

# Synthetic Genetic Interaction in Yeast genes

N. LeMeur and Z. Jiang

April 10, 2009

## 1 Introduction

Synthetic genetic interactions experiments are now being conducted to better understand cellular interactions. The generated data have already proven to be extremely valuable (Davierwala et al., 2005; A et al., 2004; Zhao et al., 2005). Synthetic lethality especially defines a genetic interaction where the combination of mutations in two or more genes leads to cell death. The implications of synthetic lethal screens have been discussed in the context of drug development as synthetic lethal pairs could be used to selectively kill cancer cells, but leave normal cells relatively unharmed.

In this package, we propose statistical and computational tools for a systems biology approach in analyzing synthetic genetic interactions. Currently, our methods can be used to find relationships between synthetic genetic interactions and cellular organizational units such as multi-protein complexes or sequence motifs.

## 2 Synthetic genetic interaction data

Several synthetic genetic datasets are now publicly available. In this package we currently propose 6 datasets:

- A et al. (2004) Systematic genetic analysis with ordered arrays of yeast deletion
- Pan et al. (2006) DNA integrity experiment in *S. cerevisiae*
- Measday et al. (2005) Systematic yeast synthetic lethal and synthetic dosage lethal screens identify genes required for chromosome segregation.
- Schuldiner et al. (2005) Genetic Interaction Data (EMAP) from the yeast early secretory pathway
- Collins et al. (2007) Functional dissection of protein complexes involved in yeast chromosome biology using a genetic interaction map.

- Chervitz et al. (1999) Synthetic genetic interaction data from as recorded by the *Saccharomyces* Genome database in January, 2007.

In this package and as reported by most authors, we use the terms *query genes* for the genes that are specifically tested by the experimenter and *array genes* for the target genes usually spotted on a array (*e.g.*, SGA, dSLAM). We note however that an analogy can be made with the concept of *bait* and *prey* terms used in proteomic experiments (*e.g.*, Y2H, APMS).

## 2.1 Synthetic genetic array data, Tong et al. (2004)

Tong et al. (2001) used the *Synthetic Genetic Array technology* or SGA to investigate synthetic genetic interaction in *S. cerevisiae*. The package **SLGI** contains both the raw and preprocessed data from A et al. (2004). To access those data you first need to load the package **SLGI** and the yeast genome annotation package (**org.Sc.sgd.db**):

```
> library("SLGI")
> library("org.Sc.sgd.db")
> data(SGA)
> data(Atong)
```

Data **SGA** contains the systematic names of all the 4655 genes tested by A et al. (2004), including both the ones that were reported as presenting synthetic genetic interactions and the ones that were not (**SGAraw** corresponds to the original list parsed from table1 of Tong et al. (2001) supplementary material).

We can verify that the genes reported by A et al. (2004) are well characterized. To that aim, we use the yeast annotation data package **org.Sc.sgd.db**:

```
> rejected <- length(intersect(SGA, org.Sc.sgdREJECTORF))
```

We note that at this time 385 genes (out of the 4655) are among the rejected ORF listed by the *Saccharomyces* Genome Database (SGD <http://www.yeastgenome.org/>). If one want to update common gene names or alias to systematic names, one can use the following:

```
> updateSGA = mget(SGA, org.Sc.sgdCOMMON2ORF, ifnotfound = NA)
```

The **tong2004raw** data.frame contains the original data reported by A et al. (2004) as Table S1 in their online supporting material. The **Atong** data contains the association matrix extracted from the **tong2004raw** data.frame. The gene names were updated for systematic gene names. They selected 132 query genes that are known involved in a chosen set of molecular functions.

There are 11 essential genes found in the query genes. A et al. (2004) pointed out that some of the query genes are partially functioning alleles of essential genes. So, we assumed these genes are fine. There are also 3 essential genes in the reported array genes that showed

synthetic lethal (SL) interaction with at least one of the query genes. We checked these three genes. Two of them, "YJL174W" and "YPL075W", are annotated both "lethal" and "viable" in the SGD database. The other gene, "YBR121C", is "lethal". We don't have the resources to tract down why this gene appears on the SGA array Tong et al. (2001).

