

Table S1: Internal validation for 17 out of 24 restricted network models.

| Model | # Genes | Validated literature pathway | Refs. | Enriched MIPS Function |
|-------|---------|---|----------------------|--|
| 0 | 109 | Kss1/Fus3-Ste12 (mating response and filamentous growth) | Elion et al. 1993 | cell fate (1.48×10^{-7}); metabolism (0.0067) |
| 1 | 69 | Sok2-Msn4 (PKA pathway) | Smith et al. 1998 | |
| 2 | 44 | Tup1/Ssn6-Nrg1 (glucose metabolism) | Park et al. 1999 | transport (1.05×10^{-5}); metabolism (5.41×10^{-4}) |
| 3 | 58 | Tup1/Ssn6- α 2/Mcm1 (mating response) | Wahi et al. 1995 | cell fate (1.12×10^{-5}) |
| 4 | 44 | Swi4-Ndd1-Ace2 (cell cycle) | Lew et al. 2001 | |
| 6 | 36 | Slt2-Rlm1/Swi4 (PKC pathway) | Jung et al. 1999 | |
| 7 | 13 | Cmd1-Cna1-Skn7 (calcium signaling) | Williams et al. 2001 | |
| 8 | 9 | | | cell defense (6.33×10^{-6}) |
| 10 | 12 | Med2-Gal11-Gal4 (general transcription) | Park et al. 2000 | |
| 12 | 7 | | | metabolism (0.026) |
| 13 | 17 | | | metabolism (1.49×10^{-5}) |
| 14 | 6 | Gcn4-Met4 (methionine synthesis) | | metabolism (2.88×10^{-4}) |
| 16 | 9 | Ste12-Mcm1 (mating response) | | cell fate (4.55×10^{-8}); homeostasis (0.0012); cell communication (0.0345) |
| 17 | 13 | Cka2-Abf1 (casein kinase pathway) | | |
| 20 | 5 | | | metabolism (0.0017) |
| 22 | 8 | Cka2-Abf1 (casein kinase pathway) | | |
| 25 | 7 | Cka2-Abf1 (casein kinase pathway) | | |

Table S2: Correlations between *swi4Δ* and *gcn4Δ* data from Rosetta and the new experiments.

| | <i>swi4Δ</i> total | <i>gcn4Δ</i> total |
|---------------------------------|----------------------------|----------------------------|
| correlation | -0.013 | 0.34 |
| correlation p-value | 0.84 | < 10 ⁻⁴ |
| rank correlation | -0.058 | 0.145 |
| rank correlation p-value | 1.0 | < 10 ⁻⁴ |
| hyper-geometric p-value | 0.188 | 4.88×10 ⁻²¹ |
| | <i>swi4Δ</i> subset | <i>gcn4Δ</i> subset |
| correlation | 0.344 | 0.831 |
| correlation p-value | 8×10 ⁻⁵ | < 10 ⁻⁵ |
| rank correlation | 0.353 | 0.705 |
| rank correlation p-value | 9×10 ⁻⁵ | < 10 ⁻⁵ |
| hyper-geometric p-value | 1.05×10 ⁻⁵ | < 1.8×10 ⁻¹³ |

Table S3: Restricted subsets used to evaluate the reproducibility.

Swi4 subset

| | | | |
|-------|--------|---------|---------|
| AAP1 | LYS20 | YAP6 | YJL225C |
| ATR1 | MNN1 | YBL029W | YJR078W |
| BAT2 | MSN4 | YBL112C | YKL051W |
| CCP1 | NCE102 | YBL113C | YLR084C |
| CLB1 | PCL7 | YDR451C | YLR463C |
| CLB2 | PDR12 | YDR545W | YLR465C |
| CLB6 | PRY2 | YEL045C | YLR466W |
| COX9 | QCR2 | YEL047C | YLR467W |
| CPA2 | RNR1 | YEL077C | YML133C |
| CSI2 | RPI1 | YER045C | YNL339C |
| CUP9 | RPL19B | YER189W | YNR067C |
| ECM13 | SAT2 | YER190W | YOL011W |
| ECM33 | SCW10 | YFR006W | YOR248W |
| ERG6 | SGA1 | YGR086C | YOR315W |
| EXG1 | SNQ2 | YGR153W | YOX1 |
| HAP1 | SOK2 | YGR296W | YPL267W |
| HAP4 | SRL1 | YHL049C | YPL283C |
| HSC82 | SVS1 | YHR048W | YPR203W |
| HTA1 | SWI4 | YIL056W | YPS4 |
| HTB1 | TRP4 | YIL177C | |
| ISU2 | UTR2 | YJL217W | |

Gcn4 subset

| | | |
|-------|-------|---------|
| ADH5 | HAD1 | UGA3 |
| APG1 | HAL2 | YER069W |
| ARG1 | HIS1 | YER073W |
| ARG11 | HIS4 | YGL184C |
| ARG3 | HOM3 | YHM1 |
| ARG7 | LEU4 | YHR122W |
| ARG8 | MET16 | YHR162W |
| ARO1 | PCL5 | YJL200C |
| ARO3 | RIB5 | YLR152C |
| CPA2 | TRP2 | YMC1 |
| GCN4 | TRP3 | YOL119C |

Table S4: Gene sets for external validation.

Msn4 subset

| | |
|---------|---------|
| ALD3 | LAP4 |
| ARA1 | PGM2 |
| CTT1 | RAS2 |
| YMR173W | SOD2 |
| DOT5 | SOL4 |
| GLK1 | SPS100 |
| GLO1 | SSA4 |
| GRE3 | TKL2 |
| GSY1 | TPS1 |
| HOR2 | TTR1 |
| HSP12 | YDL124W |
| HSP26 | YKR011C |
| HSP104 | YMR315W |
| HXK1 | YNL200C |

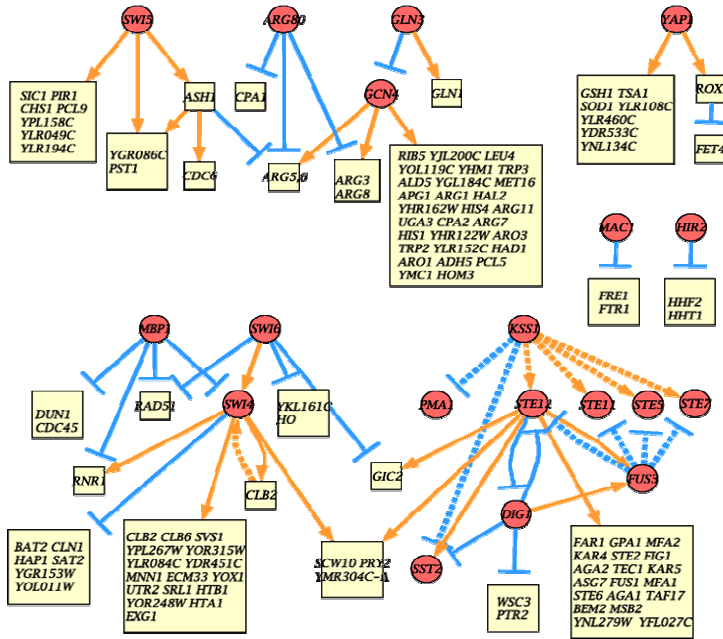
Hap4 subset

| | |
|-------|---------|
| ATP3 | COX13 |
| ATP7 | QCR7 |
| ATP16 | TUF1 |
| COX4 | QCR10 |
| COX7 | YLR294C |
| COX12 | |

