Gopalacharyulu et al.

Dynamic network topology changes in functional modules predict responses to oxidative stress in yeast

Supplementary information

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Protocol S1. Data and methods

Hubs

We used megNet to calculate degrees in and out of each node. The 20 nodes with highest degrees (i.e. sum of in- and out- degrees) were considered as hubs.

Yeast experiment

Strain and Medium

Yeast strain CEN.PK was used in this study. Strain was revived on YPD agar plate containing 10 g L^{-1} yeast extract, 20 g L^{-1} glucose monohydrate, 20 g L^{-1} peptone, and 20 g L^{-1} nutrient agar. For both pre-culture and main-culture, YPD liquid medium containing 11 g L^{-1} glucose monohydrate, 3 g L^{-1} yeast extract, 3 g L^{-1} malt extract, and 5 g L^{-1} peptone was used. Medium was sterilized by autoclaving (15 min, 121° C).

Cultivation

Initially revived cells from YPD agar plate was inoculated into 5 ml YPD medium and grown in 50 ml shake flask at 30° C, 250 rpm for 12 h. Main cultivations were carried out in 2 flasks, one for control and one for oxidative stress condition. An aliquot of over night grown culture was added to 200 ml fresh YPD medium in two separate 1000 ml shake flasks and cultivated as described above. One flask serves as a control and the other one for stress condition.

Hydrogen peroxide treatment

Cells were grown to mid-log phase and 20 ml of culture was taken out from the stress condition flask as a reference (t=0) and 20 ml of pre warmed YPD medium supplemented with H2O2 was added to give a final concentration of 0.3mM H2O2. Samples were collected at 10, 20, 30, 40, 50, 60, 80, 100, 120 and 160 min (Gasch et al 2000). The same procedure was followed in control flask but without H2O2 and collected the samples.

Chemicals

Yeast extract, malt extract, and nutrient agar were obtained from Difco (Detroit MI, USA). Peptone was obtained from Bacto (Sparks, USA). All other chemicals were of analytical grade and either purchased from Fluka (Buchs, Switzerland) or from Sigma (St. Louis, USA).

Lipidomics

Sample preparation

The collected, pre-weighed yeast cells were frozen at -20C. To the frozen pellet, approximately 250 mg of glass beads and 1 ml of chloroform:methonal (2:1) were added. Twenty microliters of labeled standard mixture was added to the mixture and shaken on a platform mixer at maximum speed (level 10) at 4C for 10 min. To this mixture, 250 µl of 0.034 % MgSO4 was added and then shaken at sub-maximum speed (level 9) for 30 min. This reaction mixture was centrifuged at 3500 rpm for 5 min at room temperature. The upper aqueous phase was discarded and 2 ml of water:methanol:choloroform (47:48:3) solution was added and mixed well. This reaction mixture was again centrifuged at 3500 rpm for 5 min at room temperature and the upper aqueous phase was discarded. The lower organic phase was transferred and evaporated the organic solvents under a constant nitrogen gas stream. The lipids were dissolved in 100 µl of chloroform:methonal (2:1) solution. Ten microliters of labelled standard mixture was added to the lipid extract.

The internal standard mixture contained the following lipid compounds (µg/ml) with heptadecanoic acid (C17:0) as the esterified fatty acid: D-*erythro*-Sphingosine-1-Phosphate (9.3 µg/ml; C17 Base, Avanti Polar Lipids), PC(17:0/0:0) (8.8 µg/ml; Avanti Polar Lipids), MG(17:0/0:0/0:0)[rac] (9.3 µg/ml; Larodan Fine Chemicals), PG(17:0/17:0)[rac] (9.6 µg/ml; Avanti Polar Lipids), Cer(d18:1/17:0) (9.2 µg/ml; Avanti Polar Lipids), PS(17:0/17:0) (8.6 µg/ml; Avanti Polar Lipids), PC(17:0/17:0) (9.9 µg/ml; Avanti Polar Lipids), PA(17:0/17:0) (8.5 µg/ml; Avanti Polar Lipids), PE(17:0/17:0) (8.9 µg/ml; Avanti Polar Lipids), DG(17:0/17:0/0:0)[rac] (10.2 µg/ml;

Larodan Fine Chemicals), and TG(17:0/17:0/17:0) (10.4µg/ml; Larodan Fine Chemicals). The labeled standard mixture consisted of PC(16:0/0:0-D3) (9.3 µg/ml; Larodan Fine Chemicals), PC(16:0/16:0-D6) (11.7 µg/ml; Larodan Fine Chemicals) and TG(16:0/16:0/16:0-^{13}C3) (10.0 µg/ml; Larodan Fine Chemicals).

Lipid analysis

Lipid extracts were analysed on a Q-ToF premier mass spectrometer (Waters) combined with an Acquity Ultra Performance Liquid chromatography (UPLC/MS). The column was an Acquity UPLC BEH C18 10x50 mm with 1.7 µm particles and kept at 50° C. The binary solvent system A included water (1% 1M NH_4Ac, 0.1% HCOOH) and solvent system B included LC/MS grade (Rathburn) acetonitrile/isopropanal (5:2, 1% 1M NH_4Ac, 0.1% HCOOH). The gradient started from 65% A/ 35% B, reached 100% B in 6 min and remained there for the next 7 min. The total run time including a 5 min re equilibration step was 18 min. The flow rate was 0.2 ml/min and injection volume 1 µl. The temperature of the sample organiser was set at 10° C. The lipid profiling was carried out using positive ion mode. The data was collected at mass range of m/z 300-2000 with scan duration of 0.2 sec. The source temperature was set at 120° C and nitrogen was used as desolvation gas (800 L/h) at 250° C. The voltages of the sampling cone and capillary were 39 V and 3.2 KV, respectively. Reserpine (50µg/L) was used as the lock spray reference compound (5 µl/min; 10 sec scan frequency).

Lipidomics data processing and analysis

The obtained data was converted into netCDF file format using Dbridge software from MASSLYNX. The converted data was processed using MZmine software version 0.60 [1]. Lipids were identified based on their retention time (RT) and mass-to-charge ratio (MZ) using our in-house built Lipid database [2]. All the identified lipids were quantified by normalizing with corresponding internal standards.

All monoacyl lipids except cholesterol esters, such as monoacylglycerols and monoacyl-glycerophospholipids were normalized with PC (17:0/0:0), all diacyl lipids except ethanolamine phospholipids were normalized with PC(17:0/17:0), the diacyl ethanolamine phospholipids were normalized with PE(17:0/17:0), and the triacylglycerols and cholesterol esters with TG(17:0/17:0/17:0). Univariate (Ttest and Wilcoxon tests) and multivariate analyses (PLS/DA) were performed using Matlab version 7.2 (Mathworks, Inc) and the PLS toolbox version 4.0 beta Matlab package (Eigenvector Research, Inc).

Primary metabolites analysis

Metabolites extraction

Approximately 8 ml of culture sample was taken and quenched immediately in 40 ml of 60% cold (-40º C) methanol. Sample was centrifuged at -19º C, 2000 g, acceleration 9 and deceleration 2 for 5 min. The supernatant (upper methanol) was discarded. Metabolites were extracted using boiling ethanol method. Approximately 20 ml of 75% ethanol was boiled in 80-100º C water bath for 4 min and added to the sample pellet and vortexed briefly. This sample mixture was boiled in water bath for 3 min, vortexed briefly and transferred on ice. Ethanol was evaporated in rapid-vap vacuum evaporator. The conditions were as follows, initially at 30° C, 48%, 70 mbar for 10 min and then at 30° C, 48%, 0 mbar, for 2½ h and finally at 30° C, 48%, 5 mbar, for 30 min. The pellet was dissolved in 0.5 ml double distilled water and transferred the suspension in 1.5 ml eppendorf tube. The sample was centrifuged at 14 000 rpm at room temperature for 5 min and transferred the supernatant to a new tube and stored at -80º C.

Chromatography

Yeast cell extracts were analyzed with HPLC-MS/MS method for quantitative analysis of phosphorous and TCA-cycle compounds [3]. The system consists of HT-Alliance HPLC (Waters, Milford, MA) working at high pH. The analytes were resolved by anion exchange chromatography

combined with post column ASRS Ultra II 2mm ion suppressor (Dionex, Sunnyvale, CA) and detected with Quattro Micro triple quadrupole mass spectrometry (Waters, Milford, MA) operating in electrospray negative ion mode. The analytical column is IonPac AS11 (2x250 mm, Dionex, Sunnyvale, CA) and guard column IonPac AG11 (2x50 mm, Dionex, Dionex Sunnyvale, CA). Flow rate is 250 µl/min and injection volume is 5 µl. The temperature of the column is 35˚ C and autosampler 10˚ C.

The compounds were detected in Multiple Reaction Monitoring (MRM) mode for optimal sensitivity and selectivity. Mass spectrometric parameters, cone voltage and collision energy are optimized for each component. A small aliquot of ^{13}C-labelled metabolites from yeast fed-batch cultivation is used as an internal standard for both calibration standards and samples. Hexose phosphates (glucose-6-phosphate, fructose-6-phosphate and mannose-6-phosphate), pentose phosphates (ribose-5-phosphate), trehalose-6-phosphate, fructose bisphosphate, glycerate-3-phosphate, phosphoenolpyruvate, 6-phosphogluconate, succinate, malate, citrate, and pyruvate are quantitatively measured with this method. Data is processed with MassLynx 4.1 software. Internal calibration curves were calculated based on response of ^{12}C analyte and ^{13}C labelled analogue.

Fatty acids analyses

Sample Preparation

Fifty micro liters of the lipid extract sample was taken and dried under the constant flow of nitrogen gas. Seven hundred micro liters of petroleum ether, 250 µL of 0.5 M sodium methoxide (NaOMe) in dry methanol and few anti-bumping granules were added to the dried sample. After vortexing for 10 s, the sample was incubated in water bath at 45° C for 5 min. To this mixture, 500 µL of 15% NaHSO4 and 200 µL of petroleum ether were added. After briefly vortexing, the upper organic phase was separated by centrifugation at 10,000 rpm for 3 min at room temperature. The sample was taken in GC vial and dried under the constant flow of nitrogen gas. Fifty micro liters of hexane

solvent was added to the dried sample and vortexed for few seconds. The sample was taken into micro insert and sealed the GC vials with air-tight caps.

Fatty acid analyses by GC-FID

GC was carried out using a HP 5890 GC-FID System equipped with HP-FFAP (25 m × 0.32 mm x 0.52 μm) that was directly connected to a FID detector (Agilent Technologies, Waldbronn, Deutschland). The injection volume was 2 μL at a carrier gas flow rate of 1.34 ml/min helium. The temperature gradient was 70° C for 1 min, 7° C/min up to 240° C. Further operation temperatures were 260° C (inlet), 300° C (detector). The obtained GC chromatograms were processed i.e., integration, base line correction etc using software. The relative percentage of fatty acids was calculated for each sample.

NOTE: Lipidomics raw data, concentrations of quantified lipids, primary metabolites, and relative % abundances of fatty acids are provided as an additional supplementary file: GopalacharyuluEtAl_DynamicModuleTopology_Supplement.xls

References

1. Katajamaa M, Miettinen J, Oresic M (2006) MZmine: toolbox for processing and visualization of mass spectrometry based molecular profile data. Bioinformatics 22: 634-636.
2. Yetukuri L, Katajamaa M, Medina-Gomez G, Seppanen-Laakso T, Vidal-Puig A, et al. (2007) Bioinformatics strategies for lipidomics analysis: characterization of obesity related hepatic steatosis. BMC Syst Biol 1: 12.
3. van Dam JC, Eman MR, Frank J, Lange HC, van Dedem GWK, et al. (2002) Analysis of glycolytic intermediates in Saccharomyces cerevisiae using anion exchange chromatography and electrospray ionization with tandem mass spectrometric detection. Anal Chim Acta 460: 209-218.

Text S1. Supplementary results

Network reconstruction

Initially, integrated network was constructed from the interaction databases. The network contained 6433 protein nodes, 401 metabolite nodes, 6104 gene nodes, 707 transcription factor binding site nodes, 17992 protein-protein interaction edges, 2648 metabolic reaction edges, 736 transcription factor binding edges, 518 gene regulation edges, and 12036 'gene encodes protein' edges, and 93 edges representing mutual interactions between transcription factors. Table 1 of the paper provides similar statistics for the networks used in the analysis i.e. reference and condition networks.

Dynamic changes in modules

Dynamic changes in modules are visualized in terms of changes in clustering coefficients in Fig. 2 of the paper. Visualization of the module networks along the time points may offer concrete understanding of module changes to a biologist. Here, we present the network images for some modules (Figure S2). For this illustration, we selected one module from each category (i.e. each subfigure in Fig. 2 of the main paper), because showing all the networks would need large space.

Multiple comparisons and confounding effects

In order to account for the multiple comparisons we corrected the raw p values by applying Bonferroni correction. Bonferroni correction is too conservative in general, therefore we calculated False Discovery Rate (FDR) q values. We checked the distributions of these p values and q values (Figure S1). We see from the histograms that p value distribution is non-uniform, which might suggest a confounding effect (although it may also be non-uniform due to true positives or due to dependencies). And, the biological validation part of the paper suggests that there is indeed a biological reason for this.

Hubs

In a network, nodes with very high degrees (much larger than average degree) are called "hubs". We identified the hubs and central nodes as explained in the *Data and Methods* section. An mRNA binding protein, JSN1/PUF1 (Uniprot: P47135), stood out as the hub in all the networks except for 40 min and 100 min networks.

In each network, we selected top 20 proteins in terms of total degree (i.e. sum of in and out degrees) for study. In the following discussion, top 20 hubs are simply called hubs and total degree is called degree. The hub proteins in the reference network had degrees ranging from 167-500 (while the average degree of all nodes in the network was 18), whereas hubs in the condition networks had their degrees in the range of 68-312. Some of the important hub proteins are discussed below:

- P47135 (JSN1/PUF1), an mRNA binding protein, showed highest degree and was present in all the networks except at 40 and 100 min.
- P29295 (HRR25) is a casein kinase I, which phosphorylates RNA polymerases, transcription factors, topoisomerases I and II, and non-histone chromatin proteins. This was not among the hubs in the reference network and from 10 to 60 min networks, but was a hub from 80 to 160 min networks. It is post-translational regulator of DNA metabolism and is also involved in regulating different mechanisms including vesicular trafficking, gene expression, and DNA repair and chromosome segregation. This might indicate that in order to face the oxidative stress insult the degree of this protein was increasing with respect to the stress condition.
- P39743 (RVS167) is a reduced viability upon starvation protein; involved in cytoskeletal reorganization in response to environmental stresses. This protein was not among the hubs

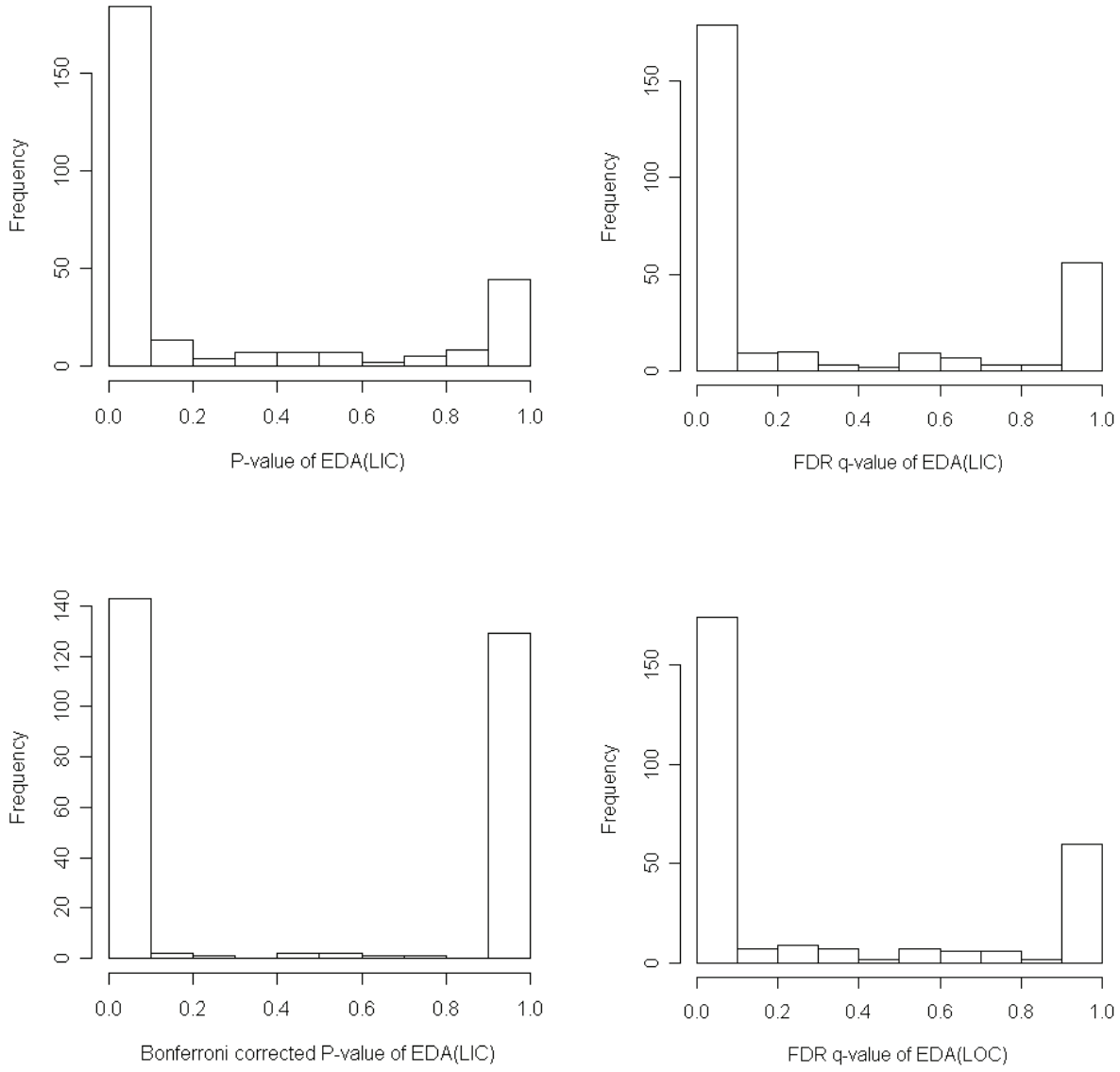
in reference network, but was a hub at 10, 20, 30 and 50 minutes. This suggests that this protein might be required during initial phase of stress condition in order to face the oxidative stress.

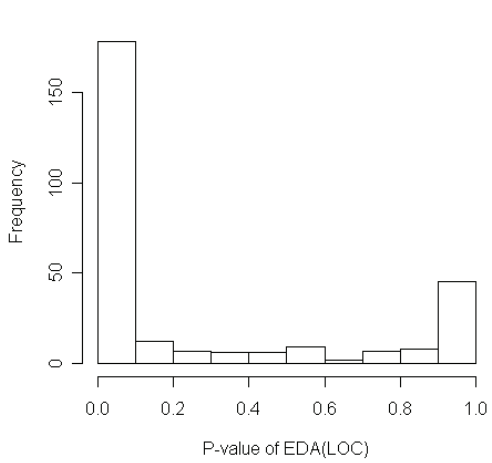
- P06787 (CMD1) - Calmodulin - is a calcium binding protein that regulates both calcium dependent (stress-activated pathways) and calcium independent (mitosis, bud growth, actin organization, endocytosis, etc) processes. This protein was a hub at 10, 20, and 100 minutes and was not among hubs in other networks.
- P38286 (IFA38), which has microsomal beta-keto-reductase activity (fatty acid elongation), was present in the reference network but absent in all the condition networks.

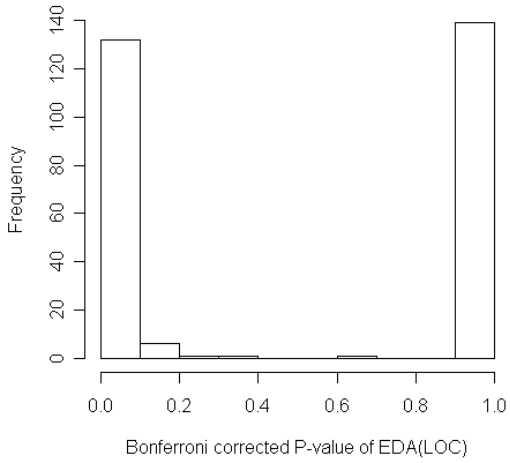
Most of the reference network hub proteins were absent in 40 and 100 min networks. Interestingly in these networks, most of the hubs were subunits of DNA directed RNA polymerases I, II and III, which are involved in transcription and ribosome biogenesis. In particular, Rpb9 protein is involved in response to DNA damage stimulus and Rpa1 is involved in double strand break repair, nucleotide excision repair, post replication repair and DNA recombination. This means that at these time points, degree of most of the RNA polymerases were increased in response to the stress condition. This indicates some specific changes at 40 and 100 min time points.

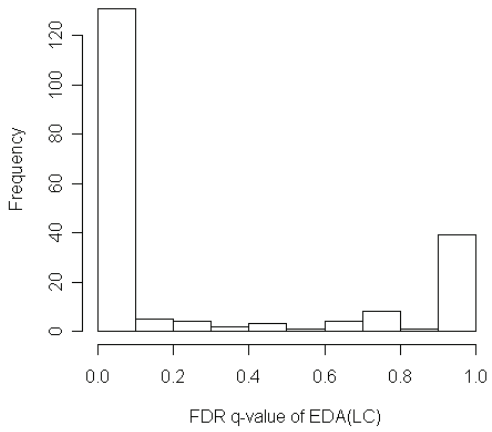
Supplementary figures and tables

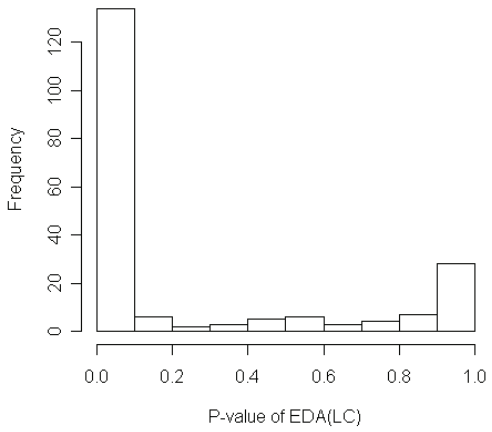
Figure S1. Histograms of raw *p* values, corrected (Bonferroni) *p* values and FDR *q* values. The distributions are not uniform. QQ plot is also used to see the difference between a theoretical uniform distribution and the *p* value distribution as an example.

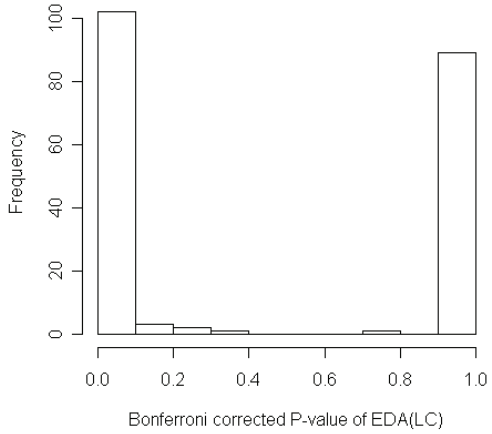



Frequency
0
50
100
150
0.0
0.2
0.4
0.6
0.8
1.0
P-value of EDA(LOC)


Frequency
0
20
40
60
80
100
120
140
0.0
0.2
0.4
0.6
0.8
1.0
Bonferroni corrected P-value of EDA(LOC)


Frequency
0
20
40
60
80
100
120
0.0
0.2
0.4
0.6
0.8
1.0
FDR q-value of EDA(LC)


Frequency
0
20
40
60
80
100
120
0.0
0.2
0.4
0.6
0.8
1.0
P-value of EDA(LC)


Frequency
0
20
40
60
80
100
0.0
0.2
0.4
0.6
0.8
1.0
Bonferroni corrected P-value of EDA(LC)

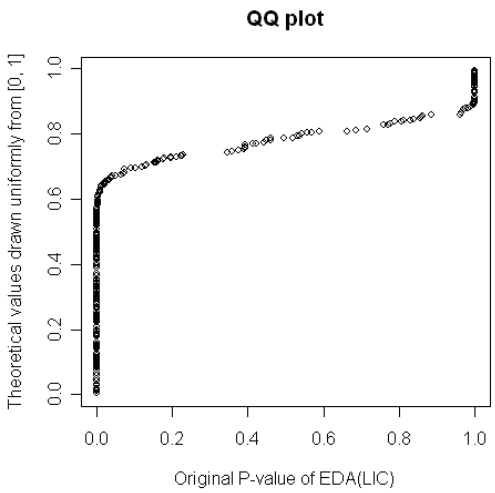
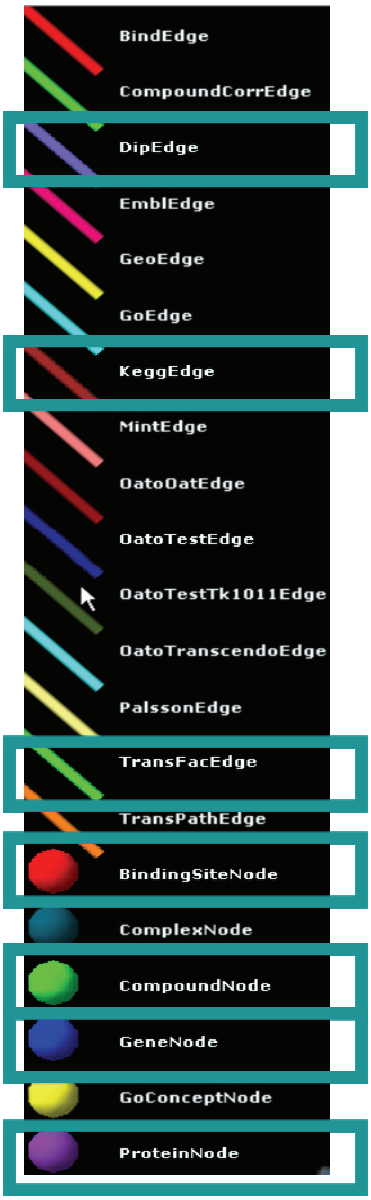
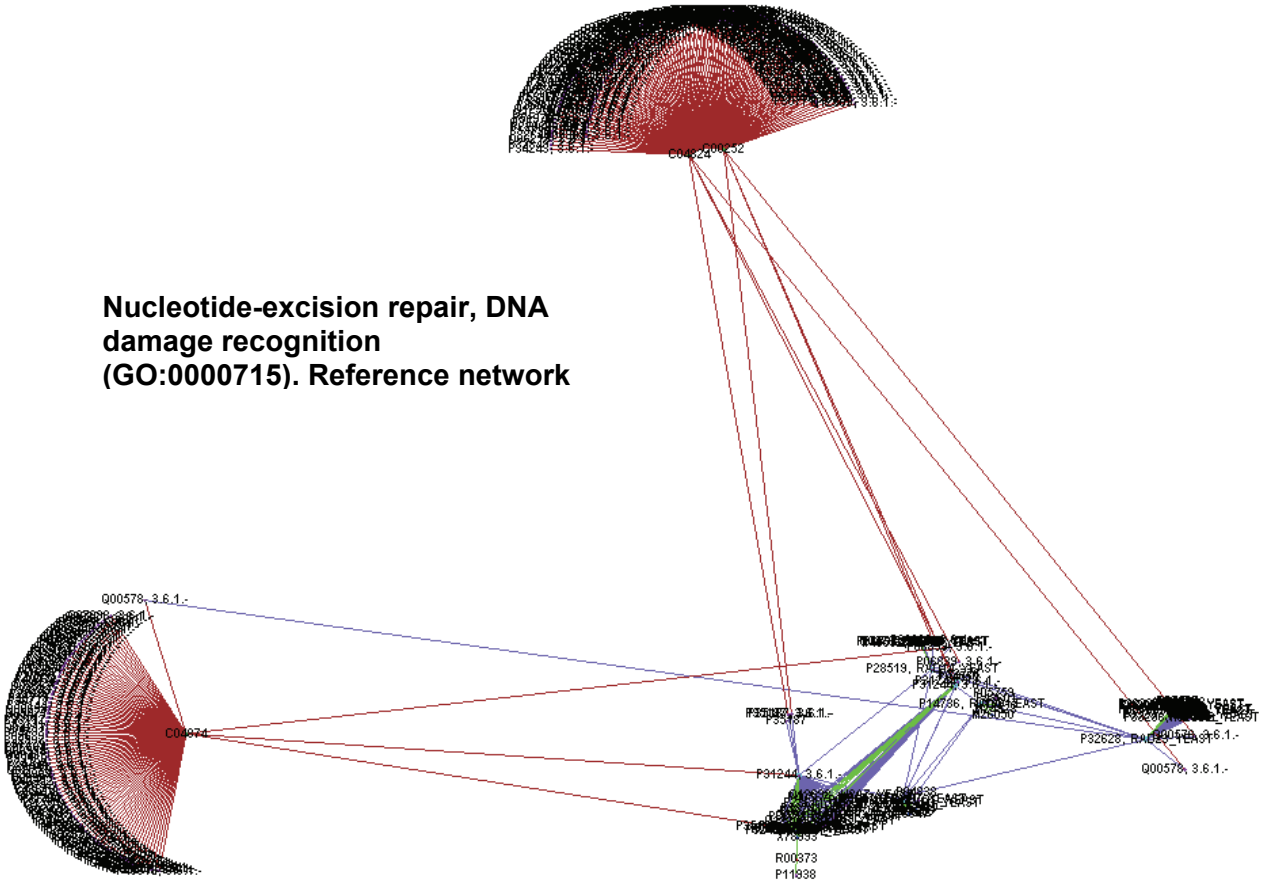

QQ plot
Theoretical values drawn uniformly from [0, 1]
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.2
0.4
0.6
0.8
1.0
Original P-value of EDA(LIC)

Figure S2. Networks of selected modules along the different time points of the oxidative stress. This provides the network view of the dynamic changes of the modules. Dynamic changes of 4 selected modules, one from each category from Fig. 2 of the manuscript, are presented here. First picture gives the *megNet* legend (color codes for edges and nodes) for the subsequent network images. In the legend the edge types and node types relevant for the current networks are highlighted.