### 2.1.1 Synthetic lethal and synthetic dosage lethal screens, Measday et al (2005)

Measday et al. (2005) perform some systematic yeast synthetic lethal and synthetic dosage lethal screens using the SGA approach (Tong et al., 2001). They first tested 14 query genes and found 84 non-essential genes that synthetically interact with at least one query gene (SLchr). Then they tested interaction between 3 query genes and the genome wide set of deletion strains under 3 different temperatures. They found 141 array genes that interact at least with one query gene (SDL). They identified genes required for chromosome segregation.

## 2.2 DNA integrity experiment in *S. cerevisiae*, Pan et al (2006)

The package contains raw and preprocessed data from Pan et al. (2006) obtained in Boeke's lab.

```
> data(Boeke2006raw)
> data(Boeke2006)
```

Boeke2006raw is a data frame with 5775 observations and Boeke2006 is an incidence matrix reporting the systematic genetic interactions identified between 74 query genes and the deletion gene set in Pan et al. (2004) (see man pages for more details).

The technology used by Boeke and collaborators is slightly different from the approach taken by Tong et al. (2001). The used heterozygote diploid-based synthetic lethality analyzed by microarray (dSLAM). The 21991 probes spotted on the dSLAM array are available by calling dSLAM.GPL1444 or dSLAM (see man pages for more details).

## 2.3 Genetic Interaction Data (EMAP), Schuldiner et al (2005) and Collins (2007)

We also collected data generated by Collins and collaborators. These data are different from the other as they have been heavily preprocessed using their own procedure, EMAP or epistatic miniarray profiles. Those data are presented as incidence matrix and are accompanied by some metadata, e.g., systematic names and mutated allele.

```
> data(gi2005)
> data(gi2005.metadata)
```

## 2.4 Saccharomyces Genome database

We provide synthetic genetic interaction data as recorded by the Saccharomyces Genome database in January, 2007. Data can be accessed using `SGD.SL`, synthetic lethal, `SGD.SynRescue`, synthetic rescue, and `SGD.SynGrowthDefect`, synthetic growth defect.

## 3 Transcription Factor data

The transcription factor binding affinities data were extracted from Lee et al. (2002). They represented as an matrix where rows are *S. cerevisiae* systematic gene names and columns known transcription factor. The value in each entry represents the p-value, as reported by Lee et al. (2002), for the transcription factor (TF) binding upstream of the gene.

```
> data(TFmat)
```

## 4 Example of analysis: Synthetic genetic interactions and multi-protein complexes

To integrate synthetic genetic interactions with multi-protein complexes, we can make use of the interactome as defined in the `ScISI` package. The `ScISI` package or *In Silico Interactome for Saccharomyces cerevisiae* provides an interactome built for computational experimentation. The `ScISI` is binary incidence matrix where the rows are indexed by the gene locus names and the columns are indexed by the identification codes for the protein complexes based on the repository from where they are obtained. This interactome is currently built from the Intact, Gene Ontology and Mips curated databases, and estimated protein complexes from the `apComplex` package. In this vignette, we will make use of a subset of the `ScISI` interactome, the `ScISIC` data, that only contains the data from the curated databases.

```
> library(ScISI)
> data(ScISIC)
> ScISIC[1:5, 1:5]
```

	EBI-913756	EBI-876785	EBI-852570	EBI-866976	EBI-1180400
EBI-913756	0	0	0	0	0
EBI-876785	0	0	0	0	0
EBI-852570	0	0	0	0	0
EBI-866976	0	0	0	0	0
EBI-1180400	0	0	0	0	0

As an example we will use the data generated by Pan et al. (2006). First, one need to reduce the interactome matrix and genetic interaction matrix to the same list of genes. This can be done using the `gi2Interactome` function.

```

> data(Boeke2006)
> data(dSLAM)
> dim(Boeke2006)

[1] 74 843

> Boeke2006red <- gi2Interactome(Boeke2006, ScISIC)
> dim(Boeke2006red)

[1] 46 320

```

Next we can identify multi-protein complexes that present synthetic interaction among their proteins (**within interaction**) or share synthetic interaction with other multi-protein complex (**between interaction**) using the `getInteraction` function. This function requires the incidence matrix, the array list and the interactome of interest.

```

> interact <- getInteraction(Boeke2006red, dSLAM, ScISIC)

