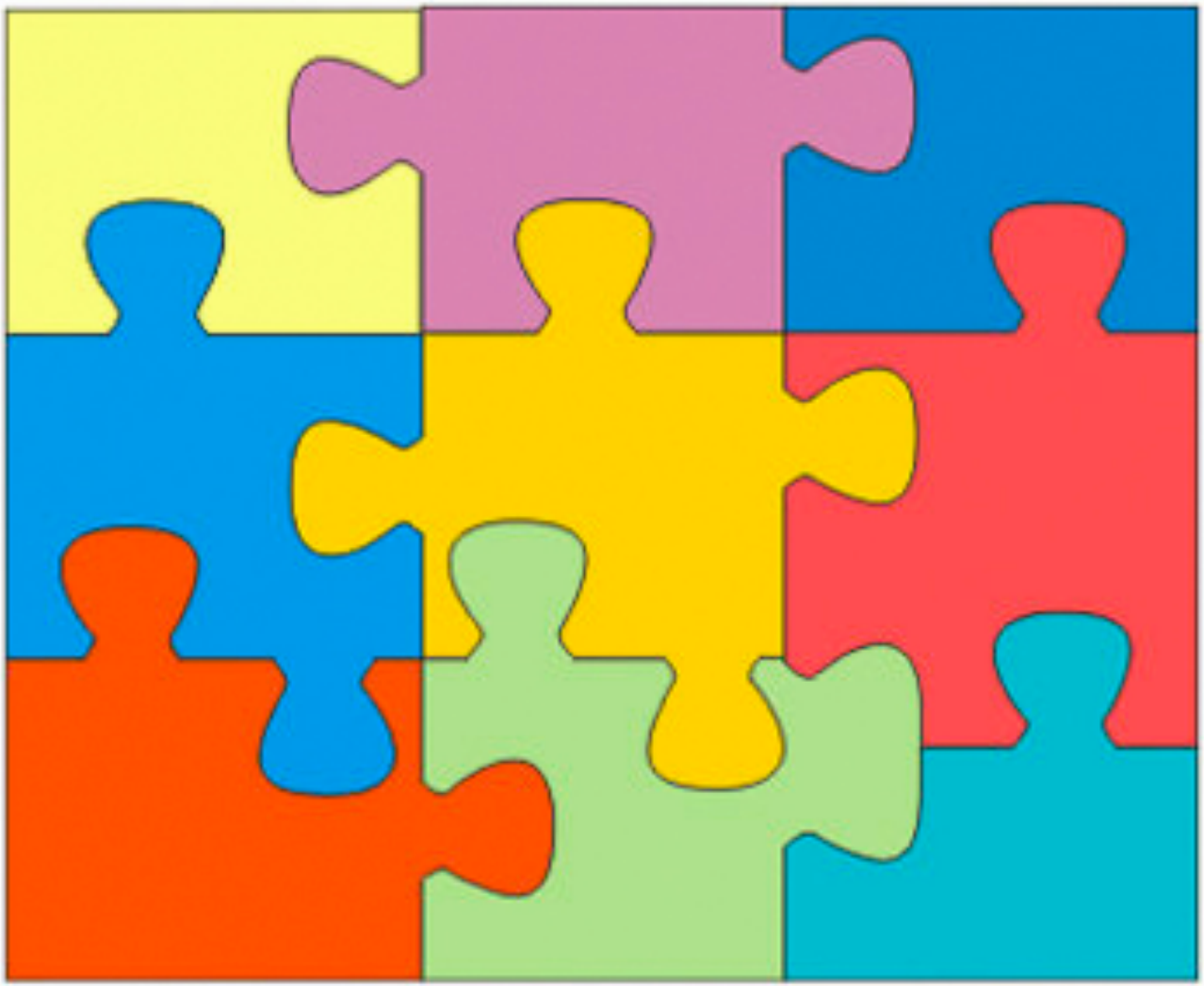
From Proteomics to Systems Biology



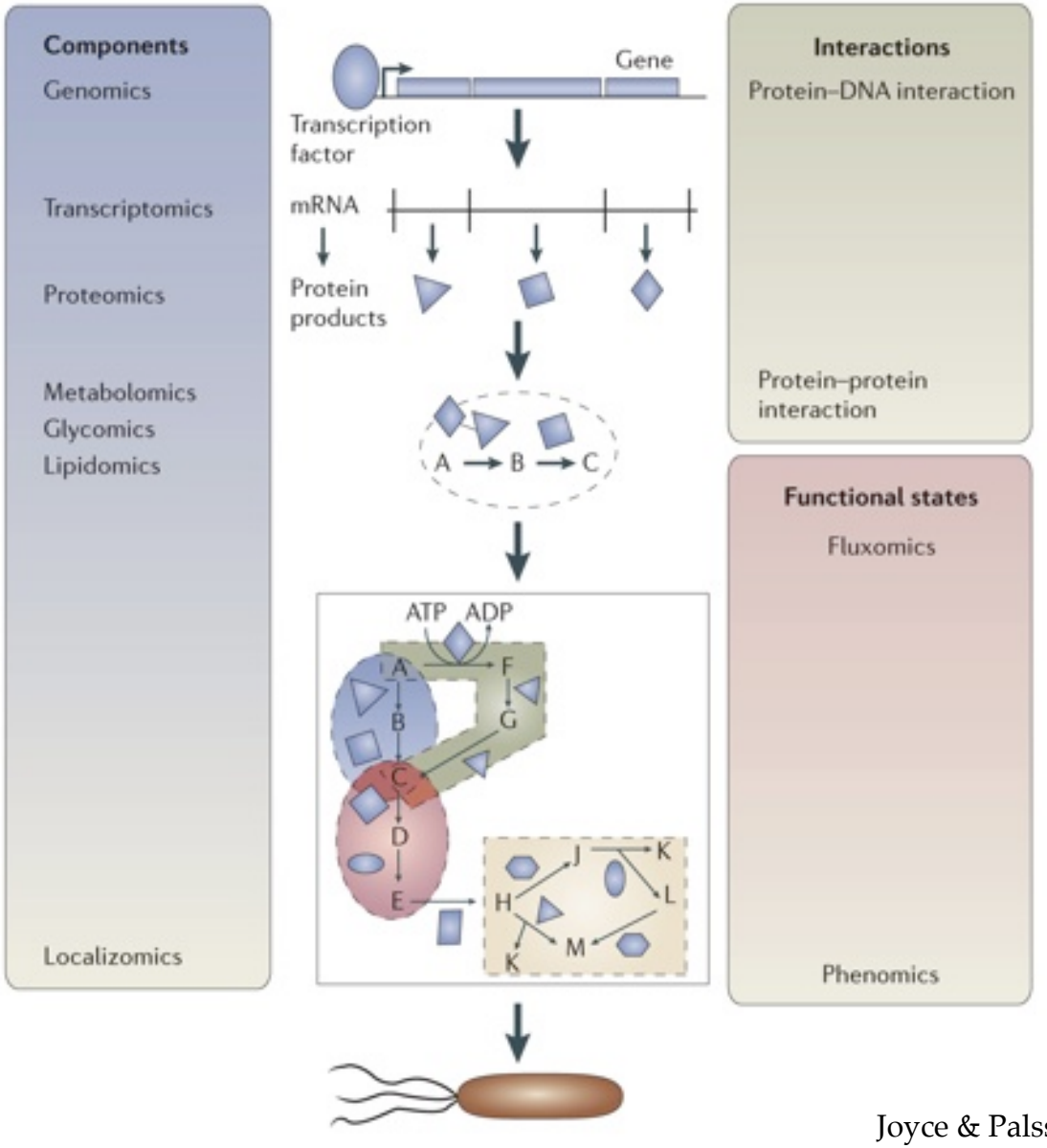
Integration of "omics"- information

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



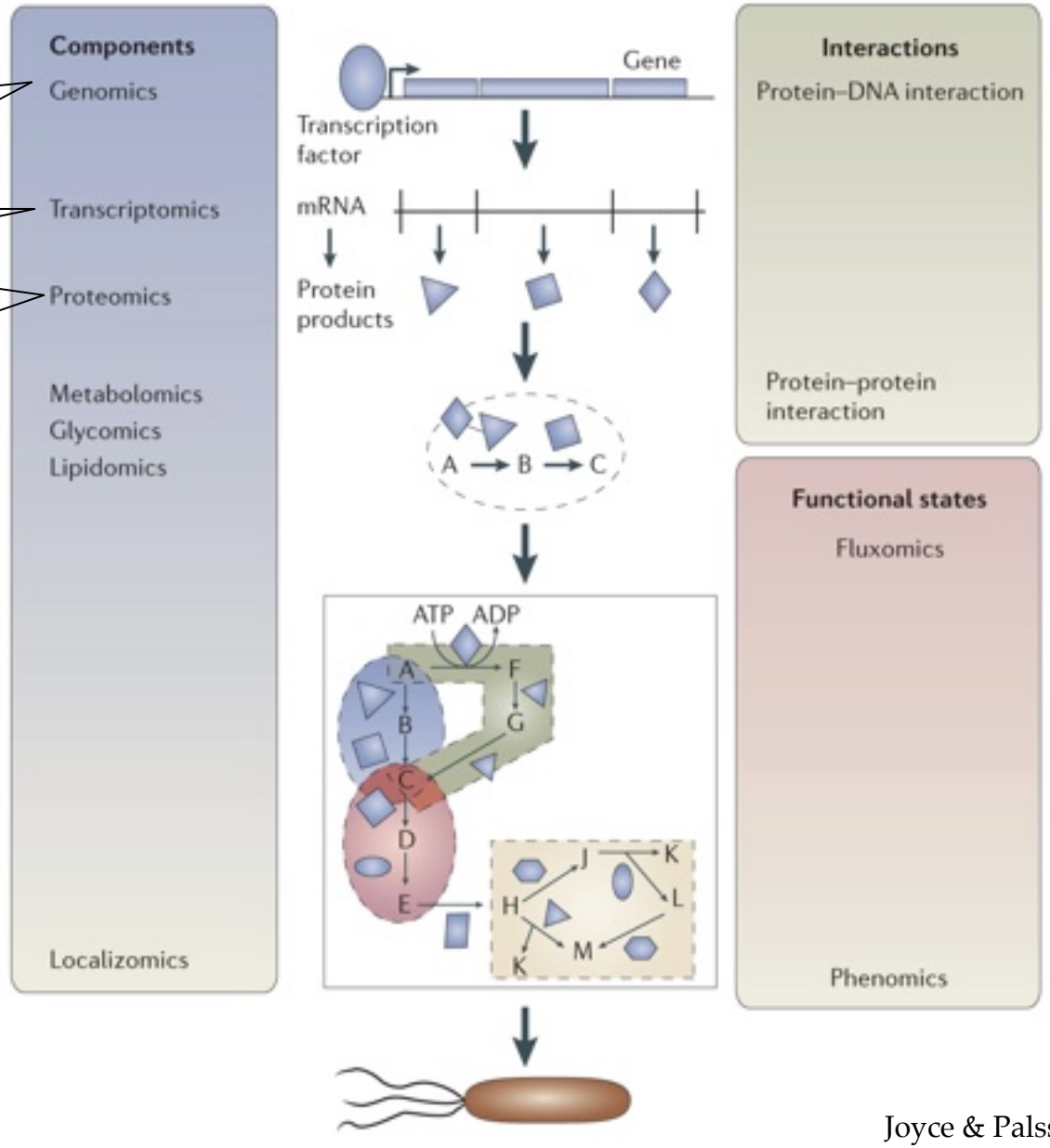
Joyce & Palsson, 2006

Omics - data provide systems-level information

Whole-genome sequencing

Microarrays

2D-electrophoresis, mass spectrometry



Joyce & Palsson, 2006

Transcriptomics (indirectly) tells about RNA-transcript abundances

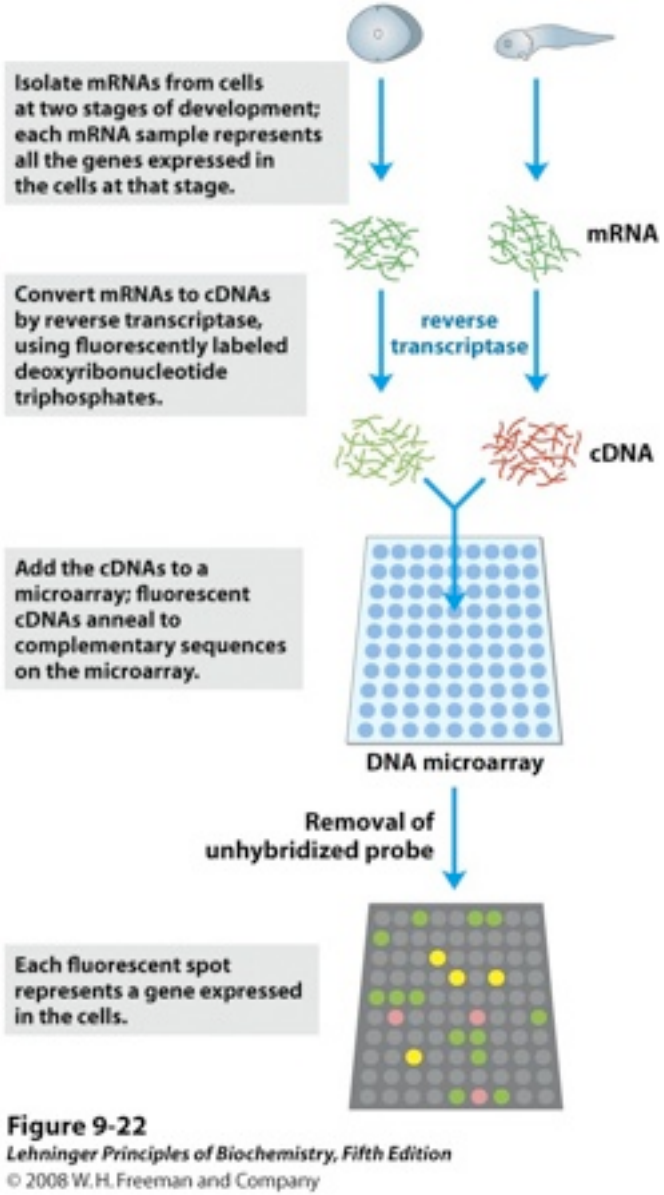