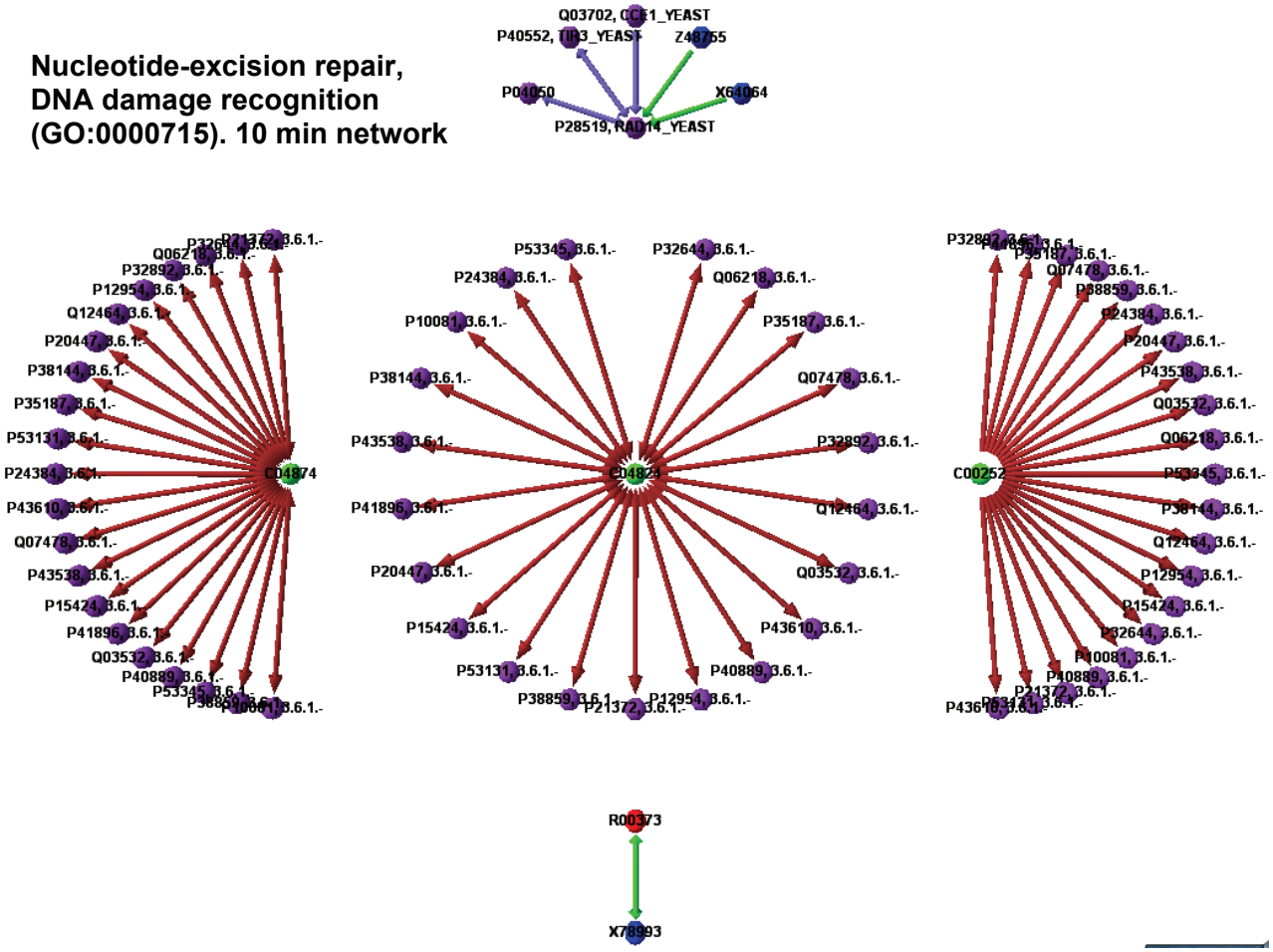


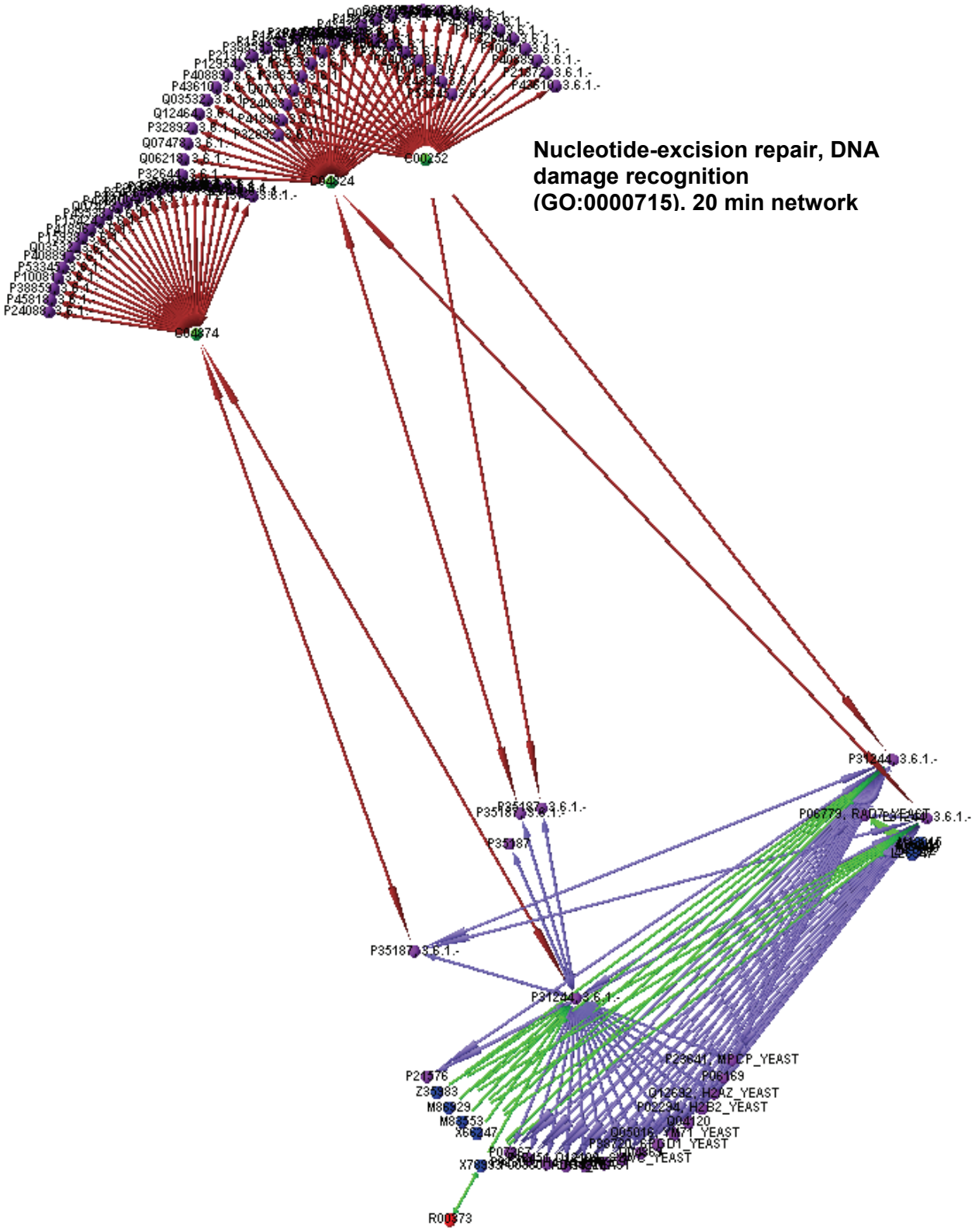
Legend for the networks.

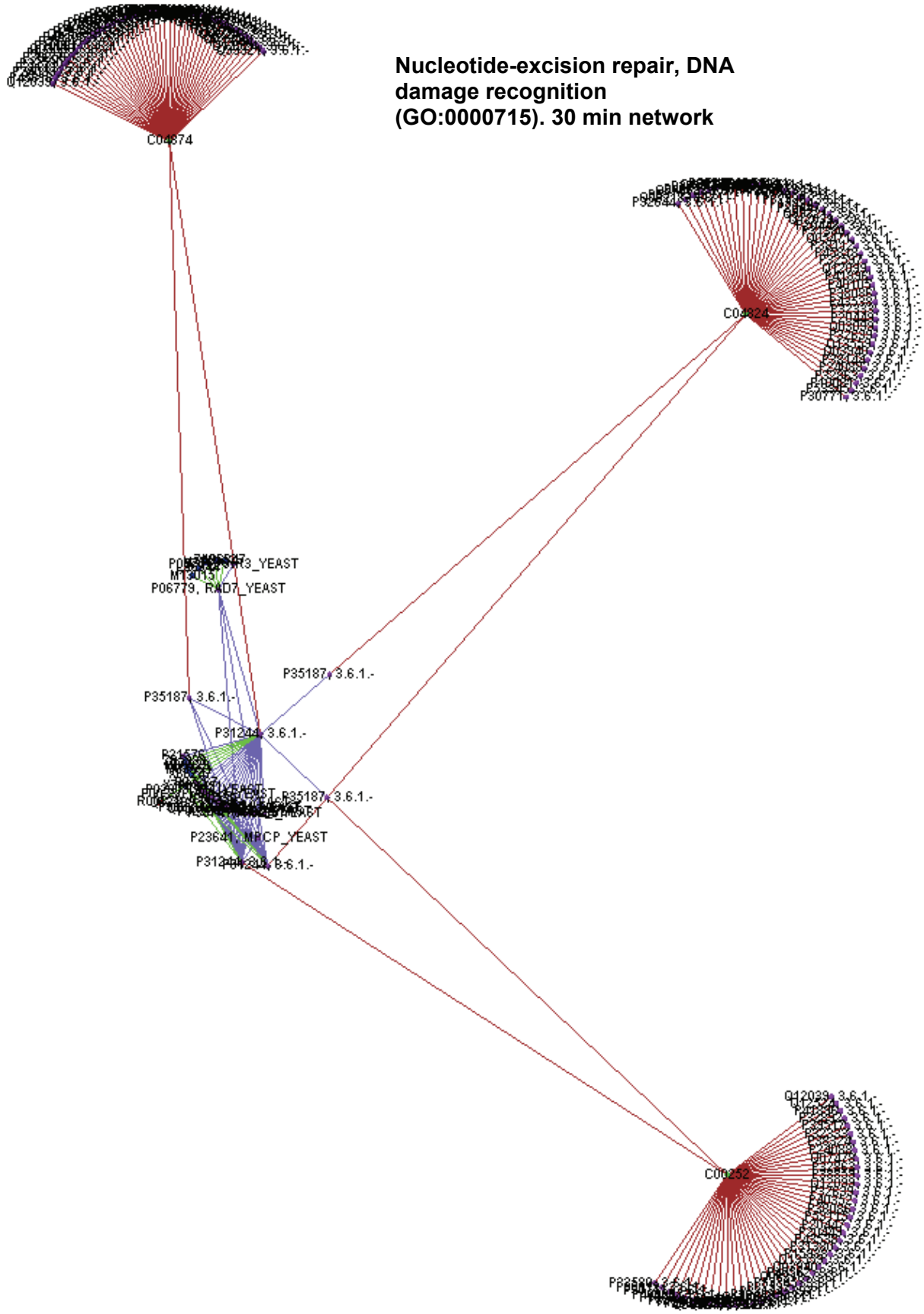
Nucleotide-excision repair, DNA damage recognition (GO:0000715). Reference network



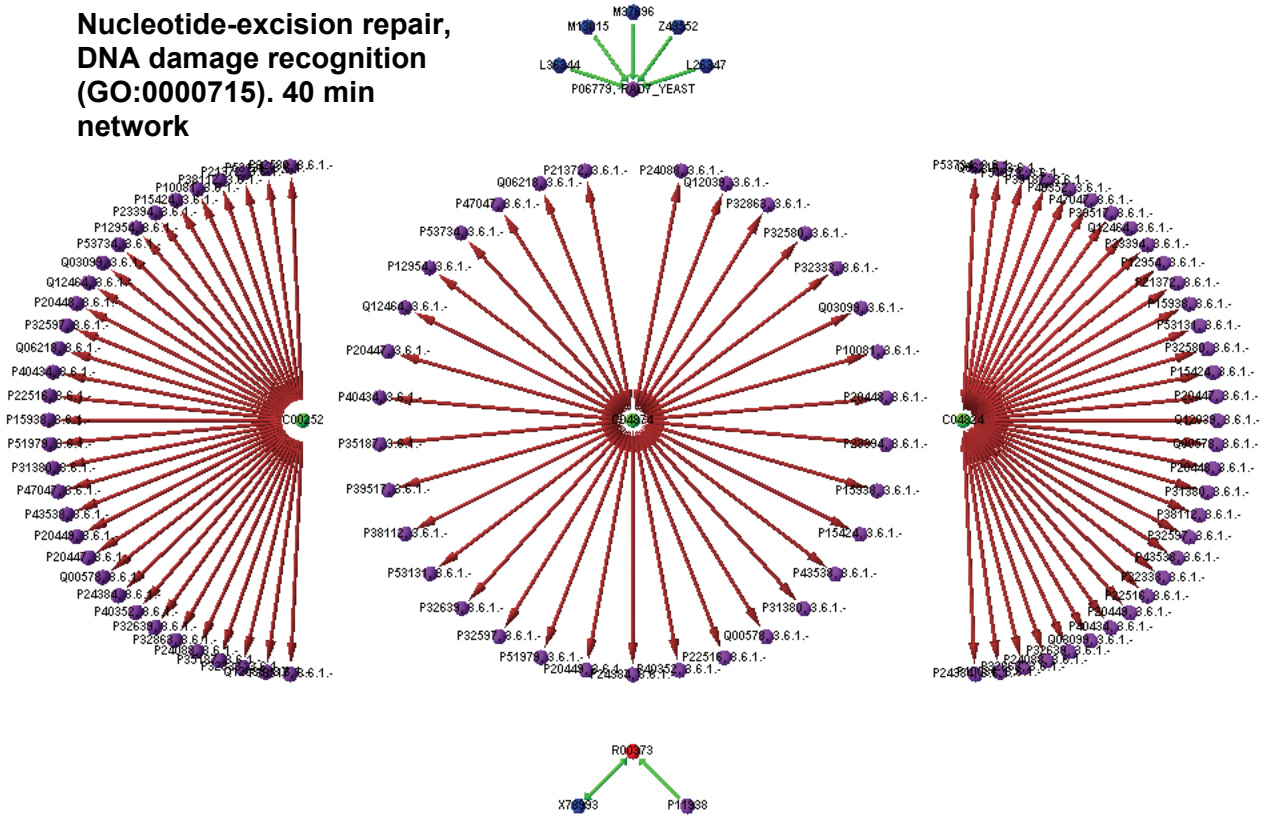
Nucleotide-excision repair, DNA damage recognition (GO:0000715). 10 min network



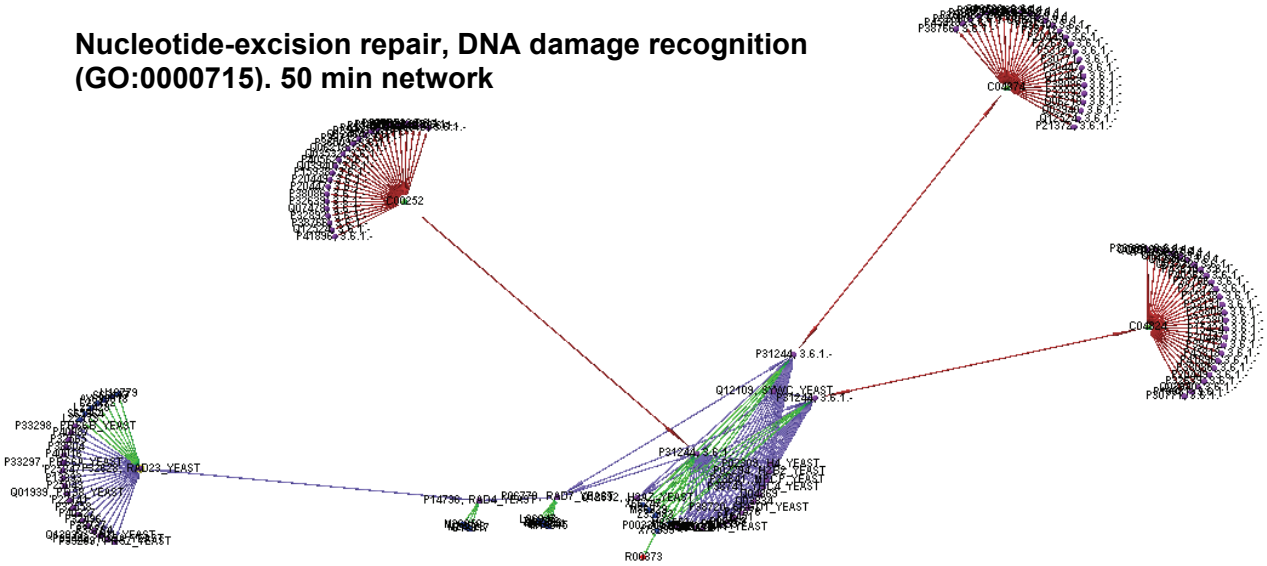

Nucleotide-excision repair, DNA damage recognition (GO:0000715). 20 min network
C00252
C04524
C04374
P31244, 3.6.1.-
P35187, 3.6.1.-
P35187
P06773, RAD7_YEAST
P23641, MPCP_YEAST
P06169
Q13682, H2AZ_YEAST
P02294, H2B2_YEAST
D04120
P21576
Z36083
M88929
M88553
R00373


Nucleotide-excision repair, DNA damage recognition (GO:0000715). 30 min network
C04874
C04824
C00252
P06779, RAD7_YEAST
P35187, 3.6.1.-
P31244, 3.6.1.-
P23641, MRCP_YEAST

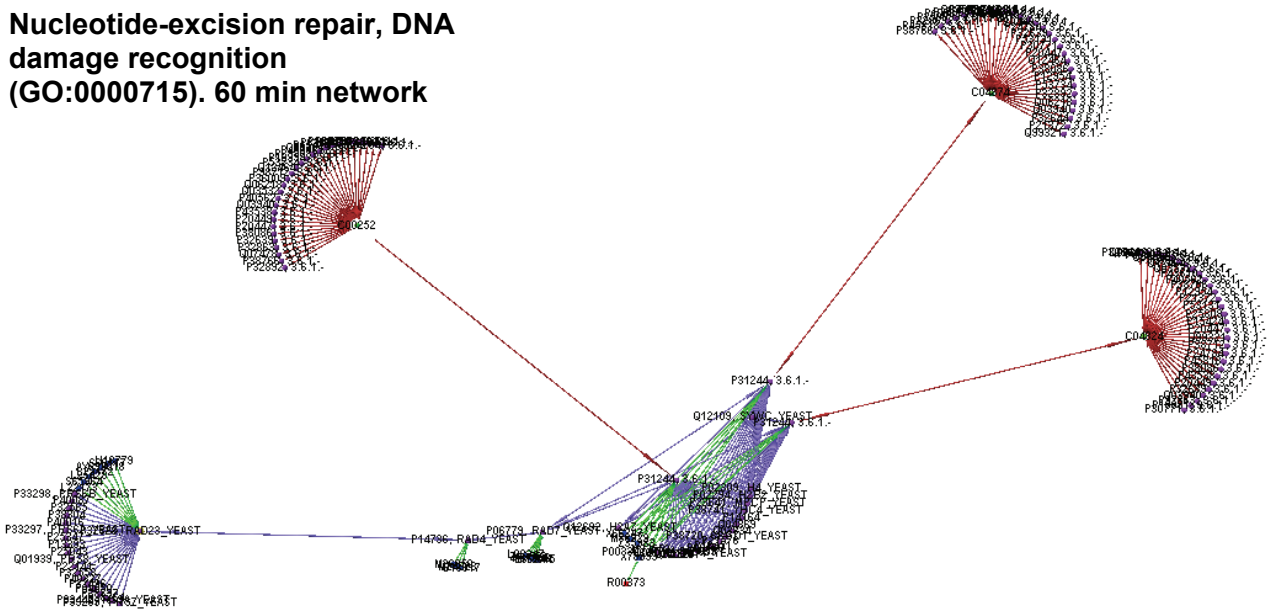
Nucleotide-excision repair, DNA damage recognition (GO:0000715). 40 min network

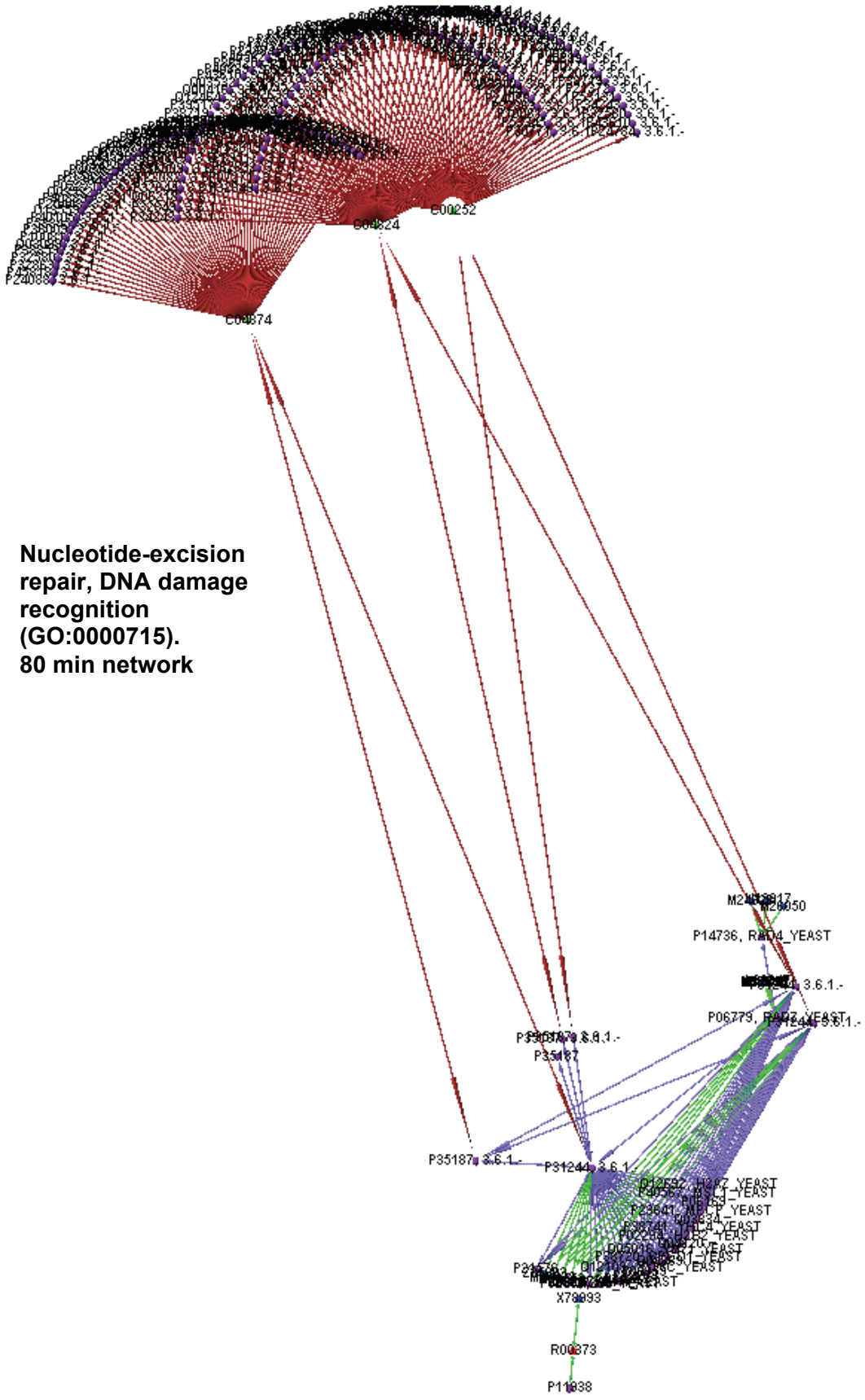


Nucleotide-excision repair, DNA damage recognition (GO:0000715). 50 min network



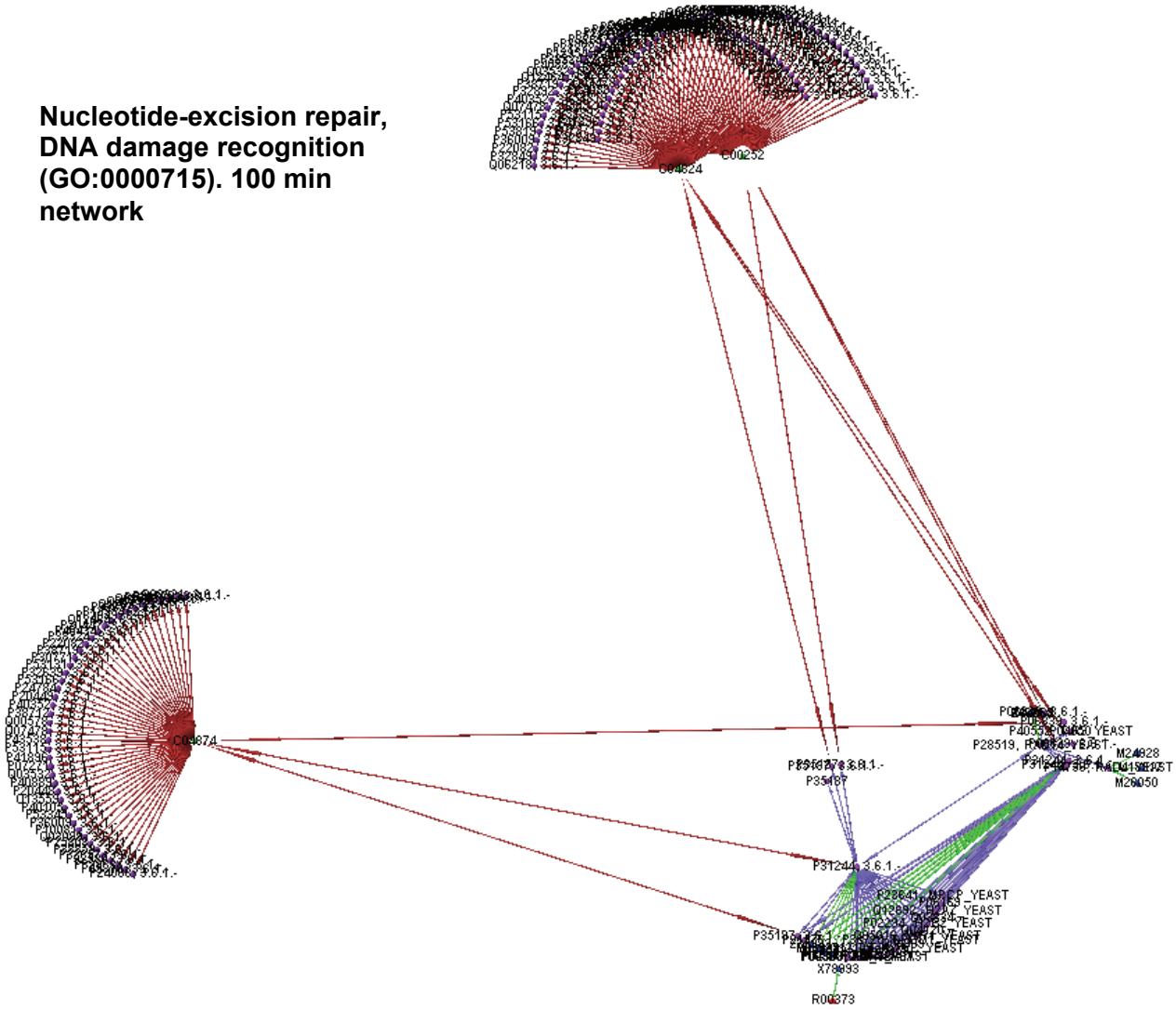
Nucleotide-excision repair, DNA damage recognition (GO:0000715). 60 min network



