

Bioinformatics 3

V7 – Function Annotation, Gene Regulation

Fri., Nov 11, 2011

Network Meta-Growth

Q: When I find a new protein and its (already known) partners in an experiment and I add that to a database, do I get a scale-free network?

Which proteins are in a database??? \Leftrightarrow the experimentally accessible ones!!!

- => costs for the experiment
- => experience for purification, methods, analysis...
- => existing assays for similar proteins
- => personal interests
 - (also for advertising: related to {cancer, HIV, Alzheimer...})

Higher probability to find proteins related to known ones
 \Leftrightarrow growing network with preferential attachment

What Does a Protein Do?

The screenshot shows the BRENDA website's classification scheme. At the top, there is a logo for BRENDA (The Comprehensive Enzyme Information System) and a logo for the TU Braunschweig Dept. of Bioinformatics. Below the header, there is a navigation bar with 'EC Explorer' and links for 'SEARCH' and 'BROWSE'. The main content is a hierarchical tree of enzyme classes:

- 1 Oxidoreductases (4042 organisms)
- 2 Transferases (3198 organisms)
 - 2.1 Transferring one-carbon groups (615 organisms)
 - 2.1.1 Methyltransferases (514 organisms)
 - 2.1.2 Hydroxymethyl-, formyl- and related transferases (82 organisms)
 - 2.1.3 Carboxy- and carbamoyltransferases (105 organisms)
 - 2.1.4 Amidinotransferases (32 organisms)
 - 2.1.4.1 glycine amidinotransferase (17 organisms)
 - 2.1.4.2 scyllo-inosamine-4-phosphate amidinotransferase (15 organisms)
 - 2.2 Transferring aldehyde or ketonic groups (91 organisms)
 - 2.3 Acyltransferases (930 organisms)
 - 2.4 Glycosyltransferases (925 organisms)
 - 2.5 Transferring alkyl or aryl groups, other than methyl groups (547 organisms)
 - 2.6 Transferring nitrogenous groups (377 organisms)
 - 2.7 Transferring phosphorus-containing groups (1343 organisms)
 - 2.8 Transferring sulfur-containing groups (276 organisms)
 - 2.9 Transferring selenium-containing groups (6 organisms)
 - 3 Hydrolases (4453 organisms)
 - 4 Lyases (2145 organisms)
 - 5 Isomerases (849 organisms)
 - 6 Ligases (686 organisms)

Enzyme Classification scheme

(from <http://www.brenda-enzymes.org/>)

MIPS FunCat

- **MIPS Functional Catalogue**
- + **M01 METABOLISM**
- + **M02 ENERGY**
- + **M04 STORAGE PROTEIN**
- + **M10 CELL CYCLE AND DNA PROCESSING**
- + **M11 TRANSCRIPTION**
- + **M12 PROTEIN SYNTHESIS**
- + **M14 PROTEIN FATE (folding, modification, destination)**
- + **M16 PROTEIN WITH BINDING FUNCTION OR COFACTOR REQUIREMENT (structural or catalytic)**
- + **M18 REGULATION OF METABOLISM AND PROTEIN FUNCTION**
- + **M20 CELLULAR TRANSPORT, TRANSPORT FACILITIES AND TRANSPORT ROUTES**
- + **M30 CELLULAR COMMUNICATION/SIGNAL TRANSDUCTION MECHANISM**
- + **M32 CELL RESCUE, DEFENSE AND VIRULENCE**
- + **M34 INTERACTION WITH THE ENVIRONMENT**
- + **M36 SYSTEMIC INTERACTION WITH THE ENVIRONMENT**
- + **M38 TRANSPOSSABLE ELEMENTS, VIRAL AND PLASMID PROTEINS**
- + **M40 CELL FATE**
- + **M41 DEVELOPMENT (Systemic)**
- + **M42 BIOGENESIS OF CELLULAR COMPONENTS**
- + **M43 CELL TYPE DIFFERENTIATION**
- + **M45 TISSUE DIFFERENTIATION**
- + **M47 ORGAN DIFFERENTIATION**
- + **M70 SUBCELLULAR LOCALIZATION**
- + **M73 CELL TYPE LOCALIZATION**
- + **M75 TISSUE LOCALIZATION**
- + **M77 ORGAN LOCALIZATION**
- + **M98 CLASSIFICATION NOT YET CLEAR-CUT**
- + **M99 UNCLASSIFIED PROTEINS**

Classification Browser from <http://mips.gsf.de/projects/funcat>

Digging Deeper



Details and Proteins

[01](#) METABOLISM [[Eukaryota](#) [Bacteria](#) [Archaea](#)]
[01.06](#) lipid, fatty acid and isoprenoid metabolism [[Eukaryota](#) [Bacteria](#) [Archaea](#)]
[01.06.02](#) membrane lipid metabolism [[Eukaryota](#) [Bacteria](#) [Archaea](#)]
[01.06.02.01](#) phospholipid metabolism [[Eukaryota](#) [Bacteria](#) [Archaea](#)]

DETAILED RESULTS:

Number:	01.06.02.01
Description:	phospholipid metabolism
Explanation	-
EC number:	-
Taxonomy:	[Eukaryota Bacteria Archaea]
Reference Link:	-
Reference PMID:	-
Funlink:	-
GO mapping:	GO:0008654

Manually Annotated Proteins:

Organism	Proteins
Helicobacter pylori KE26695	HP0190 ; HP0700 ; HP0215 ; HP0737 ; HP1071 ; HP0961 ; HP0871 ; HP1016 ; HP0201 ; <i>Co-annotated-FunCats</i>
Saccharomyces cerevisiae	
Neurospora crassa	
Listeria monocytogenes EGD	gi_16411389 ; gi_16410893 ; gi_16411991 ; gi_16409732 ; gi_16410732 ; gi_16410825 ; gi_16409367 ; gi_16411263 ; <i>Co-annotated-FunCats</i>

Un-Classified Proteins?

BIOINFORMATICS

Vol. 21 Suppl. 1 2005, pages i302–i310
doi:10.1093/bioinformatics/bti1054



Whole-proteome prediction of protein function via graph-theoretic analysis of interaction maps

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Princeton University, Princeton, NJ 08544, USA

Received on January 15, 2005; accepted on March 27, 2005

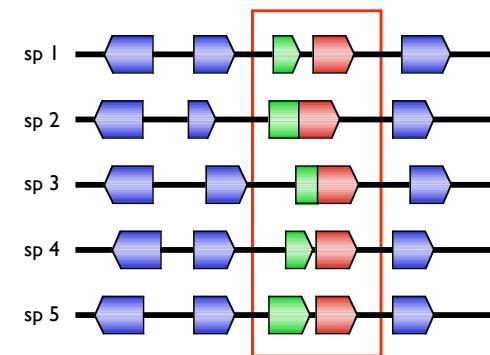
Many **unclassified proteins**:

- => estimate: ~1/3 of the yeast proteome not annotated functionally
- => BioGRID: 4495 prot. in the largest cluster of the yeast physical interaction map.
2946 have a MIPS functional annotation

Partition the Graph

Large **PPI networks** were built from:

- HT experiments (Y2H, TAP, synthetic lethality, coexpression, coregulation, ...)
 - predictions (gene profiling, gene neighborhood, phylogenetic profiles, ...)
- => proteins that are functionally linked



Identify **unknown functions** from **clustering** of these networks by, e.g.:

- shared interactions (similar neighborhood => power graphs)
- membership in a community
- similarity of shortest path vectors to all other proteins (= similar path into the rest of the network)

Protein Interactions

Nabieva et al used the *S. cerevisiae* dataset from GRID of 2005 (now BioGRID)
=> 4495 proteins and 12 531 physical interactions in the largest cluster

The screenshot shows the BioGRID website homepage. The header features a large "BioGRID" logo on the left, followed by a search bar with a dropdown menu set to "Organism: Escherichia coli K12" and a "GO" button. Below the search bar is the text "General Repository for Interaction Datasets". A red navigation bar at the top includes links for "home", "help / support", "contribute", "downloads", "mirrors", and "about us". The main content area has two columns. The left column is titled "About BioGRID" and contains a detailed description of the database's history, current size (over 198,000 interactions from six species), and features like Cytoscape integration. The right column is titled "BioGRID Links" and lists various external resources and databases.

About BioGRID

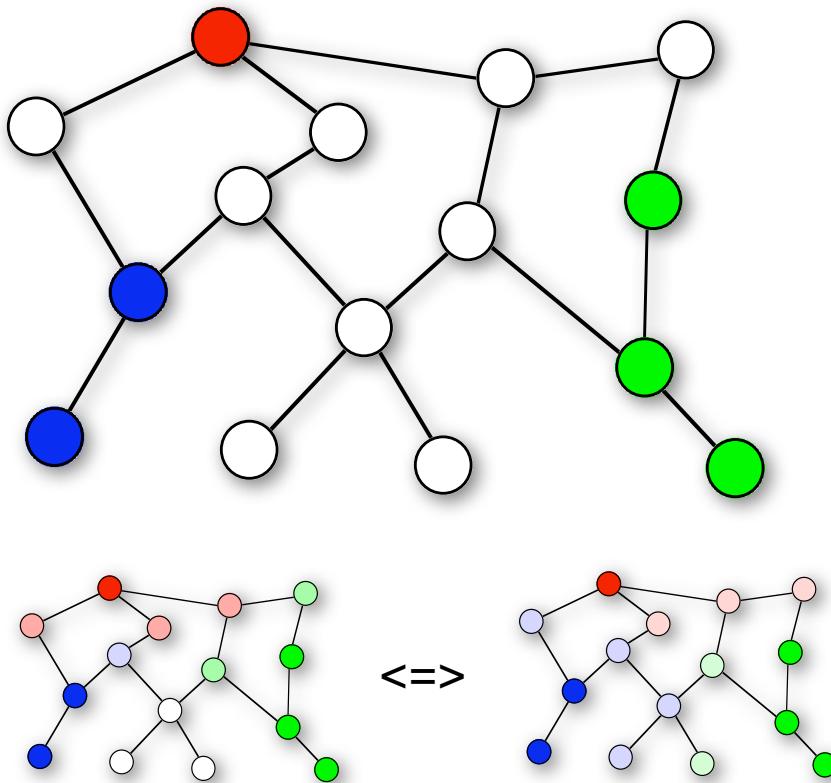
The Biological General Repository for Interaction Datasets (BioGRID) database (<http://www.thebiogrid.org>) was developed to house and distribute collections of protein and genetic interactions from major model organism species. BioGRID currently contains over 198 000 interactions from six different species, as derived from both high-throughput studies and conventional focused studies. Through comprehensive curation efforts, BioGRID now includes a virtually complete set of interactions reported to date in the primary literature for both the budding yeast *Saccharomyces cerevisiae* and the fission yeast *Schizosaccharomyces pombe*. A number of new features have been added to the BioGRID including an improved user interface to display interactions based on different attributes, a mirror site and a dedicated interaction management system to coordinate curation across different locations. The BioGRID provides interaction data with monthly updates to *Saccharomyces Genome Database*, Flybase and Entrez Gene. Source code for the BioGRID and the linked [Osprey network visualization system](#) is now freely available without restriction.

