163	$cPLA_2{}^{**} + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})cPLA_2{}^{**}$, k_f = 1.93 μmol^{-1}.L.s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac164	$(Ca^{2+})cPLA_2{}^{**} \xrightarrow{k_b} cPLA_2{}^{**} + Ca^{2+}$, k_b = 0.41 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac165	$(Ca^{2+})cPLA_2{}^P + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2cPLA_2{}^P$, k_f = 10.8 μmol^{-1}.L.s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke,

		2002)
Reac166	$(Ca^{2+})_2 cPLA_2{}^P \xrightarrow{k_b} (Ca^{2+})cPLA_2{}^P + Ca^{2+}$, k_b = 108 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac167	$(Ca^{2+})cPLA_2{**} + Ca^{2+} \xrightarrow{k_f} (Ca^{2+})_2 cPLA_2{**}$, k_f = 10.8 $\mu mol^{-1}.L.s^{-1}$	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac168	$(Ca^{2+})_2 cPLA_2{**} \xrightarrow{k_b} (Ca^{2+})cPLA_2{**} + Ca^{2+}$, k_b = 2.5 s^{-1}	(Nalefski et al., 1997; Bittova et al., 1999; Nalefski et al., 2001; Nalefski and Falke, 2002)
Reac169	$AA \xrightarrow{k_{\deg}} \varnothing$, k_{deg} = 0.4 s^{-1}	(Bhalla and Iyengar, 1999; Tanaka et al., 2007)
Reac170	$(Ca^{2+})_3 PKC^* + AMPAR_{syn} \xrightarrow{k_f} ((Ca^{2+})_3 PKC^*)AMPAR_{syn}$, f k_f = 0.4 $\mu mol^{-1}.L.s^{-1}$	(Woodgett et al., 1986)
Reac171	$((Ca^{2+})_3 PKC^*)AMPAR_{syn} \xrightarrow{k_b} (Ca^{2+})_3 PKC^* + AMPAR_{syn}$, k_b = 0.8 s^{-1}	(Woodgett et al., 1986)
Reac172	$((Ca^{2+})_3 PKC^*)AMPAR_{syn} \xrightarrow{k_{cat}} (Ca^{2+})_3 PKC^* + AMPAR^P_{syn}$, k_{cat} = 0.3 s^{-1}	(Woodgett et al., 1986)
Reac173	$(AA)PKC^* + AMPAR_{syn} \xrightarrow{k_f} ((AA)PKC^*)AMPAR_{syn}$, k_f = 0.4 $\mu mol^{-1}.L.s^{-1}$	(Woodgett et al., 1986)
Reac174	$((AA)PKC^*)AMPAR_{syn} \xrightarrow{k_b} (AA)PKC^* + AMPAR_{syn}$,	(Woodgett et al., 1986)

