From Proteomics to Systems Biology

Integration of “omics” - information
Outline and learning objectives

“Omics” science provides global analysis tools to study entire systems

• How to obtain omics - data
• What can we learn? Limitations?
• Integration of omics - data
• In-class practice:
  Omics-data visualization
Omics - data provide systems-level information

Joyce & Palsson, 2006
Omics - data provide systems-level information

Whole-genome sequencing

Microarrays

2D-electrophoresis, mass spectrometry

Joyce & Palsson, 2006
Transcriptomics (indirectly) tells about RNA-transcript abundances

⇒ primary genomic readout

Strengths:
- very good genome-wide coverage
- variety of commercial products

Drawback:
No protein-level info!!
- RNA degradation
- Post-translational modifications
⇒ validation by e.g. RT-PCR
Proteomics aims to detect and quantify a system’s entire protein content.

**Strengths:**
- Info about post-translational modifications
- High throughput possible due to increasing quality and cycle speed of mass spec instrumentation

**Limitations:**
- Coverage dependent on sample, preparation & separation method
- Bias towards most highly abundant proteins
Omics - data provide systems-level information

- Glycan arrays
- Glyco-gene chips
- Mass spec / NMR of carbohydrates

Joyce & Palsson, 2006
Metabolomics and Lipidomics

Metabolites extracted from cell lysate

Lipids
Metabolomics and Lipidomics

**Metabolomics:**
Large-scale measurement of cellular metabolites and their levels
-> combined with proteome: functional readout of a cellular state

**Limitations / challenges:**
- often low reproducibility of sample preparations
- highly diverse set of metabolites
- large dynamic range

Metabolites extracted from cell lysate
Metabolomics and Lipidomics

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**Lipidomics aim:**
To identify & classify cellular inventory of lipids and lipid interacting factors
-> pathobiological impact

**Limitations:**
- low to medium throughput
- reproducibility difficult
Glycomics identifies cellular glycan components and glycan-interacting factors

Impact:
- antigen recognition
- cell adhesion
- cancer biology

Limitations:
Methods still under development

http://www.functionalglycomics.org
Omics - data provide systems-level information

In silico predictions, organelle proteomics, histocytomics,
‘Localizomics’ tells about sub-cellular locations

Bioinformatics

TargetP
http://www.cbs.dtu.dk/services/TargetP/

PSORT
http://www.psort.org/

Expasy
-> Topology Prediction
http://www.expasy.ch/tools/#proteome

Eukaryotic protein sorting signals

Emanuelsson 2002
‘Localizomics’ tells about sub-cellular locations

**Bioinformatics**
- **TargetP**
  - http://www.cbs.dtu.dk/services/TargetP/
- **PSORT**
  - http://www.psort.org/
- **Expasy**
  - Topology Prediction

**Organellar proteomics**
- Preparation / digestion
- -> 2DE & MS

**Histocytomics**
- e.g. LSC (Laser Scanning Cytometry)
- or LES (Layered Expression Screening)

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**Microscopy techniques**
- -> tagging (GFP)
- -> antibody detection

Spalding *et al.*, 2010

Coulton, 2004
Omics - data provide systems-level information

Joyce & Palsson, 2006
Interactomics

Protein-DNA interactions
- e.g. ChIP on chips

Protein-Protein interactions
- e.g. Antibody-based protein arrays

www.avivasybio.com

Wingren_Borrebaeck_2009
Interactomics

Protein-Protein interactions

-> Yeast two-hybrid screens

All interactomics data need to be validated!!!
=> often false positives!!!
Omics - data provide systems-level information

Joyce & Palsson, 2006
Fluxomics looks at global and dynamic changes of metabolite levels over time.

metabolite identification

metabolic flux analysis

pathway reconstruction

-> integration of omics-data from other sources

http://www.nat.vu.nl/~ivo/flux/  Van Beek, Van Stokkum
Fluxomics looks at global and dynamic changes of metabolite levels over time

But:
Method suffers from same shortcomings as metabolomics:
-> sample prep reproducibility
-> wide variety of metabolites
-> large dynamic range

If $^{14}$C-label: scintillation counting

http://www.nat.vu.nl/~ivo/flux/
Omics - data provide systems-level information

Joyce & Palsson, 2006

Phenotype arrays, RNAi-screens
Phenomics

High-throughput approaches to determine cellular fitness or viability in response to genetic / environmental manipulation

Some commonly used experimental approaches:

⇒ Phenotyping microarrays

http://www.biolog.com/pmTechDesOver.html
Phenomics

=> RNAi screens
Integration of omics-data

The Challenge:
How to integrate extreme abundances of heterogeneous data from very diverse sources?

Interactomics  Phenomics  Metabolomics

Genomics  Transcriptomics  Proteomics

http://systemsbiology.ucsd.edu
Integration of omics-data: Network reconstruction

- Annotated genome
- Cell Physiology & Localizomics
- Literature
  - Known biochemical data
- Interactomics
  - Enzymatic complexes, regulatory/signaling networks
- Fluxomics & Metabolomics
  - Proteomics & Transcriptomics
  - Pathways, capacities, inferred reactions

Functional genomics
Homologies
Integration of omics-data: Network reconstruction

- Annotated genome
- Phenomics
- Cell Physiology & Localizomics
- Literature
  - Known biochemical data
- Interactomics
  - Known enzymatic complexes, regulatory/signaling networks
- Fluxomics & Metabolomics
- Proteomics & Transcriptomics
- Network reconstruction
- Metabolic model

http://systemsbiology.ucsd.edu
Integration of omics-data: Model testing and validation

Annotated genome

Homologies

Cell Physiology & Localizomics

Interactive models

Known biochemical data

Literature

Enzymatic complexes, regulatory/signalling networks

Interactomics

Pathways, capacities, inferred reactions

Fluxomics & Metabolomics

Proteomics & Transcriptomics

Metabolic model

Biochemical & genetic methods

Revised assignments & model functions

New predictions etc.
The holy grail of systems biology:

Automatically updated, genome-scale, comprehensive network reconstructions for any system of interest

=> Advanced projects for some model organisms (Human, mouse, yeast, *E. coli*)

- Toxico-genomics
- Nutri-genomics
- Metabolic disorders
- Cancer biology
- Personalized drug design
- Metabolic engineering
- Meta-Omics

Increasing medical impact