```

Then, one might want to know how what are the multi-protein complexes that share at least  $n$  interactions:

```

> intSummary <- iSummary(interact$bwMat, n = 5)

```

```

-----Count: 7 -----
GO:0031390  Ctf18 RFC-like complex
EBI-1252538  Ctf18 RFC-like complex
-----Count: 12 -----
GO:0000417  HIR complex
EBI-1236334  HIR complex
-----Count: 9 -----
GO:0030870  Mre11 complex
EBI-1236334  Mre11 complex
-----Count: 9 -----
GO:0031390  Ctf18 RFC-like complex
EBI-1236334  Ctf18 RFC-like complex
-----Count: 6 -----
GO:0031390  Ctf18 RFC-like complex
EBI-1251060  Ctf18 RFC-like complex
-----Count: 9 -----
GO:0000502  proteasome complex
GO:0000118  histone deacetylase complex
-----Count: 6 -----
GO:0030015  CCR4-NOT core complex

```

GO:0000118 histone deacetylase complex  
 -----Count: 8 -----  
 GO:0031415 NatA complex  
 GO:0000118 histone deacetylase complex  
 -----Count: 9 -----  
 GO:0043529 GET complex  
 GO:0000118 histone deacetylase complex  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0000118 histone deacetylase complex  
 -----Count: 8 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0000118 histone deacetylase complex  
 -----Count: 6 -----  
 MIPS-360 Proteasome  
 GO:0000118 histone deacetylase complex  
 -----Count: 7 -----  
 GO:0000502 proteasome complex  
 GO:0000119 mediator complex  
 -----Count: 10 -----  
 GO:0043529 GET complex  
 GO:0000119 mediator complex  
 -----Count: 6 -----  
 GO:0005694 chromosome  
 GO:0000119 mediator complex  
 -----Count: 6 -----  
 GO:0000812 SWR1 complex  
 GO:0000151 ubiquitin ligase complex  
 -----Count: 6 -----  
 GO:0030870 Mre11 complex  
 GO:0000151 ubiquitin ligase complex  
 -----Count: 6 -----  
 GO:0035267 NuA4 histone acetyltransferase complex  
 GO:0000151 ubiquitin ligase complex  
 -----Count: 7 -----  
 GO:0005694 chromosome  
 GO:0000151 ubiquitin ligase complex  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0000151 ubiquitin ligase complex  
 -----Count: 8 -----  
 GO:0030529 ribonucleoprotein complex

GO:0000417 HIR complex  
 -----Count: 6 -----  
 GO:0032806 carboxy-terminal domain protein kinase complex  
 GO:0000417 HIR complex  
 -----Count: 9 -----  
 GO:0000508 Rpd3L complex  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 GO:0016469 proton-transporting two-sector ATPase complex  
 GO:0000502 proteasome complex  
 -----Count: 15 -----  
 GO:0030529 ribonucleoprotein complex  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 GO:0030870 Mre11 complex  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 GO:0030897 HOPS complex  
 GO:0000502 proteasome complex  
 -----Count: 9 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0000502 proteasome complex  
 -----Count: 7 -----  
 GO:0033263 CORVET complex  
 GO:0000502 proteasome complex  
 -----Count: 11 -----  
 GO:0005694 chromosome  
 GO:0000502 proteasome complex  
 -----Count: 15 -----  
 GO:0005840 ribosome  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 MIPS-240.20 HDB complex  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 MIPS-260.80 Class C Vps protein complex  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 MIPS-220 H<sup>+</sup>-transporting ATPase, vacuolar  
 GO:0000502 proteasome complex  
 -----Count: 6 -----  
 GO:0030015 CCR4-NOT core complex

