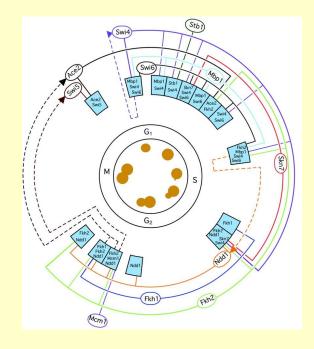


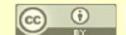
### Computational Molecular Biology Biochem 218 – BioMedical Informatics 231

http://biochem218.stanford.edu/

# Gene Regulatory Networks



Doug Brutlag
Professor Emeritus
Biochemistry & Medicine (by courtesy)





# Homework 7 Transcription Factor Motifs for Co-expressed Genes

• Choose a group of co-expressed genes from the Yeast Cell Cycle Database by first entering a single gene of interest to you and then clicking on select all co-expressed genes:

http://genome-www.stanford.edu/cgi-bin/cellcycle/search

• Collect all the names of the genes and enter them in Go Term Finder to discover common biological processes, common molecular mechanisms and common cellular components in the Saccharomyces Genome Database:

http://www.yeastgenome.org/cgi-bin/GO/goTermFinder.pl

• Using the Batch download link, collect all the gene sequences plus 1 KB upstream and enter the 1 KB upstream sequence from all the genes into MDScan and search for motifs 8, 10 or 12 bases long:

http://mdscan.stanford.edu/

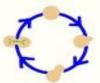
- You may have to remove simple sequences such as (tatatatata or ttttttttt or cacacacaca) by globally replacing them with an X character in order to ignore simple sequence repeats from the list of motifs found.
- Enter your list of co-expressed gene names in YeasTract web site and see if MDScan has discovered any known transcription binding sites:

http://www.yeastract.com/



# Yeast Cell Cycle Database

http://genome-www.stanford.edu/cgi-bin/cellcycle/search



### Yeast Cell Cycle Analysis Project

#### Home

Cell Cycle Analysis Home

Home | Search | Figures | Data | Info | Links |
SGD | Microarray Homepage

#### View Figures

View figures from the paper

#### Search

Search the complete dataset

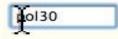
#### Download Data

Download images and primary data tables

#### Information

Information on how to use this site and scientific methods Input the name (either ORF or common e.g ACT1, YAL004W) for the gene you wish to view

You may also use a wild-card to retrieve a list of genes that match your expression, eg cdc\*.



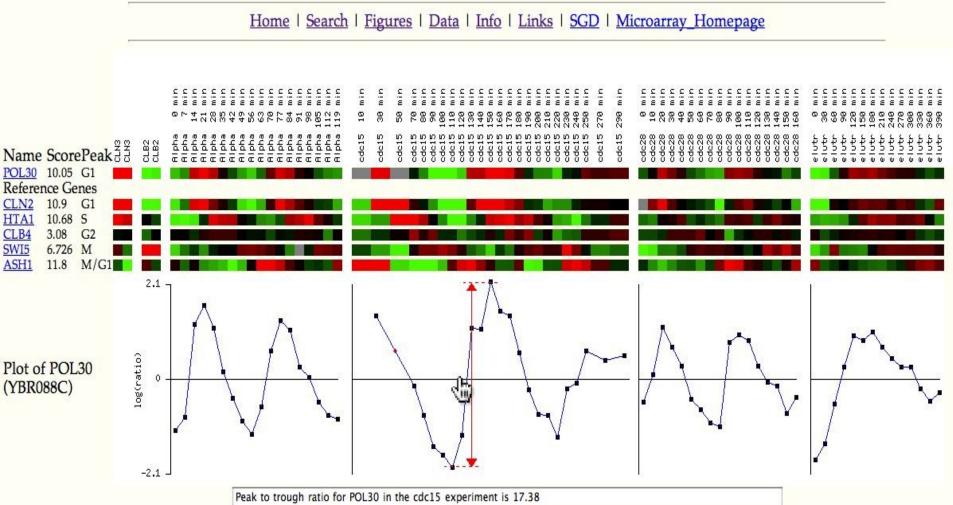
Submit



# Yeast Cell Cycle Database



### Yeast Cell Cycle Analysis Project



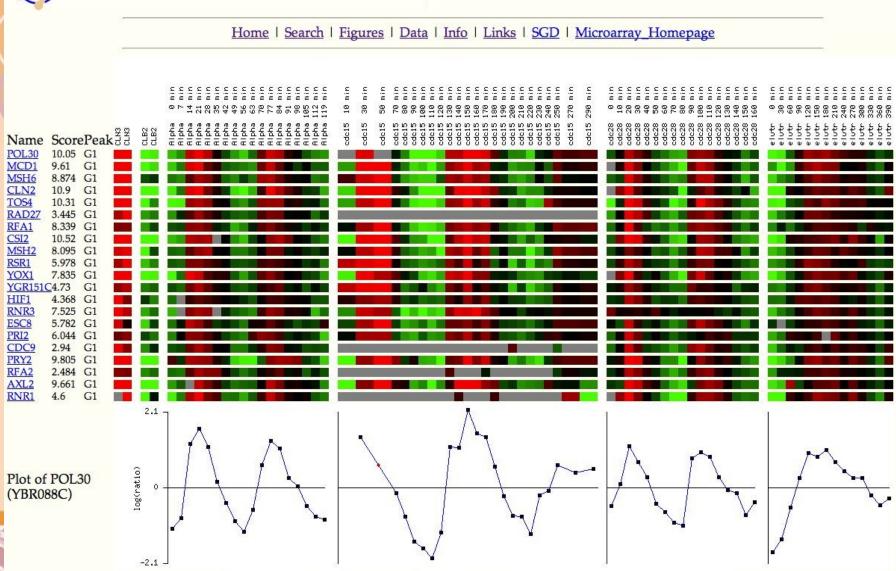
Hit submit to view 20 genes which are expressed similarly to the queried gene

## Yeast Cell Cycle Database

http://genome-www.stanford.edu/cgi-bin/cellcycle/search



### Yeast Cell Cycle Analysis Project



Put your mouse over the graphs to find out their peak to trough ratios.

### Saccharomyces Genome Database

http://www.yeastgenome.org/



### Saccharomyces Genome Database

#### Search Options

Advanced Search, Full-text Search (Textpresso), Search SGD web pages, Global Gene Hunter, Search Literature, and more.

#### Help Resources

Getting Started, Sitemap, FAQ, and more.

#### ▶ Analysis & Tools

BLAST, Gene/Seq Resources, Maps, and more.

#### ▶ Homology & Comparisons

PDB Homologs, Protein Domains/Motifs, Homologs, and more.

#### ► Function & Expression

Protein Info, Pathways, Expression Connection, and more.

#### GO Resources

GO Tutorial, What is GO?, GO Slim Mapper, GO Term Finder, and more. SGD<sup>TM</sup> is a scientific database of the molecular biology and genetics of the yeast *Saccharomyces* cerevisiae, which is commonly known as baker's or budding yeast.

### New and Noteworthy

#### SGD Quarterly Newsletter - January 29, 2010

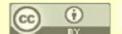
SGD sends out its quarterly newsletter to colleagues designated as contacts in SGD. An HTML version of the newsletter is available. If you would like to receive this letter in the future please use the Colleague Submission/Update form to let us know.

#### SGD Curation News

- Genome Snapshot
- New papers added to SGD this week.
- · View Genome-wide Analysis papers in SGD.
- . Do a literature search.
- Table of Gene Summary Paragraphs (new ones highlighted yellow).

#### New genetic interaction data file available for download from SGD - January 22, 2010

A large set of genetic interaction data from Costanzo et al., The Genetic Landscape of a Cell, Science 327: 425-431 (2010) is available for download from SGD's Download Data Files page and will be available via the web interface in the future. This study presents 74,984 genetic interactions, comprising a functional map of the cell. Thanks to the authors for providing their data to SGD.



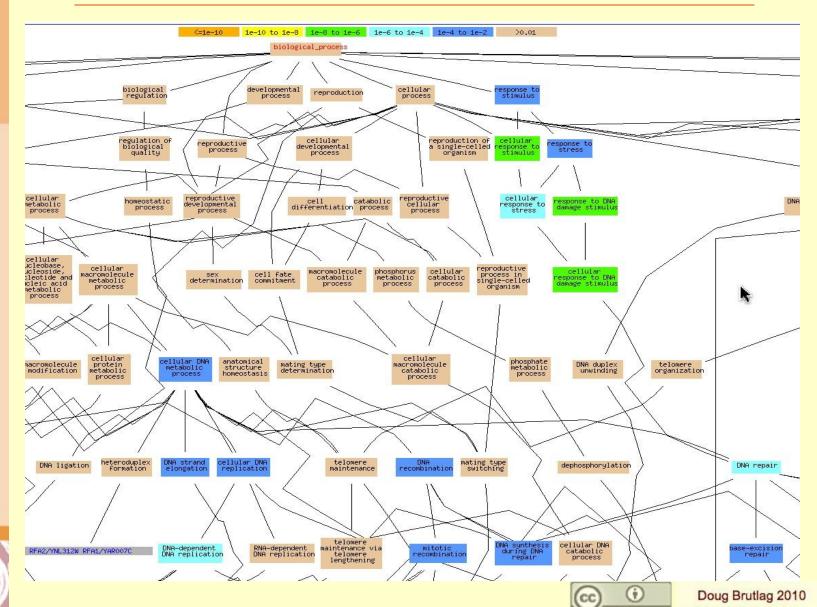
### Saccharomyces Genome Database Go Term Finder

http://www.yeastgenome.org/

7							
SGD	Search				Site Ma	ap   Search Options	s   Help   Home   =   RSS
Community Info	Submit Data	BLAST	Primers	PatMatch	Gene/Seq Resources	Advanced Search	Community Wiki
00.5 P0.00.5.00000 1 (40.00 NO 1 AVE	8 0 1 85 <b>3 1</b> 7 7 8 4 9 7 9	F1 F14 S51	IN COOR IN SEC. SEC. III		ene Ontology Ter		74 W W 180 W 170 TO 170
					or parents of those GO t ms and/or to bin them in		ibe the genes in your list to help you di se the GO Slim Mapper.
Default Settings:							
All genes/features     Manually curated     Hits with p-value	and High-through	nput annota	tion method	S			
Optional: Add a title f	or your search r	results					
Step 1: Query Set (Yo	ur Input)						
Enter Gene/ORF name (separated by a return	NG 80					OR Up	load a file of Gene/ORF names:
CDC9			A			(0	hoose File ) no file selected
PRY2							
RFA2 AXL2			<u></u>				
RNR1							
Step 2: Choose Ontol	ogy and Set Cut	toff					
● Process							
<b>○</b> Function							
○ Component							
Search using default se	ettings or use Ste	p 3, Step 4,	and/or Step	5 below to cu	stomize your options.		



# Saccharomyces Genome Database Go Term Finder Results



## Saccharomyces Genome Database Gene Sequence Resources

http://www.yeastgenome.org/cgi-bin/seqTools

Search		Site Map   Search Option	ons   Help   Hom	e   " see   N RSS
Community Info Submit Data BLAST Pri	mers PatMatch Gene/Seq R	esources Advanced Search	Community Wiki	
	Gene/S	equence Resources		Help
Submit Form				
This resource allows retrieval of a list	of options for accessing biol	ogical information, table/m	ap displays, a	nd sequence analysis tools for
<ol> <li>a named gene or seque</li> <li>a specified chromosom</li> <li>a raw DNA or protein se</li> </ol>	al region, or			
If you would like to retrieve information		genes, please go to the B	atch Downloa	d page.
nter a Name If irst few characters followed by *:  Inples: - act1 - YHR023W D - S000001855 Innk Locus - YSCHELI Innk AccNo L00683 Innk GI - gi:171655 - 70353  Illable, add flanking basepairs In and downstream	Then enter The entire of will be displentered.  Note: Enter order for the descending strand.	chromosome:  coordinates (optional): to hromosome sequence ayed if no coordinates are  coordinates in ascending Watson strand and order for the Crick	OR	3. Type or Paste a  DNA Sequence:  The sequence MUST be provided in RA format, no comments (numbers are oka

### Saccharomyces Genome Database Batch Download Tool

http://www.yeastgenome.org/cgi-bin/batchDownload

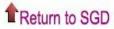
Step 1: '	Your Input
Option 1. Enter Feature/Standard Gene names (separate by return:)  POL30 MCD1 MSH6 CLN2  Examples: Gene Name - PPN1 ORF - YDR452W SGDID - S000002860  OR  Upload a file of Feature/Standard Gene names Choose File no file selected	Option 2. Pick a chromosome  Number Then enter coordinates (optional):  If no coordinates are entered all the features in the selected chromosom will be retrieved.  OR  Upload a file of chromosomal regions (coordinates are optional) with the following tab-separated columns: chr start_coordinate stop_coordinate For example:  III 1356 20455  IV 11331 18001  VI 9856 100010  Choose File no file selected
	ant to retrieve (You can select multiple types) details on the output file format.
Sequence data Genomic DNA (DNA sequence with introns) Genomic DNA + 1 kb upstream and 1 kb downstream of flanking sequence Coding Sequence (DNA sequence without introns) ORF Translation (Protein Sequence)  Other data Chromosomal Feature information including gene names, coordinates, des Gene Ontology (GO) Annotations (in gene_association file format) Phenotype Physical Interactions (in Cytoscape file format) Genetic Interactions (in Cytoscape file format)	



### Saccharomyces Genome Database Batch Download Tool

http://www.yeastgenome.org/cgi-bin/batchDownload

Download Data			
Search Search	Site Map   Search Options   He	elp   Home   Fig.   RSS	
Community Info Submit Data BLAST Primers PatMate	ch Gene/Seq Resources Adva	nced Search Community Wiki	
Dow	nload Data	Н	elp
ownloading data for 21 Feature/Gene names			
nis may take a while to run. For large gene lists, please download data fro ait	om our FTP site. Please wait		
ait			
he following file(s) contain the data you requested (please refer to the hel ata will be available at this URL for 1 hour after the request was made.	p page for details on the file format).	Please click on the file name to down	nload.
Type of Data Requested	Number of Features in the File	Name of Downloadable File	Size
Genomic DNA + 1kb upstream and 1kb downstream of flanking sequence	21	genomic1kb.fasta_643.gz	24.59 KB



Send a Message to the SGD Curators





### **MDScan**

### http://mdscan.stanford.edu/



Overview MDscan finds motif from ChIP-on-chip targets

Motif Finding Search for interesting motifs in your sequences on our server

Input Format How to specify the input parameters

Output Explanations How to look at the output file we send you

Motif Regressor An improved MDscan for download.