BioGRID Links

- [Arabidopsis Information Resource](#)
- [BioPIXIE](#)
- [Biotechnology and Biological Sciences Research Council \(BBSRC\)](#)
- [Canadian Institutes of Health Research \(CIHR\)](#)
- [Cytoscape](#)
- [Database of Interacting Proteins](#)
- [Entrez-Gene](#)
- [Flybase](#)
- [Gene DB](#)
- [Gene Ontology](#)
- [Germ Online](#)

Function Annotation

Problem: **predict** function (= functional annotation) for a protein from the **available** annotations



Similar:
How to **assign colors** to
the white nodes?

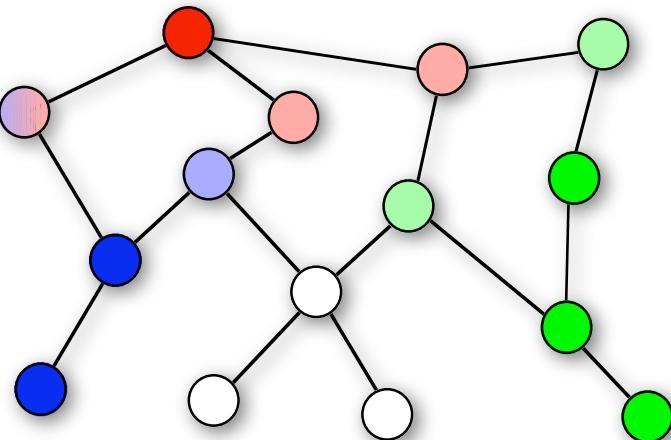
Use information on:

- distance to colored nodes
- local connectivity
- reliability of the links
- ...

Algorithm I: Majority

Schwikowski, Uetz, and Fields, "A network of protein–protein interactions in yeast"
Nat. Biotechnol. **18** (2000) 1257

Consider all neighbors and **sum** up how often a certain **annotation occurs**
=> score for an annotation = count among the direct neighbors
=> take the three most frequent functions



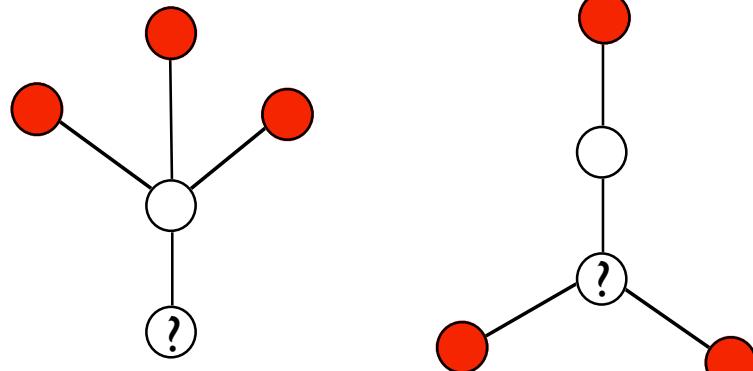
Majority makes only limited use
of the local connectivity
=> cannot assign function to
next-neighbors

For weighted graphs:
=> weighted sum

Extended Majority: Neighborhood

Hishigaki, Nakai, Ono, Tanigami, and Takagi, "Assessment of prediction accuracy of protein function from protein–protein interaction data", *Yeast* **18** (2001) 523

Look for **overrepresented** functions within a given **radius** of 1, 2, or 3 links
=> function score = value of a χ^2 -test



Neighborhood does not consider local network topology

Both examples are treated **identical** with $r = 2$

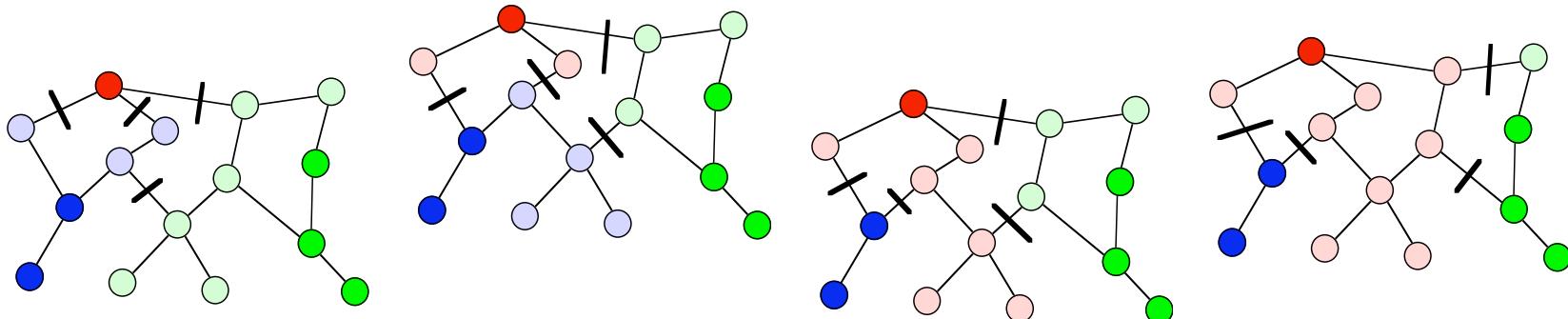
Neighborhood can not (easily) be generalized to weighted graphs!

Minimize Changes: GenMultiCut

Karaoz, Murali, Letovsky, Zheng, Ding, Cantor, and Kasif, "Whole-genome annotation by using evidence integration in functional-linkage networks" PNAS **101** (2004) 2888

"Annotate proteins so as to **minimize** the number of times that **different** functions are associated with **neighboring** proteins"

=> generalization of the multiway k -cut problem for weighted edges,
can be stated as an integer linear program (ILP)



Multiple possible solutions => scores from **frequency** of annotations

Nabieva et al: FunctionalFlow

Extend the idea of "**guilty by association**"

=> each annotated protein is a source of "function"-flow

=> simulate for a few timesteps

=> choose the annotation with the highest accumulated flow

Each node u has a reservoir $R_t(u)$, each edge a capacity constraint (= weight) $w_{u,v}$

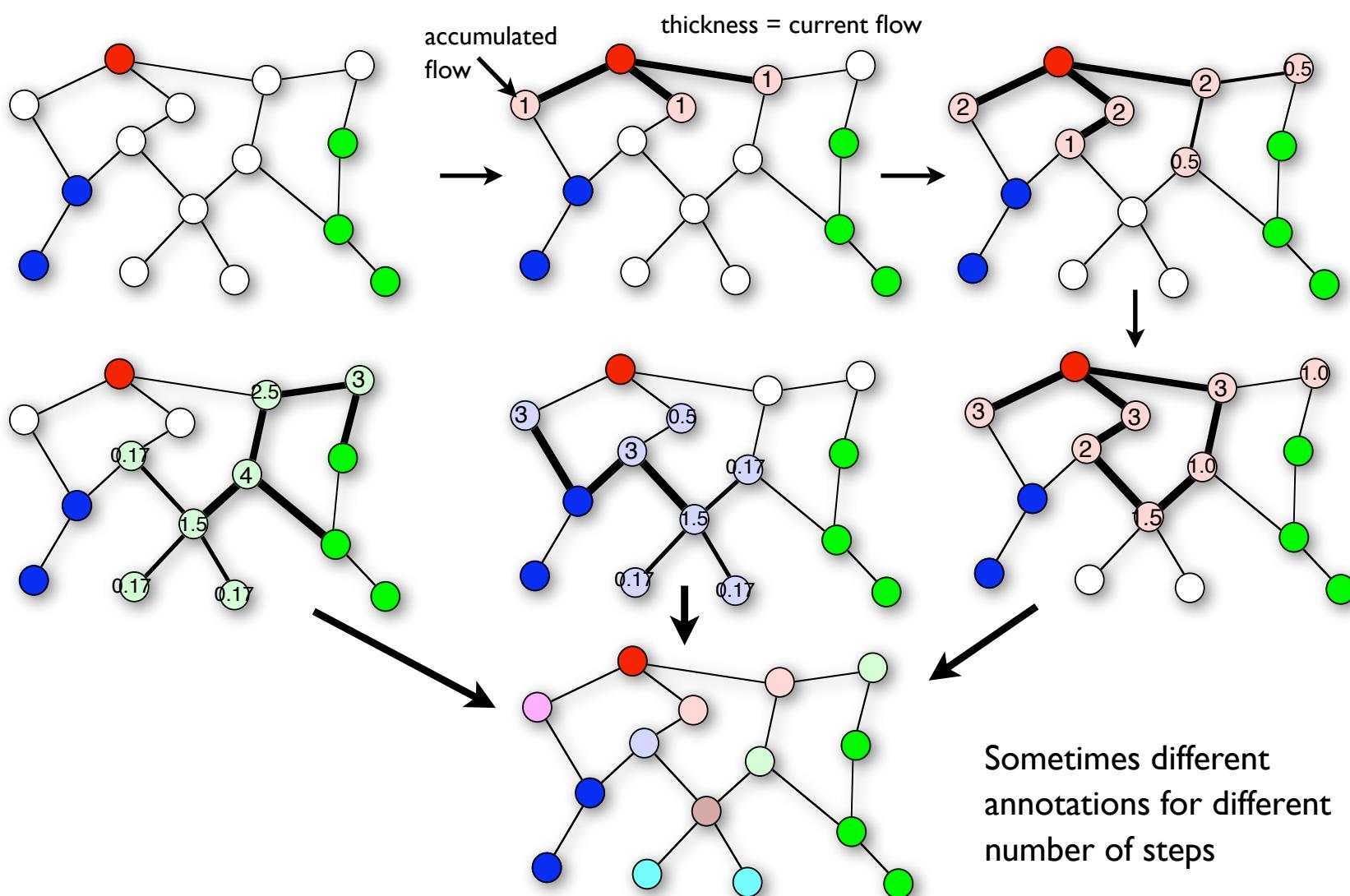
Initially: $R_0^a(u) = \begin{cases} \infty, & \text{if } u \text{ is annotated with } a, \\ 0, & \text{otherwise.} \end{cases}$ and $g_0^a(u, v) = 0$

