Supplementary Information:

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A Brief Description of the Model

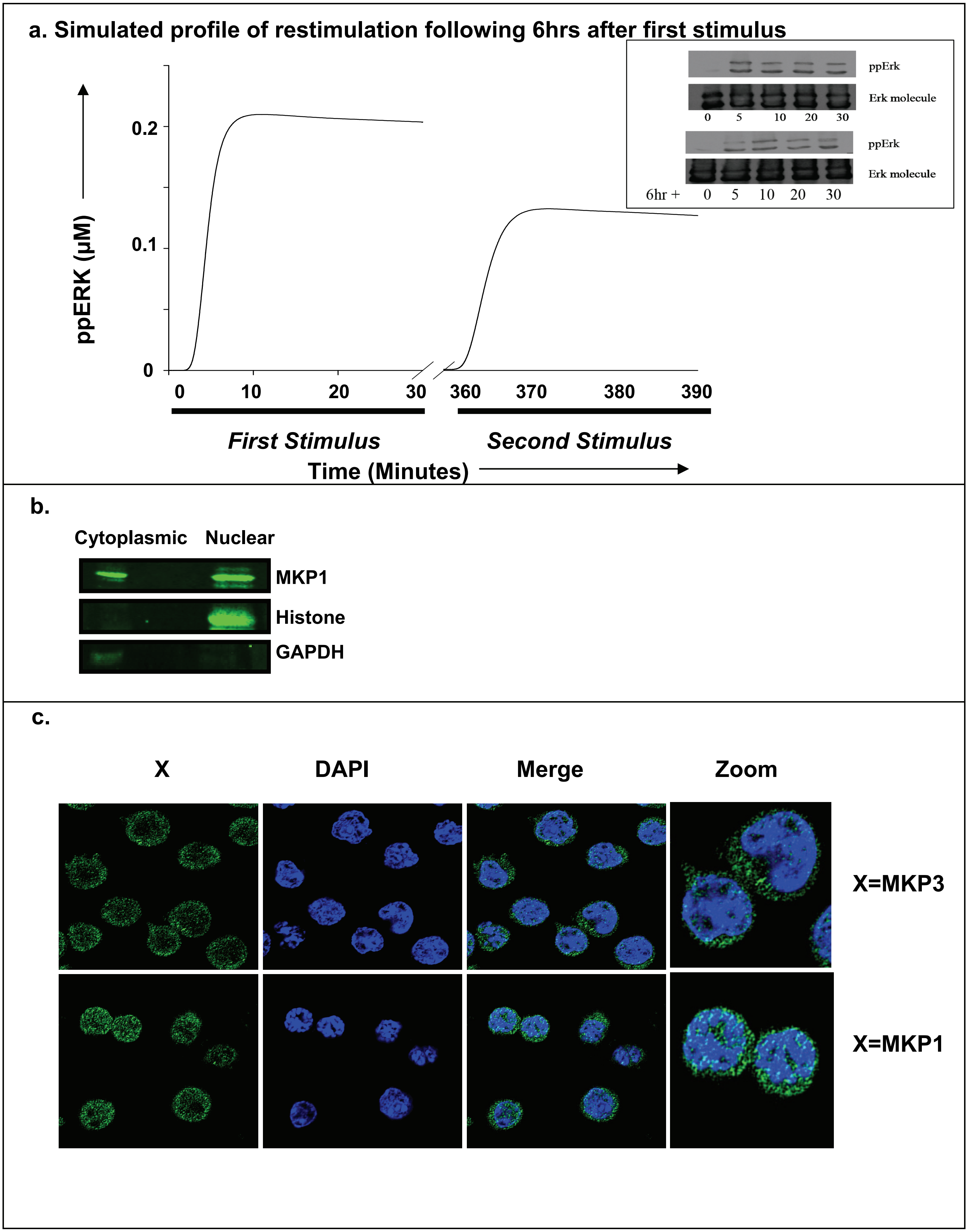
The BCR is composed of heavy and light chains and the associated immuno-tyrosine activation motifs (ITAMs). ITAMs get phosphorylated in response to BCR engagement by antigen, which then leads to cross linking of the BCR molecules. The BCR dependent phosphorylation of ITAMs is sustained through Syk dependent phosphorylation on three additional sites on the ITAMs. For simplicity, however, we have defined all stages of this multiple phosphorylated states as the doubly phosphorylated BCR (which represents- ITAM + Immunoglobulin part of the BCR). Both singly and doubly phosphorylated BCR activates the src kinase Lyn. Syk, which is immediately downstream to Lyn, is then phosphorylated in a Lyn-dependent manner. This establishes a positive feedback loop at the BCR(1). Antigen-bound BCR also undergoes internalization, although internalized receptors do not contribute towards further signaling(2). Lyn also phosphorylates CD22, a membrane anchored intermediate of B cell signaling. This, in turn, recruits the protein tyrosine phosphatase SHP1 to the membrane. Since SHP1 is a negative regulator of a majority of protein tyrosine kinases including Lyn and Syk, a negative feedback loop is established. Thus a negative and a positive feedback loop are both established in the immediate vicinity of the BCR. Both Lyn and Syk also activate Brutons' tyrosine kinase (Btk). Btk in turn phosphorylates PLCg when the latter is bound to the Syk-phopshorylated BLNK, a major scaffold protein that connects BCR initiated signaling to downstream events(3,4). Lyn via CD19, and Syk via BCAP (B Cell Adopter Protein), activate PI3-Kinase signaling with the consequent generation of PIP3. This leads to recruitment of cytoplasmic Akt and PDK to the membrane, where PDK then phosphorylates Akt(4).

Syk mediated activation of BLNK also leads to the formation of a BLNK-Grb2-SoS complex, which functions as the RasGDP-GTP exchanger in B cells. The GAP and GEF are modeled according to the scheme as described by Bhalla et. al.(5,6). We've summarized the activation of all PKC isoforms by DAG mediated PKC recruitment to the membrane. RasGTP binds to Raf and resulting complex of Raf-RasGTP is then phosphorylated by PKC. Phosphorylated Raf activates the classical Raf-MEK-ERK pathway. Although lymphocyte signaling also involves RasGRPs in activation of RasGTPs via SOS(7,8), the effect of RasGRPs are better characterized in terms of maintaining the basal levels of RasGTP activity(8). The stimulus induced effect of RasGRPs on RasGTP kinetics is still unclear. Therefore, we kept our model at the level of RasGTP simple and invoked only the classical activation pathway of RasGTP via SoS as the standard GEF. The predicted ligand dose response yielded a good match with the experimental results and more importantly the simplification of the activation pathway of RasGTP did not affect the performance of our model. ERK negatively regulates Raf by hyper phosphorylating it(6,9). In addition Raf is also negatively regulated through phosphorylation at ser259 by activated Akt (10). This process has been modeled accordingly. Dephosphorylation of activated Raf is mediated through PP2A whereas the inactivated form represented by hyperphsophorylation or Ser259 phosphorylation, is dephosphorylated by both PP1 and PP2A.

Several reports in the literature have indicated that phosphorylation of ERK1/2 is also regulated by phosphatases(6). In more recent experiments we have demonstrated that the BCR dependent phosphorylation profiles of all the three constituents of the MAPK module (i.e. Raf, MEK1/2 and ERK1/2) were profoundly influenced when cells were depleted of a range of cellular phosphatases by siRNA. Interestingly, depending upon the phosphatases that were depleted, both negative and positive effects were noted suggesting the existence of diverse modes of regulation (11). Therefore to explore this further, we also incorporated these earlier results for five phosphatases. These were PP1, PP2A, MKP1, MKP2 and MKP3. We started by linking core MAPK module recursively with the phosphatases in a manner that satisfied the experimental data. The phosphorylation profile of ERK was used as eventual output, although the simulated profiles of Raf and MEK1/2 were also compared with the experimental data for the purpose of model validation.

Whereas PP1(or, Calcineurin) was treated as an unregulated pool, the dual specificity phosphatases MKP1 and MKP3 were modeled as previously described(6), but with the modification that phosphorylation of MKP1 was modeled as a single step process. An interesting aspect of our earlier experimental results was the finding that depletion of MKP3 by siRNA resulted in contrasting effects on the BCR-stimulated phosphorylation profiles of MEK and ERK. Whereas phosphorylation of MEK-1/2 was markedly enhanced, the sensitivity of ERK-1/2 to BCR stimulation was attenuated(11). This observation could be rationalized by invoking the related finding of (12), that the PKC substrate Casein kinase2α both interacts with and phosphorylate MKP3. Thus, although MKP3 is known to negatively regulate ERK1/2 activation, the simultaneous over-expression of CK2α – however reversed this effect. This attenuating effect of CK2α on MKP3 involves phosphorylation of the latter(12). In our present system we found that MKP3 expression was up regulated upon BCR stimulation (S3c.B) and our model depicts that the interaction of CK2αwith this phosphatase modulates the MKP3-mediated co-ordination of the negative feedback loop influencing ERK-1/2 phosphorylation. Importantly our earlier results also implicated MKP1, which is positively regulated by ERK-1/2 as a direct target of MKP3. While modeling the MAPK pathway, however, the possibility that the MKP3 acted simultaneously on both ERK-1/2 and MKP1 seemed unlikely since such a proposition failed to explain the previously described experimental results. We therefore, considered the possibility that the ERK-1/2 and MKP1 may represent alternate substrate for MKP3, with substrate specificity being determined by the phosphorylation state of MKP3. Whereas the non phosphorylated MKP3 functioned as a negative regulator of ERK-1/2 activation, its phosphorylation by CK2α alters its substrate preference in favor of MKP1, with the consequent attenuation of its activity. This postulates yielded a satisfactory solution after a few optimization and simulation exercises.

Our earlier findings that the depletion of MKP3 from cells by si-RNA resulted in a marked enhancement in the BCR-dependent phosphorylation of MEK-1/2 (11) also prompted us to link phosphorylated MKP3 as a negative regulator of MEK-1/2. Consequently, while phospho-MKP3 would not be expected to directly inhibit ERK-1/2 activation this would nonetheless, be compensated by the inhibitory effect of MKP3 on the upstream kinase MEK-1/2. Further, PP2A has been described as a regulator of the phosphorylation of MEK-1/2(5,6,13). In addition, a marked increase in ERK-1/2 phosphorylation was also observed under these conditions. We accounted for


a. Simulated profile of restimulation following 6hrs after first stimulus
ppERK (µM)
0.2
0.1
0
0
10
20
30
360
370
380
390
First Stimulus
Second Stimulus
Time (Minutes)
ppErk
Erk molecule
0 5 10 20 30
ppErk
Erk molecule
6hr + 0 5 10 20 30
b.
Cytoplasmic
Nuclear
MKP1
Histone
GAPDH
c.
X
DAPI
Merge
Zoom
X=MKP3
X=MKP1

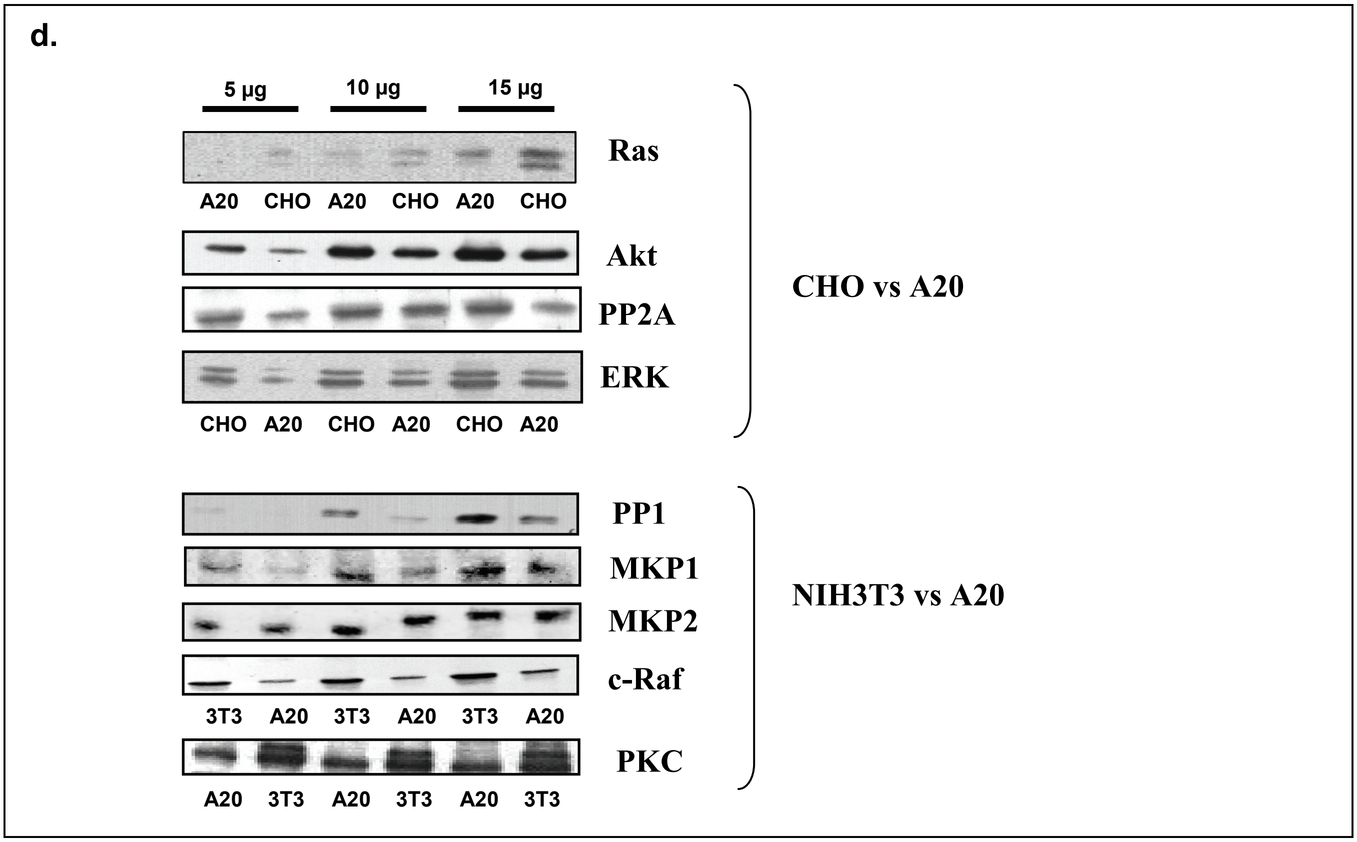


Figure S1.1: (**a**)**.** Shown here the simulation profile of ERK phosphorylation (ppERK) following a first stimulus of thirty minutes and a second stimulus 6 hours after the first stimulus. Inset in the top panel shows the Western blot from the similar experiment on A20 cells. A good correspondence between the Western blot results and the *in silico* prediction is clearly evident here. (**b**)**.** This panel shows the result of an experiment where nuclear and cytosolic fractions from A20 cells are probed for MKP1. These blots were also probed for the corresponding marker proteins for nuclear (histone) and the cytoplasmic (GAPD) fractions. While the presence of MKP1 in both fractions is evident, the selective presence of the marker proteins in the appropriate fractions confirms the absence of any cross contamination. (**c**)**.** A more direct experiment using confocal imaging further confirmed that both MKP1 and MKP3 are present in the cytoplasmic and in the nuclear compartments. For this experiment, A20 cells were fixed and stained (green color) for MKP3 (top panel) and MKP1 (lower panel). Blue color shows the nuclear stain by DAPI. (**d**)**.** Western blot-based determination of the concentration of signaling molecules in A20 cells by titrating against the corresponding lysates from NIH3T3 and CHO cells. The concentration of our molecules of interest were previously determined in either of these cell lines(1,2)). Blots shown are representative of 3 independent experiments. Indicated amounts of the total protein were loaded and the resolved lysates probed for the indicated proteins. Band intensities for each protein obtained in A20 cells were then compared with the corresponding intensities for the same protein in the lysate used as the standard (i.e CHO or NIH3T3) to calculate its relative concentration in A20 cells. The final values used represented the mean value obtained for the triplicate sets at each concentration of the total cellular protein. Further, a parallel probe for GAPD was used as the loading control and the ratio of the band intensity of the target protein versus that of GAPD in each lane was used for normalization. This procedure is similar in principle to that described earlier (3).

1. Bhalla, U. S., and Iyengar, R. (1999) *Science* **283**(5400), 381-387
2. Hatakeyama, M., Kimura, S., Naka, T., Kawasaki, T., Yumoto, N., Ichikawa, M., Kim, J. H., Saito, K., Saeki, M., Shirouzu, M., Yokoyama, S., and Konagaya, A. (2003) *Biochem J* **373**(Pt 2), 451-463
3. Schoeberl, B., Eichler-Jonsson, C., Gilles, E. D., and Muller, G. (2002) *Nat Biotechnol* **20**(4), 370-375

these unexpected findings by considering the possibility that phosphorylation of MKP3 could be reversed by the direct action of PP2A. Thus in addition to de-phosphorylating Raf and MEK-1/2, PP2A is also likely to function in regulating the balance between the phosphorylated and non-phosphorylated pools of MKP3. The resulting model for the MAPK module yielded a prediction for the time dependent phosphorylation of ERK-1/2 that was in excellent agreement with the experimentally obtained results.

Previous studies have shown that MKP1 is primarily localized within the nuclear compartment of cells. At least in A20 cells, however, we found that this phosphatase was in fact distributed between both the nuclear and the cytoplasmic and nuclear compartments. This was first revealed from experiments involving confocal microscopy where both nuclear- and cytoplasmic-localization of MKP1, with a respective distribution of 60% versus 40%, was clearly evident (Supplementary Fig. S1.1c). We further confirmed these findings through an alternate approach wherein A20 cells were lysed, and the cytoplasmic and the nuclear extract fractions were separately obtained. These fractions were then individually probed for the presence of MKP1 by a Western blot analysis. As shown in Supplementary Figure S1.1b, the presence of MKP1 could clearly be detected in both the fractions. Further, the relative distribution between the cytoplasmic and the nuclear fraction seen here was consistent with that obtained in our confocal microscopy experiments (Supplementary Fig. S1.1c). Importantly, the presence of MKP1 in both fractions in Supplementary Figure 1.1b was not due to cross contamination between the nuclear and cytoplasmic fractions. The purity of each fraction could be demonstrated by the fact that, as expected, histone H1 was present only in the nuclear but not the cytoplasmic fraction. Similarly, a Western blot analysis for GAPD revealed the selective presence of this protein in the cytoplasmic but not the nuclear fraction (Supplementary Fig. 1.1b), thus confirming the absence of any significant level of cross-contamination between the two sample sets.

The above results thus identify a cascade of phosphatases (PP2A-MKP3-MKP1) that is aligned in parallel with the MAPK cascade (Raf-MEK-ERK). ERK activation also leads to transcriptional up-regulation of MKP1 and MKP3. We have achieved the same through a reaction scheme similar to as proposed by (6), although the rates are scaled according to the present concentration of these two phosphatases. The concentrations of c-Raf, MEK, ERK, PP2A, MKP1, RasGDP-GTP total, Akt were determined by Western blot titrations that compared against corresponding levels present in NIH3T3 and CHO cells (See Supplementary Fig. S1.1d). Concentrations of the remaining molecules were estimated.

Assumptions and criteria for implementation of the model :

Few important Considerations have been taken while implementing model in mathematical form which are as follows:

1. Since a detailed description of the early signaling events at the BCR signalosome is currently unavailable, the steps were minimized and unnecessary complexity was avoided. For this, the parameters were constrained to the extent possible for describing the kinetics of these events without affecting the known outputs, and keeping the system simple. For example, phosphorylation of BLNK at multiple sites was represented by a single step. Further, the four different (1+ 3) events of phosphorylation at the ITAMs (BCR in the model) by BCR activation and Syk mediated feedback were simplified in two steps (1 by BCR engagement + 1 by Syk) keeping the positive feedback effect of Lyn-Syk-ITAM feedback loop intact.
2. Activated to unactivated ratios were maintained for different molecules in accordance with their cytoplasmic locations and mode of activation. Compartmentalization was not considered in our analysis.
3. In the case of regulation by multiple phosphatases, the experimental results obtained by Western blot analyses cannot be directly correlated to exact relative levels of activated molecules since quantitation by this technique is not linear over a large range. Thus a true regression scheme cannot be employed for phosphatase-mediated perturbations involving large variations in phosphorylation levels. Further, shifts in baseline phosphorylation levels also cause problems, which are not usually encountered in the traditional model building exercises where maximum phosphorylation levels of substrates following on receptor activation are considered as 100%, and regression is then applied for a comparatively smaller range of modulations in phospholevels. However post implementation techniques were employed for assessing regression stability of the parameters. These were Multi Parametric Sensitivity Analysis (MPSA) and Partial Rank Correlation Coefficients (PRCC), as described later in sensitivity analysis and robustness scores.
4. Parameters describing the kinetics of molecules on the network periphery were grouped together to define the representative kinetic behavior relevant to the present MAPK module.

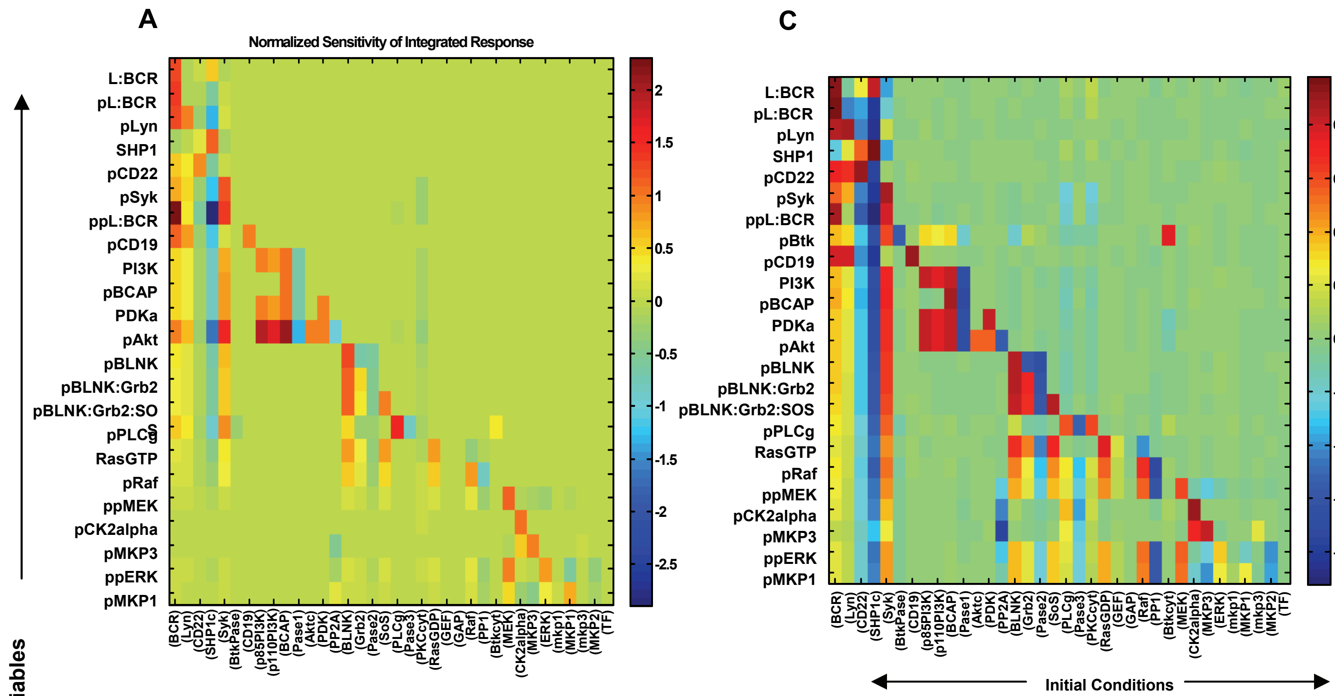
Sensitivity Analysis of the Model:

Having constructed the model, we performed an exhaustive sensitivity analysis for identifying the key regulatory features of BCR induced MAPK (ERK). Table S1.1 shows selected sensitivities and their corresponding parameters with their reaction scopes. Sensitivity analysis was done using four different methods using SBML_SAT (14) a MATLAB toolbox for sensitivity analysis of systems biology models which is based on SBML. SBML_SAT is free and available at (http://sysbio.molgen.mpg.de/SBML-SAT/).

We used four different methods of sensitivity analysis on integrated response of model output variables. All these methods of analysis identified BLNK-mediated activation of the BLNK/Grb2/SOS complex, which functions as the RasGTP-GDP exchanger uponn BCR stimulation. BLNK has a key role in B cell receptor induced signaling. It serves as a scaffold for SoS and, therefore, couples Syk with downstream signaling events of BCR signalososme (15-17). Global sensitivity analysis methods use multiple parameter variations. The scores identify the Multi-parametric Sensitivity analysis and give Kolmogorov-Smirnov (K-S) statistics values for the distance between frequencies of the acceptable and unacceptable parameter sets generated through random perturbations. That is, MPSA reveals the uncertainty of the parameter space used. Thus the K-S value here specifically revealed that kcat_123 (the enzymatic action of ppMEK on ERK) and kf_124 (binding of pERK to the ppMEK), had a significant effect on the ppERK response. This has also been reported earlier, and the consistency of these parameters found in all the methods employed suggests that this two-step phosphorylation is an important step in shaping the both integrated responses and the maximal responses of ppERK. Interestingly, the two-step phosphorylation of ppMEK does not actually give high K-S value or local sensitivity coefficient for the enzymatic action of pRaf on MEK (kcat_104), and this remains consistent on both the integrated and maximum response of ppMEK. The detailed Sensitivities of ppMEK and ppERK are provided with the parameters in S1B.

Weighted average of local sensitivity (WALS) which uses the weighted average of local sensitivity indices on parameters space and calculate the least square errors of reference simulation and perturbations. The scores of WALS here primarily identified the component important for the dose response components of present network including the main phosphatases of the model and the BCR-LYN-SYK positive feedback loop. The popular Global Sensitivity Analysis (GSA) method of regression-based rank transformation method Partial Rank Correlation Coefficient (PRCC) uniquely isolates the vm_7 (Vmax of CD22 phosphorylation) which is the part of Negative auto-regulatory loop at BCR dependent Lyn activation, and responsible for the membrane recruitment of SHP1 which negatively regulate and shapes the activity of BCR signalosome. PRCC also uniquely identified the binding of MEKpp to PP2A, the negative regulator of both MEK and Raf activity, both in the Integrated and maximum response of ppERK. This identifies that the first step of ppMEK binding to PP2A competes along with pMKP3, which is another negative regulator of MEK activity in the phosphatase cascade. In all cases of ppERK and ppMEK, the integrated response was invariably affected by the action of PP1 on pRaf, which we found to be true experimentally as well (11). PRCC also revealed the role of the initial conditions on various model output variables and is shown in figure S1.2.

Fig S1.3 to S1.8 shows the various output variables and their sensitivities for integrated and maximum responses by the different methods of LSA and GSA. The sensitivity of time dependent responses were also measured (data not shown), and this was consistent with the present results and model behavior. The model was also tested for various perturbations and combinations of the initial concentrations of Raf-MEK-ERK and we found that the solution for the SAM converged to the same response spectrum. Although we identified parameters which were sensitive to perturbations, the sensitivity of these parameters did not affect model output significantly since the cut off for the highlighted results chosen was as low as 10% of the maximum possible sensitivity in each case. Thus model was robust with respect to variations in parameters and initial conditions.



