Supplement

Analysis of dose dependence curve by using Hill function approximation

We analysed the steepness of pHER and pAKT dose dependence curves by fitting theoretical dose dependence curve to the Hill equation:

$$y = \frac{x^n}{x^n + K^n}$$

where y is output signal either pHER2 or pAKT, x – HRG concentration, n – Hill coefficient, K - half-maximal concentration of HRG.

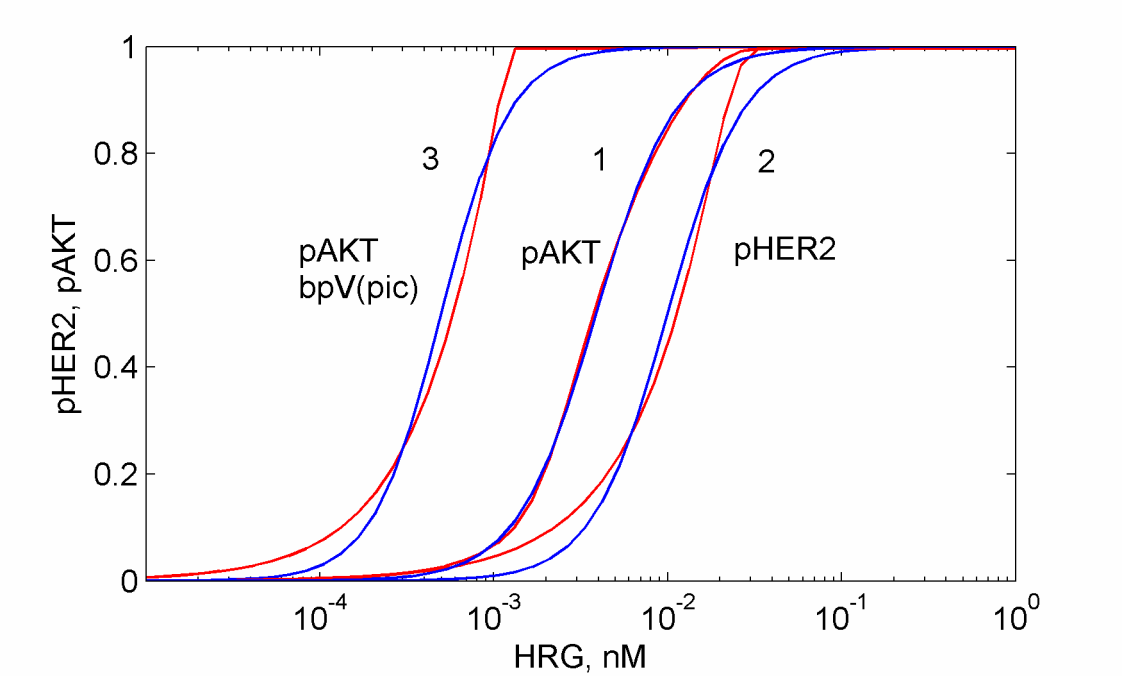

Fig. S1. Approximation of pHER2 and pAKT theoretical dose dependences (red lines) by Hill function (blue lines). Curves 1 - pAKT dose dependence. Hill coefficient n=1.9 and half-maximal concentration K=0.004. Curves 2 - pHER2 dose dependence. n=2.0, K=0.01. Curves 3 - pAKT dose dependence in the presence of PTEN inhibitor bpV(pic), 100 nM. n=2.2 and half-maximal concentration $K=5\cdot 10^{-4}$.

Input-output characteristic and sensitivity of signal transduction system of PI3K/PTEN/AKT pathway