Then: **downhill flow** with capacity constraints

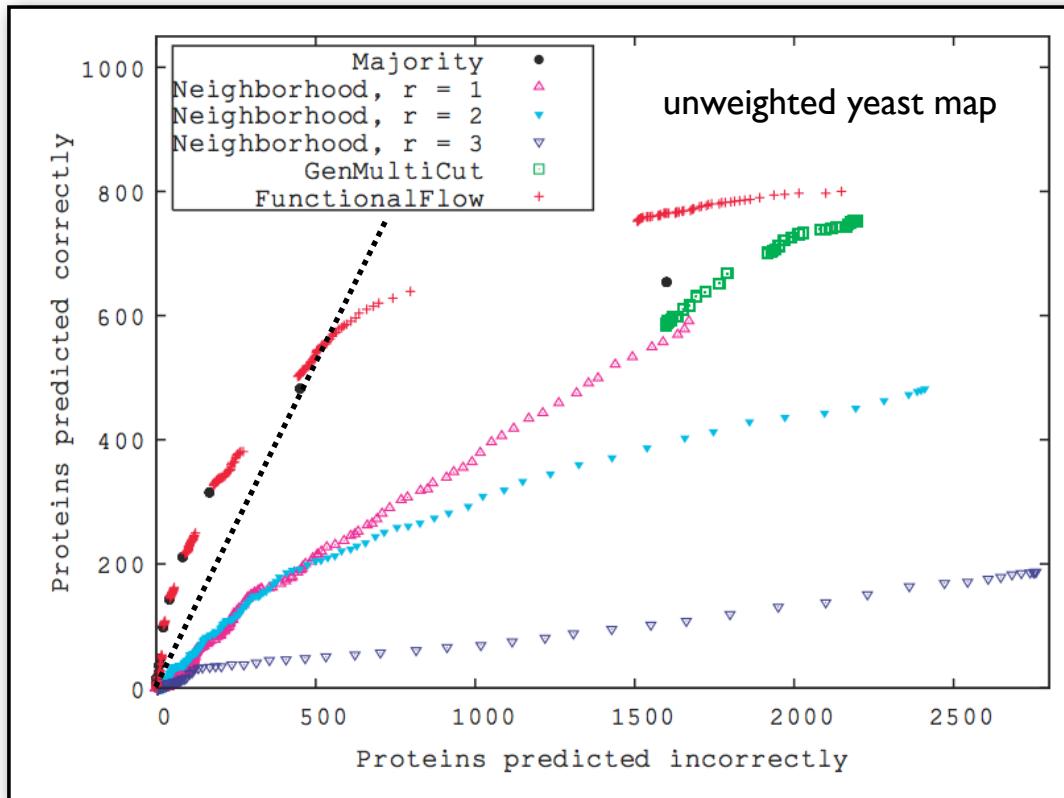
$$g_t^a(u, v) = \begin{cases} 0, & \text{if } R_{t-1}^a(u) < R_{t-1}^a(v) \\ \min\left(w_{u,v}, \frac{w_{u,v}}{\sum_{y:(u,y)\in E} w_{u,y}}\right), & \text{otherwise.} \end{cases}$$

Score from accumulated in-flow: $f_a(u) = \sum_{t=1}^d \sum_{v:(u,v)\in E} g_t^a(v, u)$

An Example



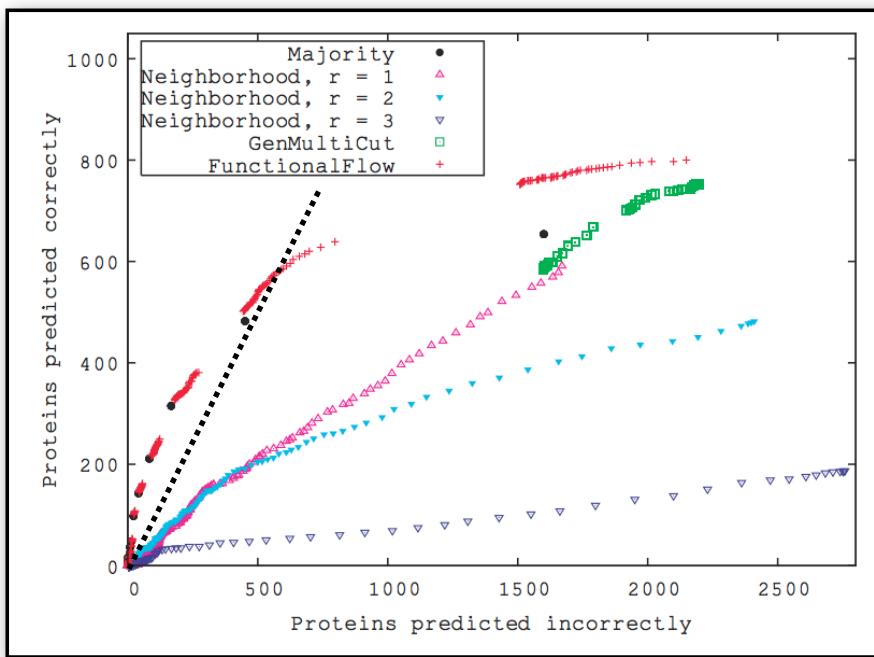
Comparison



For FunctionalFlow:
six propagation steps
(diameter of the yeast
network ≈ 12)

Change **score threshold** for accepting annotations => ratio **TP/FP**
=> **FunctionalFlow** performs **best** in the high-confidence region
=> many false predictions!!!

Comparison Details



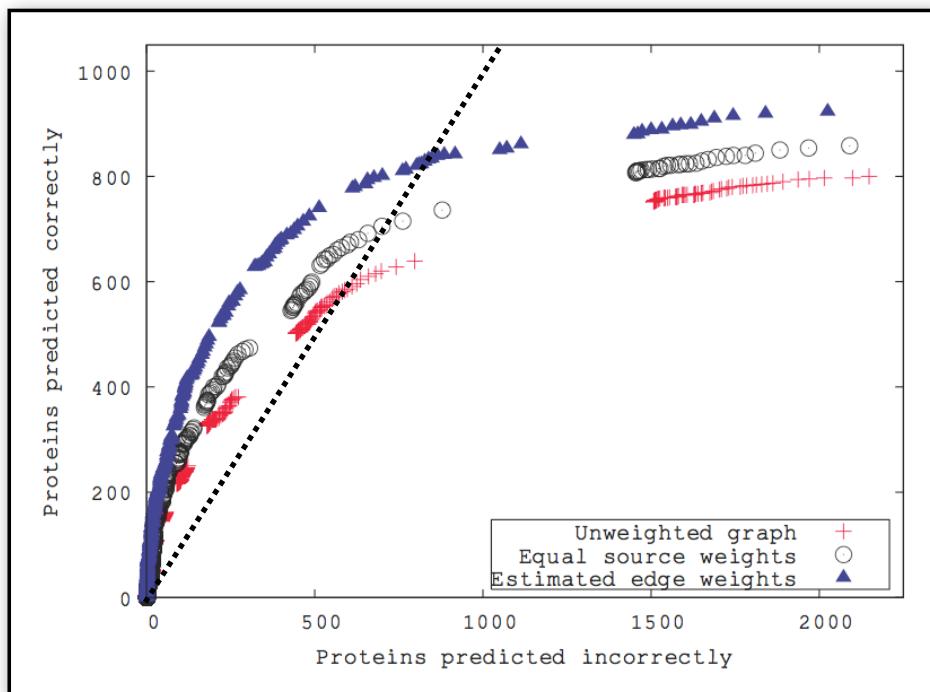
Multiple runs (solutions) of
FunctionalFlow
(with slight random perturbations
of the weights)
=> increases prediction accuracy

Majority vs. Neighborhood @ $r = 1$
=> counting neighboring
annotations is more effective
than χ^2 -test

Neighborhood with $r = 1$ or 2 comparable for high-confidence region,
performance decreases with increasing r
=> **bad** idea to **ignore** local connectivity

Weighted Graphs

Performance of FunctionalFlow with differently weighted data:

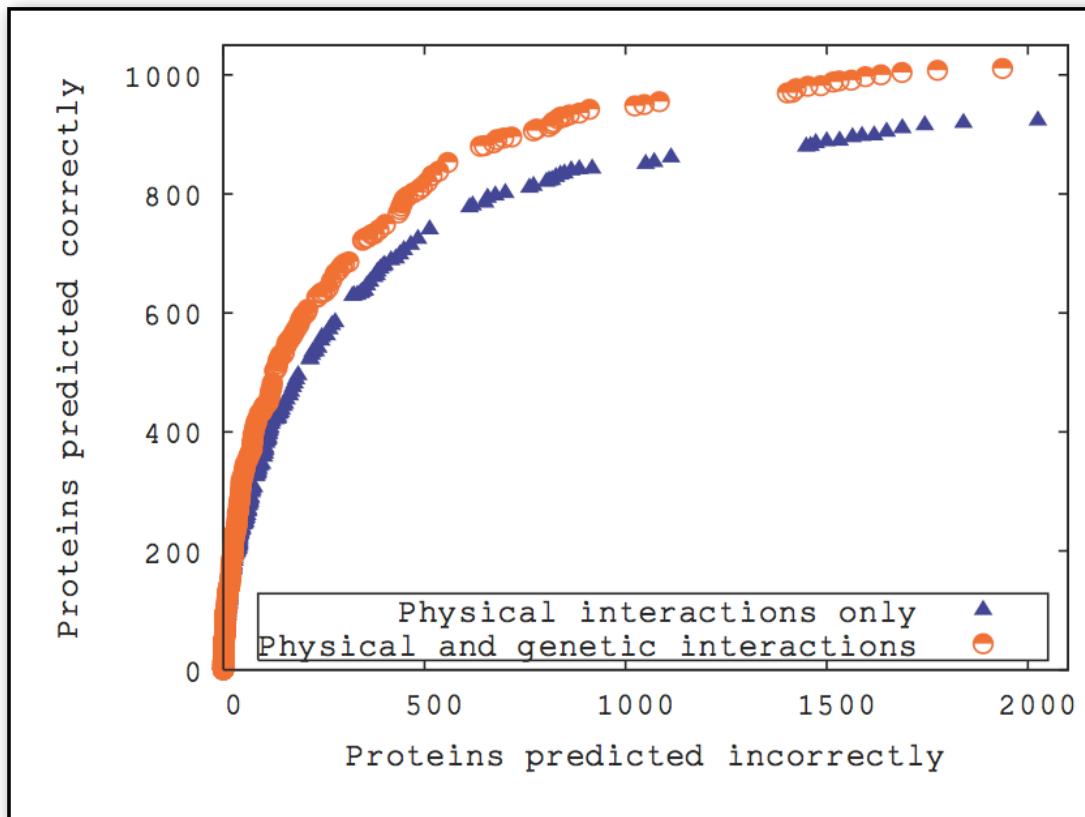


Compare:

- unweighted
- weight 0.5 per experiment
- weight for experiments according to (estimated) reliability

Largest improvement
=> individual experimental reliabilities

Additional Information



(Note the clever choice of symbols in the plot...)

Use **genetic linkage** to modify the edge **weights**
=> better performance (also for Majority and GenMultiCut)

Summary: **Static PPI-Networks**

"Proteins are **modular machines**" \Leftrightarrow How are they related to each other?

1) **Understand** "Networks"

prototypes (ER, SF, ...) and their properties ($P(k)$, $C(k)$, clustering, ...)

2) Get the **data**

experimental and theoretical techniques (Y2H, TAP, co-regulation, ...),
quality control and data integration (Bayes)

3) **Analyze** the data

compare $P(k)$, $C(k)$, clusters, ... to prototypes => highly modular, clustered
with sparse sampling => PPI networks are not scale-free

4) **Predict** missing information

network structure combined from multiple sources => functional annotation

Next step: environmental changes, cell cycle

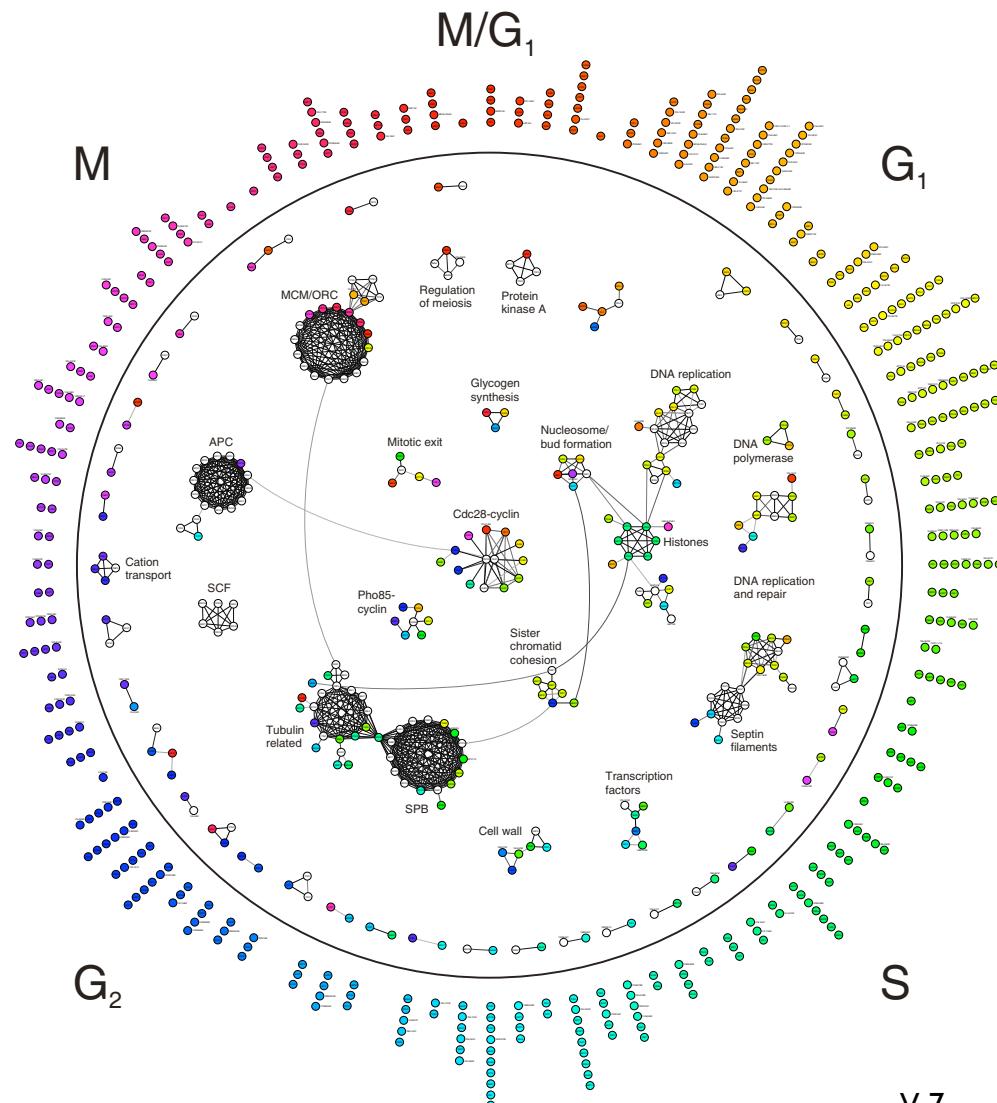
=> **changes** (dynamics) in the PPI network – **how and why?**

Turn, Turn, Turn...

From Lichtenberg et al,
Science 307 (2005) 724:

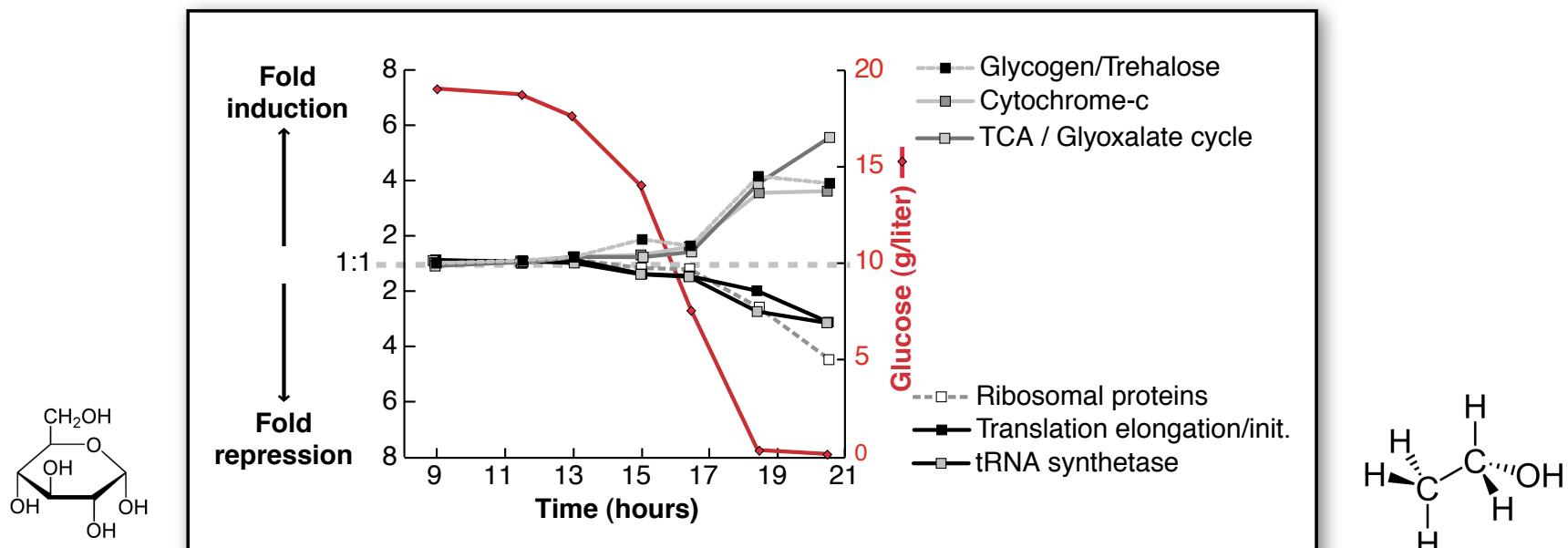
=> certain proteins only
occur during well-
defined phases in the
cell cycle

=> how is protein
expression regulated?