Figure 9-22
Lehninger Principles of Biochemistry, Fifth Edition

⇒ primary genomic readout

Strengths:

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

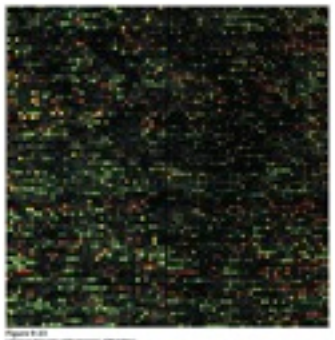
Drawback:

No protein-level info!!

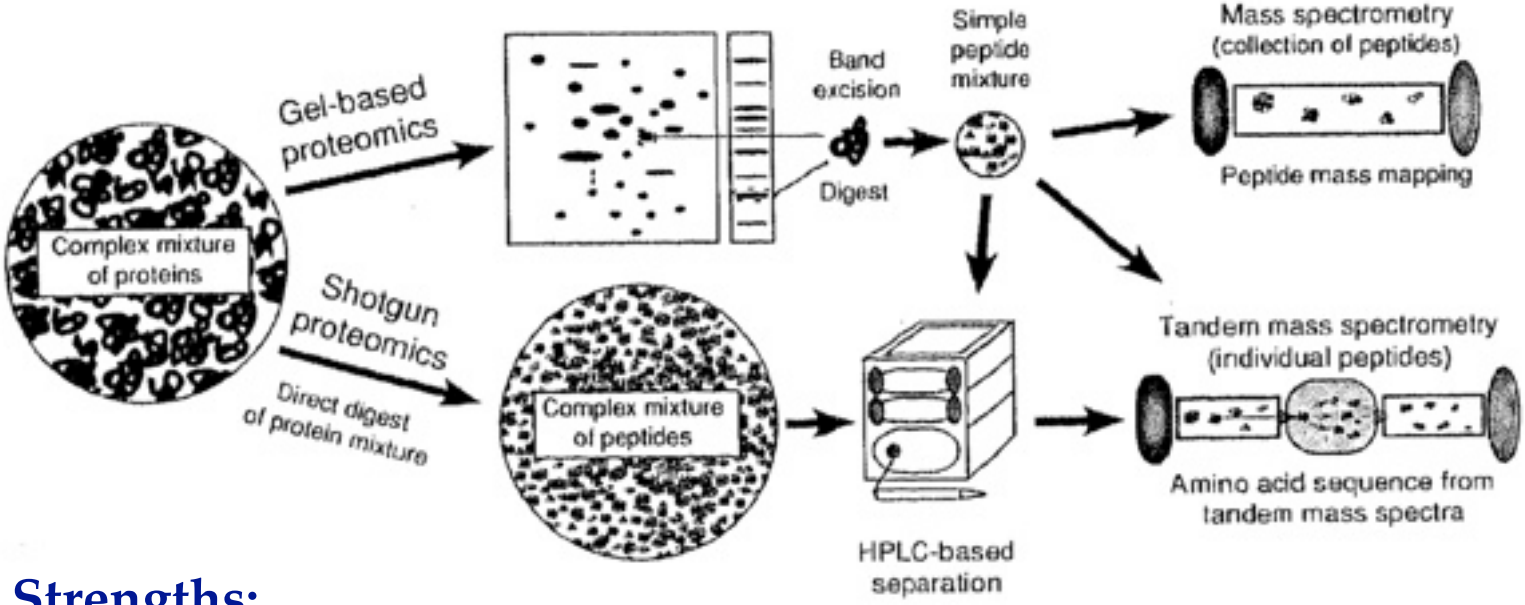
-> RNA degradation

-> Post-translational modifications

=> validation by e.g. RT-PCR



Proteomics aims to detect and quantify a system's entire protein content



Strengths:

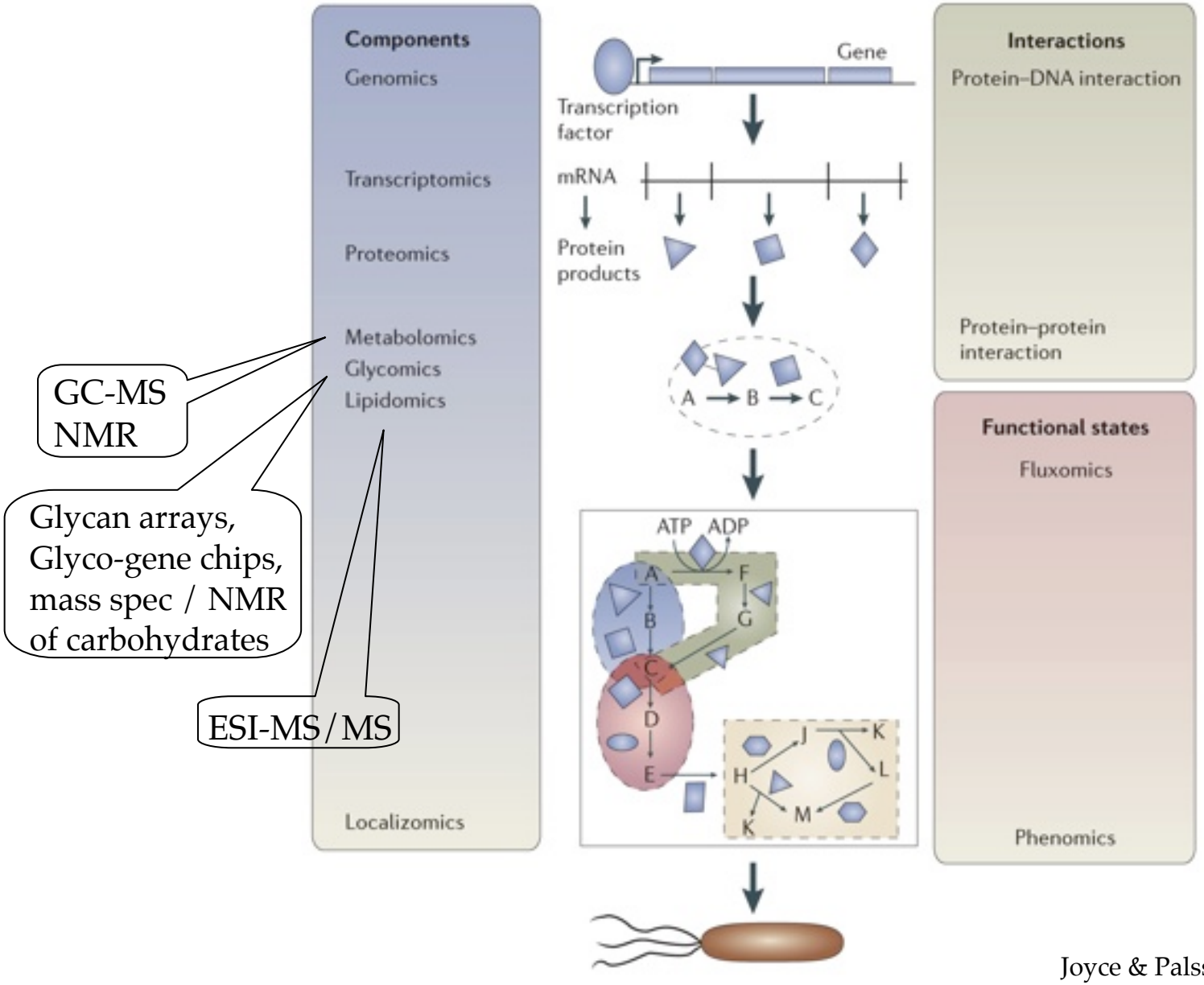
-> info about post-translational modifications