Reference Nat Biotechnol. 2002 20(8):835-9.

<u>Contacts</u> People behind the project

See other motif finding algorithms we have developed.

### MDscan

### A Fast and Accurate Motif Finding Algorithm With Applications To Chromatin Immunoprecipitation Microarray Experiments

Xiaole Shirley Liu, Douglas L. Brutlag, Jun S. Liu Stanford Medical Informatics, Stanford University

While chromatin immunoprecipitation followed by cDNA microarray (ChIP-on-chip) has become a popular procedure for studying genome-wide protein-DNA interactions and transcription regulation, it can only map the probable protein-DNA interaction loci within 1-2kb resolution. To pinpoint the interaction sites down to the base pair level, we introduce a novel computational method, Motif Discovery scan (MDscan), that examines the ChIP-array selected sequences and searches for DNA sequence motifs representing the protein-DNA interaction sites. MDscan combines the advantages of two widely adopted motif search strategies, word enumeration and position-specific weight matrix updating, and incorporates the ChIP enrichment information to accelerate the search and enhance its success rate. The intuition is to first search for similar words appearing in the sequences more likely to contain the motif (highly ChIP-enriched sequences) because these sequences have higher signal to noise ratio. Words in each similarity group can initialize a position specific motif matrix and the motif can be updated and refined with the whole input sequences (all ChIP-selected targets). The method showed both speed and accuracy advantages compared to several established motif-finding algorithms in both simulation and published yeast ChIP-on-chip experiments. MDscan can be used not only with the ChIP experiments, but also to find DNA motifs in other experiments in which a subgroup of the sequences can be inferred to contain relatively more abundant motif sites.

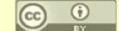
We recently developed a new program, Motif Regressor, to better utilize mRNA expression level or ChIP-on-chip enrichment information to improve the performance of MDscan. Motif Regressor first identifies a set of non-redundant candidate motifs using MDscan, and scans the promoter region of every gene in the genome with each candidate motif to measure how good a promoter matches a motif (in terms of both the number of sites and the strength of matching). It then uses linear regression analysis to select motifs whose promoter matching scores are significantly correlated with ChIP-on-chip enrichment or downstream gene expression values. When ranking motifs by linear regression p-value, Motif Regressor automatically picks the best motif and optimal motif width. Due to its computational intensity, Motif Regressor is not currently available as a web server. However, for interested users to explore the program locally, the program is available for download at: <a href="http://www.math.umass.edu/~conlon.mr.html">http://www.math.umass.edu/~conlon.mr.html</a>

#### Obtaining a local copy of MDscan:

MDscan is free-of-charge to academia. Please check out:

<u>Brutlag Bioinformatics Group Software Download</u> and

<u>Academic License Instructions</u> for details.



# MDScan Input

http://mdscan.stanford.edu/



### Overview MDscan finds motif from ChIP-on-chip targets

#### Motif Finding Search for interesting motifs in your sequences on our server

#### Input Format How to specify the input parameters

#### Output Explanations How to look at the output file we send you

### Motif Regressor An improved MDscan for

#### Reference Nat Biotechnol. 2002

download.

#### 20(8):835-9. Contacts

### People behind the project

### SeqMotifs See other motif finding algorithms we have developed.

#### Suggestions, comments, bugs to: <u>Xiaole Shirley Liu</u> Last updated 4/15/2004.

#### **MDscan Search**

#### Please don't submit more than one job at a time!!

Submit another job only if one of the following is true:

- You have received answer from your previous submission.
   Your previous job was submitted more than one day ago.
- User information

Please specify your email so we can send the search result to you brutlag@stanford.edu

#### Run information

Please specify a run name (will be included in the result email)
Pol30 1KB upstream -TATATATATA - TTTTTTTTTT

#### Input Sequences

#### **Background Model**

You can use the input sequence as background if you don't specify any of the following. Or you can specify a background sequence file

Choose File no file selected

Or paste background sequences below:

Or use the precomputed genome background model

#### Motif Model

Motif width 8 Number of top sequences to look for candidate motifs 10 Number of candidate motifs for scanning the rest sequences 20 Report the top final 5 motifs found

Submit Search Request





### MDScan Output

MDscan Search Result Pm 0.2639 Minimum match (6/8) The highest scoring 5 motifs are: Motif 1: Wid 8; Score 4.276; Sites 68; Con AAACGCGT; RCon ACGCGTTT rCon Deg rDeg 47.78 7.85 6.44 37.93 Y 47.78 7.85 27.57 16.80 97.08 0.81 0.81 1.31 1.31 96.58 0.81 1.31 1.31 0.81 96.58 1.31 C 1.31 96.58 0.81 1.31 1.31 0.81 96.58 1.31 28.07 0.81 0.81 70.32 YPL256C CLN2 SGDID:S000006177, Chr XVI from 67614-63977, reverse complement, Verified ORF Len 1020 Site #1 r 36 **TGACGCGA** Len 1000 Site #1 f 494 YML027W YOX1 SGDID:S000004489, Chr XIII from 220406-223563, Verified ORF YML027W Y0X1 SGDID:S000004489, Chr XIII from 220406-223563, Verified ORF Len 1000 Site #2 r 496 TTACGCGT YML027W Y0X1 SGDID:S000004489, Chr XIII from 220406-223563, Verified ORF Len 1000 Site #3 f 555 **AGACGCGA** YML027W Y0X1 SGDID:S000004489, Chr XIII from 220406-223563, Verified ORF Len 1000 Site #4 f 760 AAACGCGA Site #1 r 695 YER070W RNR1 SGDID:S000000872. Chr V from 297948-302614. Verified ORF Len 1020 TTACGCGT YER070W RNR1 SGDID:S000000872, Chr V from 297948-302614, Verified ORF Len 1020 Site #2 r 630 TGACGCGT Site #3 r 559 YER070W RNR1 SGDID:S000000872, Chr V from 297948-302614, Verified ORF Len 1020 TTACGCGT YER070W RNR1 SGDID:S000000872, Chr V from 297948-302614, Verified ORF Len 1020 Site #4 r 509 AAACGCGT YER070W RNR1 SGDID: S0000000872, Chr V from 297948-302614, Verified ORF Len 1020 Site #5 f 507 TTACGCGT Site #6 f 557 YER070W RNR1 SGDID:S000000872, Chr V from 297948-302614, Verified ORF Len 1020 AAACGCGT YER070W RNR1 SGDID:S000000872, Chr V from 297948-302614, Verified ORF Len 1020 Site #7 f 628 AAACGCGT YER070W RNR1 SGDID:S000000872, Chr V from 297948-302614, Verified ORF Len 1020 Site #8 f 693





# YeasTract Transcription Factor Database http://www.yeastract.com/





Contact Us - Tutorial - @

Welcome to YEASTRACT

Quick search...

DISCOVERER NEW

#### Regulatory Associations:

- Search for TFs
- Search for Genes
- Search for Associations

#### Group genes:

- Group by TF
- Group by GO

#### Pattern Matching:

- Search by DNA Motif
- Find TF Binding Site(s)
- Search Motifs on Motifs

#### **Utilities:**

- ORF List ⇔ Gene List
- IUPAC Code Generation
- Generate Regulation Matrix

#### Retrieve:

- TF-Consensus List
- Upstream Sequence
- Flat files

#### About Yeastract:

- Contact Us
- Cite YEASTRACT
- Acknowledgments
- Credits

#### Support & suggestions:

veastract@kdbio.inesc-id.pt

YEASTRACT (Yeast Search for Transcriptional Regulators And Consensus Tracking) is a curated repository of more than 34469 regulatory associations between transcription factors (TF) and target genes in Saccharomyces cerevisiae, based on more than 1000 bibliographic references. It also includes the description of 291 specific DNA binding sites for more than a hundred characterized TFs. Further information about each Yeast gene has been extracted from the Saccharomyces Genome Database (SGD) as per the latest release, version 1.1438, from Apr 11, 2009. For each gene the associated Gene Ontology (GO) terms and their hierarchy in GO was obtained from the GO consortium as per the OBO flat file from Apr 24, 2009. Currently, YEASTRACT maintains a total of 27250 terms from GO. The nucleotide sequences of the promoter and coding regions for Yeast genes were obtained from Regulatory Sequence Analysis Tools (RSAT). All the information in YEASTRACT will be updated regularly to match the latest data from SGD, GO consortium, RSA Tools and recent literature on yeast regulatory networks.

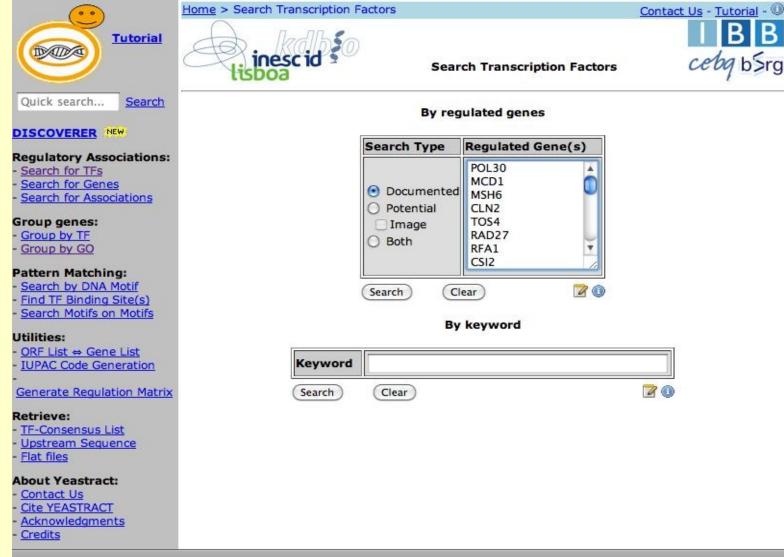
YEASTRACT now includes DISCOVERER, a set of tools that can be used to identify complex motifs found to be over-represented in the promoter regions of co-regulated genes. DISCOVERER is based on the MUSA and RISO algorithms. These algorithms take as input a list of genes and identify over-represented motifs, which can then be compared with transcription factor binding sites described in the YEASTRACT database.

Facilities are also provided to enable the exploitation of the gathered data when solving a number of biological questions, as exemplified in the Tutorial. YEASTRACT allows the identification of documented or potential transcription regulators of a given gene and of documented or potential regulons for each transcription factor. It also renders possible the comparison between DNA motifs and the transcription factor binding sites described in the literature. The system also provides a useful mechanism for grouping a list of genes (for instance a set of genes with similar expression profiles as revealed by microarray analysis) based on their regulatory associations with known transcription factors.

YEASTRACT provides a set of queries to search and retrieve important biological information from the gathered data and to predict transcription regulation networks in yeast from data emerging from gene-by-gene analysis or global approaches.



# YeasTract Transcription Factor Search http://www.yeastract.com/formfindregulators.php







## YeasTract Transcription Factor Search Results

http://www.yeastract.com/formfindregulators.php





Home > Search Transcription Factors > Result

Search Transcription Factors



Jump to

Quick search...