	k_b = 0.8 s^{-1}	
Reac175	$((AA)PKC^{*})AMPAR_{syn} \xrightarrow{k_{cat}} (AA)PKC^{*} + AMPAR_{syn}^{P}$, k_{cat} = 0.3 s^{-1}	(Woodgett et al., 1986)
Reac176	$(AA)(Ca^{2+})PKC^{*} + AMPAR_{syn} \xrightarrow{k_f} ((AA)(Ca^{2+})PKC^{*})AMPAR_{syn}$, k_f = 0.4 $\mu mol^{-1}.L.s^{-1}$	(Woodgett et al., 1986)
Reac177	$((AA)(Ca^{2+})PKC^{*})AMPAR_{syn} \xrightarrow{k_b} (AA)(Ca^{2+})PKC^{*} + AMPAR_{syn}$, k_b = 0.8 s^{-1}	(Woodgett et al., 1986)
Reac178	$((AA)(Ca^{2+})PKC^{*})AMPAR_{syn} \xrightarrow{k_{cat}} (AA)(Ca^{2+})PKC^{*} + AMPAR_{syn}^{P}$, k_{cat} = 0.3 s^{-1}	(Woodgett et al., 1986)
Reac179	$(AA)(Ca^{2+})_3PKC^{*} + AMPAR_{syn} \xrightarrow{k_f} ((AA)(Ca^{2+})_3PKC^{*})AMPAR_{syn}$, k_f = 0.4 $\mu mol^{-1}.L.s^{-1}$	(Woodgett et al., 1986)
Reac180	$((AA)(Ca^{2+})_3PKC^{*})AMPAR_{syn} \xrightarrow{k_b} (AA)(Ca^{2+})_3PKC^{*} + AMPAR_{syn}$, k_b = 0.8 s^{-1}	(Woodgett et al., 1986)
Reac181	$((AA)(Ca^{2+})_3PKC^{*})AMPAR_{syn} \xrightarrow{k_{cat}} (AA)(Ca^{2+})_3PKC^{*} + AMPAR_{syn}^{P}$, k_{cat} = 0.3 s^{-1}	(Woodgett et al., 1986)
Reac182	$PP2A + AMPAR_{syn}^{P} \xrightarrow{k_f} (PP2A)AMPAR_{syn}^{P}$, k_f = 0.6 $\mu mol^{-1}.L.s^{-1}$	(Donella Deana et al., 1990)
Reac183	$(PP2A)AMPAR_{syn}^{P} \xrightarrow{k_b} PP2A + AMPAR_{syn}^{P}$, k_b = 0.17 s^{-1}	(Donella Deana et al., 1990)
Reac184	$(PP2A)AMPAR_{syn}^{P} \xrightarrow{k_{cat}} PP2A + AMPAR_{syn}$, k_{cat} = 0.25 s^{-1}	(Donella Deana et al., 1990)
Reac185	$GRIP + AMPAR_{syn} \xrightarrow{k_f} (GRIP)AMPAR_{syn}$, k_f = 1.0 $\mu mol^{-1}.L.s^{-1}$	(Gianni et al., 2005; Gianni et al., 2006; Launey, 2007)
Reac186	$(GRIP)AMPAR_{syn} \xrightarrow{k_b} GRIP + AMPAR_{syn}$, k_b = 7 s^{-1}	(Gianni et al., 2005; Gianni et al., 2006; Launey, 2007)
Reac187	$GRIP + AMPAR_{syn}^{P} \xrightarrow{k_f} (GRIP)AMPAR_{syn}^{P}$, k_f = 1.0 $\mu mol^{-1}.L.s^{-1}$	(Matsuda et al., 1999; Chung et al., 2003;

		Launey, 2007)
Reac188	$(GRIP)AMPAR^{P}_{syn} \xrightarrow{k_b} GRIP + AMPAR^{P}_{syn}$, k_b = 70 s^{-1}	(Matsuda et al., 1999; Chung et al., 2003; Launey, 2007)
Reac189	$AMPAR_{syn} \xrightarrow{k_f} AMPAR_{extra-syn}$, f k_f = 0.1 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac190	$AMPAR_{extra-syn} \xrightarrow{k_b} AMPAR_{syn}$, k_b = 0.02 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac191	$AMPAR^{P}_{syn} \xrightarrow{k_f} AMPAR^{P}_{extra-syn}$, k_f = 0.1 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac192	$AMPAR^{P}_{extra-syn} \xrightarrow{k_b} AMPAR^{P}_{syn}$, k_b = 0.025 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac193	$PP2A + AMPAR^{P}_{extra-syn} \xrightarrow{k_f} (PP2A)AMPAR^{P}_{extra-syn}$, k_f = 0.6 $\mu mol^{-1}.L.s^{-1}$	(Donella Deana et al., 1990)
Reac194	$(PP2A)AMPAR^{P}_{extra-syn} \xrightarrow{k_b} PP2A + AMPAR^{P}_{extra-syn}$, k_b = 0.17 s^{-1}	(Donella Deana et al., 1990)
Reac195	$(PP2A)AMPAR^{P}_{extra-syn} \xrightarrow{k_{cat}} PP2A + AMPAR_{extra-syn}$, k_{cat} = 0.25 s^{-1}	(Donella Deana et al., 1990)
Reac196	$AMPAR_{extra-syn} \xrightarrow{k_f} AMPAR_{dend}$, f k_f = 0.02 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac197	$AMPAR_{dend} \xrightarrow{k_b} AMPAR_{extra-syn}$, k_b = 0.00025 s^{-1}	(Borgdorff and Choquet, 2002; Bats