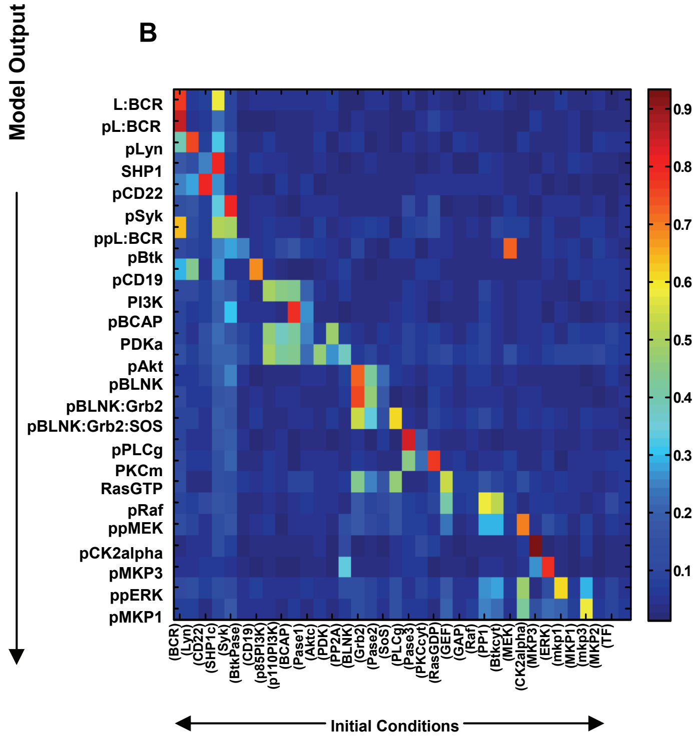


Figure S1. 2 : Sensitivity Analysis of Model output Variables for initial conditions : The three panels are showing the result of Sensitivity analysis performed on Initial conditions by three different methods (A) Local Sensitivity Analysis (LSA), (B) Multi Parametric Sensitivity Analysis (MPSA), (C) Partial Rank Correlation Coefficient (PRCC). Sensitivity analysis was performed against initial condition variation and Sensitivity measured for different model output variables for their integrated reponses.

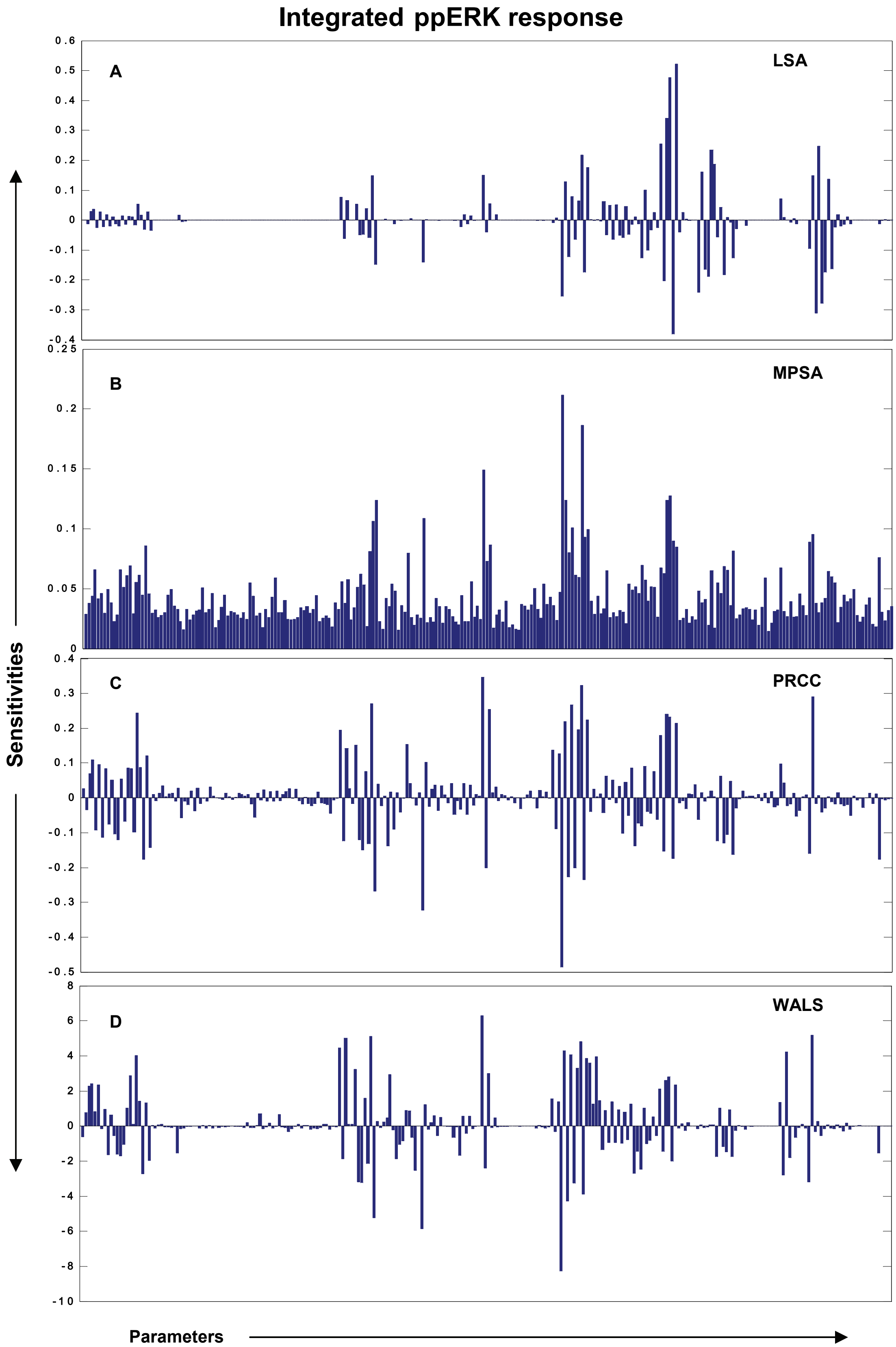


Figure S1. 3: Sensitivities of Integrated response of ppERK to Parameters variations as measured by four different methods of local and global sensitivity analysis. (A) Local Sensitivity Analysis (LSA) (B) Multi Parametric Sensitivity Analysis (MPSA) (C) Partial Rank Correlation Coefficient (PRCC), and (D) Weighted Average of Local Sensitivities (WALS) In all cases parameters location on the X-axis is in the order of their serial nos.

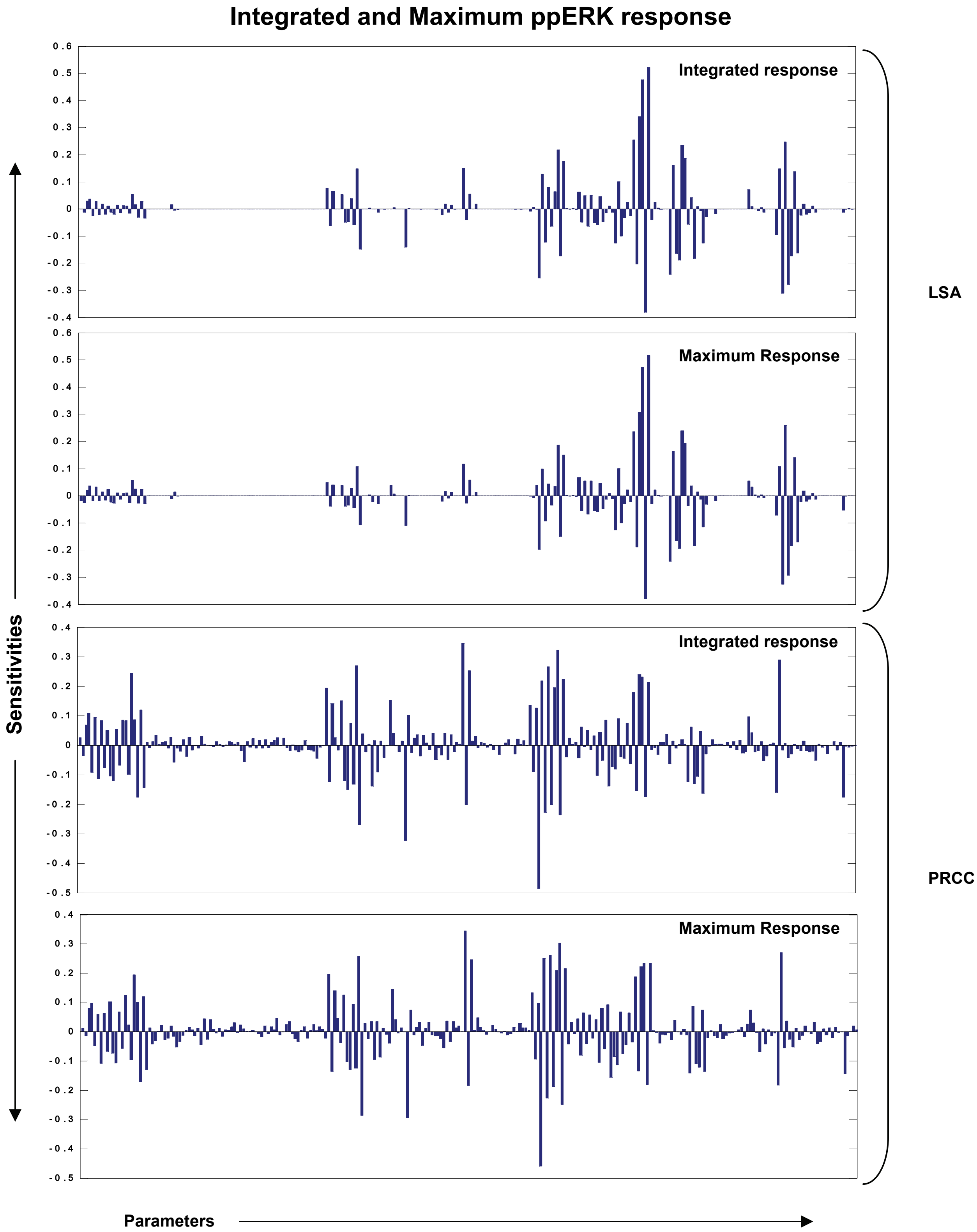


Figure S1. 4: Comparison of sensitivities of integrated response and sensitivities of maximum response of ppERK to Parameter variations as measured by local and global sensitivity analysis. Fully Normalized Sensitivities from Local Sensitivity Analysis (LSA) and Global Sensitivity Analysis by Partial Rank Correlation Coefficients (PRCC).

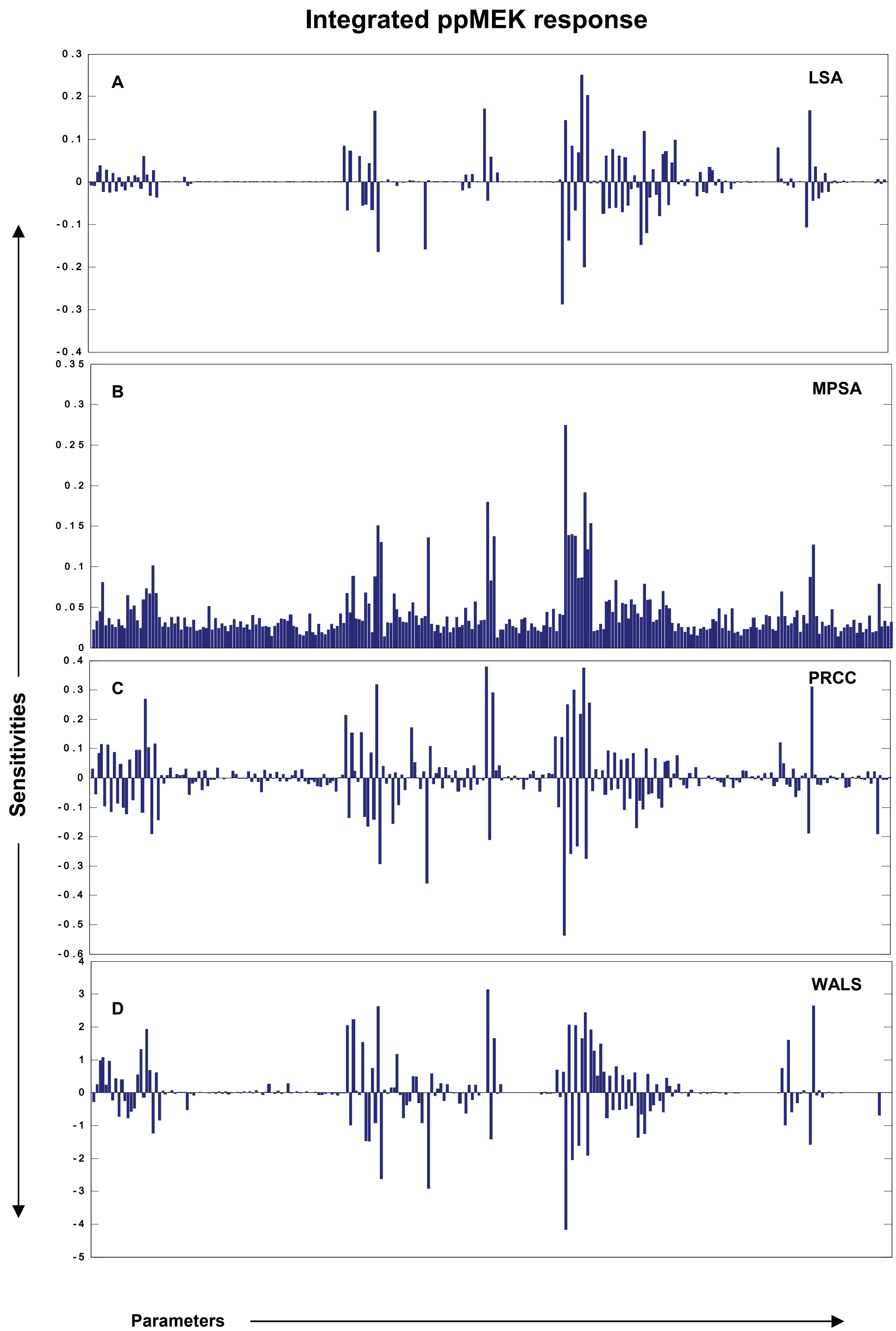


Figure S1. 5: Sensitivities of Integrated response of ppMEK to Parameter variations as measured by four different methods of local and global sensitivity analysis. (A) Local Sensitivity Analysis (LSA) (B) Multi Parametric Sensitivity Analysis (MPSA) (C) Partial Rank Correlation Coefficient (PRCC), and (D) Weighted Average of Local Sensitivities (WALS)

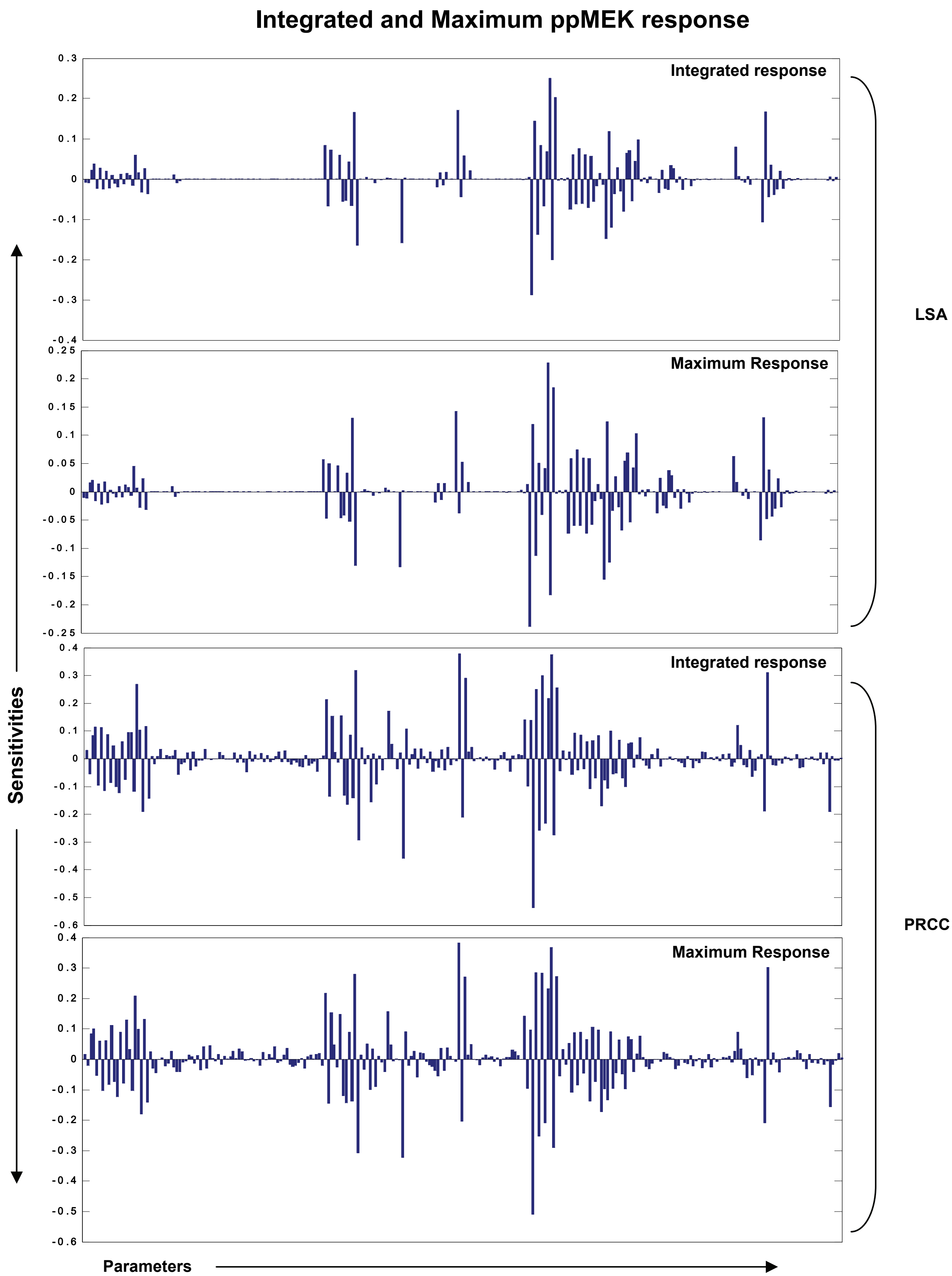


Figure S1. 6: Comparison of sensitivities of integrated response and sensitivities of maximum response of ppMEK to Parameter variations as measured by local and global sensitivity analysis. Fully normalized sensitivities from Local Sensitivity Analysis (LSA) and Global Sensitivity Analysis by Partial Rank Correlation Coefficients (PRCC) .

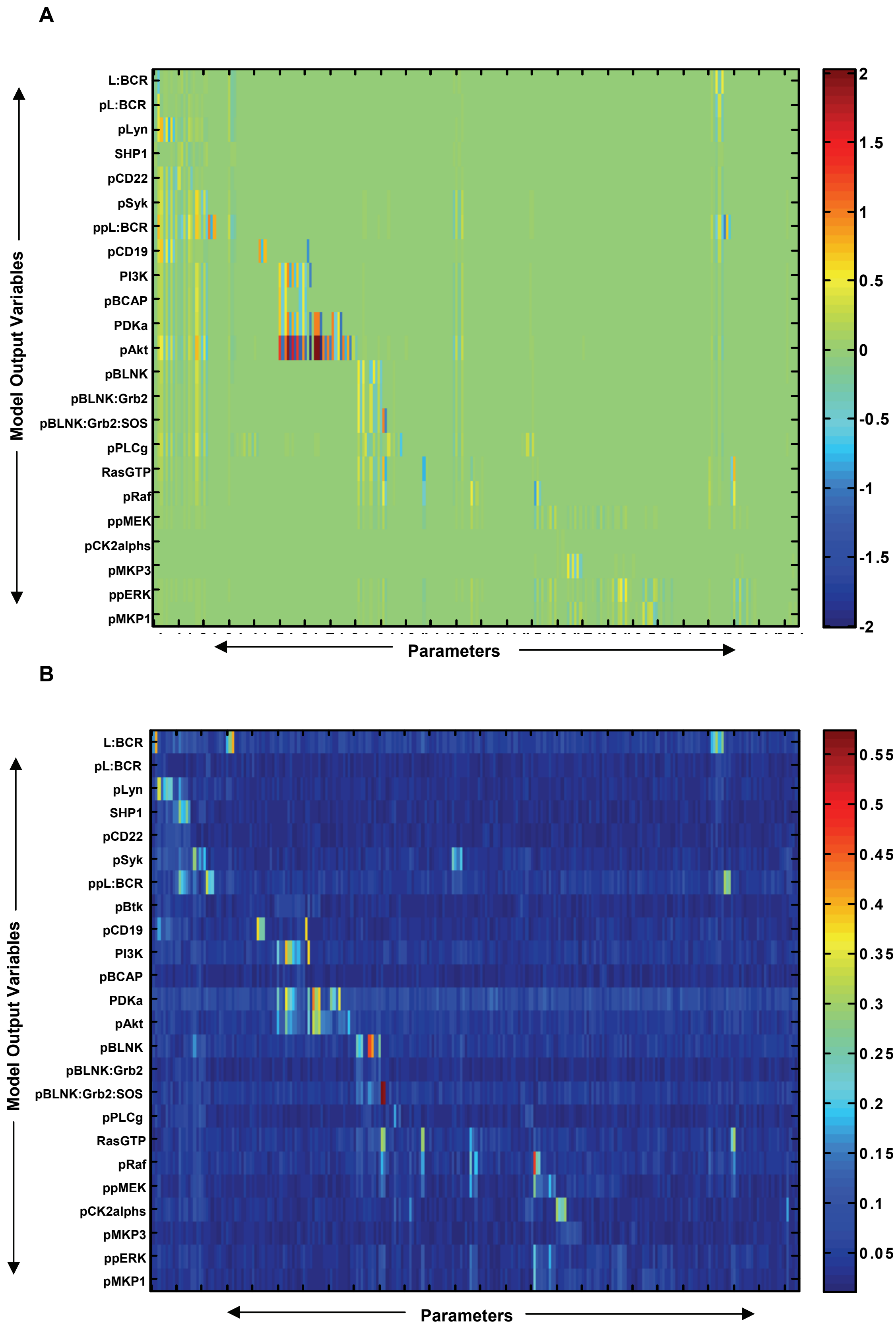


Figure S1. 7: Comparison of sensitivities of integrated response of different model output variables for Parameter variations as measured by local and global sensitivity analysis. (A) Local Sensitivity Analysis (LSA) and (B) Global Sensitivity Analysis by Multi-Parametric Sensitivity analysis .

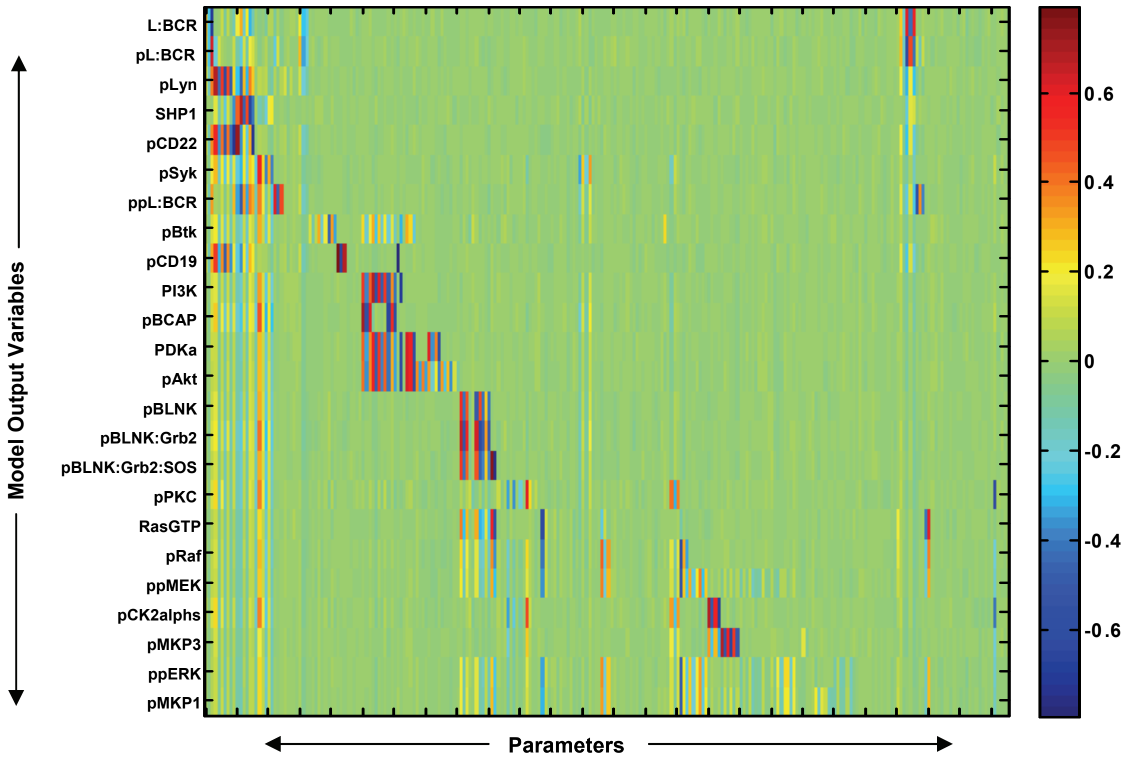


Figure S1. 8: Sensitivities of integrated response of different model output variables for Parameter variations as measured by global sensitivity analysis by Partial Rank Correlation Coefficients (PRCC) Method .