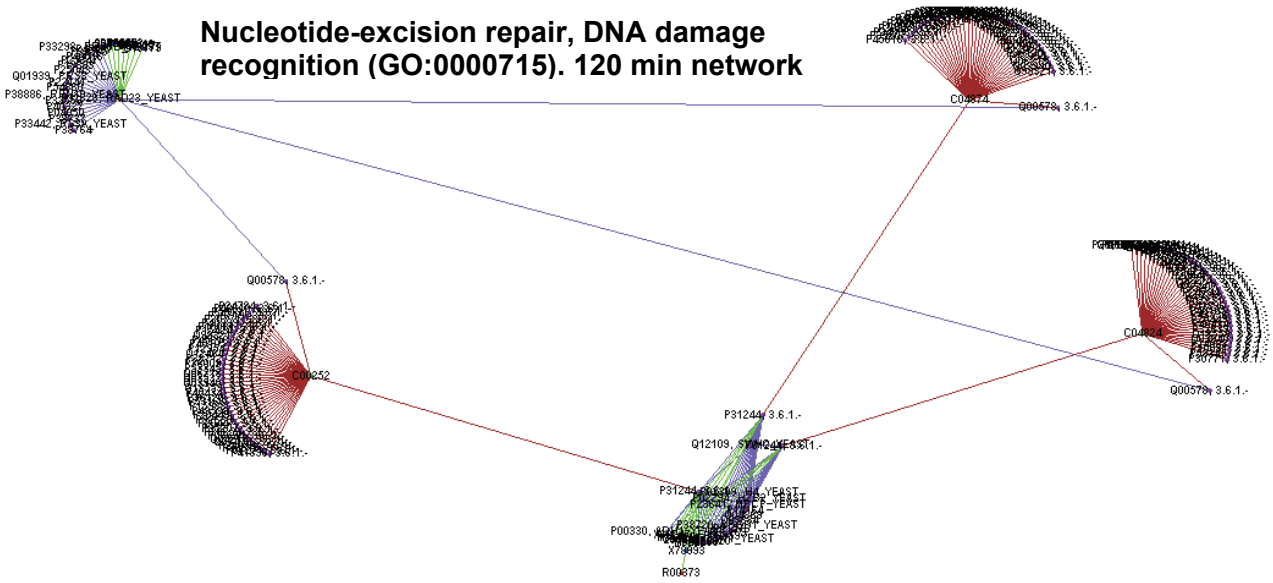


Nucleotide-excision repair, DNA damage recognition (GO:0000715). 80 min network

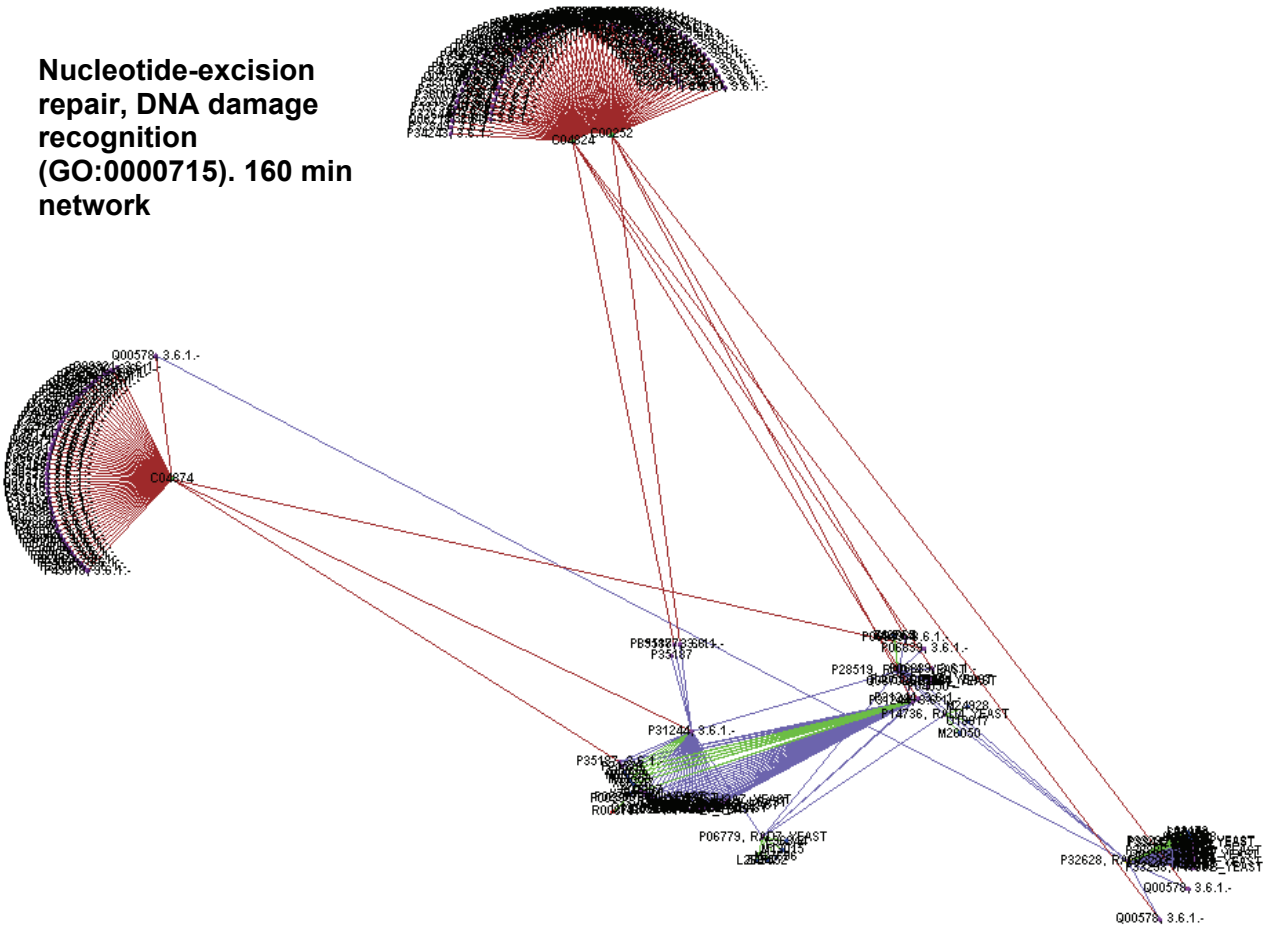
Nucleotide-excision repair, DNA damage recognition (GO:0000715). 100 min network



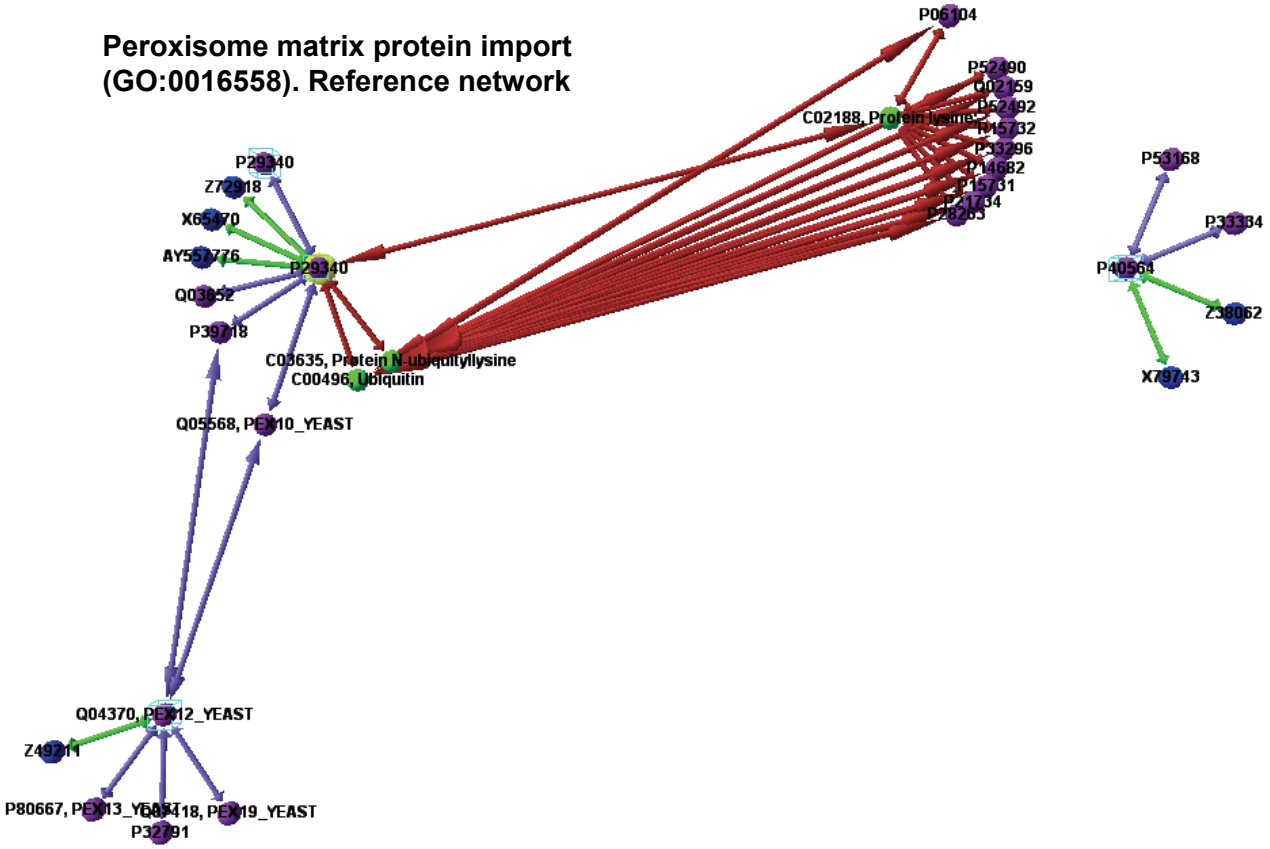
Nucleotide-excision repair, DNA damage recognition (GO:0000715). 120 min network



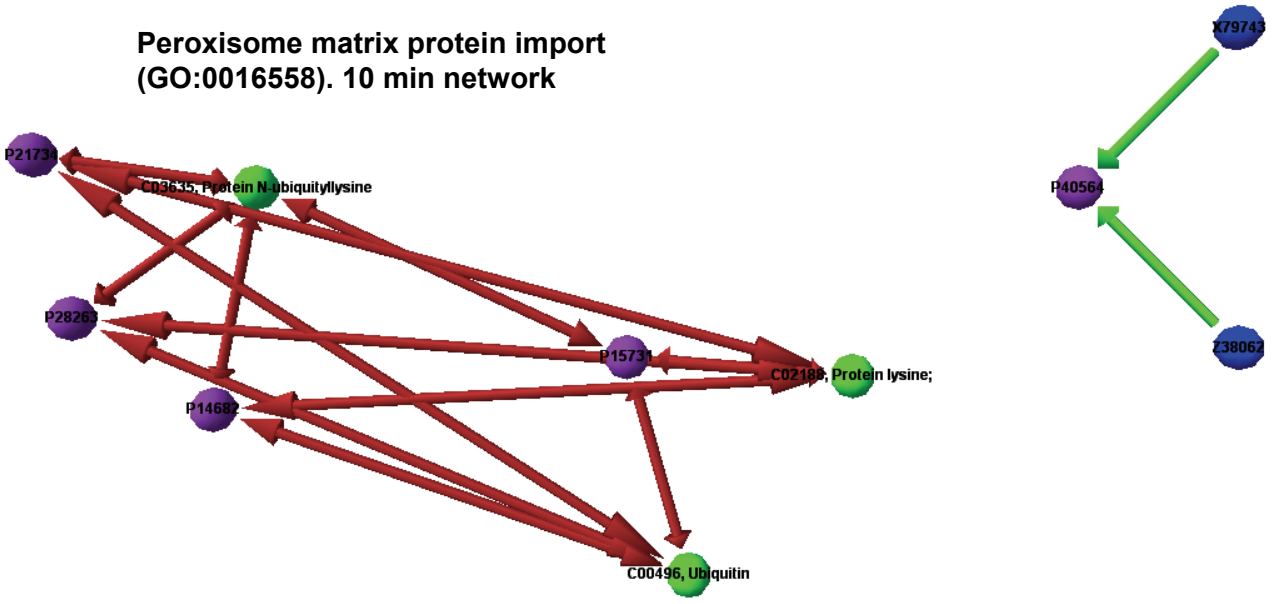
Nucleotide-excision repair, DNA damage recognition (GO:0000715). 160 min network

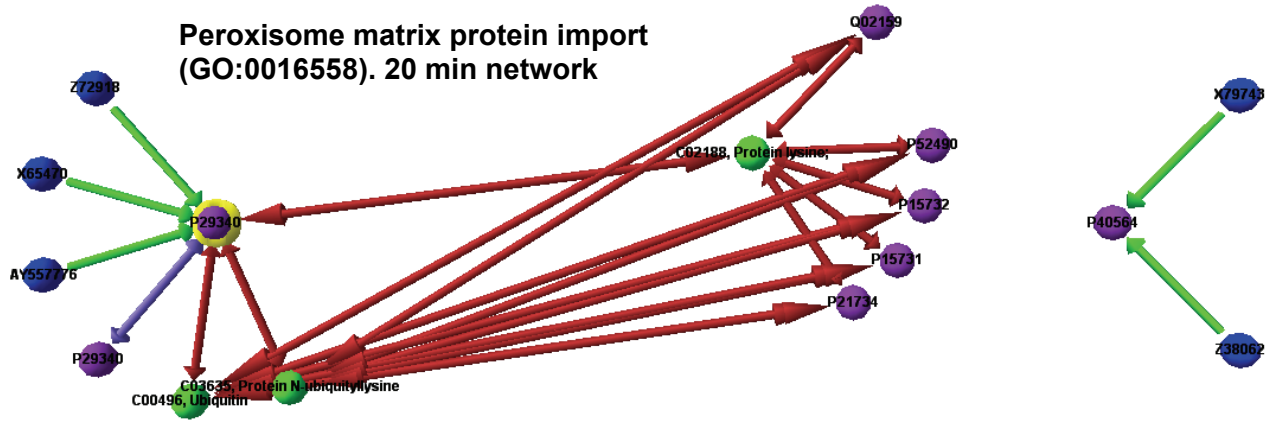


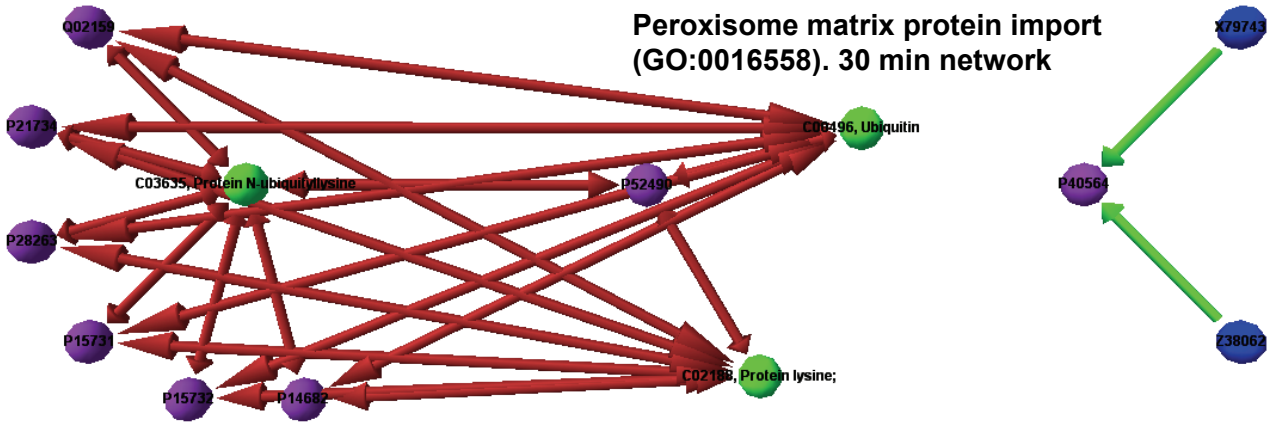
Peroxisome matrix protein import (GO:0016558). Reference network

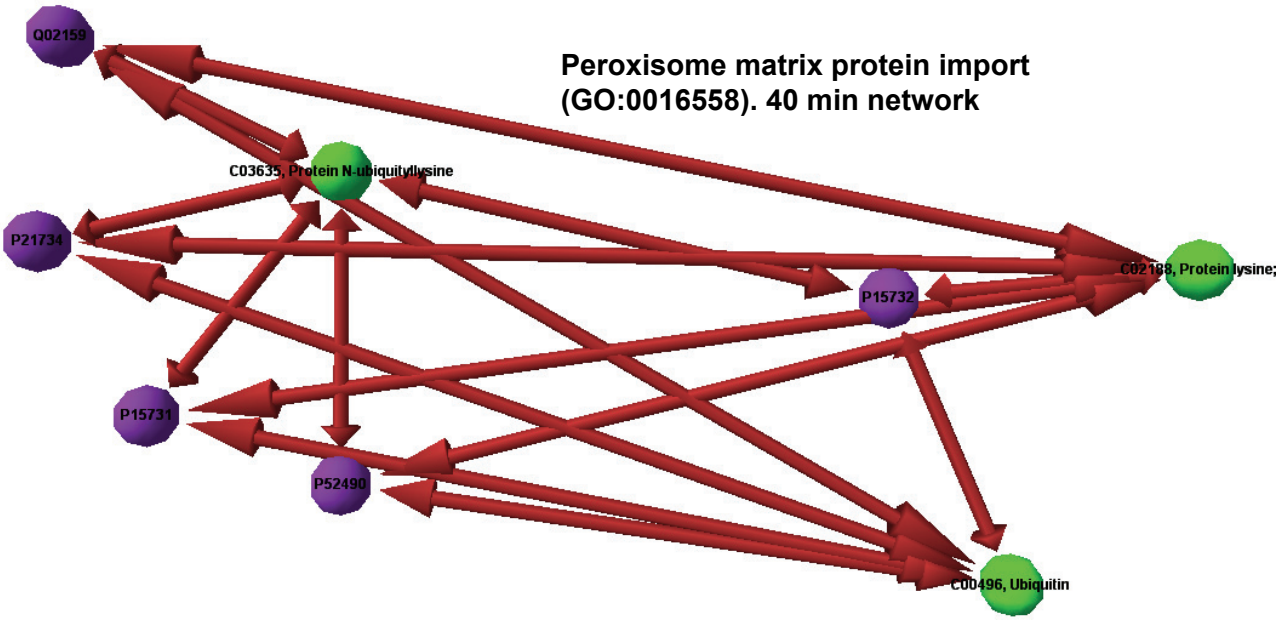


Peroxisome matrix protein import (GO:0016558). 10 min network




Peroxisome matrix protein import
(GO:0016558). 20 min network
Q02159
Z72918
X65470
P29340
AY557776
P29340
C03635, Protein N-ubiquitinyllysine
C00496, Ubiquitin
C02188, Protein lysine;
P52490
P15732
P15731
P21734
X79743
P40564
Z38062


Peroxisome matrix protein import
(GO:0016558). 30 min network
Q02159
P21734
C03635, Protein N-ubiquitinyllysine
P28263
P15731
P15732
P14682
C00496, Ubiquitin
P52490
C02188, Protein lysine;
X79743
P40564
Z38062


Peroxisome matrix protein import
(GO:0016558). 40 min network
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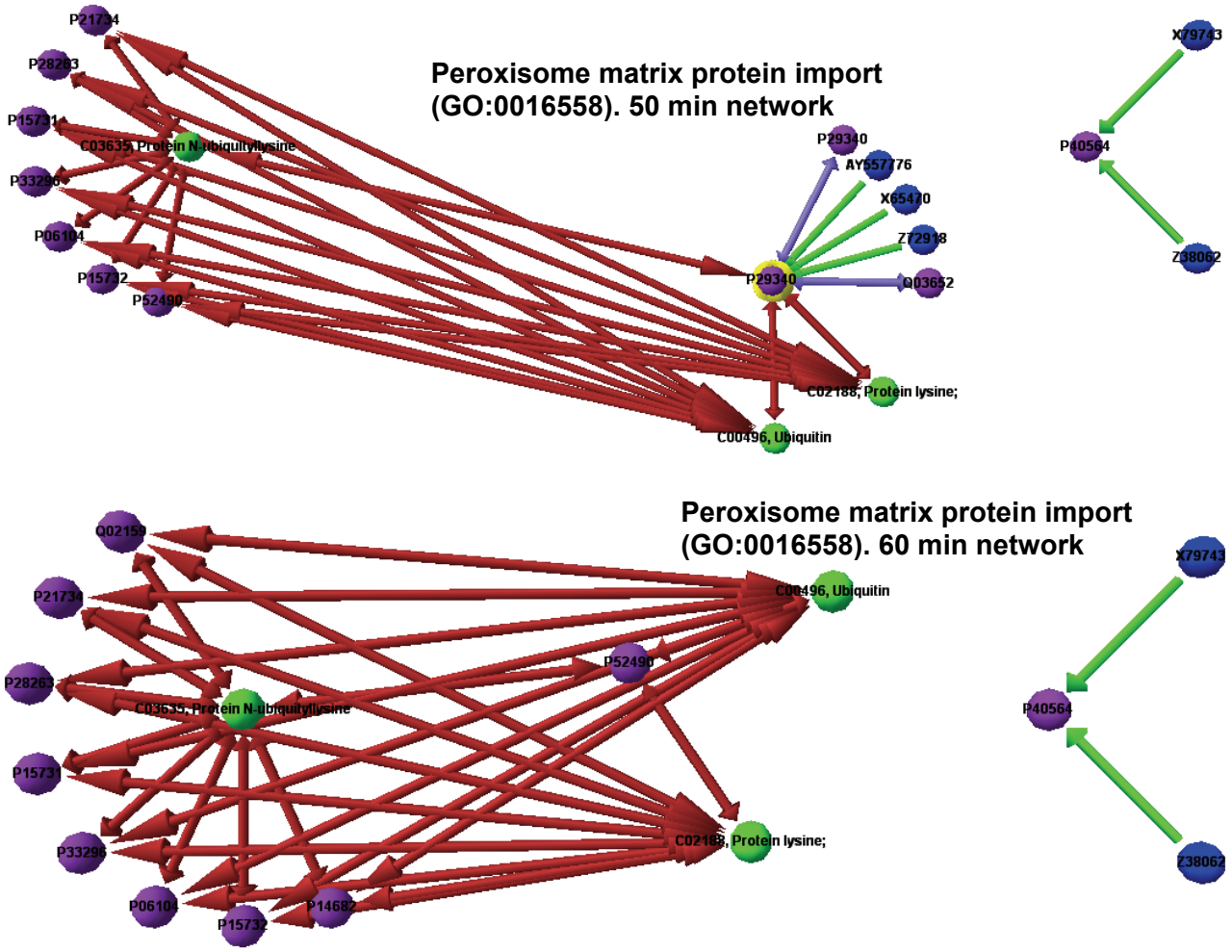
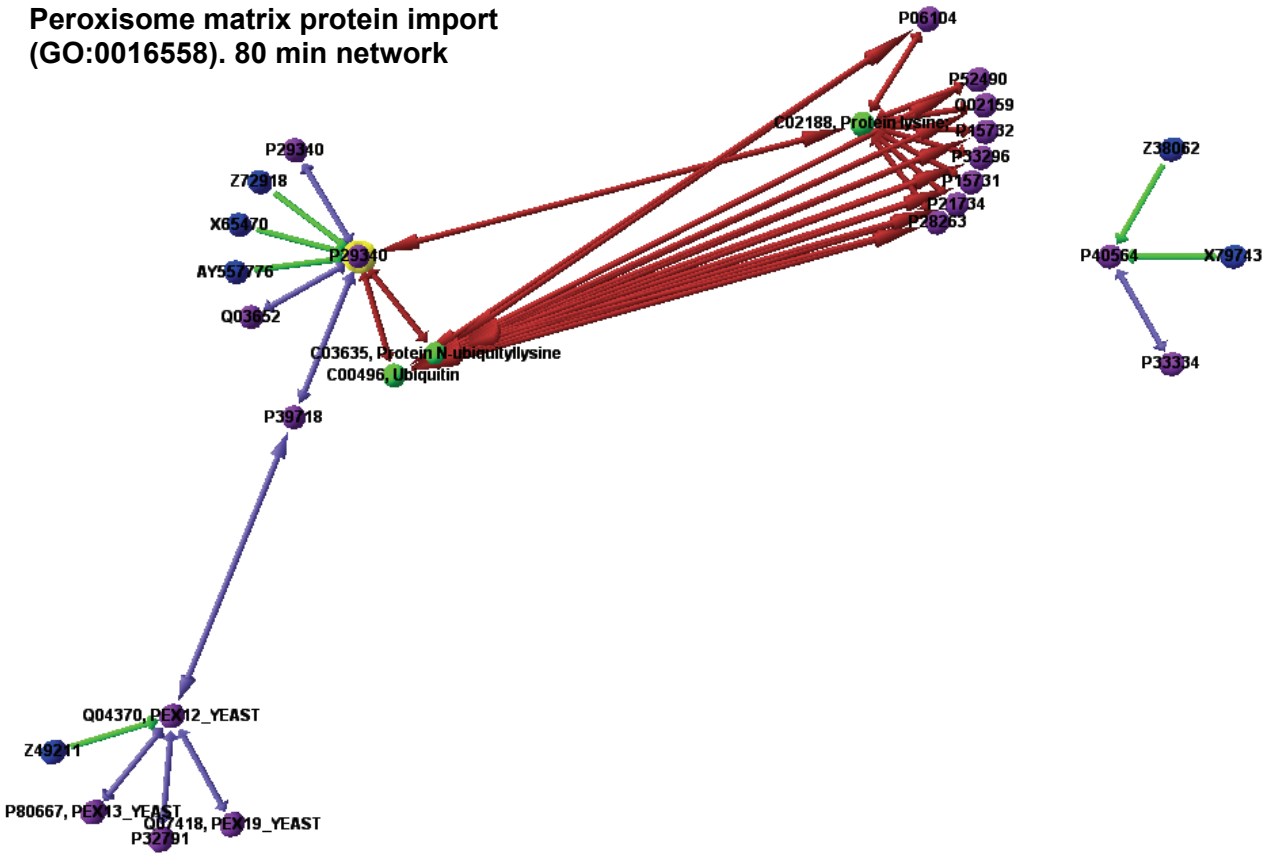
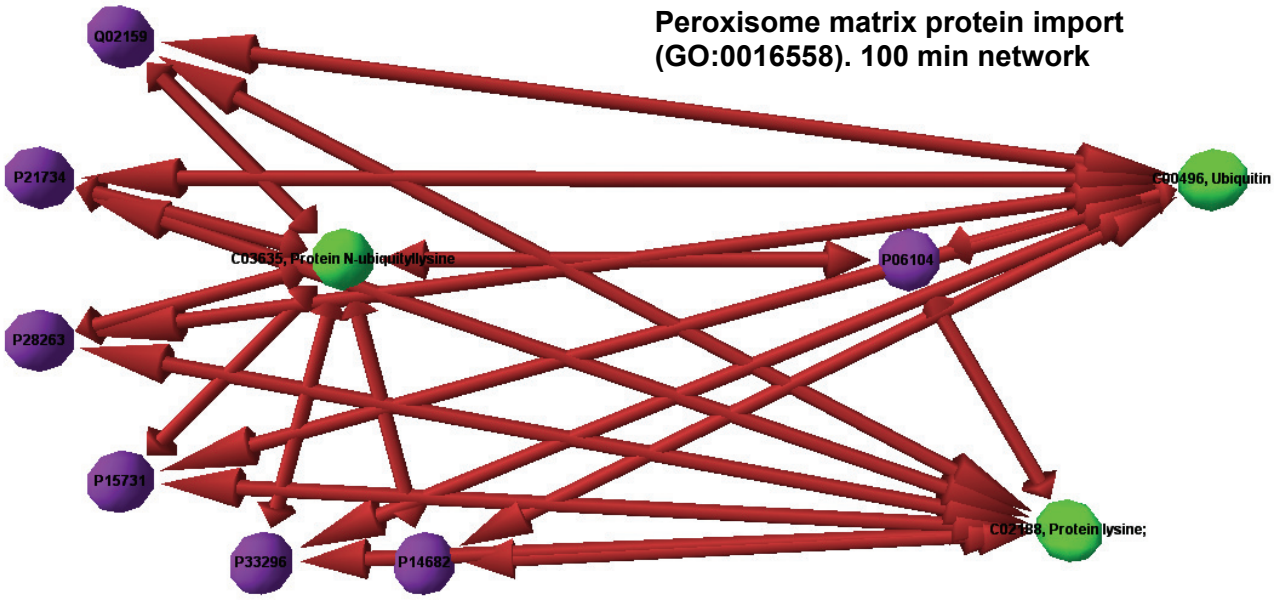
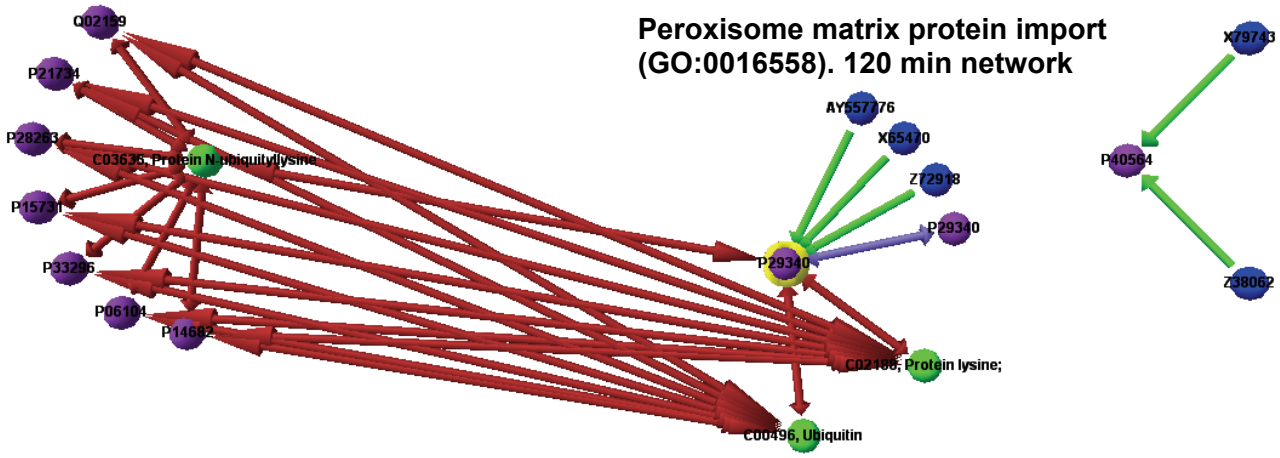
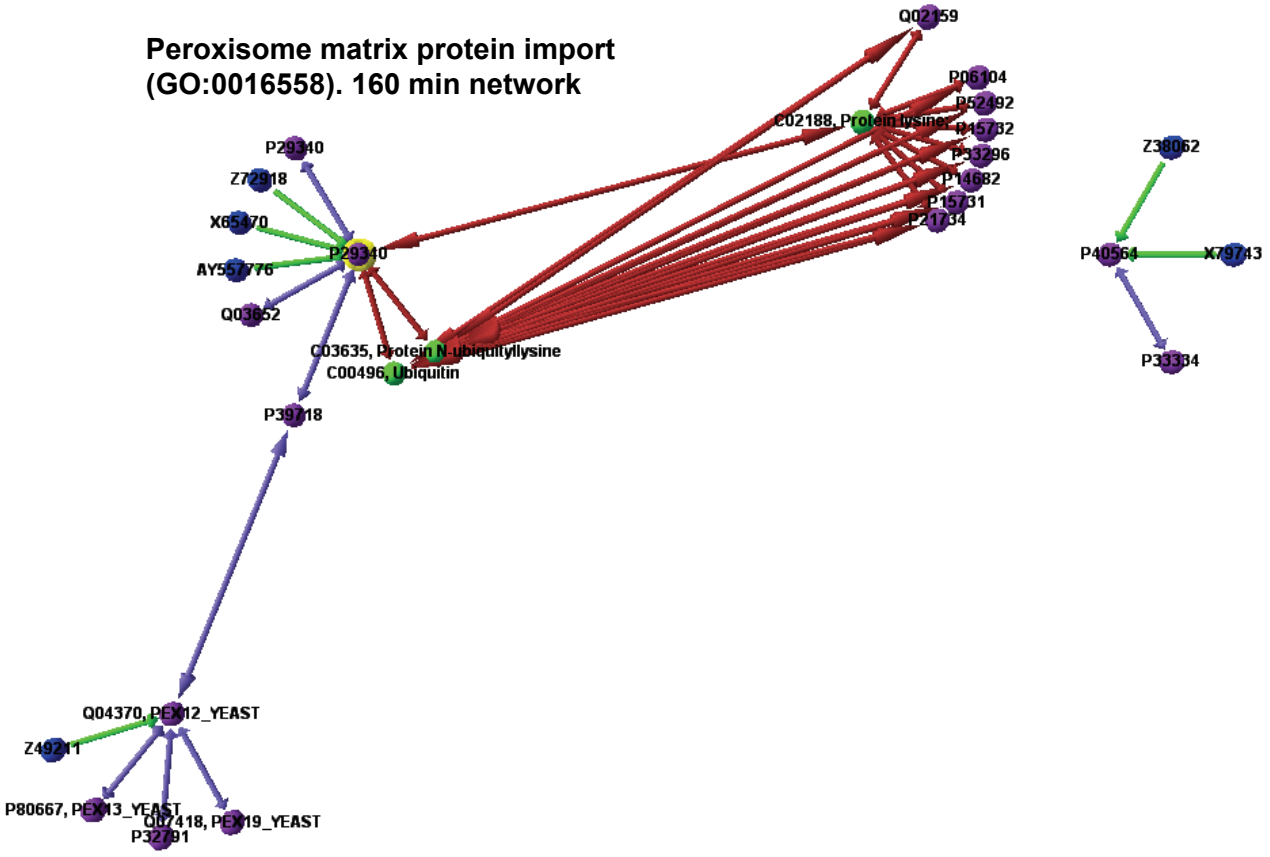
P21734
P15731
P52490
P15732
C02188, Protein lysine;
C00496, Ubiquitin