-> 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



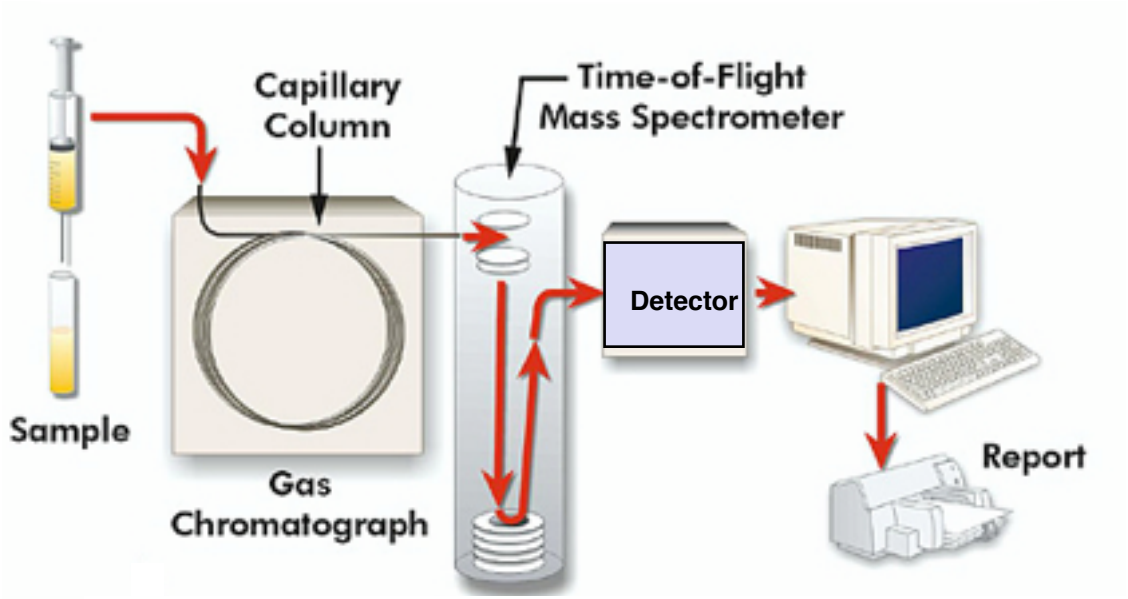
Joyce & Palsson, 2006

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

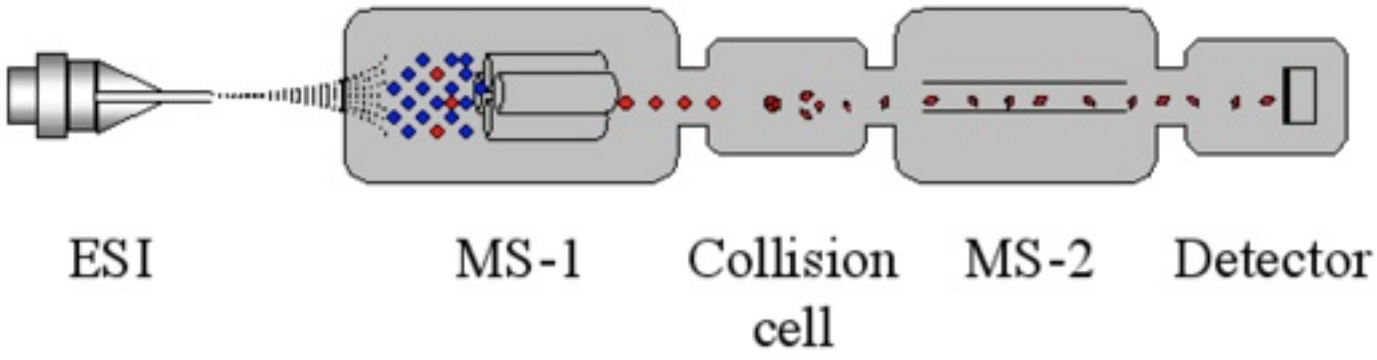
Limitations / challenges:

- often low reproducibility of sample preparations
- highly divers set of metabolites
- large dynamic range

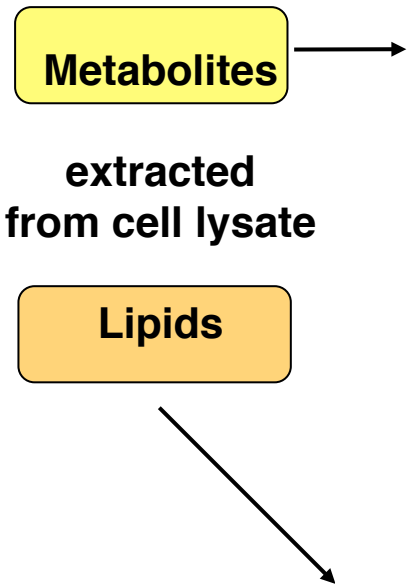
Metabolites

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 divers set of metabolites
- large dynamic range

Lipidomics aim:

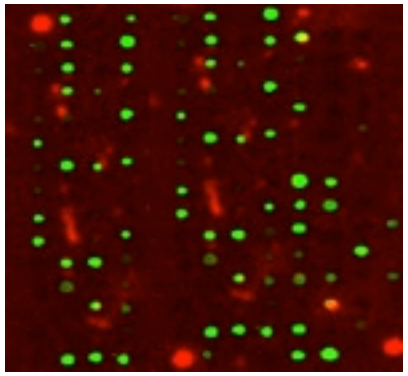
To identify & classify cellular inventory of lipids and lipid interacting factors

-> pathobiological impact

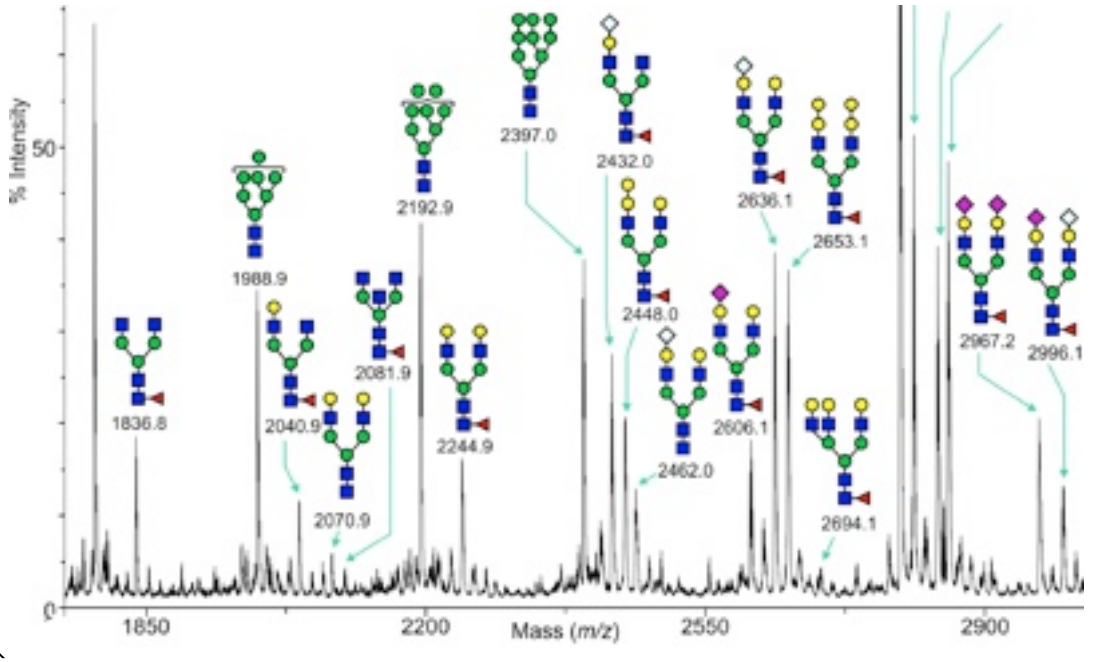
Limitations:

- low to medium throughput
- reproducibility difficult

Glycomics identifies cellular glycan components and glycan-interacting factors



Glycan-array
-> glycan-recognition proteins

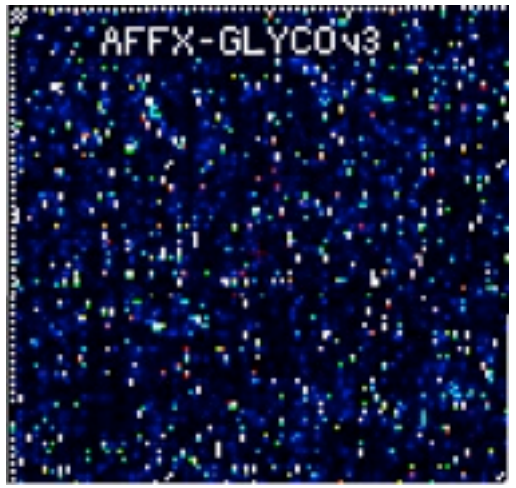


Impact:

- antigen recognition
- cell adhesion
- cancer biology

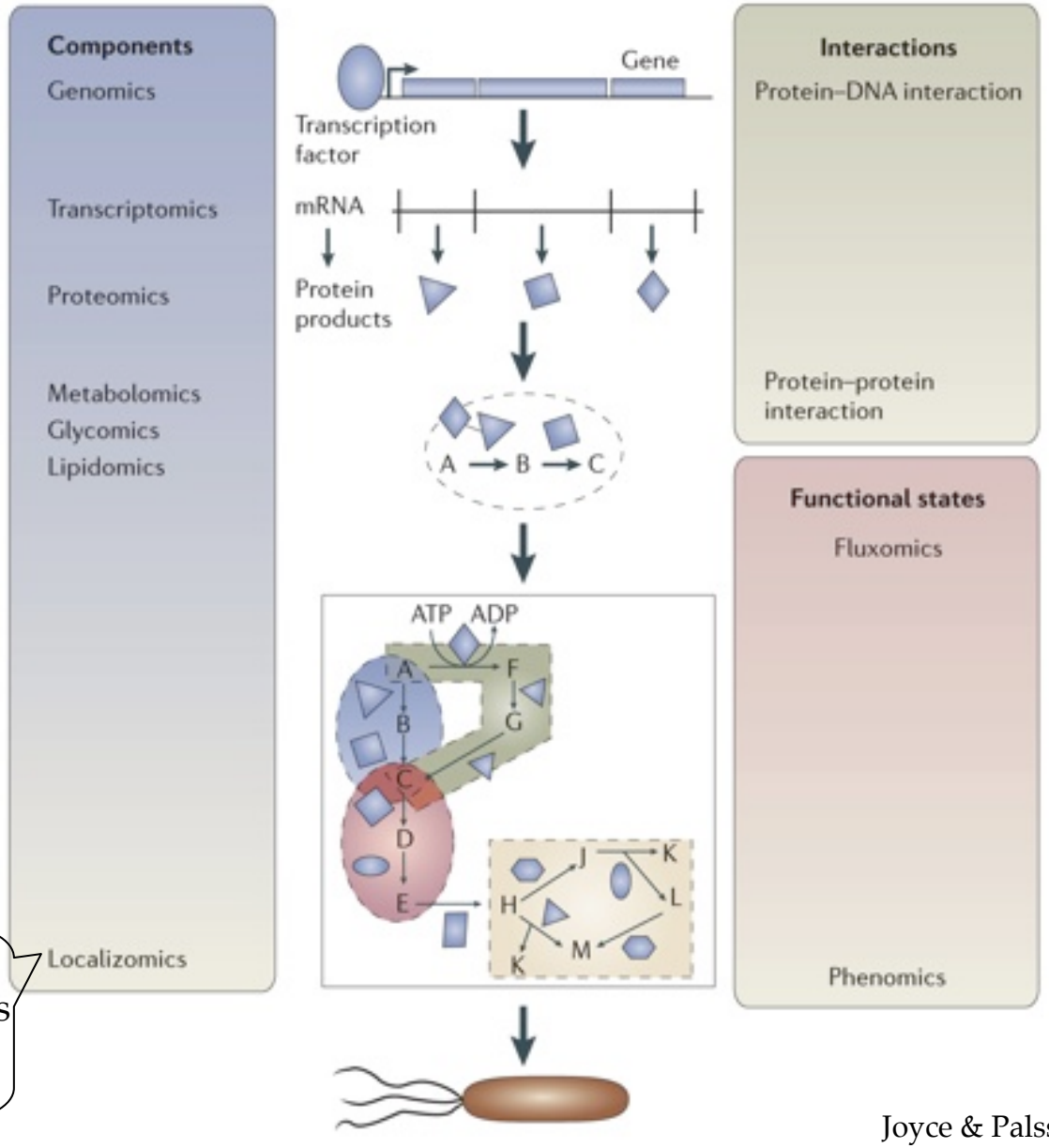
***Limitations*:**

Methods still under development



http://www.functionalglycomics.org

Omics - data provide systems-level information



In silico predictions, organelle proteomics histocytomics,

Joyce & Palsson, 2006

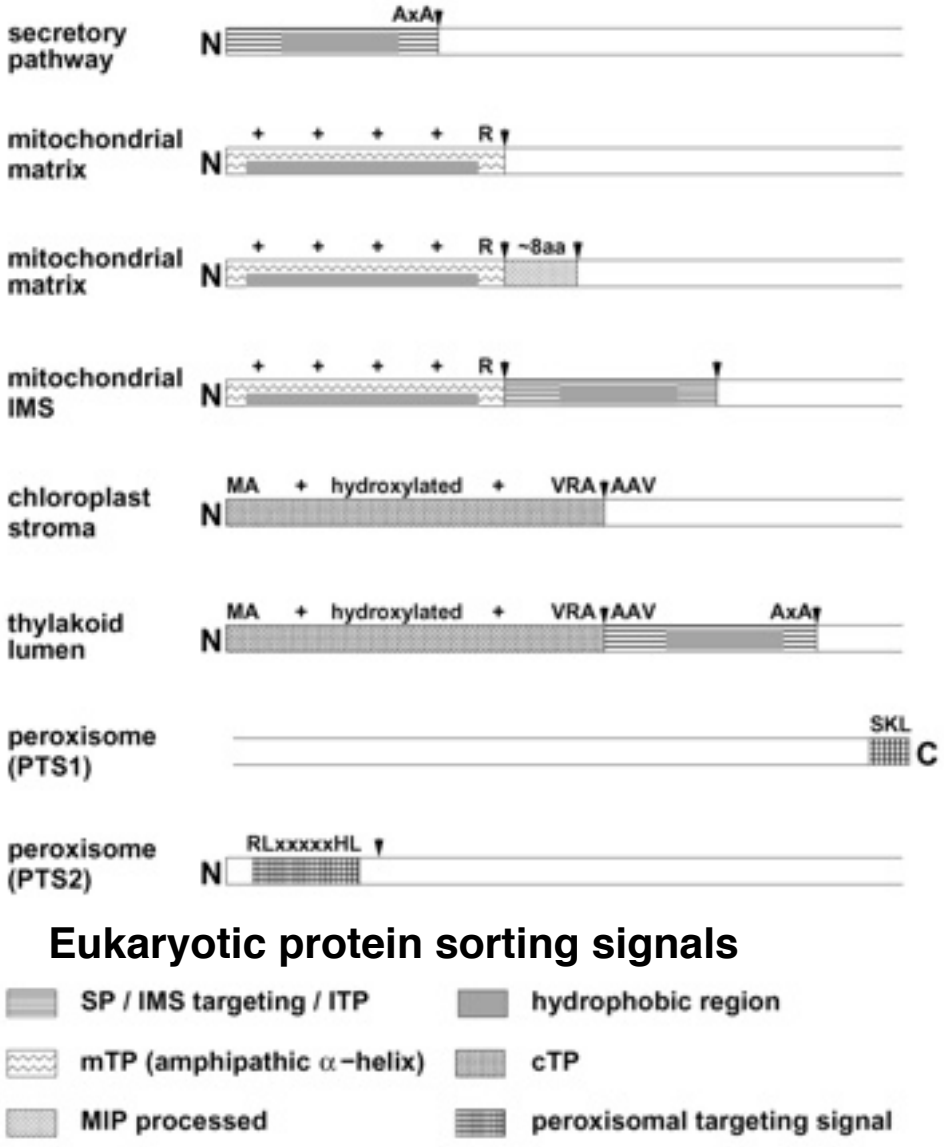
‘Localizomics’ tells about sub-cellular locations

Bioinformatics

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

PSORT
http://www.psort.org/

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



Emanuelsson 2002

‘Localizomics’ tells about sub-cellular locations

Bioinformatics

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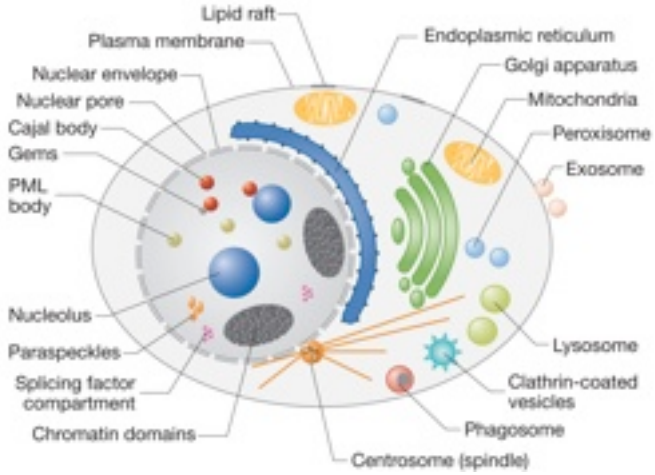