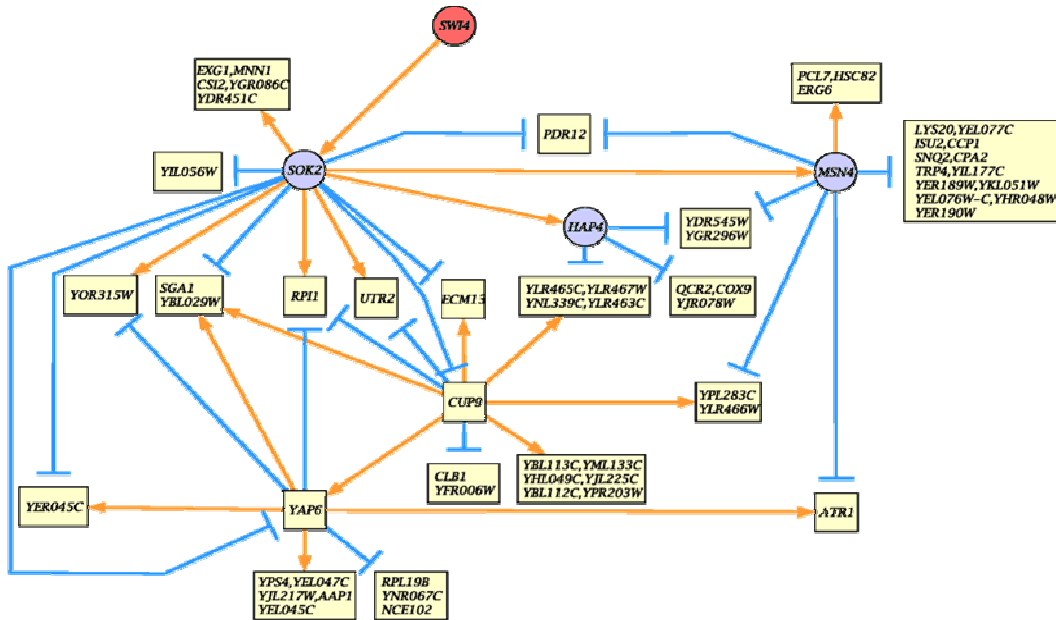
Wiring diagrams for all inferred physical regulatory models

Note: Model 0 contains interactions for which the annotations (activator/repressor) could be uniquely determined. Models 1-44 (38 total) contain ambiguous interactions. Hence, we show only one of many possible sets of annotations that are consistent with the original knockout data.