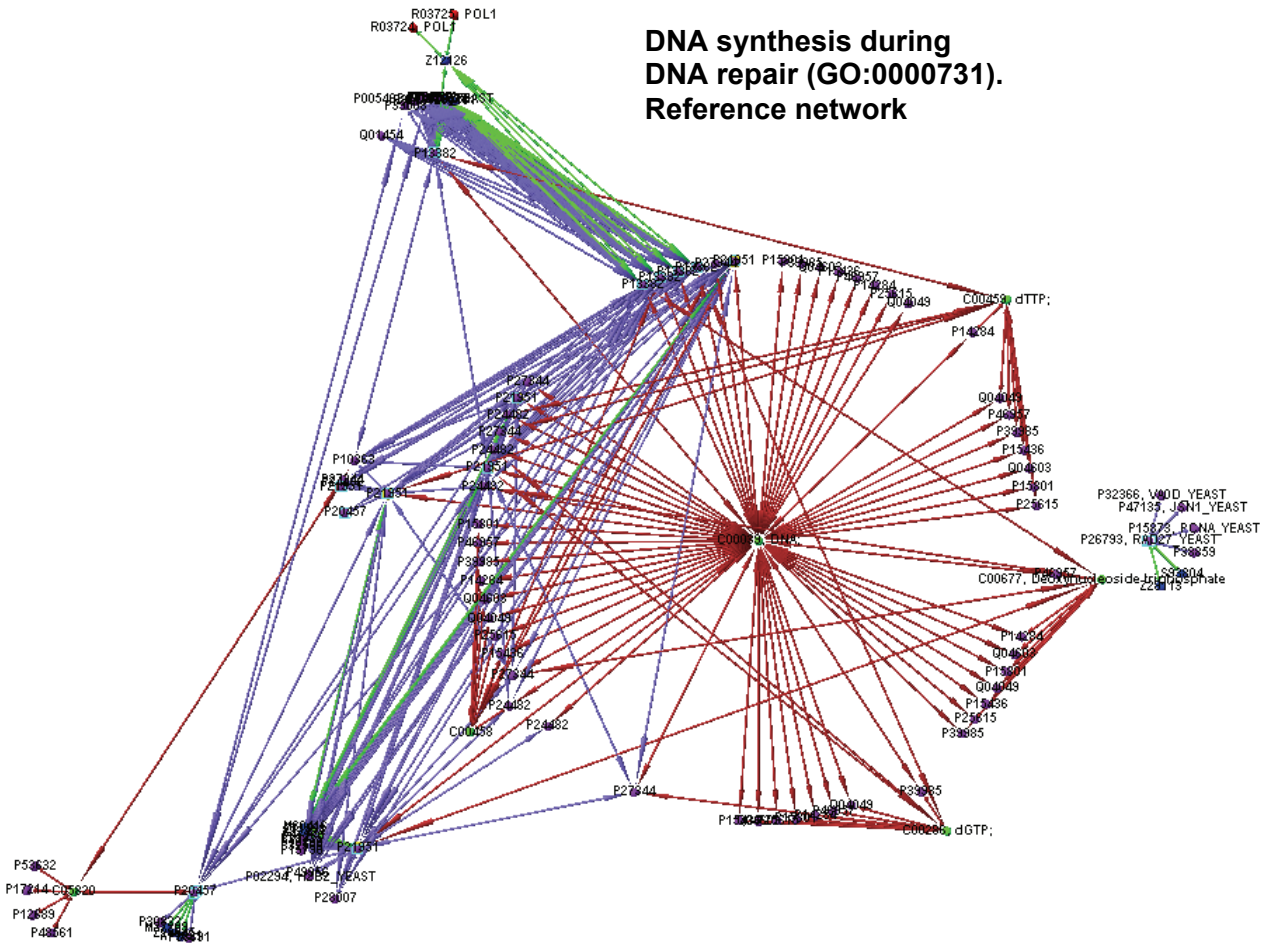

Peroxisome matrix protein import
(GO:0016558). 50 min network
P21734
P28263
P15731
C03635, Protein N-ubiquitinyllysine
P33298
P06104
P15732
P52490
P29340
AY557776
X65470
Z72918
Q03652
C02188, Protein lysine;
C00496, Ubiquitin
X79743
P40564
Z38062
Peroxisome matrix protein import
(GO:0016558). 60 min network
Q02159
P21734
P28263
C03635, Protein N-ubiquitinyllysine
P15731
P33298
P06104
P15732
P14682
P52490
C00496, Ubiquitin
C02188, Protein lysine;
X79743
P40564
Z38062

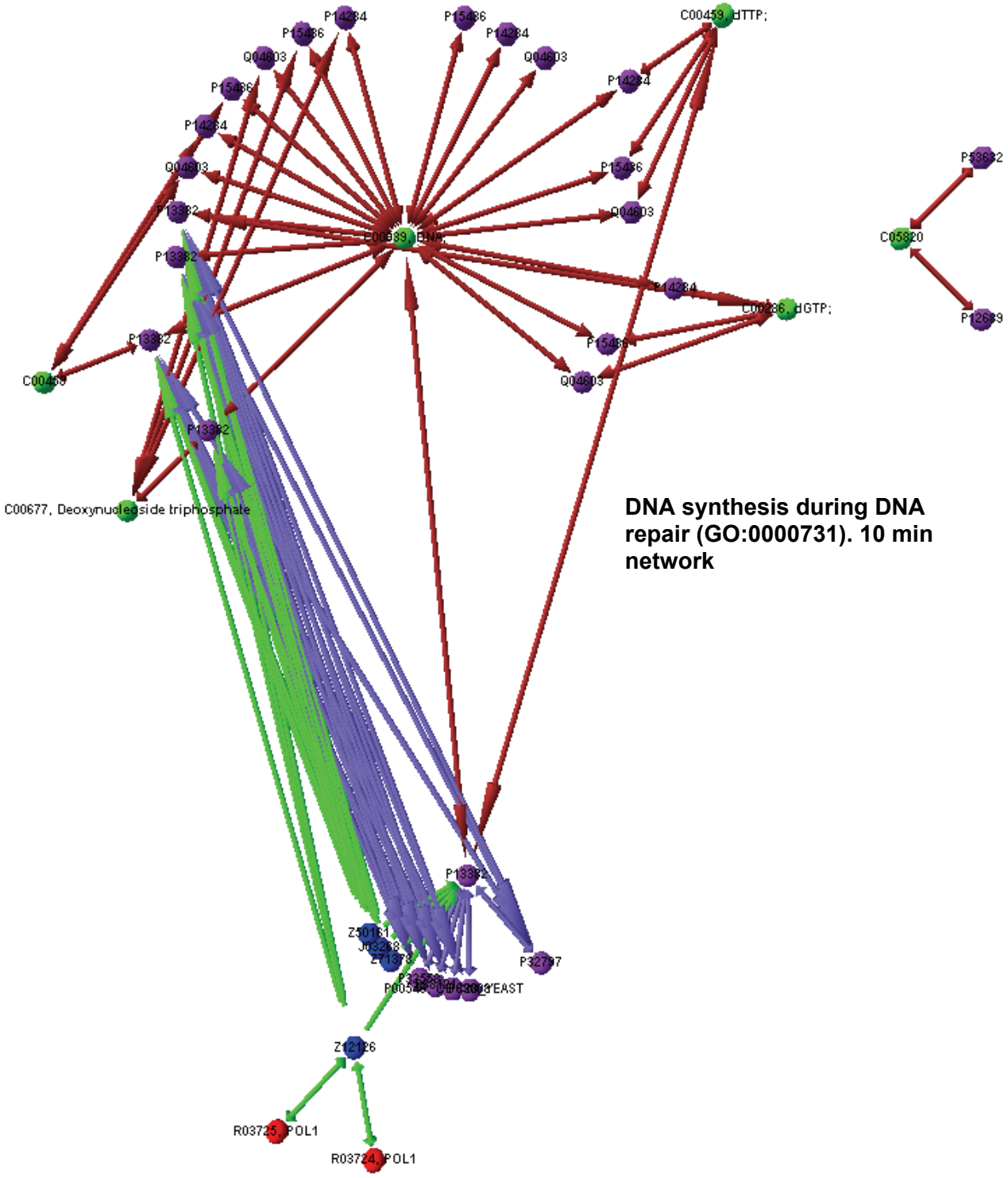

Peroxisome matrix protein import
(GO:0016558). 80 min network
P06104
P52490
Q02159
C02188, Protein lysine;
P15732
P33296
P15731
P21734
P28263
P29340
Z72818
X65470
AY557776
Q03652
P29340
C03635, Protein N-ubiquitinyllysine
C00496, Ubiquitin
P39718
Z38062
P40564
X79743
P33334
Q04370, PEX12_YEAST
Z49211
P80667, PEX13_YEAST
Q07418, PEX19_YEAST
P32791


Peroxisome matrix protein import
(GO:0016558). 100 min network
Q02159
P21734
C00496, Ubiquitin
C03635, Protein N-ubiquitinyllysine
P06104
P28263
P15731
C02188, Protein lysine;
P33296
P14682


Peroxisome matrix protein import
(GO:0016558). 120 min network
Q02159
P21734
P28263
C03635, Protein N-ubiquitinyllysine
P15731
P33296
P06104
P14682
AY557776
X65470
Z72918
P29340
P29340
C02188, Protein lysine;
C00496, Ubiquitin
X79743
P40564
Z38062


Peroxisome matrix protein import
(GO:0016558). 160 min network
Q02159
P06104
P52492
P15732
P33296
P14682
P15731
P21734
C02188, Protein lysine;
P29340
Z72918
X65470
AY557776
P29340
Q03652
C03635, Protein N-ubiquitinyllysine
C00496, Ubiquitin
P39718
Q04370, PEX12_YEAST
Z49241
P80667, PEX13_YEAST
Q07418, PEX19_YEAST
P32791
Z38062
P40564
X79743
P33334


DNA synthesis during
DNA repair (GO:0000731).
Reference network
R03725, POL1
R03724, POL1
Z12126
Q01454
P13882
C00459, dTTP;
P14284
P32366, VOD_YEAST
P47135, JEN1_YEAST
P15873, RONA_YEAST
P26793, RAD27_YEAST
P38859
C00677, Deoxyribonucleoside triphosphate
C00458
P27344
C00286, dGTP;
P53632
P17444, CDC20
P20457
P48061



DNA synthesis during DNA repair (GO:0000731). 10 min network

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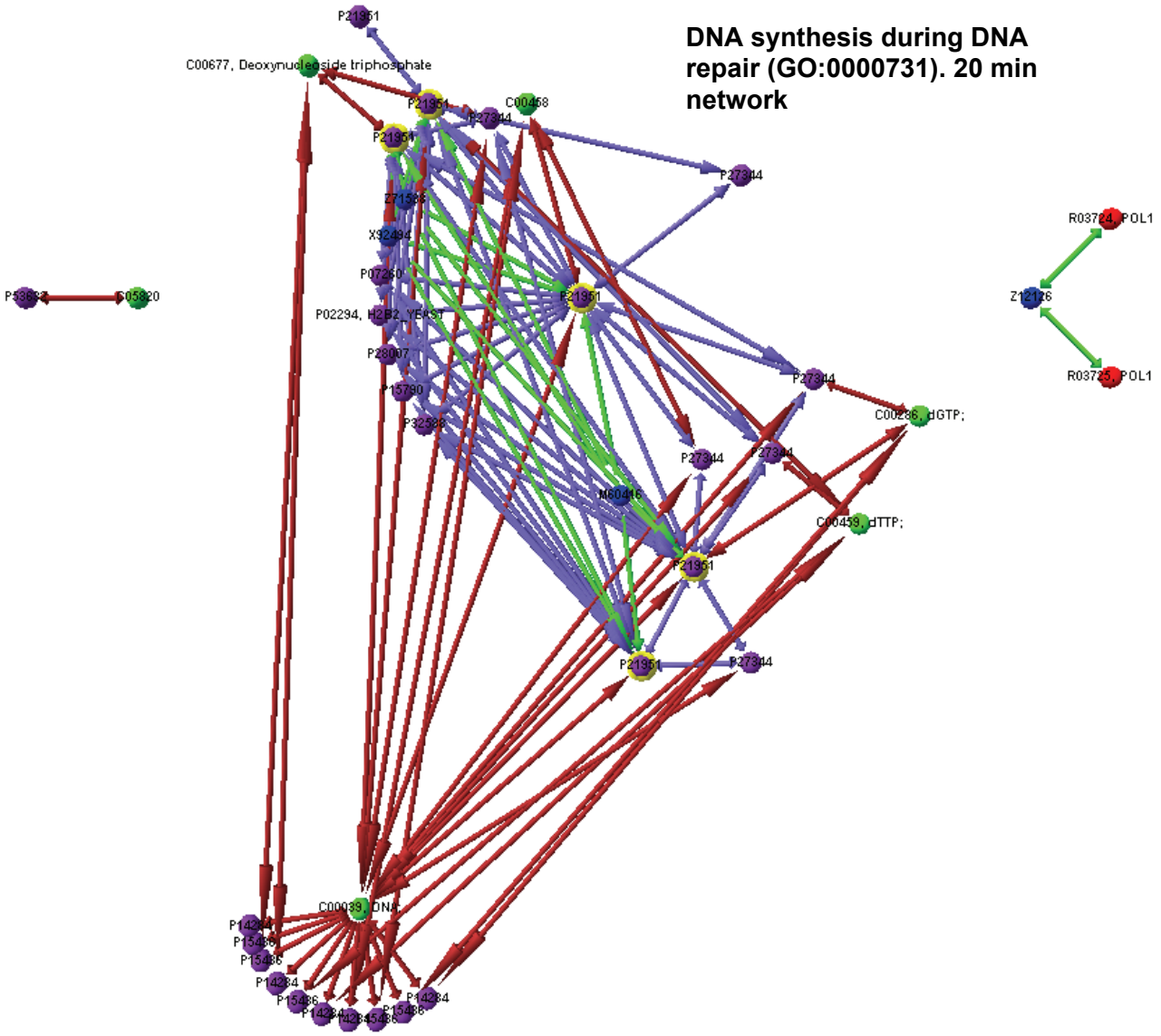
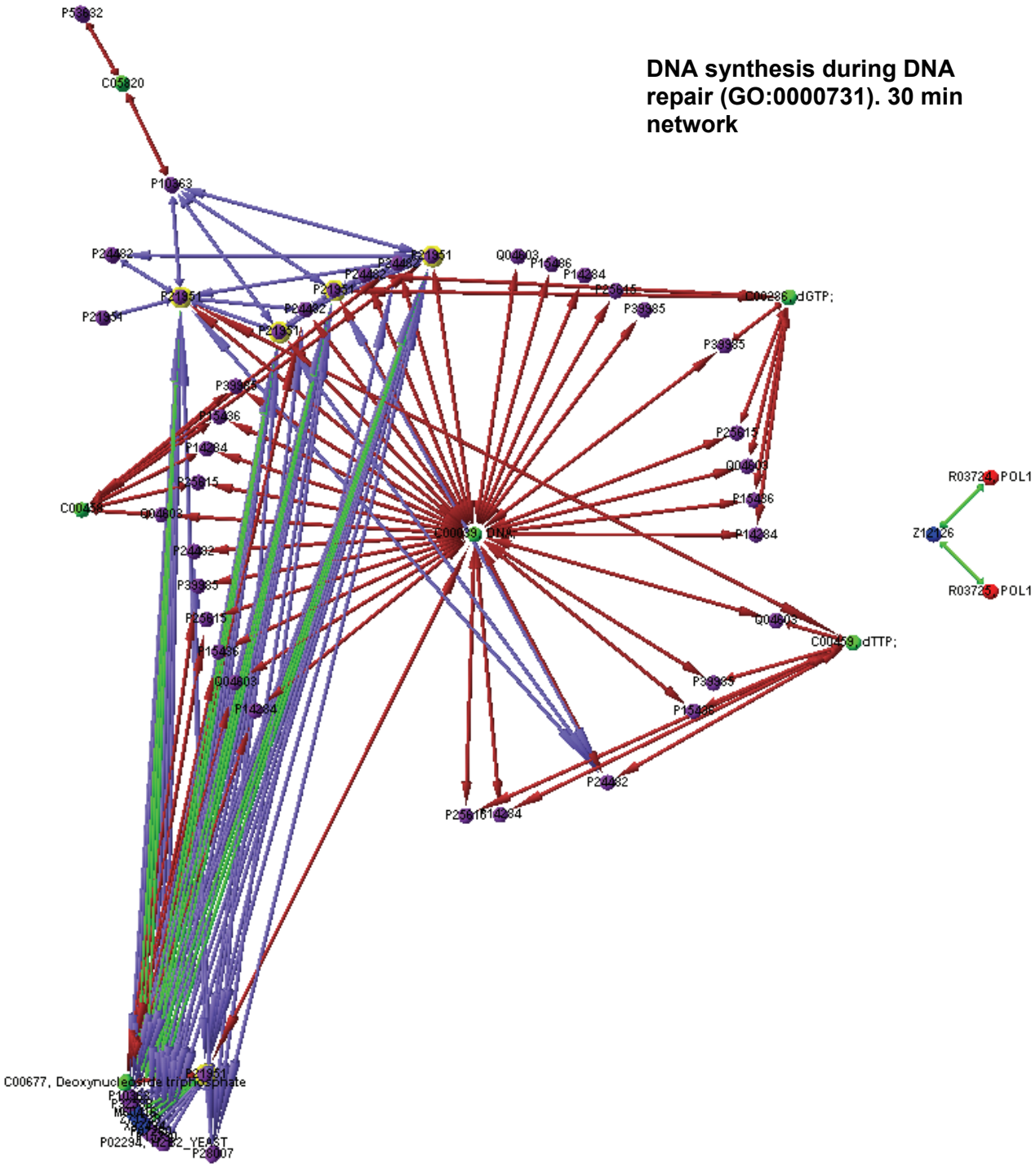
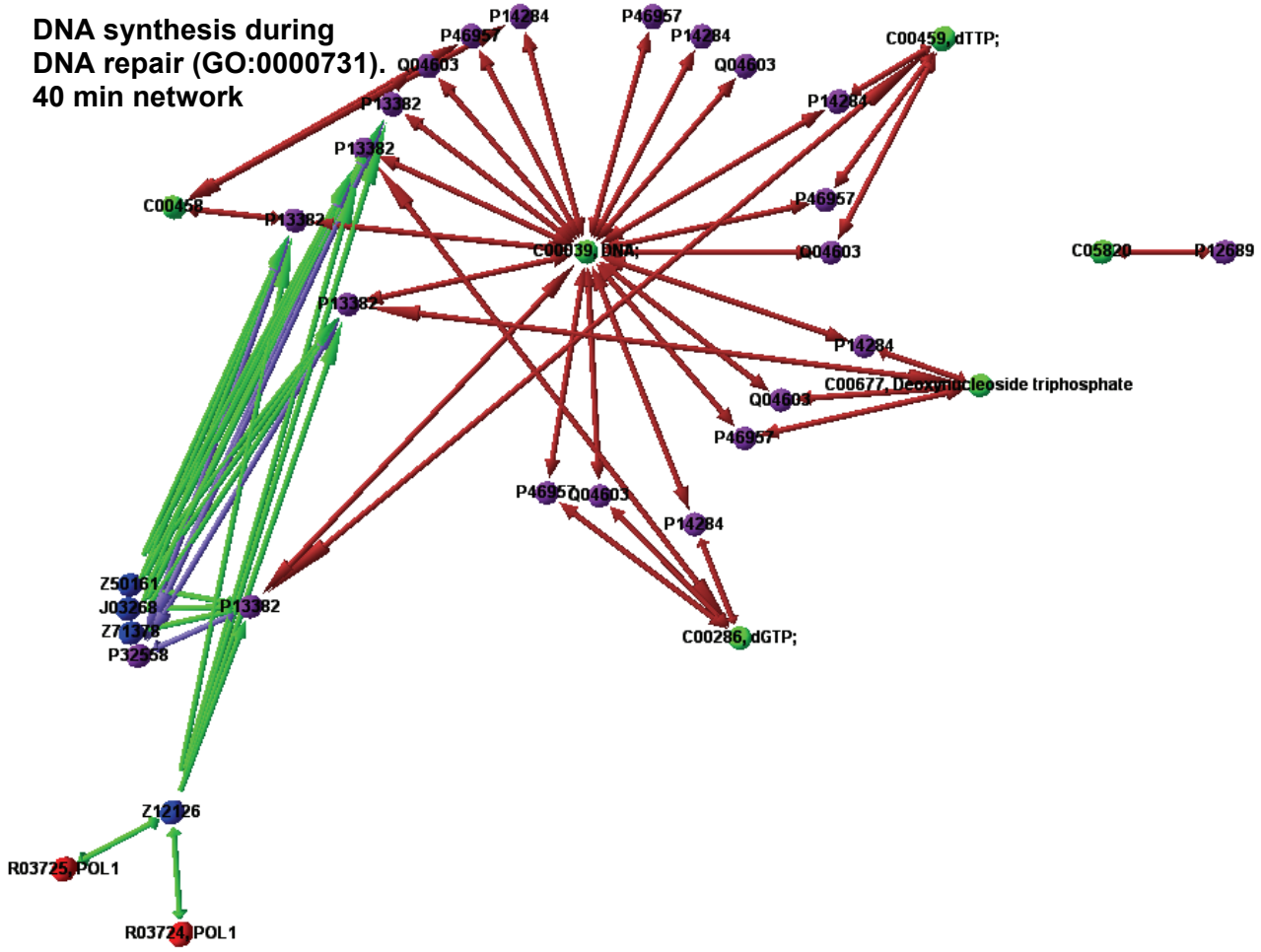
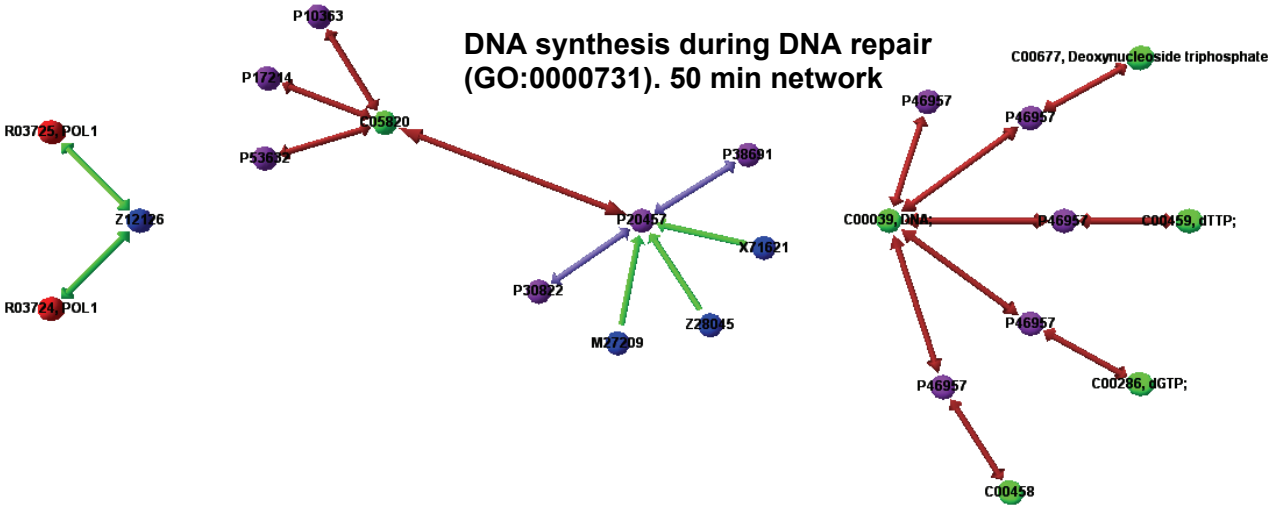


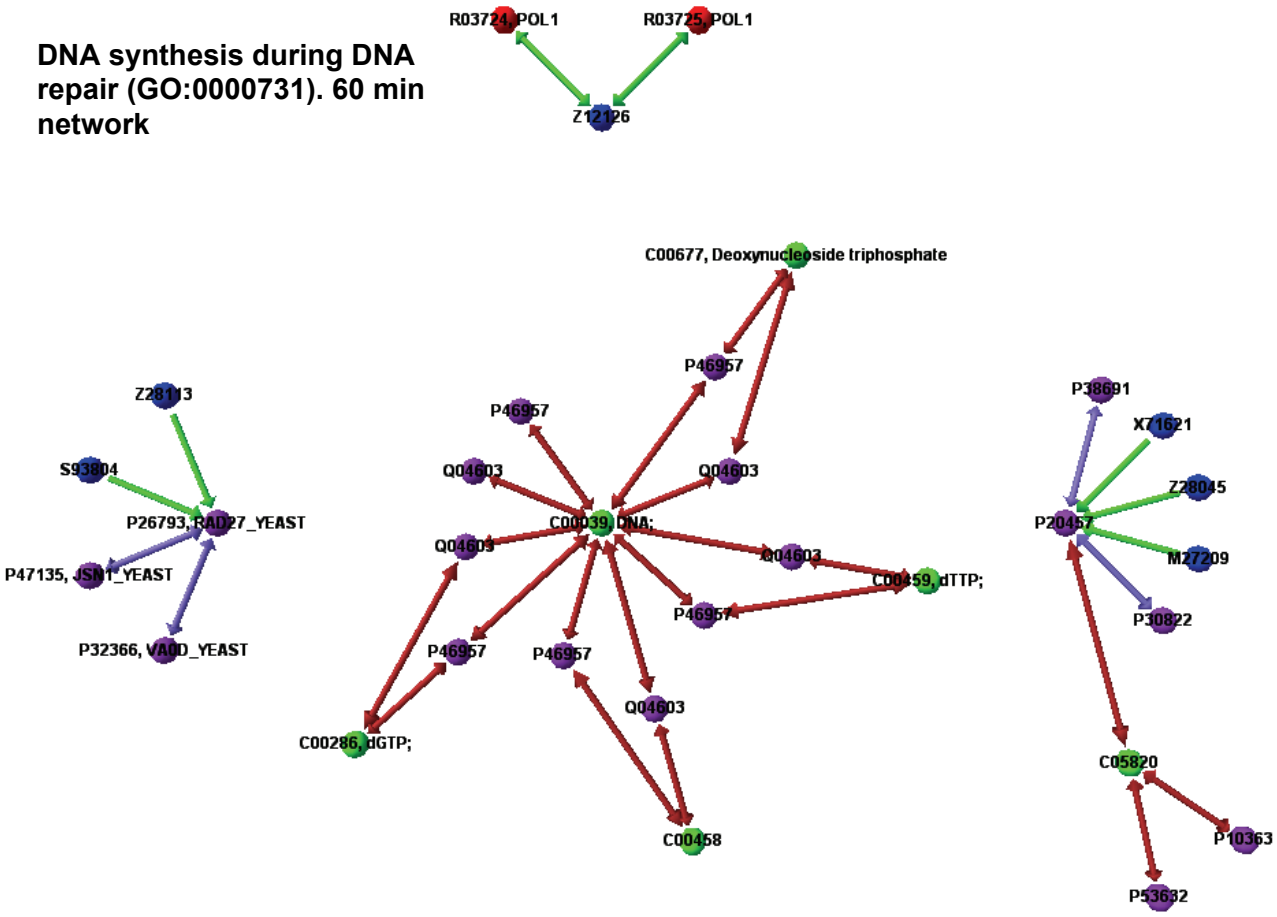
DNA synthesis during DNA repair (GO:0000731). 30 min network

