

Extended model of PI3K, Erk MAPK, PKC and AMPK signalling systems

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Overview

1 Network

2 Insulin Simulations

- +/- Amino acids
- Amino acids +/- insulin
- PI3K inhibition
- Akt Inhibition
- mTORC1 Inhibition
- TSC2 Knockdown

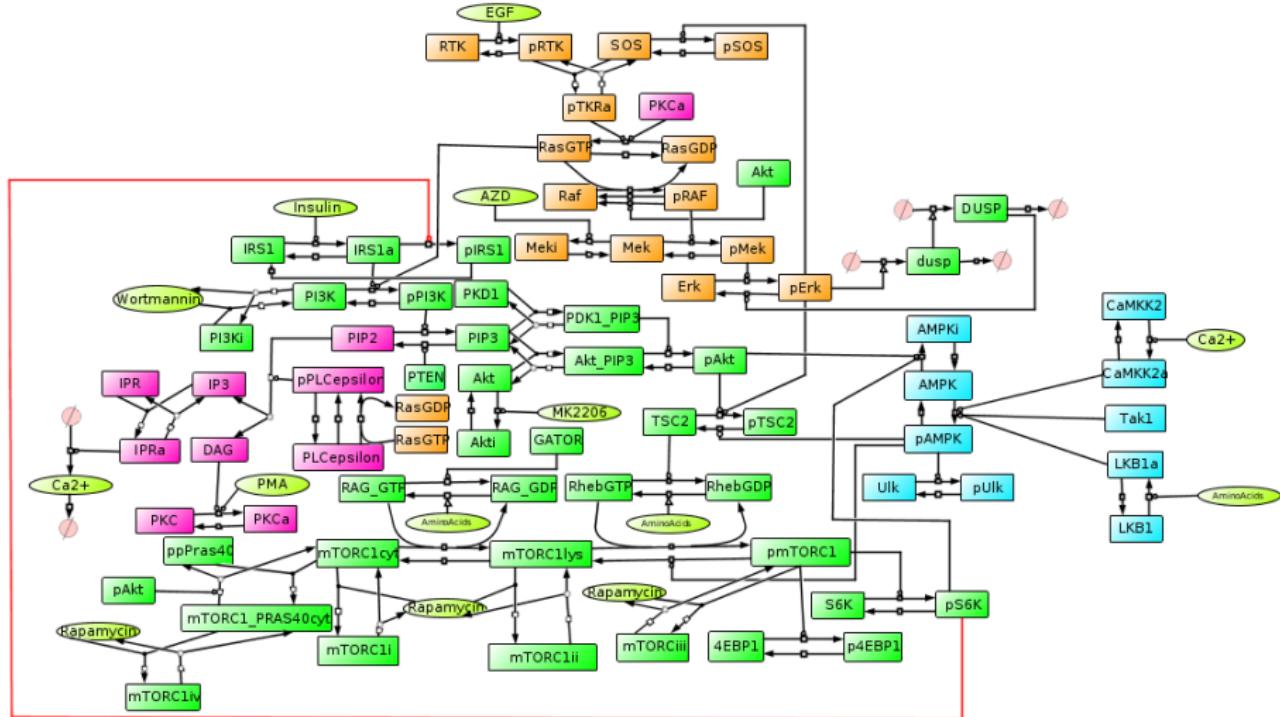
3 EGF Stimulation

- +/- EGF Stimulation
- +/- Mek Inhibition

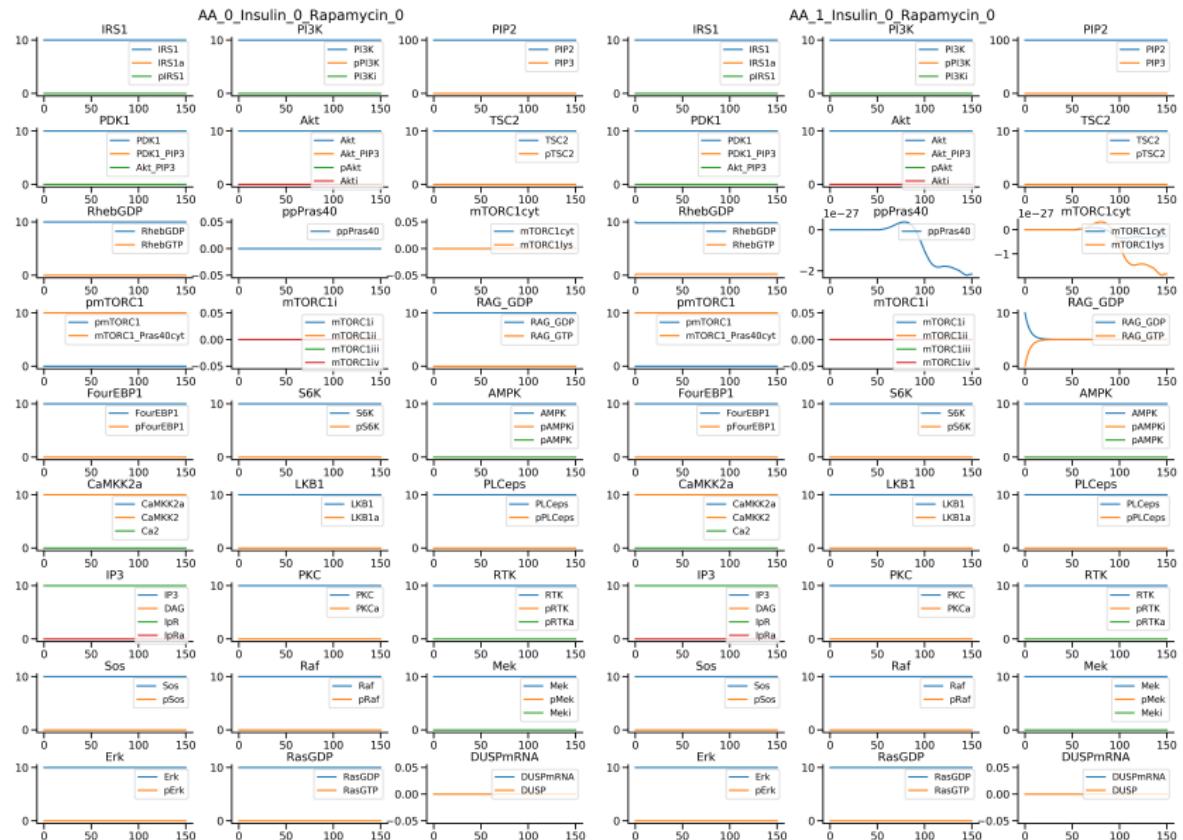