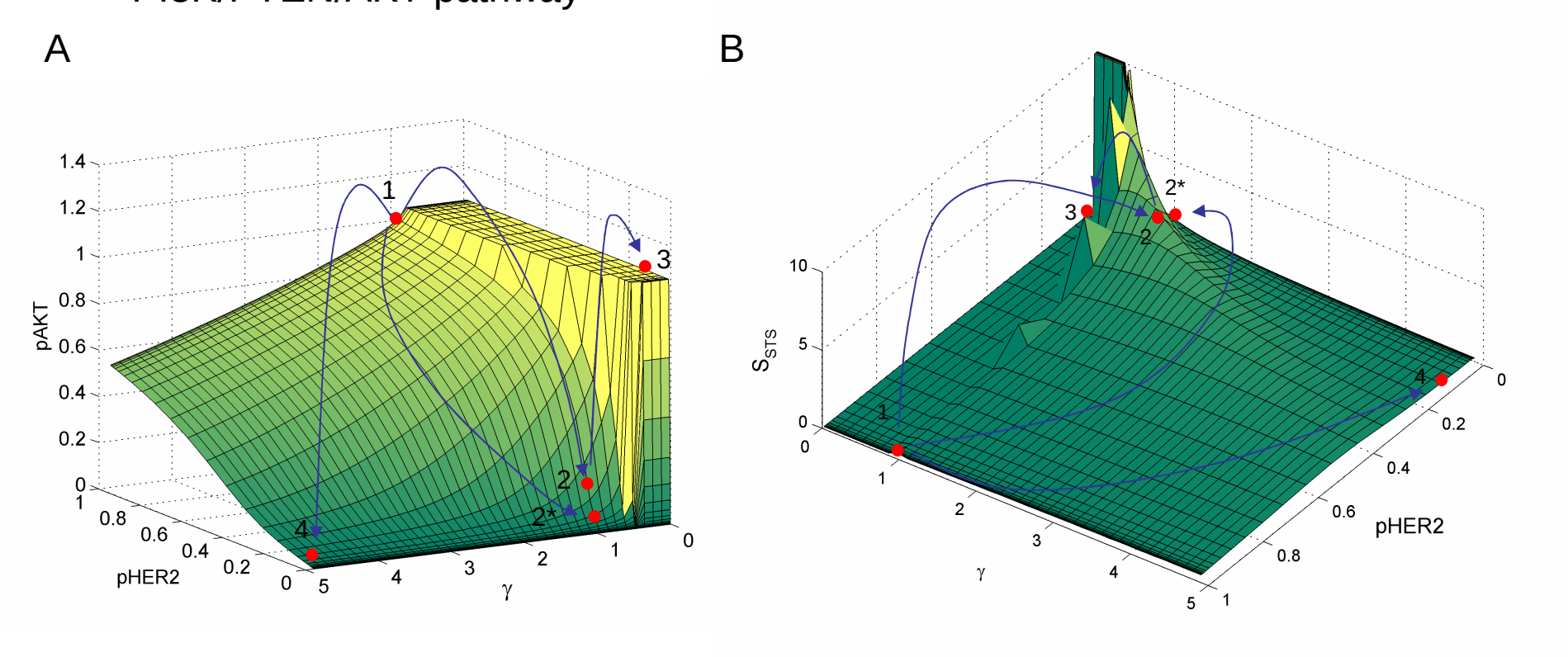

Fig. S2. Dependence of pAKT (A) and sensitivity S_{STS} (B) on pHER2 input signal and control parameter γ. Arrows show trajectories of the pAKT (A) and sensitivity S_{STS} (B) changes at RTK inhibition by pertuzumab and γ changes as a result of PTEN activity alteration. Trajectory (1-2) shows HER2 inhibition by pertuzumab; (2-3) – γ change corresponding the loss of PTEN activity; (1-4) – combination of HER2 inhibition by pertuzumab and PI3K inhibition by LY294002; (1-2*) - 95% inhibition of HER2. The concentrations of pHER2 and pAKT are normalized to their maximal concentrations.

Effects of HER2 inhibition, *PIK3CA* mutation, and AKT overexpression on sensitivity of signal transduction system, $S_{STS,i}$