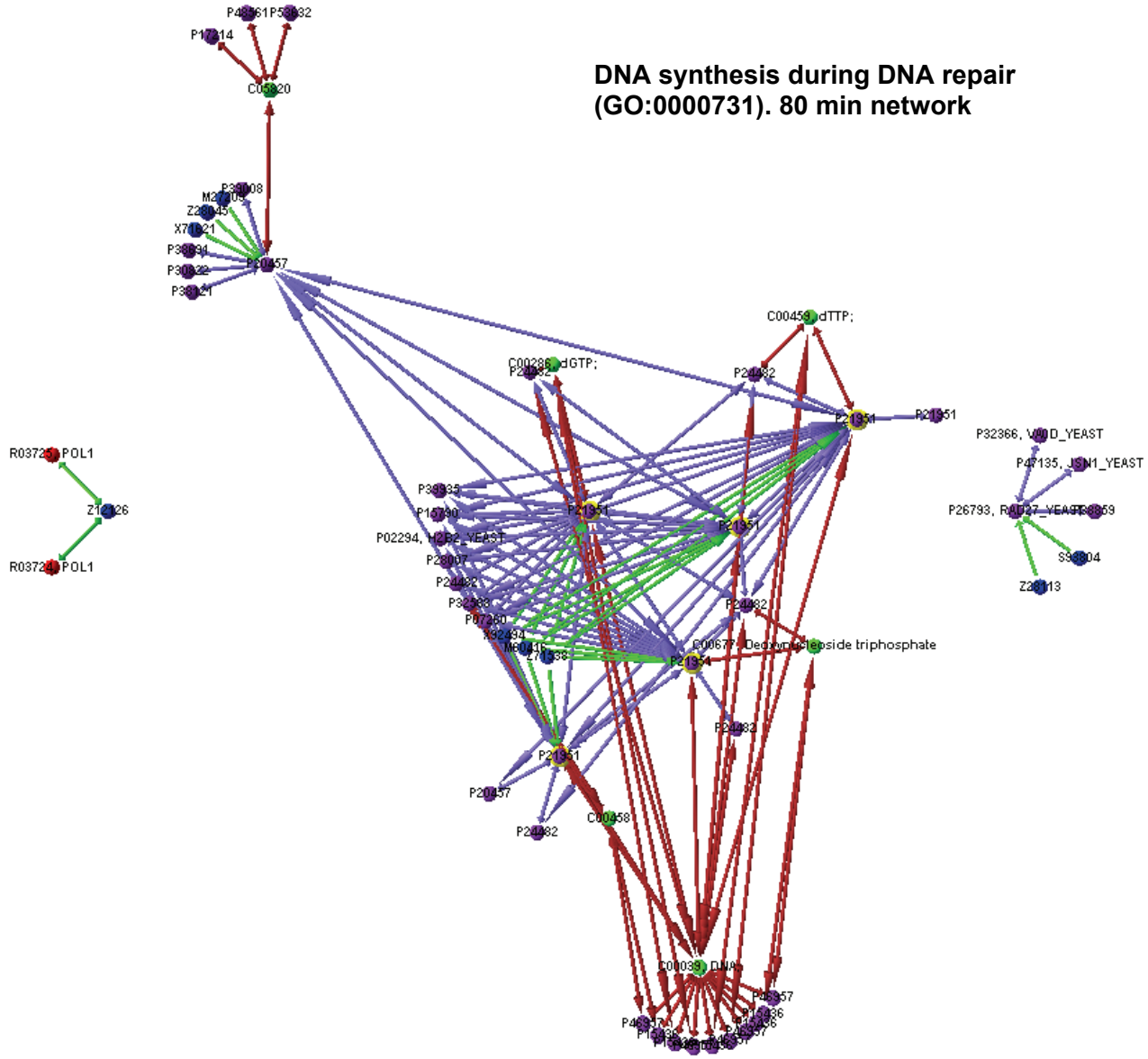



DNA synthesis during
DNA repair (GO:0000731).
40 min network
P14284
P46957
P46957
P14284
C00459, dTTP;
Q04603
Q04603
P13382
P14284
P13382
P46957
C00458
P13382
C00039, DNA;
Q04603
C05820
P12689
P13382
P14284
C00677, Deoxynucleoside triphosphate
Q04603
P46957
P46957
Q04603
P14284
C00286, dGTP;
Z50161
J03268
Z71378
P32558
P13382
Z12126
R03725, POL1
R03724, POL1

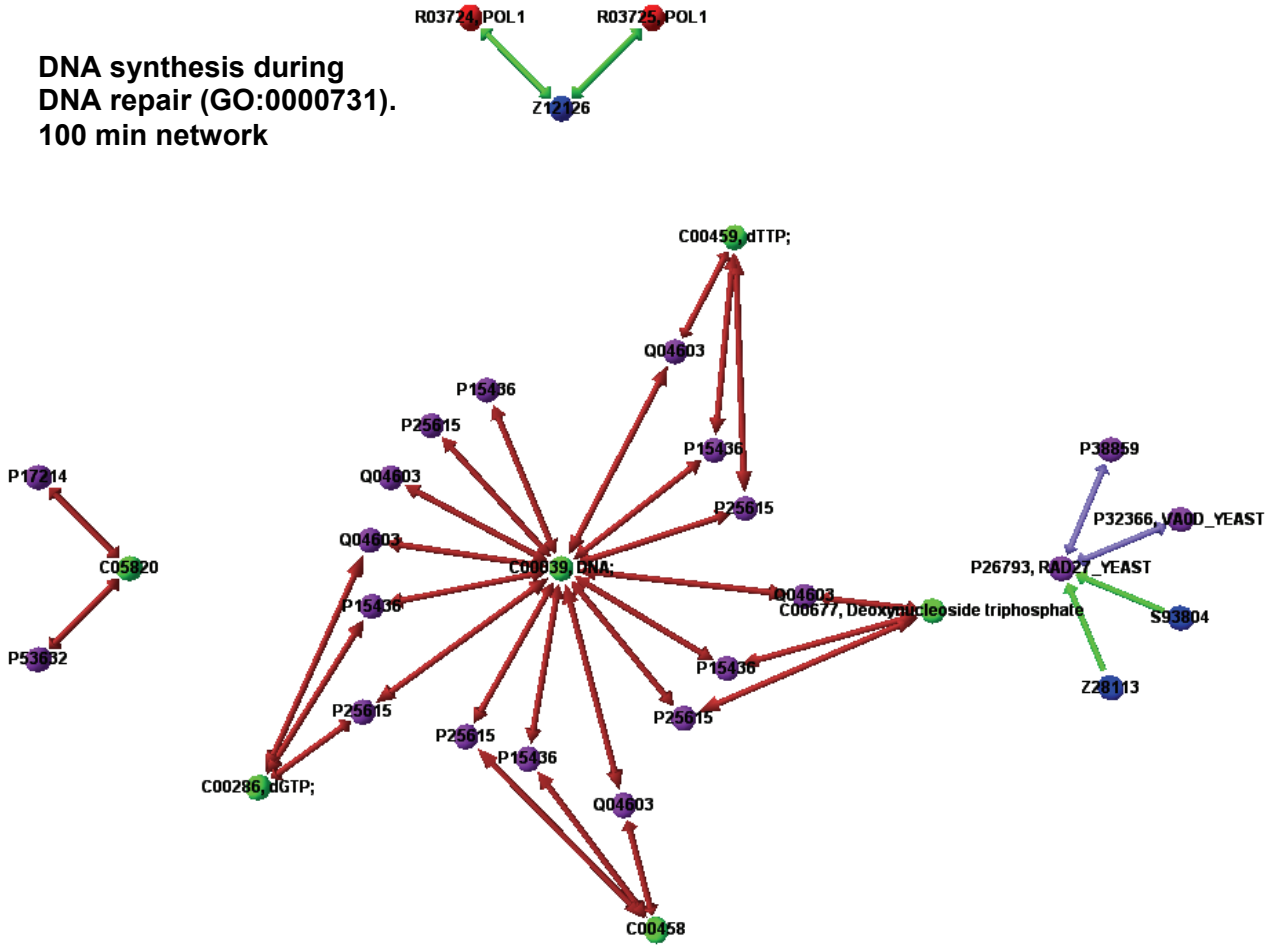

DNA synthesis during DNA repair
(GO:0000731). 50 min network
P10363
P17214
C05820
P53692
R03725, POL1
Z12126
R03724, POL1
P38691
P20457
X71621
P30822
Z28045
M27209
C00677, Deoxynucleoside triphosphate
P46957
P46957
C00039, DNA;
P46957
C00459, dTTP;
P46957
P46957
C00286, dGTP;
C00458

DNA synthesis during DNA repair (GO:0000731). 60 min network

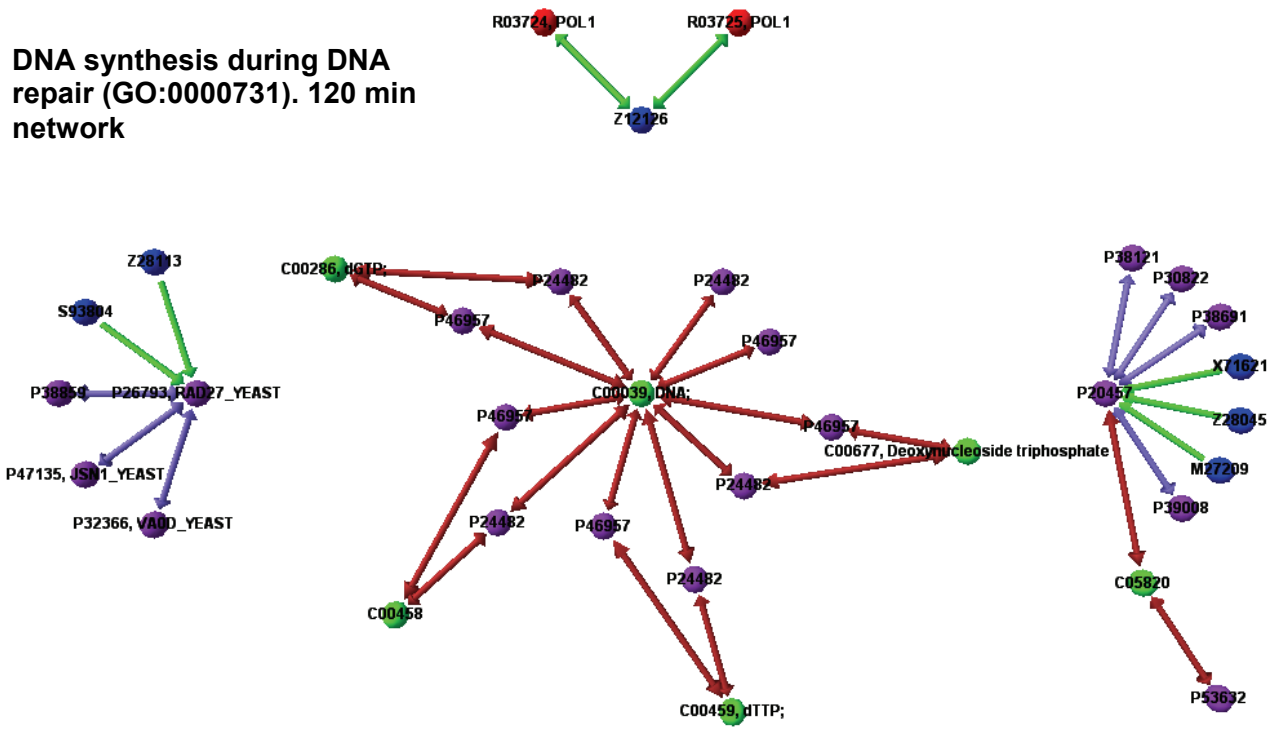



DNA synthesis during DNA repair
(GO:0000731). 80 min network
C00459, dTTP;
C00286, dGTP;
C00677, Deoxynucleoside triphosphate
C00039, DNA
P21951
P24482
P20457
C00458
R03724, POL1
Z12126
R03724, POL1
P32366, VMD_YEAST
P47135, JSN1_YEAST
P26793, RAD27_YEAST
S93804
Z26113
P02294, H2B2_YEAST

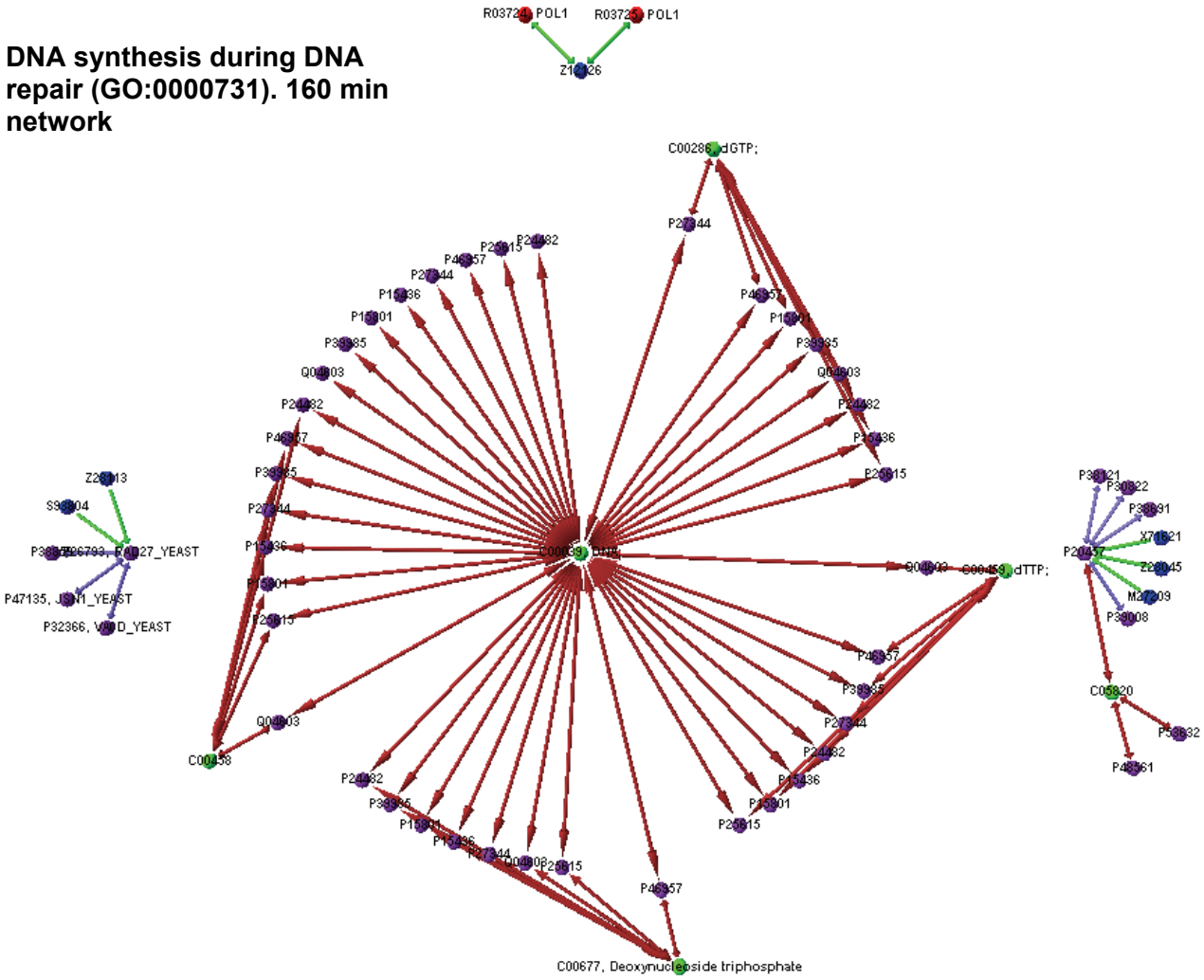
DNA synthesis during DNA repair (GO:0000731). 100 min network

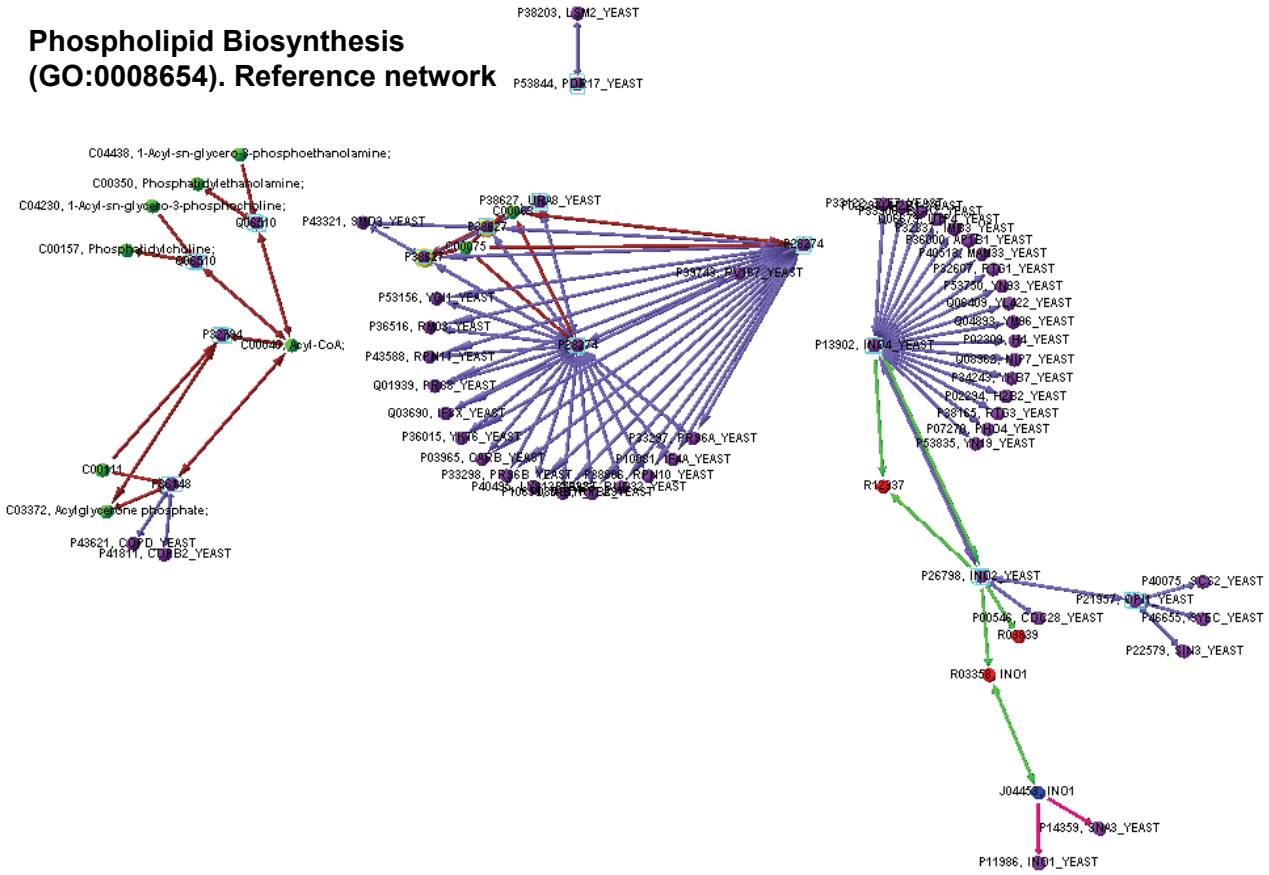


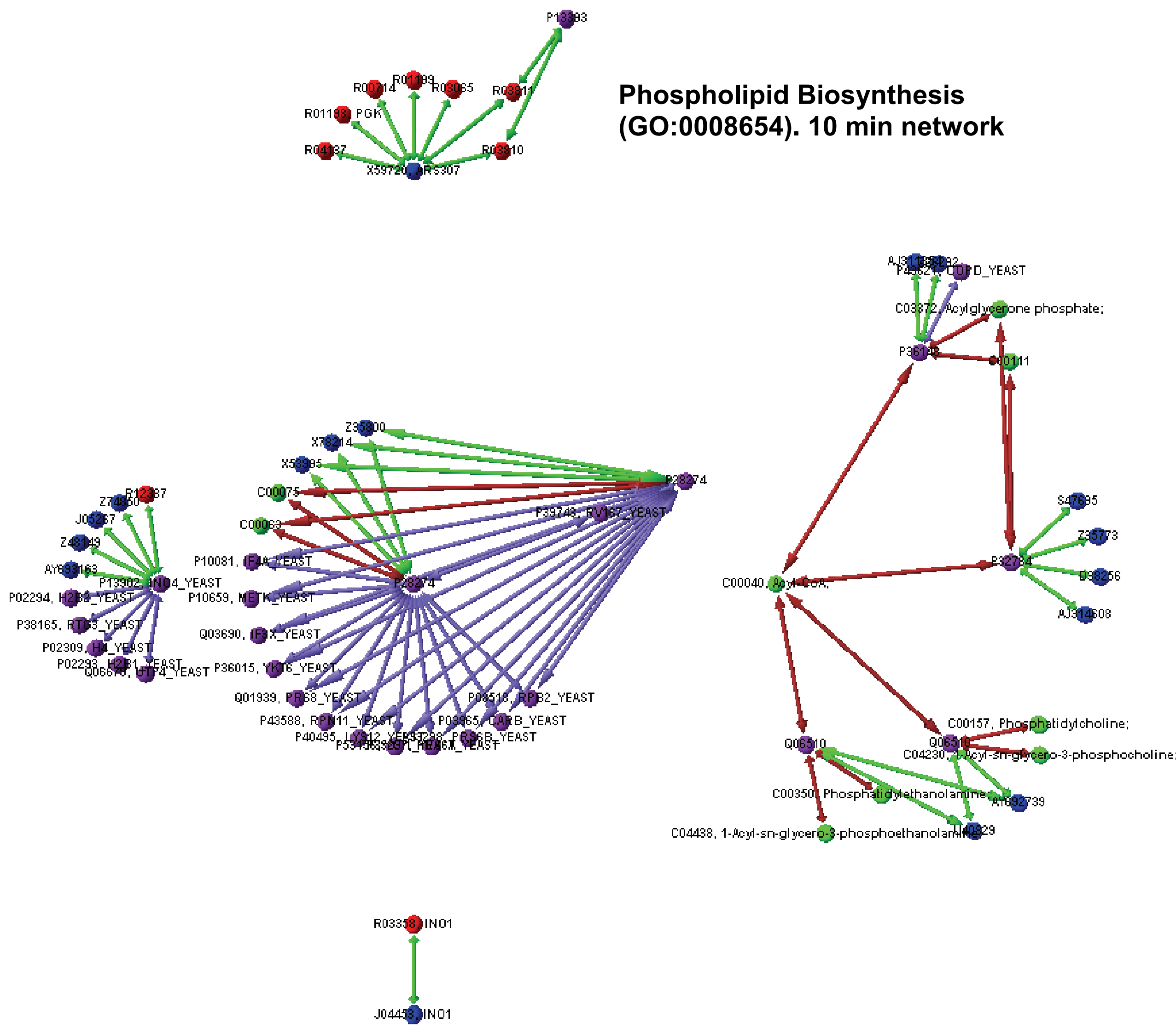
DNA synthesis during DNA repair (GO:0000731). 120 min network

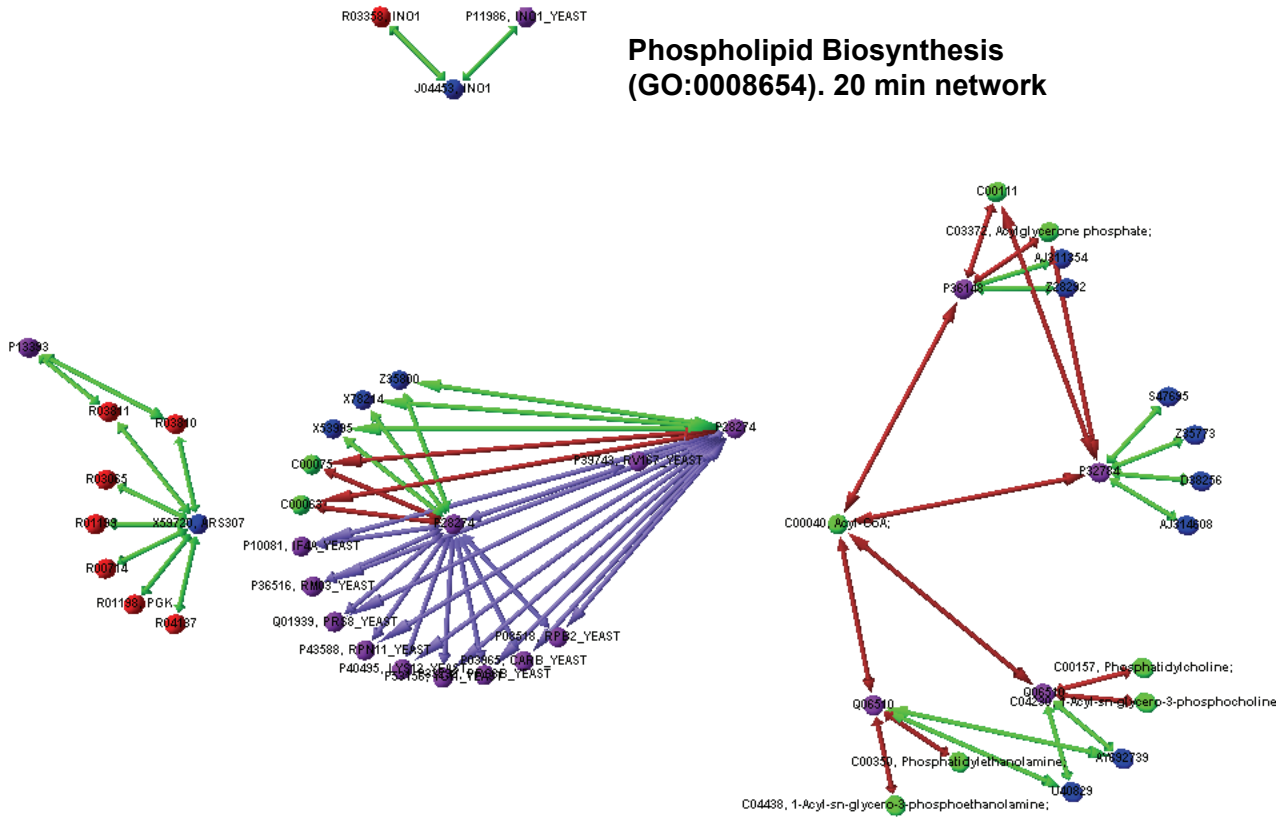


DNA synthesis during DNA repair (GO:0000731). 160 min network




Phospholipid Biosynthesis
(GO:0008654). Reference network
P38203, LSM2_YEAST
P53844, PDR17_YEAST
C04438, 1-Acyl-sn-glycero-3-phosphoethanolamine;
C00350, Phosphatidylethanolamine;
C04230, 1-Acyl-sn-glycero-3-phosphocholine;
C00157, Phosphatidylcholine;
C00010, CoA;
C00111
C03372, Acylglycerone phosphate;
P38274
P43321, SNX3_YEAST
P38627, LIP8_YEAST
P38827
P53156, YDL1_YEAST
P36516, RTC3_YEAST
P43588, RCN1_YEAST
Q01939, PP88_YEAST
Q03690, IES3_YEAST
P36015, YMR6_YEAST
P03965, CAPB_YEAST
P33298, PR26B_YEAST
P33297, PR26A_YEAST
P10081, IE4A_YEAST
P38998, RPN10_YEAST
P13902, IN04_YEAST
R12937
P26798, IN02_YEAST
P40075, SIC2_YEAST
P21357, OPI1_YEAST
P00546, CDC28_YEAST
R03339
P46655, SWC5_YEAST
P22579, SIN3_YEAST
R03358, INO1
J04456, INO1
P14359, SIN3_YEAST
P11986, IN01_YEAST


Phospholipid Biosynthesis
(GO:0008654). 10 min network
C03372, Acylglycerone phosphate;
C00040, Acyl-CoA;
C00157, Phosphatidylcholine;
C04230, 1-Acyl-sn-glycero-3-phosphocholine;
C00350, Phosphatidylethanolamine;
C04438, 1-Acyl-sn-glycero-3-phosphoethanolamine;
P10081, IF4A_YEAST
P10659, METK_YEAST
Q03690, IF3X_YEAST
P36015, YKT6_YEAST
Q01939, PRS8_YEAST
P43588, RPN11_YEAST
P08518, RPB2_YEAST
P03965, CARB_YEAST
P39743, RV167_YEAST
P13902, INO4_YEAST
P02294, H2B2_YEAST
P38165, RTT3_YEAST
P02309, H4_YEAST
R03358, INO1
J04453, INO1


R03358, INO1
P11986, INO1_YEAST
J04453, INO1
Phospholipid Biosynthesis
(GO:0008654). 20 min network
C00111
C03372, Acyldihydroxyacetone phosphate;
AJ311654
P36116
Z48292
P13393
R03841
R03840
R03365
R01188
X59720, ARS307
R00714
R01198, PGK
R04187
Z35800
X78214
X53385
C00075
C00083
P38274
P39743, RVB1_YEAST
P10081, FAA1_YEAST
P36516, RIM3_YEAST
Q01939, PRS8_YEAST
P43588, RPM11_YEAST
P40495, LYS12_YEAST
P06518, RPB2_YEAST
R03865, CARB_YEAST
S47695
Z35773
P32784
D38256
AJ314608
C00040, Acyl-CoA;
C00157, Phosphatidylcholine;
Q06510
C04230, 1-Acyl-sn-glycero-3-phosphocholine
AJ832739
C00350, Phosphatidylethanolamine;
D40829
C04438, 1-Acyl-sn-glycero-3-phosphoethanolamine;