GO:0000508 Rpd3L complex  
 -----Count: 9 -----  
 GO:0031415 NatA complex  
 GO:0000508 Rpd3L complex  
 -----Count: 14 -----  
 GO:0043529 GET complex  
 GO:0000508 Rpd3L complex  
 -----Count: 7 -----  
 GO:0005694 chromosome  
 GO:0000508 Rpd3L complex  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0000508 Rpd3L complex  
 -----Count: 9 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0000508 Rpd3L complex  
 -----Count: 8 -----  
 GO:0030015 CCR4-NOT core complex  
 GO:0000812 SWR1 complex  
 -----Count: 8 -----  
 GO:0031415 NatA complex  
 GO:0000812 SWR1 complex  
 -----Count: 6 -----  
 GO:0043529 GET complex  
 GO:0000812 SWR1 complex  
 -----Count: 6 -----  
 GO:0005694 chromosome  
 GO:0000812 SWR1 complex  
 -----Count: 8 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0000812 SWR1 complex  
 -----Count: 8 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0000812 SWR1 complex  
 -----Count: 9 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0000814 ESCRT II complex  
 -----Count: 6 -----  
 GO:0031415 NatA complex  
 GO:0000814 ESCRT II complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase



GO:0000814 ESCRT II complex  
 -----Count: 6 -----  
 MIPS-360 Proteasome  
 GO:0000814 ESCRT II complex  
 -----Count: 6 -----  
 GO:0030015 CCR4-NOT core complex  
 GO:0000815 ESCRT III complex  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0000815 ESCRT III complex  
 -----Count: 6 -----  
 GO:0043529 GET complex  
 GO:0000938 GARP complex  
 -----Count: 8 -----  
 GO:0043529 GET complex  
 GO:0005667 transcription factor complex  
 -----Count: 6 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0005678 chromatin assembly complex  
 -----Count: 6 -----  
 GO:0033263 CORVET complex  
 GO:0005678 chromatin assembly complex  
 -----Count: 8 -----  
 GO:0005694 chromosome  
 GO:0005678 chromatin assembly complex  
 -----Count: 7 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0005680 anaphase-promoting complex  
 -----Count: 6 -----  
 GO:0030870 Mre11 complex  
 GO:0005732 small nucleolar ribonucleoprotein complex  
 -----Count: 9 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0005871 kinesin complex  
 -----Count: 6 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0005875 microtubule associated complex  
 -----Count: 6 -----  
 GO:0043529 GET complex  
 GO:0008023 transcription elongation factor complex  
 -----Count: 7 -----  
 GO:0005694 chromosome

GO:0008540 proteasome regulatory particle, base subcomplex  
 -----Count: 16 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0016272 prefoldin complex  
 -----Count: 9 -----  
 GO:0031415 NatA complex  
 GO:0016272 prefoldin complex  
 -----Count: 6 -----  
 GO:0005838 proteasome regulatory particle  
 GO:0016272 prefoldin complex  
 -----Count: 9 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0016272 prefoldin complex  
 -----Count: 6 -----  
 MIPS-360 Proteasome  
 GO:0016272 prefoldin complex  
 -----Count: 10 -----  
 GO:0030015 CCR4-NOT core complex  
 GO:0016469 proton-transporting two-sector ATPase complex  
 -----Count: 6 -----  
 GO:0031415 NatA complex  
 GO:0016469 proton-transporting two-sector ATPase complex  
 -----Count: 16 -----  
 GO:0043529 GET complex  
 GO:0016469 proton-transporting two-sector ATPase complex  
 -----Count: 10 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0016469 proton-transporting two-sector ATPase complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0016469 proton-transporting two-sector ATPase complex  
 -----Count: 6 -----  
 GO:0031415 NatA complex  
 GO:0016514 SWI/SNF complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0016514 SWI/SNF complex  
 -----Count: 8 -----  
 GO:0031415 NatA complex  
 GO:0016585 chromatin remodeling complex  
 -----Count: 8 -----  
 MIPS-370 Protein N-acetyltransferase

GO:0016585 chromatin remodeling complex  
 -----Count: 10 -----  
 GO:0043529 GET complex  
 GO:0017119 Golgi transport complex  
 -----Count: 11 -----  
 GO:0030529 ribonucleoprotein complex  
 GO:0030015 CCR4-NOT core complex  
 -----Count: 6 -----  
 GO:0030870 Mre11 complex  
 GO:0030015 CCR4-NOT core complex  
 -----Count: 6 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0030015 CCR4-NOT core complex  
 -----Count: 6 -----  
 GO:0000274 mitochondrial proton-transporting ATP synthase, stator stalk  
 GO:0030015 CCR4-NOT core complex  
 -----Count: 6 -----  
 MIPS-240.20 HDB complex  
 GO:0030015 CCR4-NOT core complex  
 -----Count: 9 -----  
 MIPS-420.50 F0/F1 ATP synthase (complex V)  
 GO:0030015 CCR4-NOT core complex  
 -----Count: 12 -----  
 GO:0030870 Mre11 complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 9 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 18 -----  
 GO:0031415 NatA complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 9 -----  
 GO:0033062 Rhp55-Rhp57 complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 8 -----  
 GO:0033551 monopolin complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 11 -----  
 GO:0043529 GET complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 13 -----  
 GO:0005694 chromosome