		et al., 2007)
Reac198	$AMPAR^{P}_{extra-syn} \xrightarrow{k_f} AMPAR^{P}_{dend}$, k_f = 0.02 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac199	$AMPAR^{P}_{dend} \xrightarrow{k_b} AMPAR^{P}_{extra-syn}$, k_b = 0.00025 s^{-1}	(Borgdorff and Choquet, 2002; Bats et al., 2007)
Reac200	$PP2A + AMPAR^{P}_{dend} \xrightarrow{k_f} (PP2A)AMPAR^{P}_{dend}$, k_f = 0.6 $\mu mol^{-1}.L.s^{-1}$	(Donella Deana et al., 1990)
Reac201	$(PP2A)AMPAR^{P}_{dend} \xrightarrow{k_b} PP2A + AMPAR^{P}_{dend}$, k_b = 0.17 s^{-1}	(Donella Deana et al., 1990)
Reac202	$(PP2A)AMPAR^{P}_{dend} \xrightarrow{k_{cat}} PP2A + AMPAR_{dend}$, k_{cat} = 0.25 s^{-1}	(Donella Deana et al., 1990)
Reac203	$AMPAR^{P}_{dend} \xrightarrow{k_f} AMPAR^{P}_{cyt}$, [f] k_f = 0.003 s^{-1}	(Ehlers, 2000; Lin et al., 2000; Passafaro et al., 2001)
Reac204	$AMPAR^{P}_{cyt} \xrightarrow{k_b} AMPAR^{P}_{dend}$, k_b = 0.002 s^{-1}	(Ehlers, 2000; Passafaro et al., 2001)
Reac205	$PP2A + AMPAR^{P}_{cyt} \xrightarrow{k_f} (PP2A)AMPAR^{P}_{cyt}$, k_f = 0.6 $\mu mol^{-1}.L.s^{-1}$	(Donella Deana et al., 1990)
Reac206	$(PP2A)AMPAR^{P}_{cyt} \xrightarrow{k_b} PP2A + AMPAR^{P}_{cyt}$, k_b = 0.17 s^{-1}	(Donella Deana et al., 1990)
Reac207	$(PP2A)AMPAR^{P}_{cyt} \xrightarrow{k_{cat}} PP2A + AMPAR_{cyt}$, k_{cat} = 0.25 s^{-1}	(Donella Deana et al., 1990)

[a] 1μmol.L^{-1} corresponds to ~ 49 molecules
[b] Parenthesis indicates complex formation
[c] The presence of * or ** indicates activated form of the species considered
[d] The letter ^{P} indicates phosphorylation without activation
[e] The term *memb* refers to membrane

[f] The terms $AMPAR_{syn}$, $AMPAR_{extra\text{-}syn}$, $AMPAR_{dend}$, $AMPAR_{cyt}$ refer, respectively, to synaptic AMPAR, extra-synaptic AMPAR in the spine, dendritic AMPAR and cytosolic AMPAR.

Table 1 References

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Table 2 Sensitivity analysis of the biochemical population size of the components of the positive feedback loop used in the model. Parameters (n_{Hill}, $K_{1/2}$, LTD_{max}) were estimated with 95% confidence interval by nonlinear least square regression to Equation 1.

Specie	n_{Hill}	$K_{1/2}$ (μmol.L^{-1})	LTD_{max} (%)
Optimal model	5.72	1.50	32.80
PKC +10%	5.29 (7.52 %)[a]	1.36 (9.34 %)	33.36 (1.70 %)
PKC -10%	5.28 (7.69 %)	1.64 (9.34 %)	29.62 (9.65 %)
Raf-act +10%	5.84 (2.09)	1.43 (4.67 %)	31.99 (2.47 %)
Raf-act -10%	5.69 (0.52 %)	1.56 (4.00 %)	30.95 (6.04 %)
Raf +10%	5.59 (2.27 %)	1.39 (7.34 %)	33.83 (3.14 %)
Raf -10%	5.79 (1.22 %)	1.64 (9.34 %)	28.28 (13.78 %)
MEK +10%	5.46 (4.55 %)	1.40 (6.67 %)	32.61 (0.58 %)
MEK -10%	6.23 (8.91 %)	1.58 (5.34 %)	30.17 (8.02 %)
ERK +10%	5.99 (4.72 %)	1.44 (4.00 %)	31.88 (2.80 %)
ERK -10%	5.56 (2.79 %)	1.55 (3.34 %)	30.09 (8.26 %)
$cPLA_2$ +10%	5.41 (5.41 %)	1.44 (4.00 %)	31.91 (2.71 %)
$cPLA_2$ -10%	6.04 (5.59 %)	1.59 (6.00 %)	30.16 (8.05 %)
PP1 +10%	5.52 (3.49 %)	1.48 (1.34 %)	31.94 (2.62 %)
PP1 -10%	5.61 (1.92 %)	1.51 (0.67 %)	31.28 (4.63 %)
PP5 +10%	6.29 (9.96 %)	1.55 (3.34 %)	29.38 (10.43 %)
PP5 -10%	5.47 (4.37 %)	1.35 (10.0 %)	31.96 (2.56 %)
PP2A +10%	6.50 (13.63 %)	1.65 (10.0 %)	24.51 (25.27 %)
PP2A-10%	6.04 (5.59 %)	1.36 (9.34 %)	35.22 (7.37 %)
MKP +10%	6.07 (6.11 %)	1.52 (1.34 %)	28.12 (14.26 %)
MKP -10%	5.79 (1.22 %)	1.41 (6.00 %)	32.15 (1.98 %)

