From Genome Function to Biomedical Insight: ENCODE and beyond

Understanding basic biology using functional genomics: solving the genotype-phenotype problem

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What have we done?

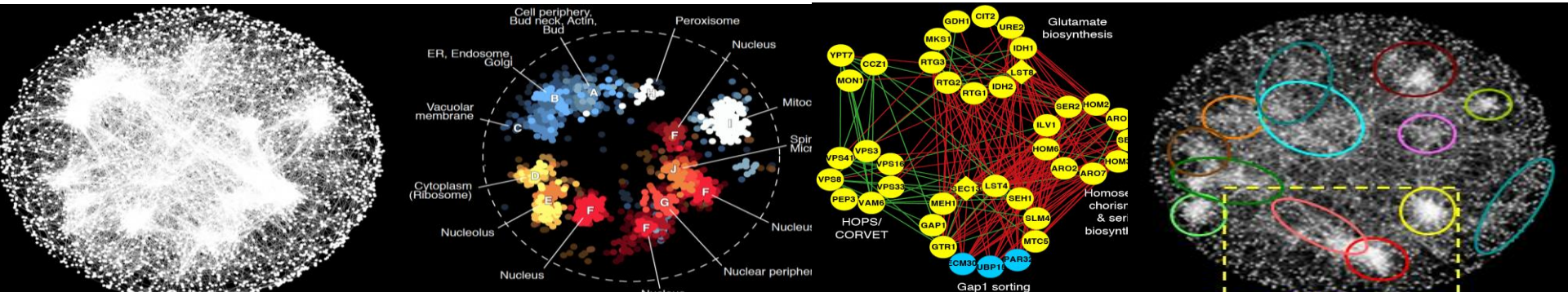
Generated data that predicts functional elements in the human genome (and selected model genomes)

What do we need to do?

- Generate unbiased, genome-scale <u>functional</u> data that will enable useful modeling of biological processes
- Develop methods to examine regulatory events across the genome on timescales relevant to molecular mechanisms – explore combinatorial perturbations
- enable development of quantitative, predictive models

How do we do it?

- Engage model organism and human genetics communities in a joint effort to systematically define the genotype-phenotype relationship



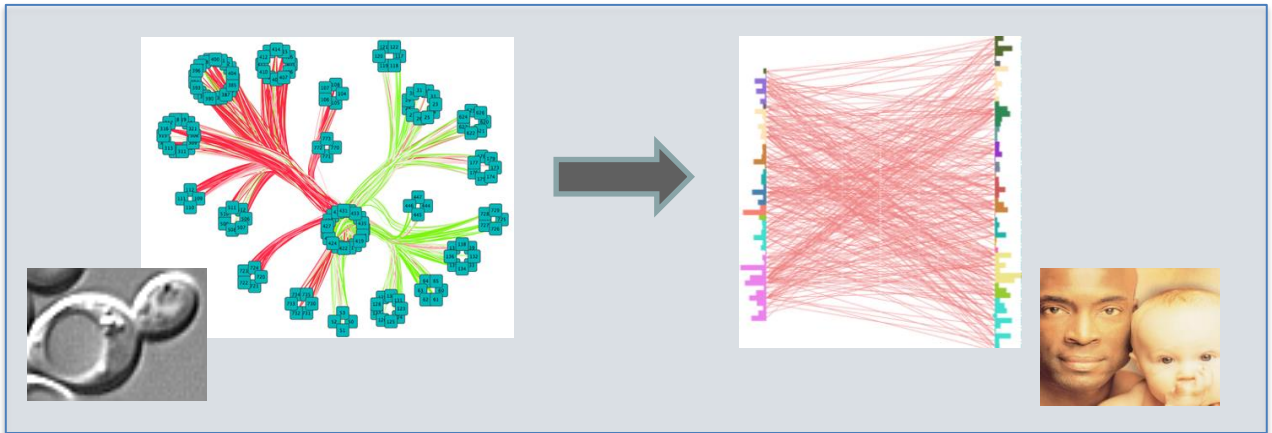
A model project: analysis of genetic interactions in yeast

Reagents for systematic genetics in yeast

- **Deletion array – non-essential genes**
- **Arrays of conditional alleles of essential genes**

- Most single genetic perturbations are of little phenotypic consequence
- The eukaryotic cell is highly genetically buffered
- Need methods for systematic study of genetic interactions
- Need sensitive assays to assess phenotypes in mutant backgrounds

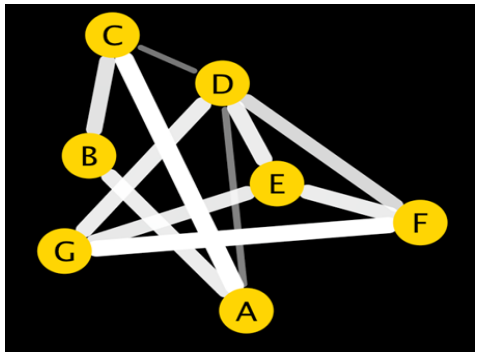
GFP-collection



Assaying Genetic Interactions

<u>Overall Project Goal</u>:

Use yeast mutant arrays to systematically explore genetic interactions



A **Genetic Interaction** occurs if an allele of one gene combines with the allele of another gene to generate an unexpected double mutant phenotype.