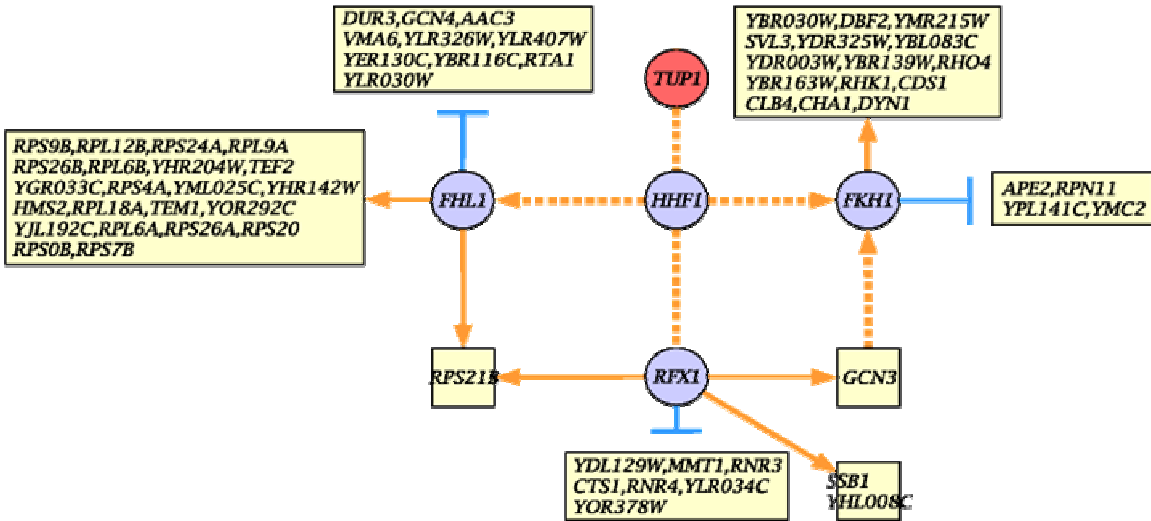
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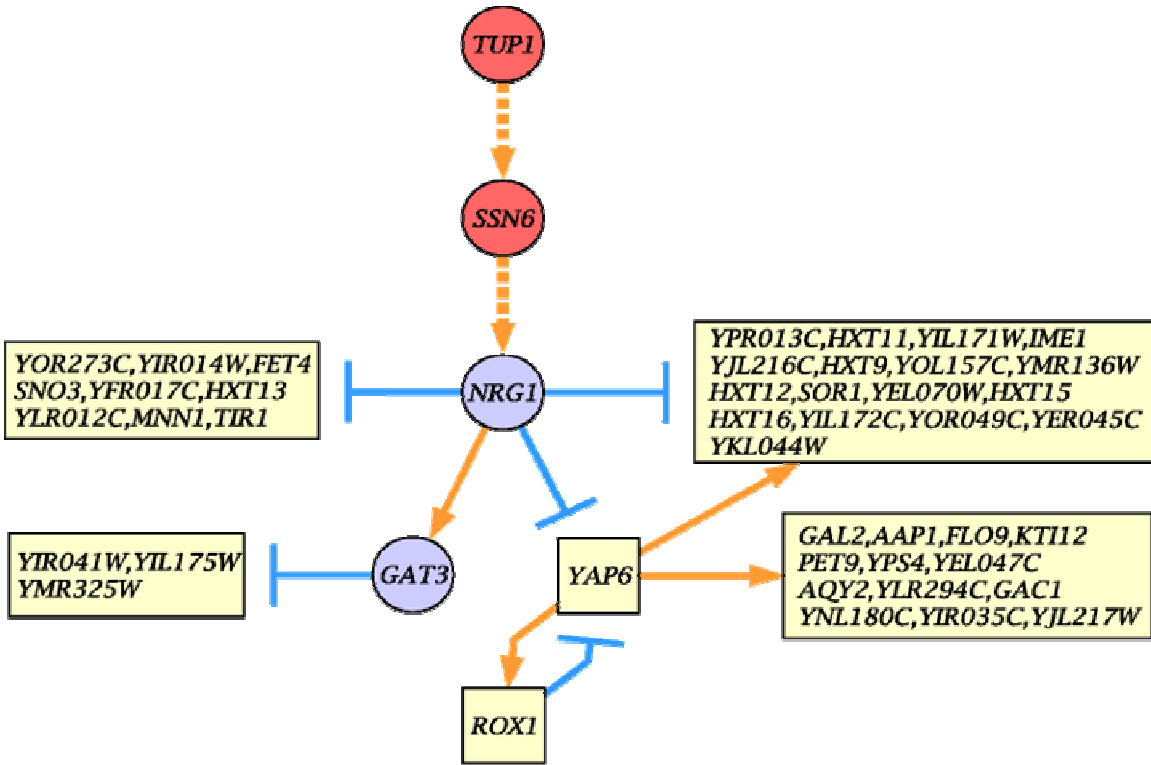
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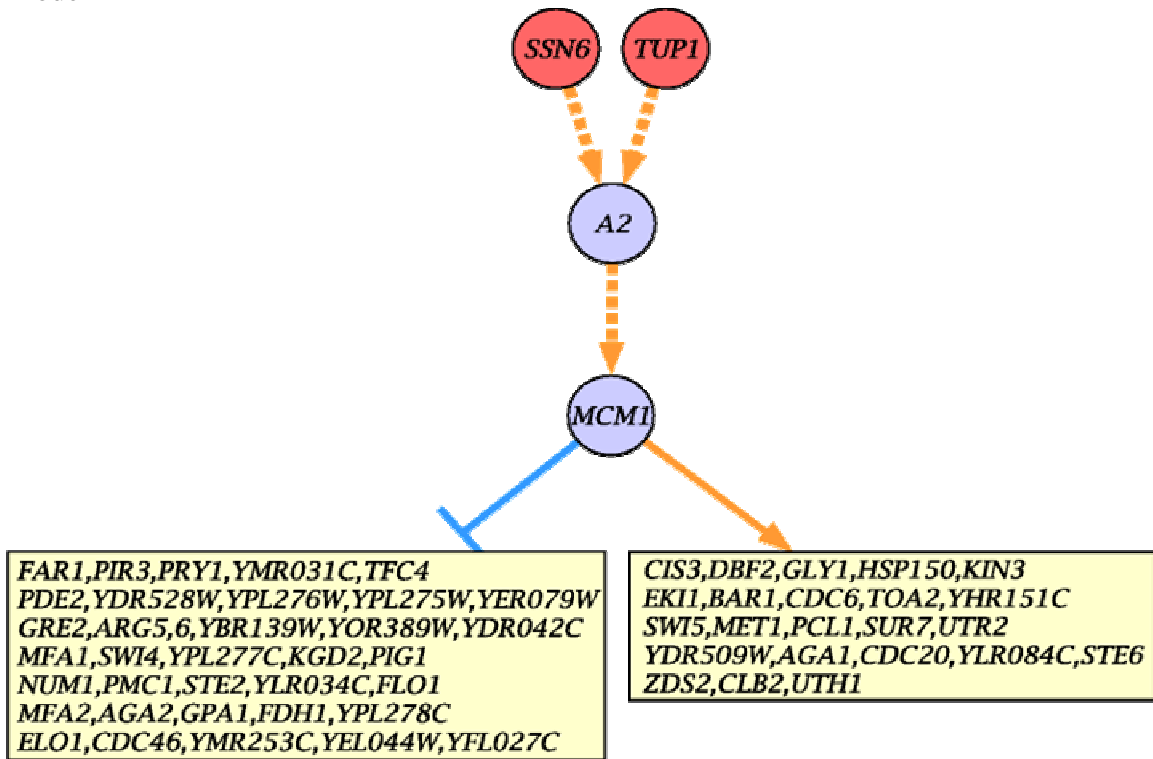
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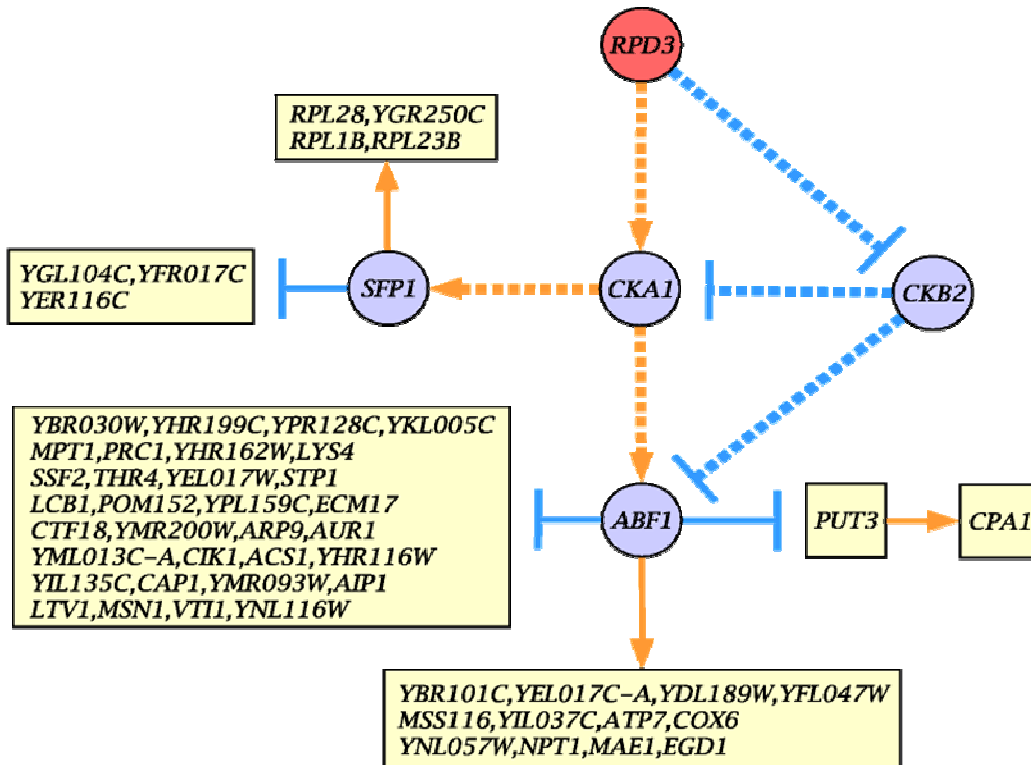
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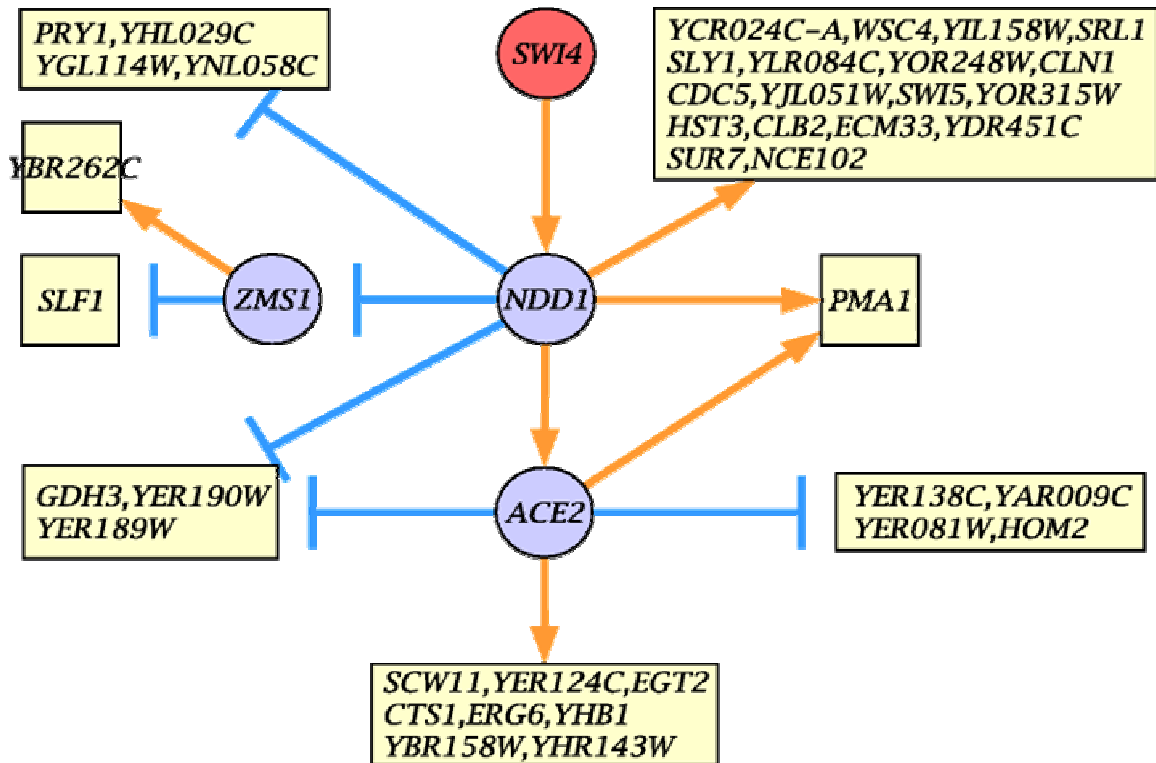
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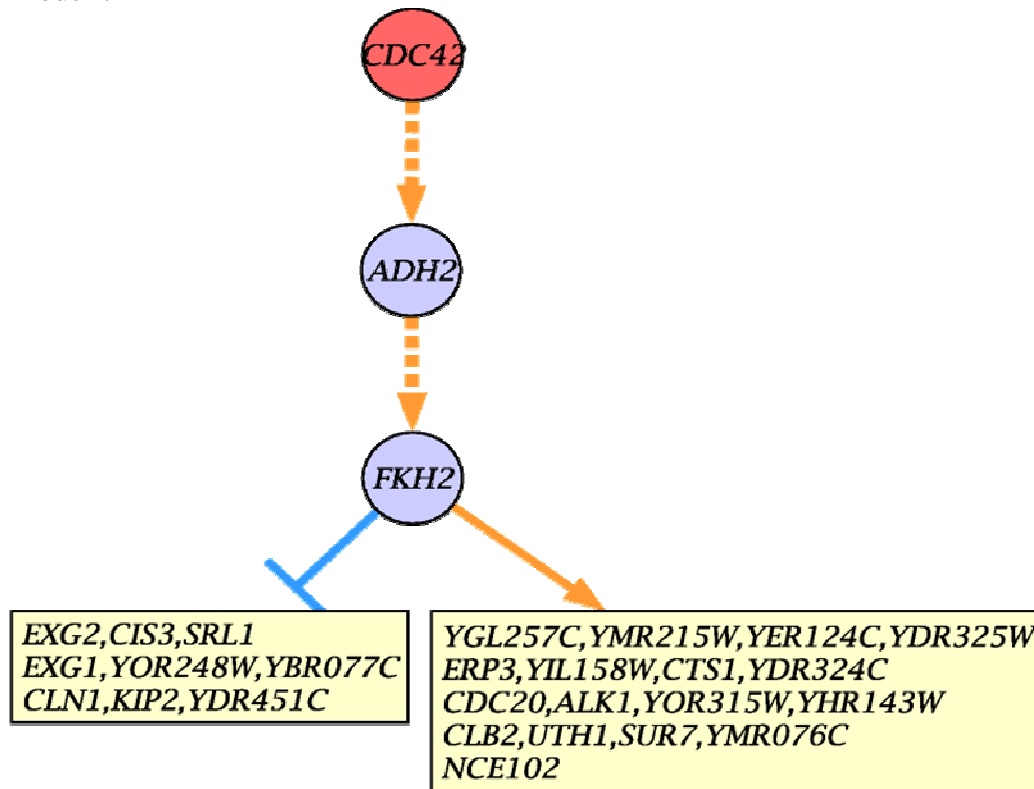