4 PMA Stimulation

5 Observations

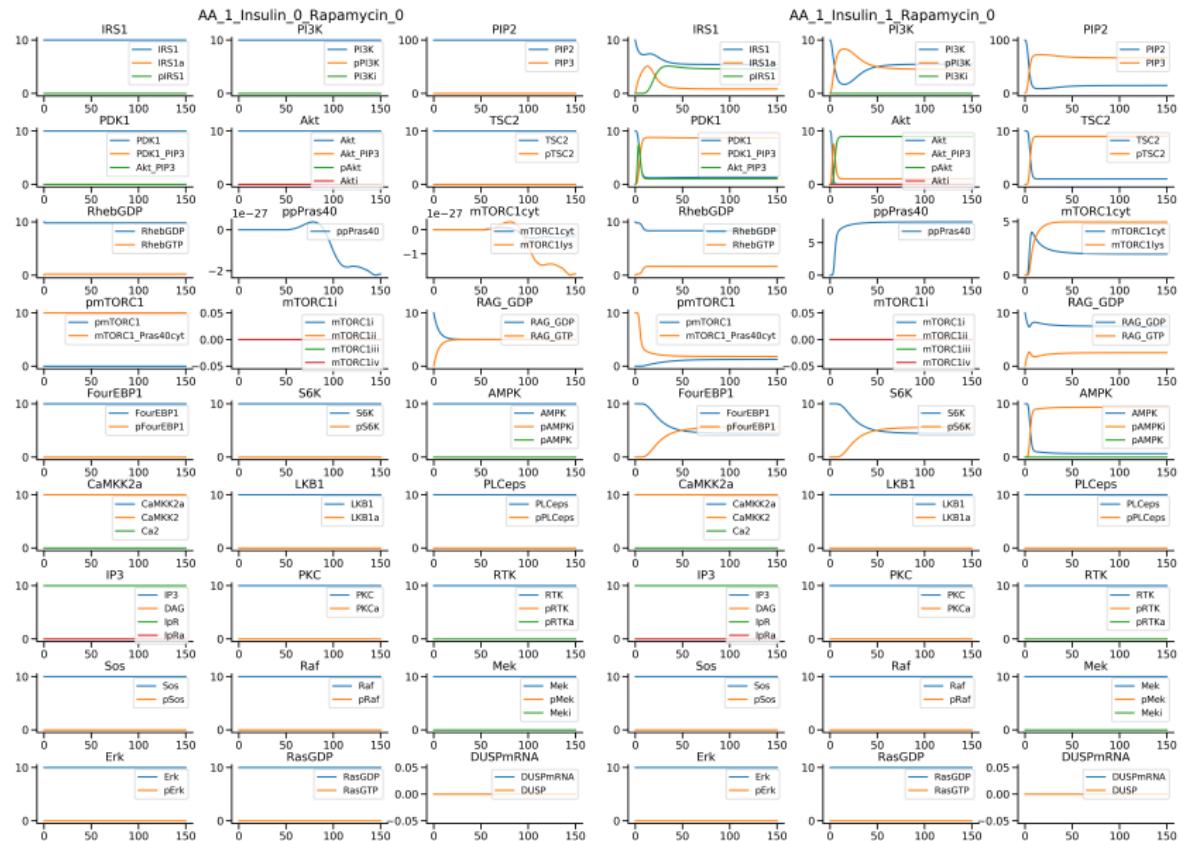
Network



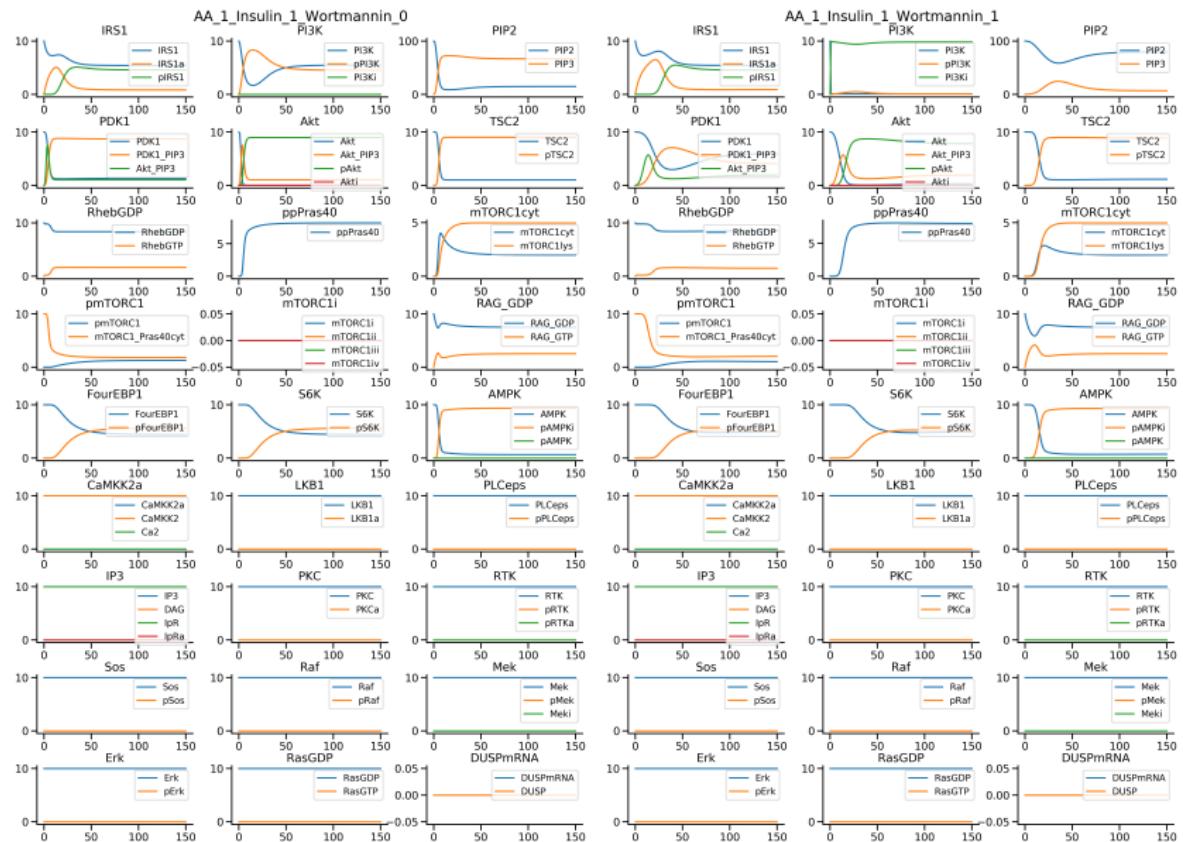