Table S1.1: List of Sensitive parameters for ppERK response, identified by multiple sensitive analysis methods. (Highlighted values are chosen by low cut-off of the scores in each method. Both negative and positive values are selected in cases wherever required)

Parameter no.	Name	Scope (Reaction)	Value	INTEGRATED RESPONSE ppERK				MAXIMUM RESPONSE ppERK	
				LSA	MPSA	PRCC	WALS	LSA	PRCC
3	kf_2	[L:BCR] -> [L:BCRp]	0.99	0.029204	0.043819	0.070292	2.2845	0.020365	0.081712
4	kon_3	[L:BCRp] + Lyn <-> [L:BCRp:Lyn]	0.8857	0.037552	0.065934	0.10865	2.4007	0.037694	0.097706
6	kcat_4	[L:BCRp:Lyn] -> [L:BCRp] + Lynp	0.515	0.028499	0.046031	0.096054	2.3485	0.032711	0.058961
7	kon_5	Lynp + SHP1 <-> [Lynp:SHP1]	7	-0.02222	0.029844	-0.11401	-0.15307	-0.01859	-0.10919
8	koff_5	Lynp + SHP1 <-> [Lynp:SHP1]	7.9716	0.017748	0.049554	0.084544	0.96652	0.01486	0.063383
9	kcat_6	[Lynp:SHP1] -> Lyn + SHP1	2	-0.01922	0.038369	-0.07513	-1.6353	-0.01607	-0.06662
10	km_7	Lynp + CD22 -> Lynp + CD22p	1.933	0.01182	0.02282	0.05168	0.61933	0.02376	0.10261
11	vm_7	Lynp + CD22 -> Lynp + CD22p	5.4291	-0.01237	0.028449	-0.10304	-0.54861	-0.02388	-0.0735
12	kf_8	CD22p + SHP1c <-> [CD22p:SHP1c]	0.7532	-0.01929	0.066175	-0.12033	-1.611	-0.02785	-0.10627
13	kb_8	CD22p + SHP1c <-> [CD22p:SHP1c]	1.201	0.014022	0.051081	0.054348	-1.7142	0.012024	0.068158
14	kcat_9	[CD22p:SHP1c] -> CD22p + SHP1	0.9426	-0.01476	0.060674	-0.06679	-1.0386	-0.01242	-0.05681
15	kf_10	SHP1 -> SHP1c	0.01	0.012677	0.069115	0.086093	1.0282	0.010086	0.12424
16	kf_11	CD22p -> CD22	0.0943	0.011214	0.02936	0.08423	2.8871	0.010491	0.023539
18	kf_12	Lynp + Syk <-> [Lynp:Syk]	0.448	0.053245	0.061226	0.24421	4.0278	0.057128	0.19438
19	kcat_13	[Lynp:Syk] -> Lynp + Sykp	21.56515	0.016662	0.044864	0.0879	1.4256	0.026035	0.10032
20	kf_14	Sykp + SHP1 <-> [Sykp:SHP1]	20	-0.03165	0.085495	-0.17647	-2.7199	-0.02746	-0.17125
21	kb_14	Sykp + SHP1 <-> [Sykp:SHP1]	3.6	0.02689	0.045941	0.12013	1.31	0.023202	0.12074
31	kon_22	2 [L:BCR1] <-> [L:BCR]	10	0.016718	0.022684	0.027805	-1.5481	-0.01006	-0.01625
82	kf_55	Sykp + BLNK <-> [Sykp:BLNK]	2.4	0.07698	0.055654	0.19513	4.4512	0.05042	0.19611
83	kb_55	Sykp + BLNK <-> [Sykp:BLNK]	4	-0.06144	0.038016	-0.1235	-1.8585	-0.03912	-0.13691
84	kcat_56	[Sykp:BLNK] -> Sykp + BLNKp	1	0.065816	0.057549	0.14234	5.0224	0.041205	0.14063
87	kf_58	BLNKp + Grb2 <-> [BLNKp:Grb2]	1	0.053132	0.051447	0.15254	3.236	0.037963	0.12557
88	kb_58	BLNKp + Grb2 <-> [BLNKp:Grb2]	0.05	-0.0494	0.062139	-0.11943	-3.2013	-0.03794	-0.10347
89	kf_59	BLNKp + Pase2 <-> [BLNKp:Pase2]	222	-0.04783	0.053274	-0.14956	-3.2291	-0.03444	-0.13002
90	kb_59	BLNKp + Pase2 <-> [BLNKp:Pase2]	3.68	0.038179	0.018583	0.075944	1.5954	0.027512	0.094075
91	kcat_60	[BLNKp:Pase2] -> BLNK + Pase2	0.926	-0.0586	0.081336	-0.13187	-2.1264	-0.04382	-0.12428
92	kf_61	[BLNKp:Grb2] + SoS <-> [BLNKp:Grb2:SoS]	0.05	0.14803	0.10632	0.27137	5.1205	0.10744	0.25726
93	kb_61	[BLNKp:Grb2] + SoS <-> [BLNKp:Grb2:SoS]	1	-0.14749	0.12379	-0.26859	-5.224	-0.10744	-0.28619
97	kf_64	PLCgp + Pase3 <-> [PLCgp:Pase3]	52	5.99E-05	0.035205	-0.13772	0.46904	-0.02243	-0.09551
98	kb_64	PLCgp + Pase3 <-> [PLCgp:Pase3]	0.54	0.000371	0.05392	0.016948	2.9354	0.000139	0.034664
108	kf_71	RasGTP -> RasGDP	0.25	-0.14	0.10863	-0.32322	-5.8548	-0.10986	-0.29429
109	kf_72	GEFp + RasGDP <-> [GEFp:RasGDP]	0.08	0.002824	0.021912	0.10295	1.2201	0.001874	0.075113
120	kf_80	PKCm + Sykp <-> [PKCm:Sykp]	0.25	-0.02158	0.044368	-0.03314	-1.6908	-0.01976	-0.05608
127	kf_85	Raf + RasGTP <-> [Raf:RasGTP]	100	0.15104	0.14929	0.34641	6.2859	0.11765	0.34396
128	kb_85	Raf + RasGTP <-> [Raf:RasGTP]	2	-0.03933	0.072863	-0.20153	-2.3882	-0.02812	-0.1836
129	kf_86	[Raf:RasGTP] + PKCm <-> [Raf:RasGTP:PKCm]	8	0.054611	0.086794	0.25403	3.0138	0.059179	0.24523
149	kf_99	Sykp + PLCg <-> [Sykp:PLCg]	10	-0.00864	0.036119	0.13652	1.5703	-0.00194	0.13414
151	kcat_100	[Sykp:PLCg] -> Sykp + PLCgp	4	-0.00205	0.047205	0.12754	1.3759	0.03828	0.098158
152	kf_101	Rafp + PP1 <-> [Rafp:PP1]	3	-0.2553	0.21149	-0.48536	-8.2838	-0.1968	-0.45958
153	kb_101	Rafp + PP1 <-> [Rafp:PP1]	4	0.12761	0.12365	0.21967	4.2975	0.098391	0.25047
154	kcat_102	[Rafp:PP1] -> Raf + PP1	4	-0.12192	0.080181	-0.22685	-4.2892	-0.09364	-0.22694
155	kf_103	Rafp + MEK <-> [Rafp:MEK]	6.8	0.078856	0.10069	0.26756	4.0473	0.044245	0.26303
156	kb_103	Rafp + MEK <-> [Rafp:MEK]	9.62	-0.06309	0.061531	-0.2007	-3.2638	-0.0354	-0.18786
157	kcat_104	[Rafp:MEK] -> Rafp + MEKp	2.405	0.063937	0.059647	0.19725	3.2865	0.035856	0.20891
158	kf_105	Rafp + MEKp <-> [Rafp:MEKp]	6.8	0.21811	0.18623	0.32331	4.805	0.18673	0.30276
159	kb_105	Rafp + MEKp <-> [Rafp:MEKp]	9.62	-0.17448	0.093219	-0.23512	-3.8752	-0.14939	-0.24828
160	kcat_106	[Rafp:MEKp] -> Rafp + MEKpp	2.405	0.17634	0.099473	0.22414	3.8703	0.15091	0.21605

161	kf_107	PKCm + CK2alpha <-> [PKCm:CK2alpha]	2	0.00215	0.039536	-0.03877	3.6096	0.002523	-0.04317
162	kb_107	PKCm + CK2alpha <-> [PKCm:CK2alpha]	8	-0.00161	0.028508	0.024229	1.2526	-0.00189	0.032473
163	kcat_108	[PKCm:CK2alpha] -> PKCm + CK2alphap	2.667	0.001957	0.043663	0.003555	3.9474	0.002263	-0.00634
164	kf_109	CK2alphap -> CK2alpha	0.333	-0.00263	0.029098	0.01183	1.4589	-0.00289	0.044563
165	kf_110	CK2alphap + MKP3 <-> [CK2alphap:MKP3]	1	0.062408	0.033284	-0.04216	-1.3307	0.067634	-0.07989
167	kcat_111	[CK2alphap:MKP3] -> CK2alpha + MKP3p	1.16	0.050177	0.026022	-0.00492	-0.94637	0.054468	-0.04071
168	kf_112	MKP3p + PP2A <-> [MKP3p:PP2A]	15	-0.06344	0.030185	0.051785	1.399	-0.06806	0.058377
169	kb_112	MKP3p + PP2A <-> [MKP3p:PP2A]	16	0.050754	0.026687	-0.01522	-0.95654	0.054448	-0.02305
171	kf_114	MEKpp + PP2A <-> [MEKpp:PP2A]	1.31	-0.05791	0.03069	-0.10188	-0.97887	-0.05763	-0.10585
174	kf_116	MEKp + PP2A <-> [MEKp:PP2A]	1.31	-0.01488	0.049138	0.085984	1.254	-0.01278	0.092898
175	kb_116	MEKp + PP2A <-> [MEKp:PP2A]	4	0.0119	0.051496	-0.13872	-2.6973	0.010226	-0.15639
176	kcat_117	[MEKp:PP2A] -> MEK + PP2A	1	-0.0121	0.046098	-0.07203	-1.4551	-0.01047	-0.08579
177	kf_118	MEKpp + MKP3p <-> [MEKpp:MKP3p]	26	-0.12597	0.069778	-0.08032	-2.4753	-0.12682	-0.11419
178	kb_118	MEKpp + MKP3p <-> [MEKpp:MKP3p]	64	0.10078	0.057211	0.090769	1.0251	0.10146	0.06711
179	kcat_119	[MEKpp:MKP3p] -> MEKp + MKP3p	16	-0.10037	0.039735	-0.03907	-1.0278	-0.10101	-0.07616
183	kf_122	ERK + MEKpp <-> [ERK:MEKpp]	1.6	0.25499	0.067188	0.17925	2.1096	0.23681	0.18892
184	kb_122	ERK + MEKpp <-> [ERK:MEKpp]	1	-0.20391	0.062512	-0.1526	-1.4375	-0.18915	-0.13563
185	kcat_123	[ERK:MEKpp] -> ERKp + MEKpp	0.25	0.34169	0.12394	0.24024	2.6227	0.30825	0.22344
186	kf_124	ERKp + MEKpp <-> [ERKp:MEKpp]	1.6	0.47591	0.12742	0.23206	2.8028	0.47353	0.23443
187	kb_124	ERKp + MEKpp <-> [ERKp:MEKpp]	1	-0.38052	0.089974	-0.17524	-2.0164	-0.37883	-0.18166
188	kcat_125	[ERKp:MEKpp] -> ERKpp + MEKpp	0.25	0.52203	0.084564	0.21452	2.3409	0.51628	0.23496
195	kf_130	ERKpp + MKP1 <-> [ERKpp:MKP1]	0.30101	-0.24219	0.047866	-0.06191	-0.15167	-0.24239	-0.02741
196	kb_130	ERKpp + MKP1 <-> [ERKpp:MKP1]	4.44	0.16201	0.038562	0.015221	0.074303	0.16317	0.039771
197	kcat_131	[ERKpp:MKP1] -> ERKpp + MKP1p	2.2	-0.16438	0.040929	-0.00984	-0.10902	-0.16571	-0.00138
198	kb_132	MKP1p + MKP3p <-> [MKP1p:MKP3p]	108	-0.18802	0.019547	0.002995	-0.06317	-0.19406	-0.01
199	kf_132	MKP1p + MKP3p <-> [MKP1p:MKP3p]	141	0.2349	0.064807	0.020359	0.065316	0.2409	0.00806
200	kcat_133	[MKP1p:MKP3p] -> MKP1 + MKP3p	27	0.18783	0.017308	0.003829	0.055951	0.19385	-0.01054
201	kf_134	ERKpp + MKP2 <-> [ERKpp:MKP2]	76	-0.05673	0.05477	-0.12398	-1.7391	-0.03585	-0.14203
202	kb_134	ERKpp + MKP2 <-> [ERKpp:MKP2]	4	0.042128	0.045962	0.06242	1.0312	0.036957	0.088384
203	kcat_135	[ERKpp:MKP2] -> ERKp + MKP2	1	-0.18257	0.068503	-0.12992	-1.1808	-0.18475	-0.11008
204	kf_136	ERKp + MKP2 <-> [ERKp:MKP2]	76	0.009324	0.065293	-0.10452	-1.4809	0.014826	-0.12148
205	kb_136	ERKp + MKP2 <-> [ERKp:MKP2]	4	-0.00785	0.036169	0.048345	0.92584	-0.0131	0.074341
206	kcat_137	[ERKp:MKP2] -> ERK + MKP2	1	-0.12558	0.081798	-0.16248	-1.7516	-0.11475	-0.13575
221	kf_148	[Rafp:RasGTP] -> Rafp + RasGTP	1	0.071143	0.06721	0.097229	1.3666	0.054611	0.074144
222	kf_149	[L:BCR1] + BCR <-> [L:BCR]	10	0.008757	0.031247	0.042901	-2.7834	0.033819	0.029415
223	kb_149	[L:BCR1] + BCR <-> [L:BCR]	2	0.00016	0.027101	-0.02317	4.2148	0.004053	-0.00312
224	kf_150	[L:BCRp] + SHP1 <-> [L:BCRp:SHP1]	83	-0.00764	0.039382	-0.01822	-1.8154	-0.00518	-0.06862
230	km_154	[BLNKp:Grb2:SoS] + RasGDP -> [BLNKp:Grb2:SoS] + RasGTP	0.050505	-0.0953	0.088828	-0.15972	-3.1803	-0.07055	-0.18217
231	vm_154	[BLNKp:Grb2:SoS] + RasGDP -> [BLNKp:Grb2:SoS] + RasGTP	22	0.14926	0.095559	0.28961	5.1958	0.10841	0.27124
232	kf_155	ERKpp + MKP1p <-> [ERKpp:MKP1p]	450	-0.3104	0.038073	-0.01653	-0.3368	-0.32582	-0.05521
233	kb_155	ERKpp + MKP1p <-> [ERKpp:MKP1p]	600	0.24832	0.030035	0.007364	0.28074	0.26066	0.036606
234	kcat_156	[ERKpp:MKP1p] -> ERKp + MKP1p	150	-0.27853	0.038234	-0.04164	-0.54174	-0.2936	-0.02657
235	kf_157	ERKp + MKP1p <-> [ERKp:MKP1p]	450	-0.17439	0.042172	-0.02909	-0.15417	-0.18474	-0.05329
236	kb_157	ERKp + MKP1p <-> [ERKp:MKP1p]	600	0.13698	0.06439	0.002892	0.083899	0.14117	0.011061
237	kcat_158	[ERKp:MKP1p] -> ERK + MKP1p	150	-0.16366	0.059964	-0.01193	-0.12975	-0.16943	-0.0273

Robustness of the Model:

Our present model was unique in that it also modeled active regulation by phosphatases. It included active regulation of phosphatase by the kinase components of the network, which in turn was negatively regulated by these active phosphatases. Thus it became important to test the model for its robustness to the parameter variations, at least to the extent that it compared well with existing models. Robustness is a fundamental property of biological systems, which allows the systems to maintain its behavior against random perturbations (18,19). We preformed the Robustness analysis by SBML_SAT (14). Robustness analysis was performed as described (20,21), and Robustness scores measured as Total Parameter Variations (TPV) by randomly generated parameters by Latin Hypercube Sampling method.

Table S1.2: Comparison of the robustness scores of various Models of MAPK :

Model Name	**Receptor/ Activator**	**RasGTP**	**pMAPKKK**	**ppMAPKK**	**pMAPK**	**Phosphatase Regulation**
Huang Ferrell	-0.00543320	-------	-0.662038	-0.961861	-1.23605	**No**
Kholodenko 2000	-------	-------	-0.537109	-1.00071	-1.25602	**No**
Levchenko With scaffold	-------	-------	-0.344902	-0.67925	-1.11045	**No**
Levcheno No Scaffold	-------	-------	-0.561329	-1.3463	-2.80383	**No**
Hatakeyama 2003	-0.58779	-1.53691	-1.59975	-1.78692	-3.52799	**Phosphatases Buffered**
Sasagawa	-0.472733	-0.79791	-0.875844 **(cRaf)** -0.980000 **(BRaf)**	-1.2053	-1.99484	**Phosphatases Buffered**
Bhalla 2002	-1.44197e-034	-0.158336	-0.88649	-3.01403	-5.13613	**MKP1 Regulation by MAPK**
Present Study	-0.386837	-0.980019	-1.34911	-2.27352	-4.98263	**Active phosphatase cascade.**

The R scores (Robustness scores) of a biological model assumes a negative value and the closer this value is to zero, the more robust the model. Here we compared some of the models for the MAPK pathways in the literature with our present model. The corresponding R scores of MAPK components of those models, calculated under identical conditions of perturbations, are given in Table S1.2. As is evident here, the robustness score of our model compares well with that of the others, particularly with those that take phosphatases into consideration. Our model shows a particularly good agreement with that of *Bhalla et.al.* (2002); the only other model that incorporates active regulation of the phosphatase MKP1.

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Supplementary Data S1B

Model details:

1. **Abbreviations and Initial Conditions**
2. **Rate Constants and Parameters and Sensitivities of Parameters**
3. **Reactions and Reactions Rate Equations**
4. **Parameter Sensitivities for ppMEK response**
5. **Parameter Sensitivities for ppERK response**

S1. MODEL DETAILS.

1. Abbreviations:

Sr. No.	Abbreviations	InitialAmount	Names
1	L	**0.25**	Ligand
2	BCR	0.05	B Cell Receptor
3	L:BCR	0	Ligand bound to receptor pair, Crosslinkin of BCR and subsequent activation of ITAM
4	L:BCRp	0	Mono Phosphorylated Activated BCR
5	Lyn	0.24	Src Kinase Lyn
6	L:BCRp:Lyn	0	Lyn Bound ot the Monophosphorylated Receptor
7	Lynp	0	Activated Lyn
8	SHP1	0	Membrane localized SHP1
9	Lynp:SHP1	0	SHP1 bound to Lyn
10	Li	0	Inactivated ligand
11	BCRi	0	Inactivated or Internalized BCR
12	CD22	0.18	Membrane Anchored CD22
13	CD22p	0	CD22 activated
14	SHP1c	0.014	Cytosolic SHP1
15	CD22p:SHP1c	0	Cytosolic SHP1 bound to phosphorylated CD22
16	Syk	0.2	SYK kinase
17	Lynp:Syk	0	Activated Lyn bound to Syk
18	Sykp	0	Activated SYK
19	Sykp:SHP1	0	Activated Syk bound to SHP1
20	L:BCRp:Sykp	0	SYK kinase bound to Mono phosphorylated ITAM of ligand activated BCR
21	L:BCRpp	0	Completely activated BCR, ITAM's Phosphorylated at multiple sites
22	L:BCRpp:Lyn	0	Completely activated BCR bound to the Lyn
23	BCRpro	**0.05**	BCR precursor
24	L:BCR1	0	Ligand bound to receptor as non crosslinked form; Single BCR bound to single molecule of antigen
25	Btk	0	Bruton's Tyrosine Kinase
26	Btk:Lynp	0	Bruton's Tyrosine Kinase (Btk)bound to activated Lyn
27	Btkp	0	Activated Btk
28	Btk:Sykp	0	Btk bound to activated Syk
29	BtkPase	0.04	Btk phosphatase
30	Btkp:BtkPase	0	Btk bound ot Btk phosphatase
31	CD19	0.12	Membrane bound CD19
32	Lynp:CD19	0	Activated Lynp bound to CD19
33	CD19p	0	Activated CD19
34	p85PI3K	0.134	p85 subunit of Phosphoinositol-3 kinase
35	CD19p:p85PI3K	0	CD19p bound to p85subunit of PI3K
36	p110PI3K	0.134	p110 subunit of Phosphoinositol-3 kinase
37	PI3K	0	Complete holoenzyme PI3K
38	CD19p:p85PI3K:p110PI3K	0	CD19p bound to p85subunit and p110subunit of PI3K
39	BCAP	0.2	Membrane anchored B cell adopter protein for PI3K signaling
40	Sykp:BCAP	0	Sykp bound to BCAP
41	BCAPp	0	Phosphorylated BCAP
42	BCAPp:p85PI3K	0	Phosphorylated BCAP bound to p85 subunit of PI3K

43	BCAPp:p85PI3K:p110PI3K	0	Phosphorylated BCAP bound to p85 and p110 subunit of PI3K
44	Pase1	0.02	Phosphatase for BCAP
45	BCAPp:Pase1	0	Phosphatase for BCAP bound to BCAPp
46	PIP2	**10**	PIP2
47	PIP3	0	PIP3
48	Aktc	0.0058	Cytosolic Akt
49	Aktm	0	Membrane localized Akt
50	PIP3:Aktc	0	PIP3 bound to Akt
51	PDK	0.18	PDK kinase
52	PIP3:PDK	0	PIP3 bound to PDK
53	PDKa	0	Activated PDK
54	PDKa:Aktm	0	PDK bound to membrane localized Akt
55	Aktp	0	Akt phosphorylated
56	PP2A	0.0071	Protein Phosphatase 2 A
57	Aktp:PP2A	0	Akt phosphorylated bound to PP2A
58	BLNK	0.34	B cell Linker Protein BLNK
59	Sykp:BLNK	0	Sykp bound to BLNK
60	BLNKp	0	BLNK phosphorylated
61	BLNKp:Btkp	0	BLNKp bound to Btkp
62	Grb2	1	Adapter Protein Grb2
63	BLNKp:Grb2	0	BLNKp bound to Grb2
64	Pase2	0.01	Phosphatase 2
65	BLNKp:Pase2	0	Phosphatase 2 bound to BLNK
66	SoS	0.01	Son of Sevenless exchanger protein for GDP GTP exchange
67	BLNKp:Grb2:SoS	0	Complete complex for lymphocyte RasGTP exchanger
68	PLCg	0.8	Phospholipase C gamma2
69	BLNKp:Btkp:PLCg	0	BLNKp bound to Btkp and PLCg
70	PLCgp	0	Phosphorylated PLCg
71	IP3	0	IP3
72	DAG	0	Diacyl glycerol
73	Pase3	0.02	Phosphatase 3
74	PLCgp:Pase3	0	PLCgp bound to Phosphatase3
75	ip3deg	0	IP3 degradation product
76	dagdeg	0	DAG degradation product
77	PKCcyt	0.7884	Cytosolic Protein kinase C
78	PKCcyt:DAG	0	PKC bound to DAG
79	PKCm	0	Membrane localized PKC
80	RasGDP	0.0454	Ras bound with GDP
81	RasGTP	0	Ras bound with GTP
82	GEF	0.01	Guanine exchange factor
83	GEFp	0	GEF phosphorylated
84	GEFp:RasGDP	0	GEFp bound to RasGDP
85	GEF:PKCm	0	GEF bound to PKC
86	GAP	0.002	GTPase activating Protein
87	PKCm:GAP	0	PKCm bound to the GAP
88	GAPp	0	GAP phosphorylated
89	PKCm:Sykp	0	Membrane localized PKC bound to Sykp
90	Sykpp	0	Inhibited Double phosphorylated Syk
91	GAP:RasGTP	0	GAP bound to RasGTP
92	Raf	0.0885	Raf

93	Raf:RasGTP	0	Raf bound to RasGTP
94	Raf:RasGTP:PKCm	0	RafRasGTP bound to PKC
95	Rafp	0	Raf phosphorylated
96	Rafser259	0	Raf phosphorylated at inhibitory serine259
97	Raf:Aktp	0	Raf bound to Akt
98	PP1	0.4748	Protein Phosphatase 1
99	Rafser259:PP1	0	RafSer259 bound to PP1
100	Rafp:Aktp	0	Rafp bound to Aktp
101	Rafpp	0	Raf double phosphorylated
102	Rafpp:PP1	0	Rafpp bound to PP1
103	Rafp:PP2A	0	Rafp bound to PP2A
104	Btkcyt	0.126	Btk cytoplasmic
105	Sykp:PLCg	0	Sykp bound to PLCg
106	Rafp:PP1	0	Rafp bound to PP1
107	MEK	0.0886	MEK kinase
108	Rafp:MEK	0	Rafp bound to MEK
109	MEKp	0	MEK phosphorylated
110	Rafp:MEKp	0	Rafp bound to MEKp
111	MEKpp	0	MEK double phosphorylated and completely activated form
112	CK2alpha	0.12	Casein kinase 2 Alpha
113	PKCm:CK2alpha	0	Membrane localized PKC bound to Casein kinase 2 alpha
114	CK2alphap	0	CK2alpha phosphorylated
115	MKP3	0.0015	DUSP6 of MAPkinase phosphatase3
116	CK2alphap:MKP3	0	CK2alpha phoaphorylated bound to MKP3
117	MKP3p	0	phosphorylated MKP3
118	MKP3p:PP2A	0	MKP3p bound to PP2A
119	MEKpp:PP2A	0	MEKpp bound to PP2A
120	MEKp:PP2A	0	MEKp bound to PP2A
121	MEKpp:MKP3p	0	MEKpp bound to MKP3p
122	MEKp:MKP3p	0	MEKpbound to MKP3p
123	ERK	0.5674	Extracellular signal regulated Kinase
124	ERK:MEKpp	0	ERK bound to MEKpp
125	ERKp	0	ERK phsophorylated
126	ERKp:MEKpp	0	ERKp bound to MEKpp
127	ERKpp	0	ERK double phosphorylated and completely activated form
128	mkp1	0.00005	MKP1 mRNA
129	MKP1	0.0002	MAPkinase phophatase 1
130	mkp3	0.000375	MKP3 mRNA
131	mkp1ubi	0	MKP1 degradation product
132	mkp3ubi	0	MKP3 degradation product
133	ERKpp:MKP1	0	ERKpp bound to MKP1
134	MKP1p	0	MKP1 phosphorylated
135	MKP1p:MKP3p	0	MKP1p bound to MKP3p
136	MKP2	0.002	MAPkinase phophatase 2
137	ERKpp:MKP2	0	ERKpp bound to MKP2
138	ERKp:MKP2	0	ERKp bound to MKP2
139	ERKpp:MKP3	0	ERKpp Bound to MKP3
140	ERKp:MKP3	0	ERKp bound to MKP3
141	TrCmplx	**1**	Transcriptional complex
142	Rafp:ERKpp	0	Rafp bound to ERKpp

143	Rafser259:PP2A	0	Rafser259 bound to PP2A
144	Rafpp:PP2A	0	Rafpp bound to PP2A
145	ERKtrns	0	ERK
146	Rafp:RasGTP	0	RafpRasGTP complex
147	L:BCRp:SHP1	0	SHP1 bound to ITAM at the first phosphorylation site
148	L:BCRpp:SHP1	0	SHP1 bound to ITAM at other site which are later phosphorylated by Syk
149	ERKp:MKP1p	0	ERKpp bound to MKP1p
150	ERKpp:MKP1p	0	ERKp bound to MKP1p
151	MKP1:ERKpp	0	MKP1 bound to ERKpp
152	MKP1:ERKp	0	MKP1 bound to ERKp
153	TF	0.05	Trancription Factor
154	ERKpp:TF	0	ERKpp bound to TF
155	TFa	0	Transcription Factor activated
156	NT	**1**	Nucleotide representing DNA
157	TFa:NT	0	TFa bound to the DNA(Representing active transcription)
158	MKP3x	0	ERK mediated MKP3' s phophorylated form prone to ubiquitination
159	MKP3:ERKpp	0	ERKpp bound to MKP3 where ERK is acting as an enzyme

All concentrations are in micromoles.

Initial amount in red color represents buffered/constant amount throughout the simulation

Lignad Unit conversion => 25 micro gram/ml ~= 0.05 micro moles
Concentrations of Raf, MEK, ERK, MKP1, PP2A, PP1, Akt,MKP2, RasGDP(total) are experimentally estimated. Rest of the concentrations are Estimated to best fit.

