**Supplementary material**

**Cancerous perturbations within the ERK, PI3K/Akt, and Wnt/β-catenin signaling network constitutively activate inter-pathway positive feedback loops**

Rahul Rao Padala†, Rishabh Karnawat†, Satish Bharathwaj Viswanathan†, Abhishek Vijay Thakkar† and Asim Bikas Das\*

Department of Biotechnology, National Institute of Technology Warangal, Warangal: 506004, Telangana, India.

(†Authors have contributed equally)

\*Corresponding author:

Dr. Asim Bikas Das

Assistant Professor

Department of Biotechnology,

National Institute of Technology Warangal,

Warangal 506004, Telangana, India

E-mail: bikasasim@gmail.com, asimbikas@nitw.ac.in,

Tel No: +91-8106311048/+91-8332969440

**Note*:*** The SBML file of ERK, PI3K/Akt, and Wnt/β-catenin crosstalk model has been submitted, which can be simulated using JWS Online (https://jjj.bio.vu.nl/models/upload/) or COPASI.

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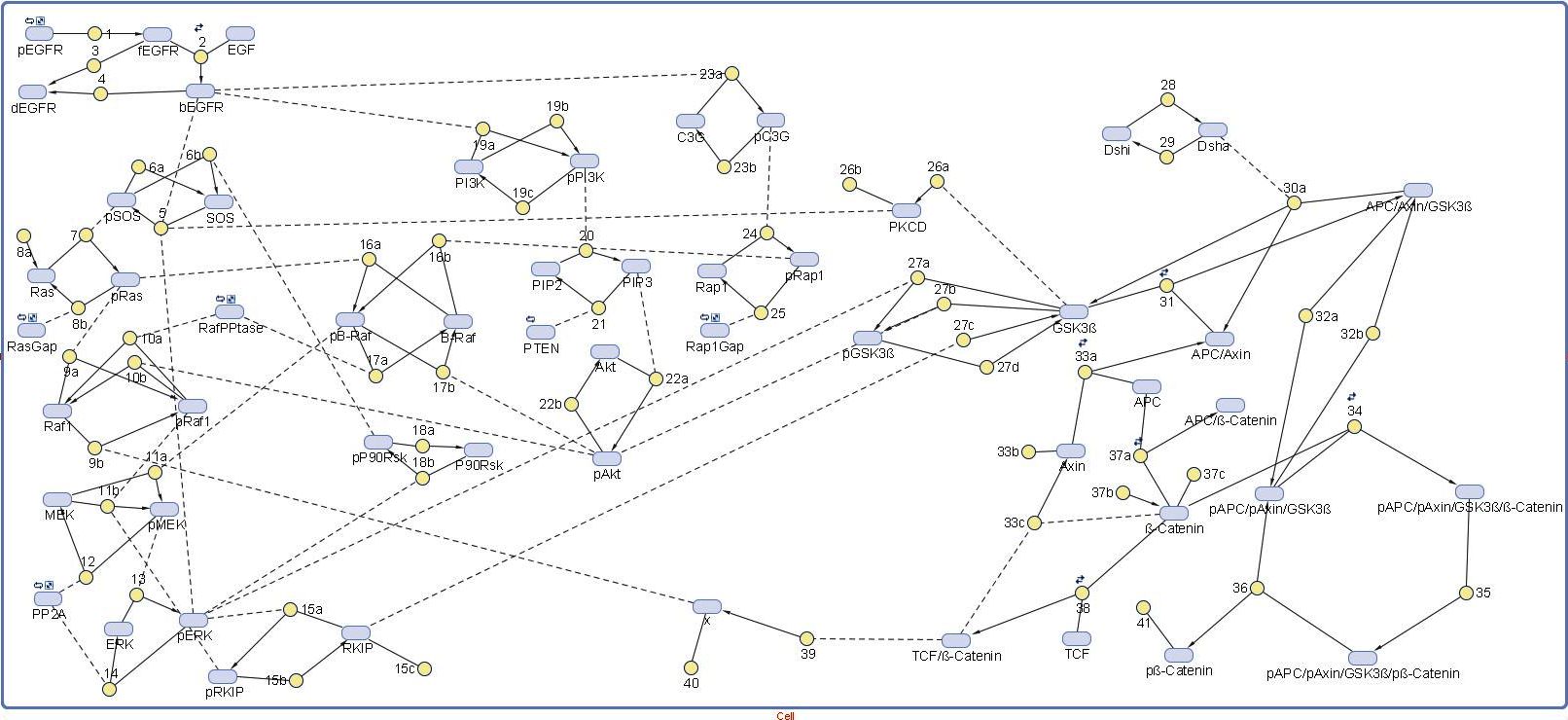


Figure S1: Schematic diagram of ERK, PI3K /Akt, and Wnt/β-catenin signaling network and crosstalk.