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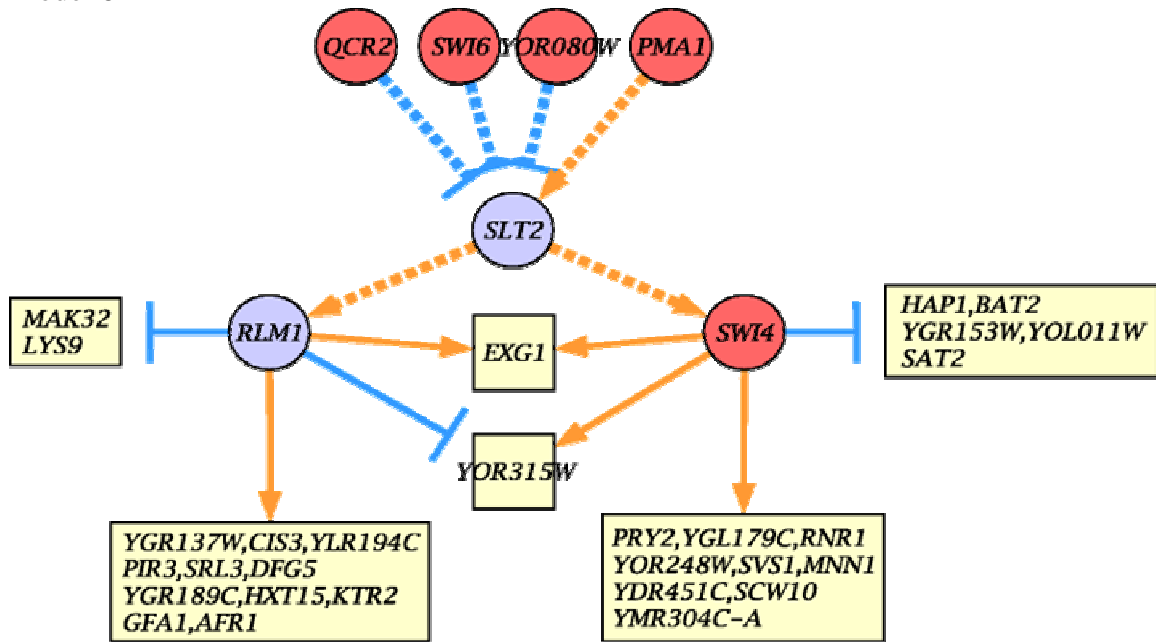
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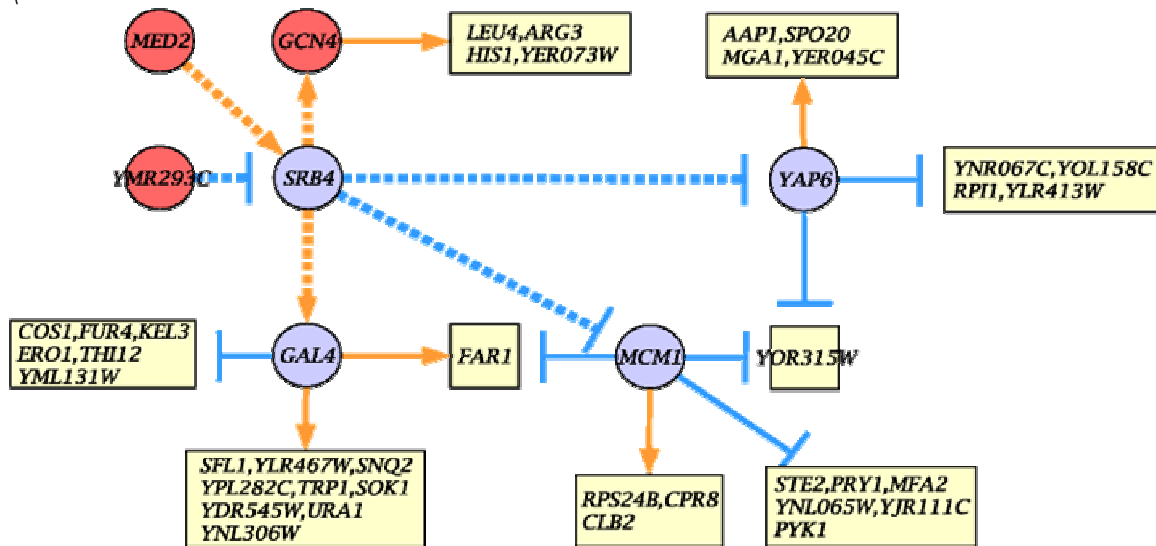
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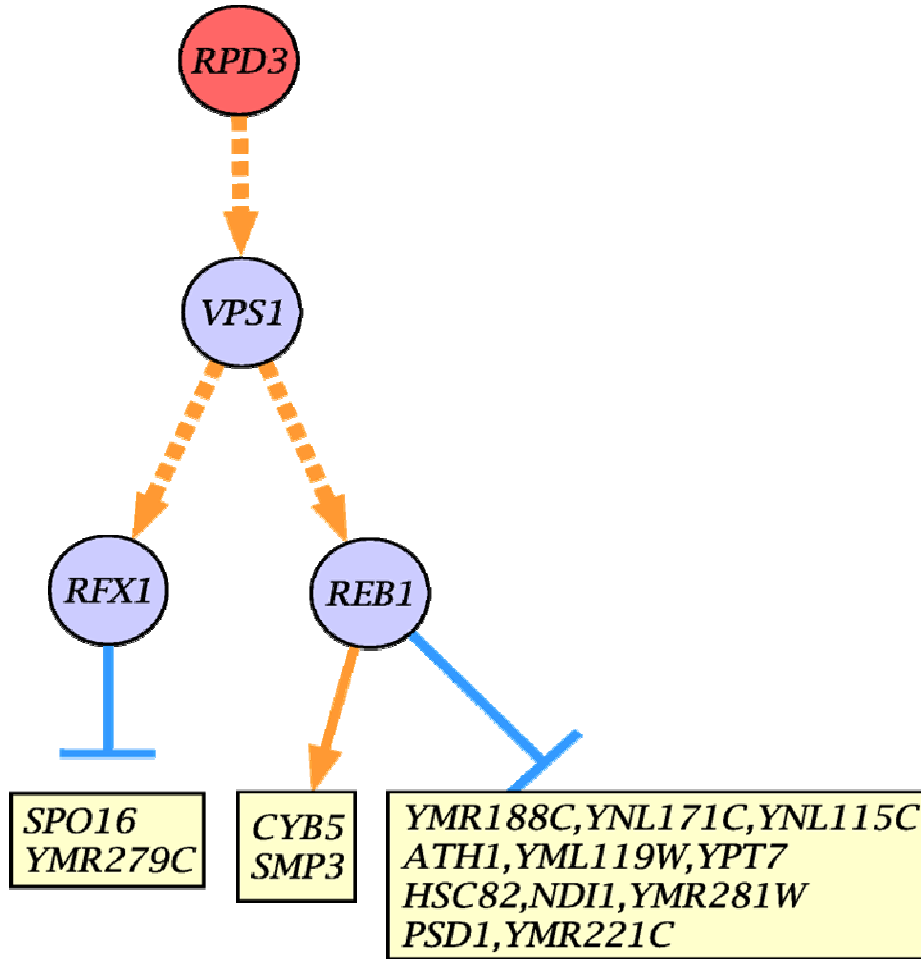
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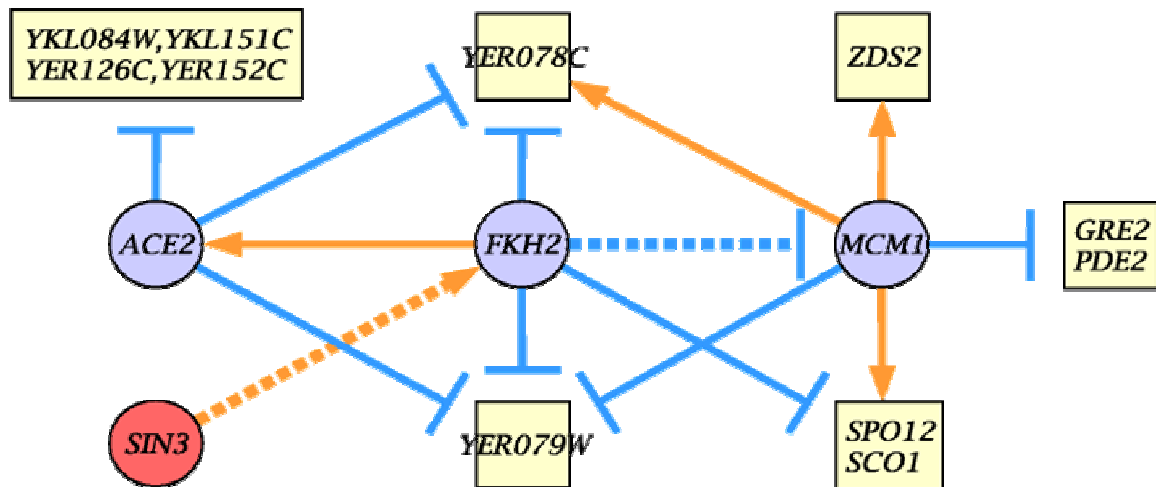
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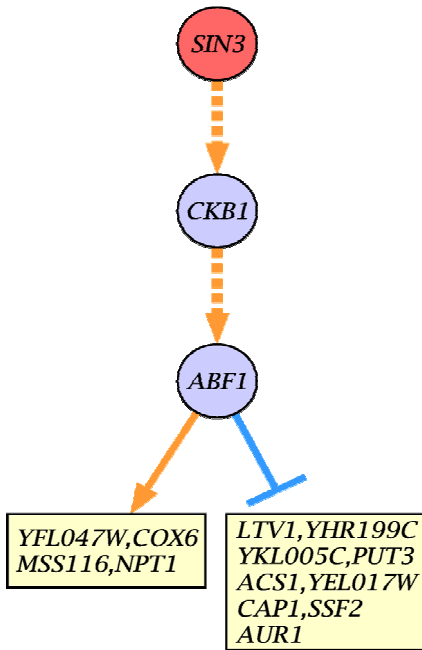
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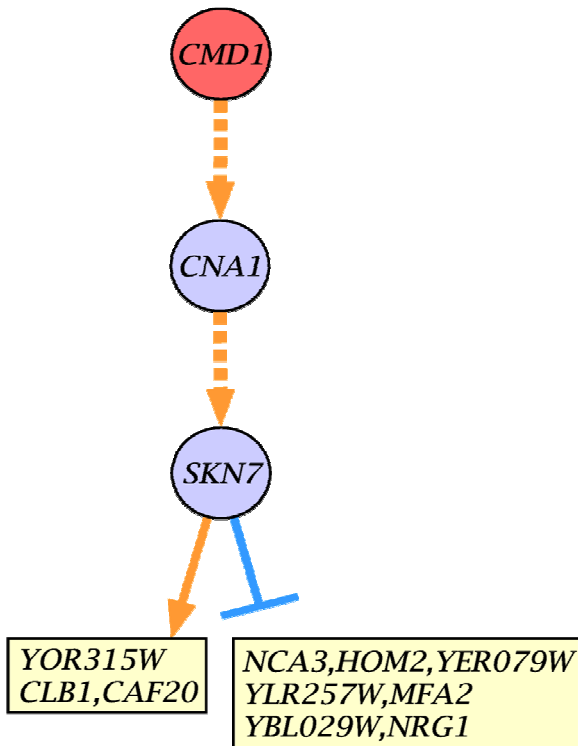