2. Reaction scheme and Reaction Rates:

	Reaction	Reaction Rate
1	L + BCR <-> [L:BCR1]	kon_1*L*BCR - koff_1*[L:BCR1]
2	[L:BCR] -> [L:BCRp]	kf_2*[L:BCR]/(0.25 + [L:BCR])
3	[L:BCRp] + Lyn <-> [L:BCRp:Lyn]	kon_3*[L:BCRp]*Lyn - koff_3*[L:BCRp:Lyn]
4	[L:BCRp:Lyn] -> [L:BCRp] + Lynp	kcat_4*[L:BCRp:Lyn]
5	Lynp + SHP1 <-> [Lynp:SHP1]	kon_5*Lynp*SHP1 - koff_5*[Lynp:SHP1]
6	[Lynp:SHP1] -> Lyn + SHP1	kcat_6*[Lynp:SHP1]
7	Lynp + CD22 -> Lynp + CD22p	vm_7*Lynp*CD22/(km_7+CD22)
8	CD22p + SHP1c <-> [CD22p:SHP1c]	kf_8*CD22p*SHP1c - kb_8*[CD22p:SHP1c]
9	[CD22p:SHP1c] -> CD22p + SHP1	kcat_9*[CD22p:SHP1c]
10	SHP1 -> SHP1c	kf_10*SHP1
11	CD22p -> CD22	kf_11*CD22p
12	Lynp + Syk <-> [Lynp:Syk]	kf_12*Lynp*Syk - kb_12*[Lynp:Syk]
13	[Lynp:Syk] -> Lynp + Sykp	kcat_13*[Lynp:Syk]
14	Sykp + SHP1 <-> [Sykp:SHP1]	kf_14*Sykp*SHP1 - kb_14*[Sykp:SHP1]
15	[Sykp:SHP1] -> Syk + SHP1	kcat_15*[Sykp:SHP1]
16	[L:BCRp] + Sykp <-> [L:BCRp:Sykp]	kf_16*[L:BCRp]*Sykp - kb_16*[L:BCRp:Sykp]
17	[L:BCRp:Sykp] -> [L:BCRpp] + Sykp	kcat_17*[L:BCRp:Sykp]
18	[L:BCRpp] + Lyn <-> [L:BCRpp:Lyn]	kf_18*[L:BCRpp]*Lyn - kb_18*[L:BCRpp:Lyn]
19	[L:BCRpp:Lyn] -> [L:BCRpp] + Lynp	kcat_19*[L:BCRpp:Lyn]
20	BCRpro -> BCR	kf_20*BCRpro
21	BCR -> BCRi	kf_21*BCR
22	2 [L:BCR1] <-> [L:BCR]	kon_22*[L:BCR1]^2 - koff_22*[L:BCR]
23	[L:BCR] -> BCRi + Li	kf_23*[L:BCR]
24	Btk + Lynp <-> [Btk:Lynp]	kf_24*Btk*Lynp - kb_24*[Btk:Lynp]
25	[Btk:Lynp] -> Btkp + Lynp	kcat_25*[Btk:Lynp]
26	Btk + Sykp <-> [Btk:Sykp]	kf_26*Btk*Sykp - kb_26*[Btk:Sykp]
27	[Btk:Sykp] -> Btkp + Sykp	kcat_27*[Btk:Sykp]
28	Btkp + BtkPase <-> [Btkp:BtkPase]	kf_28*Btkp*BtkPase - kb_28*[Btkp:BtkPase]
29	[Btkp:BtkPase] -> Btk + BtkPase	kcat_29*[Btkp:BtkPase]
30	Lynp + CD19 <-> [Lynp:CD19]	kf_30*Lynp*CD19 - kb_30*[Lynp:CD19]
31	[Lynp:CD19] -> Lynp + CD19p	kcat_31*[Lynp:CD19]
32	CD19p + p85PI3K <-> [CD19p:p85PI3K]	kf_32*CD19p*p85PI3K - kb_32*[CD19p:p85PI3K]
33	[CD19p:p85PI3K] + p110PI3K <-> [CD19p:p85PI3K:p110PI3K]	kf_33*[CD19p:p85PI3K]*p110PI3K - kb_33*[CD19p:p85PI3K:p110PI3K]
34	[CD19p:p85PI3K:p110PI3K] -> CD19p + PI3K	kcat_34*[CD19p:p85PI3K:p110PI3K]
35	Sykp + BCAP <-> [Sykp:BCAP]	kf_35*Sykp*BCAP - kb_36*[Sykp:BCAP]
36	[Sykp:BCAP] -> Sykp + BCAPp	kcat_36*[Sykp:BCAP]
37	BCAPp + p85PI3K <-> [BCAPp:p85PI3K]	kf_37*BCAPp*p85PI3K - kb_37*[BCAPp:p85PI3K]
38	[BCAPp:p85PI3K] + p110PI3K <-> [BCAPp:p85PI3K:p110PI3K]	kf_38*[BCAPp:p85PI3K]*p110PI3K - kb_38*[BCAPp:p85PI3K:p110PI3K]
39	[BCAPp:p85PI3K:p110PI3K] -> BCAPp + PI3K	kcat_39*[BCAPp:p85PI3K:p110PI3K]
40	BCAPp + Pase1 <-> [BCAPp:Pase1]	kf_40*BCAPp*Pase1 - kb_40*[BCAPp:Pase1]
41	[BCAPp:Pase1] -> BCAP + Pase1	kcat_41*[BCAPp:Pase1]
42	CD19p -> CD19	kf_42*CD19p
43	PI3K -> p85PI3K + p110PI3K	kf_43*PI3K
44	PIP2 + PI3K -> PIP3 + PI3K	vm_44 * PIP2 * PI3K/(km_44 + PIP2)
45	PIP3 -> PIP2	vm_45*PIP3/(km_45+PIP3)
46	PIP3 + Aktc <-> [PIP3:Aktc]	kf_46*PIP3*Aktc - kb_46*[PIP3:Aktc]

47	[PIP3:Aktc] <-> Aktm	kf_47*[PIP3:Aktc] - kb_47*Aktm
48	PIP3 + PDK <-> [PIP3:PDK]	kf_48*PIP3*PDK - kb_48*[PIP3:PDK]
49	[PIP3:PDK] -> PDKa	kf_49*[PIP3:PDK]
50	PDKa -> PDK + PIP3	kf_50*PDKa
51	PDKa + Aktm <-> [PDKa:Aktm]	kf_51*PDKa*Aktm - kb_51*[PDKa:Aktm]
52	[PDKa:Aktm] -> PDKa + Aktp	kcat_52*[PDKa:Aktm]
53	Aktp + PP2A <-> [Aktp:PP2A]	kf_53*Aktp*PP2A - kb_53*[Aktp:PP2A]
54	[Aktp:PP2A] -> Aktm + PP2A	kcat_54*[Aktp:PP2A]
55	Sykp + BLNK <-> [Sykp:BLNK]	kf_55*Sykp*BLNK - kb_55*[Sykp:BLNK]
56	[Sykp:BLNK] -> Sykp + BLNKp	kcat_56*[Sykp:BLNK]
57	BLNKp + Btkp <-> [BLNKp:Btkp]	kf_57*BLNKp*Btkp - kb_57*[BLNKp:Btkp]
58	BLNKp + Grb2 <-> [BLNKp:Grb2]	kf_58*BLNKp*Grb2 - kb_58*[BLNKp:Grb2]
59	BLNKp + Pase2 <-> [BLNKp:Pase2]	kf_59*BLNKp*Pase2 - kb_59*[BLNKp:Pase2]
60	[BLNKp:Pase2] -> BLNK + Pase2	kcat_60*[BLNKp:Pase2]
61	[BLNKp:Grb2] + SoS <-> [BLNKp:Grb2:SoS]	kf_61*[BLNKp:Grb2]*SoS - kb_61*[BLNKp:Grb2:SoS]
62	[BLNKp:Btkp] + PLCg <-> [BLNKp:Btkp:PLCg]	kf_62*[BLNKp:Btkp]*PLCg - kb_62*[BLNKp:Btkp:PLCg]
63	[BLNKp:Btkp:PLCg] -> [BLNKp:Btkp] + PLCgp	kcat_63*[BLNKp:Btkp:PLCg]
64	PLCgp + Pase3 <-> [PLCgp:Pase3]	kf_64*PLCgp*Pase3 - kb_64*[PLCgp:Pase3]
65	[PLCgp:Pase3] -> PLCg + Pase3	kcat_65*[PLCgp:Pase3]
66	IP3 -> ip3deg	kdeg_66*IP3
67	DAG -> dagdeg	kdeg_67*DAG
68	PLCgp + PIP2 -> PLCgp + IP3 + DAG	vm_68 * PIP2 * PLCgp/(km_68 +PIP2)
69	PKCcyt + DAG <-> [PKCcyt:DAG]	kf_69*PKCcyt*DAG - kb_69*[PKCcyt:DAG]
70	[PKCcyt:DAG] <-> PKCm	kf_70*[PKCcyt:DAG] - kb_70*PKCm
71	RasGTP -> RasGDP	kf_71*RasGTP
72	GEFp + RasGDP <-> [GEFp:RasGDP]	kf_72*GEFp*RasGDP - kb_72*[GEFp:RasGDP]
73	[GEFp:RasGDP] -> GEFp + RasGTP	kcat_73*[GEFp:RasGDP]
74	GEF + PKCm <-> [GEF:PKCm]	kf_74*GEF*PKCm - kb_74*[GEF:PKCm]
75	[GEF:PKCm] -> GEFp + PKCm	kcat_75*[GEF:PKCm]
76	PKCm + GAP <-> [PKCm:GAP]	kf_76*PKCm*GAP - kb_76*[PKCm:GAP]
77	[PKCm:GAP] -> PKCm + GAPp	kcat_77*[PKCm:GAP]
78	GEFp -> GEF	kf_78*GEFp
79	GAPp -> GAP	kf_79*GAPp
80	PKCm + Sykp <-> [PKCm:Sykp]	kf_80*PKCm*Sykp - kb_80*[PKCm:Sykp]
81	[PKCm:Sykp] -> PKCm + Sykpp	kcat_81*[PKCm:Sykp]
82	Sykpp -> Sykp	kf_82*Sykpp
83	GAP + RasGTP <-> [GAP:RasGTP]	kf_83*GAP*RasGTP - kb_83*[GAP:RasGTP]
84	[GAP:RasGTP] -> GAP + RasGDP	kcat_84*[GAP:RasGTP]
85	Raf + RasGTP <-> [Raf:RasGTP]	kf_85*Raf*RasGTP - kb_85*[Raf:RasGTP]
86	[Raf:RasGTP] + PKCm <-> [Raf:RasGTP:PKCm]	kf_86*[Raf:RasGTP]*PKCm - kb_86*[Raf:RasGTP:PKCm]
87	[Raf:RasGTP:PKCm] -> [Rafp:RasGTP] + PKCm	kcat_87*[Raf:RasGTP:PKCm]
88	Raf + Aktp <-> [Raf:Aktp]	kf_88*Raf*Aktp - kb_88*[Raf:Aktp]
89	[Raf:Aktp] -> Rafser259 + Aktp	kcat_89*[Raf:Aktp]
90	Rafser259 + PP1 <-> [Rafser259:PP1]	kf_90*Rafser259*PP1 - kb_90*[Rafser259:PP1]
91	[Rafser259:PP1] -> Raf + PP1	kcat_91*[Rafser259:PP1]
92	Rafp + Aktp <-> [Rafp:Aktp]	kf_92*Rafp*Aktp - kb_92*[Rafp:Aktp]
93	[Rafp:Aktp] -> Rafpp + Aktp	kcat_93*[Rafp:Aktp]
94	Rafpp + PP1 <-> [Rafpp:PP1]	kf_94*Rafpp*PP1 - kb_94*[Rafpp:PP1]
95	[Rafpp:PP1] -> Rafp + PP1	kcat_95*[Rafpp:PP1]
96	Rafp + PP2A <-> [Rafp:PP2A]	kf_96*Rafp*PP2A - kb_96*[Rafp:PP2A]

97	[Rafp:PP2A] -> Raf + PP2A	kcat_97*[Rafp:PP2A]
98	Btkcyt + PIP3 <-> Btk	kf_98*Btkcyt*PIP3 - kb_98*Btk
99	Sykp + PLCg <-> [Sykp:PLCg]	kf_99*Sykp*PLCg - kb_99*[Sykp:PLCg]
100	[Sykp:PLCg] -> Sykp + PLCgp	kcat_100*[Sykp:PLCg]
101	Rafp + PP1 <-> [Rafp:PP1]	kf_101*Rafp*PP1 - kb_101*[Rafp:PP1]
102	[Rafp:PP1] -> Raf + PP1	kcat_102*[Rafp:PP1]
103	Rafp + MEK <-> [Rafp:MEK]	kf_103*Rafp*MEK - kb_103*[Rafp:MEK]
104	[Rafp:MEK] -> Rafp + MEKp	kcat_104*[Rafp:MEK]
105	Rafp + MEKp <-> [Rafp:MEKp]	kf_105*Rafp*MEKp - kb_105*[Rafp:MEKp]
106	[Rafp:MEKp] -> Rafp + MEKpp	kcat_106*[Rafp:MEKp]
107	PKCm + CK2alpha <-> [PKCm:CK2alpha]	kf_107*PKCm*CK2alpha - kb_107*[PKCm:CK2alpha]
108	[PKCm:CK2alpha] -> PKCm + CK2alphap	kcat_108*[PKCm:CK2alpha]
109	CK2alphap -> CK2alpha	kf_109 * CK2alphap * PP2A/(0.05 + CK2alphap)
110	CK2alphap + MKP3 <-> [CK2alphap:MKP3]	kf_110*CK2alphap*MKP3 - kb_110*[CK2alphap:MKP3]
111	[CK2alphap:MKP3] -> CK2alphap + MKP3p	kcat_111*[CK2alphap:MKP3]
112	MKP3p + PP2A <-> [MKP3p:PP2A]	kf_112*MKP3p*PP2A - kb_112*[MKP3p:PP2A]
113	[MKP3p:PP2A] -> MKP3 + PP2A	kcat_113*[MKP3p:PP2A]
114	MEKpp + PP2A <-> [MEKpp:PP2A]	kf_114*MEKpp*PP2A - kb_114*[MEKpp:PP2A]
115	[MEKpp:PP2A] -> MEKp + PP2A	kcat_115*[MEKpp:PP2A]
116	MEKp + PP2A <-> [MEKp:PP2A]	kf_116*MEKp*PP2A - kb_116*[MEKp:PP2A]
117	[MEKp:PP2A] -> MEK + PP2A	kcat_117*[MEKp:PP2A]
118	MEKpp + MKP3p <-> [MEKpp:MKP3p]	kf_118*MEKpp*MKP3p - kb_118*[MEKpp:MKP3p]
119	[MEKpp:MKP3p] -> MEKp + MKP3p	kcat_119*[MEKpp:MKP3p]
120	MEKp + MKP3p <-> [MEKp:MKP3p]	kf_120*MEKp*MKP3p - kb_120*[MEKp:MKP3p]
121	[MEKp:MKP3p] -> MEK + MKP3p	kcat_21*[MEKp:MKP3p]
122	ERK + MEKpp <-> [ERK:MEKpp]	kf_122*ERK*MEKpp - kb_122*[ERK:MEKpp]
123	[ERK:MEKpp] -> ERKp + MEKpp	kcat_123*[ERK:MEKpp]
124	ERKp + MEKpp <-> [ERKp:MEKpp]	kf_124*ERKp*MEKpp - kb_124*[ERKp:MEKpp]
125	[ERKp:MEKpp] -> ERKpp + MEKpp	kcat_125*[ERKp:MEKpp]
126	mkp1 <-> MKP1	kf_126*mkp1 - kb_126*MKP1
127	mkp3 <-> MKP3	kf_127*mkp3 - kb_127*MKP3
128	MKP1 -> mkp1ubi	kf_128*MKP1
129	MKP3 -> mkp3ubi	kf_129*MKP3
130	ERKpp + MKP1 <-> [ERKpp:MKP1]	kf_130*ERKpp*MKP1 - kb_130*[ERKpp:MKP1]
131	[ERKpp:MKP1] -> ERKpp + MKP1p	kcat_131*[ERKpp:MKP1]
132	MKP1p + MKP3p <-> [MKP1p:MKP3p]	kf_132*MKP1p*MKP3p - kb_132*[MKP1p:MKP3p]
133	[MKP1p:MKP3p] -> MKP1 + MKP3p	kcat_133*[MKP1p:MKP3p]
134	ERKpp + MKP2 <-> [ERKpp:MKP2]	kf_134*ERKpp*MKP2 - kb_134*[ERKpp:MKP2]
135	[ERKpp:MKP2] -> ERKp + MKP2	kcat_135*[ERKpp:MKP2]
136	ERKp + MKP2 <-> [ERKp:MKP2]	kf_136*ERKp*MKP2 - kb_136*[ERKp:MKP2]
137	[ERKp:MKP2] -> ERK + MKP2	kcat_137*[ERKp:MKP2]
138	ERKpp + MKP3 <-> [ERKpp:MKP3p]	kf_138*ERKpp*MKP3 - kb_138*[ERKpp:MKP3p]
139	[ERKpp:MKP3p] -> ERKp + MKP3	kcat_139*[ERKpp:MKP3p]
140	ERKp + MKP3 <-> [ERKp:MKP3p]	kf_140*ERKp*MKP3 - kb_140*[ERKp:MKP3p]
141	[ERKp:MKP3p] -> ERK + MKP3	kcat_141*[ERKp:MKP3p]
142	TrCmplx -> mkp1	kf_142*TrCmplx
143	TrCmplx -> mkp3	kf_143*TrCmplx
144	Rafp + ERKpp <-> [Rafp:ERKpp]	kf_144*Rafp*ERKpp - kb_144*[Rafp:ERKpp]
145	[Rafp:ERKpp] -> Rafpp + ERKpp	kcat_145*[Rafp:ERKpp]
146	Rafser259 + PP2A <-> [Rafser259:PP2A]	kf_146*Rafser259*PP2A - kb_147*[Rafser259:PP2A]

147	[Rafser259:PP2A] -> Raf + PP2A	kcat_147*[Rafser259:PP2A]
148	[Rafp:RasGTP] -> Rafp + RasGTP	kf_148*[Rafp:RasGTP]
149	[L:BCR1] + BCR <-> [L:BCR]	kf_149*[L:BCR1]*BCR - kb_149*[L:BCR]
150	[L:BCRp] + SHP1 <-> [L:BCRp:SHP1]	kf_150*[L:BCRp]*SHP1 - kb_150*[L:BCRp:SHP1]
151	[L:BCRp:SHP1] -> [L:BCR] + SHP1	kcat_151*[L:BCRp:SHP1]
152	[L:BCRpp] + SHP1 <-> [L:BCRpp:SHP1]	kf_152*[L:BCRpp]*SHP1 - kb_152*[L:BCRpp:SHP1]
153	[L:BCRpp:SHP1] -> [L:BCRp] + SHP1	kcat_153*[L:BCRpp:SHP1]
154	[BLNKp:Grb2:SoS] + RasGDP -> [BLNKp:Grb2:SoS] + RasGTP	vm_154*RasGDP*[BLNKp:Grb2:SoS]/(km_154+RasGDP)
155	ERKpp + MKP1p <-> [ERKpp:MKP1p]	kf_155*ERKpp*MKP1p - kb_155*[ERKpp:MKP1p]
156	[ERKpp:MKP1p] -> ERKp + MKP1p	kcat_156*[ERKpp:MKP1p]
157	ERKp + MKP1p <-> [ERKp:MKP1p]	kf_157*ERKp*MKP1p - kb_157*[ERKp:MKP1p]
158	[ERKp:MKP1p] -> ERK + MKP1p	kcat_158*[ERKp:MKP1p]
159	ERKpp + MKP1 <-> [MKP1:ERKpp]	kf_159*ERKpp*MKP1 - kb_159*[MKP1:ERKpp]
160	[MKP1:ERKpp] -> MKP1 + ERKp	kcat_160*[MKP1:ERKpp]
161	ERKp + MKP1 <-> [MKP1:ERKp]	kf_161*ERKp*MKP1 - kb_161*[MKP1:ERKp]
162	[MKP1:ERKp] -> MKP1 + ERK	kcat_162*[MKP1:ERKp]
163	ERKpp + TF <-> [ERKpp:TF]	kf_163*ERKpp*TF - kb_163*[ERKpp:TF]
164	[ERKpp:TF] -> ERKpp + TFa	kcat_164*[ERKpp:TF]
165	TFa + NT <-> [TFa:NT]	kf_165*TFa*NT - kb_165*[TFa:NT]
166	TFa -> TF	kf_166*TFa
167	NT -> mkp1	trnsc_167*NT* [TFa:NT]
168	NT -> mkp3	trnsc_168* NT * [TFa:NT]
169	PKCm -> PKCcyt	kf_169*PKCm
170	MKP3 + ERKpp <-> [MKP3:ERKpp]	kf_170*MKP3*ERKpp - kb_170*[MKP3:ERKpp]
171	[MKP3:ERKpp] -> MKP3x + ERKpp	kcat_171*[MKP3:ERKpp]
172	MKP3x -> mkp3xubi	kf_172*MKP3x

3. Parameter Details:

Sr. No.	Parameter	Scope (Reaction)	Value
1	kon_1	L + BCR <-> [L:BCR1]	50
2	koff_1	L + BCR <-> [L:BCR1]	10
3	kf_2	[L:BCR] -> [L:BCRp]	0.99
4	kon_3	[L:BCRp] + Lyn <-> [L:BCRp:Lyn]	0.8857
5	koff_3	[L:BCRp] + Lyn <-> [L:BCRp:Lyn]	0.8766
6	kcat_4	[L:BCRp:Lyn] -> [L:BCRp] + Lynp	0.515
7	kon_5	Lynp + SHP1 <-> [Lynp:SHP1]	7
8	koff_5	Lynp + SHP1 <-> [Lynp:SHP1]	7.9716
9	kcat_6	[Lynp:SHP1] -> Lyn + SHP1	2
10	km_7	Lynp + CD22 -> Lynp + CD22p	1.933
11	vm_7	Lynp + CD22 -> Lynp + CD22p	5.4291
12	kf_8	CD22p + SHP1c <-> [CD22p:SHP1c]	0.7532
13	kb_8	CD22p + SHP1c <-> [CD22p:SHP1c]	1.201
14	kcat_9	[CD22p:SHP1c] -> CD22p + SHP1	0.9426
15	kf_10	SHP1 -> SHP1c	0.01
16	kf_11	CD22p -> CD22	0.0943
17	kb_12	Lynp + Syk <-> [Lynp:Syk]	8.7948
18	kf_12	Lynp + Syk <-> [Lynp:Syk]	0.448
19	kcat_13	[Lynp:Syk] -> Lynp + Sykp	21.56515
20	kf_14	Sykp + SHP1 <-> [Sykp:SHP1]	20
21	kb_14	Sykp + SHP1 <-> [Sykp:SHP1]	3.6
22	kcat_15	[Sykp:SHP1] -> Syk + SHP1	0.9
23	kf_16	[L:BCRp] + Sykp <-> [L:BCRp:Sykp]	0.3143
24	kb_16	[L:BCRp] + Sykp <-> [L:BCRp:Sykp]	1.2092
25	kcat_17	[L:BCRp:Sykp] -> [L:BCRpp] + Sykp	0.3023
26	kf_18	[L:BCRpp] + Lyn <-> [L:BCRpp:Lyn]	0.899
27	kb_18	[L:BCRpp] + Lyn <-> [L:BCRpp:Lyn]	0.8766
28	kcat_19	[L:BCRpp:Lyn] -> [L:BCRpp] + Lynp	0.6915
29	kf_20	BCRpro -> BCR	1.5E-06
30	kf_21	BCR -> BCRi	1.5E-06
31	kon_22	2 [L:BCR1] <-> [L:BCR]	10
32	koff_22	2 [L:BCR1] <-> [L:BCR]	5
33	kf_23	[L:BCR] -> BCRi + Li	0.0067
34	kf_24	Btk + Lynp <-> [Btk:Lynp]	0.645
35	kb_24	Btk + Lynp <-> [Btk:Lynp]	4
36	kcat_25	[Btk:Lynp] -> Btkp + Lynp	1
37	kf_26	Btk + Sykp <-> [Btk:Sykp]	2.4
38	kb_26	Btk + Sykp <-> [Btk:Sykp]	4
39	kcat_27	[Btk:Sykp] -> Btkp + Sykp	4
40	kf_28	Btkp + BtkPase <-> [Btkp:BtkPase]	12
41	kb_28	Btkp + BtkPase <-> [Btkp:BtkPase]	16
42	kcat_29	[Btkp:BtkPase] -> Btk + BtkPase	4
43	kf_30	Lynp + CD19 <-> [Lynp:CD19]	1.2245
44	kb_30	Lynp + CD19 <-> [Lynp:CD19]	12
45	kcat_31	[Lynp:CD19] -> Lynp + CD19p	3
46	kf_32	CD19p + p85PI3K <-> [CD19p:p85PI3K]	0.00345
47	kb_32	CD19p + p85PI3K <-> [CD19p:p85PI3K]	1.064

