Section I: Discussion of reaction rate constants and initial concentrations used in our simulations

The reaction rate constants used in our simulations are identical to those used by Schoeberl et al. with the following exceptions: i) k_6 (EGF receptor internalization rate) was set to $5 \cdot 10^{-4}$/s and k_{-23} (Shc phosphorylation rate) was 0.06/s, in order to remain consistent with published data on internalization and other reaction rate data (Starbuck and Lauffenburger 1992; Kholodenko, Demin et al. 1999); ii) k_{30} was set to equal k_{20} and k_{38} was set to equal k_{24} since these are similar reactions. These reactions account for Ras-GTP and Grb2 binding to receptor complex. Errors in rate equations v_{44}, v_{46}, v_{52} and v_{54} (reactions in module D) were corrected in the downloaded "rates.dat" file in order to remain consistent with nomenclature in Eq. 1 of main manuscript. Initial concentrations of reactants (given in Supplemental Table II of (Schoeberl, Eichler-Jonsson et al. 2002)) were changed to those reported by (Kholodenko, Demin et al. 1999): Grb_{total}=85nM, Shc_{total}=150nM, SOS_{total}= 34nM. We also used an initial Ras-GDP value of 68nM, since it closely matches values provided elsewhere for mammalian cells (Ferrell 1998). The complete list of reaction rate constants and initial concentrations is provided with Supplemental Material (Table S1). These changes allowed us to fit the experimental trends of (Schoeberl, Eichler-Jonsson et al. 2002) reasonably well, though exact fits were not possible.

Section II: Detailed derivation for sensitivity coefficient

Sensitivity coefficients are derived for forward and reverse rate constants independently. For forward rates:

$$Z_{ij}^{f} \equiv \partial C_i / \partial k_j^{f} \tag{S1}$$

The partial derivative in Eq. S1 is taken with all other forward and reverse rate constants held constant. Differentiating the above equation with respect to time and substituting $\partial C_i / \partial t = f_i$ (from Eq. 2, main manuscript), we obtain:

$$\frac{dZ_{ij}^{f}}{dt} = \frac{\partial f_i}{\partial k_j^{f}} + \sum_{l=1}^{m} \frac{\partial f_i}{\partial C_l} \frac{\partial C_l}{\partial k_j^{f}} \tag{S2}$$

The last partial derivative on the right side is, by definition, Z_{lj}^{f}. Rewriting Eq. S2 in matrix format and substituting $\boldsymbol{f} = \boldsymbol{\alpha}^{\mathrm{T}}\boldsymbol{v}$, we have:

$$\frac{d\,\boldsymbol{Z}^{f}}{dt} = \boldsymbol{\alpha}^{T}\left(\frac{\partial \boldsymbol{v}}{\partial \boldsymbol{k}^{f}} + \frac{\partial \boldsymbol{v}}{\partial \boldsymbol{C}} \cdot \boldsymbol{Z}^{f} \right) \tag{S3}$$

Here, $\partial \boldsymbol{v} / \partial \boldsymbol{k}^{f}$ and $\partial \boldsymbol{v} / \partial \boldsymbol{C}$ are $n \times n$ and $n \times m$ Jacobian matrices in which the i,j element contains the partial derivative of v_i with respect to k_j^{f} and C_j, respectively. Upon differentiating the rate expression (Eq. 1, main manuscript) with respect to k_j^{f} and C_j, it follows that:

$$\frac{\partial v_i}{\partial k_j^{f}} = \begin{cases} \prod_{l=1}^{m} C_l^{\mu_{il}^{f}} = \dfrac{r_i^{f}}{k_j^{f}} & \mathrm{i} = \mathrm{j} \\ 0 & \mathrm{i} \neq \mathrm{j} \end{cases} \tag{S4}$$

$$\frac{\partial v_i}{\partial C_j} = \frac{\mu_{ij}^{f} k_i^{f} \prod_{l=1}^{n} C_l^{\mu_{il}^{f}} - \mu_{ij}^{r} k_i^{r} \prod_{l=1}^{n} C_l^{\mu_{il}^{r}}}{C_j} = \frac{\mu_{ij}^{f} r_i^{f} - \mu_{ij}^{r} r_i^{r}}{C_j} \tag{S5}$$

Combining Eq. S3, S4 and S5 and writing the result in matrix format we get Eq. 3a in the main manuscript.

Section III: Details of Principal Component Analysis (PCA)

For PCA, we are interested in studying the effect of variation in reaction rate constant on biological mechanism using the response function, Q:

$$Q(\boldsymbol{k}) = \sum_{h=1}^{q}\sum_{g=1}^{p}\sum_{i=1}^{m}\left[\frac{C_i(t_h, EGF_g, \boldsymbol{k}) - C_i(t_h, EGF_g, \boldsymbol{k^0})}{C_i(t_h, EGF_g, \boldsymbol{k^0})}\right]^2 \quad \text{(S6)}$$