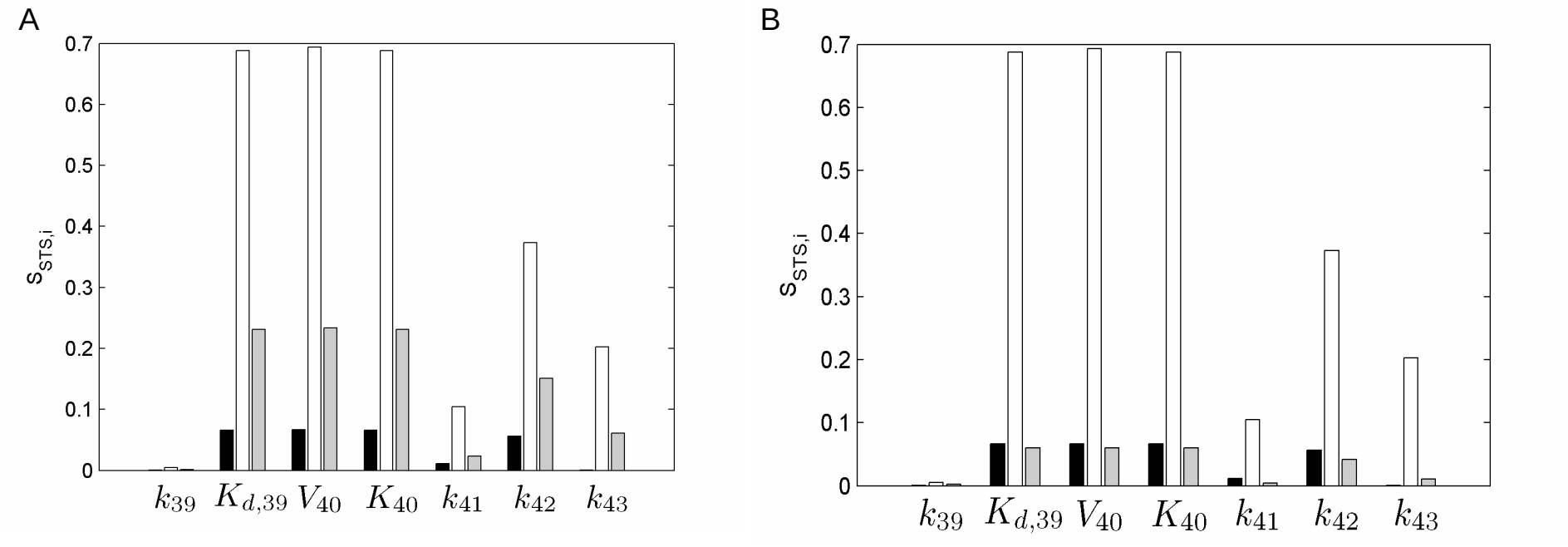

Fig. S3. Effects of HER2 inhibition, *PIK3CA* mutation (A) and 10 times AKT overexpression (B) on sensitivity $S_{STS,i}$ to the kinetic parameters of the enzymes involved in AKT phosphorylation. Black bars – no pertuzumab, white bars – 100 nM pertuzumab, grey bars - 100 nM pertuzumab and PTEN inhibition by bpV(pic). *PIK3CA* mutation was modeled by three times increase in PI3K activity.

Post-translation modification of PTEN and sensitivity-to-resistance transition due to CK2/GSK3 amplification

