

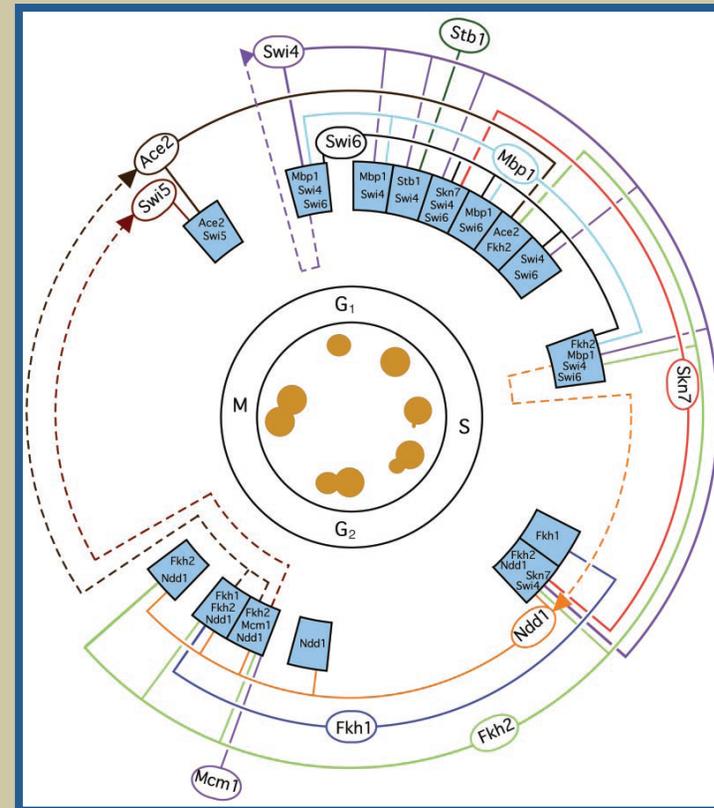
Transcriptional Regulatory Networks  
in *Saccharomyces cerevisiae*

Tong Ihn Lee et al. 2002

Bryan Heck

# Purpose

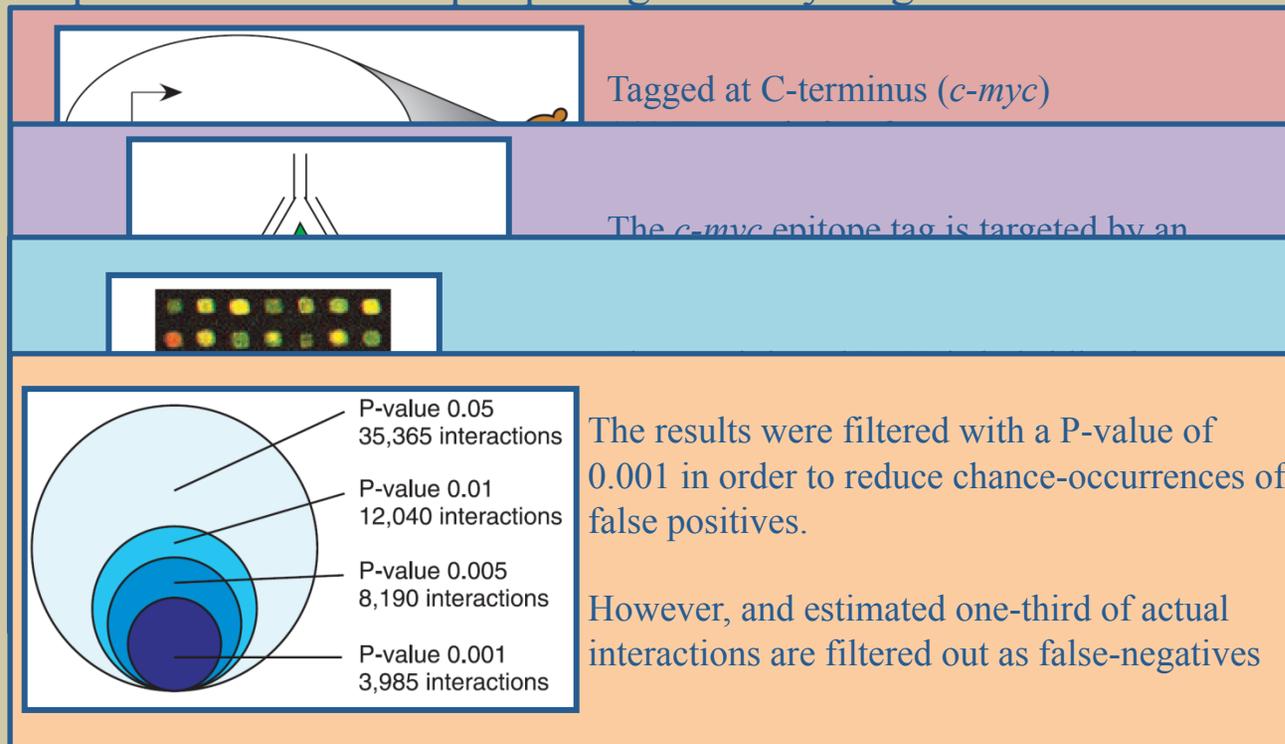
To catalogue and characterize every promoter-bound regulator that exists in *S. cerevisiae* and to apply computer algorithms to determine function and coordination of regulatory networks independent of previous knowledge and experiments.