48	kf_33	[CD19p:p85PI3K] + p110PI3K <-> [CD19p:p85PI3K:p110PI3K]	0.2
49	kb_33	[CD19p:p85PI3K] + p110PI3K <-> [CD19p:p85PI3K:p110PI3K]	4
50	kcat_34	[CD19p:p85PI3K:p110PI3K] -> CD19p + PI3K	1
51	kf_35	Sykp + BCAP <-> [Sykp:BCAP]	4.8699
52	kb_36	Sykp + BCAP <-> [Sykp:BCAP]	14
53	kcat_36	[Sykp:BCAP] -> Sykp + BCAPp	3.5
54	kf_37	BCAPp + p85PI3K <-> [BCAPp:p85PI3K]	0.5
55	kb_37	BCAPp + p85PI3K <-> [BCAPp:p85PI3K]	3
56	kf_38	[BCAPp:p85PI3K] + p110PI3K <-> [BCAPp:p85PI3K:p110PI3K]	22
57	kb_38	[BCAPp:p85PI3K] + p110PI3K <-> [BCAPp:p85PI3K:p110PI3K]	24
58	kcat_39	[BCAPp:p85PI3K:p110PI3K] -> BCAPp + PI3K	6
59	kf_40	BCAPp + Pase1 <-> [BCAPp:Pase1]	22
60	kb_40	BCAPp + Pase1 <-> [BCAPp:Pase1]	8
61	kcat_41	[BCAPp:Pase1] -> BCAP + Pase1	2
62	kf_42	CD19p -> CD19	0.1
63	kf_43	PI3K -> p85PI3K + p110PI3K	0.251829
64	km_44	PIP2 + PI3K -> PIP3 + PI3K	0.00391
65	vm_44	PIP2 + PI3K -> PIP3 + PI3K	1.69
66	km_45	PIP3 -> PIP2	0.092
67	vm_45	PIP3 -> PIP2	1.7
68	kf_46	PIP3 + Aktc <-> [PIP3:Aktc]	6
69	kb_46	PIP3 + Aktc <-> [PIP3:Aktc]	12
70	kf_47	[PIP3:Aktc] <-> Aktm	3
71	kb_47	[PIP3:Aktc] <-> Aktm	0.3
72	kf_48	PIP3 + PDK <-> [PIP3:PDK]	2.0408
73	kb_48	PIP3 + PDK <-> [PIP3:PDK]	4.2
74	kf_49	[PIP3:PDK] -> PDKa	3.5261
75	kf_50	PDKa -> PDK + PIP3	0.9597
76	kf_51	PDKa + Aktm <-> [PDKa:Aktm]	1200
77	kb_51	PDKa + Aktm <-> [PDKa:Aktm]	4
78	kcat_52	[PDKa:Aktm] -> PDKa + Aktp	1
79	kf_53	Aktp + PP2A <-> [Aktp:PP2A]	12
80	kb_53	Aktp + PP2A <-> [Aktp:PP2A]	0.65
81	kcat_54	[Aktp:PP2A] -> Aktm + PP2A	2
82	kf_55	Sykp + BLNK <-> [Sykp:BLNK]	2.4
83	kb_55	Sykp + BLNK <-> [Sykp:BLNK]	4
84	kcat_56	[Sykp:BLNK] -> Sykp + BLNKp	1
85	kf_57	BLNKp + Btkp <-> [BLNKp:Btkp]	2.723833
86	kb_57	BLNKp + Btkp <-> [BLNKp:Btkp]	1.8372
87	kf_58	BLNKp + Grb2 <-> [BLNKp:Grb2]	1
88	kb_58	BLNKp + Grb2 <-> [BLNKp:Grb2]	0.05
89	kf_59	BLNKp + Pase2 <-> [BLNKp:Pase2]	222
90	kb_59	BLNKp + Pase2 <-> [BLNKp:Pase2]	3.68
91	kcat_60	[BLNKp:Pase2] -> BLNK + Pase2	0.926
92	kf_61	[BLNKp:Grb2] + SoS <-> [BLNKp:Grb2:SoS]	0.05
93	kb_61	[BLNKp:Grb2] + SoS <-> [BLNKp:Grb2:SoS]	1
94	kf_62	[BLNKp:Btkp] + PLCg <-> [BLNKp:Btkp:PLCg]	200
95	kb_62	[BLNKp:Btkp] + PLCg <-> [BLNKp:Btkp:PLCg]	0.6333
96	kcat_63	[BLNKp:Btkp:PLCg] -> [BLNKp:Btkp] + PLCgp	4
97	kf_64	PLCgp + Pase3 <-> [PLCgp:Pase3]	52

98	kb_64	PLCgp + Pase3 <-> [PLCgp:Pase3]	0.54
99	kcat_65	[PLCgp:Pase3] -> PLCg + Pase3	4
100	kdeg_66	IP3 -> ip3deg	0.021
101	kdeg_67	DAG -> dagdeg	0.0225
102	km_68	PLCgp + PIP2 -> PLCgp + IP3 + DAG	0.05
103	vm_68	PLCgp + PIP2 -> PLCgp + IP3 + DAG	0.48
104	kf_69	PKCcyt + DAG <-> [PKCcyt:DAG]	0.45
105	kb_69	PKCcyt + DAG <-> [PKCcyt:DAG]	0.226
106	kf_70	[PKCcyt:DAG] <-> PKCm	9.9
107	kb_70	[PKCcyt:DAG] <-> PKCm	0.005
108	kf_71	RasGTP -> RasGDP	0.25
109	kf_72	GEFp + RasGDP <-> [GEFp:RasGDP]	0.08
110	kb_72	GEFp + RasGDP <-> [GEFp:RasGDP]	0.033
111	kcat_73	[GEFp:RasGDP] -> GEFp + RasGTP	0.2
112	kf_74	GEF + PKCm <-> [GEF:PKCm]	1.5
113	kb_74	GEF + PKCm <-> [GEF:PKCm]	16
114	kcat_75	[GEF:PKCm] -> GEFp + PKCm	4
115	kf_76	PKCm + GAP <-> [PKCm:GAP]	1.3125
116	kb_76	PKCm + GAP <-> [PKCm:GAP]	100
117	kcat_77	[PKCm:GAP] -> PKCm + GAPp	25
118	kf_78	GEFp -> GEF	0.1
119	kf_79	GAPp -> GAP	0.1
120	kf_80	PKCm + Sykp <-> [PKCm:Sykp]	0.25
121	kb_80	PKCm + Sykp <-> [PKCm:Sykp]	3.92
122	kcat_81	[PKCm:Sykp] -> PKCm + Sykpp	0.98
123	kf_82	Sykpp -> Sykp	0.041
124	kf_83	GAP + RasGTP <-> [GAP:RasGTP]	2.1666
125	kb_83	GAP + RasGTP <-> [GAP:RasGTP]	1
126	kcat_84	[GAP:RasGTP] -> GAP + RasGDP	10
127	kf_85	Raf + RasGTP <-> [Raf:RasGTP]	100
128	kb_85	Raf + RasGTP <-> [Raf:RasGTP]	2
129	kf_86	[Raf:RasGTP] + PKCm <-> [Raf:RasGTP:PKCm]	8
130	kb_86	[Raf:RasGTP] + PKCm <-> [Raf:RasGTP:PKCm]	0.0444
131	kcat_87	[Raf:RasGTP:PKCm] -> [Rafp:RasGTP] + PKCm	4
132	kf_88	Raf + Aktp <-> [Raf:Aktp]	2.5
133	kb_88	Raf + Aktp <-> [Raf:Aktp]	4
134	kcat_89	[Raf:Aktp] -> Rafser259 + Aktp	1
135	kf_90	Rafser259 + PP1 <-> [Rafser259:PP1]	12.85
136	kb_90	Rafser259 + PP1 <-> [Rafser259:PP1]	9
137	kcat_91	[Rafser259:PP1] -> Raf + PP1	3
138	kf_92	Rafp + Aktp <-> [Rafp:Aktp]	0.89
139	kb_92	Rafp + Aktp <-> [Rafp:Aktp]	2
140	kcat_93	[Rafp:Aktp] -> Rafpp + Aktp	0.5
141	kf_94	Rafpp + PP1 <-> [Rafpp:PP1]	9.88
142	kb_94	Rafpp + PP1 <-> [Rafpp:PP1]	13.6
143	kcat_95	[Rafpp:PP1] -> Rafp + PP1	3.4
144	kf_96	Rafp + PP2A <-> [Rafp:PP2A]	2.2
145	kb_96	Rafp + PP2A <-> [Rafp:PP2A]	16
146	kcat_97	[Rafp:PP2A] -> Raf + PP2A	4
147	kf_98	Btkcyt + PIP3 <-> Btk	90

148	kb_98	Btkcyt + PIP3 <-> Btk	0.00034
149	kf_99	Sykp + PLCg <-> [Sykp:PLCg]	10
150	kb_99	Sykp + PLCg <-> [Sykp:PLCg]	16
151	kcat_100	[Sykp:PLCg] -> Sykp + PLCgp	4
152	kf_101	Rafp + PP1 <-> [Rafp:PP1]	3
153	kb_101	Rafp + PP1 <-> [Rafp:PP1]	4
154	kcat_102	[Rafp:PP1] -> Raf + PP1	4
155	kf_103	Rafp + MEK <-> [Rafp:MEK]	6.8
156	kb_103	Rafp + MEK <-> [Rafp:MEK]	9.62
157	kcat_104	[Rafp:MEK] -> Rafp + MEKp	2.405
158	kf_105	Rafp + MEKp <-> [Rafp:MEKp]	6.8
159	kb_105	Rafp + MEKp <-> [Rafp:MEKp]	9.62
160	kcat_106	[Rafp:MEKp] -> Rafp + MEKpp	2.405
161	kf_107	PKCm + CK2alpha <-> [PKCm:CK2alpha]	2
162	kb_107	PKCm + CK2alpha <-> [PKCm:CK2alpha]	8
163	kcat_108	[PKCm:CK2alpha] -> PKCm + CK2alphap	2.667
164	kf_109	CK2alphap -> CK2alpha	0.333
165	kf_110	CK2alphap + MKP3 <-> [CK2alphap:MKP3]	1
166	kb_110	CK2alphap + MKP3 <-> [CK2alphap:MKP3]	4.64
167	kcat_111	[CK2alphap:MKP3] -> CK2alphap + MKP3p	1.16
168	kf_112	MKP3p + PP2A <-> [MKP3p:PP2A]	15
169	kb_112	MKP3p + PP2A <-> [MKP3p:PP2A]	16
170	kcat_113	[MKP3p:PP2A] -> MKP3 + PP2A	4
171	kf_114	MEKpp + PP2A <-> [MEKpp:PP2A]	1.31
172	kb_114	MEKpp + PP2A <-> [MEKpp:PP2A]	4
173	kcat_115	[MEKpp:PP2A] -> MEKp + PP2A	1
174	kf_116	MEKp + PP2A <-> [MEKp:PP2A]	1.31
175	kb_116	MEKp + PP2A <-> [MEKp:PP2A]	4
176	kcat_117	[MEKp:PP2A] -> MEK + PP2A	1
177	kf_118	MEKpp + MKP3p <-> [MEKpp:MKP3p]	26
178	kb_118	MEKpp + MKP3p <-> [MEKpp:MKP3p]	64
179	kcat_119	[MEKpp:MKP3p] -> MEKp + MKP3p	16
180	kf_120	MEKp + MKP3p <-> [MEKp:MKP3p]	26
181	kb_120	MEKp + MKP3p <-> [MEKp:MKP3p]	64
182	kcat_21	[MEKp:MKP3p] -> MEK + MKP3p	16
183	kf_122	ERK + MEKpp <-> [ERK:MEKpp]	1.6
184	kb_122	ERK + MEKpp <-> [ERK:MEKpp]	1
185	kcat_123	[ERK:MEKpp] -> ERKp + MEKpp	0.25
186	kf_124	ERKp + MEKpp <-> [ERKp:MEKpp]	1.6
187	kb_124	ERKp + MEKpp <-> [ERKp:MEKpp]	1
188	kcat_125	[ERKp:MEKpp] -> ERKpp + MEKpp	0.25
189	kf_126	mkp1 <-> MKP1	0.0004
190	kb_126	mkp1 <-> MKP1	0.0001
191	kf_127	mkp3 <-> MKP3	0.0004
192	kb_127	mkp3 <-> MKP3	0.0001
193	kf_128	MKP1 -> mkp1ubi	3.7E-16
194	kf_129	MKP3 -> mkp3ubi	3.7E-16
195	kf_130	ERKpp + MKP1 <-> [ERKpp:MKP1]	0.30101
196	kb_130	ERKpp + MKP1 <-> [ERKpp:MKP1]	4.44
197	kcat_131	[ERKpp:MKP1] -> ERKpp + MKP1p	2.2

198	kb_132	MKP1p + MKP3p <-> [MKP1p:MKP3p]	108
199	kf_132	MKP1p + MKP3p <-> [MKP1p:MKP3p]	141
200	kcat_133	[MKP1p:MKP3p] -> MKP1 + MKP3p	27
201	kf_134	ERKpp + MKP2 <-> [ERKpp:MKP2]	76
202	kb_134	ERKpp + MKP2 <-> [ERKpp:MKP2]	4
203	kcat_135	[ERKpp:MKP2] -> ERKp + MKP2	1
204	kf_136	ERKp + MKP2 <-> [ERKp:MKP2]	76
205	kb_136	ERKp + MKP2 <-> [ERKp:MKP2]	4
206	kcat_137	[ERKp:MKP2] -> ERK + MKP2	1
207	kf_138	ERKpp + MKP3 <-> [ERKpp:MKP3p]	1
208	kb_138	ERKpp + MKP3 <-> [ERKpp:MKP3p]	0.25
209	kcat_139	[ERKpp:MKP3p] -> ERKp + MKP3	9
210	kf_140	ERKp + MKP3 <-> [ERKp:MKP3p]	1
211	kb_140	ERKp + MKP3 <-> [ERKp:MKP3p]	0.25
212	kcat_141	[ERKp:MKP3p] -> ERK + MKP3	9
213	kf_142	TrCmplx -> mkp1	1E-18
214	kf_143	TrCmplx -> mkp3	1E-18
215	kf_144	Rafp + ERKpp <-> [Rafp:ERKpp]	0.05
216	kb_144	Rafp + ERKpp <-> [Rafp:ERKpp]	2
217	kcat_145	[Rafp:ERKpp] -> Rafpp + ERKpp	0.5
218	kf_146	Rafser259 + PP2A <-> [Rafser259:PP2A]	2.25
219	kb_147	Rafser259 + PP2A <-> [Rafser259:PP2A]	8
220	kcat_147	[Rafser259:PP2A] -> Raf + PP2A	4
221	kf_148	[Rafp:RasGTP] -> Rafp + RasGTP	1
222	kf_149	[L:BCR1] + BCR <-> [L:BCR]	10
223	kb_149	[L:BCR1] + BCR <-> [L:BCR]	2
224	kf_150	[L:BCRp] + SHP1 <-> [L:BCRp:SHP1]	83
225	kb_150	[L:BCRp] + SHP1 <-> [L:BCRp:SHP1]	2.77
226	kcat_151	[L:BCRp:SHP1] -> [L:BCR] + SHP1	1
227	kf_152	[L:BCRpp] + SHP1 <-> [L:BCRpp:SHP1]	240
228	kb_152	[L:BCRpp] + SHP1 <-> [L:BCRpp:SHP1]	2
229	kcat_153	[L:BCRpp:SHP1] -> [L:BCRp] + SHP1	1
230	km_154	[BLNKp:Grb2:SoS] + RasGDP -> [BLNKp:Grb2:SoS] + RasGTP	0.050505
231	vm_154	[BLNKp:Grb2:SoS] + RasGDP -> [BLNKp:Grb2:SoS] + RasGTP	22
232	kf_155	ERKpp + MKP1p <-> [ERKpp:MKP1p]	450
233	kb_155	ERKpp + MKP1p <-> [ERKpp:MKP1p]	600
234	kcat_156	[ERKpp:MKP1p] -> ERKp + MKP1p	150
235	kf_157	ERKp + MKP1p <-> [ERKp:MKP1p]	450
236	kb_157	ERKp + MKP1p <-> [ERKp:MKP1p]	600
237	kcat_158	[ERKp:MKP1p] -> ERK + MKP1p	150
238	kf_159	ERKpp + MKP1 <-> [MKP1:ERKpp]	30
239	kb_159	ERKpp + MKP1 <-> [MKP1:ERKpp]	600
240	kcat_160	[MKP1:ERKpp] -> MKP1 + ERKp	150
241	kf_161	ERKp + MKP1 <-> [MKP1:ERKp]	30
242	kb_161	ERKp + MKP1 <-> [MKP1:ERKp]	600
243	kcat_162	[MKP1:ERKp] -> MKP1 + ERK	150
244	kf_163	ERKpp + TF <-> [ERKpp:TF]	4
245	kb_163	ERKpp + TF <-> [ERKpp:TF]	0.000335
246	kcat_164	[ERKpp:TF] -> ERKpp + TFa	1
247	kf_165	TFa + NT <-> [TFa:NT]	0.0001

248	kb_165	TFa + NT <-> [TFa:NT]	0.0002
249	kf_166	TFa -> TF	1E-25
250	trnsc_167	NT -> mkp1	2E-07
251	trnsc_168	NT -> mkp3	0.000002
252	kf_169	PKCm -> PKCcyt	0.1
253	kf_170	MKP3 + ERKpp <-> [MKP3:ERKpp]	0.0034
254	kb_170	MKP3 + ERKpp <-> [MKP3:ERKpp]	1
255	kcat_171	[MKP3:ERKpp] -> MKP3x + ERKpp	0.25
256	kf_172	MKP3x -> mkp3xubi	1.5E-15

Units of rate Constants

kf * => micromoles sec^{-1} (for second order reactions), minromoles $^{-1}$ sec $^{-1}$ (for first order reactions)

kb* => sec^{-1}

kcat* => sec^{-1}

km* => micromoles

vm* => sec^{-1}

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4. Parameter Sensitivities for ppMEK response:

			Integrated response				Maximum Response	
Sr. No.	Parameter		LSA	MPSA	PRCC	WALS	LSA	PRCC
1	kon_1	50	-0.0081007	0.022403	0.030766	-0.28509	-0.010141	0.016148
2	koff_1	10	-0.0097747	0.033039	-0.05571	0.25103	-0.011007	-0.021017
3	kf_2	0.99	0.021816	0.044462	0.083205	0.97754	0.015703	0.083893
4	kon_3	0.8857	0.037961	0.080739	0.11452	1.068	0.020371	0.1011
5	koff_3	0.8766	-0.024094	0.027268	-0.095774	0.23895	-0.016402	-0.053244
6	kcat_4	0.515	0.028017	0.036089	0.11286	0.96209	0.014187	0.059698
7	kon_5	7	-0.025633	0.028756	-0.11493	-0.23063	-0.022721	-0.10261
8	koff_5	7.9716	0.020485	0.025379	0.086825	0.43516	0.018164	0.061516
9	kcat_6	2	-0.022173	0.034916	-0.086118	-0.72688	-0.019634	-0.082868
10	km_7	1.933	0.0099632	0.027374	0.04697	0.40499	0.0032908	0.11102
11	vm_7	5.4291	-0.010466	0.024241	-0.10115	-0.24109	-0.0034468	-0.074296
12	kf_8	0.7532	-0.019452	0.06456	-0.12269	-0.77121	-0.0094957	-0.12217
13	kb_8	1.201	0.011778	0.04732	0.062739	-0.57419	0.0094012	0.089788
14	kcat_9	0.9426	-0.012544	0.051637	-0.075791	-0.48004	-0.0098686	-0.078189
15	kf_10	0.01	0.014677	0.033638	0.094215	0.55321	0.012396	0.13037
16	kf_11	0.0943	0.0090196	0.02416	0.09529	1.3283	0.0076195	0.031896
17	kb_12	8.7948	-0.016071	0.059304	-0.11806	-0.14312	-0.0071009	-0.10356
18	kf_12	0.448	0.059742	0.073009	0.26925	1.9264	0.044916	0.20798
19	kcat_13	21.56515	0.016559	0.066563	0.104	0.68319	0.0071351	0.099252
20	kf_14	20	-0.03284	0.10139	-0.1909	-1.2296	-0.028173	-0.17908
21	kb_14	3.6	0.026695	0.067496	0.11745	0.61331	0.023037	0.13203
22	kcat_15	0.9	-0.036143	0.037746	-0.14269	-0.84015	-0.031294	-0.1405
23	kf_16	0.3143	-4.55E-05	0.026157	0.008245	0.050476	-3.06E-05	0.02577
24	kb_16	1.2092	3.62E-05	0.030967	-0.018818	-0.046604	2.48E-05	-0.029067
25	kcat_17	0.3023	0.0002029	0.025217	0.008797	0.021398	0.0001578	-0.043619
26	kf_18	0.899	0.0001714	0.037701	0.034444	0.067749	0.0001263	0.000524
27	kb_18	0.8766	-9.48E-05	0.030194	0.001578	-0.031537	-7.01E-05	0.005192
28	kcat_19	0.6915	0.0001085	0.038444	0.012872	0.016004	7.89E-05	-0.022479
29	kf_20	0.0000015	5.64E-05	0.02248	0.00906	0.014351	2.88E-05	-0.013605
30	kf_21	0.0000015	-1.04E-05	0.037115	0.011271	0.015617	-5.21E-06	0.027675
31	kon_22	10	0.010295	0.025772	0.030361	-0.53256	0.009538	-0.025329
32	koff_22	5	-0.0092921	0.025515	-0.056159	-0.037192	-0.0083819	-0.040964
33	kf_23	0.0067	-0.0039535	0.03418	-0.019015	-0.073003	-0.0020674	-0.040448
34	kf_24	0.645	-7.72E-05	0.020666	-0.013823	0.006173	-5.79E-05	-0.008806
35	kb_24	4	6.27E-05	0.022342	0.022475	0.025535	4.71E-05	-0.006567
36	kcat_25	1	2.41E-05	0.02522	-0.039585	0.008775	3.23E-06	0.013814
37	kf_26	2.4	-0.0003707	0.02418	0.024793	-0.002274	-0.0004054	0.008076
38	kb_26	4	0.0001856	0.050836	-0.027158	-0.014835	0.0002027	-0.013369
39	kcat_27	4	0.000247	0.022313	-0.005519	0.020469	0.0001306	0.012264
40	kf_28	12	-1.23E-05	0.036251	-0.005939	-0.03654	8.33E-05	-0.035589
41	kb_28	16	9.87E-06	0.024293	0.034774	0.030026	-6.64E-05	0.041715
42	kcat_29	4	-1.45E-05	0.029715	0.000681	-0.030381	6.18E-05	-0.029219
43	kf_30	1.2245	-0.0001795	0.026945	-0.004385	0.032754	-4.51E-05	0.045795
44	kb_30	12	0.000144	0.020191	-0.000206	-0.045476	3.65E-05	0.003205
45	kcat_31	3	5.28E-05	0.028023	-0.000349	-0.009227	1.55E-05	-0.006234
46	kf_32	0.00345	-1.85E-08	0.034965	0.022738	0.002182	3.75E-08	0.016258

47	kb_32	1.064	1.50E-07	0.025267	0.013023	0.015458	2.73E-07	-0.017255
48	kf_33	0.2	2.78E-08	0.032351	-0.001672	-0.007182	5.21E-08	0.010171
49	kb_33	4	-1.72E-07	0.024641	-0.001804	0.034612	-2.19E-07	0.002049
50	kcat_34	1	7.41E-07	0.02884	-0.001708	0.007776	5.67E-07	0.009812
51	kf_35	4.8699	-0.0006919	0.022182	0.021453	0.030564	-0.0003385	0.026789
52	kb_36	14	0.0005531	0.040409	-0.013835	-0.009489	0.0002706	0.004046
53	kcat_36	3.5	0.0005476	0.02858	0.014906	0.068369	0.0002958	0.033874
54	kf_37	0.5	2.38E-05	0.036503	-0.013383	-0.000978	-1.04E-05	0.024591
55	kb_37	3	-2.02E-05	0.026298	-0.047085	-0.058536	7.90E-06	-0.004178
56	kf_38	22	1.49E-05	0.026599	0.027291	0.019746	-1.23E-05	-0.002128
57	kb_38	24	-1.08E-05	0.025441	-0.009106	0.26488	1.06E-05	0.003194
58	kcat_39	6	1.03E-05	0.014389	0.01513	0.009044	-1.12E-05	-0.005399
59	kf_40	22	-0.0003056	0.026418	-0.002026	-0.022647	-0.0001913	-0.002242
60	kb_40	8	0.000246	0.030341	0.019099	0.059647	0.0001544	-0.01942
61	kcat_41	2	-0.0002974	0.035801	-0.010917	-0.024509	-0.0001911	0.02435
62	kf_42	0.1	-1.33E-05	0.034853	0.012684	0.004526	-4.82E-06	-0.002631
63	kf_43	0.251829	-8.94E-06	0.032853	-0.011761	0.28347	1.37E-05	0.017002
64	km_44	0.00391	9.07E-08	0.040798	-0.003569	-0.006459	1.00E-07	0.005645
65	vm_44	1.69	1.88E-05	0.02641	0.008777	0.000495	-1.42E-05	0.042244
66	km_45	0.092	2.60E-06	0.025296	0.025464	0.03401	-1.23E-05	-0.010526
67	vm_45	1.7	-2.40E-06	0.016611	-0.010711	-0.019648	1.24E-05	-0.005837
68	kf_46	6	-3.06E-07	0.015403	0.029552	0.005601	-2.78E-07	0.015314
69	kb_46	12	1.04E-07	0.020258	-0.010916	0.029996	1.07E-07	0.036318
70	kf_47	3	-1.73E-07	0.042033	-0.020752	0.004163	-1.85E-07	-0.01643
71	kb_47	0.3	1.90E-07	0.019009	-0.004889	0.000489	1.92E-07	-0.023401
72	kf_48	2.0408	-3.40E-07	0.016039	-0.012581	0.014474	-3.35E-07	-0.021143
73	kb_48	4.2	1.57E-07	0.029244	-0.027622	-0.061275	1.43E-07	-0.01159
74	kf_49	3.5261	-1.20E-08	0.018756	-0.029149	-0.055838	9.84E-08	0.003425
75	kf_50	0.9597	1.53E-07	0.016205	0.012683	-0.029933	4.76E-08	-0.029584
76	kf_51	1200	-3.09E-07	0.021994	-0.02335	0.005884	-3.03E-07	0.008312
77	kb_51	4	8.34E-08	0.028978	-0.016963	-0.04249	5.10E-08	0.013871
78	kcat_52	1	-7.09E-08	0.023352	-0.009594	-0.012118	8.66E-09	0.002017
79	kf_53	12	2.82E-07	0.026666	-0.045314	-0.077526	3.12E-07	0.01637
80	kb_53	0.65	3.31E-08	0.042162	0.002515	-0.012459	5.69E-08	0.020096
81	kcat_54	2	6.71E-08	0.030469	0.010531	-0.011082	1.02E-07	-0.020774
82	kf_55	2.4	0.084507	0.067528	0.21466	2.0514	0.057408	0.21748
83	kb_55	4	-0.067551	0.043507	-0.13647	-0.99112	-0.047301	-0.14495
84	kcat_56	1	0.07204	0.088226	0.15297	2.2352	0.049755	0.15322
85	kf_57	2.7238333	-0.0002458	0.03567	0.023539	0.059673	-0.0003869	0.047195
86	kb_57	1.8372	0.0003112	0.034905	-0.013382	-0.066059	0.0003838	-0.025567
87	kf_58	1	0.059796	0.033322	0.15621	1.5302	0.046601	0.14802
88	kb_58	0.05	-0.056217	0.067657	-0.13204	-1.467	-0.046559	-0.11973
89	kf_59	222	-0.053608	0.054183	-0.16429	-1.479	-0.041738	-0.14247
90	kb_59	3.68	0.042794	0.018876	0.085365	0.73743	0.033346	0.090356
91	kcat_60	0.926	-0.065972	0.087676	-0.14135	-0.91761	-0.053069	-0.13675
92	kf_61	0.05	0.16555	0.15072	0.31814	2.6254	0.13034	0.2806
93	kb_61	1	-0.16503	0.1301	-0.29333	-2.6232	-0.13034	-0.30855
94	kf_62	200	1.65E-05	0.014152	0.040494	0.079545	-9.12E-05	0.014737
95	kb_62	0.6333	-2.20E-06	0.031056	-0.017738	-0.023986	1.23E-05	-0.033858
96	kcat_63	4	0.0047462	0.030768	0.012046	0.14859	0.0039523	0.051016

