INFERRING KINASE ACTIVITY PROFILES FROM PHOSPHOPROTEOMIC DATA

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ESTIMATING ENRICHMENT IN A KINASE NETWORK

Weighted kinase-substrate network → prune → Binary network → hypergeometric p-value
ESTIMATING ENRICHMENT IN A KINASE NETWORK

Weighted kinase-substrate network

Kinase-Substrate Networks: NetworKIN (Horn et al., Nature Methods, 2014)

prune

50

Binary network

hypergeometric

p-value

Median p-value

FDR 0.05

FDR corrected

Fraction Significant >0.5
Why Heuristic Pruning, Binary Graphs?
- Limits the number of kinases a single site gives evidence for
- Increases discriminability of kinase-substrate networks
- Limits bias of individual site emphasis
- Theoretical null distribution
APPLICATION: BCR-ABL DRIVEN CML TREATMENT

Example kinase activity predictions, where CML treated with 20-minute treatment with dasatinib (EoE) followed by rest for (3 Hr) or (6 Hr), and before treatment (Pre).

*Phosphoproteomic data from Asmussen et al. (2014) Cancer Discovery*
Comparison of HER2-status with predicted HER2-activity for breast cancer patients.

*Phosphoproteomic data from Mertins et al. (2016) Nature (1053 pTyr sites x 107 patients)*

44% of HER2- tumors are detected as HER2-active

26% of HER2+ tumors are not HER2-active
PDX Breast cancer phosphoproteomics

WHIM 8, 35, 6, 14 treated with lapatinib, *responded
HER2+ patients phosphoproteomics from microscaled biopsies. Treatment on chemo and HER2 therapy

Satpathy et al., Nat Commun. (2020)
FUTURE WORK

• FDR – correction is overly stringent
• How to combine kinase network predictions (see Bingjie Xue Poster)
• Predicting sensitivity via kinase activity profiles