+/- Amino acids



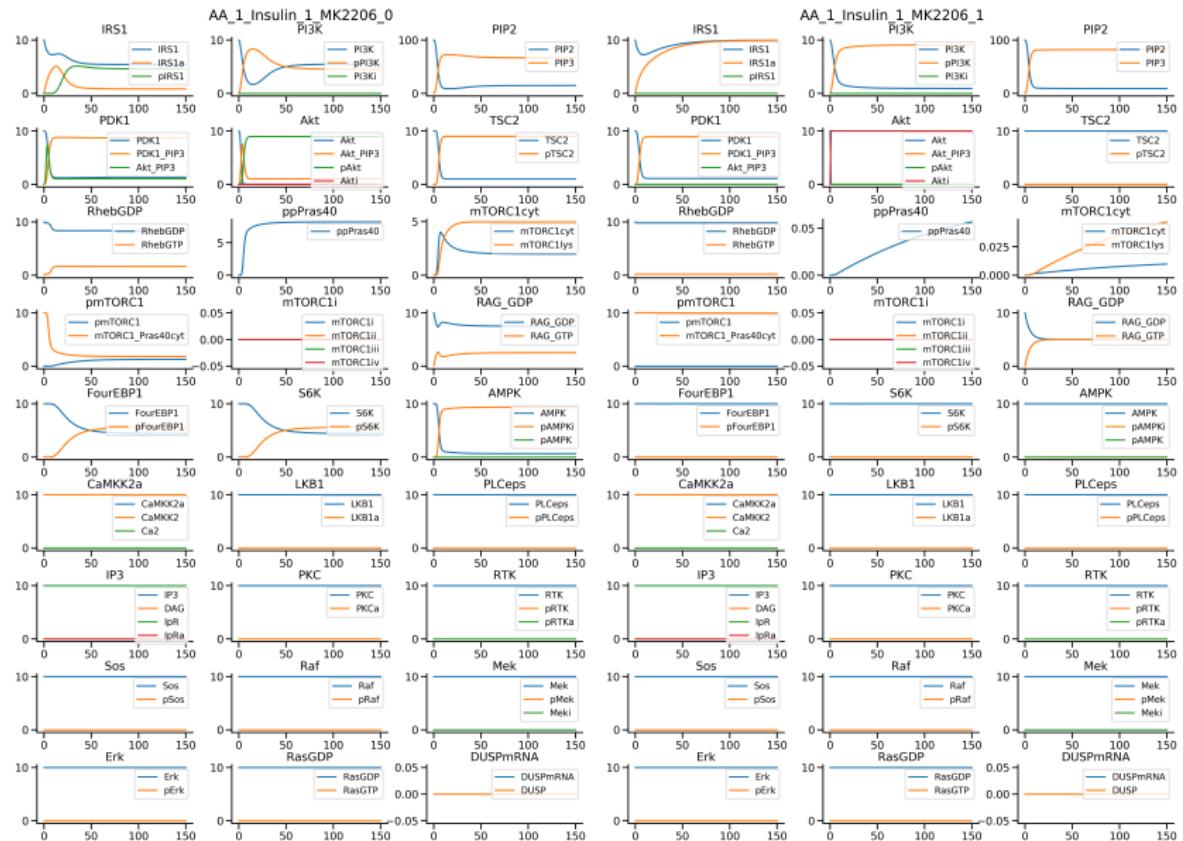
Amino acids with insulin



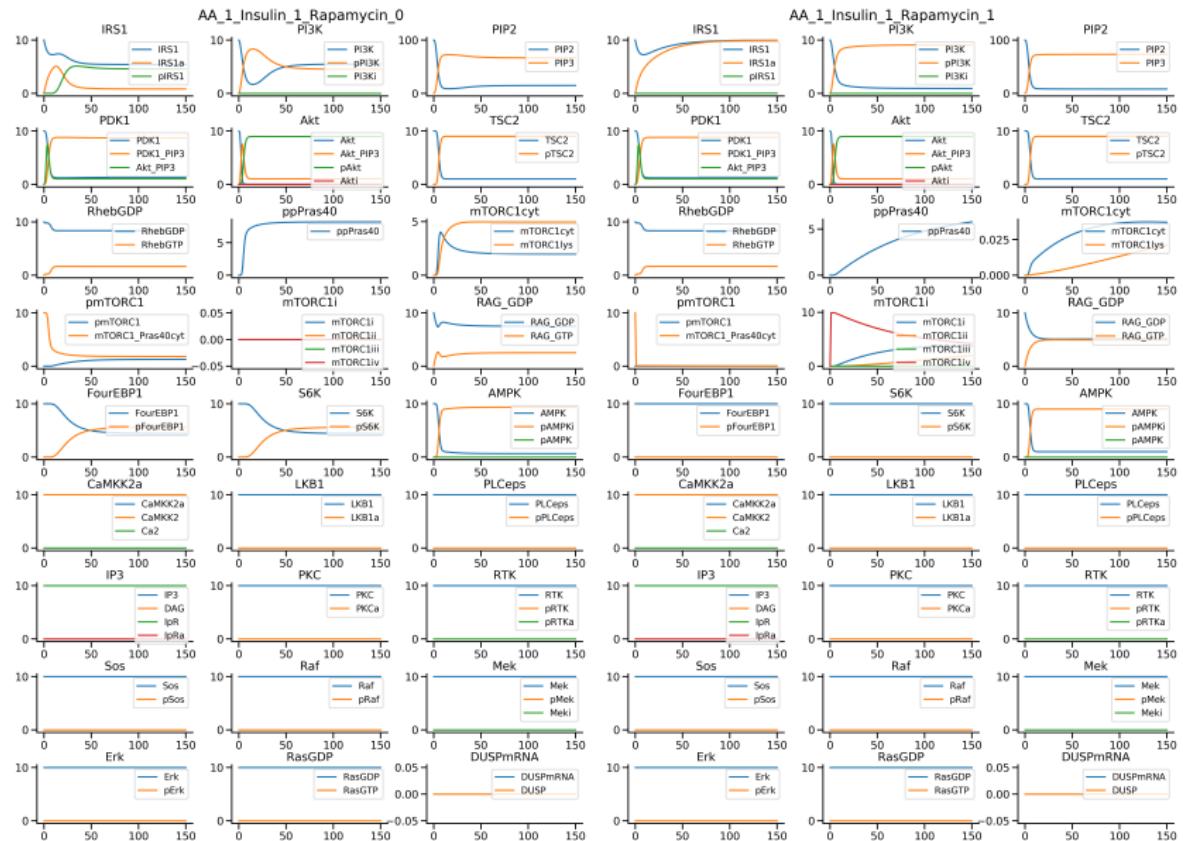