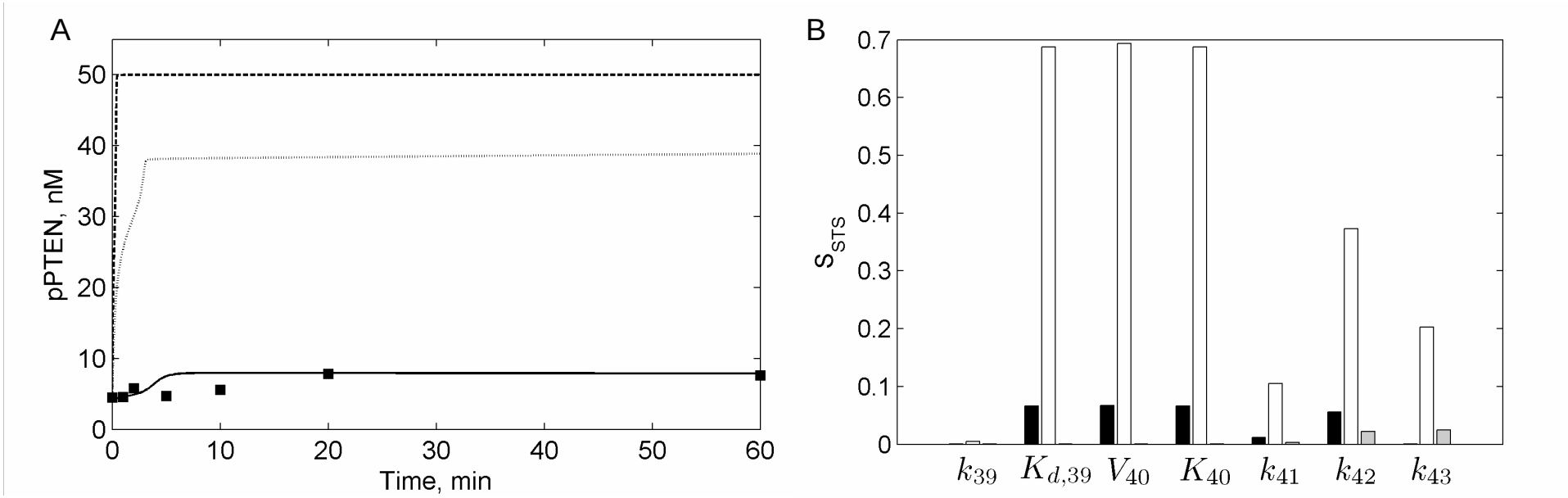

Fig. S4. (A) Kinetics of pPTEN accumulation at HRG activation (solid line). Effect of three times increase in activity of CK2/GSK3β reaction of PTEN phosphorylation (dashed line) and PTEN inhibition by bpV(pic) (dotted line) on pPTEN kinetics. Points – experimental data [1]. (B) Effects of HER2 inhibition and three times increase in activity of CK2/GSK3β reaction on sensitivity $S_{STS,i}$ to the kinetic parameters of the enzymes involved in AKT phosphorylation. Black bars – no pertuzumab, white bars – 100 nM pertuzumab, grey bars - 100 nM pertuzumab and CK2/GSK3β overexpression.

Comparison of the response-signal characteristic of signal transduction system of PE04 ovarian carcinoma cell line and NIH 3T3 fibroblasts

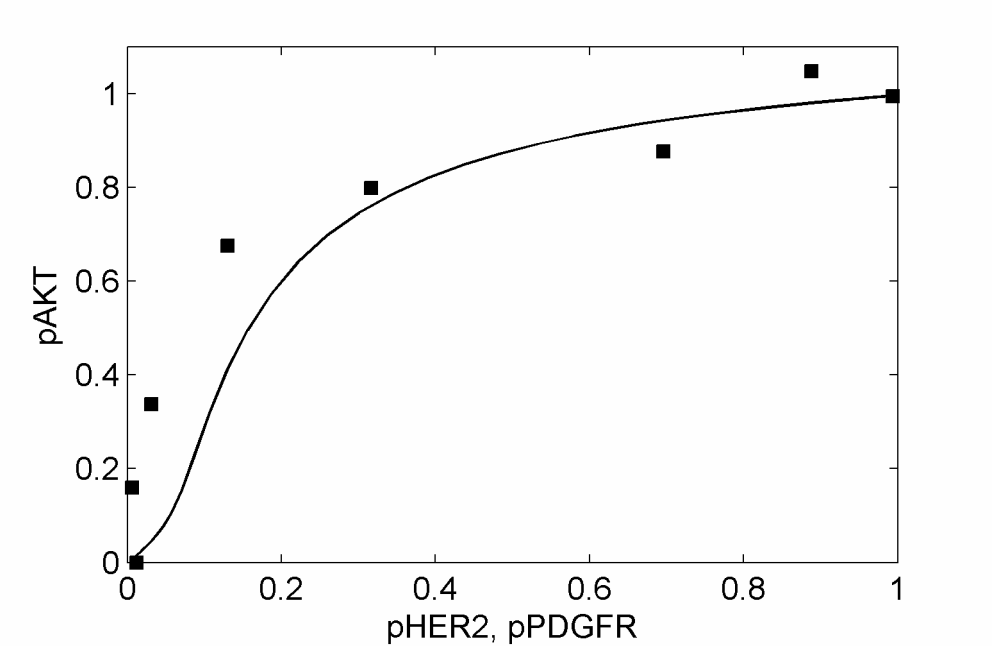

Fig. S5. Comparison of the theoretical pAKT dose dependence on pHER2 signal for PE04 ovarian carcinoma cell line with experimental pAKT dose dependence on phosphorylated platelet-derived growth factor receptor, pPDGFR (time-integrated) for NIH 3T3 fibroblasts [2].

References

1. D. Faratian, A. Goltsov, G. Lebedeva, S. Moodie, P. Mullen, C. Kay, I. H. Um, S. Langdon, I. Goryanin, D.J. Harrison, Cancer Res. 69 (2009) 6713.
2. Park CS, Schneider IC, Haugh JM. J. Biol. Chem. 278 (2003) 37064.