External Triggers

Re-routing of metabolic fluxes during the diauxic shift in *S. cerevisiae*
=> changes in protein abundances (measured via mRNA levels)

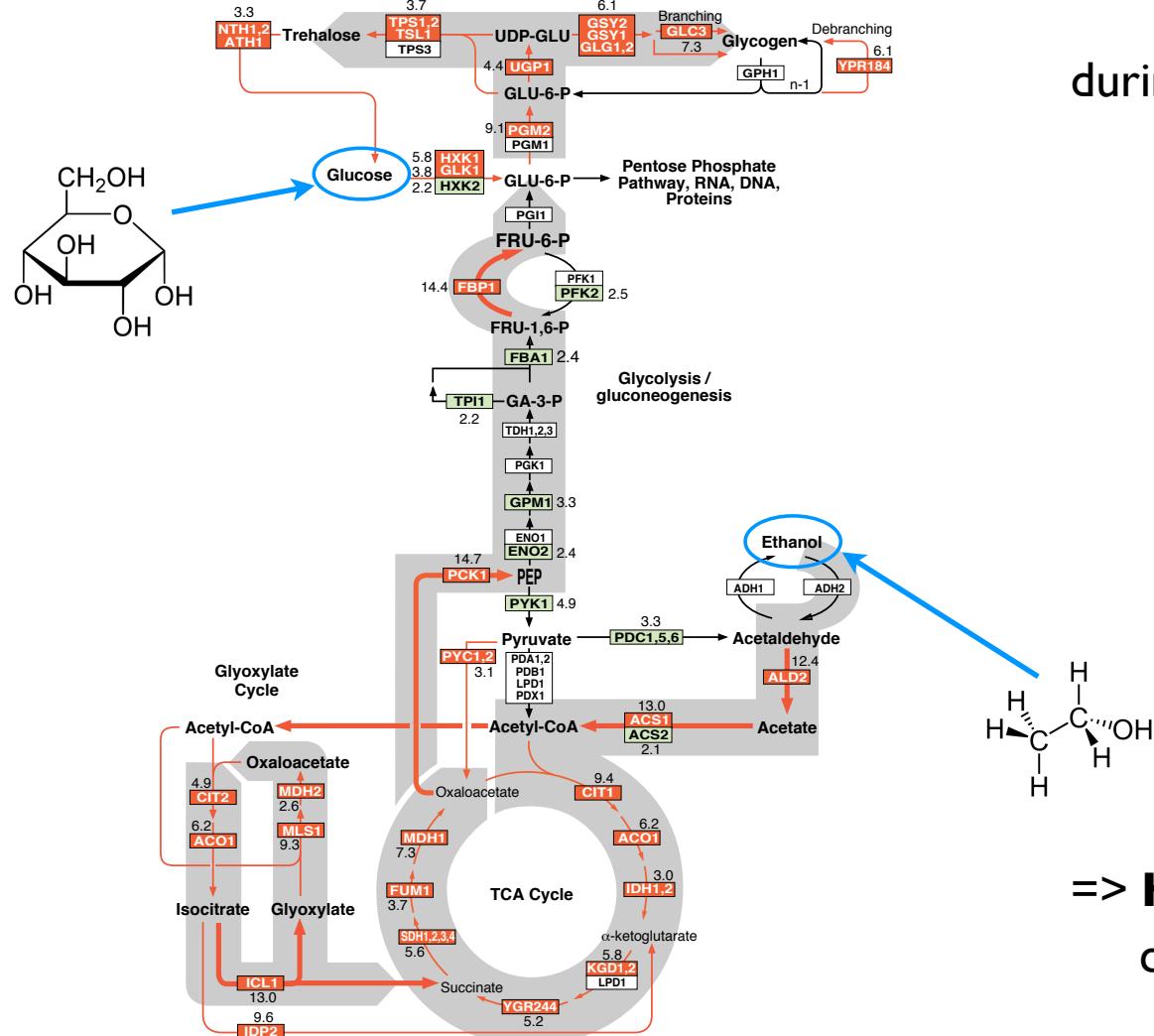


anaerobic fermentation:
fast growth on glucose => ethanol

aerobic respiration:
ethanol as carbons source

Note: "quorum sensing" — different bacteria have different strategies

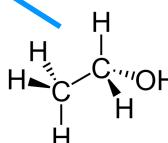
Flux Re-Routing



during diauxic shift:

- fold change
expression increases
- expression unchanged
- expression diminishes

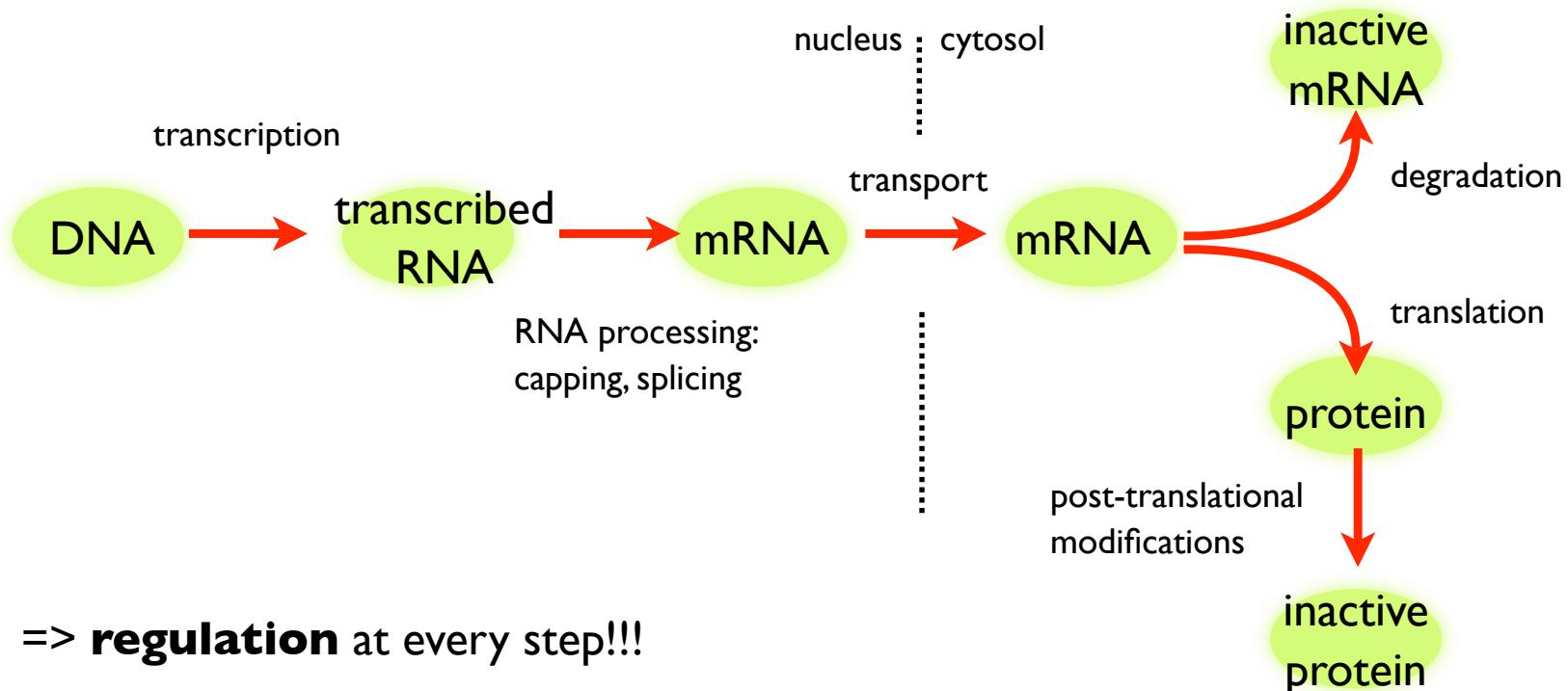
metabolic flux increases



=> how are these changes coordinated?

Gene Expression

Sequence of processes: from DNA to functional proteins



=> **regulation** at every step!!!

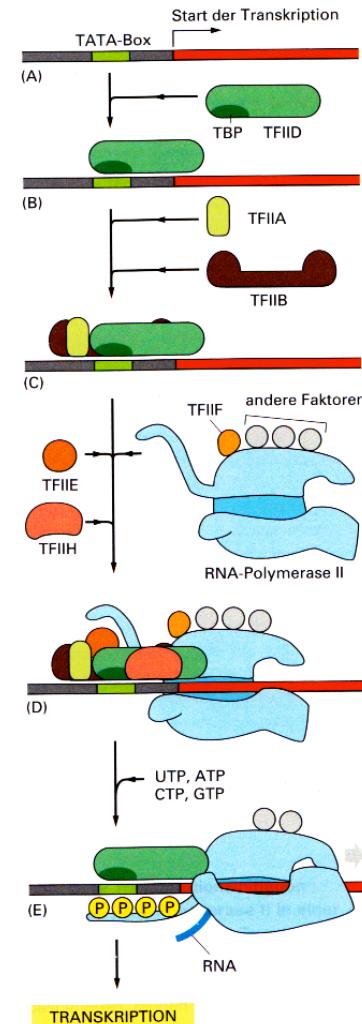
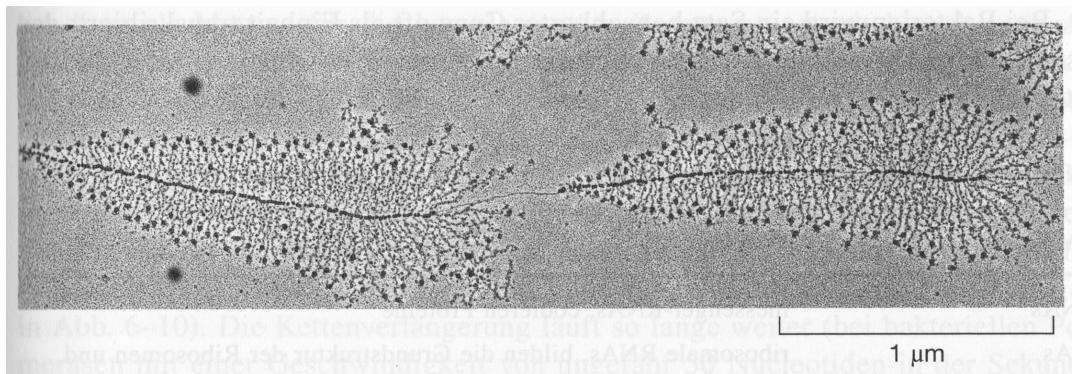
most **prominent**:

activation or repression of the transcription initiation

Transcription Initiation

In eucaryotes:

- several **general** transcription factors **have** to bind
- **specific** enhancers or repressors **may** bind
- then the RNA polymerase binds
- and starts transcription