#### DISCOVERER NEW

Search

#### Regulatory Associations:

- Search for TFs
- Search for Genes
- Search for Associations

#### Group genes:

- Group by TF
- Group by GO

#### Pattern Matching:

- Search by DNA Motif
- Find TF Binding Site(s)
- Search Motifs on Motifs

#### **Utilities:**

- ORF List ⇔ Gene List
- IUPAC Code Generation

Generate Regulation Matrix

#### Retrieve:

- TF-Consensus List
- Upstream Sequence
- Flat files

#### **About Yeastract:**

- Contact Us
- Cite YEASTRACT
- Acknowledgments
- Credits

ODE/Come Name	Documented			
ORF/Gene Name	Transcription Factor - Reference			
YBR088c/POL30 Back to top •	Mbp1p - Reference	+		
*	Sfp1p - Reference			
	Swi4p - Reference	8		
YDL003w/MCD1 Back to top ▲	Cin5p - Reference	+		
Dack to top =	Mbp1p - Reference			
	Sfp1p - Reference			
	Swi4p - Reference			
YDR097c/MSH6 Back to top	Dot6p - Reference	+		
Dack to top =	Mbp1p - Reference			
	Sfp1p - Reference			
	Swi6p - Reference			
YPL256c/CLN2	Gcn4p - Reference	+		
Back to top 🔺	Gcr1p - Reference			
	Mbp1p - Reference			
	Mcm1p - Reference			
	Rme1p - Reference			

YBR088c - POL30
YDL003w - MCDI
YDR097c - MSH6
YPL256c - CLN2
YLR183c - TOS4
YKLII3c - RAD27
YAROO7c - RFAI
YOL007c - CSI2
YOLO9Ow - MSH2
YGR152c - RSR1
YML027w - YOXI
YGR151c
YLL022c - HIF1
YILO66c - RNR3
YOLOI7w - ESC8
YKLO45w - PRIZ
YDL164c - CDC9
YKROI3w - PRY2
YNL312w - RFA2
YILI40w - AXL2
YERO70w - RNRI



### What is Systems Biology? http://en.wikipedia.org/wiki/Systems\_biology article discussion edit this page history Systems biology From Wikipedia, the free encyclopedia Wikipedia The Free Encyclopedia navigation Main Page

Systems biology is a relatively new biological study field that focuses on the systematic study of complex interactions in biological systems, thus using a new perspective (integration instead of reduction) to study them. Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. Because the scientific method has been used primarily toward reductionism, one of the goals of systems biology is to discover new emergent properties that may arise from the systemic view used by this discipline in order to understand better the entirety of processes that happen in a biological system.

#### interaction

Contents

Featured content

Current events Random article

- About Wikipedia
- Community portal
- Recent changes
- Contact Wikipedia
- Donate to Wikipedia
- Help

#### search



#### toolbox

- What links here
- Related changes
- Upload file
- Special pages
- Printable version
- Permanent link

#### Contents [hide]

- 1 Overview
- 2 History
- 3 Techniques associated with systems biology
- 4 See also
- 5 Bibliography
  - 5.1 Books
  - 5.2 Articles
- 6 External links
- 7 References

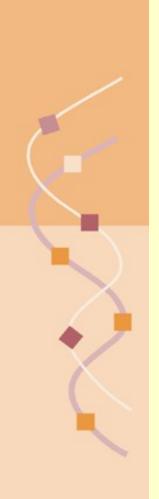
Overview

Systems biology can be considered from a number of different aspects:

 Some sources discuss systems biology as a field of study, particularly, the study of the interactions between the components of biological systems, and how these interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway).[1][2]

Log in / create account

[edit]

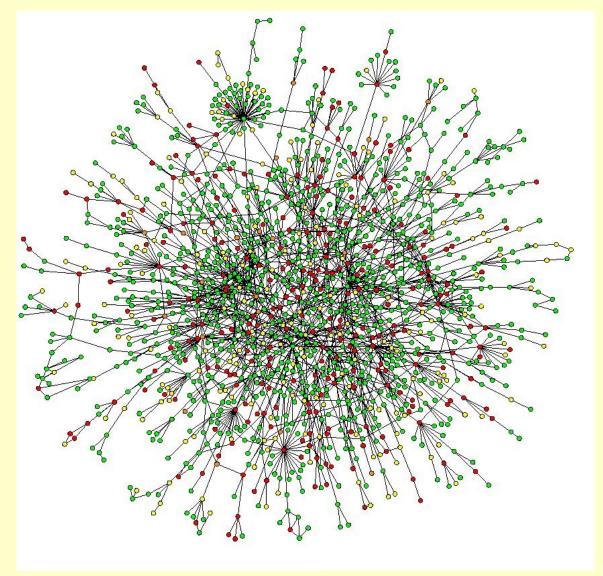


# What is Systems Biology?

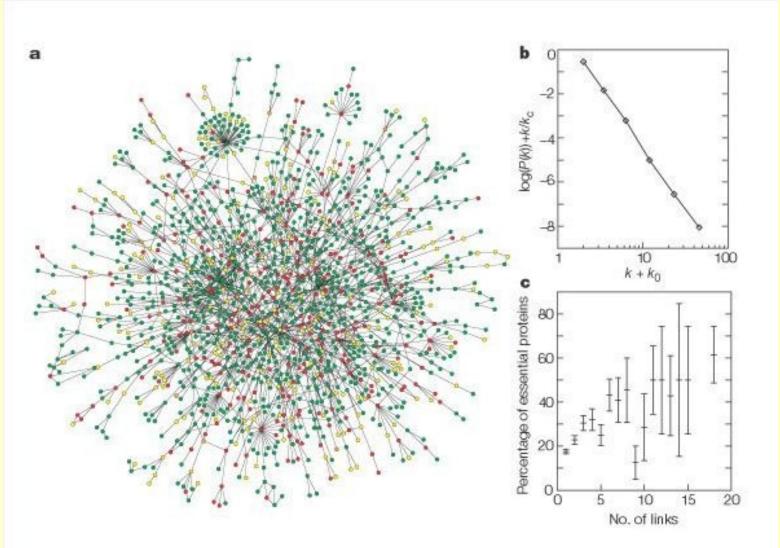
- Systematic approach to biology
  - Protein networks involving all protein-protein interactions
  - Metabolic networks involving all enzymes & pathways
  - Gene regulation involving all regulatory interactions
  - Cell behavior involving all environmental responses
  - Population biology involving all selectable traits.
- Challenges of System Biology
  - Identifying all selectable traits, all regulatory interactions, all protein complexes, all metabolic pathways, all regulatory pathways, all selectable traits
  - Computationally representing and simulating cell structures, metabolism, regulation, behavior and selection
  - Usually approached by simplification, studying one protein complex, one metabolic pathway, one regulatory network or one trait at a time. Then combining individual examples to represent the entire cell or organism.

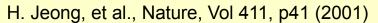


# Yeast Protein Interaction Network H. Jeong, et al., Nature, Vol 411, p41 (2001)



# Yeast Protein Interaction Network H. Jeong, et al., Nature, Vol 411, p41 (2001)







Hunter B. Fraser, 1\*† Aaron E. Hirsh, 2\* Lars M. Steinmetz, 3

Curt Scharfe, 3 Marcus W. Feldman 2

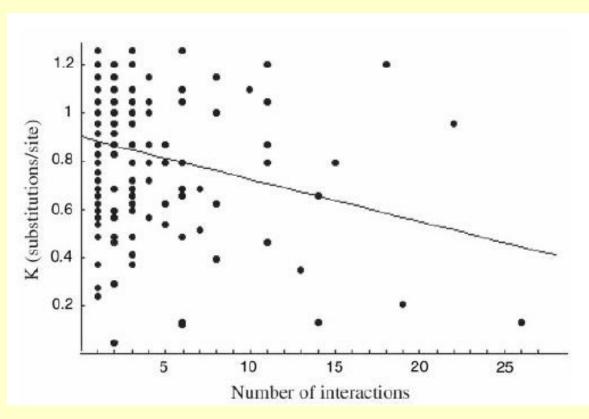
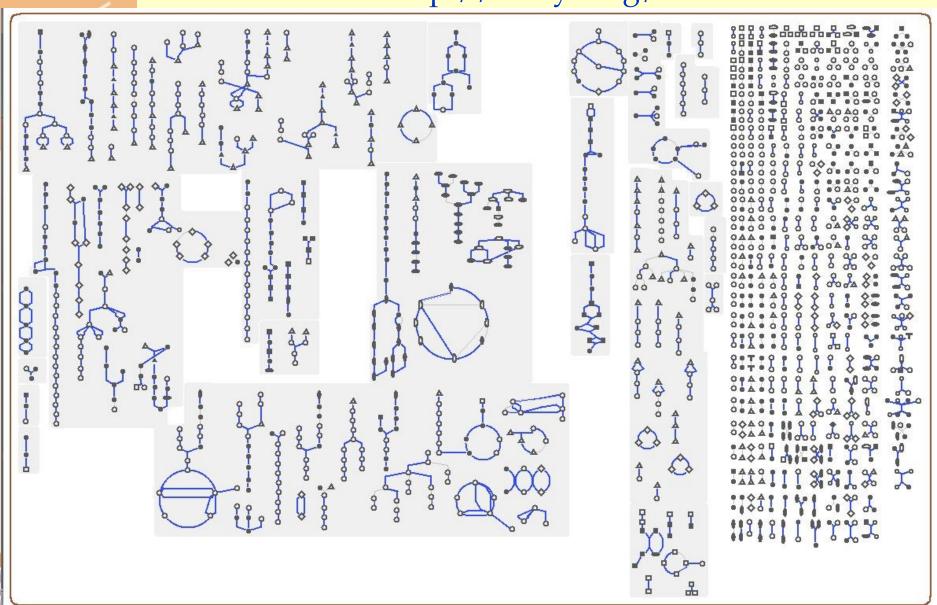


Fig. 1. The relation between the number of protein-protein interactions (I) in which a yeast protein participates and that protein's evolutionary rate, as estimated by the evolutionary distance (K) to the protein's well-conserved ortholog in the nematode C. elegans.

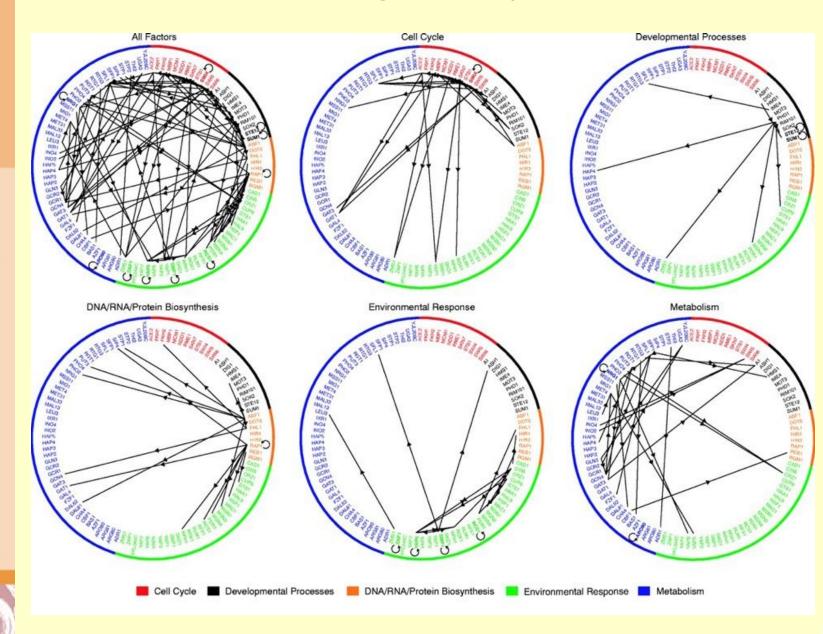


# Yeast Metabolic Pathways

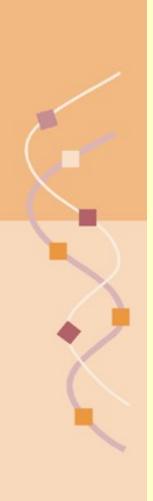
http://biocyc.org/



# Yeast Gene Regulatory Networks





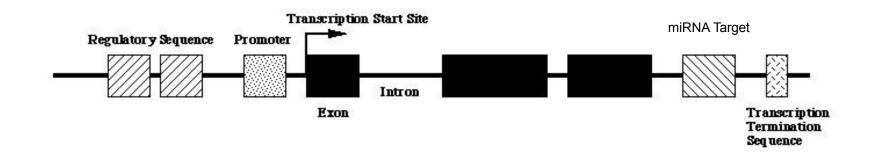


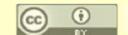
### Genomics Provides

- Location and number of genes
  - By mapping messenger RNAs (cDNAs or ESTs)
  - By computational gene finding programs
    - Glimmer
    - GenScan
    - Grail & Grail EXP
    - FGENESH
    - GeneMark & GenMarkHMM
  - By homology and conservation
- Gene expression and regulation information
  - From tissue specific mRNAs (cDNAs or ESTs)
  - From DNA chips or microarrays
    - Gene probes and tiling arrays
  - ChIP-Chip experiments
  - Stanford Microarray Database
  - NCBI GEO
  - EBI ArrayExpress
- Gene regulatory sequences
  - Promoter signals near beginning (5' end) of transcripts
  - Transcription factor binding sites
  - Transcription start sites (TSS)
  - Transcription termination signals (TTS)
  - RNA processing signals
    - Splice donor and acceptor sites
    - 5' Cap site
    - 3' polyAdemylation