Here, t_h is the h^{th} time point, q is the total number of time points, and EGF_g denotes one of the p EGF dosages considered. $\boldsymbol{k^0}$ and $\boldsymbol{k}$ are $2n$-dimensional vectors containing both the n forward and n reverse rate constants, prior to and following perturbation respectively. This response function incorporates information on changes in all species concentrations, at all times and for all stimulus dosages included in the analysis. If $\boldsymbol{\Delta\kappa}$ is a $2n$-dimensional vector whose elements are the logarithmic perturbations in the rate constants, either $\ln(k^f_j/k^{f\,0}_j)$ or $\ln(k^r_j/k^{r\,0}_j)$ (j=1..n), then the above response function can be approximated as (Vajda, Valvko et al. 1985) :

$$Q(\boldsymbol{k}) \approx \boldsymbol{Q}(\Delta\kappa) = (\Delta\kappa)^T \boldsymbol{S}^T \boldsymbol{S} (\Delta\kappa) \quad \text{(S7)}$$

Here, the form of the scaled sensitivity coefficient matrix $\boldsymbol{S}$ (and its transpose $\boldsymbol{S^T}$) depends on the definition of the response function. For example, if we consider the response function at q time points, three EGF dosages (p=3) and with respect to the system output, $C_{ERK\text{-}PP}$ (i is fixed), then $\boldsymbol{S}$ has dimensions of $(3q)\times(2n)$. The first q rows of this matrix have the elements of $W_{59,j}$ with respect to both the forward and reverse rate constants, at various times and at a fixed EGF dosage (say the lowest dose). The next q rows have the same data at the intermediate EGF concentration and the final rows have this information at the highest EGF dose. Similarly, if in addition to the above, PCA is to be performed while equally weighting the effect of reaction rate perturbation on all of the m network products (i varying from 1 to m), the matrix $\boldsymbol{S}$ will have dimensions of $(3qm)\times(2n)$. Regardless of the dimensions of $\boldsymbol{S}$, the product of $\boldsymbol{S^T S}$ always has dimensions of $(2n)\times(2n)$.

The matrix $\boldsymbol{S^T S}$ can be diagonalized using its eigenvalues and eigenvectors as shown in S8, where the individual eigenvalues (λ_l) form the diagonal elements of the diagonal matrix $\boldsymbol{\Lambda}$, and $\boldsymbol{U}$ denotes the matrix whose columns are the normalized eigenvectors. u_{jl} represents an element of $\boldsymbol{U}$.

$$\boldsymbol{S^T S = U \Lambda U^T} \quad \text{(S8)}$$

The eigenvectors represent the principle axes of the response function, in terms of the list of reactions. $\Delta\boldsymbol{\Psi} = \boldsymbol{U^T} \cdot \Delta\boldsymbol{\kappa}$ is the linear transformation of the perturbation vector, $\Delta\boldsymbol{\kappa}$, to the principle axes. With this definition, the response function is given by $Q(\Delta\boldsymbol{\kappa}) = \Delta\boldsymbol{\Psi^T \Lambda \Delta \Psi} = \sum_{i=1}^{2n} \lambda_i (\Delta\Psi_i)^2$. The response function is thus most sensitive to changes in rate constants along the principal axis corresponding to the largest eigenvalue and is least sensitive to changes along the principal axis corresponding to the smallest eigenvalue. In such analysis, the eigenvalue provides an absolute measure of the significance of some part of the biological system that is composed of strongly coupled reactions. Each eigenvector is a linear combination of reactions, and the relative magnitude of the elements of each eigenvector measures the relative importance of each reaction for the corresponding eigenvalue. Here, we use the PCA parameter e_j ($= \sum_{l=1}^{2n} \lambda_l u_{jl} / \sum_{l=1}^{2n} \lambda_l$) as a measure of the importance of the j^{th} reaction. Taken together, eigenvalues and eigenvectors of $\boldsymbol{S^T S}$ evaluated using PCA provide a measure of the significance of individual reactions.

Reference:

Ferrell, J. E., Jr. (1998) How regulated protein translocation can produce switch-like responses, *Trends Biochem. Sci.*, **23**(12), 461-5.

Kholodenko, B. N., Demin, O. V., Moehren, G. and Hoek, J. B. (1999) Quantification of short term signaling by the epidermal growth factor receptor, *J. Biol. Chem.*, **274**(42), 30169-81.

Schoeberl, B., Eichler-Jonsson, C., Gilles, E. D. and Muller, G. (2002) Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors, *Nat. Biotechnol.*, **20**(4), 370-5.

Starbuck, C. and Lauffenburger, D. A. (1992) Mathematical model for the effects of epidermal growth factor receptor trafficking dynamics on fibroblast proliferation responses, *Biotechnol. Prog.*, **8**(2), 132-43.

Vajda, S., Valvko, P. and Turanyi, T. (1985) Principal Component Analysis of Kinetic Models, *International Journal of Chemical Kinetics*, **17**, 55-81.

Table S1 Reaction equations, kinetic parameters and initial protein concentrations

Panel A.125 reaction equations, and kinetic parameters in our model.