GO:0030529 ribonucleoprotein complex  
 -----Count: 12 -----  
 GO:0005838 proteasome regulatory particle  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 11 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 18 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 12 -----  
 MIPS-360 Proteasome  
 GO:0030529 ribonucleoprotein complex  
 -----Count: 9 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 GO:0031415 NatA complex  
 GO:0030870 Mre11 complex  
 -----Count: 9 -----  
 GO:0032806 carboxy-terminal domain protein kinase complex  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 GO:0033551 monopolin complex  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 GO:0043234 protein complex  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 GO:0043529 GET complex  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 GO:0046540 U4/U6 x U5 tri-snRNP complex  
 GO:0030870 Mre11 complex  
 -----Count: 10 -----  
 GO:0005694 chromosome  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0030870 Mre11 complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase

GO:0030870 Mre11 complex  
 -----Count: 9 -----  
 MIPS-360 Proteasome  
 GO:0030870 Mre11 complex  
 -----Count: 9 -----  
 GO:0031390 Ctf18 RFC-like complex  
 GO:0030897 HOPS complex  
 -----Count: 6 -----  
 GO:0031415 NatA complex  
 GO:0030897 HOPS complex  
 -----Count: 8 -----  
 GO:0043529 GET complex  
 GO:0030897 HOPS complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0030897 HOPS complex  
 -----Count: 6 -----  
 GO:0031415 NatA complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 GO:0032806 carboxy-terminal domain protein kinase complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 12 -----  
 GO:0033263 CORVET complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 GO:0033551 monopolin complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 9 -----  
 GO:0033597 mitotic checkpoint complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 GO:0035267 NuA4 histone acetyltransferase complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 GO:0043529 GET complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 GO:0046695 SLIK (SAGA-like) complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 GO:0000786 nucleosome

GO:0031390 Ctf18 RFC-like complex  
 -----Count: 13 -----  
 GO:0005694 chromosome  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 MIPS-125.10.10 Ddc1p-Mec3p complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 9 -----  
 MIPS-260.80 Class C Vps protein complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 MIPS-310 Nuclear pore complex (NPC)  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 9 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 6 -----  
 MIPS-360 Proteasome  
 GO:0031390 Ctf18 RFC-like complex  
 -----Count: 8 -----  
 GO:0033263 CORVET complex  
 GO:0031415 NatA complex  
 -----Count: 6 -----  
 GO:0046540 U4/U6 x U5 tri-snRNP complex  
 GO:0031415 NatA complex  
 -----Count: 12 -----  
 GO:0005681 spliceosome  
 GO:0031415 NatA complex  
 -----Count: 13 -----  
 GO:0005694 chromosome  
 GO:0031415 NatA complex  
 -----Count: 6 -----  
 GO:0005840 ribosome  
 GO:0031415 NatA complex  
 -----Count: 6 -----  
 MIPS-240.20 HDB complex  
 GO:0031415 NatA complex  
 -----Count: 6 -----  
 MIPS-260.80 Class C Vps protein complex

