1 Introduction

Synthetic genetic interactions experiments are now being conduct 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 were 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 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
- Schuldiner et al. (2005) Genetic Interaction Data (EMAP) from the yeast early secretory pathway

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):

```r
> 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 (SGAr raw 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:

```r
> 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:

```r
> 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 be 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]

<table>
<thead>
<tr>
<th></th>
<th>EBI-913756</th>
<th>EBI-876785</th>
<th>EBI-852570</th>
<th>EBI-866976</th>
<th>EBI-1180400</th>
</tr>
</thead>
<tbody>
<tr>
<td>YLR274W</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>YGL201C</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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] 40 261

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: 6 --------
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: 8 ---------
GO:0005830 Not found (possibly deprecated)
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: 8 ---------
GO:0043529 GET complex
GO:0000119 mediator 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: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 ---------
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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+-transporting ATPase, vacuolar
GO:0000502 proteasome complex
---------Count: 6 ---------
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GO:0000508 Rpd3L complex
---------Count: 9 ---------
GO:0031415 NatA complex
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---------Count: 8 ---------
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GO:0000812 SWR1 complex
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GO:0031415 NatA complex
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GO:0043529 GET complex
GO:0000812 SWR1 complex
---------Count: 8 ---------
GO:0005830 Not found (possibly deprecated)
GO:0000812 SWR1 complex
---------Count: 8 ---------
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GO:0000812 SWR1 complex
---------Count: 8 ---------
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GO:0000812 SWR1 complex
----------Count: 9 ----------
GO:0000814 ESCRT II complex
----------Count: 6 ----------
GO:0031390 Ctf18 RFC-like complex
GO:0031415 NatA complex
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----------Count: 6 ----------
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GO:0000814 ESCRT II complex
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----------Count: 6 ----------
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----------Count: 6 ----------
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GO:0000815 ESCRT III complex
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GO:0000815 ESCRT III complex
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----------Count: 6 ----------
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GO:0005667 transcription factor complex
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GO:0005678 chromatin assembly complex
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GO:0030870 Mre11 complex
GO:0005732 small nucleolar ribonucleoprotein complex
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<tr>
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<td></td>
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<td>Proteasome</td>
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<td></td>
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<tr>
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<td>Not found (possibly deprecated)</td>
<td>Count: 6</td>
</tr>
<tr>
<td>GO:0016514</td>
<td>SWI/SNF complex</td>
<td>Count: 6</td>
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<tr>
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<td>Count: 6</td>
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<tr>
<td>GO:0016514</td>
<td>SWI/SNF complex</td>
<td></td>
</tr>
<tr>
<td>GO:0031415</td>
<td>NatA complex</td>
<td></td>
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GO:0030015  CCR4-NOT core complex
----------Count: 6 ----------
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GO:0030015  CCR4-NOT core complex
----------Count: 6 ----------
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GO:0030015  CCR4-NOT core complex
----------Count: 6 ----------
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GO:0030015  CCR4-NOT core complex
----------Count: 9 ----------
MIPS-420.50  FO/F1 ATP synthase (complex V)
GO:0030015  CCR4-NOT core 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:0043529  GET complex
GO:0030870  Mre11 complex
----------Count: 6 ----------
GO:0046540  U4/U6 x U5 tri-snRNP complex
GO:0030870  Mre11 complex
----------Count: 6 ----------
GO:0005830  Not found (possibly deprecated)
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
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---------Count: 9 ---------
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GO:0030897 HOPS complex
---------Count: 6 ---------
GO:0005830 Not found (possibly deprecated)
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: 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: 19 ---------
GO:0000778 condensed nuclear chromosome kinetochore
GO:0031390  Ctf18 RFC-like complex
---------Count: 6 ---------
GO:0000794  condensed nuclear chromosome
GO:0031390  Ctf18 RFC-like complex
---------Count: 6 ---------
GO:0005830  Not found (possibly deprecated)
GO:0031390  Ctf18 RFC-like complex
---------Count: 11 ---------
GO:0000776  kinetochore
GO:0031390  Ctf18 RFC-like complex
---------Count: 6 ---------
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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: 6 ---------
GO:0000778  condensed nuclear chromosome kinetochore
GO:0031415  NatA complex
---------Count: 6 ---------
GO:0000776  kinetochore
GO:0031415  NatA complex
---------Count: 6 ---------
MIPS-240.20  HDB complex
GO:0031415 NatA complex
---------Count: 6 ---------
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MIPS-360 Proteasome
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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: 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+-transporting ATPase, vacuolar
GO:0043529  GET complex
----------Count: 12 ----------
MIPS-510.40  RNA polymerase II holoenzyme
GO:0043529  GET complex
----------Count:  6 ----------
GO:0005830 Not found (possibly deprecated)
GO:0046540  U4/U6 x U5 tri-snRNP complex
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MIPS-370  Protein N-acetyltransferase
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MIPS-510.190.110  CCR4 complex
GO:0000274  mitochondrial proton-transporting ATP synthase, stator stalk
----------Count:  6 ----------
GO:0005830 Not found (possibly deprecated)
GO:0000778  condensed nuclear chromosome kinetochore
----------Count:  6 ----------
MIPS-370  Protein N-acetyltransferase
GO:0000778  condensed nuclear chromosome kinetochore
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GO:0000776  kinetochore
GO:0005830 Not found (possibly deprecated)
----------Count:  6 ----------
MIPS-240.20  HDB complex
GO:0005830 Not found (possibly deprecated)
----------Count:  6 ----------
MIPS-260.80  Class C Vps protein complex
GO:0005830 Not found (possibly deprecated)
----------Count:  6 ----------
MIPS-510.190.50  SWI/SNF transcription activator complex
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.

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

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

```r
> 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 an 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:

```r
> 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$tested, Interact = testedInteract$interact),
+   sum(Boeke), nrow(Boeke2006red) * length(dSLAM))
```

References