Insulin and amino acids +/- wortmannin



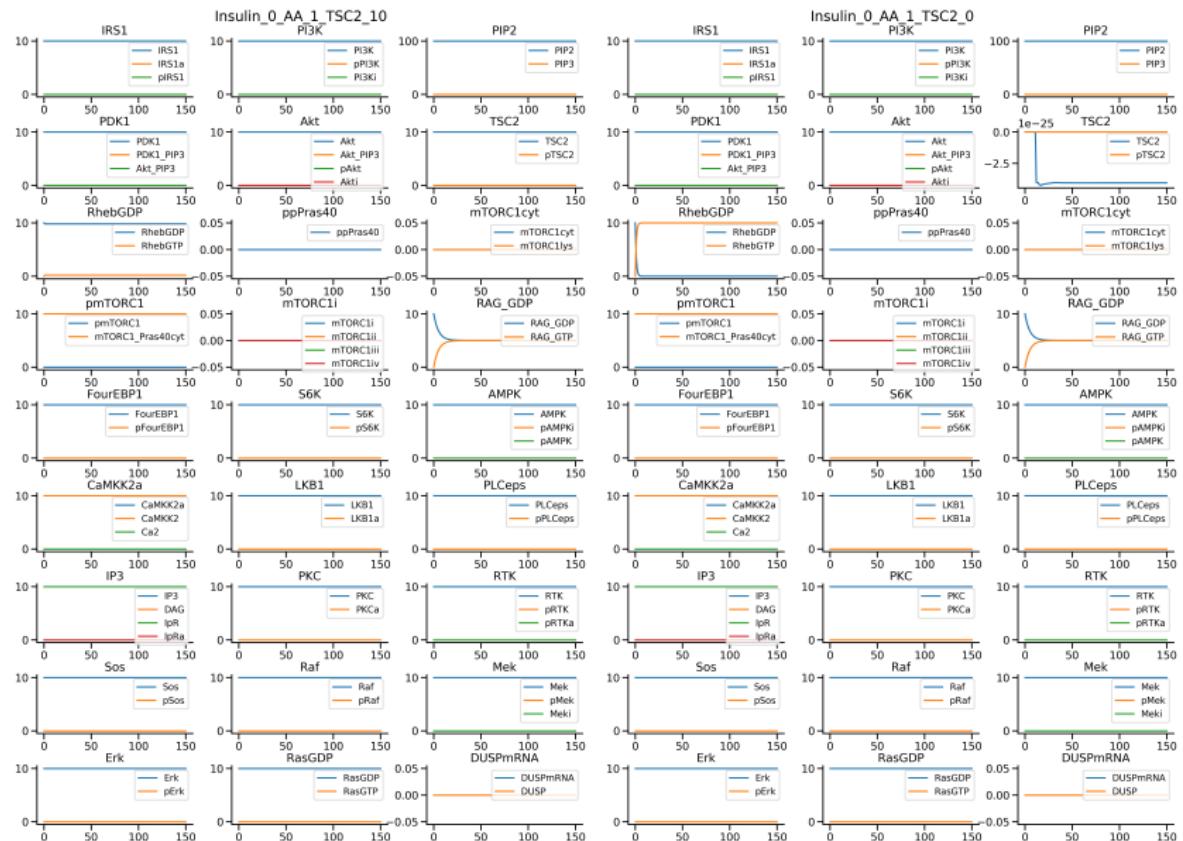
Insulin and amino acids +/- MK2206



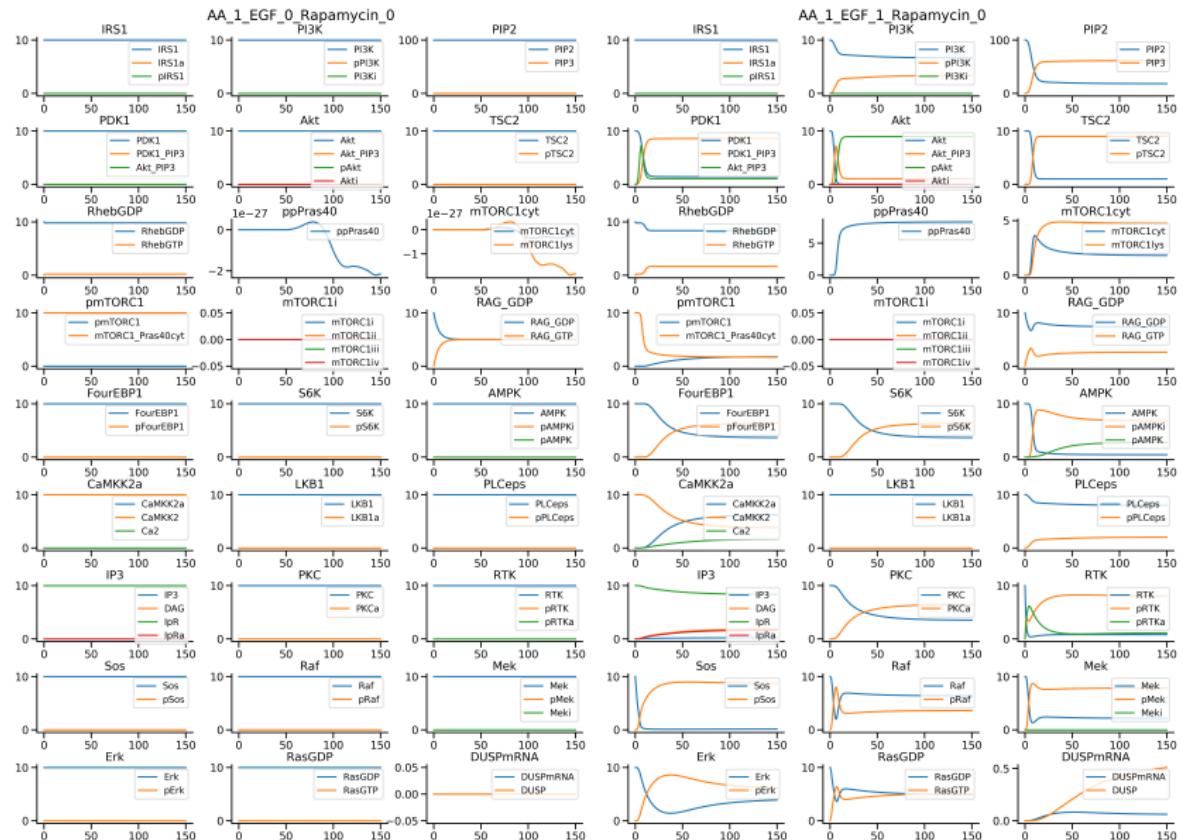