97	kf_64	52	-0.0006759	0.066439	-0.15653	0.15303	0.0009184	-0.099227
98	kb_64	0.54	0.0002757	0.046968	0.018127	1.1699	0.0001216	0.033951
99	kcat_65	4	-0.010009	0.037886	-0.092374	-0.057761	-0.0072862	-0.090736
100	kdeg_66	0.021	-1.46E-06	0.031987	0.010141	-0.76679	-2.42E-06	0.011001
101	kdeg_67	0.0225	-0.0012852	0.031137	-0.040575	-0.38332	-0.0027138	-0.009067
102	km_68	0.05	-1.55E-05	0.044846	0.001108	-0.25419	-6.72E-06	-0.040297
103	vm_68	0.48	0.0025718	0.055777	0.17255	0.50494	0.006883	0.15701
104	kf_69	0.45	0.0021416	0.039427	0.052864	0.47996	0.0034885	0.047312
105	kb_69	0.226	-3.88E-05	0.027736	0.002461	-0.30246	-2.23E-05	-0.005787
106	kf_70	9.9	0.0003948	0.036398	-0.036564	-0.91618	0.0003122	0.00214
107	kb_70	0.005	-1.88E-05	0.038958	0.022158	-0.001745	-1.49E-05	-0.001318
108	kf_71	0.25	-0.15838	0.13601	-0.36002	-2.9114	-0.13316	-0.32298
109	kf_72	0.08	0.0031314	0.02923	0.10845	0.57407	0.0022836	0.091192
110	kb_72	0.033	-0.0004375	0.020573	-0.019816	-0.10206	-0.0003232	-0.019927
111	kcat_73	0.2	0.0007472	0.027924	0.015986	0.11354	0.0005423	0.011046
112	kf_74	1.5	0.0010712	0.018398	0.036148	0.28172	0.0006921	0.027498
113	kb_74	16	-0.0008564	0.026341	-0.03477	-0.24441	-0.0005534	-0.05821
114	kcat_75	4	0.000915	0.038077	0.036829	0.24458	0.0005978	0.022197
115	kf_76	1.3125	0.0005638	0.019033	0.009826	0.018185	0.0004701	0.019829
116	kb_76	100	-0.0004493	0.024594	-0.01473	-0.00582	-0.0003747	-0.008242
117	kcat_77	25	0.0004487	0.037734	0.025288	0.001449	0.0003741	-0.017991
118	kf_78	0.1	-0.0010568	0.025383	-0.045759	-0.31922	-0.0007359	-0.024292
119	kf_79	0.1	-0.0005553	0.028063	-0.007982	-0.005937	-0.0004674	-0.037156
120	kf_80	0.25	-0.020501	0.049154	-0.030604	-0.61675	-0.018605	-0.055916
121	kb_80	3.92	0.016446	0.033186	0.03353	0.23343	0.015383	0.036008
122	kcat_81	0.98	-0.015035	0.023076	-0.039594	-0.20713	-0.013901	-0.036685
123	kf_82	0.041	0.017463	0.057226	0.041368	0.23883	0.015355	0.037553
124	kf_83	2.1666	-0.0008646	0.028601	-0.021954	-0.074246	-0.0007075	0.010554
125	kb_83	1	7.86E-05	0.0335	-0.002537	0.005102	6.45E-05	-0.000459
126	kcat_84	10	-7.73E-05	0.034494	-0.006884	-0.00454	-6.32E-05	-0.008214
127	kf_85	100	0.1706	0.17984	0.37923	3.1422	0.14257	0.38261
128	kb_85	2	-0.044226	0.082439	-0.21159	-1.42	-0.037753	-0.20289
129	kf_86	8	0.058344	0.13731	0.29131	1.6454	0.052247	0.27129
130	kb_86	0.0444	-0.0006361	0.012261	0.024898	-0.030974	-0.0005144	0.013967
131	kcat_87	4	0.020687	0.02238	0.041833	0.24231	0.016645	0.048821
132	kf_88	2.5	-2.84E-07	0.021931	-0.006838	0.003138	-2.73E-07	-0.000347
133	kb_88	4	9.06E-08	0.029569	0.002431	0.002751	7.60E-08	-0.002636
134	kcat_89	1	-1.46E-07	0.035084	0.005132	0.004996	-1.61E-07	-0.017665
135	kf_90	12.85	2.03E-07	0.026895	-0.007505	4.76E-07	2.29E-07	0.004556
136	kb_90	9	-8.18E-08	0.024841	0.007525	0.003813	-8.72E-08	0.014412
137	kcat_91	3	1.02E-07	0.017775	-0.005111	0.002428	1.10E-07	0.004818
138	kf_92	0.89	-2.13E-10	0.03496	-0.002488	0.003616	4.11E-08	0.009263
139	kb_92	2	-3.65E-08	0.036712	-0.03837	0.005026	-2.41E-08	-0.008294
140	kcat_93	0.5	6.30E-08	0.020813	-0.006537	0.006241	5.52E-08	0.004558
141	kf_94	9.88	8.07E-05	0.030187	0.01203	0.0027	8.88E-05	-0.021754
142	kb_94	13.6	-6.45E-05	0.025656	0.024208	-0.003039	-7.10E-05	0.000941
143	kcat_95	3.4	8.23E-05	0.021207	-0.006336	0.001455	9.06E-05	0.006671
144	kf_96	2.2	-0.0012373	0.019476	-0.045117	-0.051256	-0.0010168	0.007938
145	kb_96	16	0.0009899	0.02722	0.011317	0.017039	0.0008136	0.03118
146	kcat_97	4	-0.000972	0.044008	-6.93E-05	-0.025903	-0.000804	0.025397

147	kf_98	90	2.51E-06	0.025577	0.015559	-0.025799	-1.25E-05	0.012253
148	kb_98	0.00034	6.26E-06	0.048208	0.012356	-0.009749	5.95E-06	-0.000387
149	kf_99	10	-0.0016795	0.020295	0.14018	0.69939	0.0032466	0.1432
150	kb_99	16	0.0008394	0.041507	-0.098647	-0.13161	-0.0020411	-0.096032
151	kcat_100	4	0.0046884	0.040482	0.13839	0.62902	0.013448	0.097011
152	kf_101	3	-0.28775	0.27431	-0.53628	-4.1607	-0.23837	-0.51013
153	kb_101	4	0.14384	0.13875	0.25064	2.065	0.11919	0.28641
154	kcat_102	4	-0.13735	0.13974	-0.25901	-2.0457	-0.11344	-0.25337
155	kf_103	6.8	0.084216	0.13803	0.30069	2.04	0.051161	0.28427
156	kb_103	9.62	-0.067372	0.085683	-0.23344	-1.6206	-0.040931	-0.20989
157	kcat_104	2.405	0.068277	0.086782	0.21866	1.6508	0.041463	0.23179
158	kf_105	6.8	0.25104	0.19112	0.37532	2.4397	0.22869	0.36726
159	kb_105	9.62	-0.20082	0.12102	-0.27515	-1.9073	-0.18295	-0.28955
160	kcat_106	2.405	0.20293	0.15362	0.25556	1.9228	0.18482	0.27306
161	kf_107	2	-0.0030366	0.020352	-0.043678	1.2685	-0.002793	-0.055079
162	kb_107	8	0.0022751	0.021267	0.029998	0.51711	0.002093	0.03207
163	kcat_108	2.667	-0.0026499	0.029568	-0.002955	1.4809	-0.0024564	-0.017403
164	kf_109	0.333	0.0032352	0.022589	0.025321	0.63201	0.0030952	0.052559
165	kf_110	1	-0.075606	0.056745	-0.056998	-0.77733	-0.073326	-0.10843
166	kb_110	4.64	0.060485	0.059167	0.093508	0.51967	0.058661	0.087935
167	kcat_111	1.16	-0.061842	0.044281	-0.040174	-0.53032	-0.060068	-0.084478
168	kf_112	15	0.076617	0.083297	0.085802	0.78986	0.075052	0.089444
169	kb_112	16	-0.061293	0.03127	-0.036926	-0.5291	-0.060042	-0.046627
170	kcat_113	4	0.060895	0.05477	0.061596	0.53001	0.059627	0.065627
171	kf_114	1.31	-0.070998	0.054035	-0.10887	-0.49226	-0.073514	-0.13775
172	kb_114	4	0.056792	0.035797	0.064997	0.40359	0.058811	0.10523
173	kcat_115	1	-0.055765	0.059567	-0.068876	-0.3949	-0.0578	-0.073666
174	kf_116	1.31	-0.017696	0.053137	0.083994	0.61501	-0.016094	0.096386
175	kb_116	4	0.014156	0.042247	-0.16965	-1.3698	0.012875	-0.17224
176	kcat_117	1	-0.013832	0.037863	-0.076313	-0.64973	-0.012591	-0.096726
177	kf_118	26	-0.14849	0.078676	-0.10598	-1.2496	-0.15527	-0.13409
178	kb_118	64	0.11879	0.059039	0.09988	0.56563	0.12422	0.091137
179	kcat_119	16	-0.11979	0.059495	-0.055217	-0.56153	-0.12532	-0.095375
180	kf_120	26	-0.03666	0.031977	-0.051822	-0.37643	-0.033821	-0.044329
181	kb_120	64	0.029328	0.034419	0.067018	0.24551	0.027057	0.063881
182	kcat_21	16	-0.029635	0.047234	-0.069218	-0.25026	-0.027357	-0.047819
183	kf_122	1.6	-0.080765	0.0698	-0.10175	-0.5927	-0.068192	-0.098153
184	kb_122	1	0.06458	0.052491	0.055008	0.44854	0.054201	0.074379
185	kcat_123	0.25	0.071661	0.048263	0.059197	0.20813	0.069415	0.065595
186	kf_124	1.6	-0.054872	0.030285	-0.032202	-0.11154	-0.053369	-0.039879
187	kb_124	1	0.043874	0.020189	0.014454	0.089205	0.042697	0.017726
188	kcat_125	0.25	0.097726	0.030194	0.076255	0.27107	0.10312	0.077188
189	kf_126	0.0004	-0.0057482	0.025099	-0.005144	-0.016928	-0.0045085	0.007136
190	kb_126	0.0001	0.0036841	0.019477	-0.024192	0.014355	0.0032128	-0.023242
191	kf_127	0.0004	-0.010006	0.025682	-0.034882	-0.10484	-0.0077134	-0.031745
192	kb_127	0.0001	0.0054678	0.016531	0.016799	0.090767	0.0041986	-0.013104
193	kf_128	3.7E-16	-5.94E-08	0.025976	0.002486	0.000225	-8.90E-08	0.000169
194	kf_129	3.7E-16	1.45E-07	0.015293	0.036646	-0.000275	1.98E-07	-0.000896
195	kf_130	0.30101	-0.034466	0.023344	-0.028005	-0.029255	-0.037925	-0.008014
196	kb_130	4.44	0.023048	0.025675	-0.002783	0.024428	0.024193	0.023683

197	kcat_131	2.2	-0.023386	0.021914	-0.001845	-0.024469	-0.02457	0.019003
198	kb_132	108	-0.026781	0.023778	0.006384	-0.015103	-0.028865	0.006609
199	kf_132	141	0.033471	0.034785	-0.003464	0.026385	0.037825	0.001857
200	kcat_133	27	0.026747	0.032376	0.000972	0.015405	0.028827	-0.030914
201	kf_134	76	-0.008096	0.04845	-0.00934	-0.014447	-0.010422	-0.020146
202	kb_134	4	0.0057399	0.023857	-0.015157	0.005245	0.0037814	4.92E-06
203	kcat_135	1	-0.025795	0.041152	-0.028786	-0.044778	-0.029344	-0.011677
204	kf_136	76	0.0013348	0.02104	0.008073	-0.000529	0.003683	-0.015132
205	kb_136	4	-0.0011046	0.048719	-0.004518	-0.000627	-0.0034481	0.012515
206	kcat_137	1	-0.01777	0.018143	-0.033046	-0.021765	-0.019217	-0.022748
207	kf_138	1	-0.002673	0.019801	-0.007835	-0.006778	-0.0028333	-0.004818
208	kb_138	0.25	7.23E-05	0.014837	-0.014085	0.000532	7.66E-05	0.002946
209	kcat_139	9	-0.001431	0.022593	0.025262	-0.001424	-0.0016791	-0.026943
210	kf_140	1	-0.0012223	0.022736	0.024223	-0.005078	-0.0012274	-0.009059
211	kb_140	0.25	3.32E-05	0.025104	0.000754	0.006616	3.33E-05	0.016889
212	kcat_141	9	-0.0012958	0.036893	0.005492	-0.00332	-0.0014189	-0.026456
213	kf_142	1E-18	-7.49E-08	0.024645	-0.004358	-3.80E-06	-1.32E-07	0.003162
214	kf_143	1E-18	8.64E-08	0.021896	0.00768	0.000742	9.91E-08	-0.008422
215	kf_144	0.05	-0.0002234	0.028846	-0.008331	-0.001035	-0.0002452	0.000469
216	kb_144	2	0.0001786	0.040474	0.016558	-0.000351	0.0001961	0.007956
217	kcat_145	0.5	-5.40E-05	0.039206	-0.002028	-0.000655	-5.95E-05	0.004906
218	kf_146	2.25	-1.12E-07	0.022574	0.018009	0.00159	-1.71E-07	0.009926
219	kb_147	8	-6.86E-08	0.020701	-0.027488	0.01021	-1.05E-07	-0.009306
220	kcat_147	4	-1.50E-07	0.03858	-0.012577	-0.007866	-1.70E-07	0.027756
221	kf_148	1	0.079646	0.068924	0.12061	0.7409	0.062357	0.090164
222	kf_149	10	0.0071355	0.039084	0.049115	-0.99418	0.016586	0.0344
223	kb_149	2	-0.0033108	0.027599	-0.021312	1.6064	-0.0002372	-0.016419
224	kf_150	83	-0.0088509	0.029732	-0.030353	-0.58671	-0.0064601	-0.060096
225	kb_150	2.77	0.0064875	0.037419	0.031823	-0.00091	0.0047456	0.004328
226	kcat_151	1	-0.013847	0.046059	-0.06453	-0.31664	-0.012329	-0.050558
227	kf_152	240	-6.56E-05	0.01935	-0.04165	-0.031782	-5.30E-05	0.006149
228	kb_152	2	4.68E-05	0.039969	0.008003	0.06267	3.78E-05	-0.020358
229	kcat_153	1	-0.000167	0.0297	0.015396	-0.018814	-0.0001344	-0.008286
230	km_154	0.050505	-0.10684	0.087358	-0.18936	-1.5772	-0.085552	-0.20989
231	vm_154	22	0.16694	0.12677	0.3109	2.6449	0.13152	0.30177
232	kf_155	450	-0.043964	0.038956	0.01054	-0.08083	-0.048177	-0.016164
233	kb_155	600	0.035171	0.016977	-0.021424	0.062297	0.038541	0.021694
234	kcat_156	150	-0.039483	0.031823	-0.024057	-0.13797	-0.043447	-0.008861
235	kf_157	450	-0.025062	0.026409	-0.006232	-0.018867	-0.029313	-0.042677
236	kb_157	600	0.019712	0.027853	-0.016527	0.015241	0.023188	0.001388
237	kcat_158	150	-0.023517	0.047143	0.00717	-0.017892	-0.027396	0.002912
238	kf_159	30	-0.0032042	0.025583	0.003402	-0.002411	-0.0033118	0.007436
239	kb_159	600	0.0025633	0.014072	-0.005176	0.002849	0.0026494	0.001563
240	kcat_160	150	-0.0028585	0.020103	-0.000807	-0.005655	-0.0029817	0.0076
241	kf_161	30	-0.00198	0.024936	0.016092	0.002387	-0.0018715	0.029912
242	kb_161	600	0.0015841	0.02843	-0.033539	-0.003241	0.0014973	0.019732
243	kcat_162	150	-0.0018492	0.025495	-0.029315	-0.003998	-0.0017808	-0.007019
244	kf_163	4	-1.25E-06	0.034533	0.002698	0.007176	-1.19E-06	-0.030927
245	kb_163	0.000335	1.66E-07	0.018618	-0.00263	0.000448	1.67E-07	0.0162
246	kcat_164	1	-1.24E-05	0.030777	0.006325	0.001464	-1.17E-07	-0.010511

247	kf_165	0.0001	-6.83E-05	0.018888	-0.00406	-0.00023	-7.05E-06	-0.002669
248	kb_165	0.0002	4.15E-06	0.022969	-0.006545	7.70E-05	3.56E-08	-0.01371
249	kf_166	1E-25	0	0.039454	0.021777	4.25E-08	0	0.002925
250	trnsc_167	0.0000002	-2.08E-05	0.018938	-0.017971	-0.000206	-2.19E-06	-0.016251
251	trnsc_168	0.000002	-4.95E-05	0.020271	0.021407	-0.000137	-4.85E-06	-0.004812
252	kf_169	0.1	-0.0035418	0.079119	-0.1901	-0.69458	-0.0030874	-0.15644
253	kf_170	0.0034	0.0063752	0.025977	0.008179	0.009153	0.003166	-0.016343
254	kb_170	1	-0.0050946	0.033084	-0.00499	-0.003123	-0.0025264	-0.004438
255	kcat_171	0.25	0.0050673	0.027004	-0.00502	0.00326	0.0024941	0.019901
256	kf_172	1.5E-15	0	0.031695	0.003677	0	0	0.005965

5. Parameter Sensitivities for ppERK response:

Sr. No.	Parameter		Integrated response				Maximum Response	
			LSA	MPSA	PRCC	WALS	LSA	PRCC
1	kon_1	50	-0.0002445	0.028809	0.026461	-0.62101	-0.017606	0.012334
2	koff_1	10	-0.013296	0.037958	-0.033887	0.76302	-0.024822	-0.013979
3	kf_2	0.99	0.029204	0.043819	0.070292	2.2845	0.020365	0.081712
4	kon_3	0.8857	0.037552	0.065934	0.10865	2.4007	0.037694	0.097706
5	koff_3	0.8766	-0.025257	0.041595	-0.092315	0.83788	-0.017666	-0.04944
6	kcat_4	0.515	0.028499	0.046031	0.096054	2.3485	0.032711	0.058961
7	kon_5	7	-0.022215	0.029844	-0.11401	-0.15307	-0.018594	-0.10919
8	koff_5	7.9716	0.017748	0.049554	0.084544	0.96652	0.01486	0.063383
9	kcat_6	2	-0.019224	0.038369	-0.075128	-1.6353	-0.016067	-0.066618
10	km_7	1.933	0.01182	0.02282	0.05168	0.61933	0.02376	0.10261
11	vm_7	5.4291	-0.012374	0.028449	-0.10304	-0.54861	-0.023876	-0.073504
12	kf_8	0.7532	-0.019288	0.066175	-0.12033	-1.611	-0.027851	-0.10627
13	kb_8	1.201	0.014022	0.051081	0.054348	-1.7142	0.012024	0.068158
14	kcat_9	0.9426	-0.014758	0.060674	-0.066793	-1.0386	-0.012419	-0.05681
15	kf_10	0.01	0.012677	0.069115	0.086093	1.0282	0.010086	0.12424
16	kf_11	0.0943	0.011214	0.02936	0.08423	2.8871	0.010491	0.023539
17	kb_12	8.7948	-0.016332	0.055243	-0.099299	0.094175	-0.026003	-0.09638
18	kf_12	0.448	0.053245	0.061226	0.24421	4.0278	0.057128	0.19438
19	kcat_13	21.56515	0.016662	0.044864	0.0879	1.4256	0.026035	0.10032
20	kf_14	20	-0.031654	0.085495	-0.17647	-2.7199	-0.02746	-0.17125
21	kb_14	3.6	0.02689	0.045941	0.12013	1.31	0.023202	0.12074
22	kcat_15	0.9	-0.035105	0.029841	-0.14359	-1.9659	-0.029954	-0.13075
23	kf_16	0.3143	-5.61E-05	0.032611	0.010196	0.034926	-3.58E-05	0.012822
24	kb_16	1.2092	4.43E-05	0.026161	-0.007907	-0.11423	2.89E-05	-0.041825
25	kcat_17	0.3023	0.0001804	0.027664	0.0129	0.070179	0.000127	-0.031577
26	kf_18	0.899	0.0001617	0.030214	0.034899	0.10011	0.0001103	0.002745
27	kb_18	0.8766	-8.79E-05	0.044642	0.002813	-0.05821	-5.95E-05	0.021482
28	kcat_19	0.6915	0.0001009	0.04945	0.012044	-0.044509	6.68E-05	-0.028309
29	kf_20	0.0000015	4.52E-05	0.035748	0.013892	-0.089061	1.98E-05	-0.023059
30	kf_21	0.0000015	-8.92E-06	0.032903	-0.009045	-0.021167	-4.21E-06	0.020638
31	kon_22	10	0.016718	0.022684	0.027805	-1.5481	-0.010061	-0.016245
32	koff_22	5	-0.0061032	0.015857	-0.057207	-0.16041	0.014325	-0.053021
33	kf_23	0.0067	-0.0031786	0.032803	-0.009517	-0.11561	-0.0014218	-0.034756
34	kf_24	0.645	-5.20E-05	0.024062	-0.019888	-0.032664	-1.72E-05	-0.012984
35	kb_24	4	4.27E-05	0.028343	0.01981	-0.020297	1.45E-05	0.005783
36	kcat_25	1	4.29E-05	0.031602	-0.038037	-0.005075	3.52E-05	0.01481
37	kf_26	2.4	-0.0001421	0.032294	0.02882	-0.002188	-2.39E-05	0.006386
38	kb_26	4	7.23E-05	0.050997	-0.017031	-0.11756	1.36E-05	-0.013936
39	kcat_27	4	0.0003277	0.029872	-0.000645	0.022896	0.0002733	0.01185
40	kf_28	12	-0.0001684	0.032988	-0.009724	-0.14032	-0.0002208	-0.044585
41	kb_28	16	0.0001356	0.046363	0.030938	0.053232	0.0001772	0.045402
42	kcat_29	4	-0.000137	0.017666	0.005302	-0.11777	-0.0001769	-0.026617
43	kf_30	1.2245	-0.0001875	0.023575	0.000737	0.008316	-4.15E-05	0.041443
44	kb_30	12	0.0001497	0.034648	-0.00058	-0.1084	3.28E-05	0.007748
45	kcat_31	3	5.47E-05	0.044839	-0.004813	-0.034193	1.43E-05	-0.003995
46	kf_32	0.00345	1.17E-07	0.027396	0.013584	-0.06081	4.05E-07	0.011528

47	kb_32	1.064	1.34E-06	0.031035	0.00394	-0.029683	1.91E-06	-0.01559
48	kf_33	0.2	1.58E-07	0.030025	-0.005198	-0.005019	2.13E-07	0.007455
49	kb_33	4	-1.10E-06	0.028443	0.001403	-0.036614	-1.31E-06	0.004854
50	kcat_34	1	7.97E-07	0.025558	0.013921	-0.038737	6.81E-07	0.016181
51	kf_35	4.8699	-0.0005309	0.029976	0.010864	-0.01151	8.22E-05	0.031565
52	kb_36	14	0.0004241	0.024365	0.005003	-0.10924	-6.43E-05	-0.002862
53	kcat_36	3.5	0.0006703	0.054811	0.010381	0.19864	0.000559	0.02354
54	kf_37	0.5	0.0002175	0.043737	-0.01754	-0.10398	0.0004934	0.009957
55	kb_37	3	-0.0001805	0.027335	-0.055219	-0.082433	-0.0004116	0.002188
56	kf_38	22	0.0001799	0.029679	0.013475	0.028661	0.0004175	0.001568
57	kb_38	24	-0.0001429	0.017521	-0.006183	0.68237	-0.0003317	0.004557
58	kcat_39	6	0.0001427	0.032785	0.024032	-0.17348	0.0003319	-0.001322
59	kf_40	22	-0.0003898	0.025744	-0.010387	-0.049345	-0.0004377	-0.008283
60	kb_40	8	0.0003135	0.043026	0.019113	0.16896	0.0003499	-0.01864
61	kcat_41	2	-0.0003658	0.058979	-0.010036	-0.135	-0.0004067	0.020006
62	kf_42	0.1	-1.49E-05	0.030025	0.019435	-0.037675	-5.91E-06	-0.007831
63	kf_43	0.251829	-0.0001777	0.030205	-0.00731	0.65728	-0.0004724	0.017275
64	km_44	0.00391	5.67E-07	0.040132	0.01029	-0.076597	3.85E-07	0.006573
65	vm_44	1.69	0.0002209	0.024724	0.018525	-0.10296	0.0005185	0.046112
66	km_45	0.092	0.0001335	0.023942	0.026203	-0.3157	0.0003583	-0.011317
67	vm_45	1.7	-0.0001321	0.024573	-0.000698	-0.14383	-0.0003576	-0.001056
68	kf_46	6	-2.83E-08	0.026188	0.025339	-0.011709	-2.65E-08	0.024912
69	kb_46	12	-1.09E-06	0.034182	-0.00792	0.094806	-1.06E-06	0.034152
70	kf_47	3	8.64E-07	0.032132	-0.01831	-0.12595	8.31E-07	-0.007892
71	kb_47	0.3	-6.63E-07	0.035256	0.002398	0.051062	-4.80E-07	-0.023768
72	kf_48	2.0408	-3.46E-07	0.029759	-0.016615	0.042503	-2.71E-07	-0.035079
73	kb_48	4.2	-9.09E-08	0.032916	-0.022552	-0.19421	4.28E-09	0.004605
74	kf_49	3.5261	1.07E-06	0.044505	-0.015656	-0.11011	1.19E-06	0.017419
75	kf_50	0.9597	-1.04E-06	0.02279	0.017271	-0.17	-1.38E-06	-0.022626
76	kf_51	1200	-2.75E-07	0.025677	-0.014492	-0.082318	-4.32E-07	0.00539
77	kb_51	4	-1.06E-06	0.027468	-0.016605	0.099979	-1.12E-06	0.024804
78	kcat_52	1	1.07E-06	0.025539	-0.020193	0.088256	1.46E-06	0.003447
79	kf_53	12	4.86E-07	0.018353	-0.043716	-0.19348	8.77E-07	0.017494
80	kb_53	0.65	4.96E-07	0.038382	-0.006848	-0.015141	6.25E-07	0.008709
81	kcat_54	2	-3.51E-07	0.032828	-0.001809	-0.053351	-2.17E-07	-0.022539
82	kf_55	2.4	0.07698	0.055654	0.19513	4.4512	0.05042	0.19611
83	kb_55	4	-0.06144	0.038016	-0.1235	-1.8585	-0.03912	-0.13691
84	kcat_56	1	0.065816	0.057549	0.14234	5.0224	0.041205	0.14063
85	kf_57	2.7238333	8.12E-05	0.024065	0.025961	0.10239	0.0001975	0.046593
86	kb_57	1.8372	7.80E-05	0.034293	-0.016806	0.11506	-0.000103	-0.037334
87	kf_58	1	0.053132	0.051447	0.15254	3.236	0.037963	0.12557
88	kb_58	0.05	-0.049398	0.062139	-0.11943	-3.2013	-0.037943	-0.10347
89	kf_59	222	-0.047834	0.053274	-0.14956	-3.2291	-0.034439	-0.13002
90	kb_59	3.68	0.038179	0.018583	0.075944	1.5954	0.027512	0.094075
91	kcat_60	0.926	-0.058595	0.081336	-0.13187	-2.1264	-0.043824	-0.12428
92	kf_61	0.05	0.14803	0.10632	0.27137	5.1205	0.10744	0.25726
93	kb_61	1	-0.14749	0.12379	-0.26859	-5.224	-0.10744	-0.28619
94	kf_62	200	0.0002163	0.022522	0.039607	0.26265	0.0003602	0.028511
95	kb_62	0.6333	-2.98E-05	0.016266	-0.023157	-0.098571	-4.91E-05	-0.024949
96	kcat_63	4	0.0043672	0.041945	0.005476	0.22407	0.0035218	0.034216