This network model was constructed using MATLAB SimBiology Toolbox. This figure is provided to verify the connections between the nodes, reaction numbers and kinetic equations employed in the model. The numbers mentioned in the diagram indicate the reaction numbers (In the figure, PKCD and p indicate PKCδ and phosphorylated state respectively).

# Table S1. ODEs used to construct the mathematical model of ERK-PI3K/Akt-Wnt/β-catenin signaling pathways

|  |
| --- |
| **ODEs:** |
| d(Ras)/dt = (V8b - V7 + V8a) |
| d([pRas])/dt = (-V8b + V7) |
| d(Raf1)/dt = (-V9a+ V10b + V10a - V9b) |
| d([pRaf1])/dt = (V9a - V10b - V10a + V9b) |
| d(MEK)/dt = (V12 - V11a - V11b) |
| d([pMEK])/dt = (-V12 + V11a + V11b) |
| d(ERK)/dt = (-V13 + V14) |
| d([pERK])/dt = (V13 - V14) |
| d(PI3K)/dt = (V19c - V19a - V19b) |
| d(PIP2)/dt = (-V20 + V21) |
| d(PIP3)/dt = (V20 - V21) |
| d(Akt)/dt = (-V22a + V22b) |
| d(pAkt)/dt = (V22a - V22b) |
| d(Dshi)/dt = (-V28 + V29) |
| d(Dsha)/dt = (V28 - V29) |
| d([APC/Axin])/dt = (V30 - V31 + V33a) |
| d([APC/Axin/GSK3β])/dt = (-V30 + V31 + V32b - V32a) |
| d(APC)/dt = (-V33a - V37a) |
| d([APC/β -catenin])/dt = (V37a) |
| d([pAPC/pAxin/GSK3β])/dt = (V32a - V34 - V32b + V36) |
| d([pAPC/pAxin/GSK3β/β -catenin])/dt = (V34 - V35) |
| d([pAPC/pAxin/GSK3B/pΒ-catenin])/dt = (V35 - V36) |
| d([pβ -catenin])/dt = (V36 - V41) |
| d([β -catenin])/dt = (-V37a - V37c - V34 + V37b - V38) |
| d(TCF)/dt = (-V38) |
| d([TCF/β -catenin])/dt = (V38) |
| d(GSK3β)/dt = (-V27b + V27c - V27a + V27d - V31 + V30) |
| d([pGSK3β])/dt = (V27b - V27d + V27a) |
| d(Axin)/dt = (-V33a + V33c - V33b) |
| d([pPI3K])/dt = (-V19c + V19b + V19a) |
| d([pB-Raf])/dt = (-V17a + V16a + V16b - V17b) |
| d(bEGFR)/dt = (-V4 + V2) |
| d(P90Rsk)/dt = (-V18b + V18a) |
| d([pP90Rsk])/dt = (V18b - V18a) |
| d(SOS)/dt = (V6a + V6b - V5) |
| d([pSOS])/dt = (-V6a - V6b + V5) |
| d(dEGFR)/dt = (V3 + V4) |
| d(fEGFR)/dt = (V1 - V2 - V3)---- |
| d(EGF)/dt = (-V2) |
| d(B-Raf)/dt = (V17a - V16a - V16b + V17b) |
| d(C3G)/dt = (-V23a + V23b) |
| d([pC3G])/dt = (V23a - V23b) |
| d(Rap1)/dt = (-V24 + V25) |
| d([pRap1])/dt = (V24 - V25) |
| d(RKIP)/dt = (V15b - V15a - V15c) |
| d([pRKIP])/dt = (-V15b + V15a) |
| d(PKCD)/dt = (V26a - V26b) |
| d(X)/dt = (V39 - V40) |
| **Fluxes:** |
| V1 = (V1) |
| V2 = ((k12×EGF×fEGFR-k22×bEGFR)) |
| V3 = (k3×fEGFR) |
| V4 = (k4×bEGFR) |
| V5 = ((((k15×bEGFR)+k25)+k35×PKCD)/(1+[pERK]/k45)) |