Insulin and amino acids +/- rapamycin



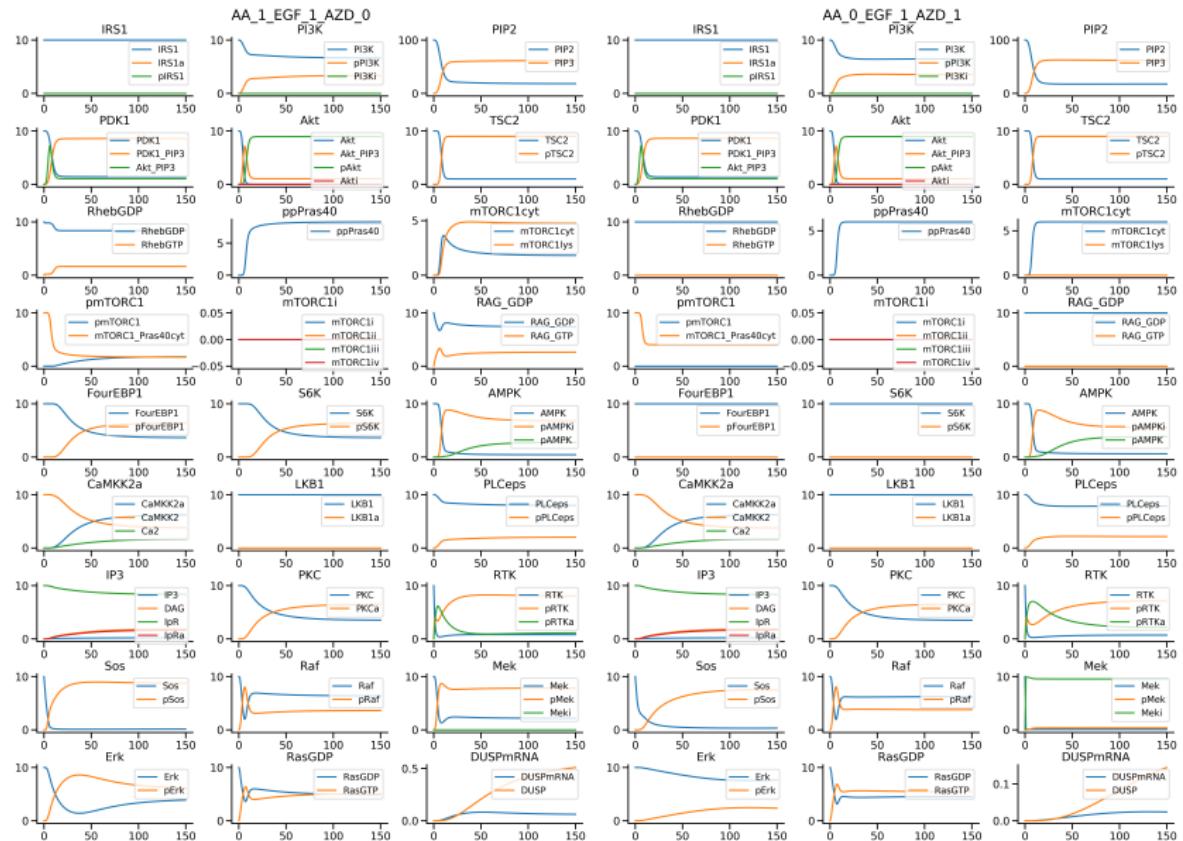
Insulin, amino acids and TSC2^{+/+} and TSC2^{-/-}