Organellar proteomics

Preparation / digestion
-> 2DE & MS

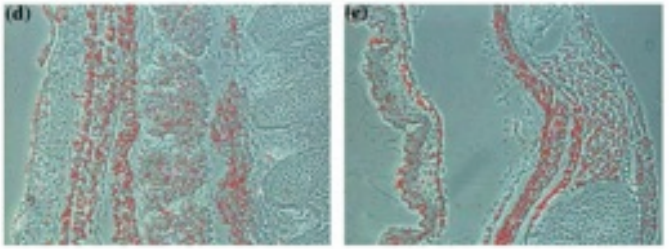
Microscopy techniques

-> tagging (GFP)
-> antibody detection

Spalding *et al.*, 2010

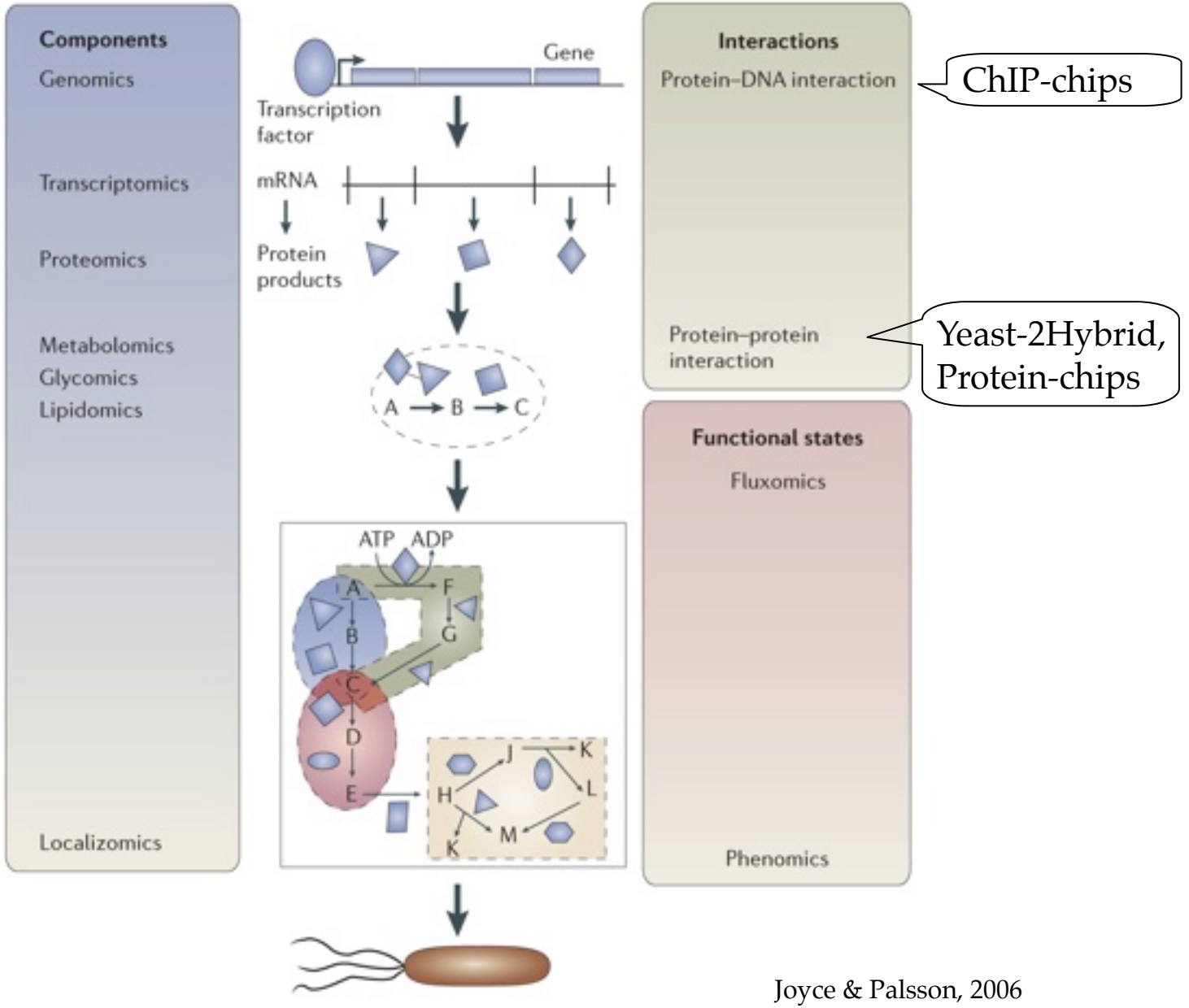
Histocytomics

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



Coulton, 2004

Omics - data provide systems-level information

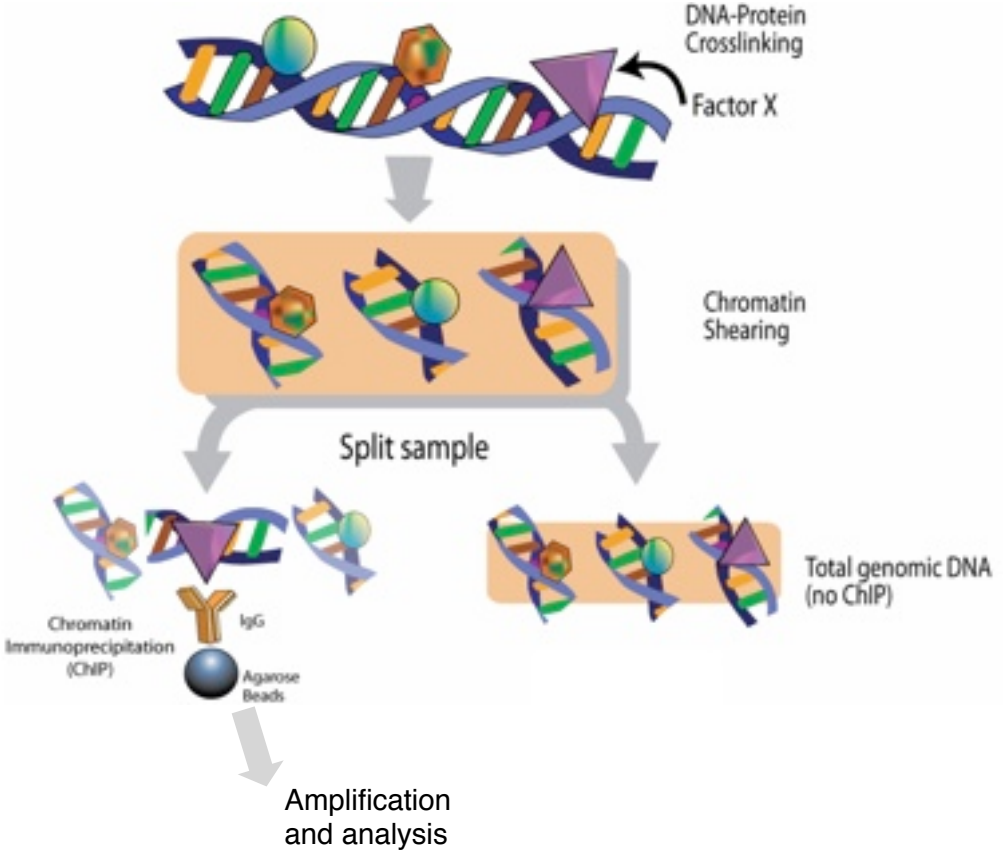


Joyce & Palsson, 2006

Interactomics

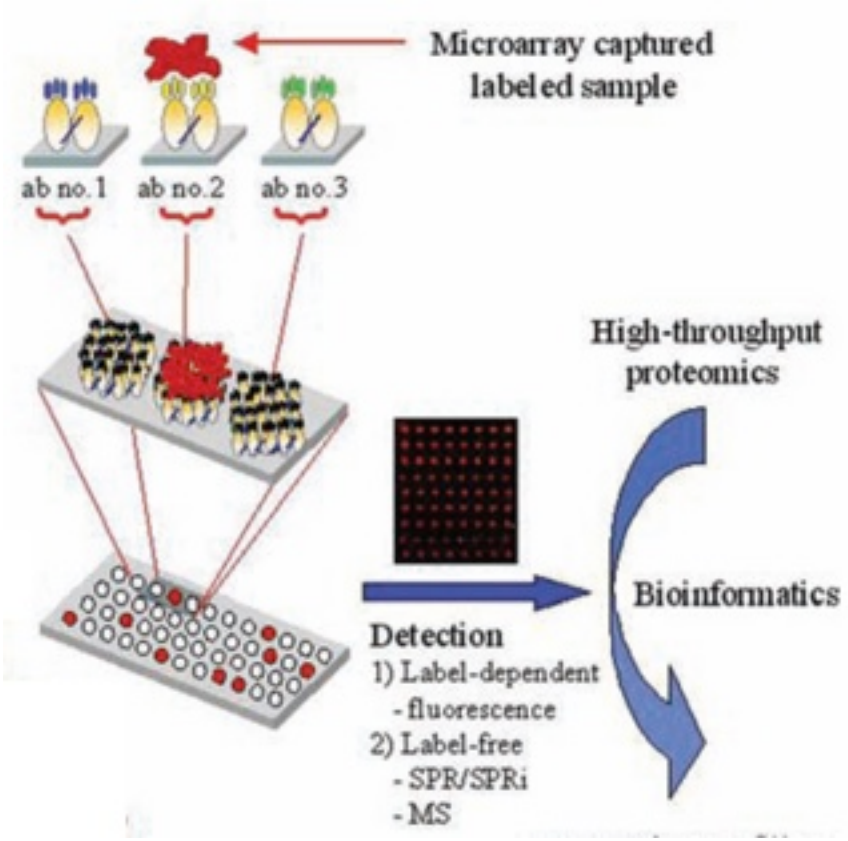
Protein-DNA interactions

-> e.g. ChIP on chips



Protein-Protein interactions

-> e.g. Antibody-based protein arrays



www.avivasysbio.com

Wingren_Borrebaeck_2009

Interactomics

Protein-Protein interactions

-> Yeast two-hybrid screens

All interactomics data need to be validated!!!
=> often false positives!!!

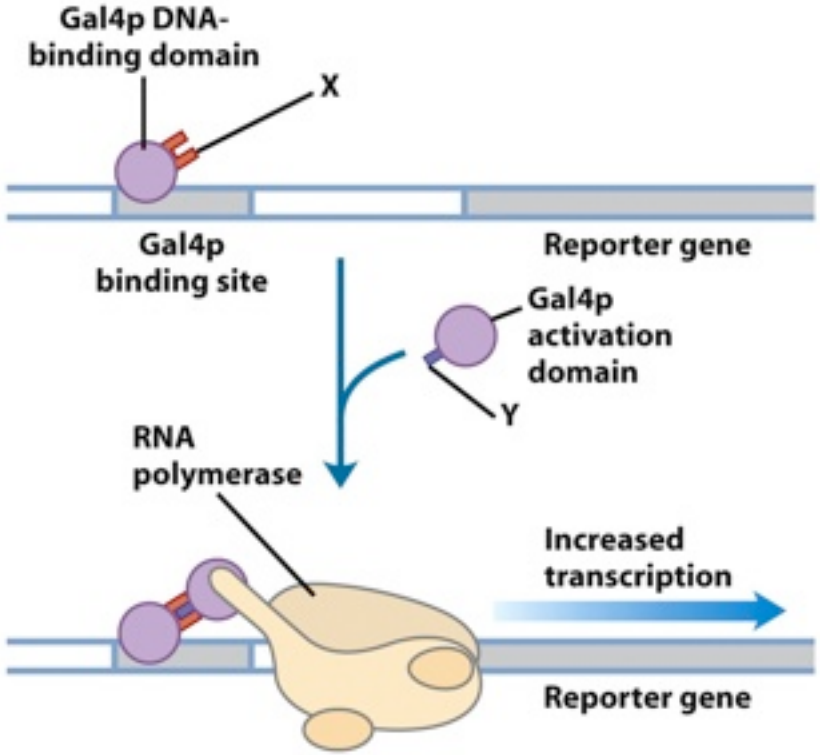


Figure 9-25a
Lehninger Principles of Biochemistry, Fifth Edition
© 2008 W. H. Freeman and Company