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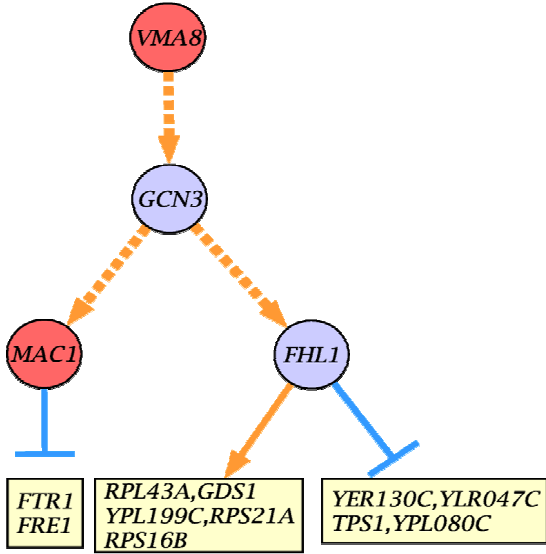
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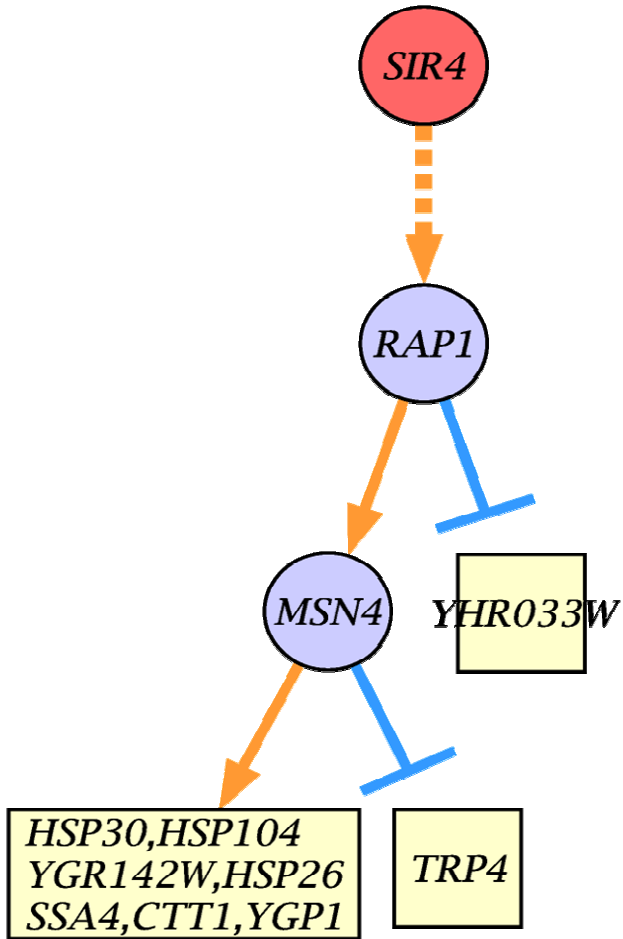
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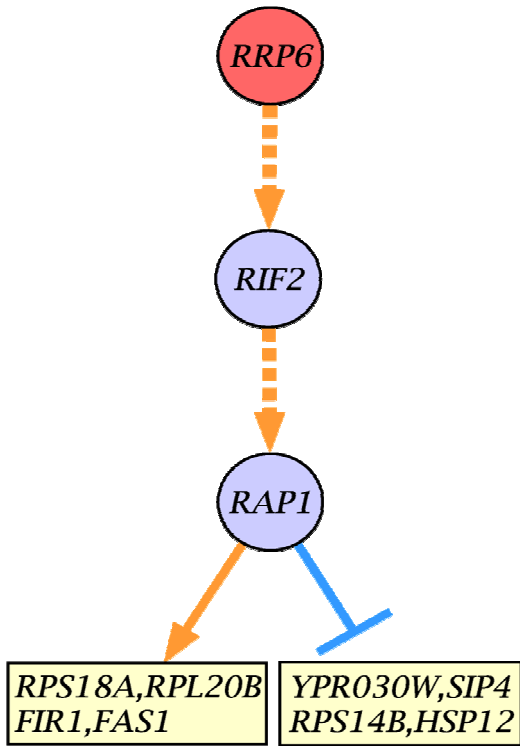
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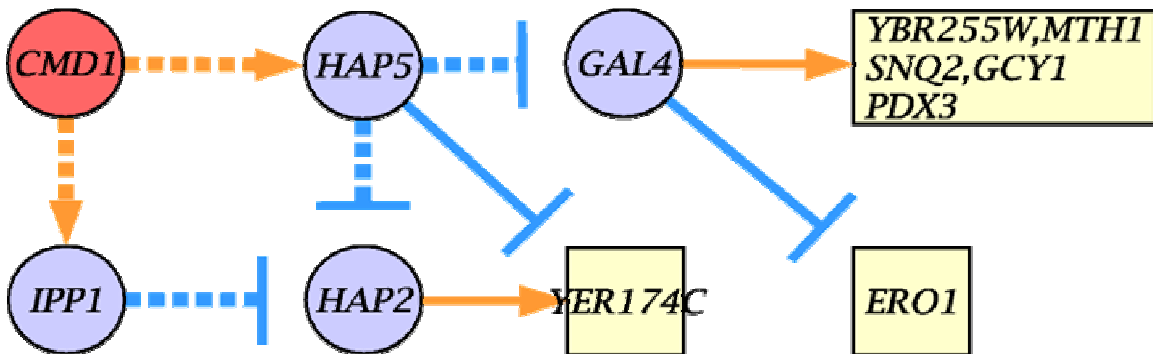
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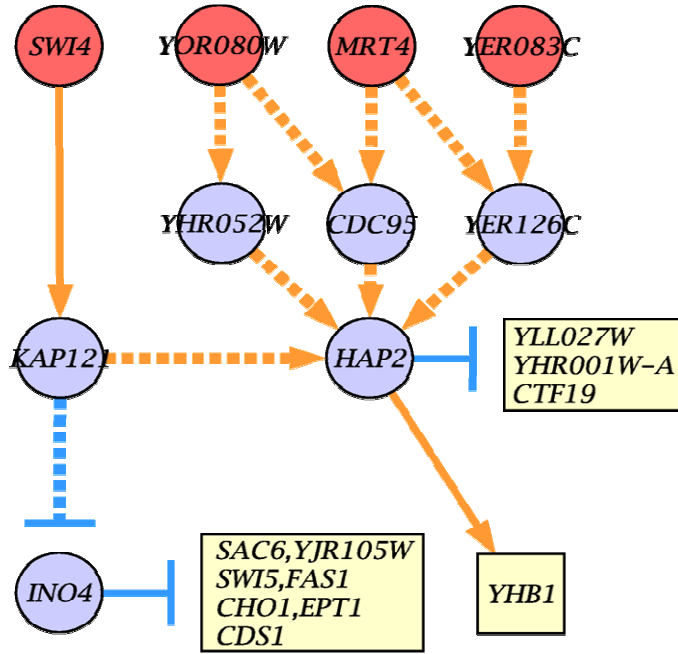
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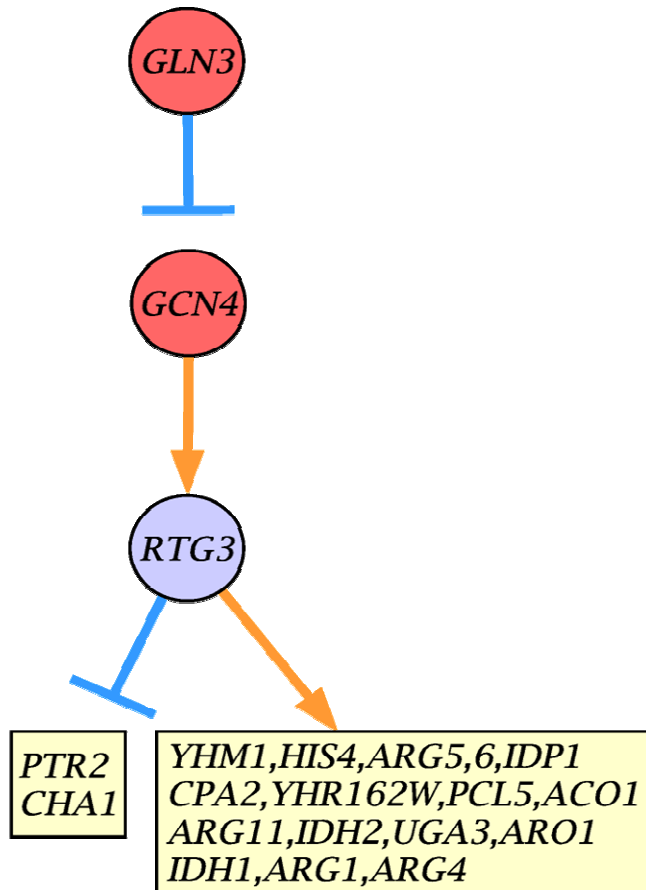