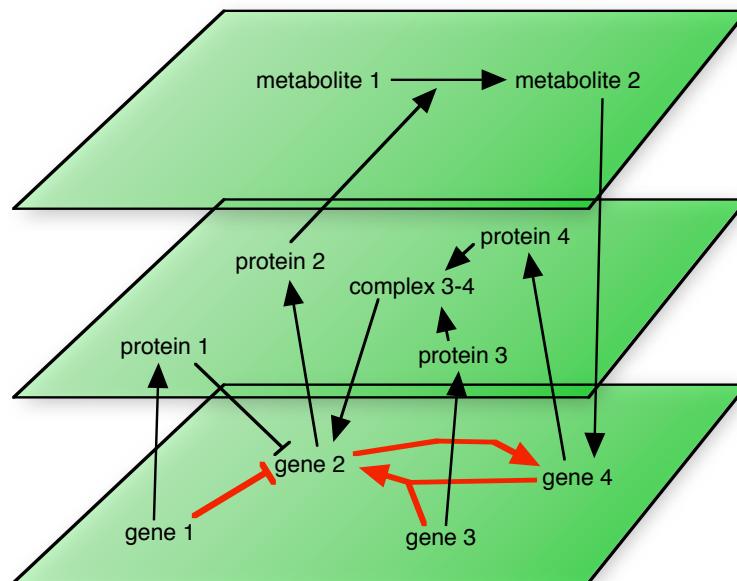


Layers upon Layers

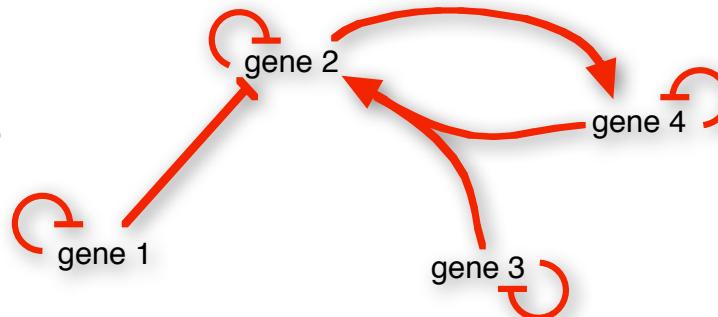
Biological regulation
via proteins and metabolites

<=>

Projected regulatory network



<=>



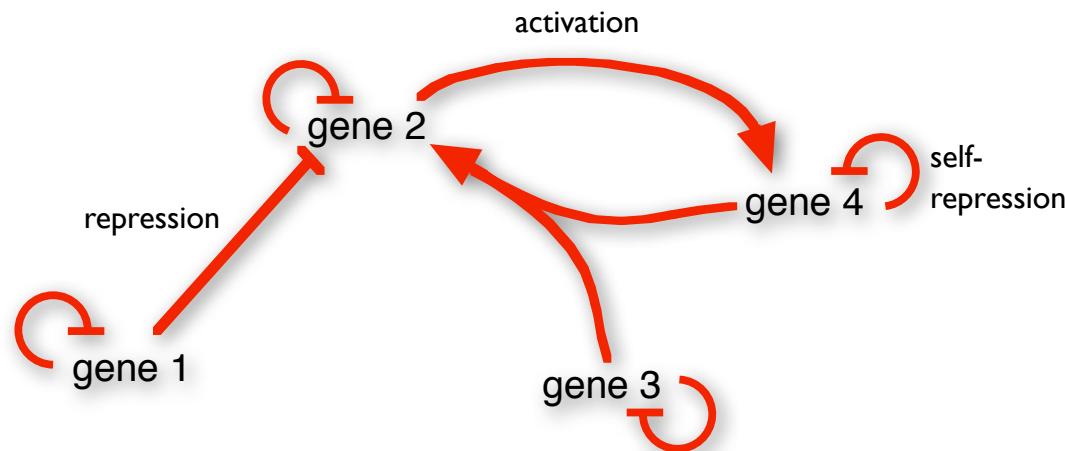
Remember:
genes do not interact directly

Graph Conventions

Nodes: genes that code for proteins which catalyze products ...
=> everything projected onto respective gene

Gene regulation networks have "cause and action"
=> **directed** networks

A gene can enhance or suppress the expression of another gene
=> **two types** of arrows



Luminescence in *V. fischeri*

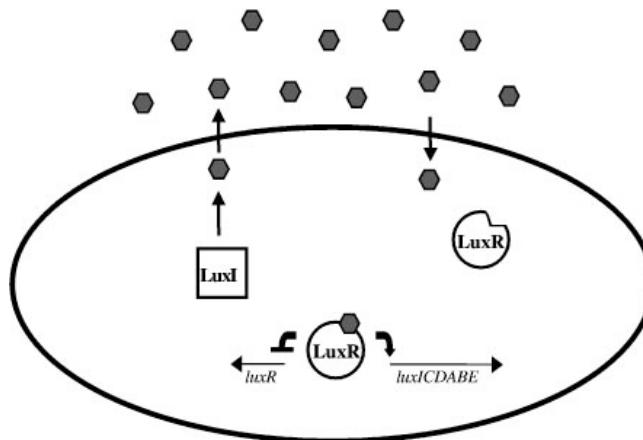
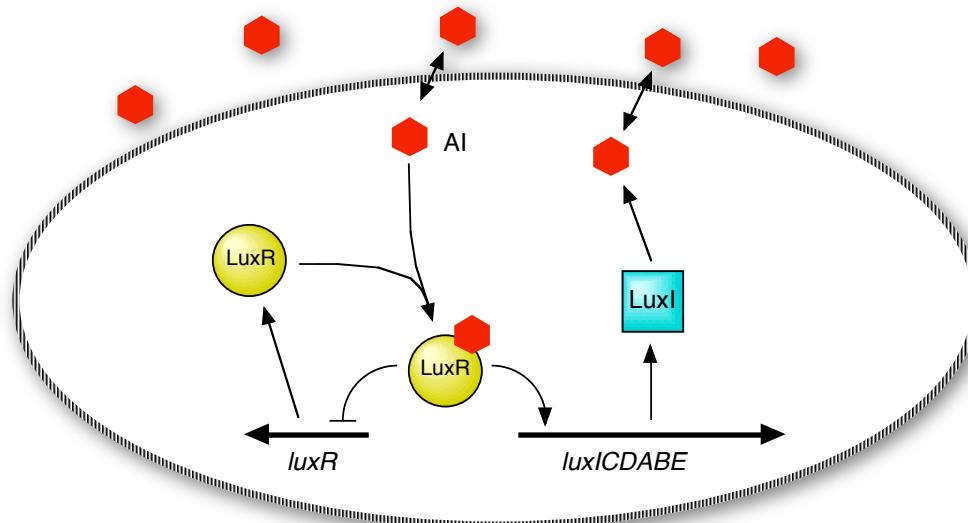


Figure 1 The *Vibrio fischeri* LuxI/LuxR quorum sensing circuit. There are five luciferase structural genes (*luxCDABE*) and two regulatory genes (*luxR* and *luxI*) required for quorum sensing-controlled light emission in *V. fischeri*. The genes are arranged in two adjacent but divergently transcribed units. *luxR* is transcribed to the left, and the *luxICDABE* operon is transcribed to the right. The LuxI protein (square) is responsible for synthesis of the HSL autoinducer *N*-(3-oxohexanoyl)-homoserine lactone (hexagons). As the cell-population density increases, the concentration of the autoinducer increases both intra- and extracellularly. At a critical autoinducer concentration, the LuxR protein (circle) binds the autoinducer. The LuxR-autoinducer complex binds at the *luxICDABE* promoter and activates transcription of this operon. This action results in an exponential increase in autoinducer synthesis via the increase in transcription of *luxI* and an exponential increase in light production via the increase in transcription of *luxCDABE*. The LuxR-autoinducer complex also binds at the *luxR* promoter, but in this case the complex represses the transcription of *luxR*. This negative action compensates for the positive action at the *luxICDABE* promoter. The oval represents a bacterial cell.

Miller, Bassler, 2001

The Complete Picture?

Sketch from Miller & Bassler used to explain the mechanism:



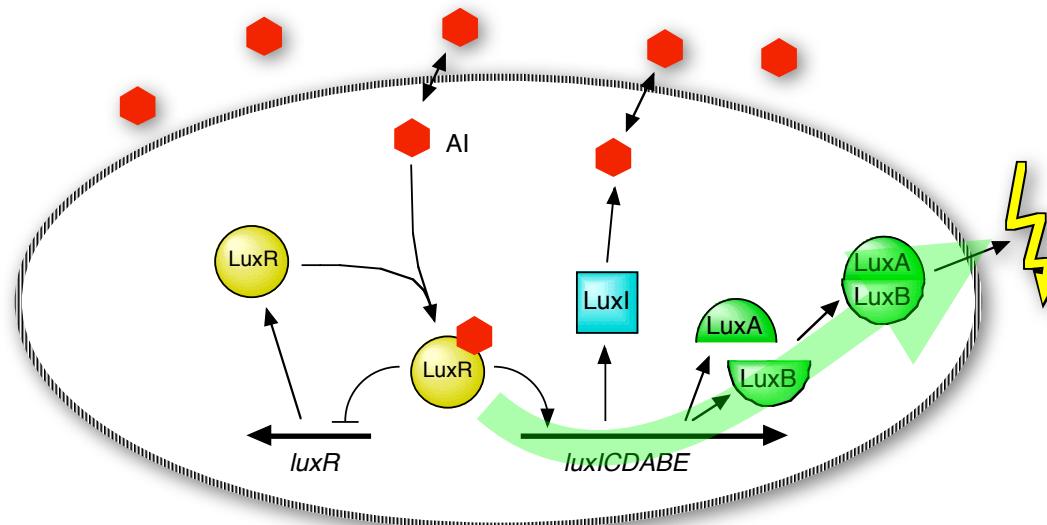
What is **missing**?