# Methods

## “Genome-Wide Location Analysis”

### Step 1: Introduce an Epitope Tag to Every Regulator



# Results

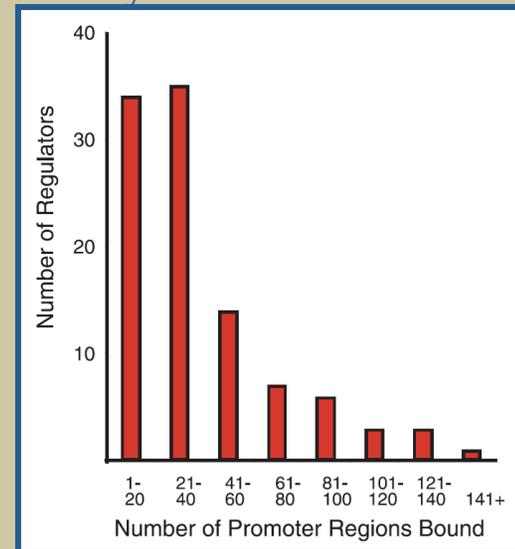
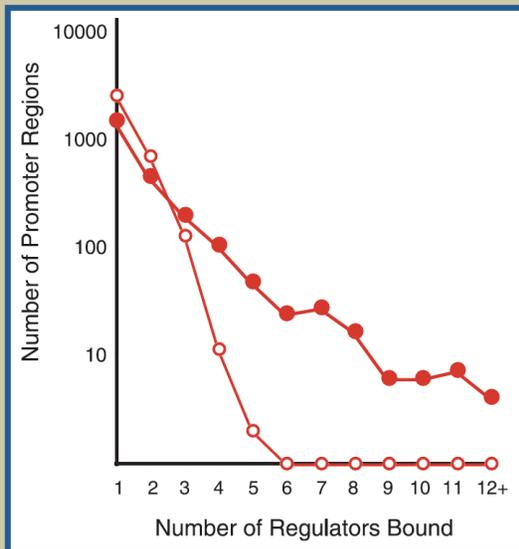
## Regulator Density

Approximately 4000 interactions at  $P = 0.001$

2343 of 6270 yeast genes had their promoters bound (37%)

More than a third of promoters bound by multiple regulators

-Feature associated with higher eukaryotes



# Results

## Regulatory Motifs

Simplest unit of transcriptional regulatory network architecture

Identified six basic behaviors:

Autoregulation	Multi-Component Loop
Single Input Motif	Multi-input Motif
Feedforward Loop	Regulator Chain

# Network Motifs

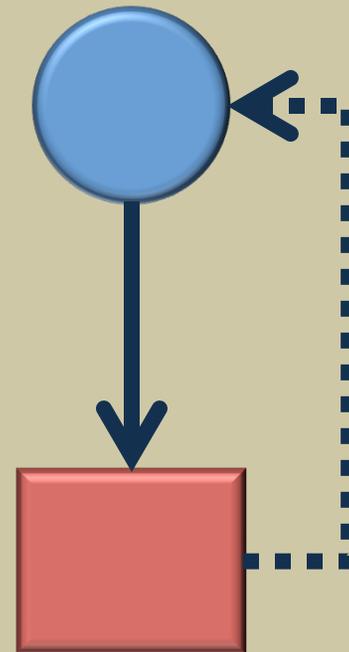
## Auto-Regulation

Regulator binds its own promoter region

10% of regulator genes are autoregulated  
In contrast to prokaryotes (52%-74%)

Benefits include:

- Reduced response time to stimuli
- Biosynthetic cost of regulation
- Stability of gene expression



# Network Motifs

## Multi-Component Loop

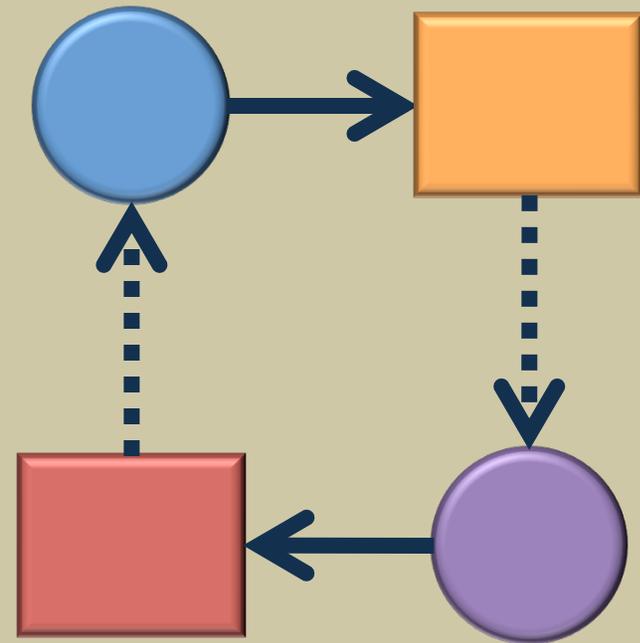
Closed regulator loop containing two or more factors

Only three instances of this motif

Not present in prokaryotes

Benefits include:

- Feedback control
- Bistable system that can switch between two alternate states



# Network Motifs

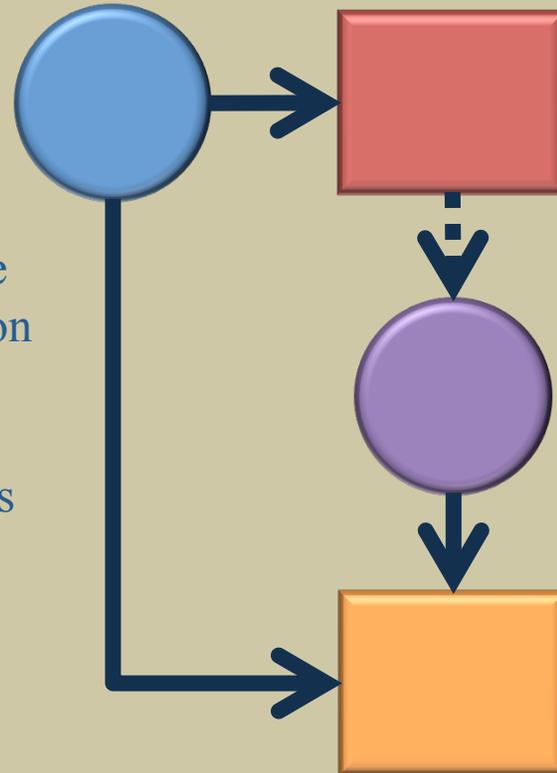
## Feed-Forward Loop

Regulator binds both its primary target and the promoter of a regulator which shares a common target