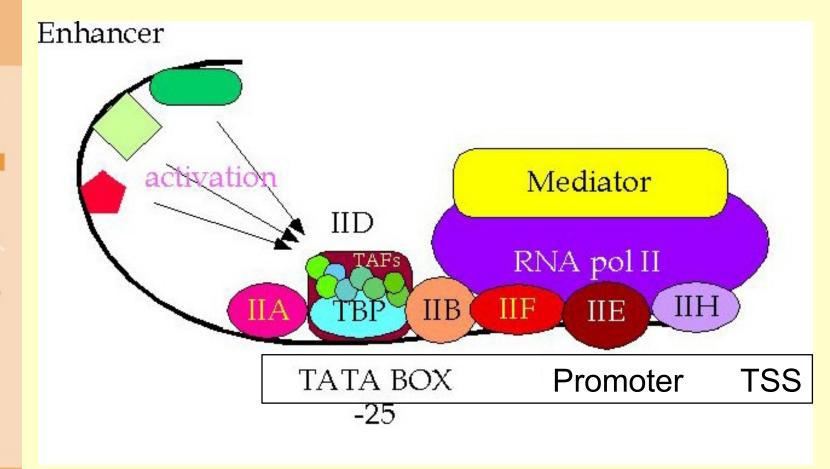


# Eukaryotic Gene Structure



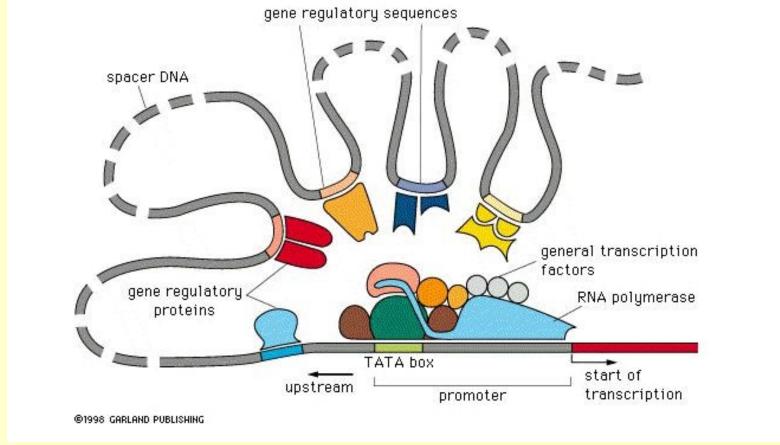


# RNA Polymerase Promoter Binding



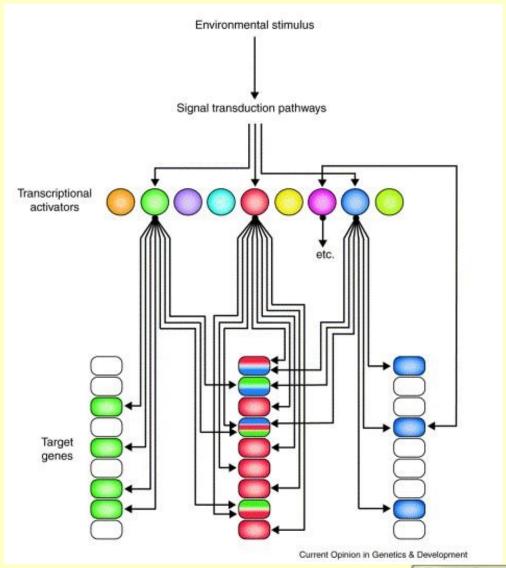


# Multiple Enhancer Sequences





# Gene Expression Regulatory Network







http://www.rcsb.org/pdb/static.do?p=education\_discussion/molecule\_of\_the\_month/pdb122\_1.html

February 2010 Molecule of the Month by David Goodsell Previous Features doi: 10.2210/rcsb\_pdb/mom\_2010\_2

#### **Enhanceosome**

keywords: transcription factor, gene expression, CBP, CREBbinding protein, transcriptional enhancers, enhanceosome

Take a moment to ponder the form of your body: the shape of your face, the color of your eyes, the length of your fingers, the perfect articulation of your bones and muscles, the way your hair grows curly or straight. Now let your imagination travel inward, and think of the complex shapes and functions of your different cells, and the teeming molecular world inside each one. Remarkably, this amazing structure and form and function is specified by information in the genome, which encodes a mere 20,000-25,000 protein-coding genes. One of the great puzzles being pieced together by scientists is the mechanism by which these genes, and the methods used to control their expression, specify all of these different aspects of life.

#### **Combinatorial Control**

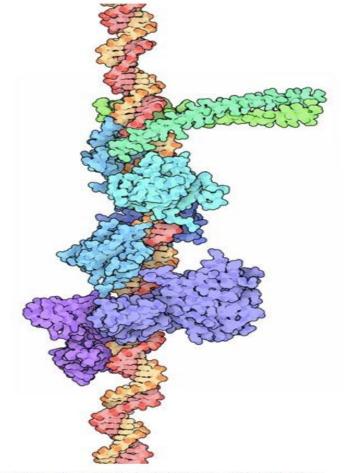
In order to specify which gene will be expressed in a given situation, your cells use a diverse collection of DNA-binding proteins to control access to the DNA. Surprisingly, there are relatively few of these proteins: by some estimates, the human genome encodes about 2,600 of them. But then, the capabilities of this limited set are greatly expanded by using them in combination, by requiring two or more to bind simultaneously to activate a gene. In this way, each protein may be used in many ways and the spectrum of responses is far more varied.

#### **Enhancing Transcription**

The assembly of DNA and proteins pictured here is a transcriptional enhanceosome (PDB entries 1t2k, 2pi0, 2o6g and 2o61) that controls expression of interferon-beta, an important protein for fighting viral infection. When the cell is infected by viruses, several different DNA-binding proteins are produced, including ATF-2/c-Jun (in green at the top),

interferon response factors (IRF, shown in turquoise at the center), and nuclear factor kB (NF-kB, shown in blue and magenta at the bottom). Individually, each one is not sufficient to activate the gene, and each one also plays other roles in the activation of other genes (for instance, Nf-kB is also important in immune responses, inflammation, apoptosis, and many other processes). But when they all bind together, they activate the gene and interferon is made.

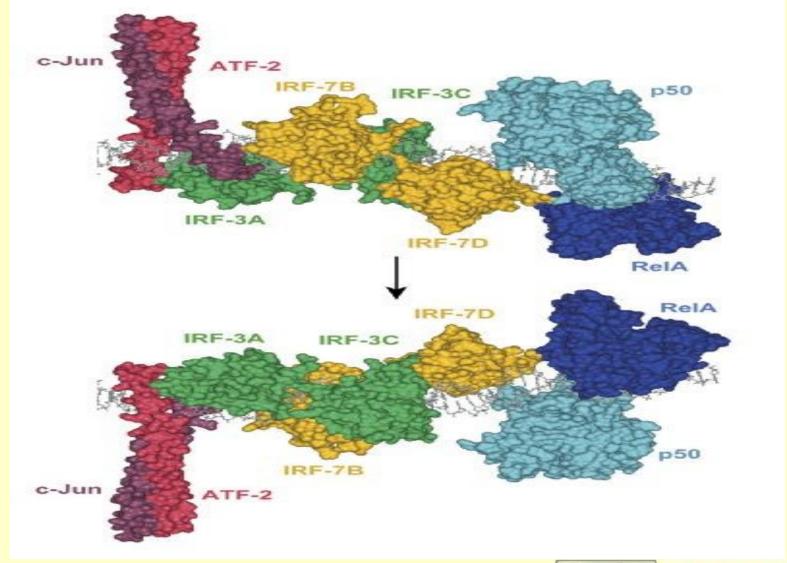
**Next: Integrating the Signal** 





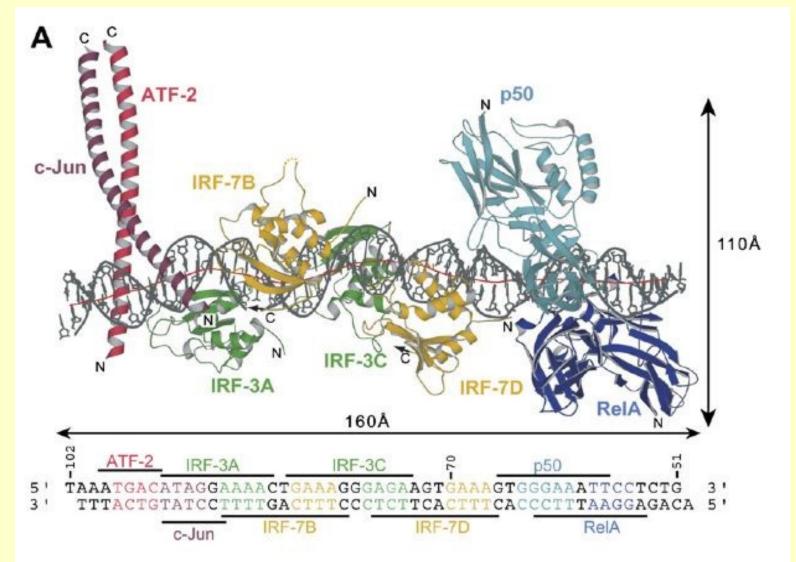
## Enhanceosome

http://www.cell.com/retrieve/pii/S0092867407006563



## Enhanceosome

http://www.cell.com/retrieve/pii/S0092867407006563

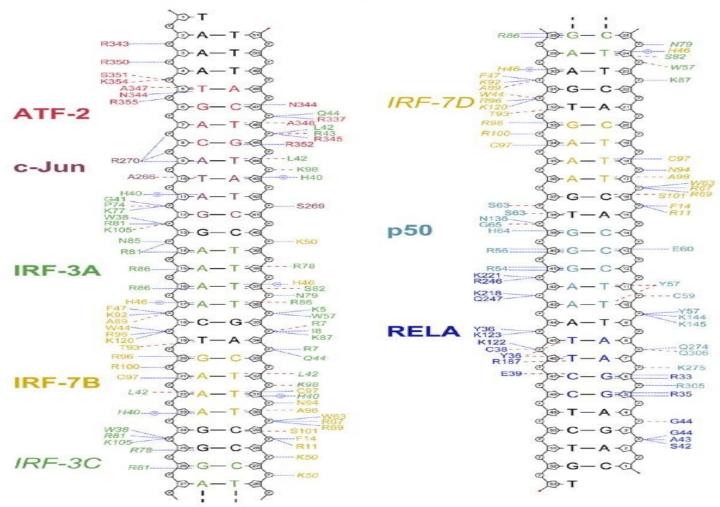




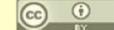
### IFN-beta Enhancer

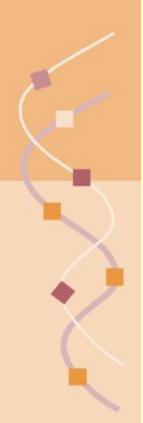
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### IFN-β enhancer

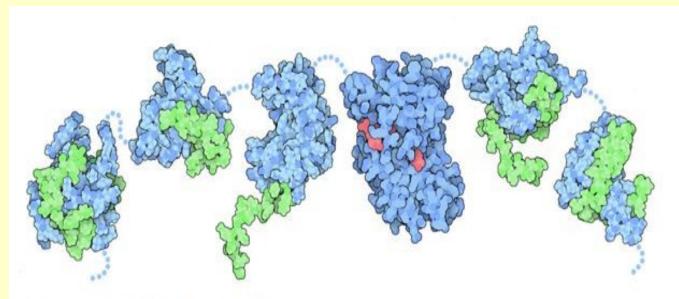








# Enhanceosome: Integrating the Signal http://www.rcsb.org/pdb/static.do?p=education\_discussion/molecule\_of\_the\_month/pdb122\_2.html