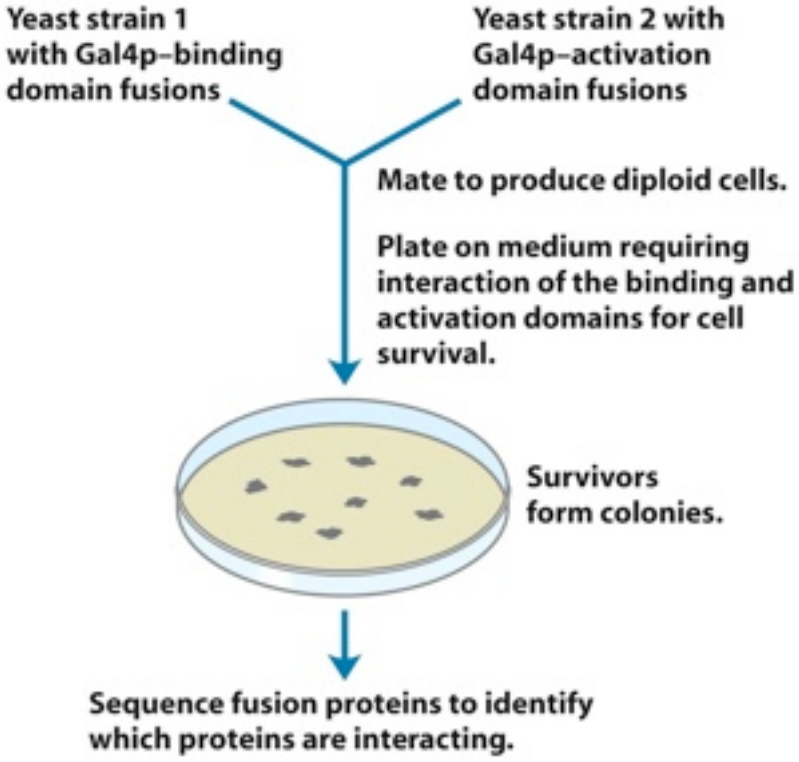


Figure 9-25b
Lehninger Principles of Biochemistry, Fifth Edition
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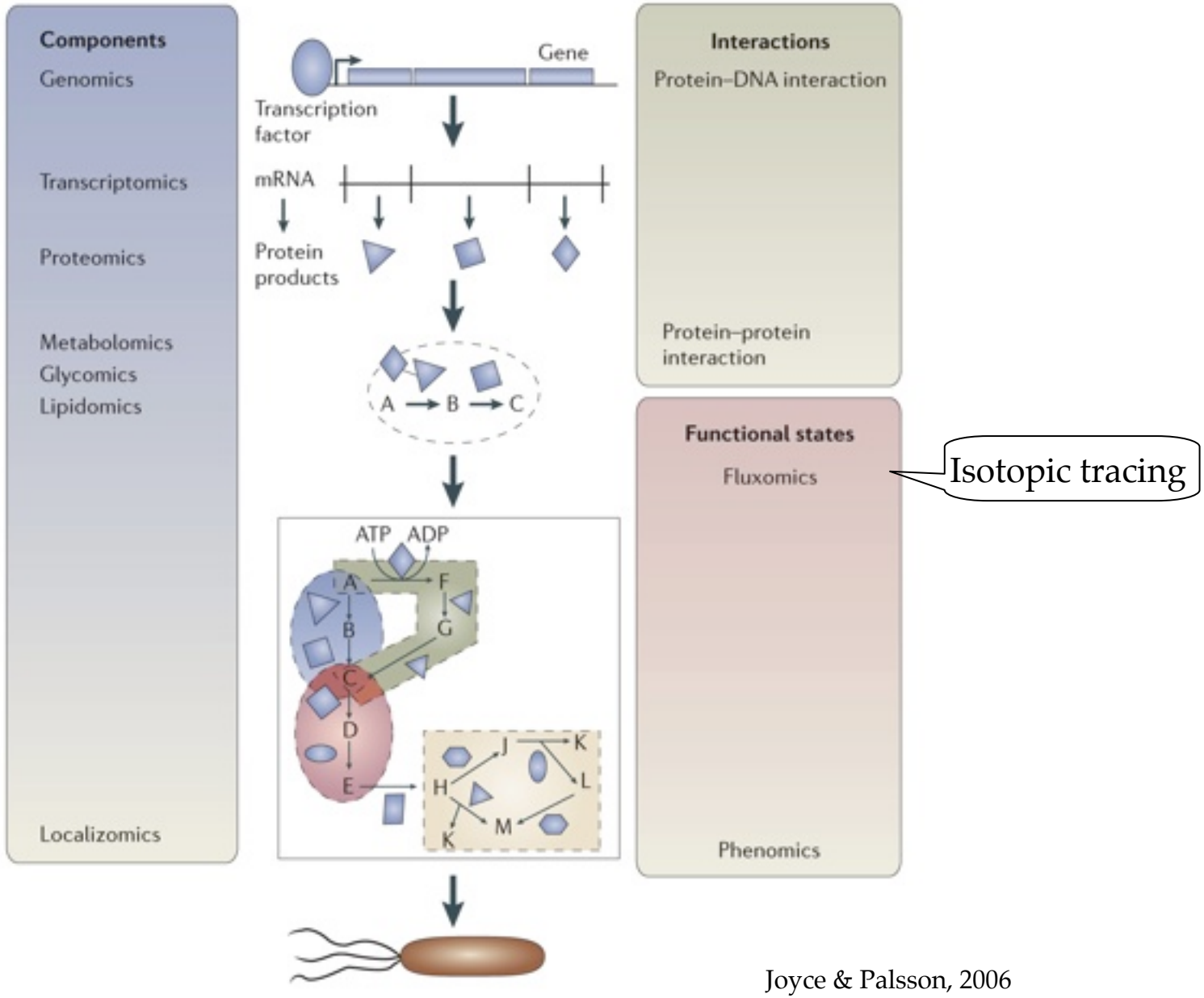
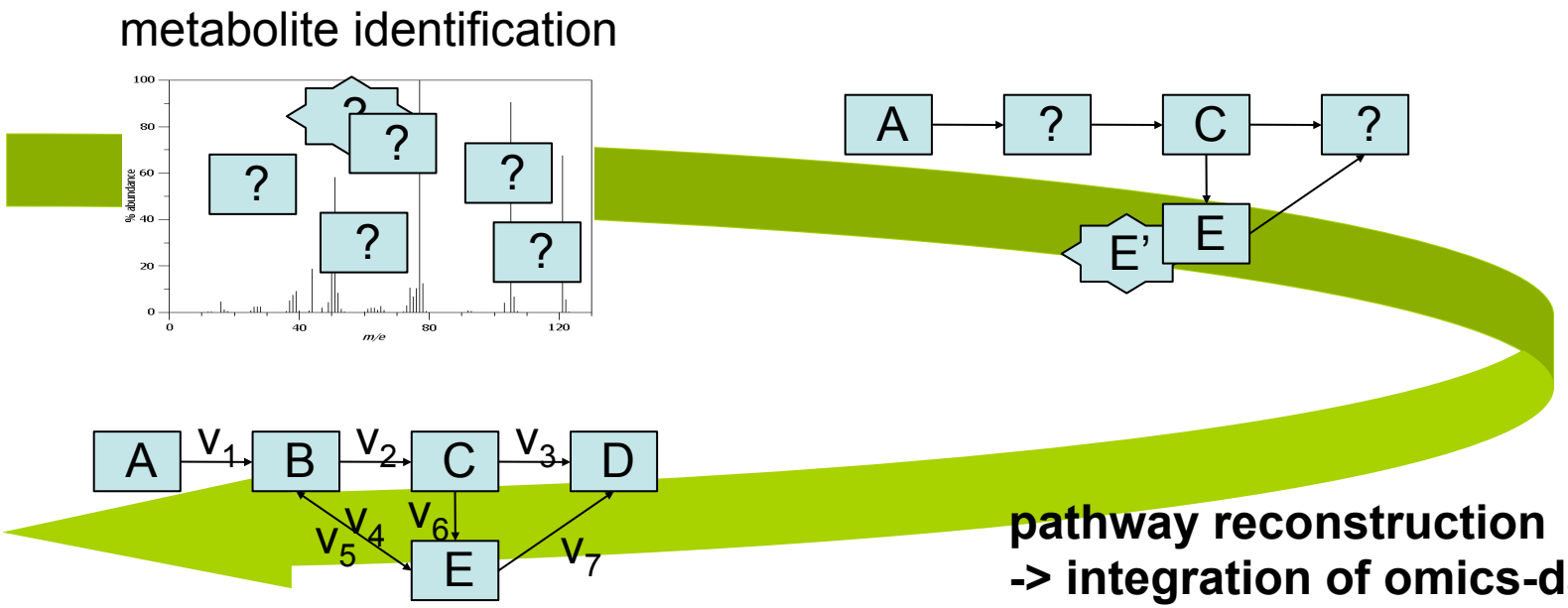
Omics - data provide systems-level information



