BST281: Genomic Data Manipulation, Spring 2017

Wednesday 13: Genetic Perturbations and Interactions

**Understanding biological systems**

* Option 1: Create a model from first principles that explains experimental observations
  + This is the domain of Mathematical Biology and Systems Biology
* Option 2: Break (or, more generally, perturb) the system and see how it responds (“reverse genetics”)
  + If you perturb gene X and phenotype Y changes, infer that X is related to Y (maybe not directly)
  + Contrast with “forward” (traditional) genetics = work backward from a phenotype to a gene

**Single-gene perturbations**

* Ways to perturb a biological system (typically via a gene or gene product)
  + Delete the gene, e.g. by CRISPR-Cas9 technology
  + Change expression of the gene (change of promoter, RNA interference)
  + Disable protein product with a drug/small molecule
* Phenotypes to measure
  + Low-dimensional phenotypes such as “alive/dead” or “relative growth/fitness”
  + High-dimensional phenotypes such as organismal/cell morphology (less common)
  + High-dimensional phenotypes such as RNA/protein expression screening (more common)
* A perturbation results in a list of measured (downstream) changes
  + We aim to reconstruct the activities (e.g. intervening regulation/pathways) in the middle
* Methods for studying changes in high-dimensional phenotypes
  + Gene set enrichment analyses
    - Are downstream perturbations enriched for known processes?
  + Network-context analyses
    - Are downstream perturbations co-localized in a known biological network?
    - Can use to define new functional modules (gene sets)
  + Clustering of phenotypic profiles
    - Another means for defining new functional modules
  + Subset structure and nested effects models
    - Infer mechanistic order (A leads to B leads to C) of perturbations

**Combinatorial perturbations**

* Single-gene perturbations often produce small effects due to evolved redundancy in biological systems
* Instead perturb pairs of genes and look for epistatic effects
  + Non-multiplicative changes in fitness (e.g. WA=0.5, WB=0.5, WAB≠WA×WB=0.25)
  + WAB>WA×WB 🡪 “not as bad as expected” 🡪 positive (or buffering) epistasis
    - Ex. Two genes in the same pathway – once pathway is “broken” it can’t get worse
  + WAB<WA×WB 🡪 “worse than expected” 🡪 negative (or antagonistic) epistasis
    - Ex. Two genes in parallel pathways – can delete one or the other but not both
  + Epistasis can also involve non-additive changes in high-dimensional phenotypes, e.g. expression
* Epistatic interactions tend to co-associate with other functional relationships (see examples above)
  + Can be used to define new functional modules
* Epistatic “covering” can help infer order information within a pathway
  + “Loss of A+B” more similar to “loss of A” than “loss of B” 🡪 A upstream of B

**Suggested reading**

* Pevsner, Ch. 14, pp. 648-670
* Costanzo, Michael, et al. "[The genetic landscape of a cell](http://science.sciencemag.org/content/327/5964/425)." Science 327.5964 (2010): 425-431.