Reaction number	Reaction equation	Kinetic parameter	
v1	[EGFR]+[EGF] ↔ [EGF-EGFR]	k1=3e7;	k-1= 3.8e-3;
v2	[EGF-EGFR]+[EGF-EGFR] ↔ [(EGF-EGFR)2]	k2=1e7;	k-2=0.1;
v3	[(EGF-EGFR)2] ↔ [(EGF-EGFR*)2]	k3=1;	k-3=0.01;
v4	[(EGF-EGFR*)2-GAP-Grb2]+[Prot] ↔ [(EGF-EGFR*)2-GAP-Grb2-Prot]	k4=1.73e-7 [Receptors/s];	k-4=1.66e-3 [1/s];
v5	[(EGF-EGFR*)2-GAP-Grb2-Prot] → [(EGF-EGFRi*)2-GAP-Grb2]+[Proti]	k5=0.03 - 0.0033 ;	
v6	[EGFR] ↔ [EGFRi]	k6=5e-4#;	k-6=5e-3;
v7	[(EGF-EGFR*)2] → [(EGF-EGFRi*)2]	k7=5e-4;	
v8	[(EGF-EGFR*)2]+[GAP] ↔ [(EGF-EGFR*)2-GAP]	k8=1e6 ;	k-8=0.2;
v9	[(EGF-EGFR*)2-GAP-Grb2] → [(EGF-EGFRi*)2-GAP-Grb2]	k9=5e-5;	
v10	[EGFRi]+[EGFi] ↔ [EGF-EGFRi]	k10=1.4e5 ;	k-10= 0.011;
v11	[EGF-EGFRi]+[EGF-EGFRi] ↔ [(EGF-EGFRi)2]	k11=1e7;	k-11=0.1;
v12	[(EGF-EGFR)2i] ↔ [(EGF-EGFRi*)2]	k12=1;	k-12=0.01;
v13	→ [EGFR]	k13=2.17 [Receptors/s];	
v14	[(EGF-EGFRi*)2]+ [GAP] ↔ [(EGF-EGFRi*)2-GAP]	k14=1e6 ;	k-14=0.2;
v15	[Proti] → [Prot]	k15=1e4;	
v16, 63	[(EGF-EGFR*)2-GAP]+[Grb2] ↔ [(EGF-EGFR*)2-GAP-Grb2]	k16=1e7;	k-16=0.055;
v17, 64	[(EGF-EGFR*)2-GAP-Grb2]+[Sos] ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos]	k17=1e7;	k-17=0.06;
v18, 65	[(EGF-EGFR*)2-GAP-Grb2-Sos]+[Ras-GDP] ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GDP]	k18=1.5e7 ;	k-18=1.3;
v19, 66	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GDP] ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos]+[Ras-GTP]	k19=0.5;	k-19=1e5;
v20, 67	[Ras-GTP*]+[(EGF-EGFR*)2-GAP-Grb2-Sos] ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GTP]	k20=2.1e6;	k-20=0.4;
v21, 68	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GTP] ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos]+[Ras-GDP]	k21=0.023;	k-21=2.2e5;
v22, 69	[(EGF-EGFR*)2-GAP]+[Shc] ↔ [(EGF-EGFR*)2-GAP-Shc]	k22=2.1e7;	k-22=0.1;
v23, 70	[(EGF-EGFR*)2-GAP-Shc] ↔ [(EGF-EGFR*)2-GAP-Shc*]	k23=6;	k-23=0.06#;
v24, 71	[(EGF-EGFR*)2-GAP-Shc*]+[Grb2] ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2]	k24=1e7;	k-24=0.55;
v25, 72	[(EGF-EGFR*)2-GAP-Shc*-Grb2]+[Sos] ↔ [(EGF-EGFR*)2-GAP-Shc-Grb2-Sos]	k25=1e7;	k-25=0.0214;
v26, 73	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos]+[Ras-GDP] ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GDP]	k26=1.5e7 ;	k-26=1.3;
v27, 74	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GDP] ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos] + [Ras-GTP]	k27=0.5;	k-27=1e5;
v28, 75	[Raf]+[Ras-GTP] ↔ [Raf-Ras-GTP]	k28=1e6;	k-28=0.0053;
v29, 76	[Raf-Ras-GTP] ↔ [Raf*]+[Ras-GTP*]	k29=1;	k-29=7e5;;
v30, 77	[Ras-GTP*]+[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos] ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GTP]	k30=2.1e6#;	k-30=0.4;
v31, 78	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GTP] ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos]+[Ras-GDP]	k31=0.023;	k-31=2.2e5;
v32, 79	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos] ↔ [(EGF-EGFR*)2-GAP]+[Shc-Grb2-Sos]	k32=0.1;	k-32=2.4e5;
v33	[Shc*-Grb2-Sos] ↔ [Grb2-Sos]+[Shc*]	k33=0.2;	k-33=2.1e7;
v34, 80	[(EGF-EGFR*)2-GAP-Grb2-Sos] ↔ [(EGF-EGFR*)2-GAP]+[Grb2-Sos]	k34=0.03;	k-34=4.5e6;
v35	[Grb2-Sos] ↔ [Grb2] +[Sos]	k35=0.0015;	k-35=4.5e6;
v36	[Shc*] ↔ [Shc]	Vmax36=1.7;	Km36=340
v37, 81	[(EGF-EGFR*)2-GAP-Shc*] ↔ [(EGF-EGFR*)2-GAP]+[Shc*]	k37=0.3;	k-37=9e5;
v38	[Shc*]+[Grb2] ↔ [Shc*-Grb2]	k38=1e7#;	k-38=0.55;
v39, 82	[(EGF-EGFR*)2-GAP-Shc*-Grb2] ↔ [(EGF-EGFR*)2-GAP]+[Shc*-Grb2]	k39=0.3;	k-39=9e5;
v40	[Shc*-Grb2]+[Sos] ↔ [Shc*-Grb2-Sos]	k40=3e7;	k-40=0.064;
v41, 83	[(EGF-EGFR*)2-GAP-Shc*] + [Grb2-Sos] ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos]	k41=3e7;	k-41=0.0429;
v42, 84	[Raf*]+[Phosphatase1] ↔ [Raf*-Phosphatase1]	k42=7.17e7;	k-42=0.2;
v43, 85	[Raf*-Phosphatase1] → [Raf]+[Phosphatase1]	k43=1;	
v44, 86	[MEK] + [Raf*] ↔ [MEK-Raf*]	k44=1.11e7;	k-44=0.01833
v45, 87	[MEK-Raf*] → [MEK-P] +[Raf*]	k45=3.5;	
v46, 88	[MEK-P]+[Raf*] ↔ [MEK-P-Raf*]	k46=1.11e7;	k-46=0.01833