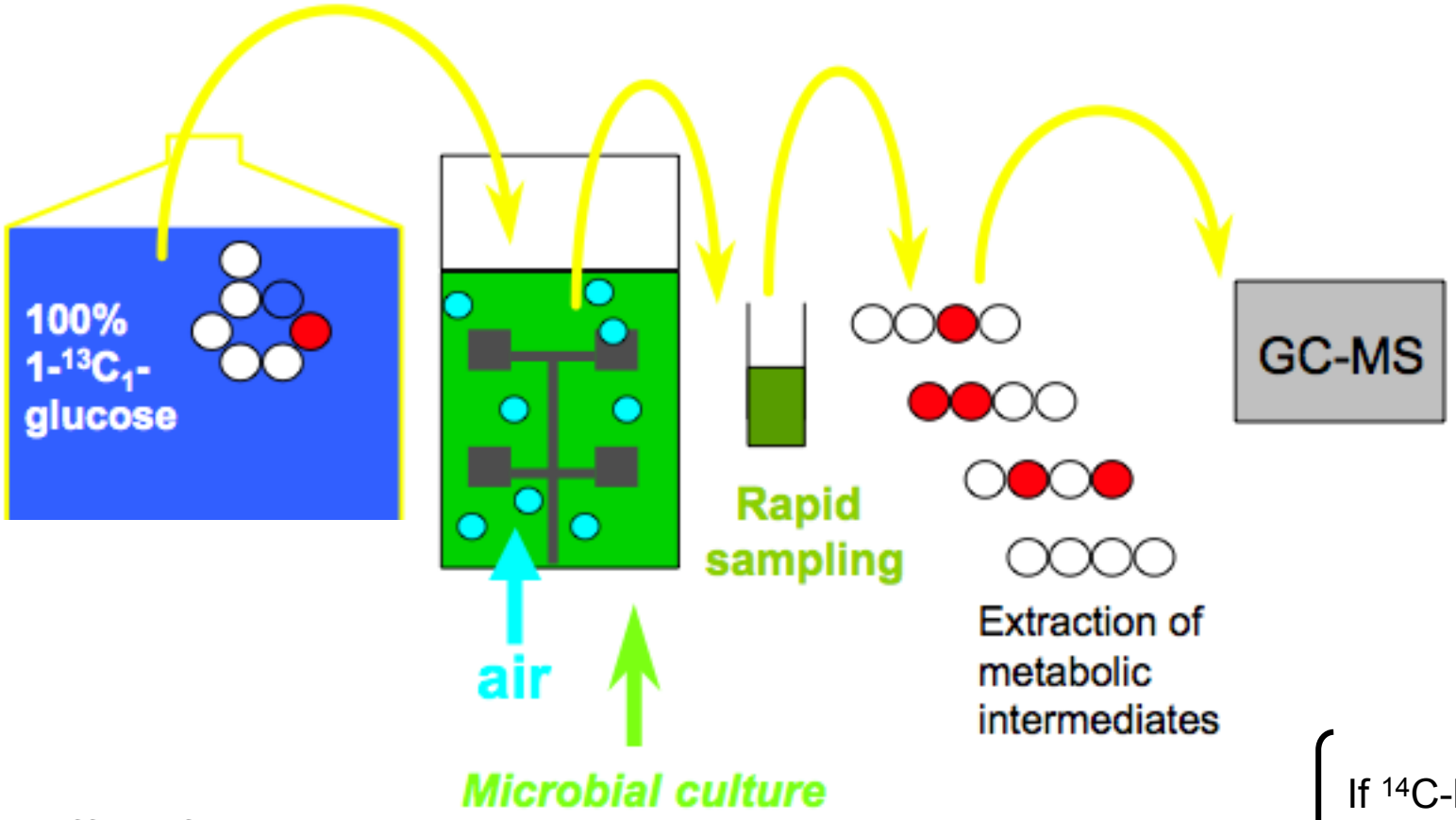
Joyce & Palsson, 2006

Fluxomics looks at global and dynamic changes of metabolite levels over time



http://www.nat.vu.nl/~ivo/flux/ Van Beek, Van Stokkum

Fluxomics looks at global and dynamic changes of metabolite levels over time

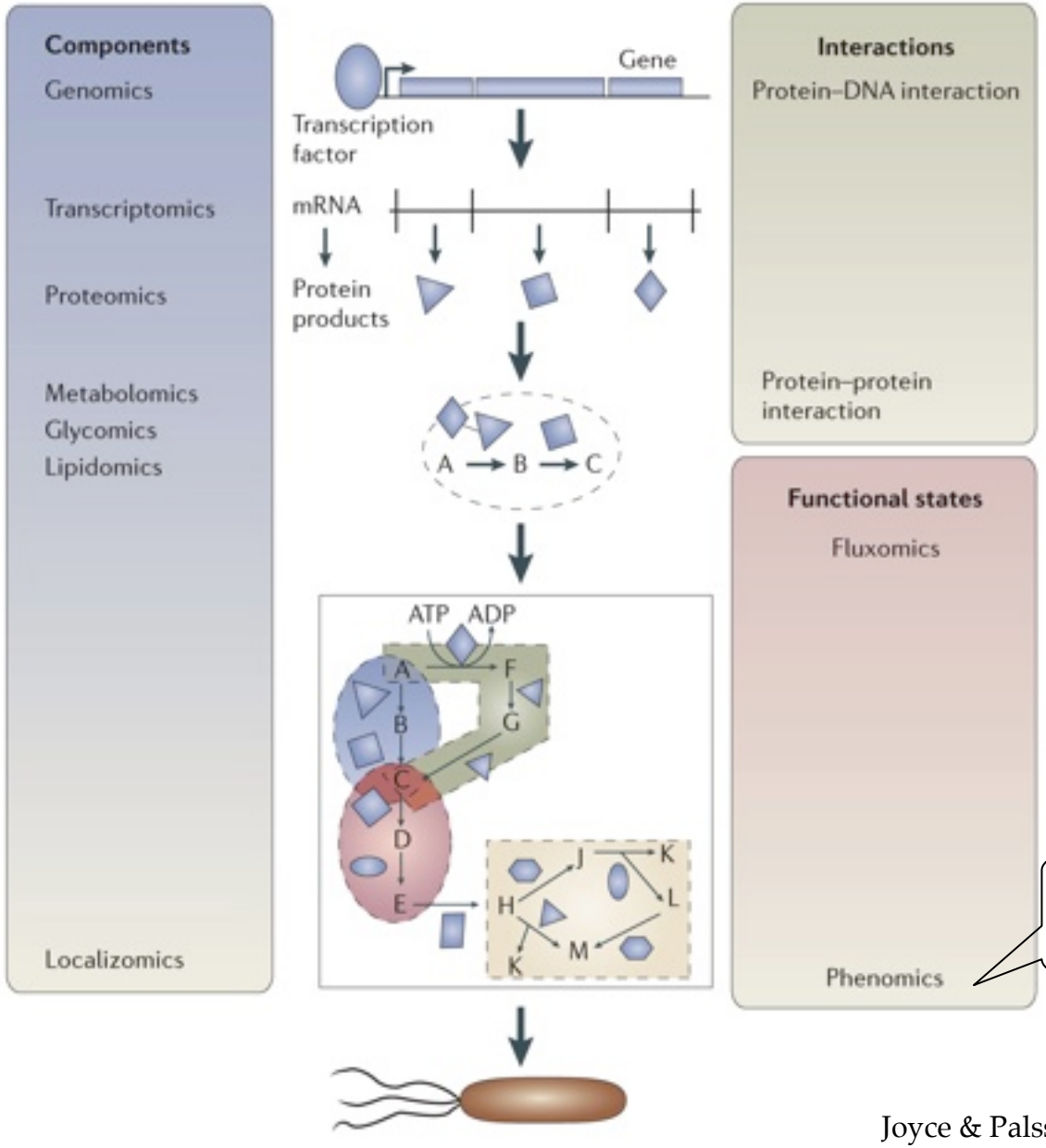


But:
Method suffers from same shortcomings as metabolomics:
-> sample prep reproducibility
-> wide variety of metabolites
-> large dynamic range

If ^{14}C-label: scintillation counting

http://www.nat.vu.nl/~ivo/flux/ Van Beek, Van Stokkum

Omics - data provide systems-level information



Joyce & Palsson, 2006

Phenomics

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

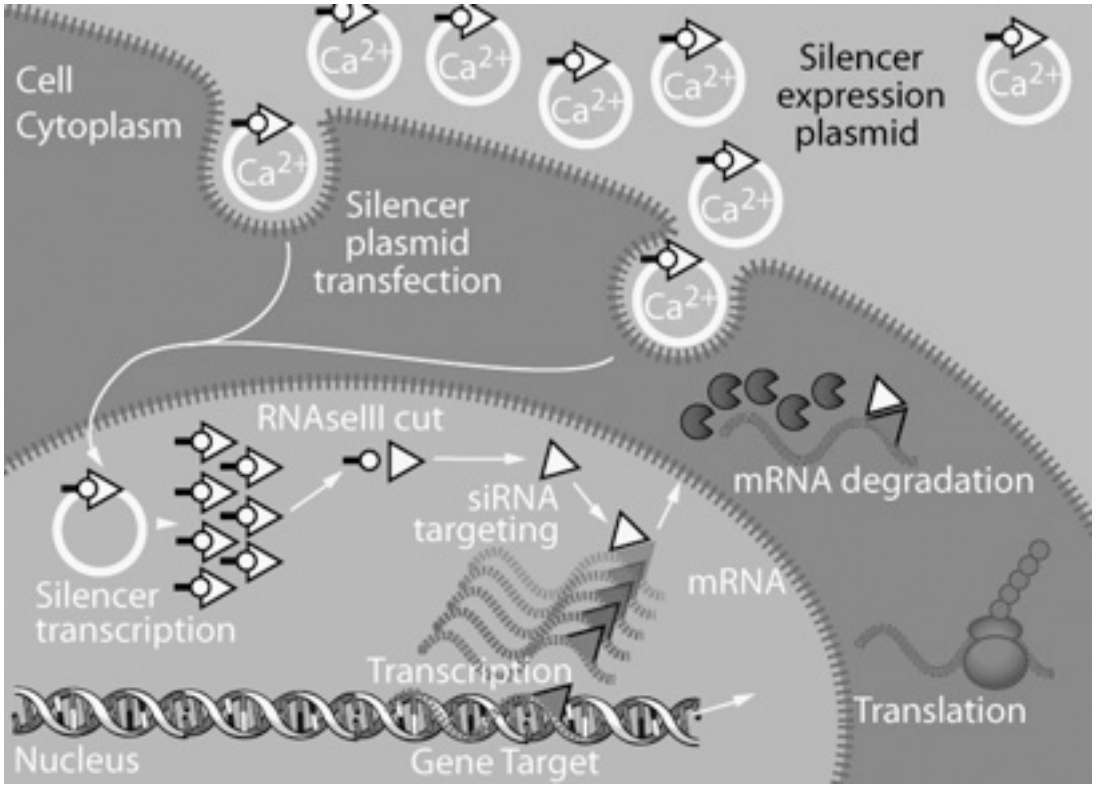
Some commonly used experimental approaches:

⇒ Phenotyping microarrays

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

Phenomics

=> RNAi screens

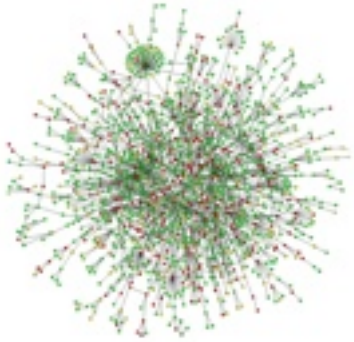


Integration of omics-data

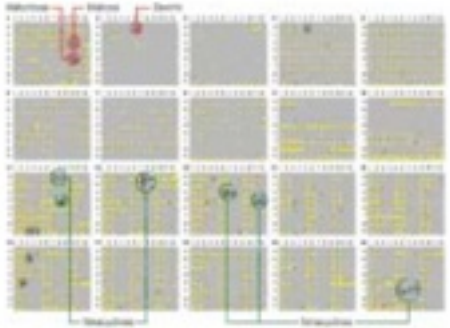
The Challenge:

How to integrate extreme abundances of heterogeneous data from very divers sources?