- light signal
- degradation of AI and proteins
- threshold
- details of the "reactions"

A Slightly More Complete Picture

Add luminescence

$\text{LuxA} + \text{LuxB} \Rightarrow \text{Luziferase} \Rightarrow \text{Light}$

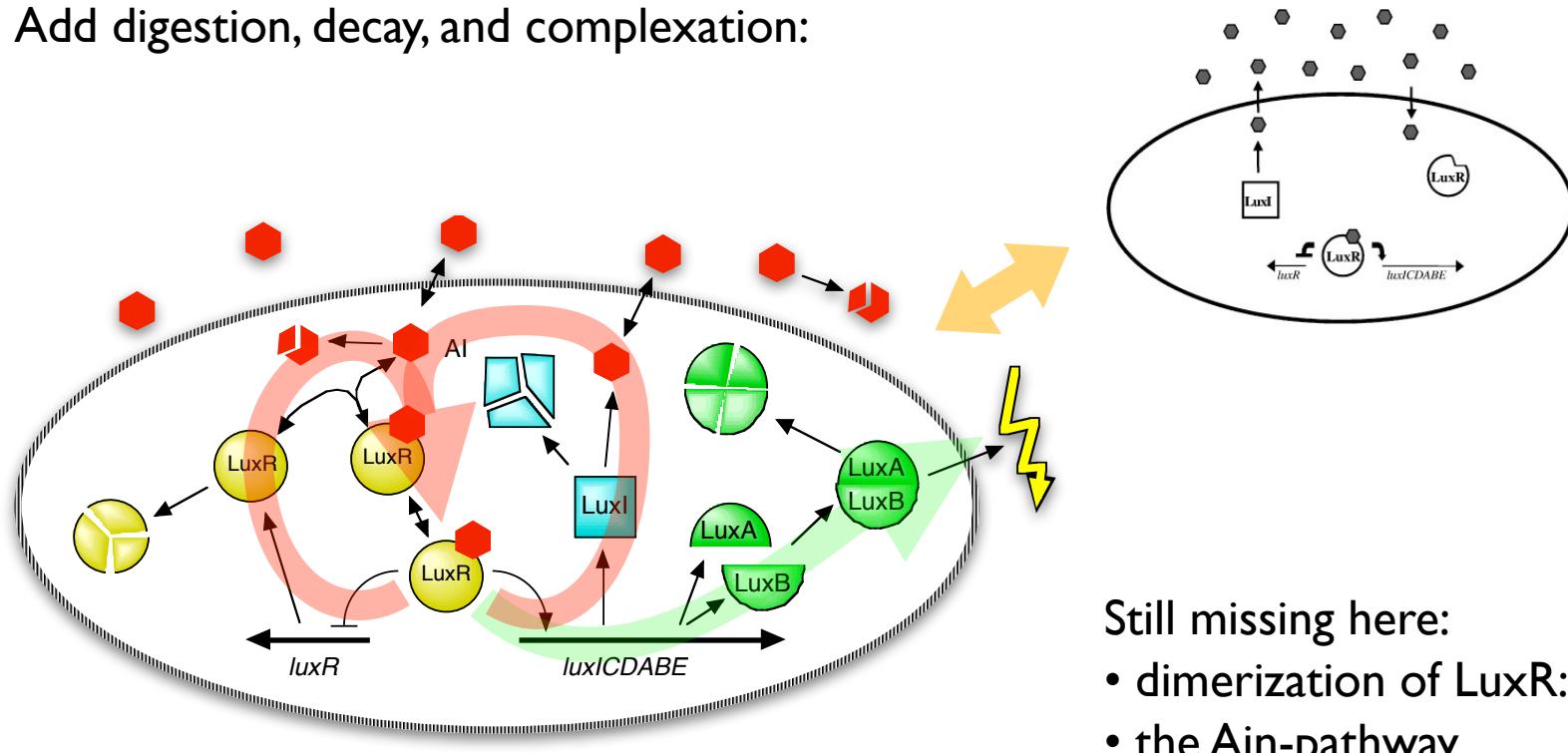


Beware: the picture contains **different reaction mechanisms**
(various associations, transcription+translation, diffusion, ...)

Task: "sort the occurring reactions into their respective categories
and discuss the notion of a TF with your neighbor ...":)

Still not the Complete Picture

Add digestion, decay, and complexation:



- Still missing here:
- dimerization of LuxR:AI
 - the Ain-pathway

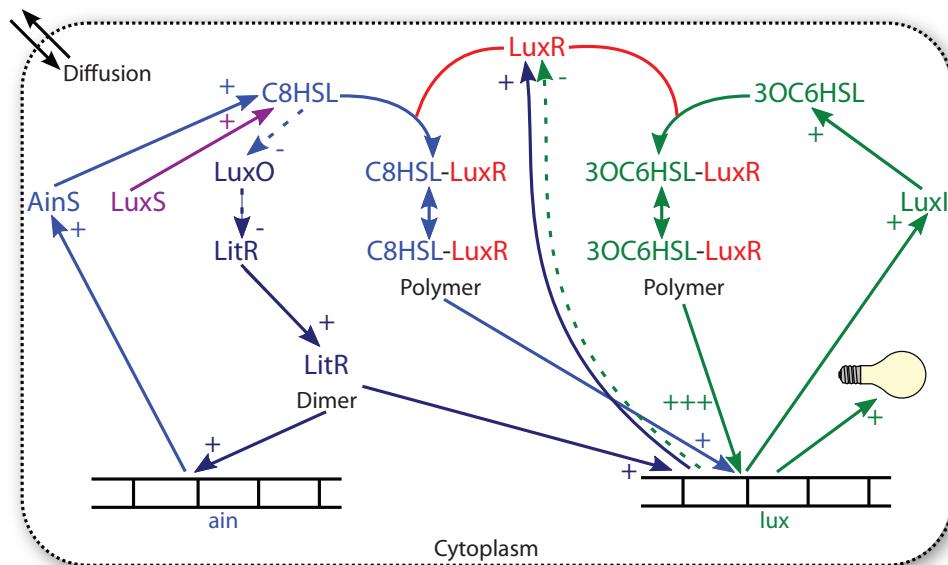
Modelling problem in biology:

=> convert hand-waving **verbal descriptions** into consistent models

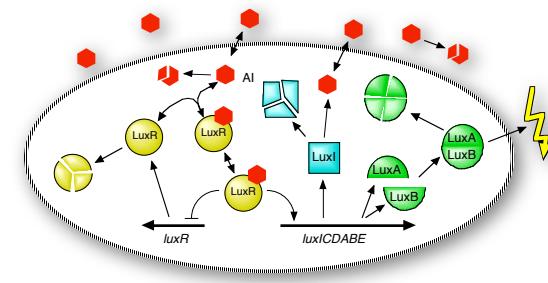
And There is One More Detail...

- two autoinducers: 3OC6HSL and C8HSL
- two genes (ain and lux)

But: the model is still incomplete



Nadine Schaad, BSc. thesis



=> which of all these reactions
are important for the
dynamic behavior of the
system?

=> is everything known?

=> systemic modell?

=> interactions with
cellular environment

=> predictions?

E. coli Regulatory Network

BMC Bioinformatics

BioMed Central

Research article

Open Access

Hierarchical structure and modules in the *Escherichia coli* transcriptional regulatory network revealed by a new top-down approach

Hong-Wu Ma¹, Jan Buer^{2,3} and An-Ping Zeng*¹

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This article is available from: <http://www.biomedcentral.com/1471-2105/5/199>

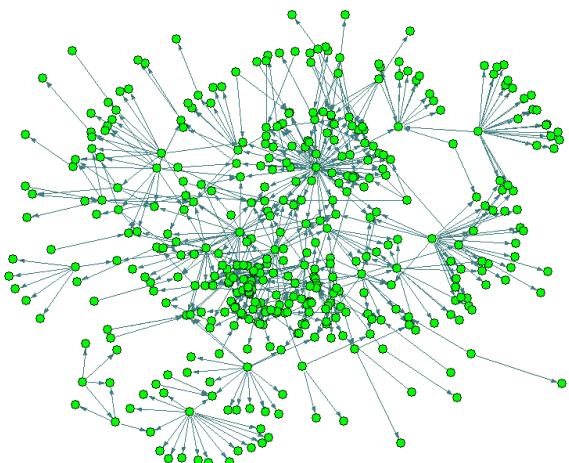
© 2004 Ma et al.; licensee BioMed Central Ltd

BMC Bioinformatics 5 (2004) 199

Hierarchies

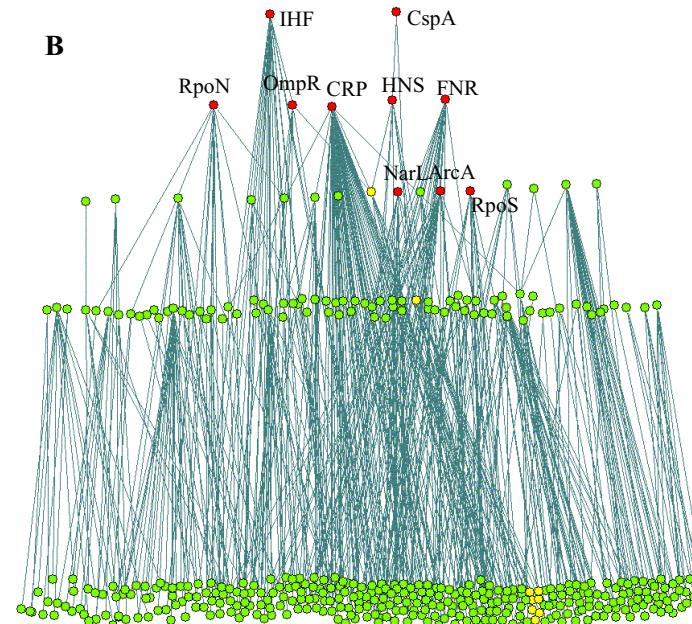
Largest WCC: 325 operons
(3/4 of the complete network)

WCC = weakly connected component (ignore directions)



Network from standard layout algorithm

=>



Network with all regulatory edges pointing downwards

=> a few global regulators (●) control all the details

Global Regulators in *E. coli*

Table I: Global regulators and their regulated operons and functions in the regulatory network of *E. coli*.