GO:0031415 NatA complex  
 -----Count: 6 -----  
 MIPS-510.190.50 SWI/SNF transcription activator complex  
 GO:0031415 NatA complex  
 -----Count: 6 -----  
 MIPS-220 H<sup>+</sup>-transporting ATPase, vacuolar  
 GO:0031415 NatA complex  
 -----Count: 6 -----  
 GO:0033551 monopolin complex  
 GO:0032806 carboxy-terminal domain protein kinase complex  
 -----Count: 6 -----  
 GO:0043529 GET complex  
 GO:0032806 carboxy-terminal domain protein kinase complex  
 -----Count: 7 -----  
 GO:0005694 chromosome  
 GO:0032806 carboxy-terminal domain protein kinase complex  
 -----Count: 8 -----  
 GO:0043529 GET complex  
 GO:0033263 CORVET complex  
 -----Count: 8 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0033263 CORVET complex  
 -----Count: 7 -----  
 MIPS-360 Proteasome  
 GO:0033263 CORVET complex  
 -----Count: 6 -----  
 GO:0005694 chromosome  
 GO:0033551 monopolin complex  
 -----Count: 10 -----  
 GO:0043529 GET complex  
 GO:0033588 Elongator holoenzyme complex  
 -----Count: 6 -----  
 GO:0005694 chromosome  
 GO:0035267 NuA4 histone acetyltransferase complex  
 -----Count: 8 -----  
 GO:0005694 chromosome  
 GO:0043234 protein complex  
 -----Count: 8 -----  
 GO:0048188 COMPASS complex  
 GO:0043529 GET complex  
 -----Count: 6 -----  
 GO:0000220 vacuolar proton-transporting V-type ATPase, V0 domain

GO:0043529 GET complex  
 -----Count: 10 -----  
 GO:0000221 vacuolar proton-transporting V-type ATPase, V1 domain  
 GO:0043529 GET complex  
 -----Count: 22 -----  
 GO:0005694 chromosome  
 GO:0043529 GET complex  
 -----Count: 6 -----  
 GO:0005840 ribosome  
 GO:0043529 GET complex  
 -----Count: 6 -----  
 MIPS-133.40 Srb10p complex  
 GO:0043529 GET complex  
 -----Count: 6 -----  
 MIPS-240.20 HDB complex  
 GO:0043529 GET complex  
 -----Count: 10 -----  
 MIPS-260.20 Clathrin-associated protein (AP) complex  
 GO:0043529 GET complex  
 -----Count: 8 -----  
 MIPS-260.80 Class C Vps protein complex  
 GO:0043529 GET complex  
 -----Count: 8 -----  
 MIPS-510.40.20 Kornberg's mediator (SRB) complex  
 GO:0043529 GET complex  
 -----Count: 16 -----  
 MIPS-220 H<sup>+</sup>-transporting ATPase, vacuolar  
 GO:0043529 GET complex  
 -----Count: 12 -----  
 MIPS-510.40 RNA polymerase II holoenzyme  
 GO:0043529 GET complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0046540 U4/U6 x U5 tri-snRNP complex  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0000274 mitochondrial proton-transporting ATP synthase, stator stalk  
 -----Count: 12 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0005681 spliceosome  
 -----Count: 6 -----  
 GO:0005694 chromosome



GO:0005694 chromosome  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 GO:0005694 chromosome  
 -----Count: 13 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0005694 chromosome  
 -----Count: 12 -----  
 MIPS-360 Proteasome  
 GO:0005694 chromosome  
 -----Count: 12 -----  
 GO:0005840 ribosome  
 GO:0005838 proteasome regulatory particle  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 GO:0005840 ribosome  
 -----Count: 13 -----  
 MIPS-360 Proteasome  
 GO:0005840 ribosome  
 -----Count: 6 -----  
 MIPS-510.190.110 CCR4 complex  
 MIPS-240.20 HDB complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 MIPS-240.20 HDB complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 MIPS-260.80 Class C Vps protein complex  
 -----Count: 9 -----  
 MIPS-510.190.110 CCR4 complex  
 MIPS-420.50 F0/F1 ATP synthase (complex V)  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 MIPS-510.190.50 SWI/SNF transcription activator complex  
 -----Count: 6 -----  
 MIPS-370 Protein N-acetyltransferase  
 MIPS-220 H<sup>+</sup>-transporting ATPase, vacuolar

Finally, we want to know if any of those interactions are statistically significant. To that aim we developed 2 approaches. First, using a graph theory approach, we test whether those interactions are randomly distributed within the interactome.

```
> modelBoeke <- modelSLGI(Boeke2006red, universe = dSLAM, interactome = ScISIC,
+   type = "intM", perm = 5)
```

A plot function allows you to visualize the result. In this case, we note that the number of observed synthetic genetic interaction is globally higher than the simulated data

```
> plot(modelBoeke, pch = 20)
```

```
■echo=FALSE,fig=TRUE■ print(plot(modelBoeke,pch=20))
```

Note that here, for computer time efficiency, we only performed 5 permutations but for really analysis 100 permutations or more are strongly recommended.