39 regulators involved in 49 feedforward loops controlling approximately 240 genes (10%)

Benefits include:

- Switch sensitive to sustained inputs, but not transient ones
- Possible temporal control
- Multistep ultrasensitivity



# Network Motifs

## Single-Input Motif

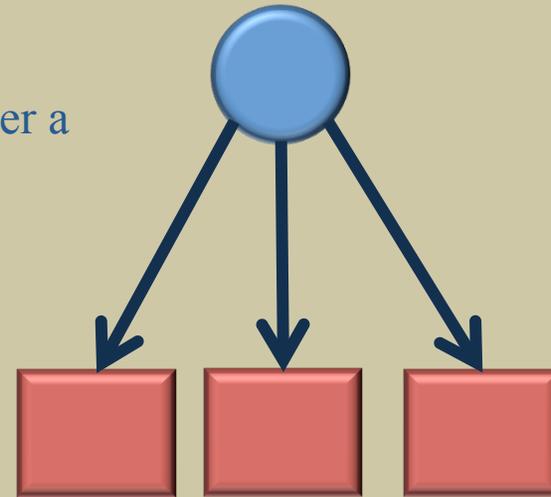
Single regulator that binds a set of genes under a specific condition

Benefits include:

Coordination of discrete biological functions

Unique finding:

Fh11, whose function was not previously known, was shown to make a single-input motif consisting of all ribosomal protein promoters but nothing else.



# Network Motifs

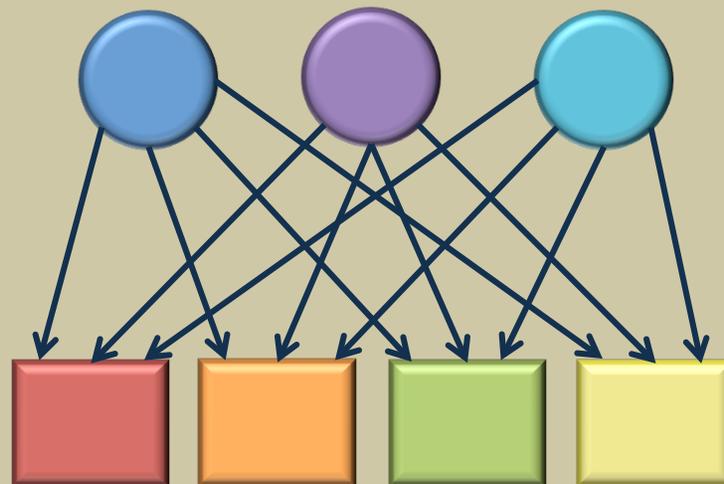
## Multi-Input Motif

Set of regulators that bind together to a common set of genes

295 combinations of regulators binding to common promoters

Benefits include:

Coordinating gene expression over a wide variety of growth conditions and cell cycle



