Data driven refinement of gene signatures for enrichment analysis and cell state characterization

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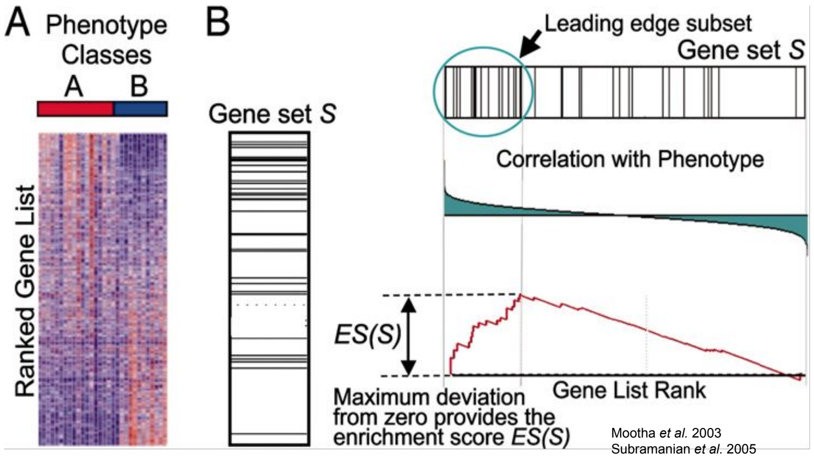
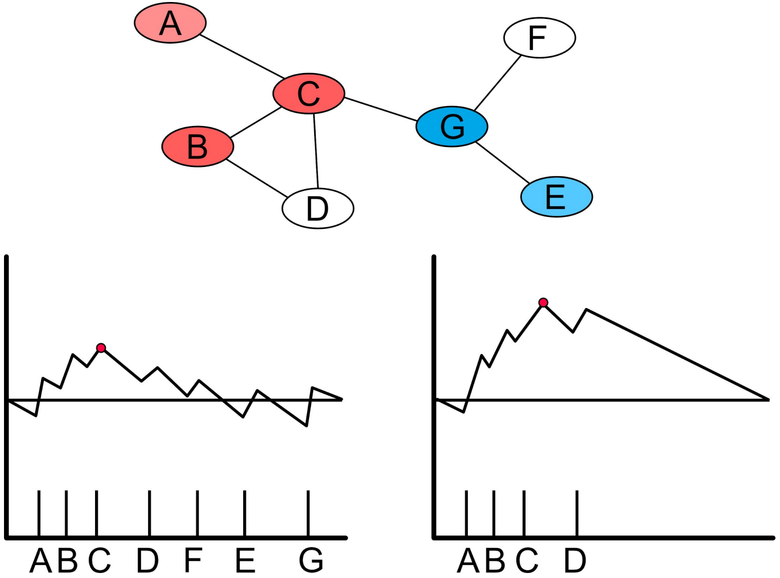
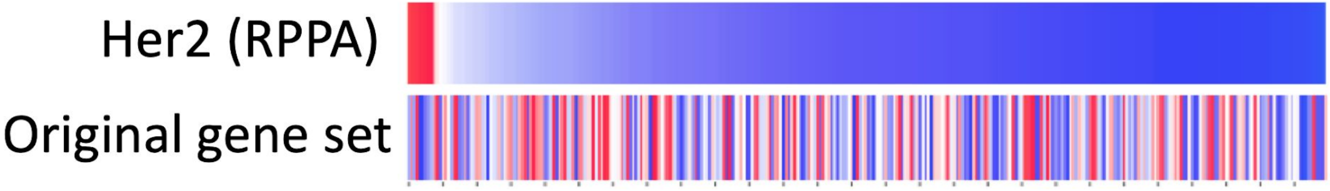
GSEA - Gene sets can lack context-specific coordinate regulation