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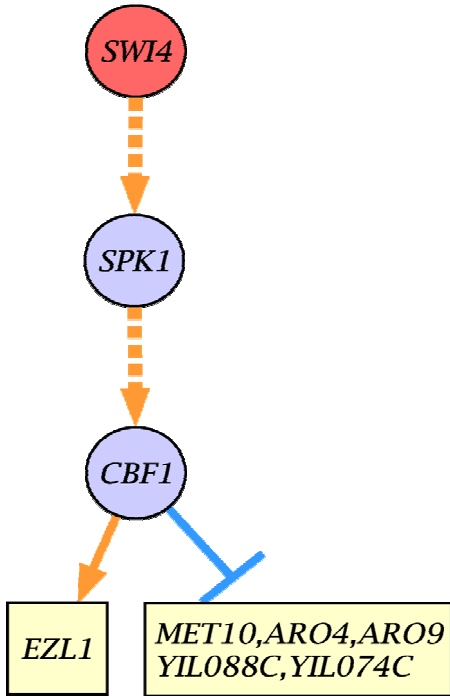
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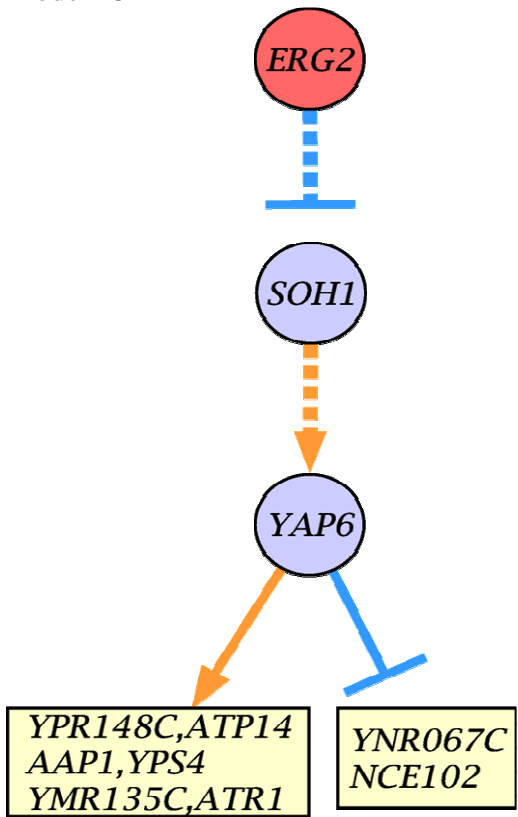
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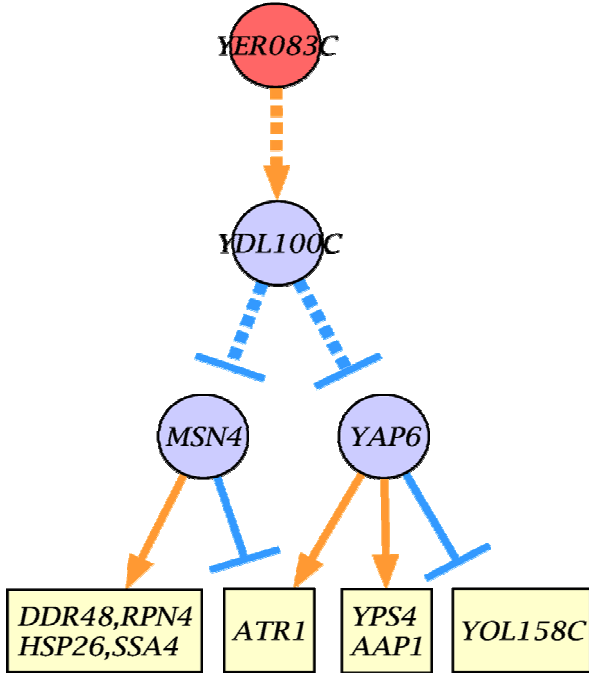
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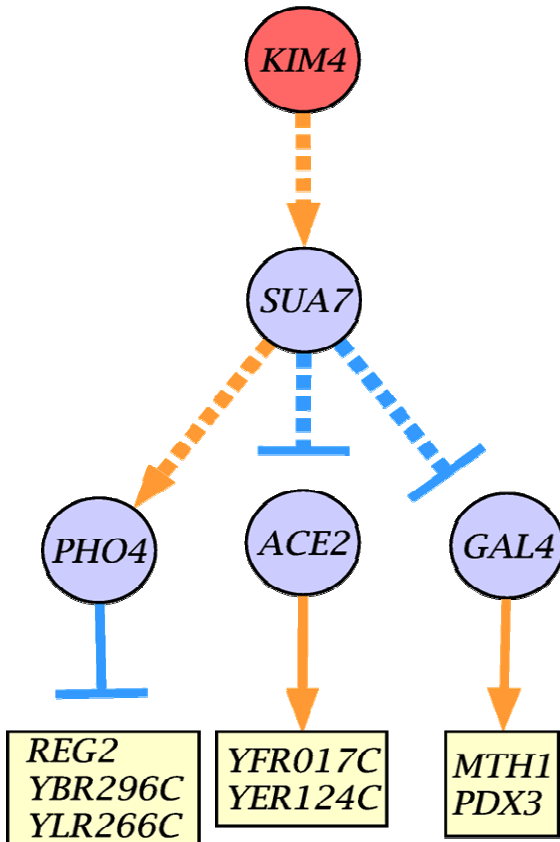
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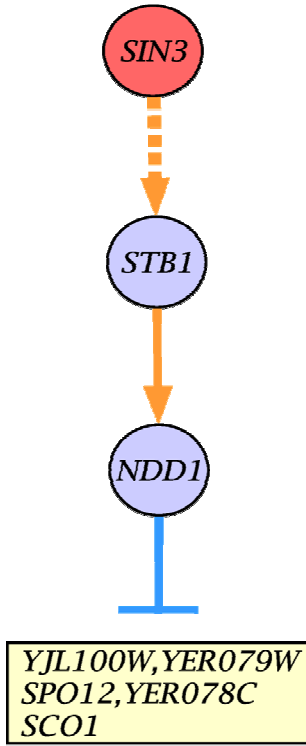
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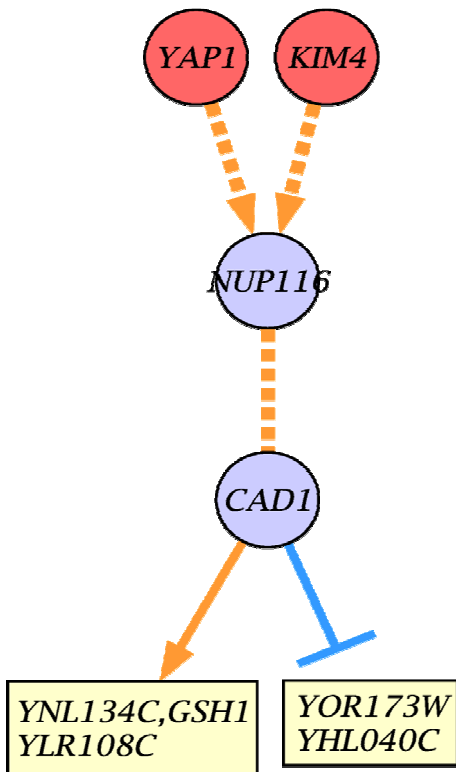