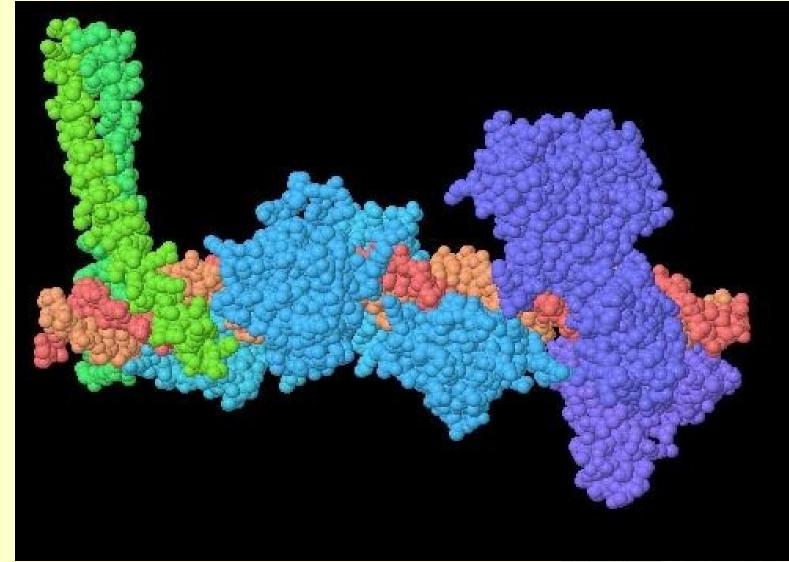
### Integrating the Signal

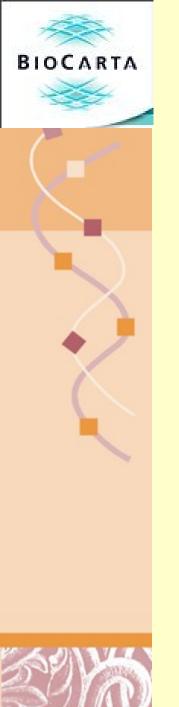
Once the transcription factors bind to the different sites in the enhancer DNA sequence, the signal must somehow be sensed and used to activate the gene. In many cases, this is performed using CREB-binding protein or the similar protein p300. This protein is composed of many connected domains, (PDB entries 118c, 1kdx, 1jsp, 3biy, 2ka6 and 1kbh), which bind to different proteins in the assembled enhanceosome. Then, a large domain in the center acts as a histone acetyltransferase, modifying histones in nucleosomes and causing them to disassemble and reveal the gene. In the intereferon-b gene, a nucleosome normally covers the start site of transcription, blocking transcription. Assembly of the enhanceosome leads to removal of this nucleosome, allowing the gene to be expressed.

Previous: Enhanceosome Home: Enhanceosome **Next: Exploring the Structure** 



# Enhanceosome: Exploring the Structure http://www.rcsb.org/pdb/static.do?p=education\_discussion/molecule\_of\_the\_month/pdb122\_2.html





PRODUCT INDEX

PRODUCT SEARCH

SEARCH (

Contains (

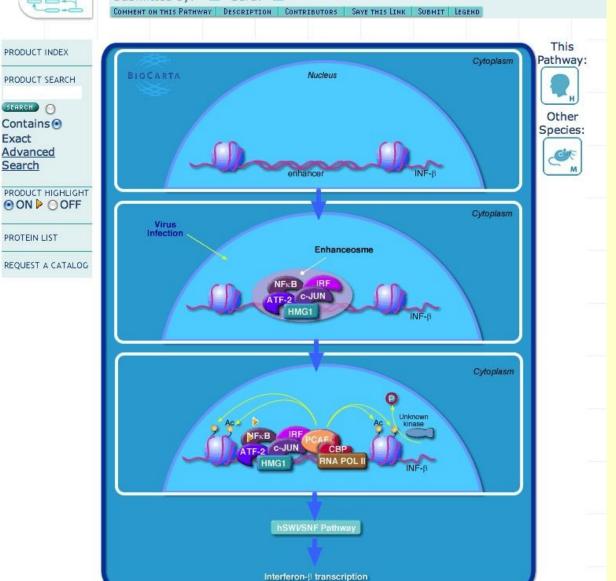
PROTEIN LIST

Exact Advanced Search



ht PATHWAY5 > The information-processing pathway at the IFN-beta enhancer



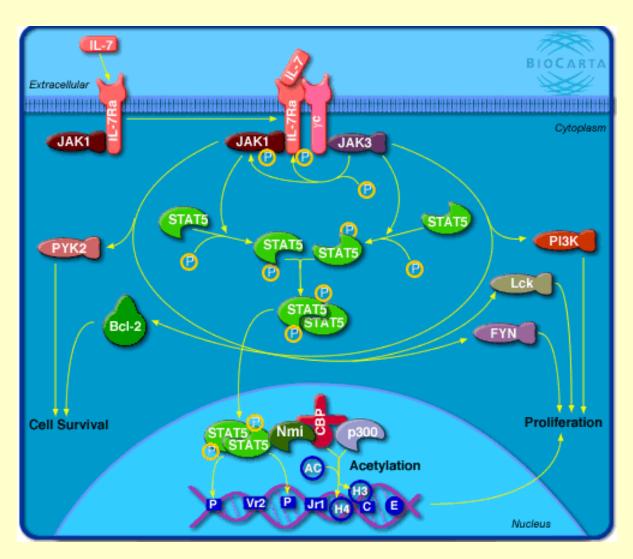


asp



## IL7 Regulatory Pathway

http://www.biocarta.com/pathfiles/h\_il7Pathway.asp/

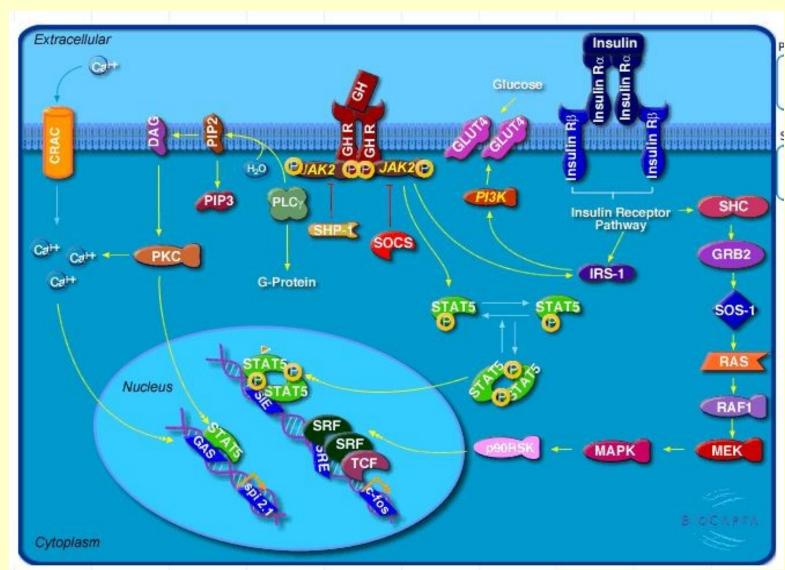






## Growth Hormone Receptor Pathway

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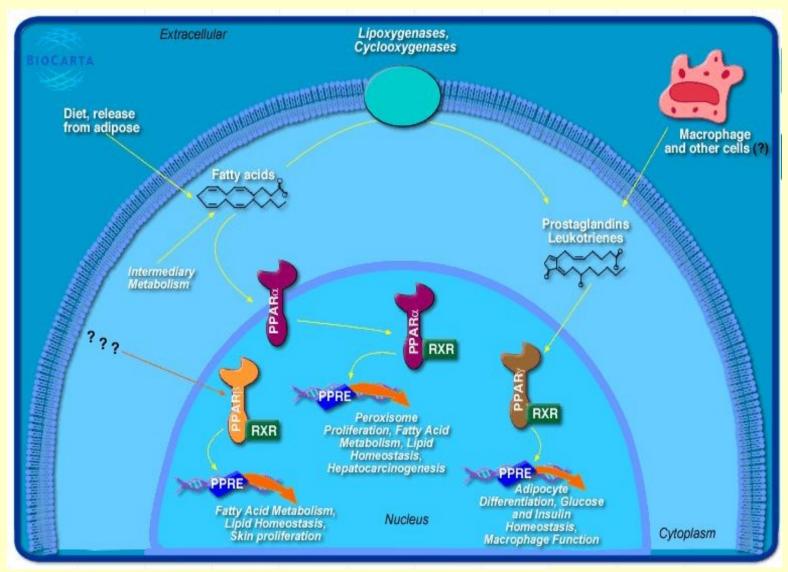






## PPAR-Mechanism of Action

http://www.biocarta.com/pathfiles/h\_pparPathway.asp

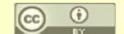




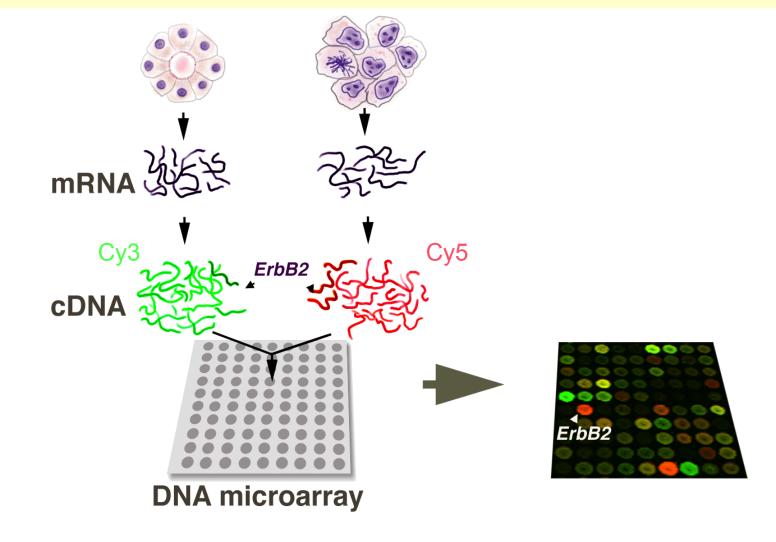


## Gene Regulatory Mechanisms

- Transcriptional Mechanisms
  - Type of promoters & RNA polymerase
  - Control of Transcription
    - Constitutive
    - Inducible
    - Repressible
  - Transcription Factors and TFBS
- RNA processing
  - Capping
  - Splicing and Alternative Splicing
  - Poly-Adenylation
  - RNA export to cytoplasm
  - RNA degradation rates
- Translational Mechanisms
  - Micro RNAs (miRNAs)
  - Silencer RNAs (siRNAs or RNAi) degrading mRNA
- Epigenetic Mechanisms
  - Chromatin remodeling
  - Histone acetylation
  - DNA methylation