Next, we can perform a Hypergeometric test to identify the multi-protein complexes that presents a unusual number of synthetic genetic interaction.

The test2Interact function allows you to summarize the genetic interactions within one cellular organizational unit or between 2 cellular organizational units, taking into account all the interactions tested (positive or negative). One can compute the global interaction matrix as follows:

```
> array <- dSLAM[dSLAM %in% rownames(ScISIC)]
> query <- rownames(Boeke2006)[rownames(Boeke2006) %in% rownames(ScISIC)]
> allInteract <- matrix(1, nrow = length(query), ncol = length(array),
+   dimnames = list(query, array))
> tested <- getInteraction(allInteract, dSLAM, ScISIC)

> testedInteract <- test2Interact(iMat = interact$bwMat, tMat = tested$bwMat,
+   interactome = ScISIC)
> significant <- hyperG(cbind(Tested = testedInteract$tested, Interact = testedInteract$
+   sum(Boeke), nrow(Boeke2006red) * length(dSLAM))
```

## References

- Tong A et al. Global mapping of the yeast genetic interaction network. *Science*, 303:808–813, Feb. 2004.
- S.A. Chervitz, E.T. Hester, C.A. Ball, et al. Using the Saccharomyces Genome Database (SGD) for analysis of protein similarities and structure. 27(1):74–78, 1999.
- SR Collins, KM Miller, NL Maas, A Roguev, J Fillingham, CS Chu, M Schuldiner, M Gebbia, J Recht, M Shales, et al. Functional dissection of protein complexes involved in yeast chromosome biology using a genetic interaction map. *Nature*, 446(7137):806–810, 2007.

- PA Davierwala, J Haynes, Z Li, RL Brost, MD Robinson, L Yu, S Mnaimneh, H Ding, H Zhu, Y Chen, X Cheng, GW Brown, C Boone, BJ Andrews, and TR Hughes. The synthetic genetic interaction spectrum of essential genes. *Nat Genet*, 37(10):1147–1152, Oct 2005.
- TI Lee, NJ Rinaldi, F Robert, et al. Transcriptional regulatory networks in *Saccharomyces cerevisiae*. *Science*, 298:799–804, 2002.
- V. Measday, K. Baetz, J. Guzzo, K. Yuen, T. Kwok, B. Sheikh, H. Ding, R. Ueta, T. Hoac, B. Cheng, et al. Systematic yeast synthetic lethal and synthetic dosage lethal screens identify genes required for chromosome segregation. *Proc Natl Acad Sci US A*, 102(39):13956–13961, 2005.
- X Pan, DS Yuan, D Xiang, X Wang, S Sookhai-Mahadeo, JS Joel S Bader, P Hieter, F Spencer, and JD Boeke. A robust toolkit for functional profiling of the yeast genome. *Mol Cell*, 16(3):487–496, 2004.
- X Pan, P Ye, DS Yuan, et al. A DNA integrity network in the yeast *Saccharomyces cerevisiae*. *Cell*, 124:1069–1081, 2006.
- M. Schuldiner, S.R. Collins, N.J. Thompson, V. Denic, A. Bhamidipati, T. Punna, J. Ihmels, B. Andrews, C. Boone, J.F. Greenblatt, et al. Exploration of the Function and Organization of the Yeast Early Secretory Pathway through an Epistatic Miniarray Profile. *Cell*, 123(3):507–519, 2005.
- AH Tong, M Evangelista, AB Parsons, H Xu, GD Bader, N Page, M Robinson, S Raghbizadeh, CW Hogue, H Bussey, B Andrews, M Tyers, and C Boone. Systematic genetic analysis with ordered arrays of yeast deletion mutants. 294 (5550):2364 – 8, 2001.
- R Zhao, M Davey, Y-C. Hsu, et al. Navigating the chaperone network: An integrative map of physical and genetic interactions mediated by the Hsp90 chaperone. *Cell*, 120:715–727, 2005.