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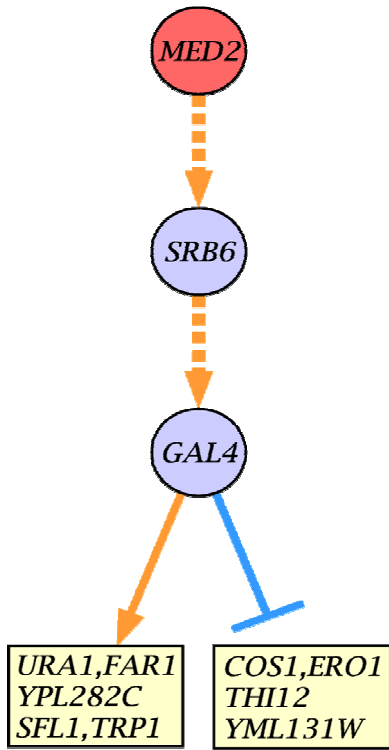
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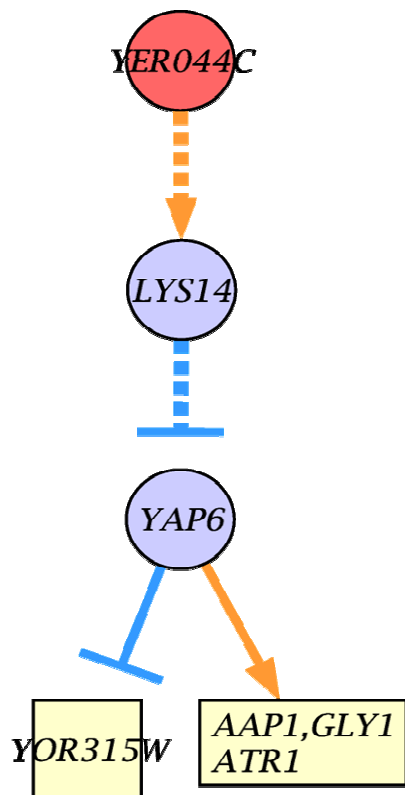
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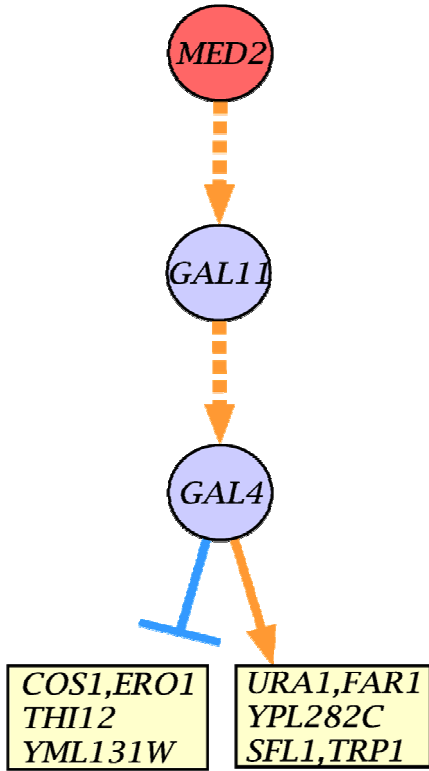
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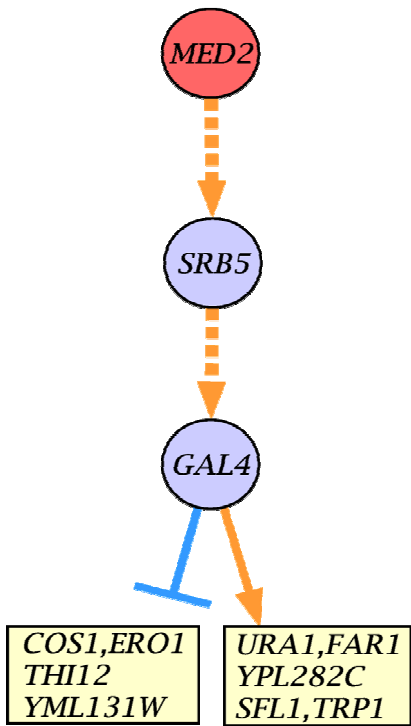
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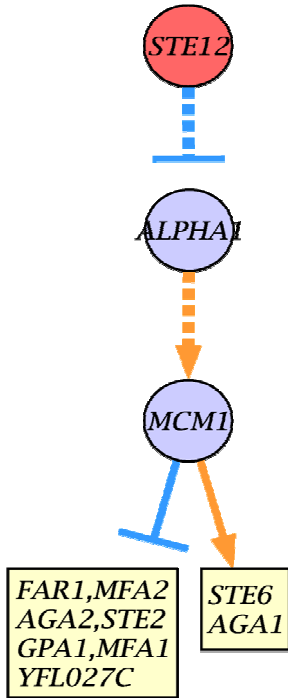
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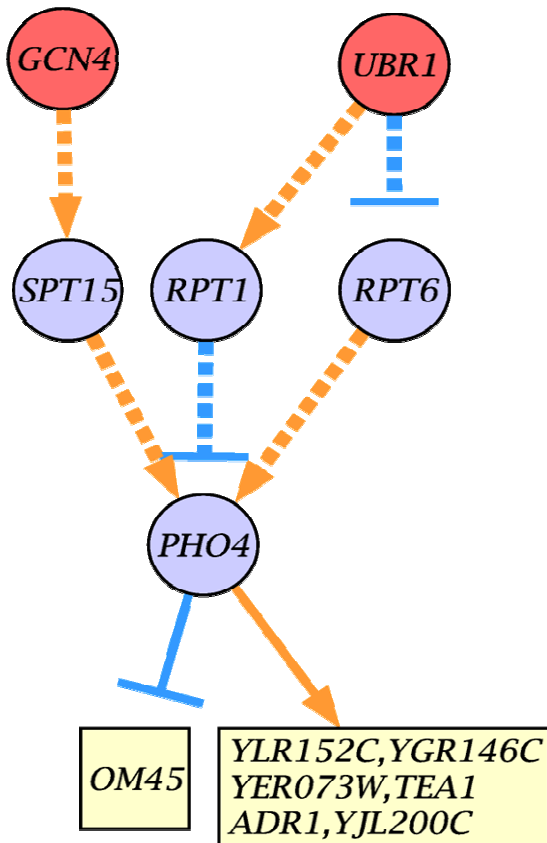