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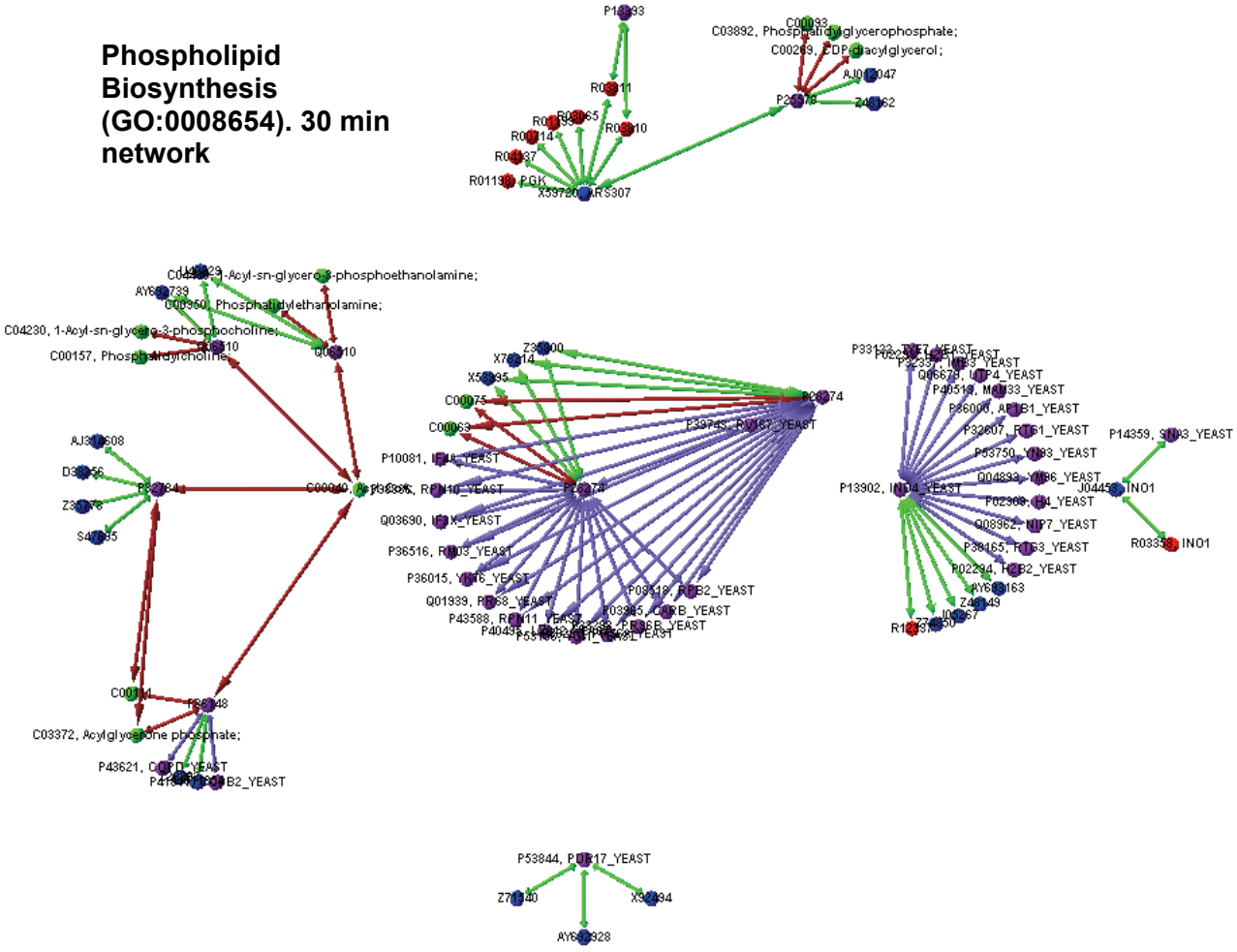
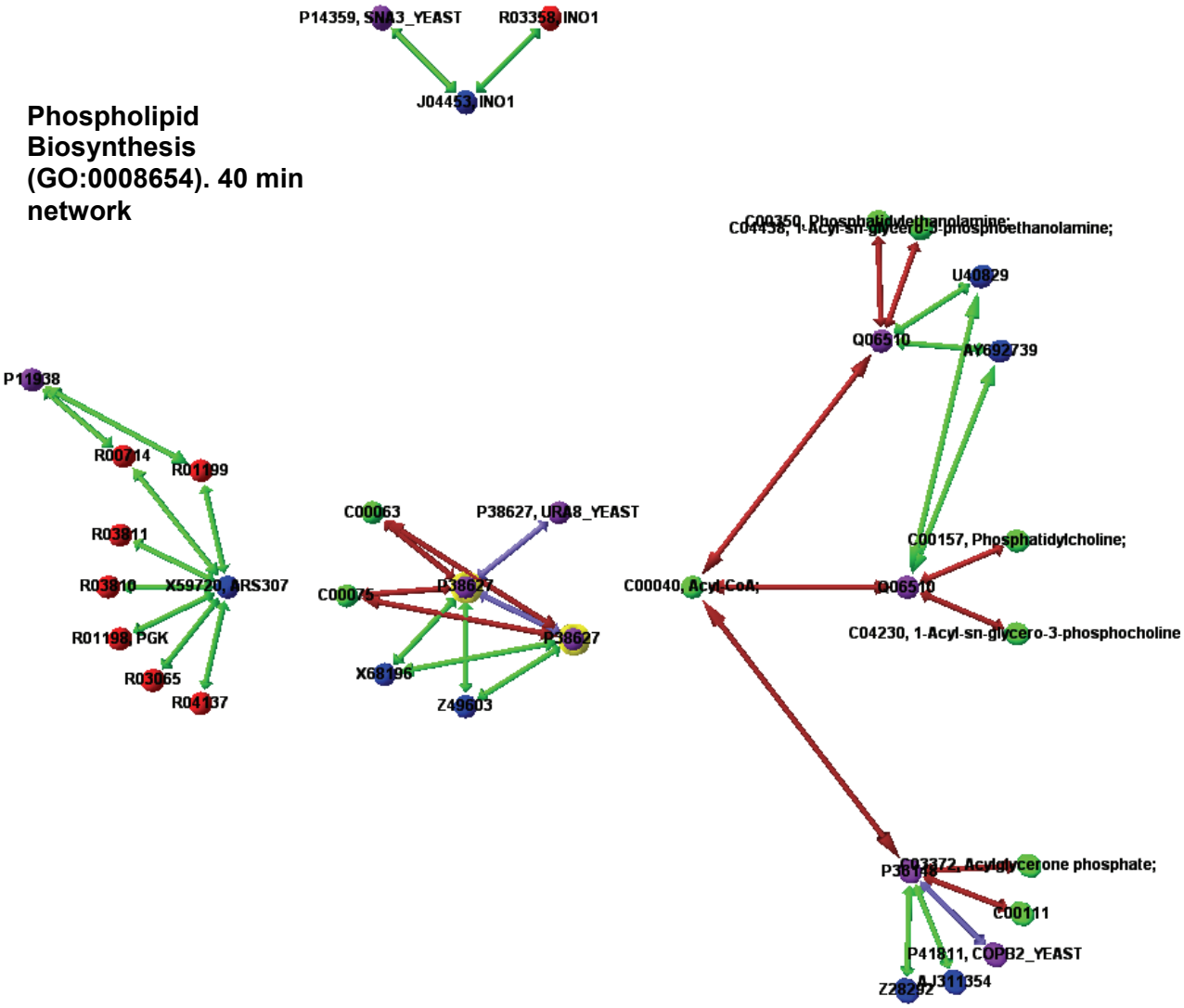
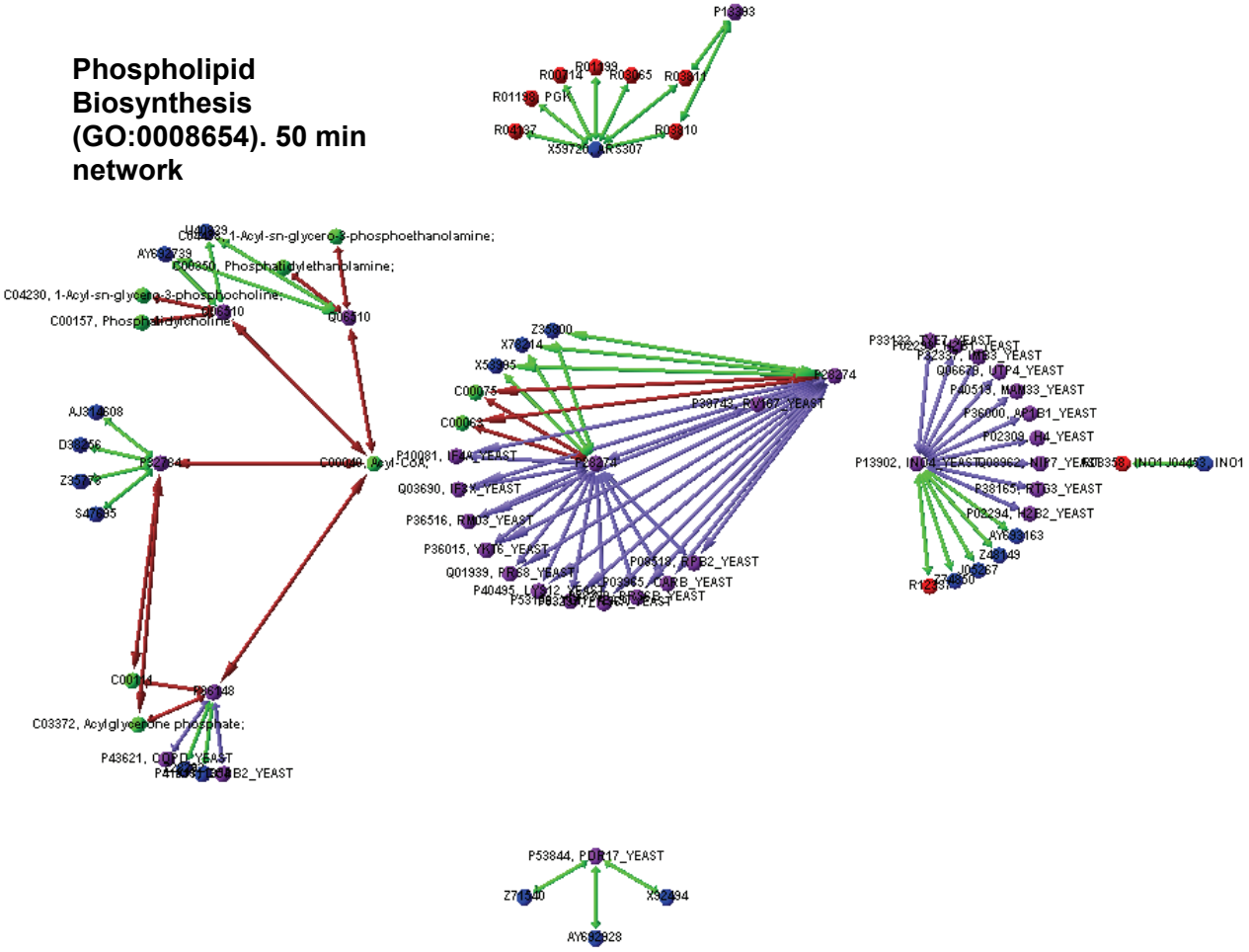
Phospholipid Biosynthesis (GO:0008654). 30 min network

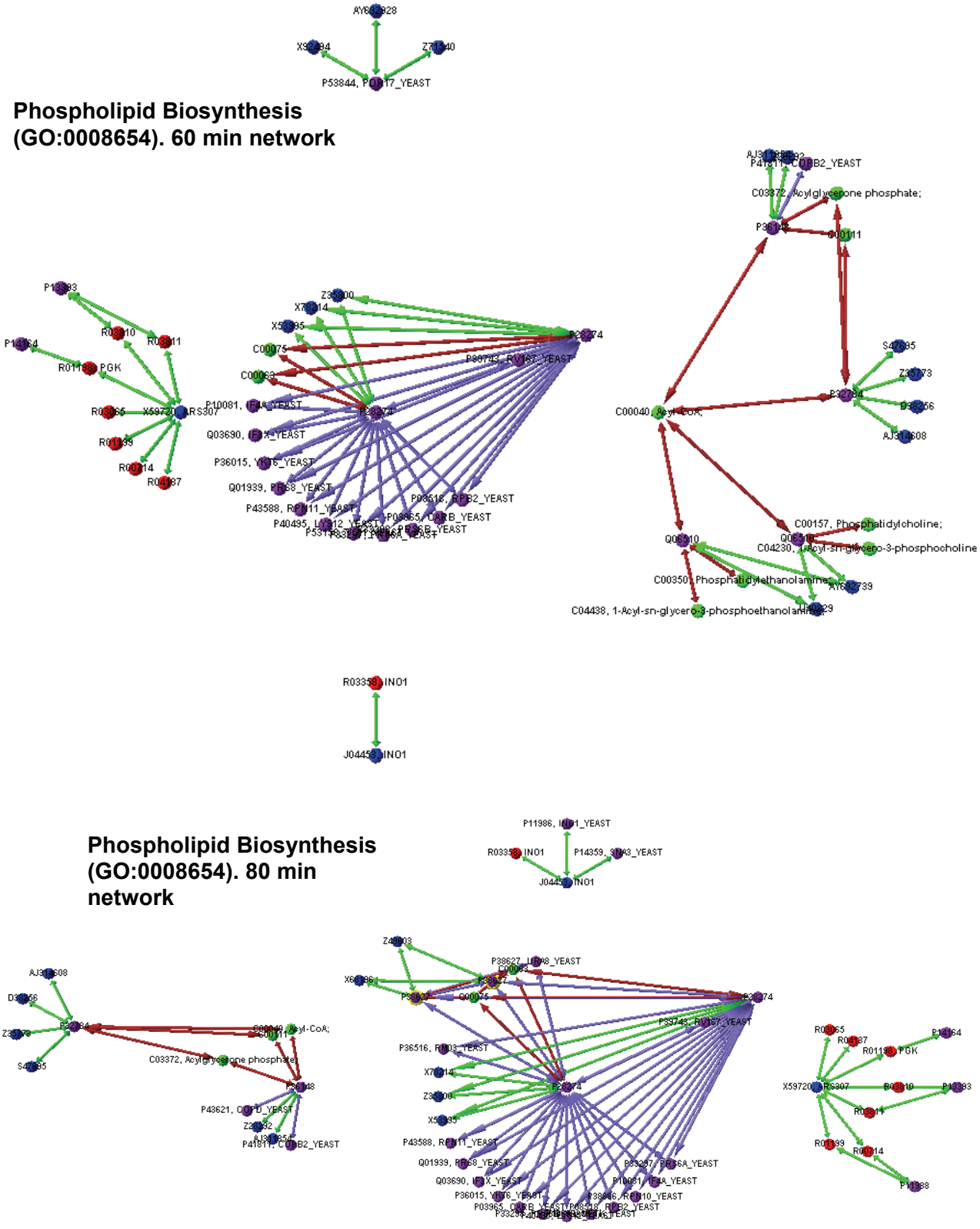


Phospholipid Biosynthesis (GO:0008654). 40 min network

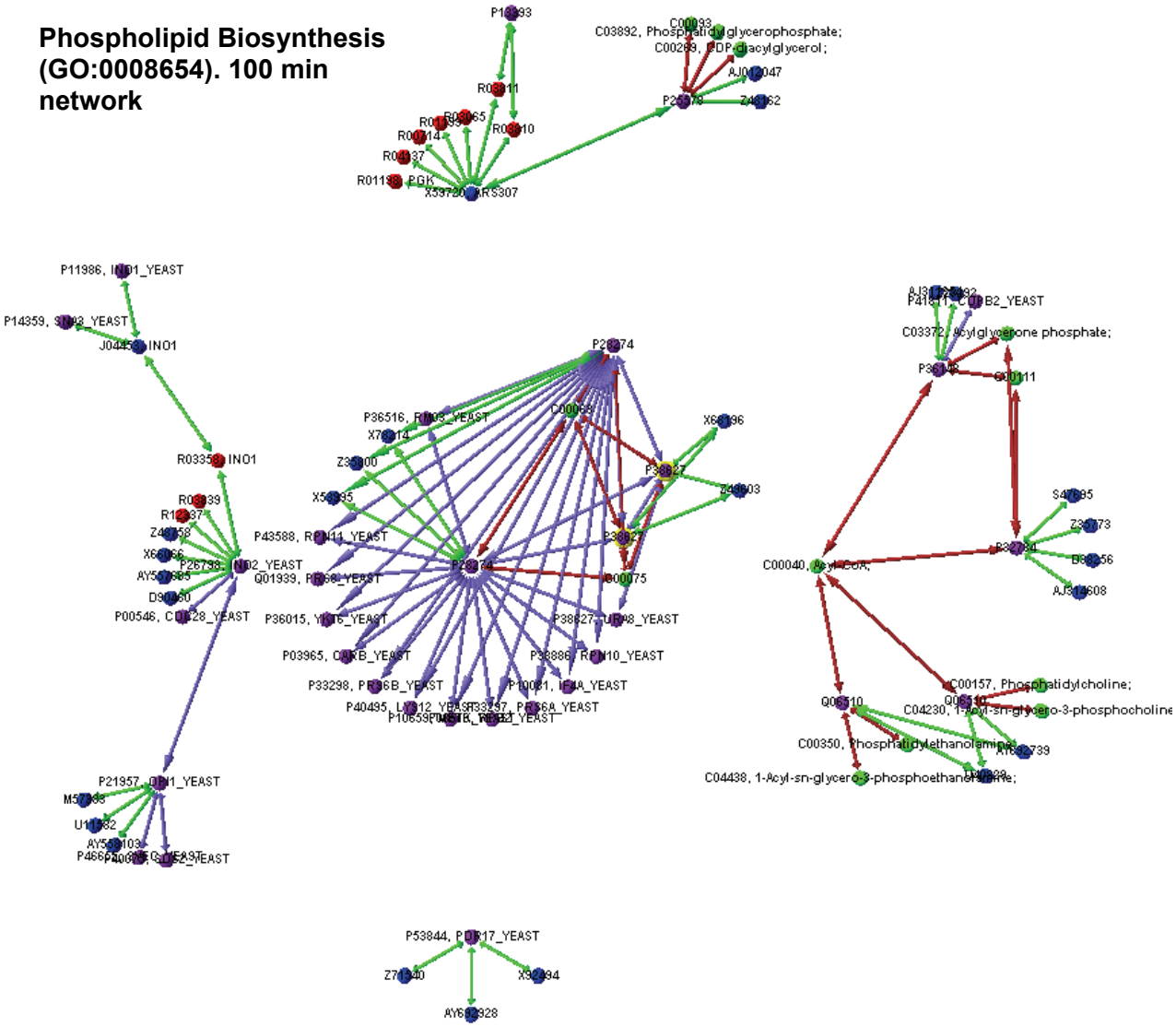


Phospholipid Biosynthesis (GO:0008654). 50 min network

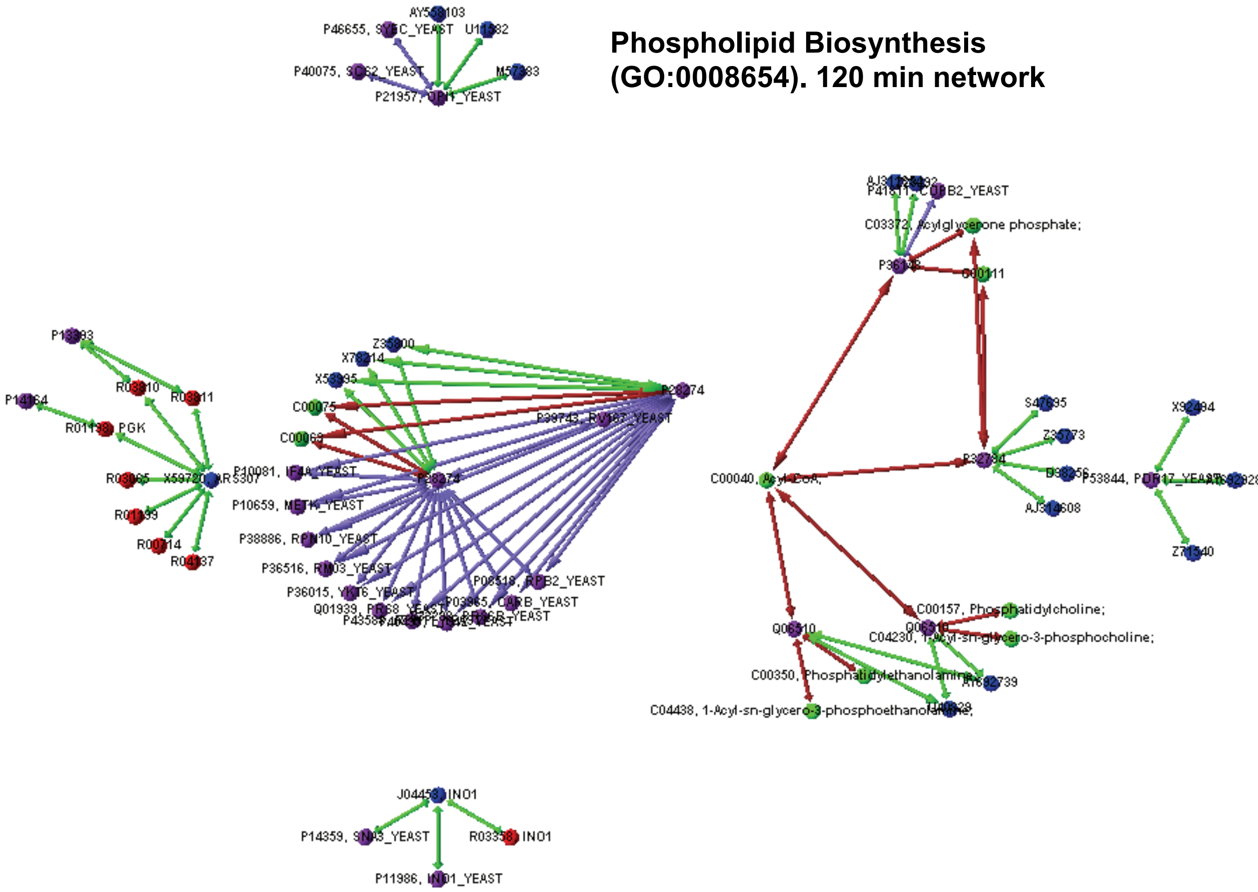



Phospholipid Biosynthesis (GO:0008654). 60 min network
P53844, PC017_YEAST
P13393
R03310
R03311
P14164
R01138, PGK
R03065
X59720, ARS307
R01139
R00714
R04187
Z35800
X78214
X58395
C00075
C00063
P38274
P38743, RVB1_YEAST
P10081, IE14_YEAST
Q03690, IE2X_YEAST
P36015, YM16_YEAST
Q01939, PRS8_YEAST
P43588, RPN11_YEAST
P03518, RPB2_YEAST
P03965, CORB_YEAST
P40495, LV312_YEAST
P53197, PRS6A_YEAST
P41811, COPB2_YEAST
C03372, Acylglycerone phosphate;
P36111
C00111
S47685
Z35873
D38256
AJ314608
C00040, Acyl-CoA;
C00157, Phosphatidylcholine;
Q06310
C04230, 1-Acyl-sn-glycero-3-phosphocholine
C00350, Phosphatidylethanolamine;
AY692739
C04438, 1-Acyl-sn-glycero-3-phosphoethanolamine
R03358, INO1
J04451, INO1
Phospholipid Biosynthesis (GO:0008654). 80 min network
P11986, IDI1_YEAST
P14359, SUA3_YEAST
AJ314608
D38256
Z35873
S47685
C00040, Acyl-CoA;
C00111
C03372, Acylglycerone phosphate;
P43621, COPD_YEAST
Z28252
AJ315854
P41811, COPB2_YEAST
Z46703
P38627, UBA3_YEAST
X64386
P38743, RVB1_YEAST
P36516, RM03_YEAST
X78214
Z35800
X58395
P43588, RPN11_YEAST
Q01939, PRS8_YEAST
Q03690, IE2X_YEAST
P36015, YM16_YEAST
P03965, CORB_YEAST
P53197, PRS6A_YEAST
P10081, IE14_YEAST
P38636, RPN10_YEAST
P03518, RPB2_YEAST
R03065
R04187
P14164
R01138, PGK
X59720, ARS307
R03310
P13393
R03314
R01139
R00714
P11988

Phospholipid Biosynthesis (GO:0008654). 100 min network



Phospholipid Biosynthesis (GO:0008654). 120 min network



Phospholipid Biosynthesis (GO:0008654). 160 min network

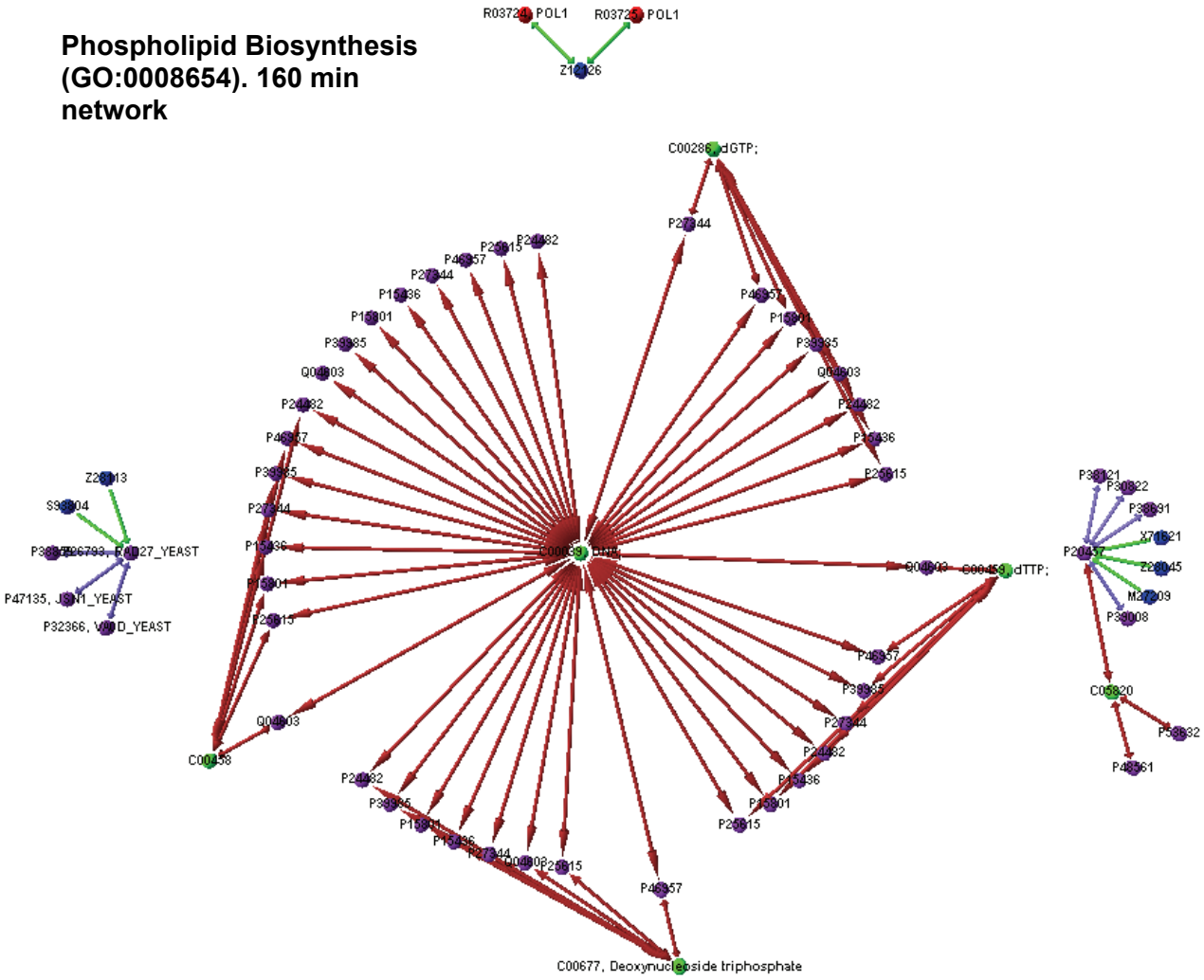


Table S1. Topological parameters for the reference and condition networks.

Time (min)	Clustering coefficient	In degree	Out degree
10	0.1890	4.0700	3.9680
20	0.1930	3.7090	3.6550
30	0.2006	5.2037	5.1053
40	0.1946	4.2845	4.2112
50	0.2073	5.0250	4.9596
60	0.2077	5.8093	5.6990
80	0.2050	6.4691	6.2924
100	0.2174	5.7163	5.6259
120	0.2129	5.6471	5.5095
160	0.2083	6.7697	6.6402
Reference	0.2000	7.9600	7.7320

Table S2. Results of heuristic method TEAFS.

TEAFS determines Topological Variation of modules. Table contains EDA values of 346 modules. When interpreting the results, one should consider FDR *q*-values as a measure for the statistical significance. *p* and *q*-values smaller than 10^{-5} are shown as < 1e-5 in the table.

LIC = Local in- connectivity. LOC = Local out- connectivity. LC = Local clustering. EDA = Extent of differential activity. P = Original *p*-value calculated by TEAFS. FDR = False Discovery Rate *q*-value (recommended significance measure). Bonferroni correction for the TEAFS *p*-values were also computed but not shown here. NES (gsea) = Normalized Enrichment Score (calculated by GSEA). P (gsea) = Nominal *p*-value (GSEA enrichment test). FDR (gsea) = False Discovery Rate *q*-value (GSEA enrichment test).

According the GSEA, positive NES score represents that the pathway is up-regulated, and the negative NES score represents that it is down-regulated.