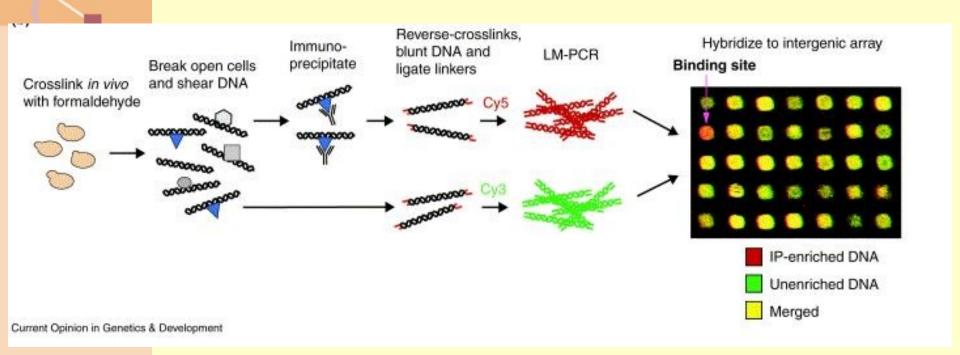


# Measuring Gene Expression with DNA Microarrays and cDNA Labeling



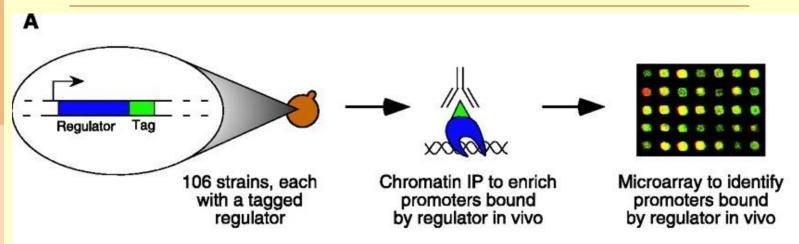


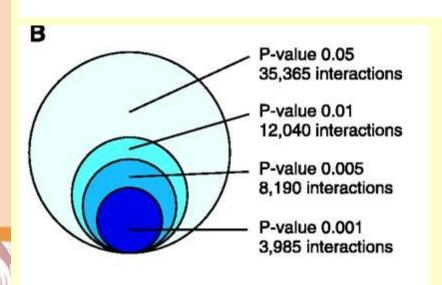
## ChIP-Chip Methodology



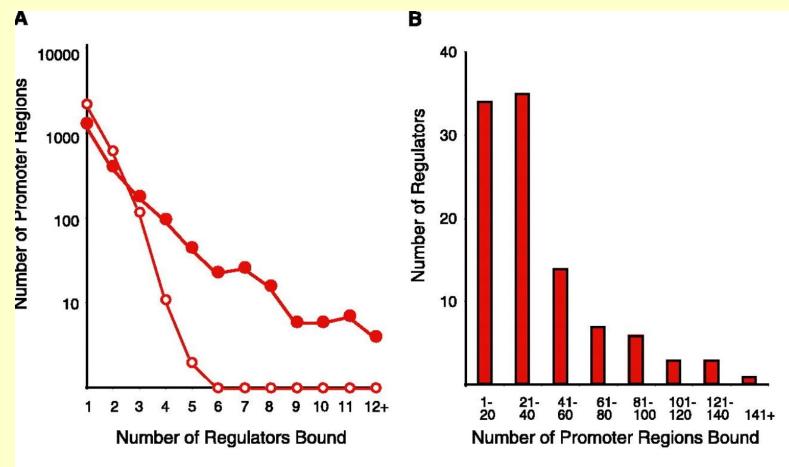


# ChIP-Chip Identification of Transcription factor Binding Sites



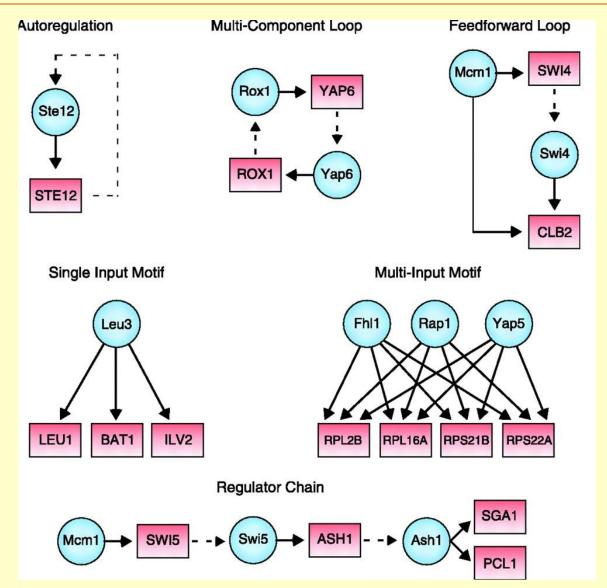


## Distribution of TFBS Among 6300 Promoters



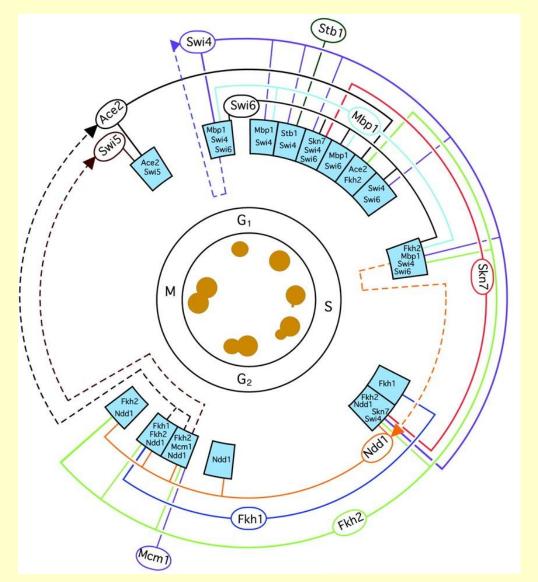


## Network Motifs in Yeast Regulatory Networks



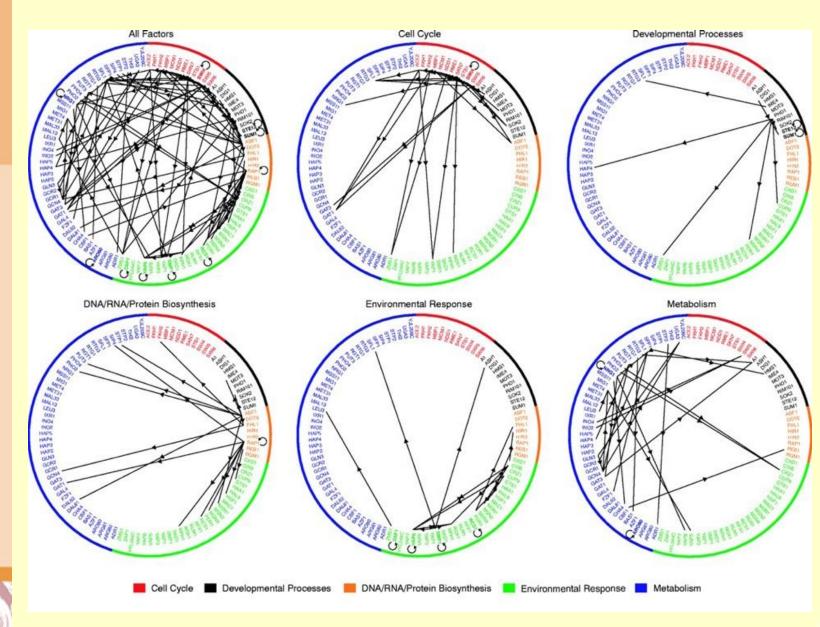


## Yeast Cell Cycle Regulatory Motifs





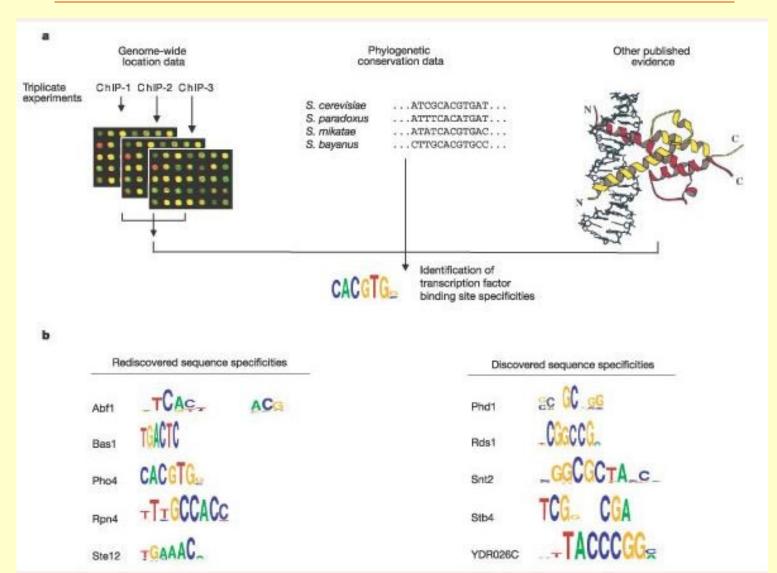
## Yeast Regulatory Motifs





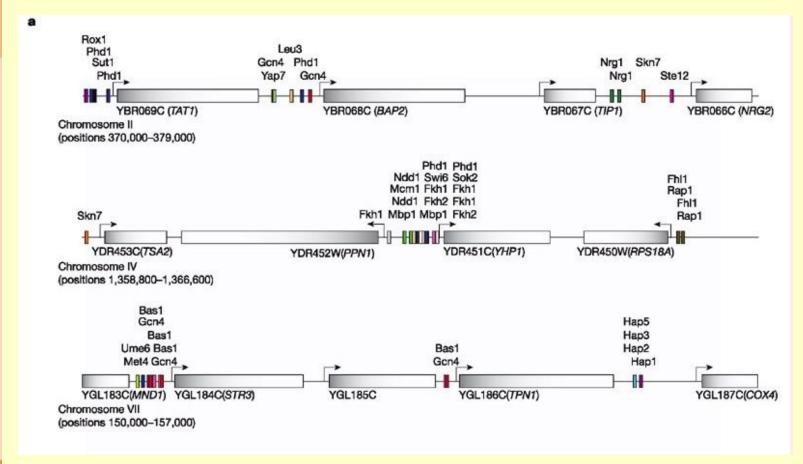


## Transcription Factor Binding Site Specificities



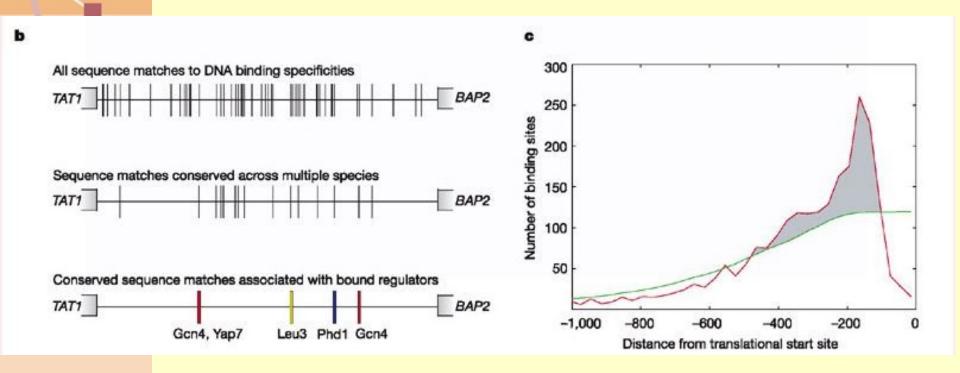


## Yeast Regulatory Map

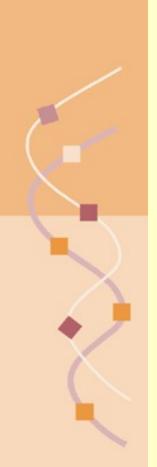




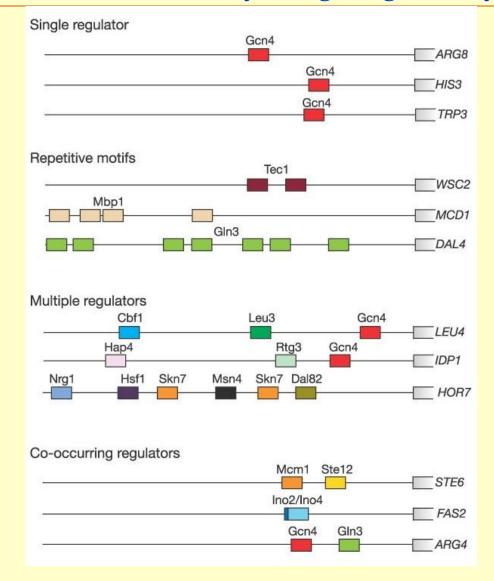
## Yeast Regulatory Map

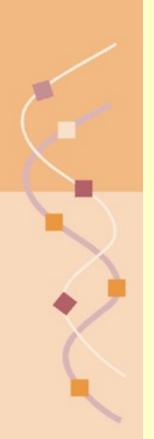




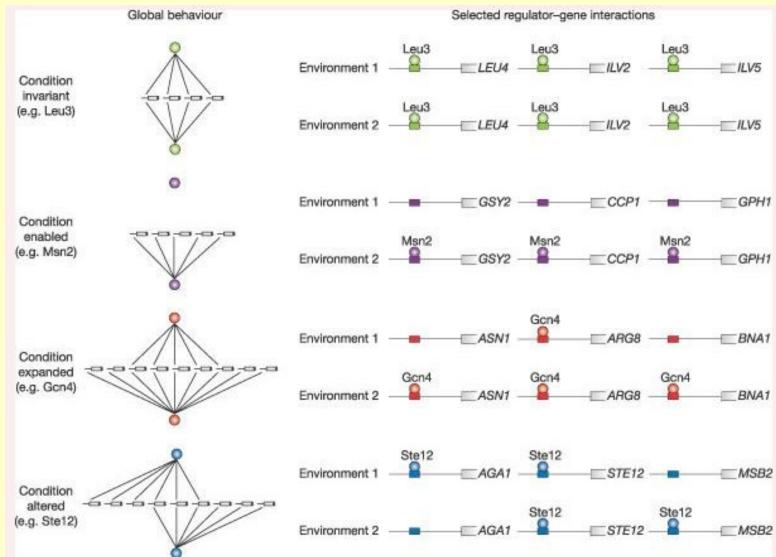


## Yeast Promoter Architecture





## Environment Specific Regulators http://web.wi.mit.edu/young/regulatory\_code/







## YeasTract Transcription Factor Database http://www.yeastract.com/





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Quick search...

DISCOVERER NEW

#### Regulatory Associations:

- Search for TFs
- Search for Genes
- Search for Associations

#### Group genes:

- Group by TF
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#### **Utilities:**

- ORF List ⇔ Gene List
- IUPAC Code Generation
- Generate Regulation Matrix

#### Retrieve:

- TF-Consensus List
- Upstream Sequence
- Flat files

#### About Yeastract:

- Contact Us
- Cite YEASTRACT
- Acknowledgments
- Credits

#### Support & suggestions:

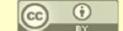
veastract@kdbio.inesc-id.pt

YEASTRACT (Yeast Search for Transcriptional Regulators And Consensus Tracking) is a curated repository of more than 34469 regulatory associations between transcription factors (TF) and target genes in Saccharomyces cerevisiae, based on more than 1000 bibliographic references. It also includes the description of 291 specific DNA binding sites for more than a hundred characterized TFs. Further information about each Yeast gene has been extracted from the Saccharomyces Genome Database (SGD) as per the latest release, version 1.1438, from Apr 11, 2009. For each gene the associated Gene Ontology (GO) terms and their hierarchy in GO was obtained from the GO consortium as per the OBO flat file from Apr 24, 2009. Currently, YEASTRACT maintains a total of 27250 terms from GO. The nucleotide sequences of the promoter and coding regions for Yeast genes were obtained from Regulatory Sequence Analysis Tools (RSAT). All the information in YEASTRACT will be updated regularly to match the latest data from SGD, GO consortium, RSA Tools and recent literature on yeast regulatory networks.