v47, 89	[MEK-P-Raf*] → [MEK-PP] + [Raf*]	k47=2.9;	
v48, 90	[MEK-PP]+[Phosphatase2] ↔ [MEK-PP-Phosphatase2]	k48=1.43e7;	k-48=0.8;
v49, 91	[MEK-PP-Phosphatase2] → [MEK-P] + [Phosphatase2]	k49=0.058;	
v50, 92	[MEK-P]+[Phosphatase2] ↔ [MEK-P-Phosphatase2]	k50=2.5e5;	k-50=0.5;
v51, 93	[MEK-P-Phosphatase2] → [MEK]+[Phosphatase2]	k51=0.058;	
v52, 94	[ERK]+[MEK-PP] ↔ [ERK-MEK-PP]	k52=1.1e5;	k-52=0.033;
v53, 95	[ERK-MEKK-PP] → [ERK-P]+[MEK-PP]	k53=16;	
v54, 96	[ERK-P]+[MEK-PP] ↔ [ERK-P-MEK-PP]	k54=1.1e5;	k-54=0.033;
v55, 97	[ERK-P-MEK-PP] → [ERK-PP]+[MEK-PP]	k55=5.7;	
v56, 98	[ERK-PP]+[Phosphatase3] ↔ [ERK-PP-Phosphatase3]	k56=1.45e7;	k-56=0.6;
v57, 99	[ERK-PP-Phosphatase3] → [ERK-P]+[Phosphatase3]	k57=0.27;	
v58,100	[ERK-P] + [Phosphatase3] ↔ [ERK-P-Phosphatase3]	k58=5e6;	k-58=0.5;
v59,101	[ERK-P-Phosphatase3] → [ERK]+[Phosphatase3]	k59=0.3;	
v60	[EGFRi] → [EGFRideg]	k60=6.67e-4;	
v61	[EGFi]→ [EGFideg]	k61=1.67e-4;	
v62	[(EGF-EGFRi*)2] ↔ [(EGF-EGFRi*)2deg]	k62=6.67e-4;	
v102	[(EGF-EGFR*)2-GAP] ↔ [(EGF-EGFRi*)2-GAP]	k102=k6;	k-102=k-6;
v103	[(EGF-EGFR*)2-GAP-Shc] ↔ [(EGF-EGFRi*)2-GAP-Shc]	k103=k6;	k-103=k-6;
v104	[(EGF-EGFR*)2-GAP-Shc*] ↔ [(EGF-EGFRi*)2-GAP-Shc*]	k104=k6;	k-104=k-6;
v105	[(EGF-EGFR*)2-GAP-Grb2-Sos] ↔ [(EGF-EGFRi*)2-GAP-Grb2-Sos]	k105=k6;	k-105=k-6;
v106	[(EGF-EGFR*)2-GAP-Grb2-Sos]+Prot ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos-Prot]	k106=k4;	k-106=k-4;
v107	[(EGF-EGFR*)2-GAP-Grb2-Sos-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Grb2-Sos]	k107=k5;	k-107=k-5;
v108	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GDP] ↔ [(EGF-EGFRi*)2-GAP-Grb2-Sos-Ras-GDP]	k108=k6;	k-108=k-6;
v109	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GDP]+Prot ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GDP-Prot]	k109=k4;	k-109=k-4;
v110	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GDP-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Grb2-Sos]	k110=k5;	k-110=k-5;
v111	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GTP] ↔ [(EGF-EGFRi*)2-GAP-Grb2-Sos-Ras-GTP]	k111=k6;	k-111=k-6;
v112	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GTP]+Prot ↔ [(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GTP-Prot]	k112=k4;	k-112=k-4;
v113	[(EGF-EGFR*)2-GAP-Grb2-Sos-Ras-GTP-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Grb2-Sos-Ras-GTP]	k113=k5;	k-113=k-5;
v114	[(EGF-EGFR*)2-GAP-Shc*-Grb2] ↔ [(EGF-EGFRi*)2-GAP-Shc*-Grb2]	k114=k6;	k-114=k-6;
v115	[(EGF-EGFR*)2-GAP-Shc*-Grb2]+Prot ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Prot]	k115=k4;	k-115=k-4;
v116	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Shc*-Grb2]	k116=k5;	k-116=k-5;
v117	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos] ↔ [(EGF-EGFRi*)2-GAP-Shc*-Grb2-Sos]	k117=k6;	k-117=k-6;
v118	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos]+Prot ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Prot]	k118=k4;	k-118=k-4;
v119	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Shc*-Grb2-Sos]	k119=k5;	k-119=k-5;
v120	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GDP] ↔ [(EGF-EGFRi*)2-GAP-Shc*-Grb2-Sos-Ras-GDP]	k120=k6;	k-120=k-6;
v121	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GDP]+Prot ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GDP-Prot]	k121=k4;	k-121=k-4;
v122	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GDP-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Shc*-Grb2-Sos-Ras-GDP]	k122=k5;	k-122=k-5;
v123	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GTP] ↔ [(EGF-EGFRi*)2-GAP-Shc*-Grb2-Sos-Ras-GTP]	k123=k6;	k-123=k-6;
v124	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GTP]+Prot ↔ [(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GTP-Prot]	k124=k4;	k-124=k-4;
v125	[(EGF-EGFR*)2-GAP-Shc*-Grb2-Sos-Ras-GTP-Prot] ↔ Proti+[(EGF-EGFRi*)2-GAP-Shc*-Grb2-Sos-Ras-GTP]	k125=k5;	k-125=k-5;