GO accession	Module name	EDA (LIC)	P	FDR	EDA (LOC)	P	FDR	EDA (LC)	P	FDR	NES (gsea)	P (gsea)	FDR (gsea)
GO:0000001	mitochondrion inheritance	406.42	0.0025	0.0046	397.58	0.0024	0.0048	23.10	< 1e-5	< 1e-5	-2.20	0.1762	0.7520
GO:0000022	mitotic spindle elongation	58.42	0.9893	1.0000	55.90	0.9999	1.0000	12.08	< 1e-5	< 1e-5	-0.40	0.6230	0.9238
GO:0000027	ribosomal large subunit assembly and maintenance	408.61	< 1e-5	< 1e-5	413.16	< 1e-5	< 1e-5	6.20	0.6884	0.8573	-2.95	0.1095	0.4461
GO:0000032	cell wall mannoprotein biosynthesis	96.68	0.3469	0.4826	122.94	0.1937	0.2855	NA	NA	NA	-0.07	0.9045	0.9823
GO:0000045	autophagic vacuole formation	28.99	0.5676	0.7217	28.99	0.5665	0.7342	NA	NA	NA	1.02	0.4396	0.9734
GO:0000055	ribosomal large subunit-nucleus export	1226.83	< 1e-5	< 1e-5	1199.25	< 1e-5	< 1e-5	NA	NA	NA	-1.76	0.0525	0.9588
GO:0000070	mitotic sister chromatid segregation	174.50	< 1e-5	< 1e-5	174.88	< 1e-5	< 1e-5	11.89	< 1e-5	< 1e-5	-0.50	0.4526	0.9315
GO:0000074	regulation of cell cycle	243.35	0.0038	0.0068	245.39	0.0078	0.0144	5.21	0.4086	0.5541	-0.34	0.6150	0.9183
GO:0000077	DNA damage checkpoint	74.35	0.9967	1.0000	69.61	0.9990	1.0000	NA	NA	NA	0.81	0.6685	0.9778
GO:0000080	G1 phase of mitotic cell cycle	37.20	0.9956	1.0000	52.59	0.8145	0.9939	2.41	0.1400	0.2023	-0.40	0.9620	0.9276
GO:0000082	G1/S transition of mitotic cell cycle	3176.25	0.0088	0.0154	3179.05	0.0147	0.0264	15.25	< 1e-5	< 1e-5	-3.28	0.0827	0.3861
GO:0000084	S phase of mitotic cell cycle	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.04	0.4836	1.0000
GO:0000086	G2/M transition of mitotic cell cycle	2400.49	0.9999	1.0000	2426.29	1.0000	1.0000	19.84	< 1e-5	< 1e-5	-0.72	0.4258	0.9370
GO:0000096	sulfur amino acid metabolism	51.29	0.9993	1.0000	54.85	0.9987	1.0000	NA	NA	NA	0.60	0.9351	0.9775
GO:0000103	sulfate assimilation	41.78	< 1e-5	< 1e-5	44.82	< 1e-5	< 1e-5	6.82	0.0745	0.1109	0.83	0.6669	0.9861
GO:0000105	histidine biosynthesis	156.55	1.0000	1.0000	219.73	0.9998	1.0000	29.90	0.9354	1.0000	-0.97	0.5024	1.0000
GO:0000114	G1-specific transcription in mitotic cell cycle	325.16	< 1e-5	< 1e-5	321.96	< 1e-5	< 1e-5	5.47	0.7892	0.9587	-0.39	0.6639	0.9243
GO:0000122	negative regulation of transcription from RNA polymerase II promoter	289.09	< 1e-5	< 1e-5	283.26	< 1e-5	< 1e-5	2.33	0.5902	0.7491	-2.10	0.1975	0.7136
GO:0000147	actin cortical patch assembly	393.71	0.9767	1.0000	384.83	0.9556	1.0000	17.18	< 1e-5	< 1e-5	0.74	0.7789	0.9986

GO:0000154	rRNA modification	276.41	0.0001	0.0002	267.27	0.0002	0.0004	9.25	0.0406	0.0633	-0.43	0.6455	0.9323
GO:0000162	tryptophan biosynthesis	188.60	< 1e-5	< 1e-5	154.34	1.0000	1.0000	30.62	< 1e-5	< 1e-5	-1.22	0.4029	0.9604
GO:0000183	chromatin silencing at ribosomal DNA	449.57	< 1e-5	< 1e-5	323.75	< 1e-5	< 1e-5	8.71	0.0011	0.0021	-0.95	0.5179	1.0000
GO:0000184	mRNA catabolism, nonsense-mediated decay	216.38	< 1e-5	< 1e-5	216.38	0.0006	0.0012	2.31	0.0057	0.0102	1.31	0.1641	0.8489
GO:0000209	protein polyubiquitination	49.24	0.3942	0.5326	47.76	0.3915	0.5427	NA	NA	NA	-0.16	0.7996	0.9542
GO:0000256	allantoin catabolism	6.81	0.9648	1.0000	5.29	0.9940	1.0000	NA	NA	NA	-1.45	0.1217	0.9667
GO:0000266	mitochondrial fission	55.05	0.0647	0.1010	128.56	0.2589	0.3699	1.03	0.5702	0.7284	-1.18	0.2916	0.9999
GO:0000288	mRNA catabolism, deadenylylation-dependent decay	169.29	0.7589	0.9436	164.74	0.7364	0.9205	0.02	< 1e-5	< 1e-5	0.87	0.6147	0.9521
GO:0000289	poly(A) tail shortening	171.50	< 1e-5	< 1e-5	169.58	< 1e-5	< 1e-5	13.05	0.6215	0.7788	0.70	0.8385	1.0000
GO:0000290	deadenylylation-dependent decapping	422.85	< 1e-5	< 1e-5	422.85	< 1e-5	< 1e-5	NA	NA	NA	0.72	0.8234	1.0000
GO:0000301	retrograde transport, vesicle recycling within Golgi	42.74	1.0000	1.0000	42.74	1.0000	1.0000	4.26	< 1e-5	< 1e-5	-0.87	0.6713	0.9832
GO:0000398	nuclear mRNA splicing, via spliceosome	826.28	< 1e-5	< 1e-5	822.05	< 1e-5	< 1e-5	8.62	0.0527	0.0806	-0.41	0.5401	0.9300
GO:0000501	flocculation (sensu Saccharomyces)	2210.44	1.0000	1.0000	1738.66	< 1e-5	< 1e-5	1.25	0.0006	0.0012	-1.47	0.2205	0.9524
GO:0000706	meiotic DNA double-strand break processing	19.86	1.0000	1.0000	15.57	1.0000	1.0000	6.91	< 1e-5	< 1e-5	-0.69	0.8677	0.9414
GO:0000715	nucleotide-excision repair, DNA damage recognition	154.73	< 1e-5	< 1e-5	153.49	< 1e-5	< 1e-5	NA	NA	NA	-0.94	0.5940	0.9955
GO:0000717	nucleotide-excision repair, DNA duplex unwinding	23.01	0.9973	1.0000	22.00	0.9986	1.0000	NA	NA	NA	-0.79	0.7128	0.9634
GO:0000722	telomerase-independent telomere maintenance	215.84	< 1e-5	< 1e-5	209.50	< 1e-5	< 1e-5	1.51	< 1e-5	< 1e-5	-1.30	0.3577	0.9698
GO:0000727	double-strand break repair via break-induced replication	46.22	1.0000	1.0000	43.16	1.0000	1.0000	6.91	< 1e-5	< 1e-5	-0.14	0.9345	0.9591
GO:0000731	DNA synthesis during DNA repair	33.23	< 1e-5	< 1e-5	33.23	< 1e-5	< 1e-5	0.22	< 1e-5	< 1e-5	1.15	0.2805	0.9043
GO:0000735	removal of nonhomologous ends	98.29	< 1e-5	< 1e-5	66.47	0.6402	0.8185	NA	NA	NA	-1.52	0.0358	0.9041
GO:0000747	conjugation with cellular fusion	708.67	0.0084	0.0148	640.58	0.0158	0.0282	NA	NA	NA	-0.26	0.6640	0.9366
GO:0000750	signal transduction during conjugation with cellular fusion	356.20	< 1e-5	< 1e-5	305.66	< 1e-5	< 1e-5	3.60	< 1e-5	< 1e-5	-0.30	0.6425	0.9269
GO:0000751	cell cycle arrest in response to pheromone	64.24	1.0000	1.0000	64.24	1.0000	1.0000	NA	NA	NA	0.54	0.9584	0.9921
GO:0000754	adaptation to pheromone during conjugation with cellular fusion	43.47	< 1e-5	< 1e-5	43.47	< 1e-5	< 1e-5	NA	NA	NA	-0.09	0.9182	0.9790
GO:0000902	cellular morphogenesis	967.70	0.9814	1.0000	909.13	0.9836	1.0000	56.75	< 1e-5	< 1e-5	-0.32	0.6557	0.9256
GO:0000903	cellular morphogenesis during vegetative growth	648.92	0.0092	0.0159	648.92	0.0077	0.0143	NA	NA	NA	-0.82	0.6886	0.9798
GO:0000910	cytokinesis	1573.19	0.0199	0.0333	1489.44	0.0301	0.0517	47.86	< 1e-5	< 1e-5	-0.77	0.3177	0.9649
GO:0000921	septin ring assembly	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.82	0.7085	0.9720
GO:0001100	negative regulation of exit from mitosis	36.53	< 1e-5	< 1e-5	36.53	< 1e-5	< 1e-5	0.03	< 1e-5	< 1e-5	0.80	0.7475	0.9888
GO:0001302	replicative cell aging	758.55	< 1e-5	< 1e-5	610.92	0.0270	0.0467	6.88	0.8393	0.9951	-3.00	0.0663	0.4823
GO:0001308	loss of chromatin silencing during replicative cell aging	186.07	1.0000	1.0000	186.07	0.9999	1.0000	0.05	1.0000	1.0000	-1.54	0.1754	0.9633
GO:0001321	age-dependent general metabolic decline during replicative cell aging	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0001402	signal transduction during filamentous growth	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.78	0.7203	0.9616
GO:0001403	invasive growth (sensu Saccharomyces)	405.96	0.0004	0.0008	367.06	0.1538	0.2353	3.30	0.1010	0.1481	-0.41	0.5256	0.9333
GO:0001718	conversion of met-tRNAf to fmet-tRNA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0005975	carbohydrate metabolism	143.20	< 1e-5	< 1e-5	152.55	< 1e-5	< 1e-5	2.44	0.4956	0.6542	-0.38	0.7290	0.9220
GO:0005977	glycogen metabolism	776.54	0.0002	0.0004	777.51	0.0001	0.0002	4.86	0.9991	1.0000	1.17	0.2751	0.9291
GO:0005980	glycogen catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.27	0.1939	0.8541
GO:0005992	trehalose biosynthesis	9.19	0.5411	0.6943	9.19	0.5437	0.7114	1.18	0.5382	0.7023	1.01	0.4760	0.9432
GO:0006000	fructose metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.35	0.1415	1.0000
GO:0006006	glucose metabolism	448.46	0.9996	1.0000	449.93	0.9987	1.0000	18.39	< 1e-5	< 1e-5	-1.16	0.4377	1.0000
GO:0006011	UDP-glucose metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

GO:0006012	galactose metabolism	80.87	< 1e-5	< 1e-5	42.28	< 1e-5	< 1e-5	6.19	0.8679	1.0000	-0.13	0.9290	0.9593
GO:0006038	cell wall chitin biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.89	0.6280	0.9919
GO:0006067	ethanol metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.41	0.0980	1.0000
GO:0006075	beta-1,3 glucan biosynthesis	NA	NA	NA	83.10	< 1e-5	< 1e-5	1.44	< 1e-5	< 1e-5	-1.26	0.2201	0.9688
GO:0006085	acetyl-CoA biosynthesis	91.92	1.0000	1.0000	103.94	1.0000	1.0000	3.02	1.0000	1.0000	-1.22	0.1823	0.9706
GO:0006090	pyruvate metabolism	43.50	0.7705	0.9538	69.62	0.1052	0.1646	3.21	0.3553	0.4885	-0.55	0.7746	0.9321
GO:0006094	gluconeogenesis	2.83	< 1e-5	< 1e-5	0.00	1.0000	1.0000	0.11	< 1e-5	< 1e-5	0.73	0.8127	1.0000
GO:0006096	glycolysis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0006097	glyoxylate cycle	438.60	< 1e-5	< 1e-5	388.40	< 1e-5	< 1e-5	7.31	< 1e-5	< 1e-5	0.93	0.5507	0.9399
GO:0006098	pentose-phosphate shunt	137.18	< 1e-5	< 1e-5	237.59	< 1e-5	< 1e-5	15.69	< 1e-5	< 1e-5	-0.64	0.8179	0.9404
GO:0006099	tricarboxylic acid cycle	914.76	< 1e-5	< 1e-5	919.20	< 1e-5	< 1e-5	11.99	0.0700	0.1050	1.10	0.3511	0.9475
GO:0006101	citrate metabolism	503.77	0.0036	0.0065	343.67	0.0689	0.1102	10.39	0.5502	0.7120	-1.26	0.2529	0.9595
GO:0006102	isocitrate metabolism	420.10	0.4608	0.6051	417.60	0.4621	0.6221	18.44	0.0168	0.0275	0.91	0.5584	0.9273
GO:0006103	2-oxoglutarate metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0006104	succinyl-CoA metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.93	0.5938	0.9889
GO:0006108	malate metabolism	95.46	0.0045	0.0080	90.51	0.0071	0.0133	6.98	< 1e-5	< 1e-5	1.31	0.1603	0.8434
GO:0006109	regulation of carbohydrate metabolism	621.45	1.0000	1.0000	600.58	1.0000	1.0000	7.15	< 1e-5	< 1e-5	-0.76	0.6676	0.9664
GO:0006114	glycerol biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.02	0.4845	1.0000
GO:0006121	mitochondrial electron transport, succinate to ubiquinone	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.07	0.3576	0.9458
GO:0006123	mitochondrial electron transport, cytochrome c to oxygen	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.23	0.8634	0.9384
GO:0006139	nucleobase, nucleoside, nucleotide and nucleic acid metabolism	27.58	1.0000	1.0000	43.13	0.9984	1.0000	3.15	0.0115	0.0198	-1.39	0.1744	1.0000
GO:0006144	purine base metabolism	116.27	< 1e-5	< 1e-5	111.00	< 1e-5	< 1e-5	14.72	< 1e-5	< 1e-5	-0.74	0.7892	0.9469
GO:0006164	purine nucleotide biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.09	0.4072	1.0000
GO:0006166	purine ribonucleoside salvage	61.44	1.0000	1.0000	124.13	1.0000	1.0000	21.71	0.6066	0.7650	-1.03	0.4864	1.0000
GO:0006183	GTP biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0006259	DNA metabolism	417.15	0.0001	0.0002	335.01	< 1e-5	< 1e-5	NA	NA	NA	-0.75	0.5953	0.9467
GO:0006260	DNA replication	688.98	0.0016	0.0031	309.68	< 1e-5	< 1e-5	NA	NA	NA	-1.91	0.2048	0.8232
GO:0006267	pre-replicative complex formation and maintenance	50.34	< 1e-5	< 1e-5	50.34	< 1e-5	< 1e-5	10.91	0.0561	0.0848	-1.00	0.4966	1.0000
GO:0006268	DNA unwinding	295.63	< 1e-5	< 1e-5	295.27	< 1e-5	< 1e-5	NA	NA	NA	-0.94	0.5119	0.9991
GO:0006269	DNA replication, synthesis of RNA primer	365.69	< 1e-5	< 1e-5	368.00	< 1e-5	< 1e-5	0.42	1.0000	1.0000	0.80	0.7204	0.9916
GO:0006270	DNA replication initiation	109.67	< 1e-5	< 1e-5	110.14	< 1e-5	< 1e-5	12.40	< 1e-5	< 1e-5	-2.21	0.1793	0.8113
GO:0006271	DNA strand elongation	250.45	0.0319	0.0512	250.55	0.0311	0.0526	NA	NA	NA	-1.59	0.1589	0.9815
GO:0006272	leading strand elongation	167.91	0.9627	1.0000	167.91	0.9682	1.0000	23.94	< 1e-5	< 1e-5	-0.94	0.5143	1.0000
GO:0006273	lagging strand elongation	245.89	< 1e-5	< 1e-5	237.17	< 1e-5	< 1e-5	19.54	< 1e-5	< 1e-5	-0.88	0.5500	0.9974
GO:0006275	regulation of DNA replication	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.89	0.5696	0.9372
GO:0006280	mutagenesis	103.75	< 1e-5	< 1e-5	106.42	< 1e-5	< 1e-5	15.75	< 1e-5	< 1e-5	-1.05	0.4388	1.0000
GO:0006281	DNA repair	700.13	0.0001	0.0002	703.33	0.0002	0.0004	4.61	0.0234	0.0377	-0.21	0.7157	0.9440
GO:0006284	base-excision repair	222.03	< 1e-5	< 1e-5	210.50	< 1e-5	< 1e-5	18.71	< 1e-5	< 1e-5	-1.14	0.3906	1.0000
GO:0006289	nucleotide-excision repair	501.53	< 1e-5	< 1e-5	491.59	< 1e-5	< 1e-5	24.76	< 1e-5	< 1e-5	-0.80	0.4811	0.9808
GO:0006298	mismatch repair	304.79	< 1e-5	< 1e-5	293.77	< 1e-5	< 1e-5	24.08	< 1e-5	< 1e-5	-0.62	0.5179	0.9437
GO:0006301	postreplication repair	424.52	< 1e-5	< 1e-5	424.58	< 1e-5	< 1e-5	20.00	< 1e-5	< 1e-5	-1.05	0.4856	1.0000
GO:0006302	double-strand break repair	239.36	0.2220	0.3135	240.06	0.2064	0.3026	NA	NA	NA	-0.93	0.5808	0.9866
GO:0006303	double-strand break repair via nonhomologous end-joining	468.21	< 1e-5	< 1e-5	465.77	< 1e-5	< 1e-5	7.43	< 1e-5	< 1e-5	-1.52	0.2901	0.9071
GO:0006310	DNA recombination	567.38	< 1e-5	< 1e-5	538.78	< 1e-5	< 1e-5	NA	NA	NA	-0.97	0.4592	0.9978
GO:0006325	establishment and/or maintenance of chromatin	311.58	< 1e-5	< 1e-5	311.58	< 1e-5	< 1e-5	NA	NA	NA	-1.41	0.3291	1.0000

	architecture												
GO:0006333	chromatin assembly or disassembly	786.84	< 1e-5	< 1e-5	778.17	< 1e-5	< 1e-5	NA	NA	NA	-1.53	0.2953	0.9273
GO:0006338	chromatin remodeling	249.61	0.9692	1.0000	235.19	0.9709	1.0000	2.38	< 1e-5	< 1e-5	-1.53	0.1498	0.9406
GO:0006342	chromatin silencing	268.64	< 1e-5	< 1e-5	269.89	< 1e-5	< 1e-5	0.35	1.0000	1.0000	0.60	0.9292	0.9770
GO:0006348	chromatin silencing at telomere	520.01	< 1e-5	< 1e-5	416.96	< 1e-5	< 1e-5	8.81	< 1e-5	< 1e-5	-0.45	0.4873	0.9329
GO:0006350	transcription	626.66	0.5563	0.7106	624.48	0.5690	0.7342	0.02	0.0309	0.0490	0.65	0.8730	0.9858
GO:0006355	regulation of transcription, DNA-dependent	53.78	0.7873	0.9661	50.92	0.7211	0.9054	3.78	1.0000	1.0000	-3.86	0.0130	0.5904
GO:0006356	regulation of transcription from RNA polymerase I promoter	1738.66	< 1e-5	< 1e-5	1738.66	< 1e-5	< 1e-5	1.25	0.0004	0.0008	-0.75	0.7932	0.9496
GO:0006357	regulation of transcription from RNA polymerase II promoter	468.30	< 1e-5	< 1e-5	456.62	< 1e-5	< 1e-5	8.76	0.5663	0.7281	-1.32	0.1722	0.9907
GO:0006359	regulation of transcription from RNA polymerase III promoter	1738.66	< 1e-5	< 1e-5	1738.66	< 1e-5	< 1e-5	1.25	0.0010	0.0019	-0.75	0.7632	0.9496
GO:0006360	transcription from RNA polymerase I promoter	186.51	0.3581	0.4957	186.51	0.3492	0.4913	NA	NA	NA	-1.19	0.4041	0.9989
GO:0006364	rRNA processing	1504.25	< 1e-5	< 1e-5	1473.73	< 1e-5	< 1e-5	21.91	0.1060	0.1543	-0.31	0.6069	0.9269
GO:0006366	transcription from RNA polymerase II promoter	618.05	< 1e-5	< 1e-5	617.13	< 1e-5	< 1e-5	6.09	< 1e-5	< 1e-5	-0.40	0.5293	0.9255
GO:0006367	transcription initiation from RNA polymerase II promoter	753.52	< 1e-5	< 1e-5	742.66	< 1e-5	< 1e-5	8.30	< 1e-5	< 1e-5	-1.18	0.2230	0.9982
GO:0006368	RNA elongation from RNA polymerase II promoter	315.98	< 1e-5	< 1e-5	315.25	< 1e-5	< 1e-5	2.97	< 1e-5	< 1e-5	-0.76	0.5905	0.9586
GO:0006378	mRNA polyadenylylation	181.08	< 1e-5	< 1e-5	190.29	< 1e-5	< 1e-5	2.55	0.3591	0.4904	-1.50	0.3024	0.9221
GO:0006379	mRNA cleavage	139.57	0.8115	0.9872	149.00	0.7810	0.9634	3.91	< 1e-5	< 1e-5	0.66	0.8497	0.9899
GO:0006388	tRNA splicing	6.36	< 1e-5	< 1e-5	6.36	< 1e-5	< 1e-5	NA	NA	NA	-0.35	0.7073	0.9184
GO:0006390	transcription from mitochondrial promoter	36.67	< 1e-5	< 1e-5	34.59	< 1e-5	< 1e-5	1.41	< 1e-5	< 1e-5	0.91	0.5859	0.9338
GO:0006402	mRNA catabolism	750.28	< 1e-5	< 1e-5	741.84	< 1e-5	< 1e-5	8.98	0.0279	0.0446	-0.07	0.8741	0.9840
GO:0006406	mRNA-nucleus export	2581.69	< 1e-5	< 1e-5	2581.74	< 1e-5	< 1e-5	15.86	< 1e-5	< 1e-5	-5.20	0.0497	0.5641
GO:0006407	rRNA-nucleus export	1618.34	0.0033	0.0060	1612.91	0.0054	0.0103	18.41	< 1e-5	< 1e-5	-3.52	0.0482	0.5671
GO:0006408	snRNA-nucleus export	1490.38	0.1557	0.2303	1484.84	0.1688	0.2537	19.09	< 1e-5	< 1e-5	-3.44	0.0316	0.4756
GO:0006409	tRNA-nucleus export	1966.89	< 1e-5	< 1e-5	1965.15	< 1e-5	< 1e-5	20.47	< 1e-5	< 1e-5	-3.93	0.0211	0.7022
GO:0006412	protein biosynthesis	1171.74	0.0732	0.1130	1085.09	0.5219	0.6959	17.63	< 1e-5	< 1e-5	-1.37	0.2522	1.0000
GO:0006413	translational initiation	895.33	< 1e-5	< 1e-5	846.97	< 1e-5	< 1e-5	4.88	1.0000	1.0000	-2.59	0.1459	0.6339
GO:0006414	translational elongation	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.21	0.3822	0.9690
GO:0006430	lysyl-tRNA aminoacylation	31.00	0.0021	0.0039	18.19	0.0010	0.0020	0.20	1.0000	1.0000	1.25	0.1231	0.8621
GO:0006431	methionyl-tRNA aminoacylation	9.43	0.9998	1.0000	20.23	0.2303	0.3324	8.16	0.9789	1.0000	-1.22	0.2608	0.9672
GO:0006432	phenylalanyl-tRNA aminoacylation	20.51	< 1e-5	< 1e-5	20.51	< 1e-5	< 1e-5	NA	NA	NA	1.06	0.3771	0.9428
GO:0006434	seryl-tRNA aminoacylation	110.08	< 1e-5	< 1e-5	49.57	< 1e-5	< 1e-5	NA	NA	NA	-0.86	0.7112	0.9849
GO:0006437	tyrosyl-tRNA aminoacylation	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.31	0.0581	0.9881
GO:0006457	protein folding	579.56	< 1e-5	< 1e-5	602.65	< 1e-5	< 1e-5	NA	NA	NA	-0.66	0.3480	0.9320
GO:0006464	protein modification	59.55	0.1201	0.1814	59.55	0.1188	0.1838	0.00	1.0000	1.0000	0.61	0.9079	0.9812
GO:0006468	protein amino acid phosphorylation	2557.66	1.0000	1.0000	2613.27	1.0000	1.0000	46.54	0.0108	0.0188	-1.70	0.1175	0.9448
GO:0006470	protein amino acid dephosphorylation	654.72	1.0000	1.0000	650.07	1.0000	1.0000	14.58	< 1e-5	< 1e-5	-0.72	0.4203	0.9368
GO:0006473	protein amino acid acetylation	302.82	< 1e-5	< 1e-5	303.54	< 1e-5	< 1e-5	NA	NA	NA	-0.61	0.6664	0.9416
GO:0006474	N-terminal protein amino acid acetylation	0.71	1.0000	1.0000	0.00	1.0000	1.0000	2.60	1.0000	1.0000	0.80	0.7536	0.9868
GO:0006486	protein amino acid glycosylation	302.61	0.3756	0.5174	215.34	0.1428	0.2197	26.82	0.8077	0.9752	0.79	0.7030	0.9822
GO:0006487	N-linked glycosylation	492.57	< 1e-5	< 1e-5	495.96	0.0007	0.0014	9.47	< 1e-5	< 1e-5	-0.14	0.7858	0.9575
GO:0006499	N-terminal protein myristoylation	62.93	0.0198	0.0333	62.93	0.0202	0.0356	NA	NA	NA	-1.49	0.0987	0.9259
GO:0006506	GPI anchor biosynthesis	188.09	0.0749	0.1150	166.88	0.0595	0.0963	0.19	< 1e-5	< 1e-5	-1.55	0.2130	0.9821
GO:0006511	ubiquitin-dependent protein catabolism	637.14	0.1789	0.2578	639.23	0.1822	0.2699	15.69	0.4862	0.6461	-0.68	0.3551	0.9365
GO:0006513	protein monoubiquitination	49.24	0.3929	0.5326	47.76	0.3945	0.5441	NA	NA	NA	-0.17	0.7717	0.9554