97	kf_64	52	5.99E-05	0.035205	-0.13772	0.46904	-0.022427	-0.095513
98	kb_64	0.54	0.0003707	0.05392	0.016948	2.9354	0.0001391	0.034664
99	kcat_65	4	-0.012177	0.048138	-0.089814	-0.21082	-0.028655	-0.087768
100	kdeg_66	0.021	9.99E-07	0.015493	0.014339	-1.8644	3.46E-05	0.011219
101	kdeg_67	0.0225	-0.0012707	0.036186	-0.040255	-1.0649	0.0007081	-0.009558
102	km_68	0.05	-2.08E-05	0.030612	-0.001641	-0.84935	-7.88E-06	-0.039796
103	vm_68	0.48	-3.62E-05	0.079658	0.15369	0.91051	0.037763	0.14547
104	kf_69	0.45	0.0053411	0.02616	0.041075	0.85641	0.0073008	0.041524
105	kb_69	0.226	-4.77E-05	0.019626	-0.002027	-0.66447	-2.55E-05	-0.005121
106	kf_70	9.9	0.0004216	0.028204	-0.020798	-2.5247	0.0003151	0.012773
107	kb_70	0.005	-1.98E-05	0.025571	0.015899	0.002089	-1.50E-05	-0.001149
108	kf_71	0.25	-0.14	0.10863	-0.32322	-5.8548	-0.10986	-0.29429
109	kf_72	0.08	0.0028244	0.021912	0.10295	1.2201	0.0018739	0.075113
110	kb_72	0.033	-0.0003935	0.025749	-0.024727	-0.18577	-0.0002644	-0.01064
111	kcat_73	0.2	0.0006747	0.022361	0.024372	0.20819	0.0004459	0.015187
112	kf_74	1.5	0.0009799	0.041967	0.036463	0.60787	0.0005658	0.032853
113	kb_74	16	-0.0007819	0.035285	-0.035968	-0.54095	-0.0004509	-0.047424
114	kcat_75	4	0.0008363	0.021386	0.03545	0.50757	0.0004889	0.011793
115	kf_76	1.3125	0.0005004	0.035109	0.007812	0.002375	0.0003893	0.032591
116	kb_76	100	-0.0003974	0.03284	-0.015232	-0.033417	-0.0003089	-0.011406
117	kcat_77	25	0.0003973	0.027027	0.041519	-0.020758	0.0003086	-0.015362
118	kf_78	0.1	-0.0009602	0.022207	-0.046823	-0.65068	-0.0006039	-0.014172
119	kf_79	0.1	-0.0004911	0.020128	-0.008305	-0.047855	-0.0003859	-0.024297
120	kf_80	0.25	-0.021578	0.044368	-0.033144	-1.6908	-0.019764	-0.056078
121	kb_80	3.92	0.017749	0.02268	0.041171	0.57301	0.017055	0.036675
122	kcat_81	0.98	-0.013544	0.022676	-0.046715	-0.4124	-0.0086007	-0.033779
123	kf_82	0.041	0.015469	0.055815	0.036387	0.56708	0.012956	0.03533
124	kf_83	2.1666	-0.0007684	0.026479	-0.020361	-0.15637	-0.0005845	0.012846
125	kb_83	1	7.00E-05	0.035623	0.01034	-0.022543	5.36E-05	0.019967
126	kcat_84	10	-6.82E-05	0.024599	0.005106	-0.005144	-5.17E-05	-0.000325
127	kf_85	100	0.15104	0.14929	0.34641	6.2859	0.11765	0.34396
128	kb_85	2	-0.039331	0.072863	-0.20153	-2.3882	-0.028121	-0.1836
129	kf_86	8	0.054611	0.086794	0.25403	3.0138	0.059179	0.24523
130	kb_86	0.0444	-0.0005707	0.017318	0.015633	-0.096379	-0.0004265	0.005264
131	kcat_87	4	0.018453	0.028314	0.032361	0.45454	0.013748	0.048793
132	kf_88	2.5	-6.52E-07	0.032188	-0.008738	-0.045535	-6.16E-07	0.014791
133	kb_88	4	-4.37E-07	0.022101	0.010248	-0.034037	-4.67E-07	0.002758
134	kcat_89	1	-6.39E-07	0.039788	0.006098	-0.017179	-7.01E-07	-0.008887
135	kf_90	12.85	1.03E-06	0.017699	-0.006845	-0.021427	1.10E-06	0.000575
136	kb_90	9	-2.33E-07	0.020025	0.004295	0.004025	-2.76E-07	0.021784
137	kcat_91	3	1.60E-07	0.016383	-0.015047	0.015938	2.37E-07	0.008545
138	kf_92	0.89	2.19E-07	0.015495	0.000735	-0.007061	1.87E-07	-0.000853
139	kb_92	2	-5.00E-07	0.037111	-0.031196	-0.021649	-5.17E-07	-0.004097
140	kcat_93	0.5	5.27E-07	0.035656	-0.001258	-0.00013	5.93E-07	0.001915
141	kf_94	9.88	6.66E-05	0.032244	0.007923	0.012932	7.07E-05	-0.011314
142	kb_94	13.6	-5.29E-05	0.0365	0.020626	0.008166	-5.60E-05	-0.00828
143	kcat_95	3.4	6.76E-05	0.050459	-0.001447	0.008902	7.17E-05	0.015508
144	kf_96	2.2	-0.0008775	0.032992	-0.02977	-0.12794	-0.0006155	0.002574
145	kb_96	16	0.0007029	0.025427	0.022487	0.049094	0.0004938	0.028364
146	kcat_97	4	-0.000907	0.054111	0.003045	-0.061078	-0.0007085	0.014067

147	kf_98	90	0.0001316	0.03684	0.015983	-0.1287	0.0003559	0.014273
148	kb_98	0.00034	3.22E-06	0.042822	-0.00107	-0.071937	1.95E-06	0.004626
149	kf_99	10	-0.0086418	0.036119	0.13652	1.5703	-0.0019416	0.13414
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151	kcat_100	4	-0.0020475	0.047205	0.12754	1.3759	0.03828	0.098158
152	kf_101	3	-0.2553	0.21149	-0.48536	-8.2838	-0.1968	-0.45958
153	kb_101	4	0.12761	0.12365	0.21967	4.2975	0.098391	0.25047
154	kcat_102	4	-0.12192	0.080181	-0.22685	-4.2892	-0.093643	-0.22694
155	kf_103	6.8	0.078856	0.10069	0.26756	4.0473	0.044245	0.26303
156	kb_103	9.62	-0.063085	0.061531	-0.2007	-3.2638	-0.035399	-0.18786
157	kcat_104	2.405	0.063937	0.059647	0.19725	3.2865	0.035856	0.20891
158	kf_105	6.8	0.21811	0.18623	0.32331	4.805	0.18673	0.30276
159	kb_105	9.62	-0.17448	0.093219	-0.23512	-3.8752	-0.14939	-0.24828
160	kcat_106	2.405	0.17634	0.099473	0.22414	3.8703	0.15091	0.21605
161	kf_107	2	0.0021496	0.039536	-0.03877	3.6096	0.0025233	-0.043165
162	kb_107	8	-0.0016139	0.028508	0.024229	1.2526	-0.0018933	0.032473
163	kcat_108	2.667	0.0019568	0.043663	0.003555	3.9474	0.0022629	-0.006336
164	kf_109	0.333	-0.0026265	0.029098	0.01183	1.4589	-0.0028891	0.044563
165	kf_110	1	0.062408	0.033284	-0.042162	-1.3307	0.067634	-0.079887
166	kb_110	4.64	-0.049928	0.065053	0.063645	0.89923	-0.05411	0.064858
167	kcat_111	1.16	0.050177	0.026022	-0.004921	-0.94637	0.054468	-0.04071
168	kf_112	15	-0.063441	0.030185	0.051785	1.399	-0.068057	0.058377
169	kb_112	16	0.050754	0.026687	-0.015219	-0.95654	0.054448	-0.023047
170	kcat_113	4	-0.050761	0.031932	0.032452	0.92415	-0.054426	0.0418
171	kf_114	1.31	-0.057912	0.03069	-0.10188	-0.97887	-0.057628	-0.10585
172	kb_114	4	0.046323	0.020824	0.045055	0.79882	0.046102	0.081665
173	kcat_115	1	-0.047126	0.054008	-0.05087	-0.79978	-0.046982	-0.059496
174	kf_116	1.31	-0.014877	0.049138	0.085984	1.254	-0.012781	0.092898
175	kb_116	4	0.0119	0.051496	-0.13872	-2.6973	0.010226	-0.15639
176	kcat_117	1	-0.012098	0.046098	-0.072029	-1.4551	-0.010467	-0.08579
177	kf_118	26	-0.12597	0.069778	-0.080323	-2.4753	-0.12682	-0.11419
178	kb_118	64	0.10078	0.057211	0.090769	1.0251	0.10146	0.06711
179	kcat_119	16	-0.10037	0.039735	-0.039069	-1.0278	-0.10101	-0.076161
180	kf_120	26	-0.032142	0.051729	-0.043952	-0.80772	-0.028273	-0.043773
181	kb_120	64	0.025715	0.051274	0.076375	0.51923	0.022621	0.064438
182	kcat_21	16	-0.02564	0.026429	-0.062547	-0.53967	-0.022499	-0.036538
183	kf_122	1.6	0.25499	0.067188	0.17925	2.1096	0.23681	0.18892
184	kb_122	1	-0.20391	0.062512	-0.1526	-1.4375	-0.18915	-0.13563
185	kcat_123	0.25	0.34169	0.12394	0.24024	2.6227	0.30825	0.22344
186	kf_124	1.6	0.47591	0.12742	0.23206	2.8028	0.47353	0.23443
187	kb_124	1	-0.38052	0.089974	-0.17524	-2.0164	-0.37883	-0.18166
188	kcat_125	0.25	0.52203	0.084564	0.21452	2.3409	0.51628	0.23496
189	kf_126	0.0004	-0.040485	0.023763	-0.015287	-0.14211	-0.02953	0.0028
190	kb_126	0.0001	0.025925	0.025376	-0.008165	0.13985	0.021294	-0.002535
191	kf_127	0.0004	0.0029471	0.032651	-0.030991	-0.26754	0.001977	-0.03936
192	kb_127	0.0001	-0.0015666	0.021198	0.011765	0.2083	-0.0010701	-0.009857
193	kf_128	3.7E-16	-3.64E-07	0.026663	0.009355	0.000281	-9.79E-07	-0.011734
194	kf_129	3.7E-16	9.91E-07	0.024019	0.037735	0.007475	1.60E-06	-0.002693
195	kf_130	0.30101	-0.24219	0.047866	-0.061908	-0.15167	-0.24239	-0.027405
196	kb_130	4.44	0.16201	0.038562	0.015221	0.074303	0.16317	0.039771

197	kcat_131	2.2	-0.16438	0.040929	-0.009838	-0.10902	-0.16571	-0.001381
198	kb_132	108	-0.18802	0.019547	0.002995	-0.063173	-0.19406	-0.010001
199	kf_132	141	0.2349	0.064807	0.020359	0.065316	0.2409	0.00806
200	kcat_133	27	0.18783	0.017308	0.003829	0.055951	0.19385	-0.01054
201	kf_134	76	-0.056728	0.05477	-0.12398	-1.7391	-0.03585	-0.14203
202	kb_134	4	0.042128	0.045962	0.06242	1.0312	0.036957	0.088384
203	kcat_135	1	-0.18257	0.068503	-0.12992	-1.1808	-0.18475	-0.11008
204	kf_136	76	0.0093235	0.065293	-0.10452	-1.4809	0.014826	-0.12148
205	kb_136	4	-0.0078524	0.036169	0.048345	0.92584	-0.013102	0.074341
206	kcat_137	1	-0.12558	0.081798	-0.16248	-1.7516	-0.11475	-0.13575
207	kf_138	1	-0.028952	0.024999	-0.028736	-0.26968	-0.030471	-0.01908
208	kb_138	0.25	0.0007829	0.028174	-0.003334	0.022071	0.0008242	0.003598
209	kcat_139	9	-0.0003553	0.033091	0.019657	-0.031332	-0.0003706	-0.01421
210	kf_140	1	-0.017745	0.034019	0.004311	-0.18293	-0.017809	-0.020977
211	kb_140	0.25	0.0004805	0.032864	0.005518	0.020795	0.0004823	0.024813
212	kcat_141	9	-0.0001453	0.024353	0.005501	-0.027268	-0.000112	-0.025162
213	kf_142	1E-18	-4.94E-07	0.032231	-0.002124	5.14E-05	-9.96E-07	-0.013479
214	kf_143	1E-18	5.96E-07	0.01968	0.010253	3.76E-05	7.72E-07	-0.004105
215	kf_144	0.05	-0.0003103	0.03454	-0.007417	-0.004521	-0.0003188	-0.003547
216	kb_144	2	0.0002476	0.05905	0.013745	-0.00257	0.0002546	0.000987
217	kcat_145	0.5	-1.96E-05	0.014695	-0.015155	-0.001342	-2.24E-05	0.006646
218	kf_146	2.25	-7.39E-07	0.021195	0.017944	-0.004493	-1.12E-06	0.015346
219	kb_147	8	-5.38E-07	0.031041	-0.026296	0.003111	-7.64E-07	-0.017512
220	kcat_147	4	-1.01E-06	0.03223	-0.020934	0.017224	-1.25E-06	0.02603
221	kf_148	1	0.071143	0.06721	0.097229	1.3666	0.054611	0.074144
222	kf_149	10	0.0087566	0.031247	0.042901	-2.7834	0.033819	0.029415
223	kb_149	2	0.0001602	0.027101	-0.023166	4.2148	0.0040527	-0.003116
224	kf_150	83	-0.0076438	0.039382	-0.018221	-1.8154	-0.0051789	-0.068616
225	kb_150	2.77	0.0055624	0.02646	0.014122	-0.025927	0.0037624	0.010615
226	kcat_151	1	-0.012049	0.026939	-0.052775	-0.6675	-0.0069036	-0.042839
227	kf_152	240	-8.74E-05	0.04559	-0.035453	-0.085032	-7.94E-05	0.007312
228	kb_152	2	5.30E-05	0.036223	0.003056	0.10991	4.58E-05	-0.015085
229	kcat_153	1	-0.0001501	0.027691	0.008836	-0.13196	-0.000112	-0.00505
230	km_154	0.050505	-0.095301	0.088828	-0.15972	-3.1803	-0.070553	-0.18217
231	vm_154	22	0.14926	0.095559	0.28961	5.1958	0.10841	0.27124
232	kf_155	450	-0.3104	0.038073	-0.016525	-0.3368	-0.32582	-0.055213
233	kb_155	600	0.24832	0.030035	0.007364	0.28074	0.26066	0.036606
234	kcat_156	150	-0.27853	0.038234	-0.041638	-0.54174	-0.2936	-0.026566
235	kf_157	450	-0.17439	0.042172	-0.029091	-0.15417	-0.18474	-0.053286
236	kb_157	600	0.13698	0.06439	0.002892	0.083899	0.14117	0.011061
237	kcat_158	150	-0.16366	0.059964	-0.011933	-0.12975	-0.16943	-0.027302
238	kf_159	30	-0.022771	0.054777	-0.018287	-0.17335	-0.022393	-0.012408
239	kb_159	600	0.018217	0.021846	0.014659	0.087858	0.017914	0.019659
240	kcat_160	150	-0.020286	0.034752	-0.017772	-0.10099	-0.020149	-0.001282
241	kf_161	30	-0.01397	0.044675	-0.023573	-0.30043	-0.012455	-0.008766
242	kb_161	600	0.011176	0.039508	-0.019148	0.16825	0.0099646	0.033562
243	kcat_162	150	-0.013037	0.041481	-0.050465	-0.18246	-0.011878	-0.041631
244	kf_163	4	1.85E-05	0.049181	0.005915	-0.03711	-4.10E-06	-0.033687
245	kb_163	0.000335	1.11E-06	0.027863	-0.00643	0.000649	1.51E-06	0.010104
246	kcat_164	1	1.44E-05	0.022503	-0.002145	0.046297	-3.48E-06	-0.011357

247	kf_165	0.0001	-0.0001266	0.026548	-0.027298	-0.000841		-1.21E-05	0.012773
248	kb_165	0.0002	7.34E-06	0.036503	0.000348	0.000227		-1.95E-07	-0.021797
249	kf_166	1E-25	0	0.042537	0.013313	4.16E-08		0	0.015404
250	trnsc_167	0.0000002	-0.000147	0.020536	-0.016945	-0.0008		-1.35E-05	-0.002638
251	trnsc_168	0.000002	1.70E-05	0.018311	0.011652	-0.000427		1.65E-06	-0.000576
252	kf_169	0.1	-0.012238	0.075928	-0.17592	-1.5572		-0.053753	-0.14442
253	kf_170	0.0034	-0.002106	0.030705	-0.003451	0.010117		-0.0008033	-0.013916
254	kb_170	1	0.0016835	0.023235	-0.006721	-0.003458		0.0006412	0.000314
255	kcat_171	0.25	-0.0016744	0.031815	-0.002969	0.003487		-0.0006317	0.019583
256	kf_172	1.5E-15	0	0.03509	-0.001996	0		0	0.006265

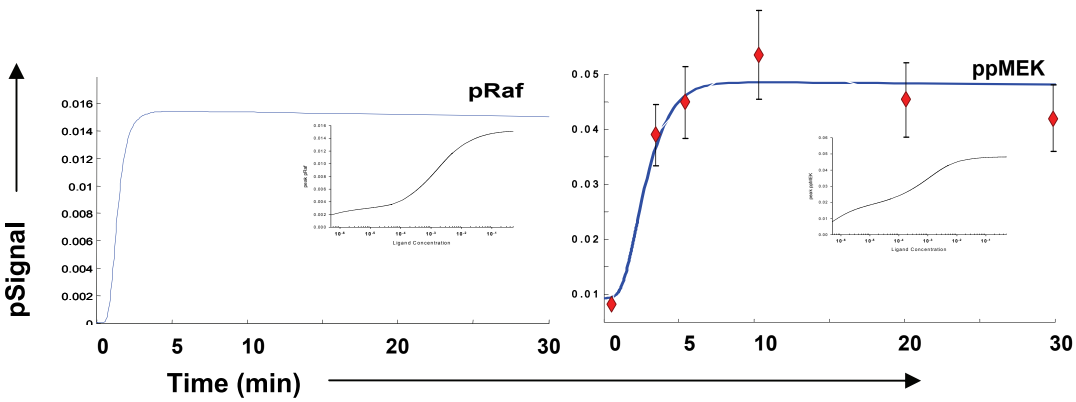


Figure S2. Shown here is a simulation of the time course of phosphorylation Raf (pRaf) and MEK (ppMEK) in cells stimulated with a saturating concentration of ligand. The inset in each panel gives the peak level of phosphorylation obtained over a wide range of ligand concentrations. These profiles are consistent with the the experimental results derived in our earlier studies(Kumar et. al., 2007, 2008) The concordance between the experimental (red diamonds, values are mean + S.D. of three experiments) and the simulated profiles is shown for ppMEK.

Supplementary Data S3

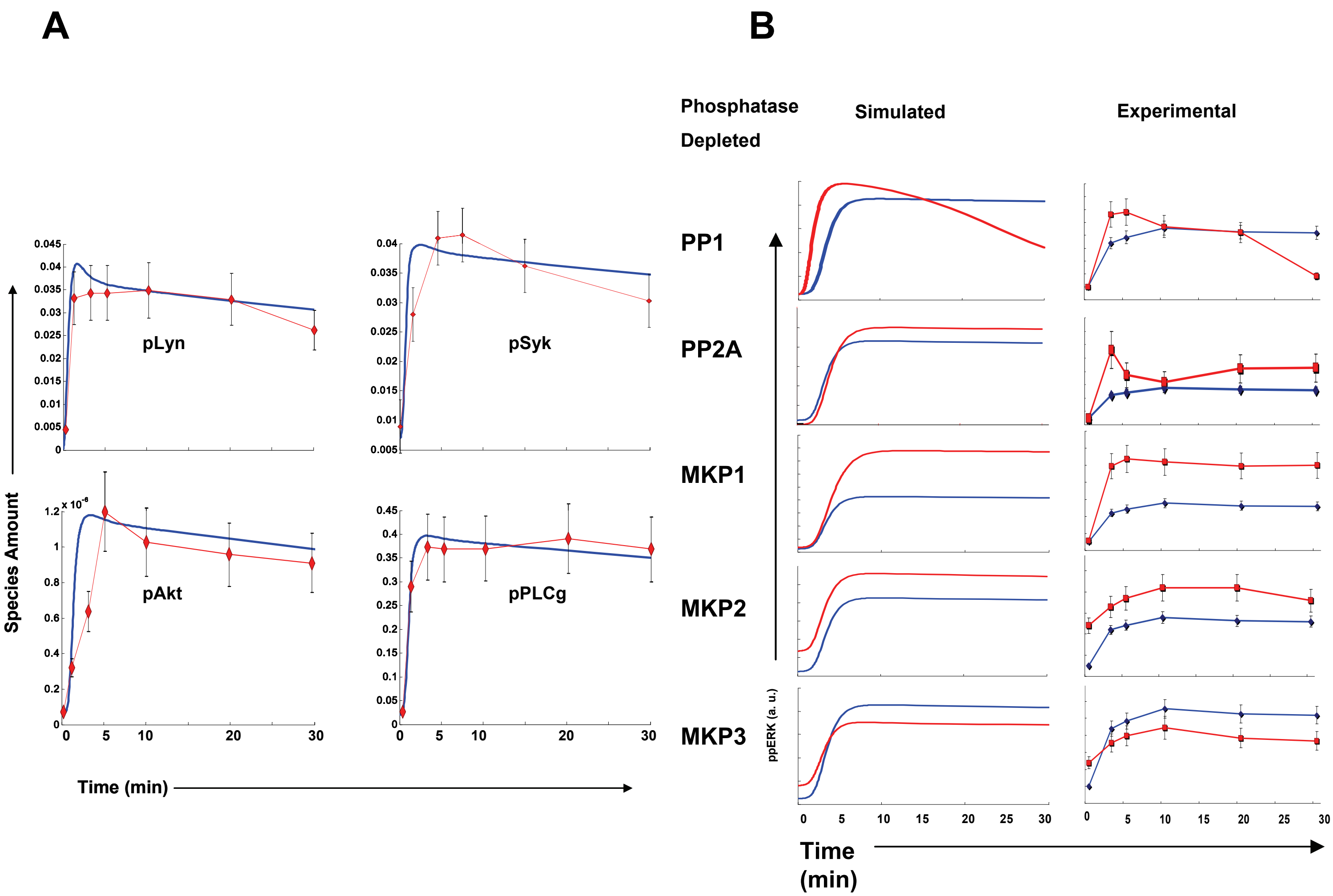
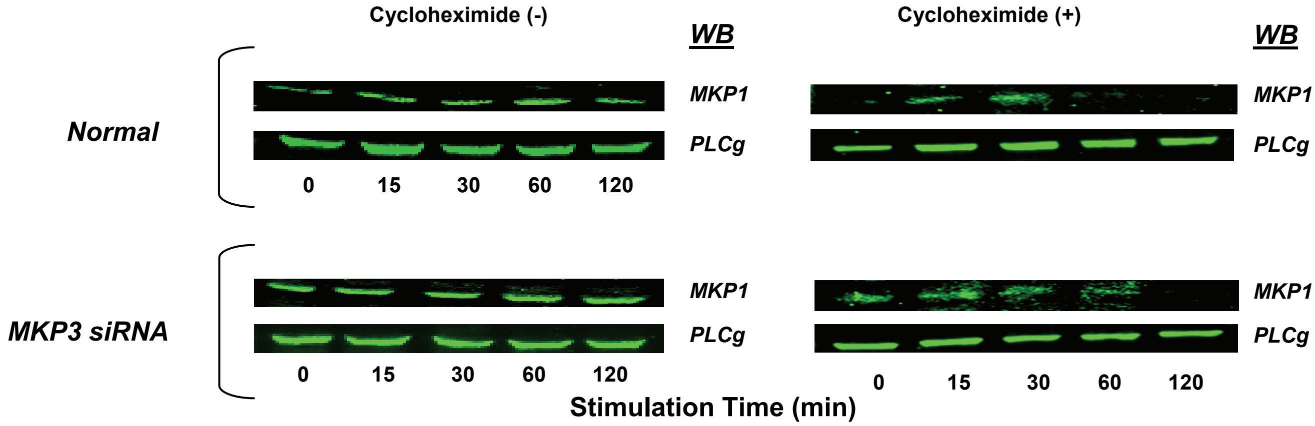


Figure S3. Panel A shows simulation of the time course of phosphorylation of the indicated molecules in cells stimulated with a saturating concentration of the ligand. For the purposes of comparison, the experimentally derived values at the various time points are also included (red diamonds, values mean ± S.D. of three experiments). These values are from our earlier study (Kumar et. al., 2007, 2008). For the *in silico* profiles simulations were first run for 3000 seconds to achieve the steady baseline levels of phosphorylations prior to stimulation. This explains the baseline levels of phospho-species seen in these profiles. Panel B compares the experimentally derived (Experimental) and *in silico* (Simulated) profiles of ERK phosphorylation following depletion of cells with the indicated phosphatases. The values for the experimental group were taken from Kumar et. al. (2008). In all cases the X-axes start from zero although the units are arbitrary. In all the panels the profiles obtained in mock (i.e. GFP-siRNA) treated cells are shown in blue whereas those for phosphatase-specific siRNA treated cells are in red. For the *in silico* profiles simulations were first run for 3000 seconds to achieve the steady baseline levels of ERK phosphorylations prior to stimulation. This explains the minor lag period seen in these profiles.