Mootha *et al.* 2003
Subramanian *et al.* 2005



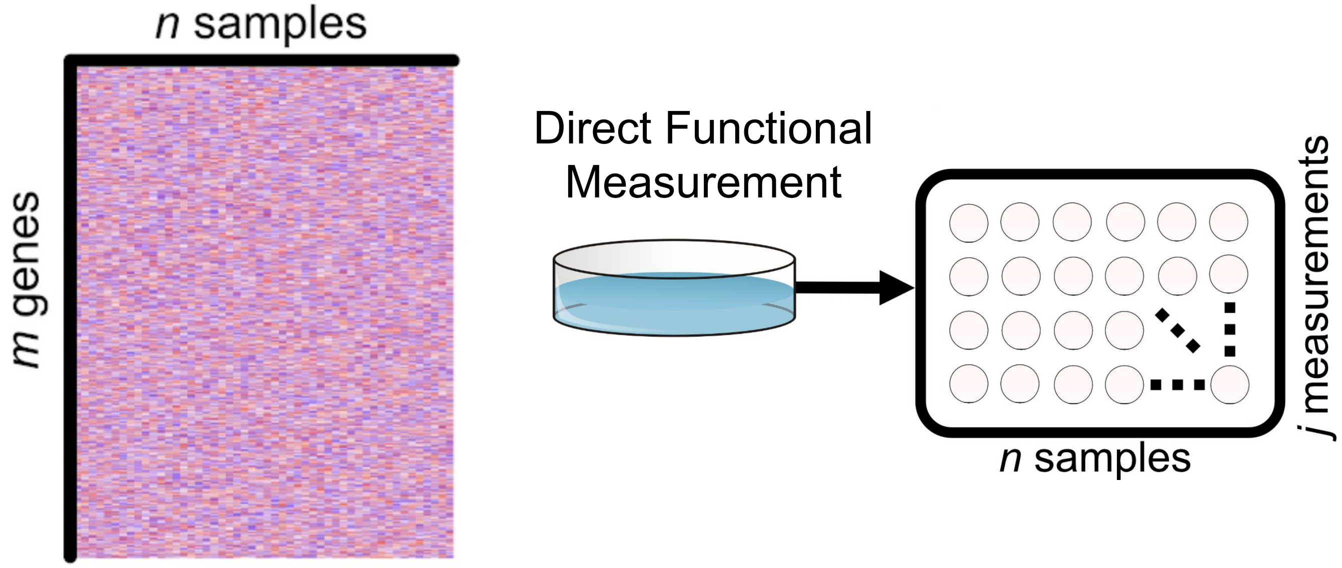
Example: REACTOME_SIGNALING_BY_ERBB2



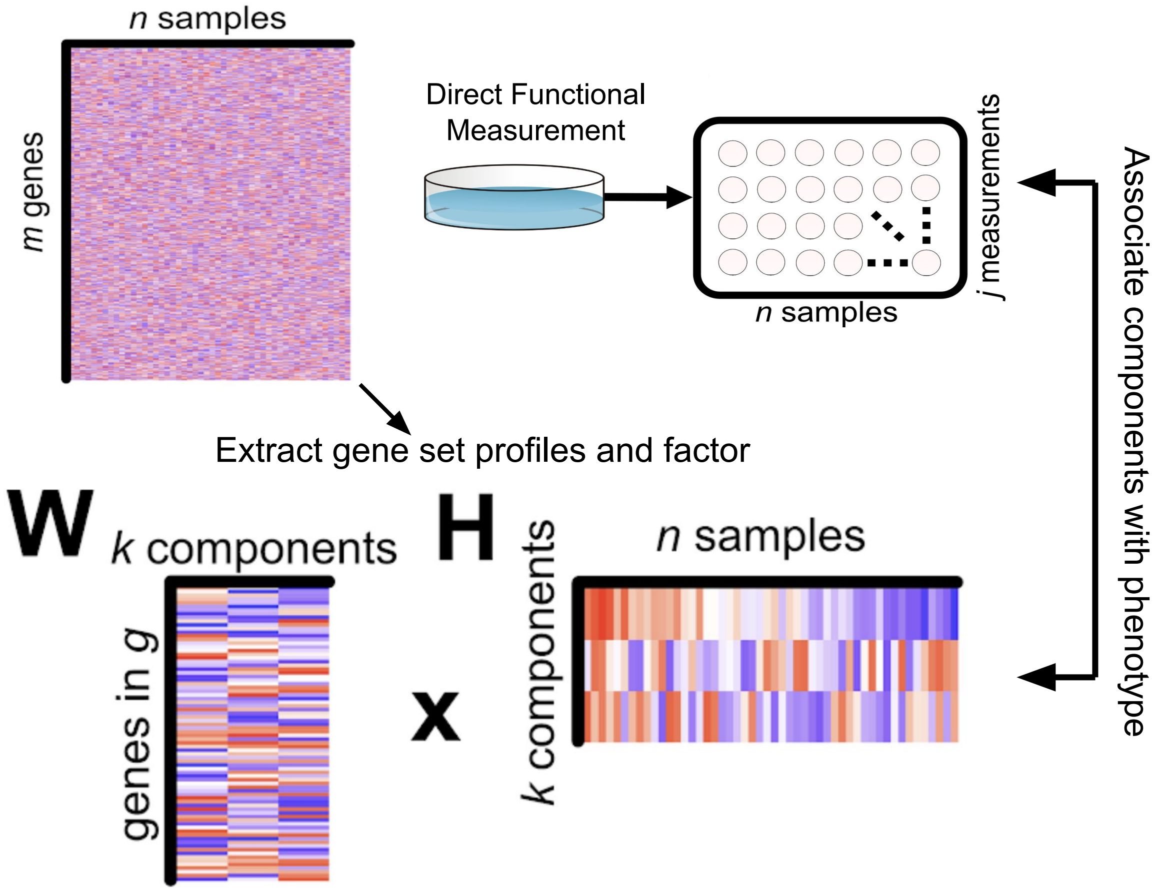
IC	p-value
0.30	0.04

Finding patterns in gene expression data

- Now we have large compendia of expression data *and* functional measurements of the same samples (RPPA, CRISPR essentiality, etc.)
- **Proposal: A data-driven method that uses these compendia to refine a gene set in order to increase its sensitivity and specificity**

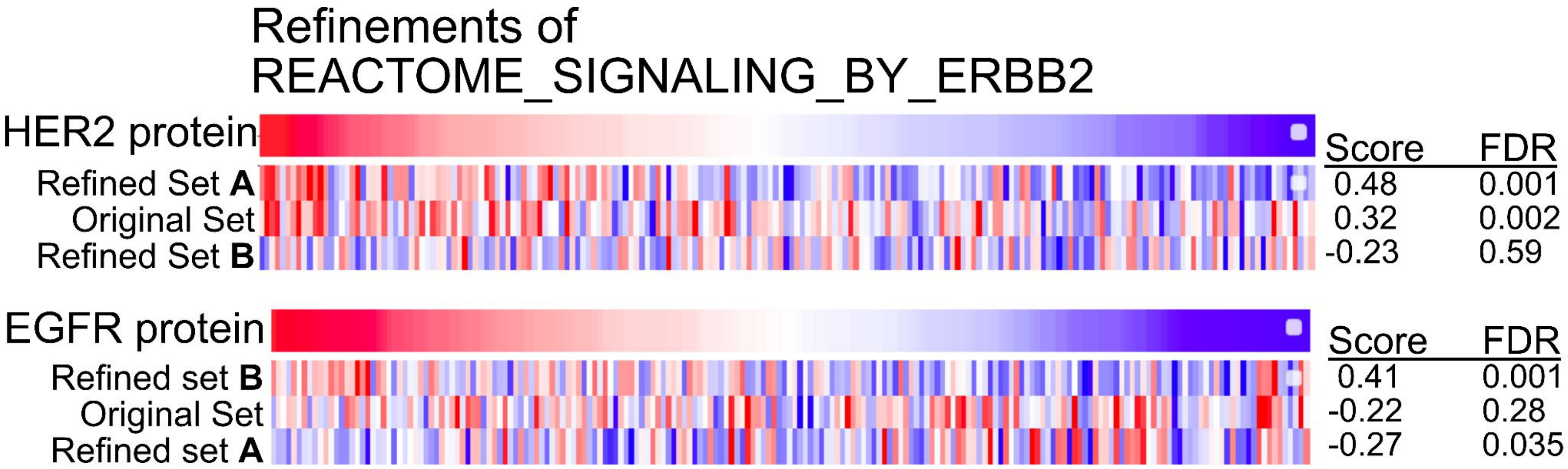


Finding patterns in gene expression data



- Non-negative matrix factorization finds lower-dimensional **patterns** in gene expression data
- Goal: Use patterns found within expression of existing gene sets to define new refined gene sets
- Decomposing gene set-defined subsets of transcriptional profiles from large compendia to identify underlying functional components.

Multi-phenotype refinement of ERBB2 signature



Refinements of REACTOME_SIGNALING_BY_ERBB2

HER2 protein	Score	FDR
Refined Set **A**	0.48	0.001
Original Set	0.32	0.002
Refined Set **B**	-0.23	0.59

EGFR protein	Score	FDR
Refined set **B**	0.41	0.001
Original Set	-0.22	0.28
Refined set **A**	-0.27	0.035

- Gene set refinement identifies two components associated with Her2 and EGFR protein abundance, respectively.
- Her2 homo-dimerizes or heterodimerizes with EGFR (Hsu & Hung 2016)
- Gene sets may represent two signaling axes

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