# Network Motifs

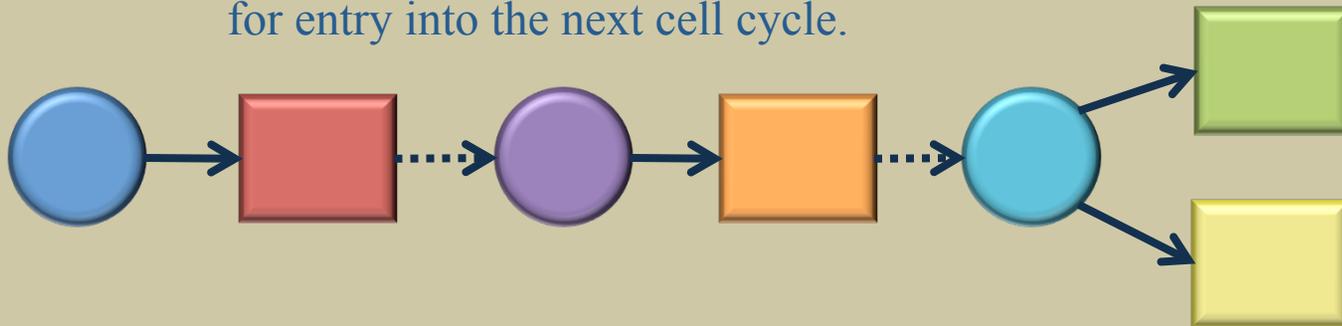
## Regulator Chain

Three or more chained regulators in which the first regulator bind the promoter of the second, etc.

188 regulator chains each involving 3-10 regulators

Benefits include:

Provides linear coordination of cell cycle;  
Regulators functioning at one stage  
regulate the expression of factors required  
for entry into the next cell cycle.



# Assembly

## MIM-CE

Multi-input motifs refined for common expression

Used genome-wide location data along with expression data from over 500 experiments to define rough groups of genes that are coordinately bound and expressed.

Fed this data into an algorithm which, given a set of genes ( $G$ ), a set of regulators ( $S$ ), and a P-value threshold (0.001):

A large set of  $G$  is used to establish a core profile

Any gene in  $G$  that varies significantly from profile is dropped

The rest of the genome is scanned against this profile

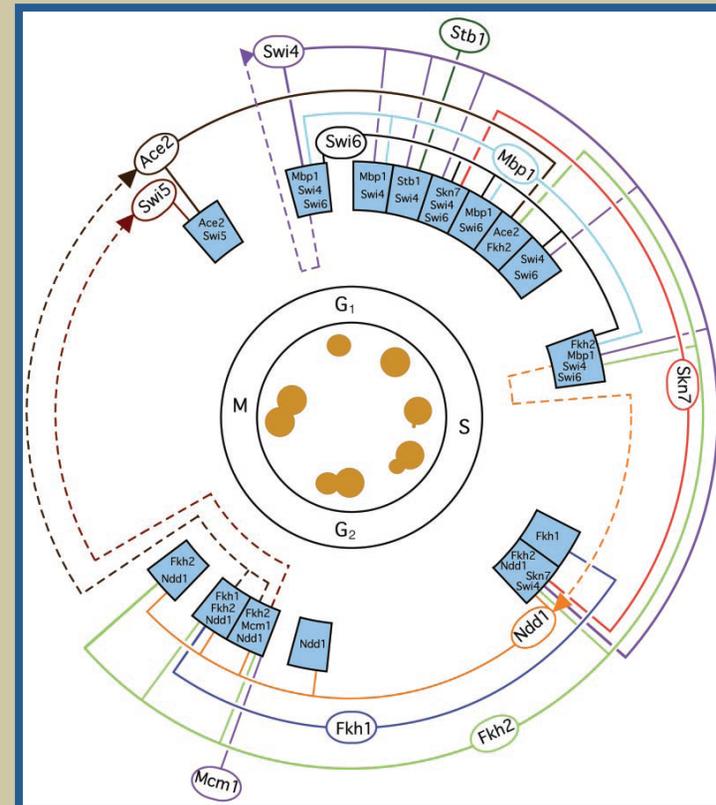
Genes with regulators bound from  $S$  are added to  $G$

P-value used for this step is based on the average of all regulators in  $S$ , not individual interactions, thus relaxing the stringency

# Assembly

## Rebuilding the Cell Cycle

- Identified MIM-CEs enriched in genes whose expression oscillates through cell cycles
- Identified the 11 regulators associated with these genes
- Used these 11 regulators to construct a new set of MIM-CEs
- Aligned the new MIM-CEs around the cell cycle based on peak expression and links with previous MIM-CEs



# Significance



Questions?