| V6a = (k6a×[pSOS]) |
| V6b = ((Kcat6b×[pP90Rsk]×[pSOS])/([pSOS]+Km6b)) |
| V7 = ((Kcat7×[pSOS]×Ras)/(Ras+Km7)) |
| V8a = V8a |
| V8b = ((Kcat8b×[RasGap]×[pRas])/([pRas]+Km8b)) |
| V9a = ((Kcat9a×[Ras×]×Raf1)/(Raf1+Km9a) |
| V9b = (k9b×W×X×Raf/(Km9b+Raf1)) |
| V10a = ((Kcat10a×RafPPtase×[pRaf1])/([pRaf1]+Km10a)) |
| V10b = ((Kcat10b×pAkt×[pRaf1])/([pRaf1]+Km10b)) |
| V11a = ((Kcat11a×[B-Raf]×MEK)/(MEK+Km11a)) |
| V11b = ((k111b×[pRaf1]×MEK)/(1+((RKIP-[pRKIP])/k211b)^2)) |
| V12 = ((Kcat12×[PP2A]×[pMEK])/([pMEK]+Km12) |
| V13 = ((Kcat13×[pMEK]×ERK)/(ERK+Km13) |
| V14 = ((Kcat14×[PP2A]×[pERK])/([pERK]+Km14)) |
| V15a = (k15a×[pERK]×(RKIP-[pRKIP])) |
| V15b = (V15b×[pRKIP]) |
| V15c = (k15c×RKIP) |
| V16a = ((Kcat16a×[pRas]×[B-Raf])/(B-Raf+[16a].Km16a)) |
| V16b = ((Kcat16b×[pRap1]×B-Raf)/(B-Raf+Km16b)) |
| V17a = ((Kcat17a×RafPPtase×[pB-Raf])/([pB-Raf]+Km17a)) |
| V17b = ((Kcat17b×pAkt×[pB-Raf])/([pB-Raf]+Km17b)) |
| V18a = (k18a×[pP90Rsk]) |
| V18b = ((Kcat18b×[pERK]×P90Rsk)/(P90Rsk+Km18b)) |
| V19a = ((Kcat19a×bEGFR×PI3K)/(PI3K+Km19a)) |
| V19b = ((Kcat19b×[pRas]×PI3K)/(PI3K+Km19b)) |
| V19c = ([k19c×[pPI3K]) |
| V20 = ((Kcat20×[pPI3K]×PIP2)/(PIP2+Km20)) |
| V21 = ((Kcat21×PTEN×PIP3)/(PIP3+Km21)) |
| V22a = ((Kcat22a×PIP3×Akt)/(Akt+Km22a) |
| V22b = (Kcat22b×Aktp/(Km22b+Aktp)) |
| V23a = ((Kcat23a×bEGFR×C3G)/(C3G+[23a].Km23a)) |
| V23b = ([k23b×[pC3G]) |
| V24 = ((Kcat24×[pC3G]×Rap1)/(Rap1+Km24)) |
| V25 = ((Kcat25×Rap1Gap×[pRap1])/([pRap1]+Km25)) |
| V26a = V/(1+(GSK3β/k26a)^2.5) |
| V26b = (k26b×PKCδ) |
| V27a = (Kcat27a×pGSK3β[pERK]) |
| V27b = (Kcat27b×GSK3β×pAkt) |
| V27c = (k27c×RKIP) |
| V27d = (Kcat27d×[pGSK3β]) |
| V28 = (k28×Dshi×W) |
| V29 = (k29×Dsha) |
| V30 = (k30×Dsha×[APC/Axin/GSK3β]) |
| V31 = (k131×GSK3β×[APC/Axin])-(k231×[APC/Axin/GSK3β]) |
| V32a = (k32a×[APC/Axin/GSK3β]) |
| V32b = (k32b×[APC×/Axin×/GSK3β]) |
| V33a = (k133a×Axin×APC)-(k233a×[APC/Axin]) |
| V33b = (k33b×Axin) |
| V33c = (k133c+k233c×([TCF/β-catenin]+[β-catenin])) |
| V34 = (k134×[pAPC/pAxin/GSK3β]×[β-catenin])-(k234×[pAPC/pAxin/GSK3β/β-catenin]) |
| V35 = (k35×[pAPC/pAxin/GSK3β /β-catenin]) |
| V36 = (k36×[pAPC/pAxin/GSK3β/pβ-catenin]) |
| V37a = (k137a×APC×[β-catenin])-(k237a×[APC/β-catenin]) |
| V37b = V37b |
| V37c = (k37c×[β-catenin]) |
| V38 = (k138×[β-catenin]×TCF)-(k238×[TCF/β-catenin]) |
| V39 = (k39×[TCF/β -catenin]^2/(Km39^2+[TCF/β-catenin]^2)) |
| V40 = (k40×X) |
| V41 = (k41×[pβ-catenin]) |