Supplementary Data S4

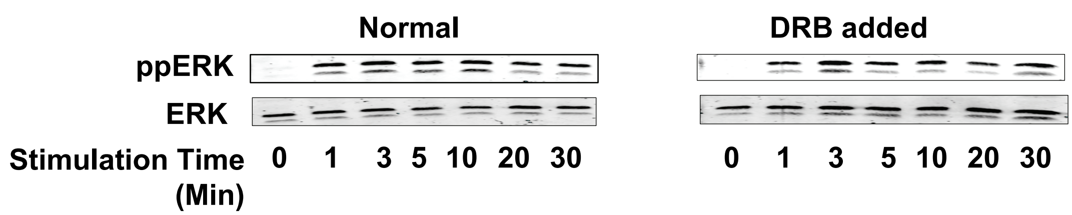
A

Effect of MKP3 knock down by siRNA on MKP1 expression level



B

Activation profiles in the presence of DRB(CK2 inhibitor)



C

Graded ERK response for various concentrations of Ligand (Fab2)

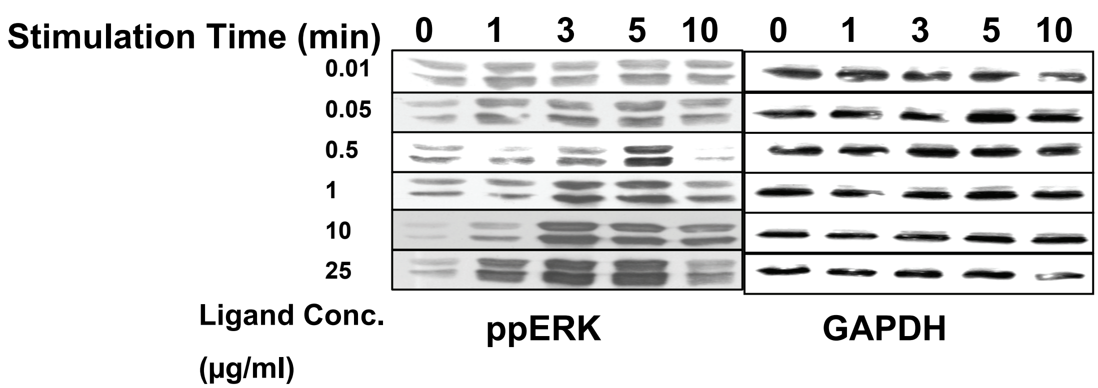


Figure S4. Panel A shows the Western blot profile of MEK in A20 cells treated either with non-silencing (GFP) siRNA (labeled Normal), or with MKP3-specific siRNA, and in the presence and absence of cycloheximide an inhibitor of protein synthesis. In both cases the cells were stimulated with the $F(ab)_2$ fragment of anti-mouse IgG for the indicated times. For quantification band intensities were normalized against that obtained for PLCg, which was used as loading control. As is evident here, MKP1 protein levels are normally defined through the balance between de novo synthesis and protein turnover. However these results also reveal that MKP3-silencing primarily affects through inducing a reduction in the rate of degradation of the MKP1 protein. **Panel B** shows the stimulation time-dependent phosphorylation profiles of ERK (ppERK) in either treated cells, or in cells pre-treated with DRB. GAPDH (Ctrl) served as the loading control for band intensity normalization in these experiments. Shown in **Panel C** are the time dependent phosphorylation profiles of ERK (ppERK) at the indicated concentrations of ligand. Here again, GAPDH was used for the loading control and for normalization of band intensities.

D

MKP3 Expression Following BCR activation

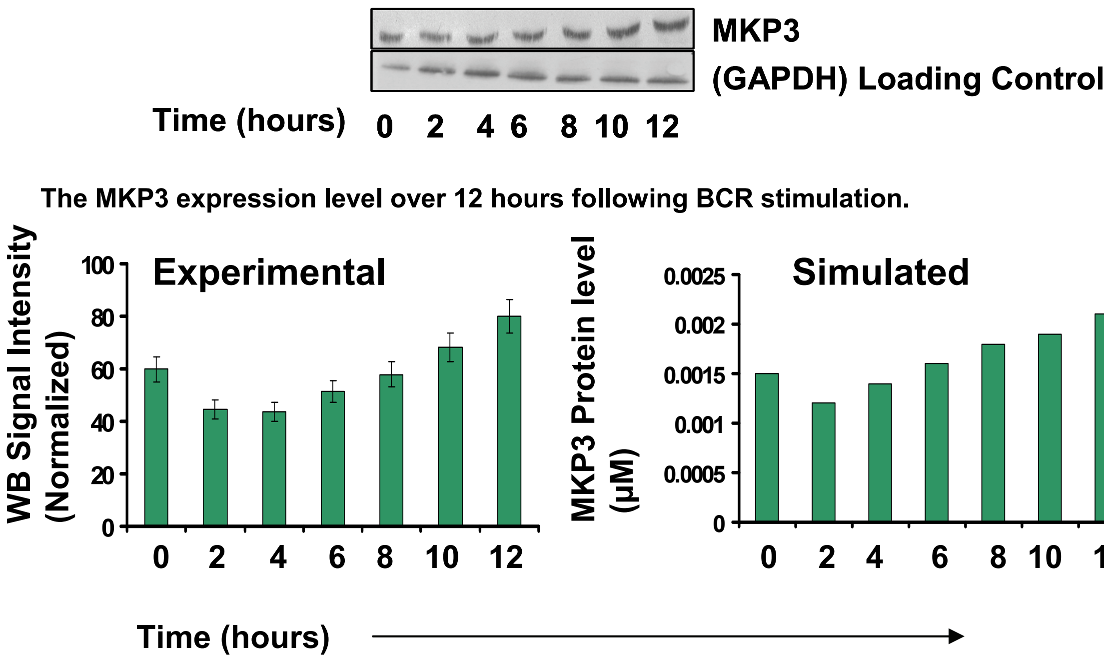


Figure S4. Panel D shows MKP3 expression level over 12 hours following BCR stimulation in A20 cells. The MKP3 expression level rises due to transcriptional up regulation by an ERK activation dependent mechanism. The model also accounts for the ERK mediated MKP3 degradation, which explains the transient decrease in MKP3 levels in response to BCR activation. Simulated versus experimental (normalized) profiles shows good agreement and thus validate the model's ability to recapitulate MKP levels in stimulus dependent manner.

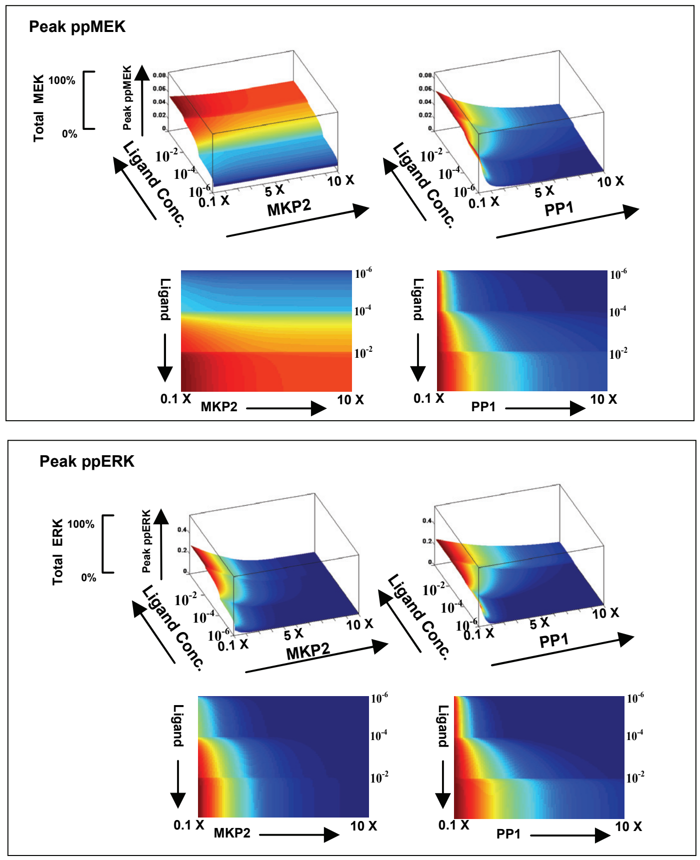


Figure S5. The peak phosphorylation of MEK (ppMEK, top subpanel) and ERK (ppERK, bottom subpanel) was determined in response to variations in concentrations of both ligand and either PP1 or MKP2. The remaining details are identical to that described for Figure 5 in the main text.

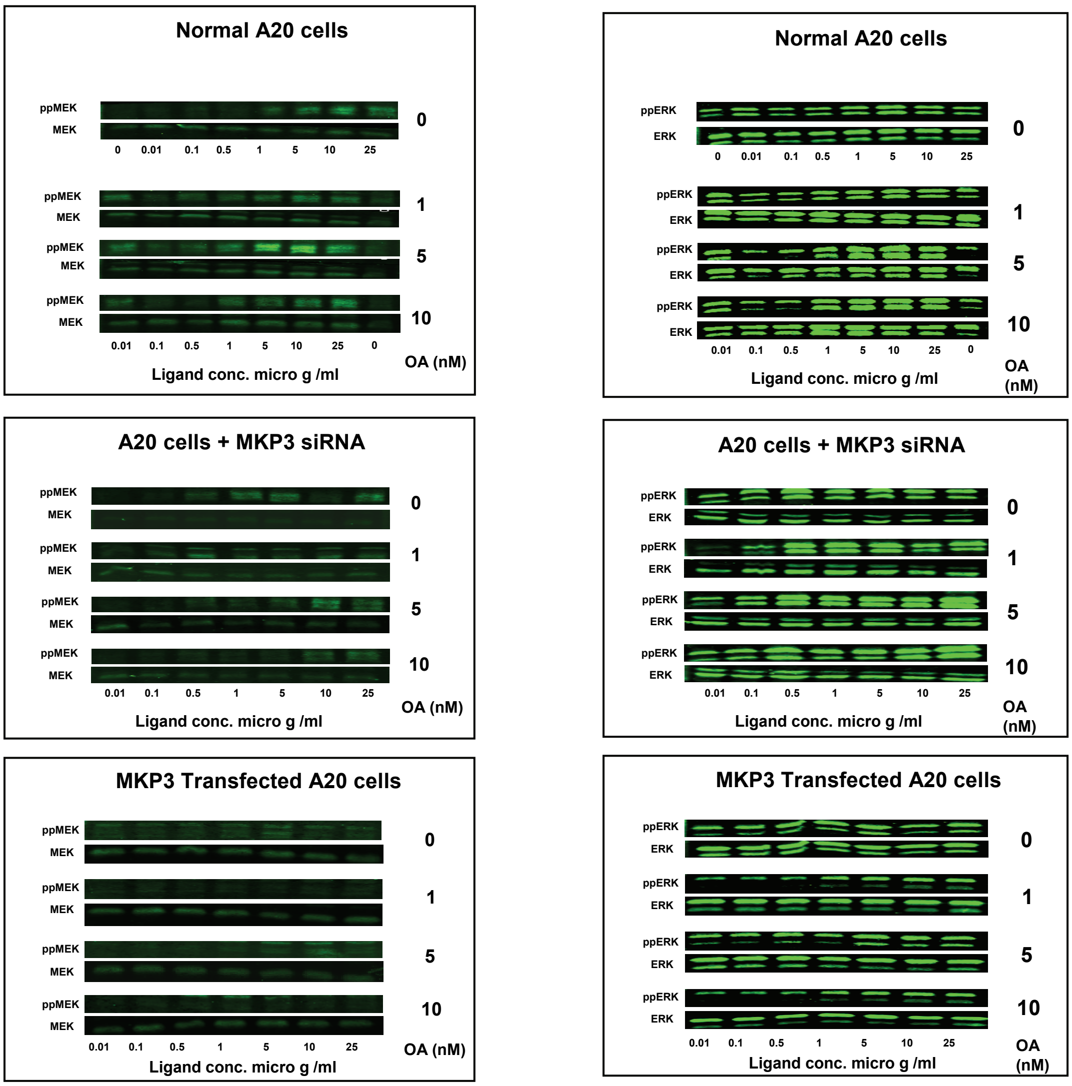
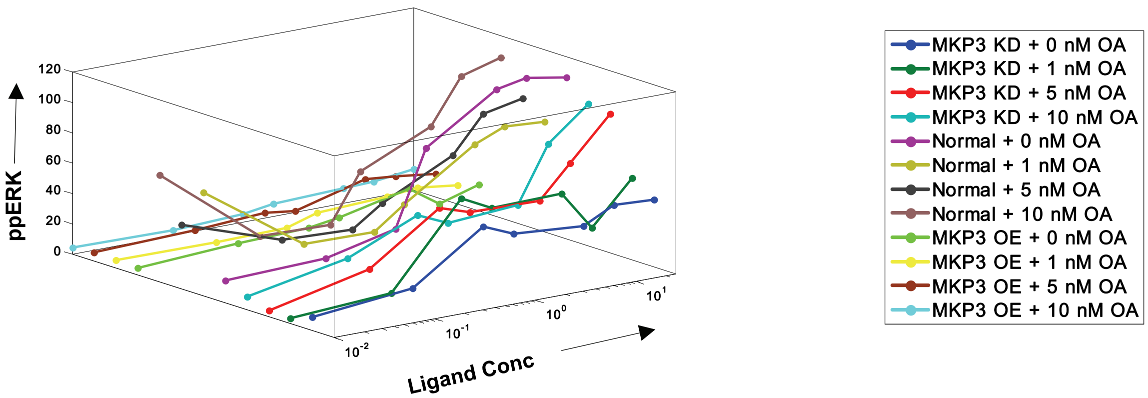
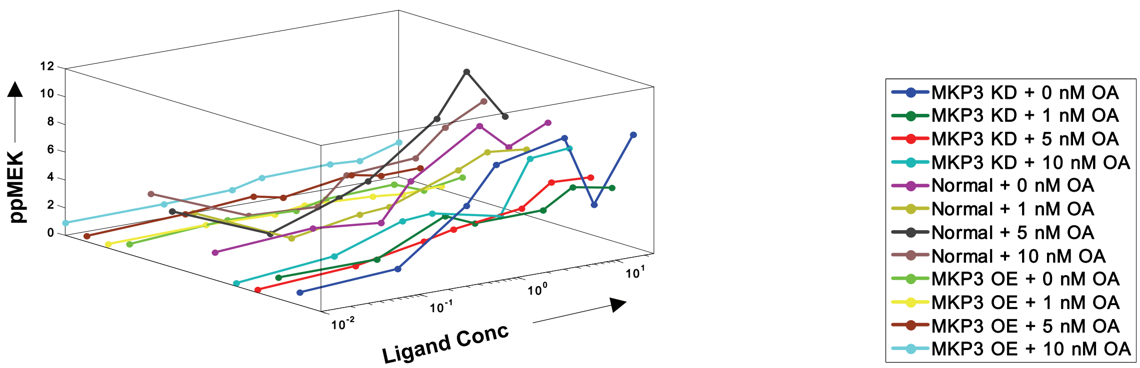


Figure S6:Ligand dose response of MEK and ERK phosphorylation to variations in levels of phosphatase activity. Shown here are the Western blot profiles for both the MEK and ERK protein, and its phosphorylated form in either normalA20 cells, in cells treated with MKP3 specific siRNA, or in cells transfected with an MKP3 bearing plasmid (see Experimental Procedures). For each group and condition, cells were stimulated with the indicated concentration of ligand, and the level of phosphorylation monitored 10 min later. The relatively lower intensities of the MEK blots are due to the fact that the concentration of this protein is about 6-fold lower than that of ERK in these cells (Supplementary Data S1)

Supplementary Data S7





FigureS7: Modulation of dose response by varying phosphatase concentrations: Western Blots in Figure S-6 were normalized and quantified using our toolbox (Gel-norm) as described earlier (Kumar et. al., 2007). The plots of these values are shown here.

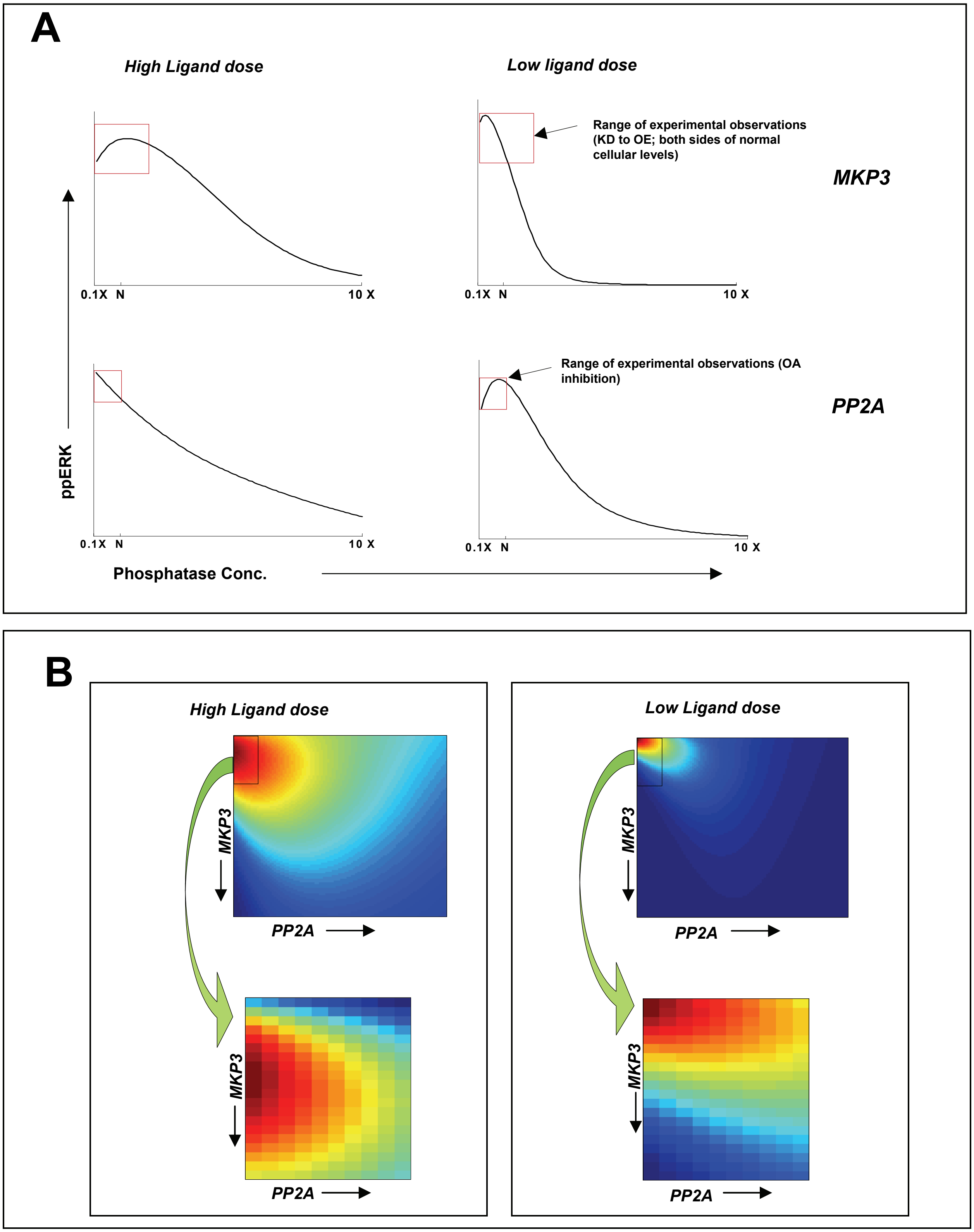


Figure S8. Panel A of this figure gives the simulated profile of peak phospho-ERK (ppERK) levels under conditions where concentrations of either MKP3 or PP2A ranged from 10-fold lower, to 10-fold higher than their respective levels in A20 cells. ERK phosphorylation responses at both high and low ligand doses are shown here. In each profile the boxed region indicates the concentration (for MKP3), or activity (for PP2A) range that was taken for the experiments described in Figure 8A of the main manuscript. Similarly MEK profile for prediction were also obtained.

Panel B shows the results of a simulation experiment where peak phospho-ERK responses were monitored under conditions where the concentrations/activities of both phosphatases were derived from the same range as described for Panel A. Here again, results obtained at high and low ligand doses are shown. The top part of this panel gives the results obtained over all the combinations of PP2A and MKP3 concentrations tested, and the boxed region identifies the range represented by the experiments in Figure 8B of the main manuscript. The lower part of this panel shows a magnification of this boxed region.

Supplementary Data S-9

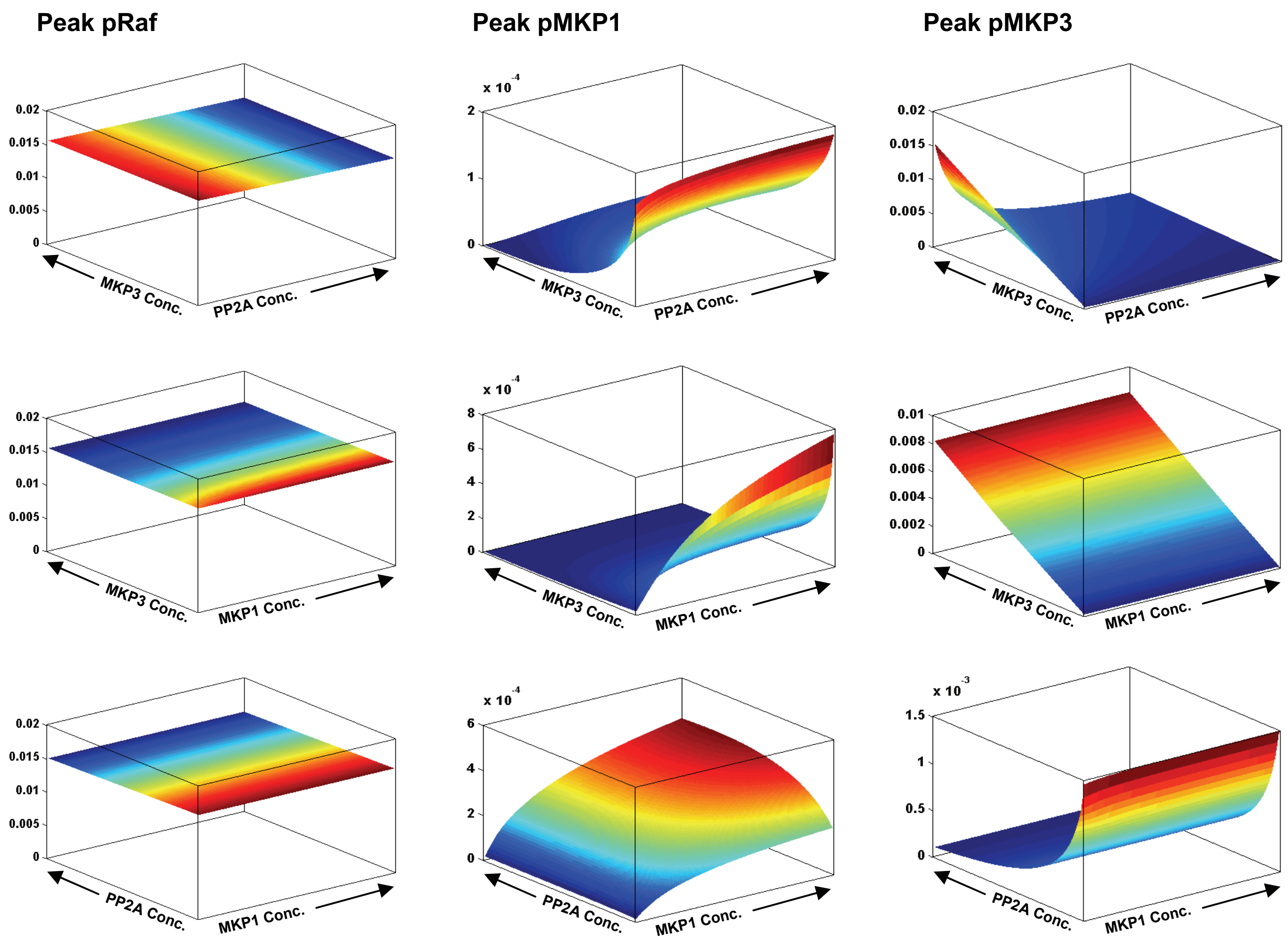
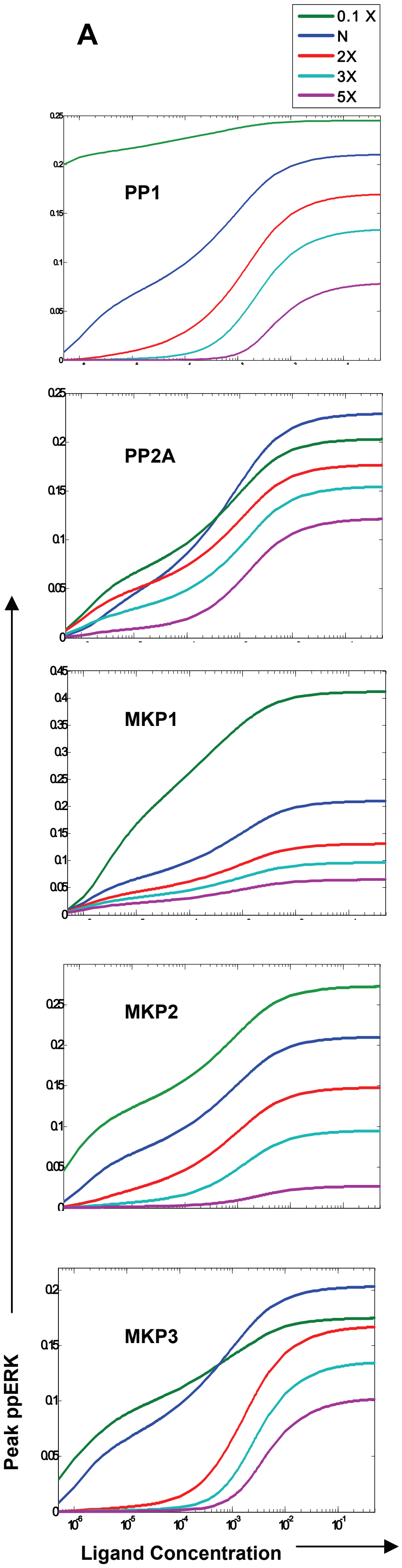


Figure S 9 : This Figure represents a part of the experiment performed in Figure 6 of the main manuscript. Shown here are the effect of variation in concentrations of the indicated phosphatase pairs on peak phosphorylation levels of Raf (pRaf), MKP1 (pMKP1), and MKP3(pMKP3). It is notable that, as per our expectations from the model in Figure 1A, the amplitude of Raf phosphorylation is only weakly sensitive to changes in concentration of PP2A. According to our model, the effect of altered PP2A levels is buffered by the excess of available PP1.(In all cases arrows showing minimum to maximum conc. of the corresponding enzymes)

Supplementary Data S-10



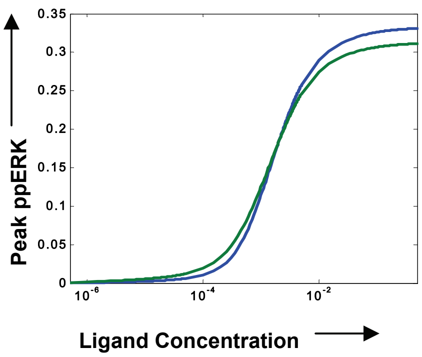


Figure S10. Panel A of this figure shows the effect of varying phosphatase concentrations on the ligand dose sensitivity of ERK phosphorylation. Here ERK phosphorylation was measured at 30 minutes of stimulation. Both the ligand dose employed and the phosphatase concentrations tested, are indicated. A marked effect of phosphatase concentration on the dose response profile is clearly evident in all the cases. However only an increase in either PP1 or MKP3 levels led to sharp increase in the slope for ERK activation. Contrary to the findings for another cell line (Bhalla et. al., 2002), modulation of MKP1 concentrations did not yield an ultrasensitive response. This is probably because of the absence of the previously described feedback loop since cPLA2 is not expressed in mature lymphocytes. Finally, no trend towards ultrasensitivity could be detected upon varying the concentrations of the MAPK pathway constituents Raf, MEK, ERK.
Panel B shows the dose response profile for ERK phosphorylation obtained following a 3- fold increase in the concentration of either PP1 (blue line) or MKP3 (Green line) under conditions where the MKP1 levels was reduced by tenfold relative to the experimentally determined values in A20 cells. Thus the shape of the ERK output response to BCR stimulation clearly reflects a combinatorial outcome of the relative concentrations of the individual MAPK pathway-associated phosphatases