YEASTRACT now includes DISCOVERER, a set of tools that can be used to identify complex motifs found to be over-represented in the promoter regions of co-regulated genes. DISCOVERER is based on the MUSA and RISO algorithms. These algorithms take as input a list of genes and identify over-represented motifs, which can then be compared with transcription factor binding sites described in the YEASTRACT database.

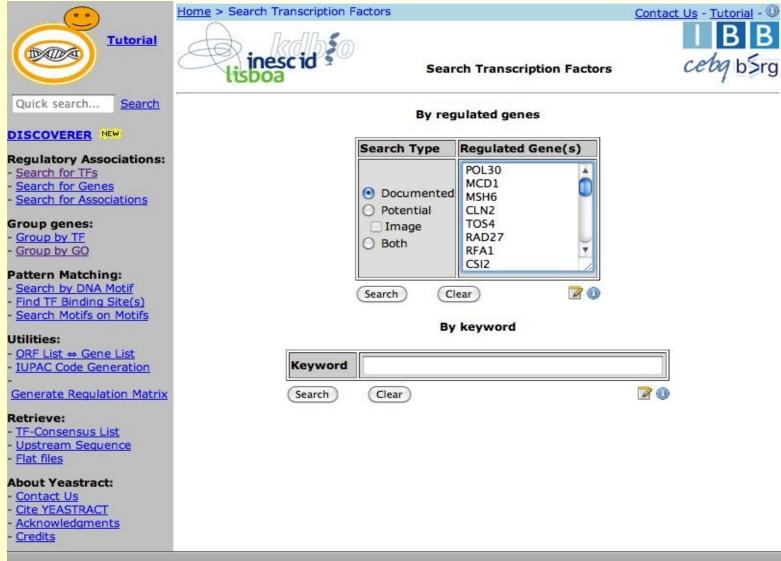
Facilities are also provided to enable the exploitation of the gathered data when solving a number of biological questions, as exemplified in the Tutorial. YEASTRACT allows the identification of documented or potential transcription regulators of a given gene and of documented or potential regulons for each transcription factor. It also renders possible the comparison between DNA motifs and the transcription factor binding sites described in the literature. The system also provides a useful mechanism for grouping a list of genes (for instance a set of genes with similar expression profiles as revealed by microarray analysis) based on their regulatory associations with known transcription factors.

YEASTRACT provides a set of queries to search and retrieve important biological information from the gathered data and to predict transcription regulation networks in yeast from data emerging from gene-by-gene analysis or global approaches.





## YeasTract Transcription Factor Search http://www.yeastract.com/formfindregulators.php







## YeasTract Transcription Factor Search Results

http://www.yeastract.com/formfindregulators.php





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Home > Search Transcription Factors > Result

Search Transcription Factors



ODE /Cons Name	Documented		
ORF/Gene Name	Transcription Factor - Reference		
YBR088c/POL30 Back to top •	Mbp1p - Reference	+	
	Sfp1p - Reference		
	Swi4p - Reference	8	
YDL003w/MCD1	Cin5p - Reference	+	
Back to top -	Mbp1p - Reference	88	
	Sfp1p - Reference		
	Swi4p - Reference		
YDR097c/MSH6	Dot6p - Reference	+	
Back to top -	Mbp1p - Reference		
	Sfp1p - Reference	33	
	Swi6p - Reference		
YPL256c/CLN2	Gcn4p - Reference	+	
Back to top -	Gcr1p - Reference		
	Mbp1p - Reference		
	Mcm1p - Reference		
	Rme1p - Reference		

YBR088c - POL30
YDL003w - MCDI
YDR097c - MSH6
YPL256c CLN2
YLR183c - TOS4
YKLII3c - RAD27
YAROO7c - RFAI
YOL007c - CS12
YOLO90w - MSH2
YGR152c - RSR1
YML027w~YOXI
YGR151c
YLL022c - HIF1
YILO66c - RNR3
YOLOI7w - ESC8
YKLO45w - PRIZ
YDL164c - CDC9
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YNL312w - RFA2
YILI40w - AXL2
YERO70w - RNRI

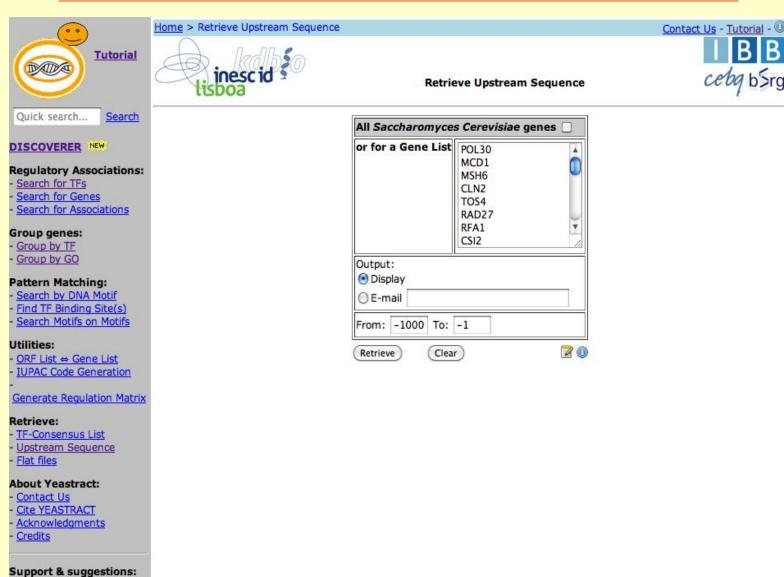
Jump to \*



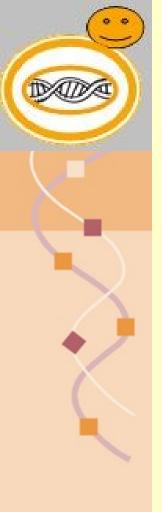




## YeasTract UpStream Sequences http://www.yeastract.com/formseqretrieval.php







## YeasTract UpStream Sequences Retrieval http://www.yeastract.com/formsegretrieval.php



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#### Retrieve:

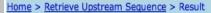
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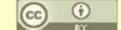
Upstream Sequence



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upstream sequence, from -1000 to -1, size 1000 GAGAAGTTAAAGAGGGGTAGACAATGATGGTAATCTTATAAACCGGCTACAATGAAGGTT GTAGCAGGAAGATGATATTTTAATACGGTTCAGGTGAAATGAAATAGCCGCCCATA ACGGCATGCTCAAGTTGTAAGTCAGGACTCTAGCTTTCTACTGTAGTATCCTCTAAAGGA ATTAACTTAGAACATTAACATATATAAAACTAGCGCTATGGCCGCAACTAAAGAAGCAAA GAGGCGGTTGTCAGCTTATATGTTCTTTGCTAATGAAAACAGAGACATTGTCCGTTCCGA GAATCCTGACGTAACTTTTGGCCAAGTAGGCAGAATATTGGGTGAGAGGTGGAAGGCCTT AACTGCTGAAGAAAAGCAACCCTATGAATCTAAGGCTCAAGCAGACAAGAAGAGATACGA ATCTGAAAAGGAATTGTACAATGCTACACGTGCTTGATCTAACAACTCAATGTTCTCTAC CTCCCATACAACGTACTTTTGAAACTTCAGAAAGAAGTTGAGTAGGTTGCATTATGTGTT TTCCTTTTTCGCACAACTTATGCTGATTCTTCAATATCTAATTATTTAGCATTTTTCTTC AAGCAGCAAGCACTAAGTACGCAGTCAAAAGAGAGAAAAA

upstream sequence, from -1000 to -1, size 1000 TACAGAAAATTTTATTATTTATATTCAAAAACAAGAAAACAAAAGAGAAAACATTAACA TGTAATTTTCATAACTAATAGTCCTAGAAAGTAATACTTTTTACAACTGTTTCTTTAAAT





### YeasTract Motif Discoverer

http://www.yeastract.com/discoverer/





Introduction MUSA

RISO Tutorial Credits Publications

Welcome to Discoverer at Yeastract

How to cite

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#### DISCOVERER NEW

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- Acknowledgments

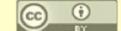
Credits

DISCOVERER provides tools for the purpose of motif extraction: the identification of de novo binding site consensus sequences from a given set of non-coding DNA sequences (such as the promoter regions of a gene). DISCOVERER contains two distinct structured motif discovery algorithms: MUSA and RISO.

Contrary to many modern motif finders, MUSA (Motif finding using an UnSupervised Approach) does not require the user to specify parameters (such as box lengths and distances between boxes) in order to extract motifs. The algorithm can therefore either be used autonomously to search for motifs, or to estimate the search parameters to be used in other motif discovery tools. Requiring as input a list of genes, MUSA returns the list of structured or simple motifs found, ordered by their p-value, and the proportion of sequences containing each motif (the guorum).

RISO, another complex motif extraction tool, searches for complex motifs with certain characteristics specified by the user, through the assignment of a set of parameters such as the number and sizes of the boxes that form the structured motif, the distances between them and the minimum quorum expected. It is also possible to specify a number of substitutions for each box. Like MUSA, RISO also requires the list of genes whose promoters are to be searched for motifs, and returns the list of motifs found and their corresponding quorums.

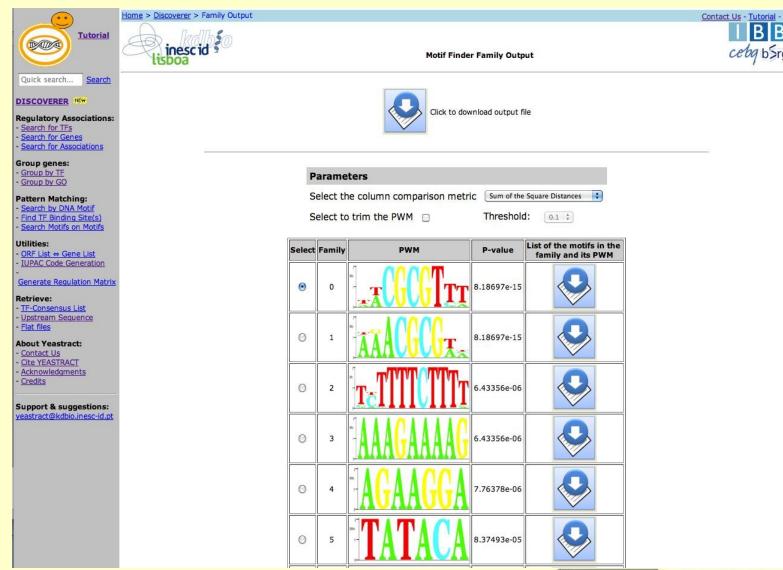






### YeasTract Motif Discoverer Results

http://www.yeastract.com/discoverer/

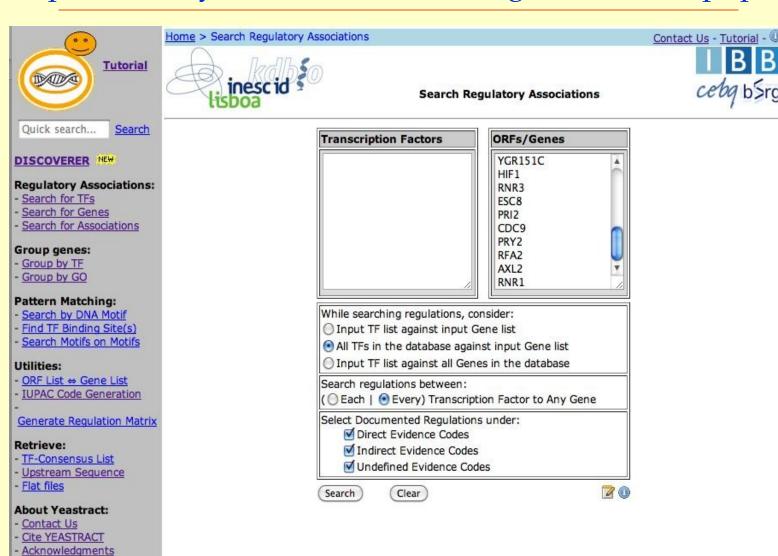








## YeasTract Transcription Factor Associations http://www.yeastract.com/formregassociations.php





Credits



## YeasTract Transcription Factor Associations http://www.yeastract.com/formregassociations.php

Home > Search Regulatory Associations > Result

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**Regulatory Associations** 



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Search

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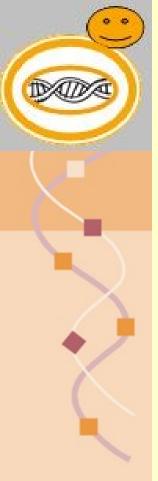
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#### Support & suggestions:

yeastract@kdbio.inesc-id.pt

Transcription Factors	<b>Documented Regulated</b>	<b>Potential Regulated</b>	
Transcription Factors	Genes - Ref	Genes - Promoter	
Abf1p  DNA binding protein with possible chromatin-reorganizing activity involved in transcriptional activation, gene silencing, and DNA replication and repair	RFA2 - Reference	HIF1 - Promoter POL30 - Promoter PRI2 - Promoter PRY2 - Promoter RAD27 - Promoter RFA1 - Promoter RFA2 - Promoter RNR1 - Promoter RNR3 - Promoter YOX1 - Promoter	
Ace2p Transcription factor that activates expression of early G1-specific genes, localizes to daughter cell nuclei after cytokinesis and delays G1 progression in daughters, localization is regulated by chosphorylation; potential Cdc28p substrate	No rows were found!	AXL2 - Promoter CDC9 - Promoter RAD27 - Promoter RFA1 - Promoter RFA2 - Promoter RNR1 - Promoter YGR151c - Promoter	
Adr1p Carbon source-responsive zinc-finger transcription factor, required for transcription of the glucose-repressed gene ADH2, of peroxisomal protein genes, and of genes required for ethanol, glycerol, and fatty acid utilization	RNR3 - Reference	CDC9 - Promoter CLN2 - Promoter CSI2 - Promoter ESC8 - Promoter MCD1 - Promoter MSH2 - Promoter MSH6 - Promoter PRI2 - Promoter RAD27 - Promoter RNR1 - Promoter TOS4 - Promoter YOX1 - Promoter	
Aft1p Transcription factor involved in iron utilization and homeostasis; binds the consensus site PyPuCACCCPu and activates the expression of target genes in response to changes in iron availability	No rows were found!	POL30 - Promoter PRI2 - Promoter RAD27 - Promoter RNR1 - Promoter	
Aft2p  Iron-regulated transcriptional activator; activates genes involved in intracellular iron use and required for iron homeostasis and resistance to oxidative stress; similar to Aft1p	No rows were found!	POL30 - Promoter PRI2 - Promoter PRY2 - Promoter RAD27 - Promoter RNR1 - Promoter	

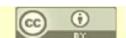


## YeasTract Group Genes by Go Terms http://www.yeastract.com/formregassociations.php

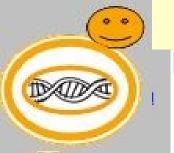




Group Genes by GO



Contact Us - Tutorial - U



Search

## YeasTract Group Genes by Go Terms

Home > Group Genes by GO > Result





GO Associations for Genes Using Biological Process at level 2

DISCOVERER	NEW
Bogulatory Ac	cociati

#### Regulatory Associations:

Search for TFs

Quick search...

- Search for Genes
- Search for Associations

#### Group genes:

- Group by TF - Group by GO
  - up by GO

#### Pattern Matching:

- Search by DNA Motif
- Find TF Binding Site(s)
   Search Motifs on Motifs

#### Utilities:

- ORF List ⇔ Gene List
- IUPAC Code Generation

Generate Regulation Matrix

#### Retrieve:

- TF-Consensus List
- Upstream Sequence
- Flat files

#### About Yeastract:

- Contact Us - Cite YEASTRACT
- Acknowledgments
- Acknowledgmen
   Credits

Go terms Percenta		N. Genes	Genes/ORF			
cellular process	90.0 %	18	Rsr1 Axl2 Yox1 Cdc9 Pri2 Rfa2 Tos4 Rad27 Cln2 Esc8 Hif1 Msh6 Pry2 Mcd1 Pol30 Msh2 Rnr1 Rnr3	+		
metabolic process	65.0 %	13	AxI2 Yox1 Cdc9 Pri2 Rfa2 Rad27 Hif1 Pry2 Pol30 Msh6 Rnr1 Rnr3 Tos4	+		
biological regulation	30.0 %	6	Cln2 Esc8 Yox1 Pol30 Rnr1 Rsr1	+		
developmental process	20.0 %	4	Axi2 Mcd1 Msh6 Rad27	+		
response to stimulus	20.0 %	4	Rnr1 Tos4 Cln2 Rnr3	+		
reproductive process	10.0 %	2	Msh6 Rad27	+		
localization	5.0 %	1	Rfa2	+		
establishment of localization	5.0 %	1	Rfa2	+		
multi-organism process	5.0 %	1	Cln2	+		
reproduction	5.0 %	1	Axi2	+		
anatomical structure formation	5.0 %	1	Hif1	+		

Go Back



Bioinformatics





## SwissRegulon Portal

Swissregulon Quick links:

Annotations

Downloads FANTOM4 results

## Services: Swissregulon **Phylogibbs** MARA TCS **Publications** Links

Contact

Swissregulon is a database of genome-wide annotations of regulatory sites. The predictions are based on Bayesian probabilistic analysis of a combination of input information including:

- Experimentally determined binding sites reported in the literature.
- Known sequence-specificities of transcription factors.
- ChIP-chip and ChIP-seq data.
- Alignments of orthologous non-coding regions.

Predictions were made using the PhyloGibbs, MotEvo, IRUS and MARA algorithms developed in our group, depending on the data available for each organism. Annotations can be viewed in a Gbrowse genome browser and can also be downloaded in flat file format.

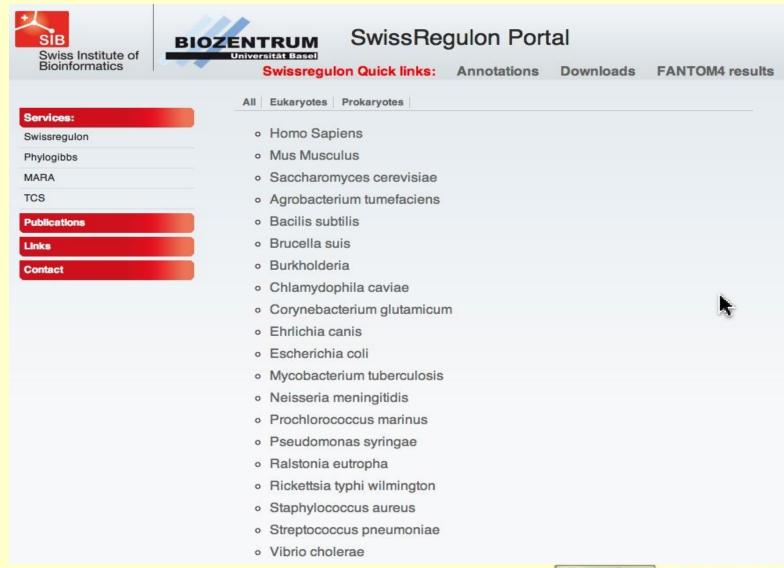
Please cite this site as following:

SwissRegulon: a database of genome-wide annotations of regulatory sites Mikhail Pachkov, Ionas Erb, Nacho Molina and Erik van Nimwegen Nucleic Acids Research, 2007, Vol. 35, Database issue D127-D131



## Swiss Regulon Organisms

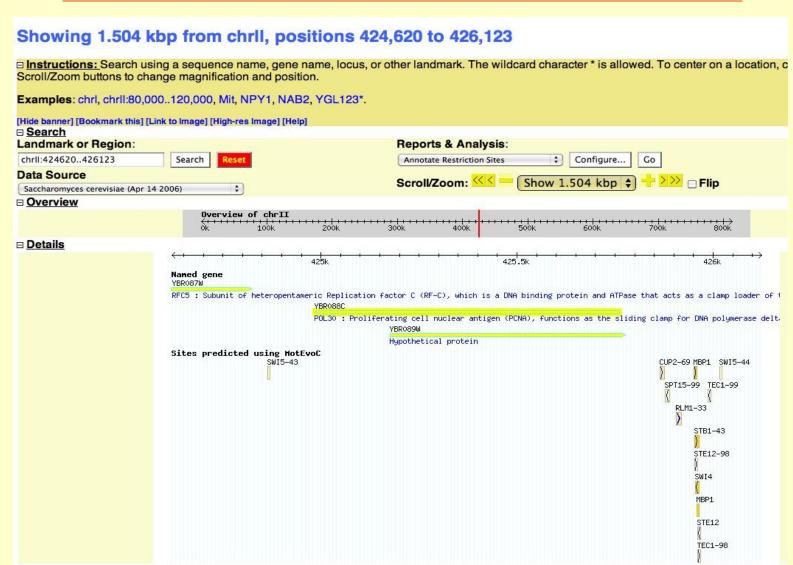
http://www.swissregulon.unibas.ch/cgi-bin/regulon

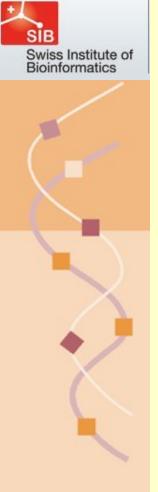




### Swiss Regulon Yeast TF Binding Sites Near Pol30

http://www.swissregulon.unibas.ch/cgi-bin/gbrowse/yeast/





### Swiss Regulon Yeast Transcription Factor Ste12

http://www.swissregulon.unibas.ch/cgi-bin/gbrowse/yeast/

#### Saccharomyces cerevisiae (Apr 14 2006)

back to main page

Name: STE12\_DIG1-68 Class: TF\_binding\_site TF\_binding\_site Type: Source: MotEvoC

Position: chrll:425967..425961 (- strand)

Lenath:

Score: 0.071272 Alias: STE12\_DIG1 Note: CGTTTTG

factor name: STE12 DIG1

weight\_matrix: 0.00 32.62 0.96 250.22 42.97 0.00 241.37 1.98 271.22 0.00 12.78 0.00 252.90 1.67 27.03 0.00 278.87 0.00 0.00 0.00 0.98 277.79 0.00 0.97 153.01 30.02 93.87 22.75

>STE12 DIG1-68 class=TF binding site position=chrII:425967..425961 (- strand) CCAAAAC

#### **Corresponding Weight Matrix**



11				
NA ST	E12 DIG1			
PO	A	C	G	T
01	0.00	32.62	0.96	250.22
02	42.97	0.00	241.37	1.98
03	271.22	0.00	12.78	0.00
04	252.90	1.67	27.03	0.00
05	278.87	0.00	0.00	0.00
06	0.98	277.79	0.00	0.97
07	153.01	30.02	93.87	22.75



## Swiss Regulon Yeast Transcription Factor Ste12 Sites

http://www.swissregulon.unibas.ch/cgi-bin/gbrowse/yeast/

#### Other locations of STE12\_DIG1 sites:

	Upstream gene	Upstream region coordinates	Site coordinates	Probability	Strai
			chrVII:878320878314	0.984212	-1
		<del></del>	chrll:408661408655	0.972057	-1
			chrlll:229021229027	0.972057	1
			chrXIV:110765110759	0.970263	-1
			chrX:585873585867	0.969271	-1
			chrlll:1311613110	0.966688	-1
			chrll:192199192193	0.966341	-1
-			chrXII:561858561864	0.966132	1
			chrXI:114864114870	0.961639	1
			chrVI:8225682262	0.958973	1
		( <del></del> )	chrXII:10416101041604	0.953367	-1
			chrX:445331445337	0.948736	1
		(Accessing to the Control of the Con	chrVII:437032437038	0.94671	1
			chrXII:790167790161	0.946707	-1
<b>&gt;</b>		( <del></del> )	chrXIII:411475411481	0.944509	1
			chrV:188204188210	0.944509	1
X		( <del></del> )	chrlll:1318813194	0.944509	1
			chrVIII:273742273748	0.942583	1
			chrlV:543992543986	0.941509	-1
_			chrXIV:276112276118	0.939875	1
		( <del></del> )	chrXIV:703355703349	0.935385	-1
			chrXVI:462194462188	0.933203	-1
		(Access)	chrVIII:273703273709	0.932334	1
			chrX:126581126587	0.931886	1
		(Access)	chrVII:516467516473	0.930058	1
			chrV:167341167335	0.930058	-1
		(Access)	chrlV:976108976102	0.92753	-1
			chrVII:437228437234	0.922055	1
		Name of the Control o	chrXIII:664436664442	0.916896	1
			chrXVI:781892781898	0.916798	1
			chrXIII:181232181226	0.914531	-1
			chrlV:5073550729	0.914278	-1
			chrXIII:659599659605	0.908352	1

#### Datafiles for download:

- PhyloGibbs predictions made using orthologs only
- PhyloGibbs predictions based on CHIP-on-chip data
   MotEvo predictions based on CHIP-on-chip data
- Weight matrices