Note: # Denotes rate constants that are different from Schoeberl et al.

Michaelis Menten constants are given in [nM], first order rate constants in 1/s and second order rate constants in [M-1 s-1].

Panel B. Comparison of initial protein concentrations in our model with that of Schoeberl et al †.

Protein	Number of molecules per cell (in Schoeberl et.al)	Number of molecules per cell (in the paper)
Receptors Total	5.00×10^4	same as Schoeberl et.al†
GAP	1.20×10^4	same as Schoeberl et.al†
Shc	1.01×10^4	1.60×10^5
Grb2	5.10×10^4	9.00×10^4
Sos	6.63×10^4	3.6×10^4
Ras-GDP Total	1.14×10^7	7.2×10^4
Raf-kinase	4.00×10^4	same as Schoeberl et.al†
Mek Total	2.20×10^4	same as Schoeberl et.al†
Erk Total	2.10×10^4	same as Schoeberl et.al†
Phosphatase 1	4.00×10^4	same as Schoeberl et.al†
Phosphatase 2	4.00×10^4	same as Schoeberl et.al†
Phosphatase 3	1.00×10^4	same as Schoeberl et.al†
Coated-Pit Protein	8.10×10^4	same as Schoeberl et.al†

† Schoeberl, B., Eichler-Jonsson, C., Gilles, E. D. and Muller, G. (2002) Nat. Biotechnol., 20(4), 370-5.

Figure legend for supplemental material:

Fig.S1 Reaction Network. EGF receptor-induced MAP kinase cascade: Reaction network adapted from Schoeberl et al. is modified to illustrate that the entire reaction scheme can be simplified into four modules. Here, each reactant is designated by a number that appears in blue. Numbers enclosed in parenthesis specify the same species after internalization, i.e. in endosomal compartments. Arrows denote reactions and green numbers prefixed with the letter *v* denote reaction velocities. Details on internalization mechanics are described elsewhere, in Supplemental Fig. 2 of Schoeberel et al.

Fig.S2 Scaled Sensitivity Coefficients. Maximum and minimum scaled sensitivity coefficients are plotted for three concentrations of EGF: 50ng/mL (panel A and B), 0.5ng/mL (panel C and D) and 0.125ng/mL (panel E and F). Panels A, C and E present data for the Phase I while B, D and F are for Phase II. Phase I lasts from 0 to 5 min. when EGF concentration is 50ng/mL, 0 to 8 min. when EGF dosage is 0.5ng/mL, and up to 12 min. when EGF dosage is 0.125ng/mL. Data in panels A and B are identical to Fig 4 in the main manuscript, except that the axes of these plots have been scaled to remain consistent with panels C-F. Squares, diamonds, triangles and circles depict W_{ij} in modules A, B, C and D respectively. Filled symbols are used for W_{ij} associated with forward rate constants (k^f), and open symbols for reverse rates (k^r). Reactions corresponding to receptor binding, signaling, degradation and internalization are marked between the panels. Reactions 6 and 7 correspond to internalization of EGF receptor or its complex via the smooth pit-pathway, and reactions 10-12, 14 correspond to signaling via these internalized molecules.

Fig.S3 Model Reduction. Simplified reaction scheme for EGF signaling obtained following model reduction (ε equals 0.07). All reactions in module C are deleted. All reactions in module D are included in the simplified model even though they are not shown here. Each reactant is designated by a number in blue. Numbers enclosed in parenthesis specify the same species after internalization. Arrows denote reactions and red numbers prefixed with the letter *v* denote reaction velocities. † and # denote components internalized via smooth-pit and coated-pit pathways respectively in the reduced model.

Fig.S1 Liu et al.