# Table S2: Parameter values used for simulation of the ERK-PI3K/Akt-Wnt/β-catenin network

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Reference** |
| V1 | 100 nM s-1 | 1 |
| k12 | 2.185e-05 s-1 | 1 |
| k22 | 0.12101 s-1 | 1 |
| k3 | 0.00125 s-1 | 1 |
| k4 | 0.2 s-1 | 1 |
| k51 | 0.003465 s-1 | 1 |
| k52 | 3.85e-05 nM s-1 | 1 |
| k53 | 2.8833e-04 s-1 | 1 |
| k54 | 1.5 nM | 1 |
| k6a | 2.5 s-1 | 1 |
| Kcat6b | 1611.97 s-1 | 2 |
| Km6b | 896896 nM | 2 |
| Kcat7 | 32.644 s-1 | 2 |
| Km7 | 35954.3 s-1 | 2 |
| Kcat8b | 1509.36 s-1 | 2 |
| Km8b | 1432410 nM | 2 |
| V8a | 7.17E-02 nmol s-1 | 3 |
| Kcat9a | 0.884096 s-1 | 2 |
| Km9a | 62464.6 nM | 2 |
| k9b | 0.025 s-1 | 4 |
| Km9b | 15 nM | 4 |
| Kcat10a | 0.12633s-1 | 4 |
| Km10a | 1061.7s-1 | 2 |
| Kcat10b | 15.1212 s-1 | 2 |
| Km10b | 119355 nM | 2 |
| Kcat11a | 185.76s-1 | 2 |
| Km11a | 4.7684e+06 nM | 2 |
| K111b | 1.1167e-05 nM­-1s-1 | Modified |
| K211b | 120 nM | Modified |
| Kcat12 | 2.8324 s-1 | 2 |
| Km12 | 5.1875e+05 nM | 2 |
| Kcat13 | 9.8537 s-1 | 2 |
| Km13 | 1.0073e+06 nM | 2 |
| Kcat14 | 8.8912 s-1 | 2 |
| Km14 | 3.4965e+06 nM | 2 |
| K15a | 1.3 nM-1 s-1 | Modified |
| V15b | 4 s-1 | Modified |
| K15c | 1.93E-03 s-1 | Modified |
| Kcat16a | 0.8841 s-1 | 2 |
| Km16a | 62645 nM | 2 |
| Kcat16b | 0.8841s-1 | 2 |
| Km16b | 62464.6 nM | 2 |
| Kcat17a | 0.12633 s-1 | 2 |
| Km17a | 1061.71 nM | 2 |
| Kcat17b | 15.1212 s-1 | 2 |
| Km17b | 119355 nM | 2 |
| K18a | 0.005 s-1 | 1 |
| Kcat18b | 0.02137 s-1 | 2 |
| Km18b | 763523 nM | 2 |
| Kcat19a | 10.6737 s-1 | 2 |
| Km19a | 184912 nM | 2 |
| Kcat19b | 0.07711 s-1 | 2 |
| Km19b | 272056 nM | 2 |
| K19c | 0.005 s-1 | 1 |
| Kcat20 | 4 s-1 | 5 |
| Km20 | 4 nM | 5 |
| Kcat21 | 5.5 s-1 | 5 |
| Km21 | 0.08 nM | 5 |
| Kcat22a | 0.33 s-1 | 6 |
| Km22a | 100 nM | 6 |
| Kcat22b | 48.667 nMs-1 | 6 |
| Km22b | 100 nM | 6 |
| Kcat23a | 694.73s-1 | 2 |
| Km23a | 6086100nM | 2 |
| K23b | 2.5s-1 | 1 |
| Kcat24 | 32.344 s-1 | 2 |
| Km24 | 35954.3 nM | 2 |
| Kcat25 | 1509.4 s-1 | 2 |
| Km25 | 1432400 nM | 2 |
| V26a | 0.00154 nM s-1 | 3 |
| k26a | 20 nM | 3 |
| K26b | 3.85E-04 s-1 | 3 |
| Kcat27a | 0.002 nM-1 s-1 | 3 |
| Kcat27b | 0.04596 nM-1 s-1 | 7 |
| K27c | 1.50E-04 s-1 | Estimated from 8 |
| Kcat27d | 0.01541 s-1 | Modified |
| W | 0 or 1 | 4 |
| k28 | 0.003s-1 | 4 |
| k29 | 0.003 s-1 | 4 |
| k30 | 0.000833 nM-1 s-1 | 4 |
| k131 | 0.001515 nM-1s-1 | 4 |
| k231 | 0.01515 s-1 | 4 |
| K32a | 0.00445 s-1 | 4 |
| K32b | 0.002217 s-1 | 4 |
| k133a | 0.01667 nM-1s-1 | 4 |
| k233a | 0.8333 s-1 | 4 |
| K33b | 0.002783 s-1 | 4 |
| k233c | 1.667E-08 s-1 | Modified |
| k133c | 1.37E-06 nM-1 s-1 | 4 |
| k134 | 0.01667 nM-1s-1 | 4 |
| k234 | 2 s-1 | 4 |
| k35 | 3.433 s-1 | 4 |
| k36 | 3.433 s-1 | 4 |
| k137a | 0.01667 nM-1s-1 | 4 |
| k237a | 20 s-1 | 4 |
| V37b | 0.00705 nmol s-1 | 4 |
| K37c | 4.283E-06 s-1 | 4 |
| k138 | 0.01667 nM-1s-1 | 4 |
| k238 | 0.5 s-1 | 4 |
| Km39 | 15 nM | 4 |
| k39 | 1.00E-02 nM s-1 | 4 |
| K40 | 2.50E-04 s-1 | 4 |
| K41 | 0.00695 s-1 | 4 |