Can we use **genetic interactions** to systematically define gene function, biological pathways; connections between bioprocesses; general principles of genetic interactions; explain the missing heritability common in genetic studies of complex diseases

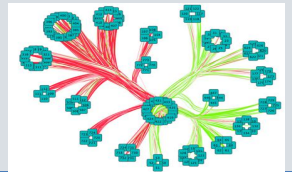
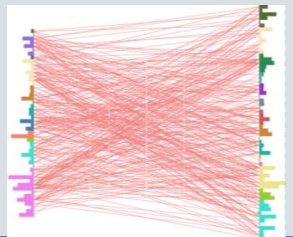
The next phase (now what?):

What areas should NHGRI support to facilitate understanding of basic biological questions/processes? What are the gaps?

"Big Picture' Gap: we need to functionally annotate the human genome through systematic perturbation, which requires considerable investment in unbiased genome-scale functional data generation, in a variety of experimental systems

Why will filling this gap be useful?

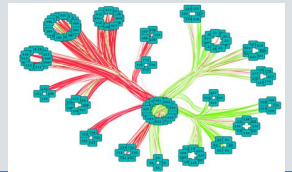
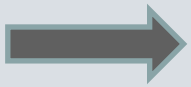
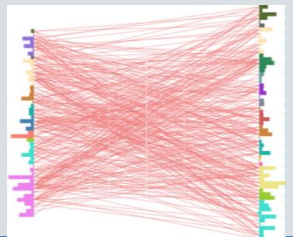
Experience from the yeast community tells us that both systems biologists and more traditional biologists benefit from large-scale, unbiased investigation - to understand the function of biomedically-relevant genes and pathways, they must be considered in their global cellular context.


How to fill the gap – technologies, data generation, projects?

Apply what we've learned about systematic functional annotation of eukaryotic genomes in yeast to human cells

-requires continued support of model system projects to develop computational methods and models and to produce reference maps and 'classifications'
-requires investment in establishing community-wide resources, like genome-scale mutant collections, for efficiently constructing and characterizing genetic perturbations
-requires tools for rapid and quantitative analysis of cell states and phenotypes automated image analysis of cell biological read-outs
-we need to consider genetic interactions, on a large-scale

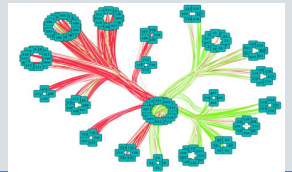
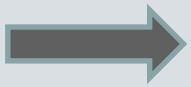
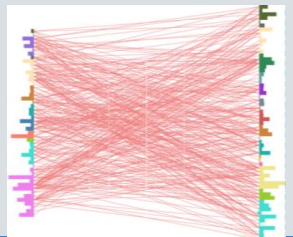






How to fill the gap – technologies, data generation, projects?

Phenotypic readouts of gene perturbation (regulatory element perturbation): Genetic interaction profiles

Genetic interaction mapping in human cells

- Continued technology development for genome engineering
- Map essential genes/measure growth rates across selected cell lines
- Use single perturbation information to choose query genes for full-genome genetic interaction screens (broad biological representation; information-rich queries)
- Functionally rich reference map for interpreting consequences of perturbing putative regulatory elements
- Combinatorial genetic perturbations will be necessary for useful functional annotation


How to fill the gap – technologies, data generation, projects?

Phenotypic readouts of gene perturbation (regulatory element perturbation): "BIG Data" cell biology

- Develop 'tool-kit' of reporters (e.g. fluorescent markers of all subcellular compartments; markers of cell cycle position; reporters of TF activity
- Produce quantitative, single cell data on reporter activity/subcellular compartment phenotypes after genetic/environmental perturbation
- Need a comprehensive set of data from accessible model system to enable intelligent selection of perturbations/conditions to choose for human cell screens
- Need serious effort to improve computational image analysis of cell images
- -move towards 'plug and play' approach (deep learning?) that can be applied to interpret any biological image

Community project (100s of labs)?