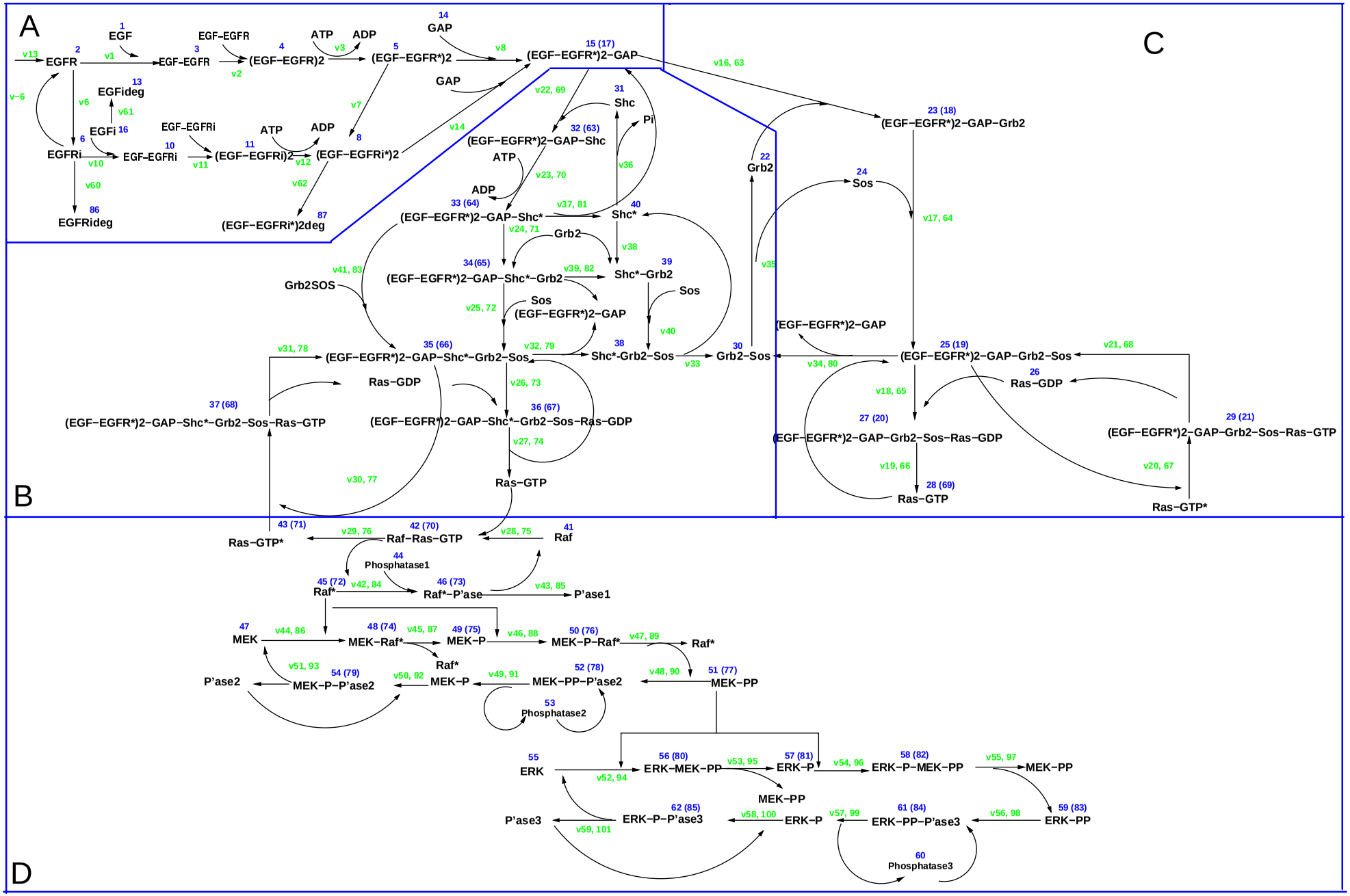

Fig.S2 A, B Liu et al.