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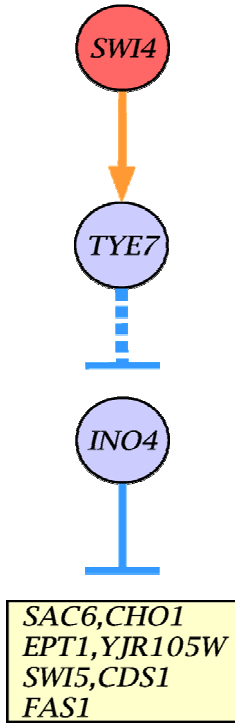
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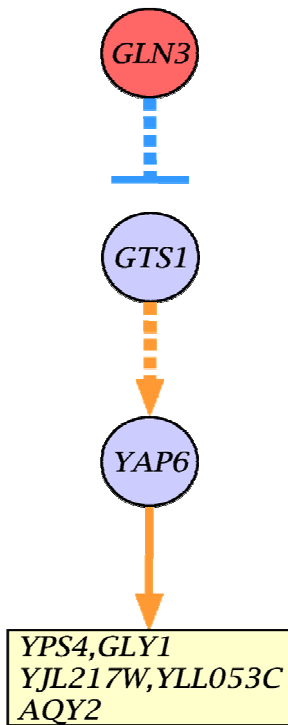
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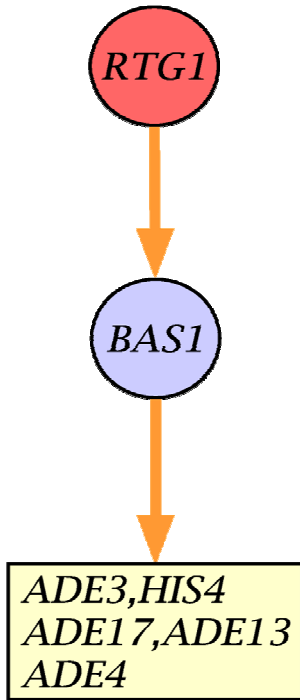
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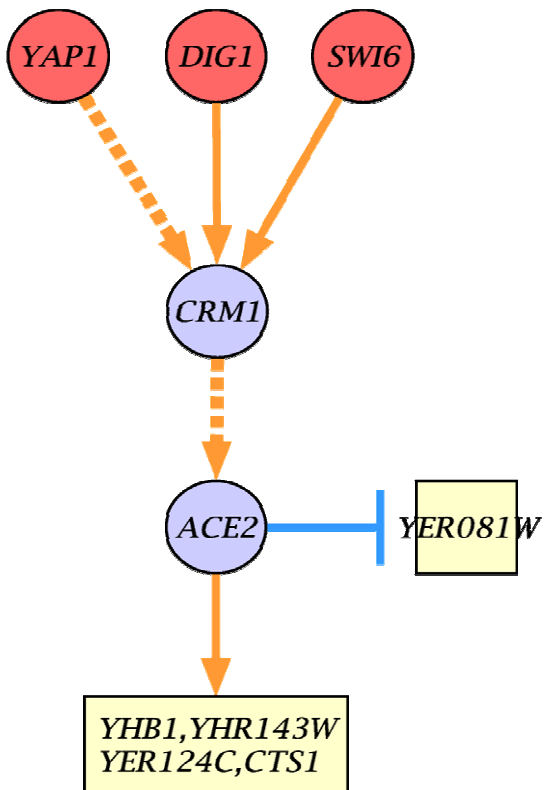
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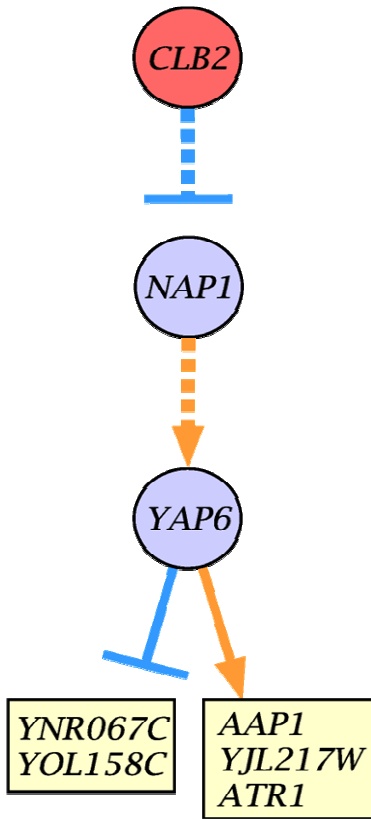
Model 40



Model 41



Model 42



Model 44