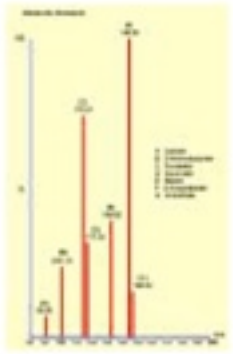
Interactomics

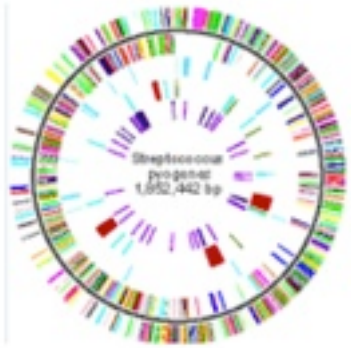


Phenomics

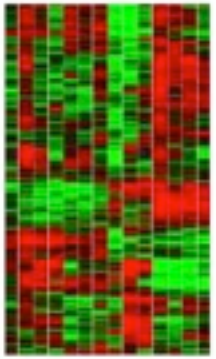


Metabolomics

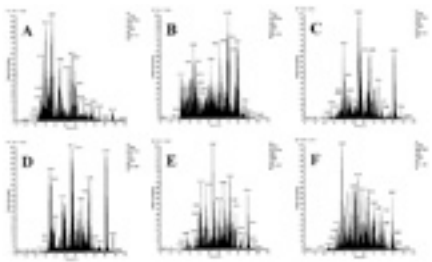




Genomics



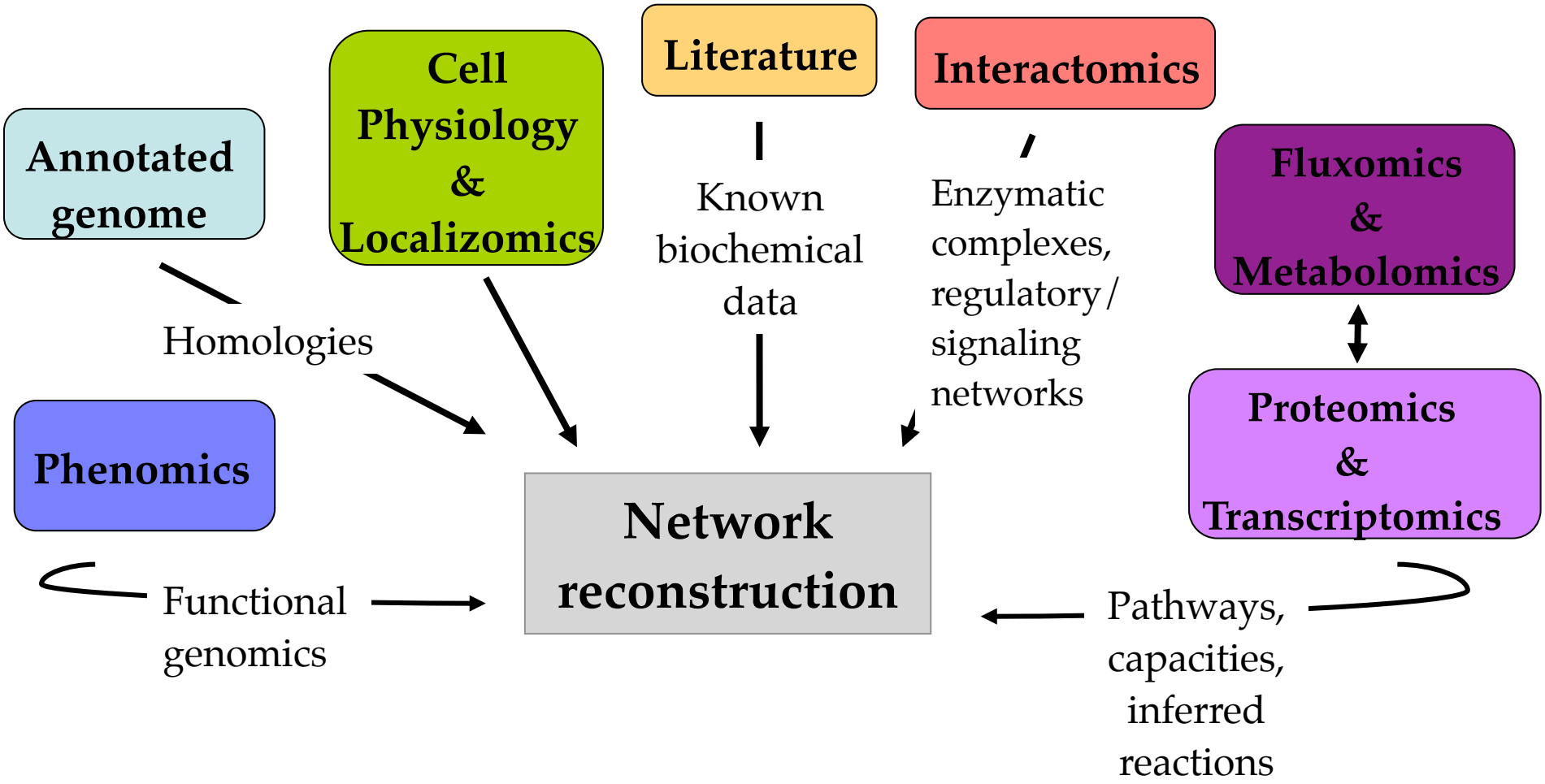
Transcriptomics



Proteomics

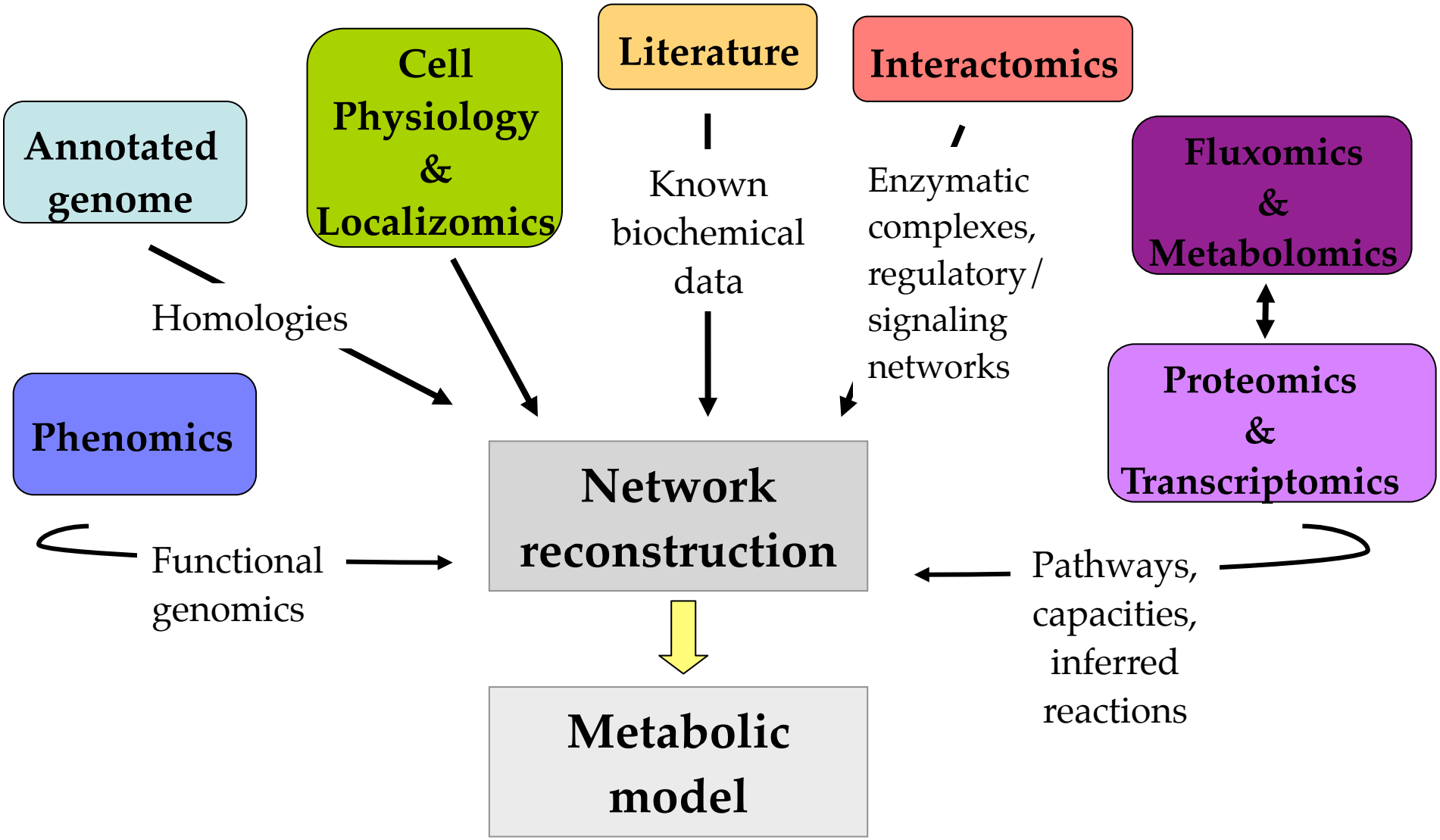
http://systemsbiology.ucsd.edu

Integration of omics-data: Network reconstruction



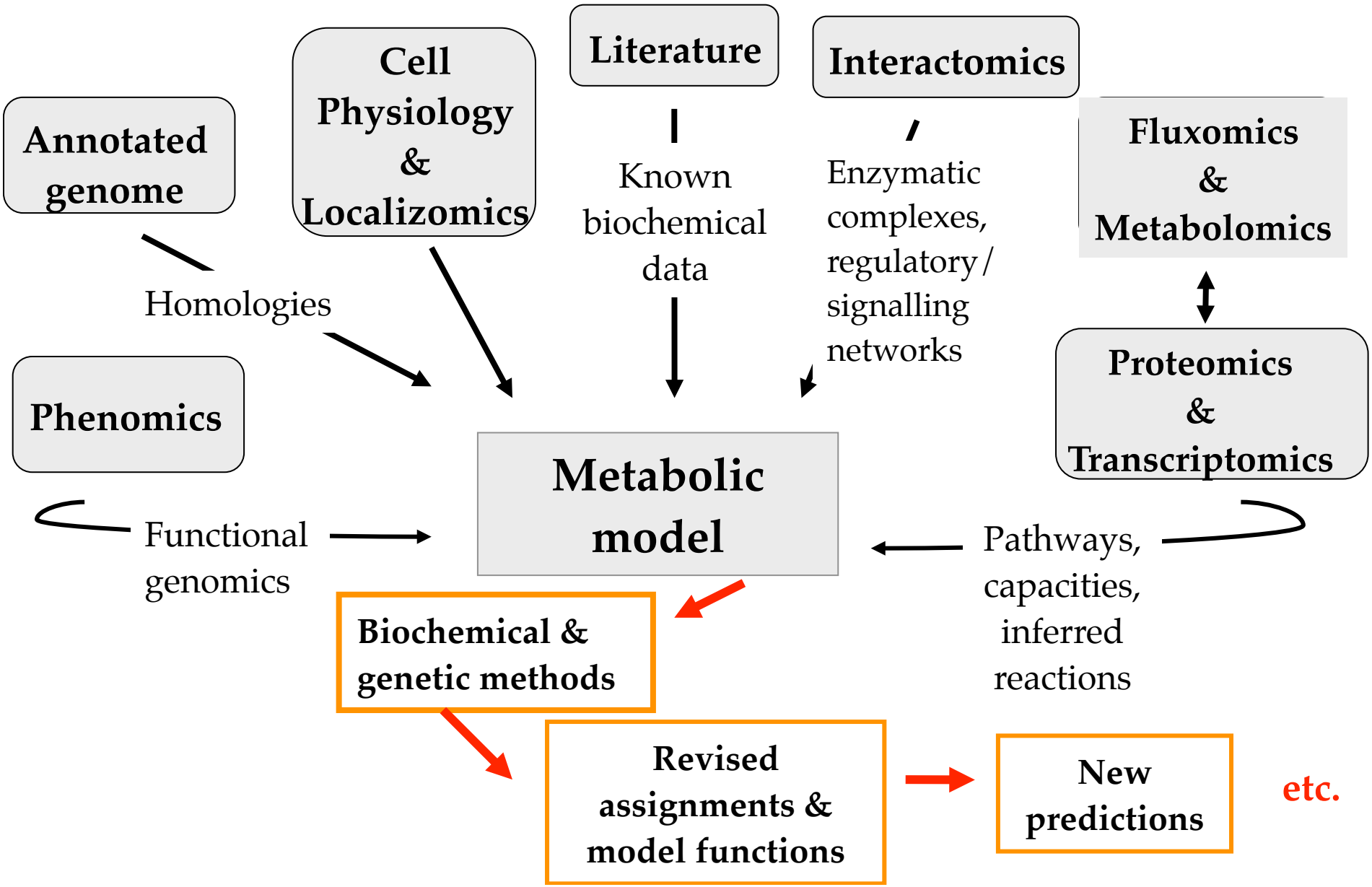
http://systemsbiology.ucsd.edu

Integration of omics-data: Network reconstruction



http://systemsbiology.ucsd.edu

Integration of omics-data: Model testing and validation



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*)