# Table S3: Species concentration at steady state for a normal system (W=0).

|  |  |
| --- | --- |
| Concentration | Reference |
| Ras = 100 nM | 9 |
| Raf1 = 100 nM | Modified |
| MEK = 680 nM | 10 |
| ERK = 260 nM | 10 |
| PI3K = 100 nM | 5 |
| PIP2 = 700 nM | 5 |
| PTEN = 270 nM | 5 |
| Akt = 200 nM | 5 |
| PP2A = 240 nM | 10 |
| Dshi = 100 nM | 4 |
| [APC/Axin] = 0.0015 nM | 4 |
| [APC/Axin/GSK3β] = 0.0076 nM | 4 |
| APC = 96.602 nM | 4 |
| [APC/β-Catenin] = 3.4392 nM | 4 |
| [pAPC/pAxin/GSK3β] = 0.0153 nM | 4 |
| [pAPC/pAxin/GSK3β/β-Catenin] = 0.002 nM | 4 |
| pAPC/pAxin/GSK3β/pβ-Catenin] = 0.002 nM | 4 |
| pβ-Catenin = 0.9881 nM | 4 |
| β-Catenin = 42.722 nM | 4 |
| TCF = 6.1879 nM | 4 |
| TCF/β-Catenin = 8.8121 nM | 4 |
| GSK3β = 49.137 nM | 4 |
| pGSK3β= 0.85544 nM | 4 |
| Axin = 0.0008 nM | 4 |
| P90Rsk = 60 nM | Modified |
| SOS = 100 nM | 9 |
| RafPPtase = 60 nM | 10 |
| fEGFR = 300 nM | 10 |
| pEGFR = 0.05 nM | Modified |
| EGF = 600 nM | Modified |
| B-Raf = 200 nM | 9 |
| C3G = 500 nM | 10 |
| Rap1 = 200 nM | 10 |
| RKIP = 20.909 nM | Modified |
| pRKIP= 0.8619 nM | Modified |
| X = 10.263 nM | 4 |
| RasGap = 100 nM | 11 |
| Rap1Gap = 12 nM | 10 |

# Parameter Sensitivity Analysis

Sensitivity analysis is a technique used to find the contribution of individual parameter values to the overall performance of a complex system. Parameter sensitivity analysis of outputs (pERK, pAkt, and β-catenin/TCF) was done in normal condition with respect to all kinetic rate constants (Kcat, Km, K, k1, and k2) in the network.