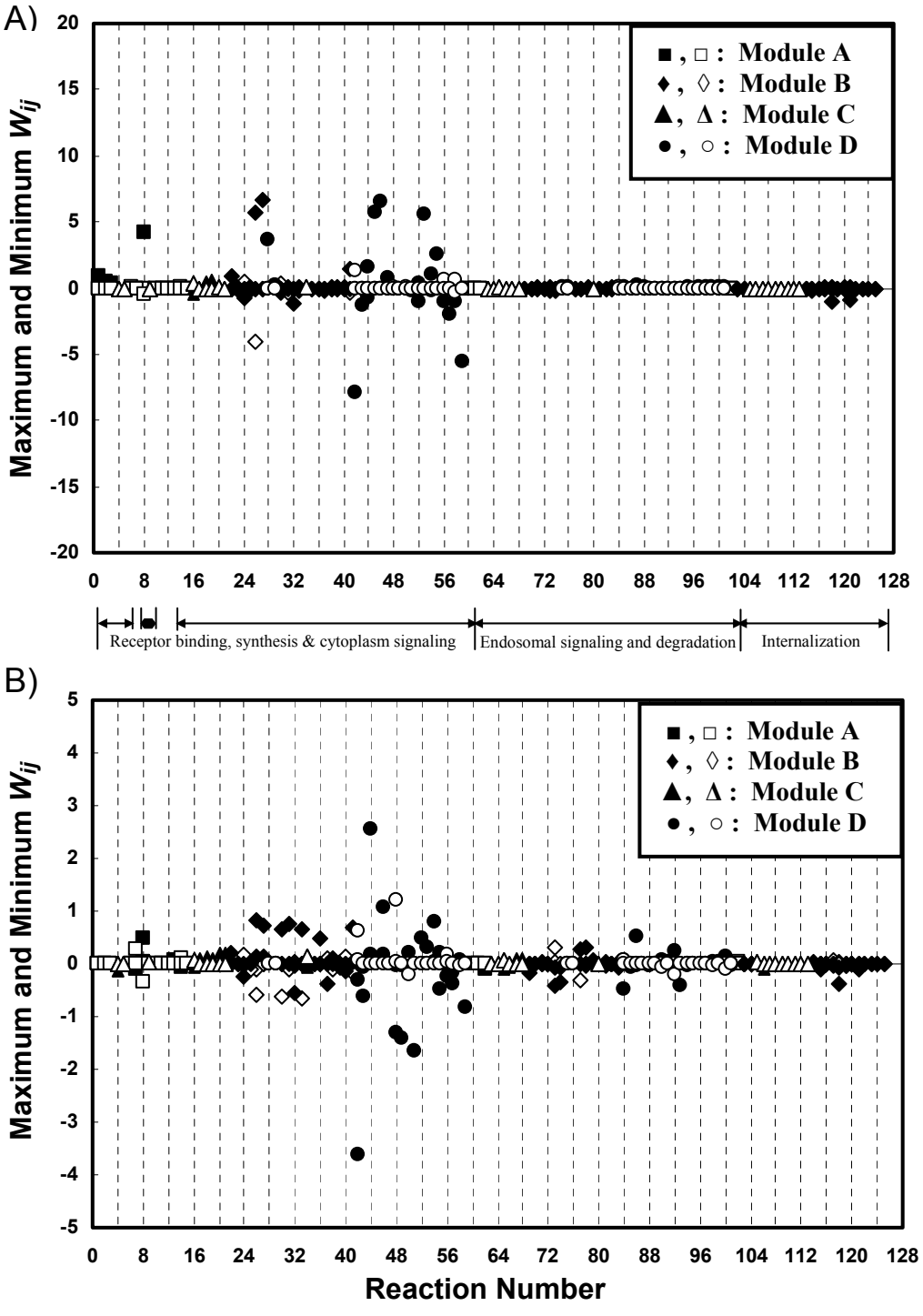

Fig.S2 C,D Liu et al.