[a]Number in parenthesis show the percentage of the deviation in comparison with the mean response calculated for 156 runs of the optimal model

Table 3 Sensitivity analysis of the unknown rate constants of the reactions of the positive feedback loop used in the model. Parameters (n_{Hill}, $K_{1/2}$, LTD_{max}) were estimated with 95% confidence interval by nonlinear least square regression to Equation 1.

Rate constant identity	n_{Hill}	$K_{1/2}$ (μmol.L^{-1})	LTD_{max} (%)
Optimal model	5.72	1.50	32.80
Rate constant 59, 62, 65 and 68[a,b] +10%	5.50 (3.85 %)[c]	1.40 (6.67 %)	31.93 (2.65 %)
Rate constant 59, 62, 65 and 68[a] -10%	6.07 (6.12 %)	1.44 (4.00 %)	29.19 (11.00 %)
Rate constant 60, 63, 66 and 69 +10%	5.98 (4.55 %)	1.50 (0.00 %)	30.48 (7.07 %)
Rate constant 60, 63, 66 and 69 -10%	6.26 (9.44 %)	1.46 (2.67 %)	30.97 (5.57 %)
Rate constant 61, 64, 67 and 70 +10%	5.75 (0.52 %)	1.48 (1.34 %)	31.94 (2.62 %)
Rate constant 61, 64, 67 and 70 -10%	5.98 (4.55 %)	1.46 (2.67 %)	30.38 (7.37 %)
Rate constant 71 +10%	6.06 (5.94 %)	1.47 (2.00 %)	30.05 (8.38 %)
Rate constant 71 -10%	5.44 (4.89 %)	1.53 (2.00 %)	32.10 (2.13 %)
Rate constant 72 +10%	6.08 (6.29 %)	1.47 (2.00 %)	32.52 (0.85 %)
Rate constant 72 -10%	6.29 (9.96 %)	1.62 (8.00 %)	30.33 (7.53%)
Rate constant 73 +10%	6.18 (8.04 %)	1.50 (0.00 %)	29.84 (9.02 %)
Rate constant 73 -10%	6.21 (8.57 %)	1.49 (0.67 %)	31.12 (5.12 %)
Rate constant 74 +10%	6.03 (5.42 %)	1.44 (4.00 %)	31.53 (3.87 %)
Rate constant 74 -10%	6.16 (7.69 %)	1.49 (0.67 %)	29.15 (11.12 %)
Rate constant 75 +10%	5.37 (6.12 %)	1.53 (2.00 %)	29.56 (9.87 %)
Rate constant 75 -10%	6.24 (9.09 %)	1.45 (3.34 %)	32.94 (0.42 %)
Rate constant 76	6.22 (8.74 %)	1.41 (6.00 %)	32.02 (2.38 %)