GO:0006525	arginine metabolism	5.66	< 1e-5	< 1e-5	21.92	0.8449	1.0000	NA	NA	NA	-0.23	0.9813	0.9373
GO:0006526	arginine biosynthesis	67.17	0.2245	0.3154	37.62	0.8164	0.9939	6.96	0.2536	0.3561	1.26	0.2030	0.8810
GO:0006529	asparagine biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.84	0.7298	0.9756
GO:0006530	asparagine catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0006534	cysteine metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.27	0.0909	0.8489
GO:0006536	glutamate metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0006537	glutamate biosynthesis	1286.21	< 1e-5	< 1e-5	1205.61	< 1e-5	< 1e-5	37.19	< 1e-5	< 1e-5	-0.54	0.6080	0.9285
GO:0006545	glycine biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.82	0.7664	0.9745
GO:0006546	glycine catabolism	145.14	< 1e-5	< 1e-5	154.86	< 1e-5	< 1e-5	30.73	< 1e-5	< 1e-5	-0.55	0.8929	0.9288
GO:0006549	isoleucine metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0006555	methionine metabolism	264.47	0.0001	0.0002	240.05	0.0012	0.0024	8.07	0.0132	0.0225	-0.05	0.9341	0.9827
GO:0006561	proline biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.85	0.6954	0.9892
GO:0006566	threonine metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.70	0.7989	0.9407
GO:0006567	threonine catabolism	35.36	1.0000	1.0000	37.48	1.0000	1.0000	1.38	1.0000	1.0000	-0.85	0.6827	0.9923
GO:0006597	spermine biosynthesis	0.00	1.0000	1.0000	0.00	1.0000	1.0000	NA	NA	NA	0.92	0.6249	0.9348
GO:0006598	polyamine catabolism	107.48	< 1e-5	< 1e-5	90.51	< 1e-5	< 1e-5	26.29	< 1e-5	< 1e-5	1.28	0.1941	0.8866
GO:0006606	protein-nucleus import	1621.36	0.9871	1.0000	1625.69	0.9765	1.0000	10.47	0.0516	0.0798	-1.13	0.3083	1.0000
GO:0006607	NLS-bearing substrate-nucleus import	1490.38	0.1628	0.2370	1484.84	0.1618	0.2450	19.09	< 1e-5	< 1e-5	-3.41	0.0290	0.3693
GO:0006608	snRNP protein-nucleus import	1490.38	0.1524	0.2266	1484.84	0.1694	0.2537	19.09	< 1e-5	< 1e-5	-3.44	0.0312	0.4312
GO:0006610	ribosomal protein-nucleus import	1490.38	0.1612	0.2359	1484.84	0.1710	0.2547	19.09	< 1e-5	< 1e-5	-3.50	0.0281	0.5092
GO:0006611	protein-nucleus export	2061.44	< 1e-5	< 1e-5	2069.84	< 1e-5	< 1e-5	20.15	< 1e-5	< 1e-5	-3.80	0.0403	0.5154
GO:0006612	protein-membrane targeting	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.89	0.5824	0.9382
GO:0006617	SRP-dependent cotranslational protein-membrane targeting, signal sequence recognition	19.09	0.5199	0.6764	19.09	0.5269	0.6992	NA	NA	NA	1.59	0.0435	0.7222
GO:0006620	posttranslational protein-membrane targeting	45.03	1.0000	1.0000	37.86	1.0000	1.0000	0.87	< 1e-5	< 1e-5	-0.85	0.6729	0.9940
GO:0006623	protein-vacuolar targeting	510.58	< 1e-5	< 1e-5	561.99	0.0004	0.0008	5.40	1.0000	1.0000	-0.82	0.3039	0.9765
GO:0006625	protein-peroxisome targeting	179.18	< 1e-5	< 1e-5	177.61	< 1e-5	< 1e-5	0.95	0.4515	0.6081	-0.38	0.8262	0.9197
GO:0006629	lipid metabolism	54.45	0.0307	0.0496	54.45	0.0312	0.0526	NA	NA	NA	-2.12	0.0413	0.7756
GO:0006631	fatty acid metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.61	0.6107	0.9399
GO:0006635	fatty acid beta-oxidation	66.11	1.0000	1.0000	71.22	1.0000	1.0000	1.67	< 1e-5	< 1e-5	1.43	0.0632	0.7618
GO:0006646	phosphatidylethanolamine biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.99	0.4645	0.9439
GO:0006672	ceramide metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.68	0.9681	0.9362
GO:0006730	one-carbon compound metabolism	141.97	< 1e-5	< 1e-5	152.74	< 1e-5	< 1e-5	28.65	< 1e-5	< 1e-5	-0.81	0.6631	0.9742
GO:0006743	ubiquinone metabolism	205.06	0.8061	0.9848	183.85	0.8024	0.9854	16.18	0.9221	1.0000	-0.30	0.8479	0.9284
GO:0006749	glutathione metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.48	0.0841	0.8575
GO:0006750	glutathione biosynthesis	17.68	1.0000	1.0000	NA	NA	NA	0.00	1.0000	1.0000	-1.26	0.1204	0.9773
GO:0006780	uroporphyrinogen III biosynthesis	22.63	< 1e-5	< 1e-5	14.14	< 1e-5	< 1e-5	1.27	< 1e-5	< 1e-5	NA	NA	NA
GO:0006783	heme biosynthesis	55.43	< 1e-5	< 1e-5	52.85	< 1e-5	< 1e-5	6.47	0.0002	0.0004	-1.25	0.3489	0.9626
GO:0006790	sulfur metabolism	30.83	< 1e-5	< 1e-5	27.59	< 1e-5	< 1e-5	0.15	< 1e-5	< 1e-5	1.41	0.0798	0.7398
GO:0006796	phosphate metabolism	56.51	< 1e-5	< 1e-5	56.51	< 1e-5	< 1e-5	NA	NA	NA	-1.31	0.2881	0.9780
GO:0006807	nitrogen compound metabolism	296.69	< 1e-5	< 1e-5	370.39	< 1e-5	< 1e-5	0.47	1.0000	1.0000	-0.92	0.5940	0.9901
GO:0006808	regulation of nitrogen utilization	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.06	0.9655	0.9805
GO:0006816	calcium ion transport	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.03	0.4203	0.9649
GO:0006817	phosphate transport	595.14	0.1592	0.2342	832.97	0.5897	0.7574	NA	NA	NA	-0.68	0.6337	0.9329
GO:0006865	amino acid transport	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.09	0.9062	0.9804
GO:0006869	lipid transport	38.18	0.0230	0.0380	38.18	0.0229	0.0401	NA	NA	NA	-1.12	0.3599	1.0000
GO:0006873	cell ion homeostasis	2026.41	< 1e-5	< 1e-5	2067.17	< 1e-5	< 1e-5	1.25	0.0007	0.0013	-1.16	0.4330	1.0000

GO:0006886	intracellular protein transport	148.19	0.0003	0.0006	301.91	< 1e-5	< 1e-5	16.21	< 1e-5	< 1e-5	-0.88	0.5143	0.9967
GO:0006887	exocytosis	264.70	0.0131	0.0223	273.64	0.0042	0.0082	NA	NA	NA	0.68	0.8457	0.9958
GO:0006888	ER to Golgi transport	1384.30	< 1e-5	< 1e-5	1087.45	< 1e-5	< 1e-5	9.37	0.0167	0.0275	-1.02	0.2257	1.0000
GO:0006890	retrograde transport, Golgi to ER	586.76	< 1e-5	< 1e-5	465.37	0.0532	0.0866	8.77	1.0000	1.0000	-1.03	0.5099	1.0000
GO:0006891	intra-Golgi transport	289.90	< 1e-5	< 1e-5	260.22	< 1e-5	< 1e-5	6.81	0.0358	0.0563	-0.44	0.5914	0.9321
GO:0006893	Golgi to plasma membrane transport	139.21	< 1e-5	< 1e-5	108.63	< 1e-5	< 1e-5	NA	NA	NA	1.22	0.2286	0.8923
GO:0006895	Golgi to endosome transport	88.34	< 1e-5	< 1e-5	145.65	0.0064	0.0121	NA	NA	NA	0.64	0.9148	0.9884
GO:0006896	Golgi to vacuole transport	141.61	< 1e-5	< 1e-5	134.36	< 1e-5	< 1e-5	NA	NA	NA	-0.36	0.6783	0.9205
GO:0006897	endocytosis	1571.39	< 1e-5	< 1e-5	1588.58	< 1e-5	< 1e-5	34.50	< 1e-5	< 1e-5	-0.16	0.7680	0.9551
GO:0006904	vesicle docking during exocytosis	94.92	0.0511	0.0802	95.32	0.0620	0.0998	NA	NA	NA	1.35	0.1482	0.8253
GO:0006906	vesicle fusion	369.70	< 1e-5	< 1e-5	321.26	< 1e-5	< 1e-5	NA	NA	NA	1.60	0.0440	0.8080
GO:0006913	nucleocytoplasmic transport	305.86	0.1968	0.2807	289.92	0.2612	0.3713	NA	NA	NA	-1.04	0.4878	1.0000
GO:0006914	autophagy	420.29	< 1e-5	< 1e-5	408.32	< 1e-5	< 1e-5	7.12	0.9598	1.0000	-1.61	0.2477	0.9817
GO:0006950	response to stress	508.17	0.4234	0.5666	486.18	0.3883	0.5409	5.27	0.8231	0.9834	-0.01	0.9726	0.9965
GO:0006970	response to osmotic stress	1397.20	< 1e-5	< 1e-5	1364.24	< 1e-5	< 1e-5	11.00	0.9785	1.0000	-0.84	0.3695	0.9852
GO:0006974	response to DNA damage stimulus	1738.66	< 1e-5	< 1e-5	1738.66	< 1e-5	< 1e-5	1.25	0.0005	0.0010	-1.65	0.2087	0.9805
GO:0006979	response to oxidative stress	147.37	0.8592	1.0000	105.65	0.9208	1.0000	NA	NA	NA	-0.02	0.9684	0.9944
GO:0006999	nuclear pore organization and biogenesis	1500.74	0.1961	0.2807	1495.14	0.2110	0.3077	19.28	< 1e-5	< 1e-5	-4.79	0.0080	0.4885
GO:0007015	actin filament organization	2237.53	< 1e-5	< 1e-5	2222.62	< 1e-5	< 1e-5	41.77	< 1e-5	< 1e-5	0.95	0.5963	0.9165
GO:0007020	microtubule nucleation	93.60	0.0019	0.0036	92.74	0.0114	0.0207	3.42	< 1e-5	< 1e-5	-0.34	0.6041	0.9205
GO:0007021	tubulin folding	14.14	0.0033	0.0060	14.14	0.0043	0.0083	NA	NA	NA	NA	NA	NA
GO:0007033	vacuole organization and biogenesis	135.25	0.0902	0.1378	272.63	0.2499	0.3588	2.83	0.1651	0.2352	-0.55	0.8170	0.9338
GO:0007034	vacuolar transport	51.62	1.0000	1.0000	35.36	1.0000	1.0000	0.11	< 1e-5	< 1e-5	1.13	0.3051	0.9083
GO:0007035	vacuolar acidification	1053.22	< 1e-5	< 1e-5	1486.41	0.0004	0.0008	28.98	0.0049	0.0088	-0.68	0.4686	0.9383
GO:0007046	ribosome biogenesis	62.99	0.9999	1.0000	57.31	0.9990	1.0000	2.13	0.3186	0.4411	-3.41	0.0027	0.4023
GO:0007047	cell wall organization and biogenesis	1562.55	< 1e-5	< 1e-5	1338.46	< 1e-5	< 1e-5	24.06	0.0140	0.0237	-0.38	0.6384	0.9158
GO:0007049	cell cycle	35.29	0.0017	0.0032	31.22	0.0076	0.0142	NA	NA	NA	-0.44	0.6236	0.9338
GO:0007059	chromosome segregation	510.21	0.4498	0.5962	502.34	0.4848	0.6495	1.15	< 1e-5	< 1e-5	-0.17	0.7488	0.9553
GO:0007062	sister chromatid cohesion	99.84	1.0000	1.0000	99.84	1.0000	1.0000	NA	NA	NA	-0.53	0.7517	0.9281
GO:0007064	mitotic sister chromatid cohesion	128.40	0.0245	0.0400	126.68	0.0305	0.0521	1.16	0.9856	1.0000	-0.84	0.5056	0.9817
GO:0007070	negative regulation of transcription from RNA polymerase II promoter, mitotic	41.61	< 1e-5	< 1e-5	41.07	< 1e-5	< 1e-5	3.65	< 1e-5	< 1e-5	-1.45	0.2307	0.9590
GO:0007091	mitotic metaphase/anaphase transition	60.28	1.0000	1.0000	58.45	1.0000	1.0000	12.08	< 1e-5	< 1e-5	0.67	0.8333	0.9941
GO:0007094	mitotic spindle checkpoint	1075.90	0.9999	1.0000	1071.78	0.9998	1.0000	14.67	< 1e-5	< 1e-5	-0.52	0.5402	0.9317
GO:0007096	regulation of exit from mitosis	329.46	< 1e-5	< 1e-5	282.53	< 1e-5	< 1e-5	12.24	< 1e-5	< 1e-5	-0.97	0.4548	0.9979
GO:0007103	spindle pole body duplication in nuclear envelope	24.33	0.0111	0.0190	24.33	0.0093	0.0170	NA	NA	NA	-1.32	0.3496	1.0000
GO:0007117	budding cell bud growth	904.57	0.0403	0.0636	896.12	0.0490	0.0802	4.48	0.0182	0.0295	-1.85	0.2220	0.8418
GO:0007118	budding cell apical bud growth	341.42	< 1e-5	< 1e-5	294.78	< 1e-5	< 1e-5	NA	NA	NA	-1.21	0.4048	0.9685
GO:0007119	budding cell isotropic bud growth	346.76	< 1e-5	< 1e-5	294.78	< 1e-5	< 1e-5	NA	NA	NA	-1.15	0.4441	1.0000
GO:0007120	axial bud site selection	677.72	< 1e-5	< 1e-5	619.15	< 1e-5	< 1e-5	10.38	< 1e-5	< 1e-5	-2.55	0.1048	0.5931
GO:0007121	bipolar bud site selection	1456.90	< 1e-5	< 1e-5	1386.19	< 1e-5	< 1e-5	14.35	< 1e-5	< 1e-5	-0.50	0.4615	0.9332
GO:0007124	pseudohyphal growth	736.32	< 1e-5	< 1e-5	679.17	< 1e-5	< 1e-5	4.53	1.0000	1.0000	-0.77	0.3024	0.9683
GO:0007126	meiosis	758.34	< 1e-5	< 1e-5	741.21	< 1e-5	< 1e-5	10.78	< 1e-5	< 1e-5	-1.53	0.1431	0.9529
GO:0007130	synaptonemal complex formation	7.78	0.4600	0.6051	7.78	0.4600	0.6221	NA	NA	NA	-1.23	0.2575	0.9920
GO:0007131	meiotic recombination	35.86	0.0250	0.0406	34.81	0.0387	0.0641	NA	NA	NA	-0.24	0.6740	0.9369

GO:0007155	cell adhesion	226.27	< 1e-5	< 1e-5	253.85	< 1e-5	< 1e-5	NA	NA	NA	-1.00	0.4862	1.0000
GO:0007165	signal transduction	739.31	< 1e-5	< 1e-5	763.33	< 1e-5	< 1e-5	12.54	< 1e-5	< 1e-5	-0.07	0.8829	0.9797
GO:0007231	osmosensory signaling pathway	48.72	< 1e-5	< 1e-5	49.77	< 1e-5	< 1e-5	4.49	0.0012	0.0022	0.96	0.4995	0.9254
GO:0007264	small GTPase mediated signal transduction	362.90	< 1e-5	< 1e-5	318.80	< 1e-5	< 1e-5	NA	NA	NA	-0.38	0.6447	0.9236
GO:0007265	Ras protein signal transduction	437.11	0.0092	0.0159	437.77	0.0046	0.0088	6.40	1.0000	1.0000	-0.25	0.7251	0.9363
GO:0007266	Rho protein signal transduction	148.49	1.0000	1.0000	150.00	1.0000	1.0000	8.49	< 1e-5	< 1e-5	-1.71	0.2230	0.9723
GO:0007569	cell aging	114.29	0.0008	0.0015	114.29	0.0005	0.0010	0.22	< 1e-5	< 1e-5	1.08	0.3680	0.9579
GO:0008033	tRNA processing	62.20	0.0002	0.0004	49.98	0.0200	0.0354	10.61	< 1e-5	< 1e-5	-0.40	0.6577	0.9269
GO:0008054	cyclin catabolism	56.69	< 1e-5	< 1e-5	56.69	< 1e-5	< 1e-5	12.08	< 1e-5	< 1e-5	0.73	0.7716	0.9978
GO:0008156	negative regulation of DNA replication	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.73	0.8944	0.9466
GO:0008295	spermidine biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.07	0.3913	0.9495
GO:0008298	intracellular mRNA localization	150.38	0.0238	0.0391	134.58	0.0043	0.0083	NA	NA	NA	-0.92	0.5632	0.9839
GO:0008299	isoprenoid biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.20	0.2029	0.9023
GO:0008614	pyridoxine metabolism	41.58	< 1e-5	< 1e-5	41.58	0.0002	0.0004	8.11	0.0016	0.0029	0.76	0.7667	0.9957
GO:0008654	phospholipid biosynthesis	140.88	0.1750	0.2535	268.97	0.8286	0.9957	4.96	0.0156	0.0260	0.98	0.4622	0.9351
GO:0008655	pyrimidine salvage	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.31	0.1636	0.8221
GO:0009060	aerobic respiration	275.72	0.0699	0.1085	242.09	0.0814	0.1288	NA	NA	NA	-1.29	0.1758	0.9637
GO:0009063	amino acid catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.17	0.2663	0.9176
GO:0009070	serine family amino acid biosynthesis	382.17	0.5894	0.7460	430.34	< 1e-5	< 1e-5	7.84	0.0965	0.1426	-1.32	0.1993	1.0000
GO:0009082	branched chain family amino acid biosynthesis	103.94	< 1e-5	< 1e-5	154.15	< 1e-5	< 1e-5	35.84	< 1e-5	< 1e-5	-1.13	0.4264	1.0000
GO:0009092	homoserine metabolism	42.67	0.2280	0.3188	42.67	0.2200	0.3192	NA	NA	NA	NA	NA	NA
GO:0009098	leucine biosynthesis	91.22	0.3934	0.5326	18.38	0.1144	0.1780	NA	NA	NA	-0.76	0.7873	0.9494
GO:0009102	biotin biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.96	0.5020	0.9341
GO:0009113	purine base biosynthesis	129.40	0.7761	0.9565	130.11	0.7786	0.9634	NA	NA	NA	-1.57	0.0971	1.0000
GO:0009117	nucleotide metabolism	268.70	0.4955	0.6476	127.28	0.5435	0.7114	0.63	0.8647	1.0000	-0.07	0.9700	0.9859
GO:0009228	thiamin biosynthesis	55.98	0.0002	0.0004	55.98	0.0001	0.0002	NA	NA	NA	0.62	0.9118	0.9785
GO:0009231	riboflavin biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.95	0.5719	1.0000
GO:0009396	folic acid and derivative biosynthesis	43.99	0.0005	0.0010	73.58	0.0265	0.0461	NA	NA	NA	-0.88	0.6444	0.9999
GO:0009408	response to heat	551.90	0.8610	1.0000	549.87	0.8269	0.9957	NA	NA	NA	-0.49	0.5828	0.9319
GO:0009435	NAD biosynthesis	16.97	0.5366	0.6917	17.68	0.7421	0.9235	0.51	0.8245	0.9834	-0.87	0.6349	0.9966
GO:0009651	response to salt stress	348.11	< 1e-5	< 1e-5	349.44	< 1e-5	< 1e-5	NA	NA	NA	-2.12	0.0717	0.7481
GO:0009749	response to glucose stimulus	73.54	1.0000	1.0000	92.63	1.0000	1.0000	32.65	< 1e-5	< 1e-5	-0.01	0.9980	0.9969
GO:0015940	pantothenate biosynthesis	60.98	0.4131	0.5554	46.96	0.4371	0.5943	10.17	< 1e-5	< 1e-5	0.97	0.4819	0.9340
GO:0015986	ATP synthesis coupled proton transport	874.44	< 1e-5	< 1e-5	1270.57	< 1e-5	< 1e-5	61.90	< 1e-5	< 1e-5	-0.56	0.6055	0.9342
GO:0015992	proton transport	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.12	0.3747	1.0000
GO:0016050	vesicle organization and biogenesis	160.41	1.0000	1.0000	160.41	1.0000	1.0000	1.84	0.0067	0.0118	-1.01	0.5243	0.9991
GO:0016070	RNA metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.69	0.8684	1.0000
GO:0016192	vesicle-mediated transport	995.56	< 1e-5	< 1e-5	980.40	< 1e-5	< 1e-5	1.73	0.4842	0.6461	1.03	0.4151	0.9798
GO:0016255	attachment of GPI anchor to protein	124.00	0.7151	0.8931	124.00	0.7109	0.9007	0.09	1.0000	1.0000	-0.85	0.6884	0.9901
GO:0016310	phosphorylation	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.05	0.4233	0.9572
GO:0016481	negative regulation of transcription	135.76	< 1e-5	< 1e-5	123.04	< 1e-5	< 1e-5	NA	NA	NA	0.99	0.4527	0.9556
GO:0016558	peroxisome matrix protein import	89.42	< 1e-5	< 1e-5	89.42	< 1e-5	< 1e-5	NA	NA	NA	-1.29	0.1967	0.9555
GO:0016567	protein ubiquitination	372.38	< 1e-5	< 1e-5	370.46	< 1e-5	< 1e-5	8.58	1.0000	1.0000	-1.09	0.3770	1.0000
GO:0016568	chromatin modification	351.08	< 1e-5	< 1e-5	347.71	< 1e-5	< 1e-5	4.27	0.8830	1.0000	-2.06	0.1596	0.7356
GO:0016571	histone methylation	41.23	0.4422	0.5889	41.23	0.4372	0.5943	0.94	1.0000	1.0000	-1.71	0.1912	0.9551
GO:0016573	histone acetylation	403.84	< 1e-5	< 1e-5	391.77	< 1e-5	< 1e-5	6.73	< 1e-5	< 1e-5	-2.58	0.1283	0.6054

GO:0016575	histone deacetylation	174.00	< 1e-5	< 1e-5	172.42	< 1e-5	< 1e-5	2.12	< 1e-5	< 1e-5	0.68	0.8425	0.9999
GO:0016584	nucleosome spacing	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.68	0.9714	0.9351
GO:0016925	protein sumoylation	47.03	0.0373	0.0592	47.03	0.0379	0.0635	NA	NA	NA	-0.97	0.5271	1.0000
GO:0018065	protein-cofactor linkage	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.40	0.1105	1.0000
GO:0019344	cysteine biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.29	0.0574	0.8583
GO:0019354	siroheme biosynthesis	15.56	< 1e-5	< 1e-5	7.07	0.5524	0.7194	1.27	< 1e-5	< 1e-5	NA	NA	NA
GO:0019413	acetate biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	-1.31	0.0678	0.9870
GO:0019415	acetate biosynthesis from carbon monoxide	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0019483	beta-alanine biosynthesis	107.48	< 1e-5	< 1e-5	90.51	< 1e-5	< 1e-5	26.29	< 1e-5	< 1e-5	1.18	0.2371	0.9464
GO:0019541	propionate metabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-2.11	< 1e-5	0.7275
GO:0019547	arginine catabolism to ornithine	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0019568	arabinose catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.73	0.8069	0.9402
GO:0019654	acetate fermentation	73.54	1.0000	1.0000	75.66	1.0000	1.0000	1.44	1.0000	1.0000	NA	NA	NA
GO:0019674	NAD metabolism	35.96	< 1e-5	< 1e-5	15.56	< 1e-5	< 1e-5	1.59	0.0154	0.0258	-1.00	0.4905	1.0000
GO:0019856	pyrimidine base biosynthesis	144.97	0.1292	0.1942	293.59	1.0000	1.0000	7.55	0.7838	0.9580	-1.04	0.4989	1.0000
GO:0019878	lysine biosynthesis, aminoadipic pathway	272.78	< 1e-5	< 1e-5	168.02	< 1e-5	< 1e-5	22.13	< 1e-5	< 1e-5	1.24	0.2244	0.8782
GO:0019933	cAMP-mediated signaling	15.56	0.0142	0.0240	4.24	0.7143	0.9009	5.92	0.0529	0.0806	-1.37	0.1272	1.0000
GO:0030100	regulation of endocytosis	12.86	< 1e-5	< 1e-5	12.86	< 1e-5	< 1e-5	NA	NA	NA	-0.68	0.8849	0.9305
GO:0030148	sphingolipid biosynthesis	830.43	0.1039	0.1578	820.62	0.0994	0.1564	NA	NA	NA	-1.19	0.4201	1.0000
GO:0030150	mitochondrial matrix protein import	243.49	< 1e-5	< 1e-5	243.49	< 1e-5	< 1e-5	NA	NA	NA	-0.24	0.7068	0.9398
GO:0030397	membrane disassembly	21.21	< 1e-5	< 1e-5	4.24	< 1e-5	< 1e-5	0.40	< 1e-5	< 1e-5	0.68	0.9744	1.0000
GO:0030437	sporulation (sensu Fungi)	563.04	0.0205	0.0341	588.46	0.0704	0.1120	9.17	0.1693	0.2394	-8.77	0.0019	0.1130
GO:0030447	filamentous growth	256.17	< 1e-5	< 1e-5	223.05	< 1e-5	< 1e-5	NA	NA	NA	-1.87	0.0600	0.8358
GO:0030466	chromatin silencing at silent mating-type cassette	240.10	0.0002	0.0004	238.04	0.0004	0.0008	7.55	0.7811	0.9580	-2.16	0.1387	0.7656
GO:0030468	establishment of cell polarity (sensu Fungi)	3583.86	< 1e-5	< 1e-5	3523.17	< 1e-5	< 1e-5	16.27	0.5391	0.7023	-0.72	0.3462	0.9330
GO:0030476	spore wall assembly (sensu Fungi)	86.22	0.3886	0.5326	50.12	0.4295	0.5895	0.00	1.0000	1.0000	-0.36	0.5594	0.9194
GO:0030488	tRNA methylation	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.91	0.5683	0.9879
GO:0030491	heteroduplex formation	204.35	0.5310	0.6876	204.35	0.5299	0.6999	NA	NA	NA	-0.79	0.7675	0.9659
GO:0030846	transcription termination from Pol II promoter, RNA polymerase(A) coupled	521.75	0.0002	0.0004	518.84	0.0002	0.0004	10.65	< 1e-5	< 1e-5	0.80	0.7053	0.9909
GO:0030847	transcription termination from Pol II promoter, RNA polymerase(A)-independent	521.75	< 1e-5	< 1e-5	518.84	0.0003	0.0006	10.65	< 1e-5	< 1e-5	0.74	0.7845	1.0000
GO:0031087	deadenylylation-independent decapping	403.76	< 1e-5	< 1e-5	403.76	< 1e-5	< 1e-5	NA	NA	NA	-0.82	0.7761	0.9751
GO:0031145	anaphase-promoting complex-dependent proteasomal ubiquitin-dependent protein catabolism	56.69	< 1e-5	< 1e-5	56.69	< 1e-5	< 1e-5	12.08	< 1e-5	< 1e-5	0.75	0.7512	0.9890
GO:0031146	SCF-dependent proteasomal ubiquitin-dependent protein catabolism	371.76	< 1e-5	< 1e-5	371.76	< 1e-5	< 1e-5	12.00	< 1e-5	< 1e-5	-0.85	0.6750	0.9861
GO:0040020	regulation of meiosis	637.04	< 1e-5	< 1e-5	625.45	< 1e-5	< 1e-5	7.04	0.0037	0.0067	-1.76	0.1679	0.9445
GO:0042138	meiotic DNA double-strand break formation	187.61	0.0036	0.0065	185.49	0.0033	0.0065	6.91	< 1e-5	< 1e-5	0.68	0.8599	1.0000
GO:0042145	homotypic vacuole fusion, non-autophagic	85.37	0.8568	1.0000	73.58	1.0000	1.0000	2.83	0.1611	0.2311	-0.81	0.7754	0.9710
GO:0042147	retrograde transport, endosome to Golgi	59.10	< 1e-5	< 1e-5	58.85	< 1e-5	< 1e-5	0.59	0.7549	0.9342	-0.29	0.8373	0.9288
GO:0042255	ribosome assembly	NA	NA	NA	NA	NA	NA	NA	NA	NA	-2.24	0.0241	0.8079
GO:0042273	ribosomal large subunit biogenesis	344.96	< 1e-5	< 1e-5	335.53	< 1e-5	< 1e-5	5.11	0.2724	0.3798	-2.20	0.1234	0.7836
GO:0042843	D-xylose catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.73	0.8124	0.9392
GO:0043044	ATP-dependent chromatin remodeling	87.68	1.0000	1.0000	62.23	1.0000	1.0000	NA	NA	NA	-0.80	0.5504	0.9723
GO:0043162	ubiquitin-dependent protein catabolism via the multivesicular body	18.38	0.8386	1.0000	NA	NA	NA	NA	NA	NA	0.63	0.8759	0.9815

	pathway												
GO:0043248	proteasome assembly	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.00	0.4563	0.9486
GO:0045003	double-strand break repair via synthesis-dependent strand annealing	202.93	0.2107	0.2990	201.69	0.3169	0.4481	1.51	< 1e-5	< 1e-5	1.57	0.0516	0.6894
GO:0045039	mitochondrial inner membrane protein import	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.58	0.7815	0.9409
GO:0045045	secretory pathway	387.07	0.1309	0.1957	429.86	0.0397	0.0654	NA	NA	NA	-1.08	0.4779	1.0000
GO:0045046	peroxisome membrane protein import	82.73	< 1e-5	< 1e-5	82.73	< 1e-5	< 1e-5	NA	NA	NA	NA	NA	NA
GO:0045047	protein-ER targeting	121.03	0.6623	0.8346	120.62	0.6630	0.8438	NA	NA	NA	1.56	0.0531	0.6532
GO:0045324	late endosome to vacuole transport	54.42	< 1e-5	< 1e-5	54.42	< 1e-5	< 1e-5	4.24	0.0094	0.0165	1.13	0.3105	0.8998
GO:0045337	farnesyl diphosphate biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0045449	regulation of transcription	123.22	0.0062	0.0110	123.47	0.0137	0.0248	NA	NA	NA	-0.60	0.5752	0.9399
GO:0045721	negative regulation of gluconeogenesis	14.77	0.0022	0.0041	10.28	0.1619	0.2450	NA	NA	NA	-0.74	0.7032	0.9466
GO:0045835	negative regulation of meiosis	174.00	< 1e-5	< 1e-5	172.42	< 1e-5	< 1e-5	2.12	< 1e-5	< 1e-5	-0.69	0.8072	0.9435
GO:0045876	positive regulation of sister chromatid cohesion	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.94	0.5925	1.0000
GO:0046459	short-chain fatty acid metabolism	NA	NA	NA	NA	NA	NA	0.71	< 1e-5	< 1e-5	-0.76	0.8600	0.9534
GO:0046513	ceramide biosynthesis	183.39	0.0371	0.0592	183.39	0.0384	0.0640	NA	NA	NA	1.36	0.1210	0.8695
GO:0046656	folic acid biosynthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GO:0046685	response to arsenic	79.90	0.8301	1.0000	78.49	0.8244	0.9957	NA	NA	NA	-0.02	0.9949	0.9948
GO:0046686	response to cadmium ion	48.79	0.8860	1.0000	48.79	0.8886	1.0000	NA	NA	NA	0.97	0.5033	0.9360
GO:0046854	phosphoinositide phosphorylation	36.92	1.0000	1.0000	15.53	1.0000	1.0000	9.49	< 1e-5	< 1e-5	1.37	0.1344	0.8928
GO:0048309	endoplasmic reticulum inheritance	118.80	0.6857	0.8602	97.64	0.3785	0.5299	NA	NA	NA	0.69	0.9611	1.0000

Table S3. GSEA parameter file.

```
producer_class        xtools.gsea.Gsea
producer_timestamp    1167380726066
param      cls        /home/belxpgo/my_gsea_data/pheno.cls#OXIDATIVE_STRESS
param      plot_top_x 20
param      norm       meandiv
param      save_rnd_lists        false
param      median     false
param      scoring_scheme        weighted
param      make_sets  true
param      gmx        /home/belxpgo/my_gsea_data/go_oln.gmt
param      gui        true
param      metric     None
param      rpt_label  my_analysis
param      help       false
param      order      descending
param      out        /home/belxpgo/gsea_home/output_folder
param      permute    tag
param      rnd_type   no_balance
param      set_min    1
param      sort       real
param      nperm      5000
param      rnd_seed   timestamp
param      zip_report false
param      set_max    500
param      res        /home/belxpgo/my_gsea_data/oxidative_stress.gct

file
/home/belxpgo/gsea_home/output_folder/my_analysis.Gsea.1167380726066/index.html
```