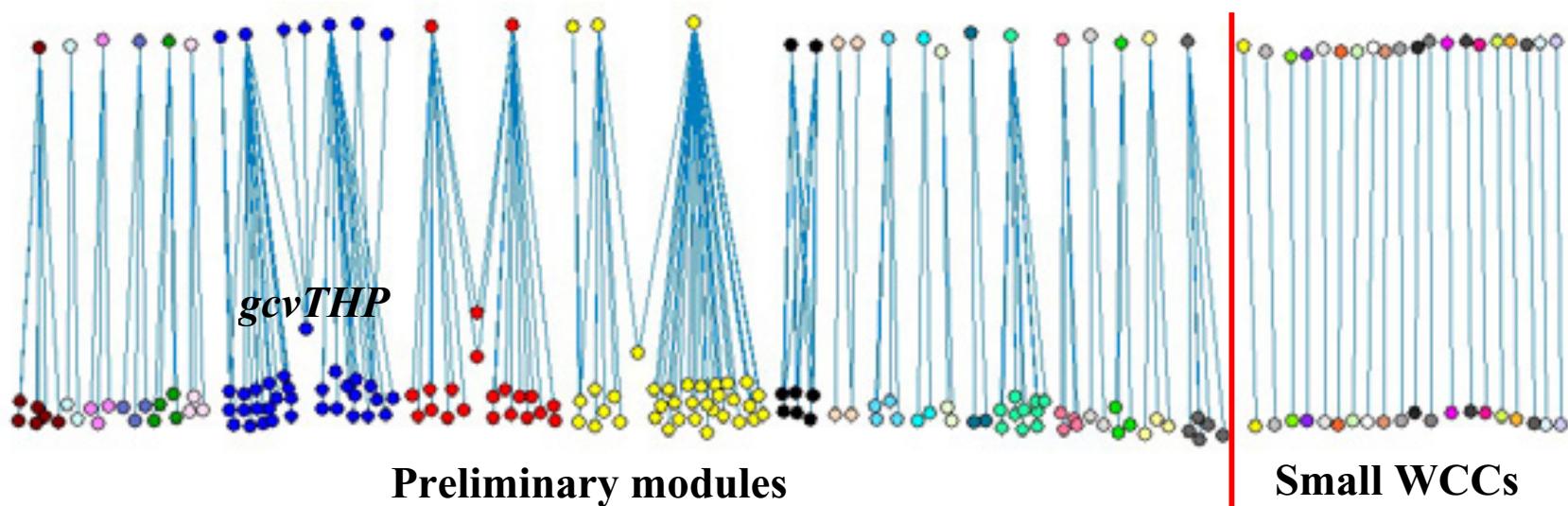
Global regulator	directly regulated Operons	Total regulated operons	Modules regulated	Function
IHF	21	39	15	integration host factor
CspA	2	24	5	Cold shock protein
CRP	72	112	21	cAMP receptor protein
FNR	22	38	16	anaerobic regulator, regulatory gene for nitrite and nitrate reductases, fumarate reductase
HNS	7	22	5	DNA-binding global regulator; involved in chromosome organization; preferentially binds bent DNA
OmpR	6	20	3	Response regulator for osmoregulation; regulates production of membrane proteins
RpoN	12	17	4	RNA polymerase sigma 54 subunit
RpoS	14	24	8	stationary phase sigma factor
ArcA	20	21	6	Response regulator protein represses aerobic genes under anaerobic growth conditions and activates some anaerobic genes
NarL	13	15	5	Two-component regulator protein for nitrate/nitrite response

Modules

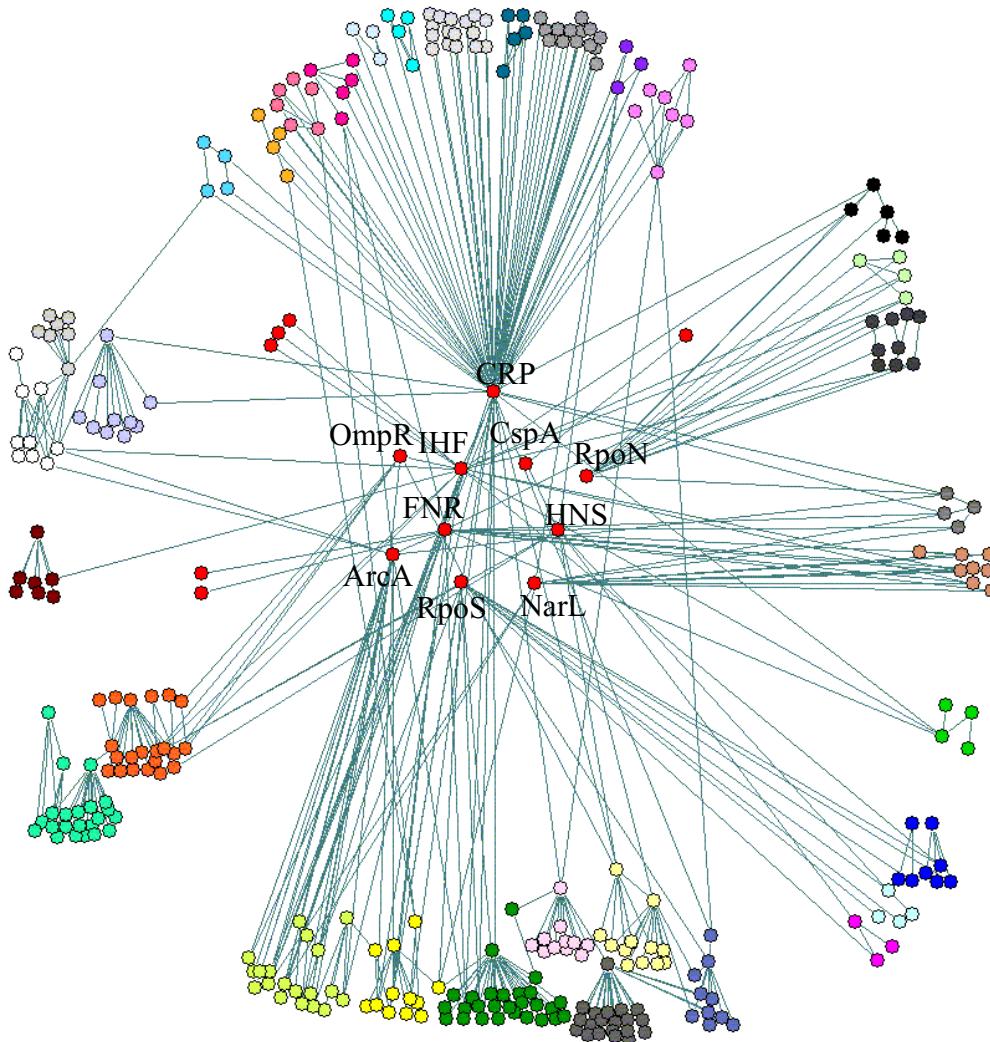
Remove top three layers and determine WCCs
=> just a few modules

B

IHF
RpoN
OmpR
CRP
HNS
ENR
CspA
NarL
ArcA
RpoS



Putting it back together



The ten global regulators are at the core of the network, some hierarchies exist between the modules

Naming a few!

Table 2: Functional investigation of modules identified.

index	Operons included	Biological function description
1	<i>aceBAK, acs, adhE, fruBKA, fruR, icdA, iclMR, mlc, ppsA, ptsG, ptsHI_crr, pykF</i>	Hexose PTS transport system, PEP generation, Acetate usage, glyoxylate shunt
2	<i>acnA, fpr, fumC, marRAB, nfo, sodA, soxR, soxS, zwf</i>	Oxidative stress response
3	<i>ada_alkB, aidB, alkA, ahpCF, dps, gorA, katG, oxyR</i>	Oxidative stress response, Alkylation
4	<i>alaWX, aldB, argU, argW, argX_hisR_leuT_prom, aspV, dnaA, leuQPV, leuX, lysT_valT_lysW, metT_leuW_glnUW_metU_glnVX, metY_yhbC_nusA_infB, nrdAB, pdhR_aceEF_lpda, pheU, pheV, proK, proL, proP, sdhCDAB_b0725_sucABCD, serT, serX, thrU_tyrU_glyT_thrT, thrW, tyrTV, valUXY_lysV, yhdG_fis</i>	rRNA, tRNA genes, DNA synthesis system, pyruvate dehydrogenase and ketoglutarate dehydrogenase system
5	<i>araBAD, araC, araE, araFGH, araJ</i>	Arabinose uptake and usage
6	<i>argCBH, argD, argE, argF, argI, argR, carAB</i>	Arginine usage, urea cycle
7	<i>caiF, caiTABCDE, fixABCX</i>	Carnitine usage
8	<i>clpP, dnaKJ, grpE, hflB, htpG, htpY, ibpAB, lon, mopA, mopB, rpoH</i>	Heat shock response
9	<i>codBA, cvpA_purF_ubiX, glnB, glyA, guaBA, metA, metH, metR, prsA, purC, purEK, purHD, purL, purMN, purR, pyrC, pyrD, speA, ycfC_purB, metC, metF, metJ</i>	Purine synthesis, purine and pyrimidine salvage pathway, methionine synthesis
10	<i>cpxAR, cpxP, dsbA, ecfI, htrA, motABcheAW, ppiA, skp_lpxDA_fabZ, tsr, xprB_dsbC_recJ</i>	Stress response, Conjugative plasmid expression, cell motility and Chemotaxis
11	<i>dctA, dcuB_fumB, frdABCD, yjdHG</i>	C4 dicarboxylate uptake
12	<i>edd_edA, gntKU, gntR, gntT</i>	Gluconate usage, ED pathway
13	<i>csgBA, csgDEFG, envY_ompT, evgA, gcvA, gcvR, gcvTHP, gltBDF, ilvIH, kbl_tdh, livJ, livKHMGF, lrp, lysU, ompC, ompF, oppABCDF, osmC, sdaA, serA, stpA</i>	Amino acid uptake and usage
14	<i>fdhF, fhlA, hydABCDEFGH, hypABCDE</i>	Formate hydrogenlyase system
15	<i>flgAMN, flgBCDEFGHIJ, flgKL, flgMN, fhlBAE, fhlDC, fliAZY, fliC, fliDST, fliE, fliFGHIJK, fliLMNOPQR, tarTapcheRBYZ</i>	Flagella motility system
16	<i>ftsQAZ, rcsAB, wza_wzb_b2060_wcaA_wcaB</i>	Capsule synthesis, cell division
17	<i>gdhA, glnALG, glnHPQ, nac, putAP</i>	Glutamine and proline utilization
18	<i>glmUS, manXYZ, nagBACD, nagE</i>	Glucosamine, mannose utilization
19	<i>glpACB, glpD, glpFK, glpR, glpTQ</i>	Glycerol phosphate utilization
20	<i>lysA, lysR, tdcABCDEF, tdcR</i>	Serine, threonine usage
21	<i>'EEC_malK_lcmR_malM_malPO_malS_malT, malZ</i>	Maltose utilization

There is no legend in the publication to identify these modules in the graphs...

Summary

- **Static** PPI networks:
=> topology, measures, data sources, ...
- **Changes** during cell cycle, adaptation to environmental changes, ...
=> Gene Regulation
=> many biological steps
=> often modelled on the gene level only

Next lecture:

- Regulatory **motifs**
=> static and dynamic behavior