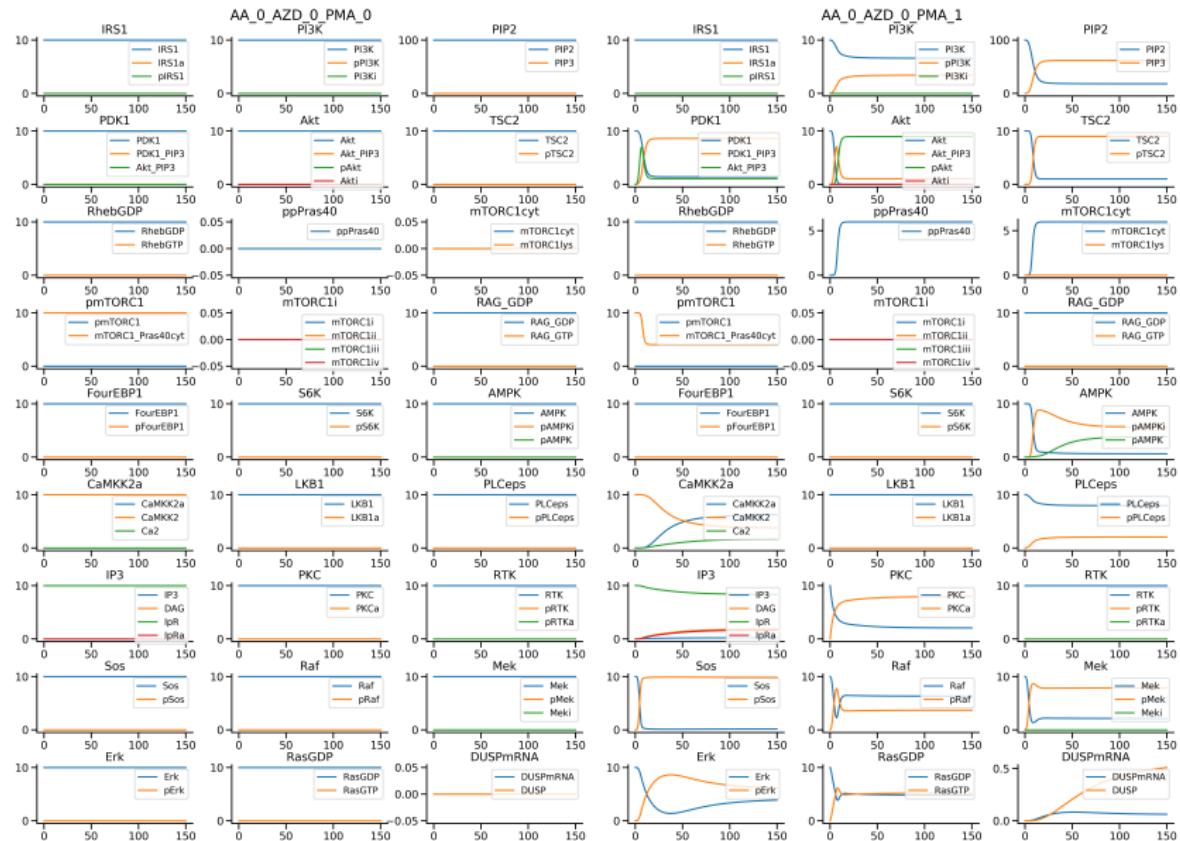
\pm - EGF stimulation (in presence of amino acids)



EGF stimulation and Mek inhibition



Stimulating PKC with PMA



[?]

- PMA causes S6K phos, Erk1/2 phos and RSK phos. Rapamycin inhibits S6K phos by PMA, but not RSK or Erk. mTORC activity is slightly inhibited by mek inhibitor
- Rheb overexpression leads to over activation of S6K
- Rheb is required for the PMA-induced activation of mTORC1 signaling

[?]

- Insulin, IGF1 and EGF all stimulate Akt phos at Ser473 after 10 minutes of stimulation
- However, in TSC2 complex knockdown the response to Insulin and IGF1 but not Erk are abrogated.
- IRS1 is regulated at the transcriptional level by its own system, as indicated by loss of this ability in TSC2 negative cells. This mechanism is not currently built into the model.