+10%			
Rate constant 76 -10%	6.60 (15.38 %)	1.55 (3.34 %)	28.91 (11.85 %)
Rate constant 77 +10%	5.53 (3.32 %)	1.52 (1.34 %)	29.71 (9.42 %)
Rate constant 77 -10%	5.61 (1.92 %)	1.51 (0.67 %)	31.56 (3.78 %)
Rate constant 84 and 87 +10%[c]	6.57 (14.86 %)	1.59 (6.00 %)	26.80 (18.29 %)
Rate constant 84 and 87 -10%	6.29 (9.96 %)	1.35 (10.00 %)	33.09 (0.88 %)
Rate constant 85 and 88 +10%	5.51 (3.67 %)	1.43 (4.67 %)	33.81 (3.07 %)
Rate constant 85 and 88 -10%	6.04 (5.59 %)	1.59 (6.00 %)	28.31 (13.69 %)
Rate constant 86 and 89 +10%	6.27 (9.61 %)	1.57 (4.67 %)	27.33 (16.68 %)
Rate constant 86 and 89 -10%	5.27 (7.86 %)	1.39 (7.34 %)	33.18 (1.16 %)
Rate constant 119, 122 and 125 +10%	5.91 (3.32 %)	1.54 (2.67 %)	31.47 (4.05 %)
Rate constant 119, 122 and 125 -10%	6.22 (8.74 %)	1.51 (0.67 %)	31.09 (5.21 %)
Rate constant 120, 123 and 126 +10%	6.19 (8.22 %)	1.47 (2.00 %)	30.67 (6.49 %)
Rate constant 120, 123 and 126 -10%	6.27 (9.61 %)	1.44 (4.00 %)	30.31 (7.59 %)
Rate constant 121, 124 and 127 +10%	6.28 (9.79 %)	1.52 (1.34 %)	30.69 (6.43 %)
Rate constant 121, 124 and 127 -10%	6.11 (6.82 %)	1.43 (4.67 %)	30.97 (5.58 %)
Rate constant 128, 131 and 134 +10%	6.19 (8.22 %)	1.51 (0.67 %)	30.42 (7.26 %)
Rate constant 128, 131 and 134 -10%	5.55 (2.97 %)	1.49 (0.67 %)	31.34 (4.45 %)
Rate constant 129, 132 and 135 +10%	5.69 (0.52 %)	1.48 (1.34 %)	31.52 (3.90 %)

Rate constant 129, 132 and 135 -10%	6.09 (6.47 %)	1.46 (2.67 %)	30.77 (6.19 %)
Rate constant 130, 133 and 136 +10%	5.56 (2.80 %)	1.47 (2.00 %)	30.14 (8.11 %)
Rate constant 130, 133 and 136 -10%	5.44 (5.39 %)	1.52 (1.34 %)	31.15 (5.03 %)
Rate constant 137, 140 and 143 +10%	6.27 (9.61 %)	1.49 (0.67 %)	30.36 (7.44 %)
Rate constant 137, 140 and 143 -10%	6.48 (13.28 %)	1.46 (2.67 %)	29.89 (8.87 %)
Rate constant 138, 141 and 144 +10%	6.14 (7.34 %)	1.43 (4.67 %)	30.86 (5.91 %)
Rate constant 138, 141 and 144 -10%	6.54 (14.33 %)	1.54 (2.67 %)	31.39 (4.29 %)
Rate constant 139, 142 and 145 +10%	5.24 (8.39 %)	1.48 (1.34 %)	31.91 (2.71 %)
Rate constant 139, 142 and 145 -10%	6.20 (8.39 %)	1.54 (2.67 %)	31.13 (5.09 %)
Rate constant 170, 173, 176 and 179 +10%	5.69 (0.52 %)	1.46 (2.67 %)	31.33 (4.48 %)
Rate constant 170, 173, 176 and 179 -10%	6.53 (14.16 %)	1.43 (4.67 %)	29.74 (9.32 %)
Rate constant 171, 174, 177 and 180 +10%	5.62 (1.75 %)	1.41 (6.00 %)	30.35 (7.47 %)
Rate constant 171, 174, 177 and 180 -10%	5.99 (4.72 %)	1.52 (1.34 %)	31.28 (4.63 %)
Rate constant 172, 175, 178 and 181 +10%	5.50 (3.85 %)	1.44 (4.00 %)	31.71 (3.32 %)
Rate constant 172, 175, 178 and 181 -10%	6.28 (9.79 %)	1.59 (6.00 %)	28.87 (11.98 %)
Rate constant 182,	6.02 (5.24 %)	1.47 (2.00 %)	29.69 (9.48 %)

193, 200 and 205 +10%			
Rate constant 182, 193, 200 and 205 -10%	6.28 (9.79 %)	1.46 (2.67 %)	31.36 (4.39 %)
Rate constant 183, 194, 201 and 206 +10%	6.13 (7.17 %)	1.49 (0.67 %)	30.65 (6.55 %)
Rate constant 183, 194, 201 and 206 -10%	6.27 (9.62 %)	1.53 (2.00 %)	30.32 (7.56 %)
Rate constant 184, 195, 202 and 207 +10%	5.20 (9.09 %)	1.54 (2.67 %)	30.72 (6.34 %)
Rate constant 184, 195, 202 and 207 -10%	5.34 (6.64 %)	1.44 (4.00 %)	31.56 (3.78 %)

[a] The identities (numbers) of the rate constants in column 1 correspond to the same identities of the reactions (reac) listed in Supplementary Table I.

[b] The parameters of analogous reactions were analyzed simultaneously.

[c] Number in parenthesis show the percentage of the deviation in comparison with the mean responses of the optimal model.