## i) pERK sensitivity with respect to all kinetic rate constants in ERK-PI3K/Akt-Wnt/β-catenin crosstalk model:

We have examined pERK sensitivity with respect to all Kcat, Km, K, k1 and k2 in ERK-PI3K/Akt-Wnt/β-catenin network in normal condition (W=0). Sensitivity analysis shows that ERK activation is highly sensitive to changes in Kcat and Km values of reactions 14, 12, 13, 17a, 11a, 7, 8a (Fig S2 & S3). This implies that pERK is more sensitive to ERK and MEK dephosphorylation by PP2A, ERK activation by MEK, dephosphorylation of B-Raf by Rafpptase, phosphorylation of RKIP by MEK, phosphorylation of Ras by SOS, and Ras deactivation by RasGap than other reactions. ERK activation also shows high sensitivity to changes in PKCδ

(reaction 26a and 26b, Fig S4). This shows that the immediate neighbors or components of ERK pathway have significant influence on ERK activation, though the network is connected via multiple levels of crosstalk.

**C:\Users\USER\Desktop\New folder\ERK sensitivity.tif**

### Figure S2: pERK sensitivity with respect to Kcat

**C:\Users\USER\Desktop\New folder\All Km ERK.tif**

### Figure S3: pERK sensitivity with respect to Km

**C:\Users\USER\Desktop\New folder\all K_ERK.tif**

### Figure S4: pERK sensitivity with respect to k

C:\Users\USER\Desktop\New folder\K1_ERK.tif

### Figure S5: pERK sensitivity with respect to k1

C:\Users\USER\Desktop\New folder\K2_erk.tif

### Figure S6: pERK sensitivity with respect to k2

ii) pAkt sensitivity with respect to all kinetic rate constants in ERK-PI3K/Akt-Wnt/β-catenin crosstalk model:

Similarly, we have examined pAkt sensitivity with respect to all Kcat, Km, K, k1 and k2 in ERK-PI3K/Akt-Wnt network in normal condition (W=0). Sensitivity analysis shows that Akt activation is most sensitive to the Kcat and Km values of reactions 21, 22b, 20, 22a, 19b, 7 and 8b (Fig S7 & S8). That is, Akt activation is most sensitive to PIP3 dephosphorylation by PTEN, phosphorylation of Akt by PIP3, phosphorylation of PIP2 by PI3K, activation of PI3K, deactivation of Ras and activation of Ras by SOS. First order reaction parameters (k) of reactions 19c(deactivation of PI3K), 26a(inhibition of PKCδ by GSK3β), and 6(dephosphorylation of SOS) show a high impact on pAkt activation (Fig S9). Even though, PKCδ and SOS are not core molecules of the PI3K/Akt pathway they still regulate Akt activation.

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### Figure S7: pAkt sensitivity with respect to Kcat

C:\Users\USER\Desktop\New folder\All Km Akt.tif

Figure S8: pAkt sensitivity with respect to Km

C:\Users\USER\Desktop\New folder\K_pAkt.tif

### Figure S9: pAkt sensitivity with respect to K

C:\Users\USER\Desktop\New folder\K1_pAkt.tif

### Figure S10: pAkt sensitivity with respect to k1

C:\Users\USER\Desktop\New folder\K2_pAkt.tif

### Figure S11: pAkt sensitivity with respect to k2

## iii) β-catenin/TCF sensitivity with respect to all kinetic rate constants in ERK-PI3K/Akt-Wnt/β-catenin crosstalk model:

The high sensitivity parameters of β-catenin/TCF formation are k1 and k2 of reactions 31, 33, and k1of reaction 34, which indicate that β-catenin/TCF is the most sensitive to formation of APC/Axin/GSK3β, APC/Axin, APC/Axin/GSK3β /β-catenin complexes (Fig S15 and S16). β-catenin/TCF formation also shows high sensitivity to first order reaction parameters (k) of reactions 32a and 32b which are associated with the formation of the destruction complex. Reactions outside Wnt pathway such as dephosphorylation of ERK ( 14 Kcat) and inhibitory phosphorylation GSK3β(27a Kcat) (Fig S12) also show moderately high sensitivity compared to others.

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### Figure S12: β-catenin/TCF sensitivity with respect to Kcat

C:\Users\USER\Desktop\New folder\All Km TCF.tif

Figure S13: β-catenin/TCF sensitivity with respect to Km

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### Figure S14: β-catenin/TCF sensitivity with respect to k

C:\Users\USER\Desktop\New folder\TCF_K1.tif

Figure S15: β-catenin/TCF sensitivity with respect to k1

C:\Users\USER\Desktop\New folder\TCF_K2.tif

### Figure S16: β-catenin/TCF sensitivity with respect to k2

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