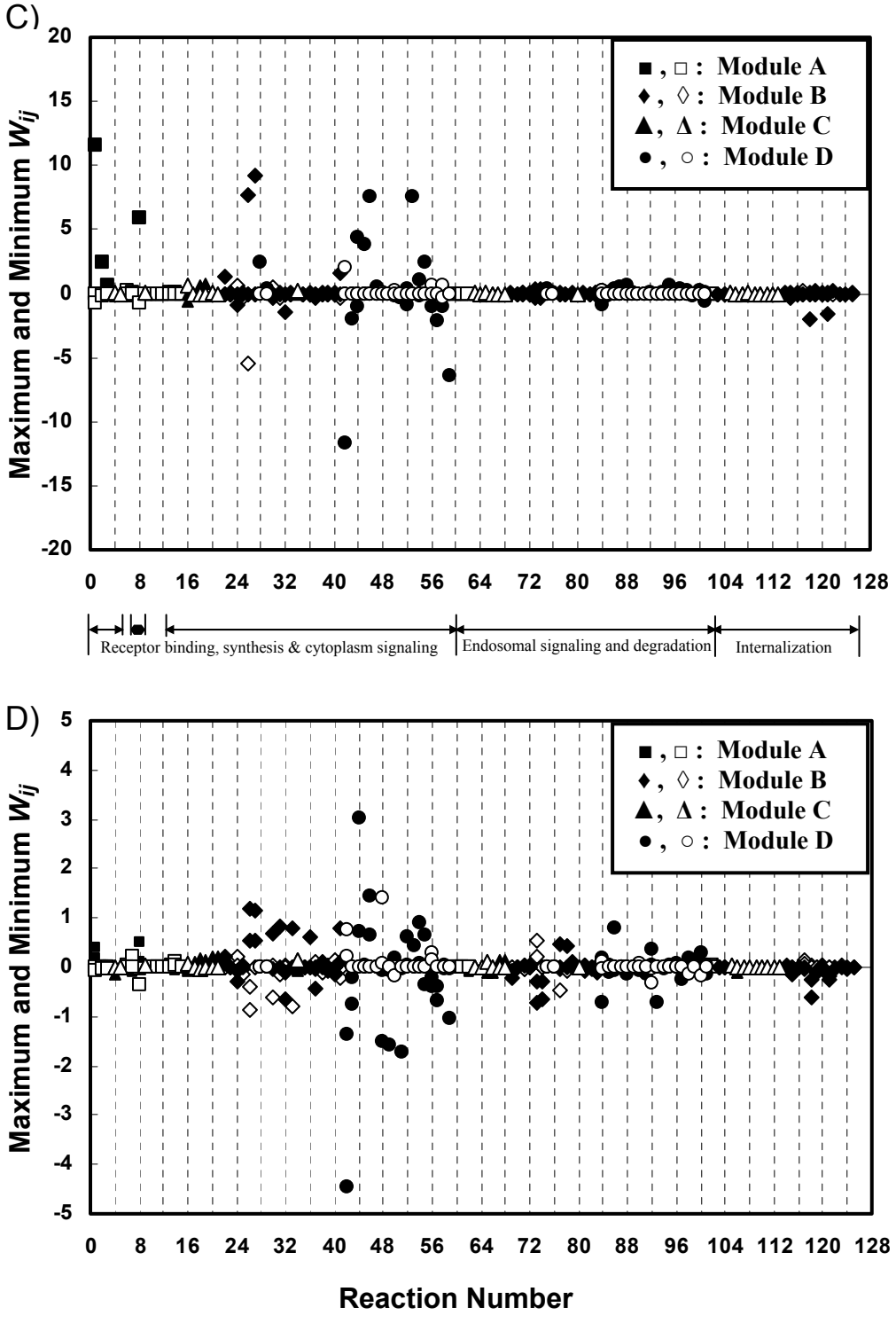

Fig.S2 E,F Liu et al.

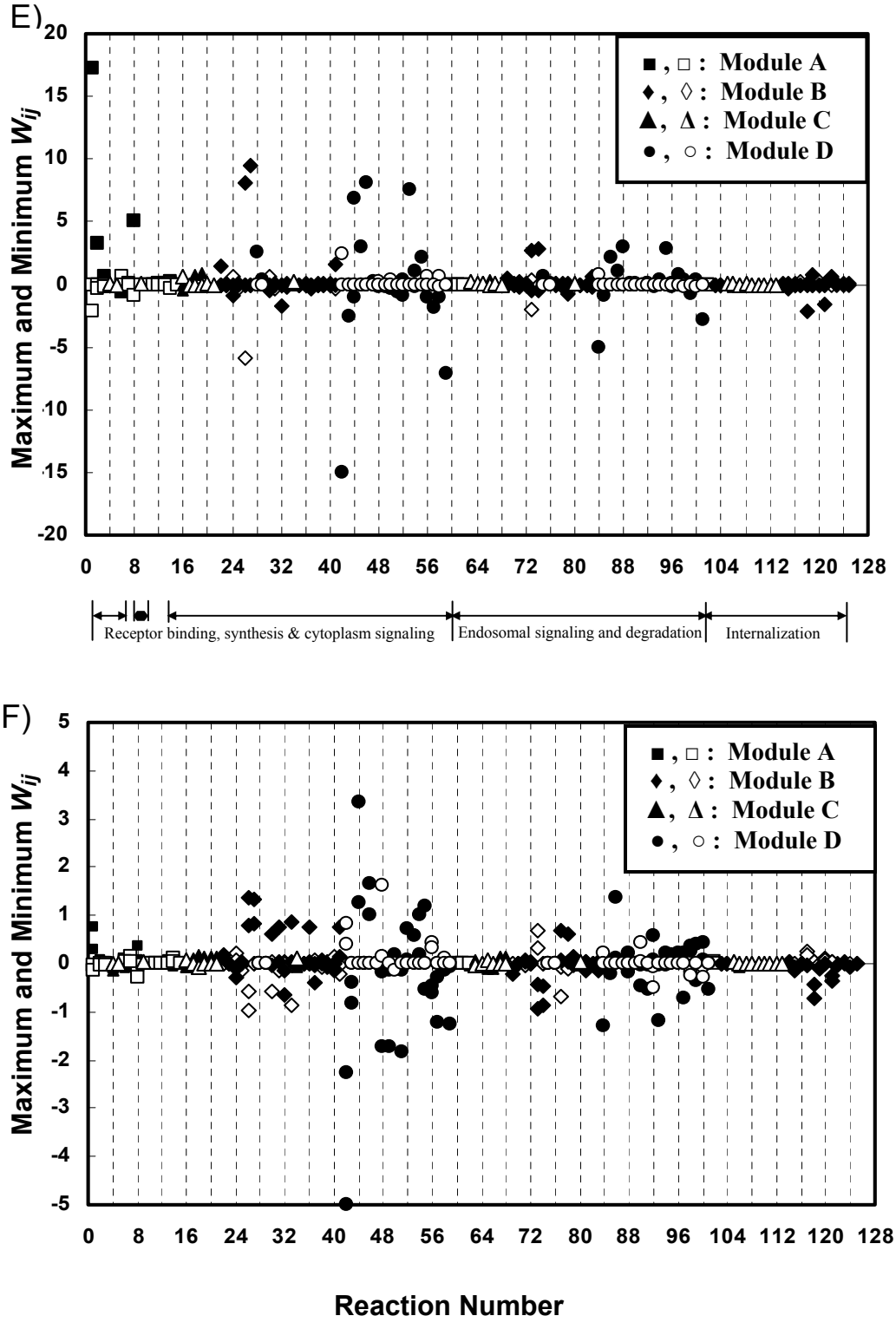

Fig.S3 Liu et al.