

PSICQUIC

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1 Introduction

PSICQUIC (the Proteomics Standard Initiative Common QUery InterfaCe, pronounced “psy-kick”) is “an effort from the HUPO Proteomics Standard Initiative (HUPO-PSI) to standardise the access to molecular interaction databases programmatically”. The Bioconductor PSICQUIC package provides a traditional R function-calling (S4) interface layered on top of the PSICQUIC REST interface, to obtain a data.frame of annotated interactions between specified proteins, each of which is typically described by the HUGO symbol of the gene which codes for the protein of interest.

PSICQUIC is loose association of web accessible databases, “providers”, linked explicitly only by virtue of being listed at the central PSICQUIC web site. Each provider supports the **MIQL** (molecular interaction query language), and each of which returns standard columns in tab-delimited text. In typical use one queries for all of the interactions in which a protein participates. Equally typical are queries for all known interactions between two specified proteins. These queries are easily constrained by **provider** (e.g., BioGrid or IntAct), by **detectionMethod**, by interaction **type**, and/or by **publicationID**.

Interactions among a set of three or more genes may also be requested. The combinations of possible pairs grows non-linearly with the number of genes, so use this option with care.

PSICQUIC may therefore be best suited to the close study of a few dozen genes or proteins of interest, rather than for obtaining interactions for hundreds or thousands of genes or proteins. For bulk interactions, we recommend that you directly download databases from individual PSICQUIC (or other) providers.

Approximately thirty databases currently implement PSICQUIC. They all

- Support the molecular interaction query language (MIQL)
- Use a controlled vocabulary describing interactions and detection methods
- Communicate via SOAP or REST
- Return results in XML or a tab-delimited form
- May be interrogated programmatically or via a URL in a web browser

```
> library(PSICQUIC)
> psicquic <- PSICQUIC()
> providers(psicquic)
```

```
[1] "BioGrid"          "bhf-ucl"          "ChEMBL"
[4] "DIP"              "HPIDb"            "InnateDB"
[7] "IntAct"           "IMEx"             "mentha"
[10] "MPIDB"            "iRefIndex"        "MatrixDB"
[13] "MINT"             "Reactome"         "Reactome-FIs"
[16] "EBI-GOA-miRNA"    "UniProt"          "MBInfo"
[19] "BindingDB"        "BAR"              "EBI-GOA-nonIntAct"
[22] "tfact2gene"
```

2 Quick Start: find interactions between Myc and Tp53

A simple example is the best introduction to this package. Here we discover that BioGrid, Intact, Reactome, STRING and BIND each report one or more interactions between human Myc and Tp53:

```
> library(Psicquic)
> psicquic <- Psicquic()
> providers(psicquic)
```

```
[1] "BioGrid"          "bhf-ucl"          "ChEMBL"
[4] "DIP"              "HPIDb"            "InnateDB"
[7] "IntAct"           "IMEx"             "mentha"
[10] "MPIDB"            "iRefIndex"        "MatrixDB"
[13] "MINT"             "Reactome"         "Reactome-FIs"
[16] "EBI-GOA-miRNA"    "UniProt"          "MBInfo"
[19] "BindingDB"        "BAR"              "EBI-GOA-nonIntAct"
[22] "tfact2gene"
```

```
> tbl <- interactions(psicquic, id=c("TP53", "MYC"), species="9606")
```

```
List of 2
```

```
$ message: chr "Unknown SSL protocol error in connection to imex.mbi.ucla.edu:443 "
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://imex.mbi.ucla.edu/xpsq-dip-all/service/soap/currentidentifier:%28TP53%20AND%20MYC%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://psicquic.curated.innatedb.com/webservices/current/search/query/identifier:%28TP53%20AND%20MYC%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://irefindex.vib.be/webservices/current/search/query/identifier:%28TP53%20AND%20MYC%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://psicquic.tfact2gene.biogateway.eu/psicquic/webservices/current/search/query/identifier:%28TP53%20AND%20MYC%29%20AND%20species:9606"
```

```
> dim(tbl)
```

```
[1] 6 16
```

Note that the several arguments to the *interactions* method are unspecified. They maintain their default values, and act as wildcards in the query.

How many of the approximately twenty-five data sources reported interactions?

```
> table(tbl$provider)
```

```

BioGrid      IMEx      IntAct Reactome-FIs      mentha
      1          1          1          1          2

```

What kind of interactions, detection methods and references were reported? (Note that the terms used in the controlled vocabularies used by the PSICQUIC data sources are often quite long, complicating the display of extractions from our data.frame. To get around this here, we extract selected columns in small groups so that the results will fit on the page.)

```
> tbl[, c("provider", "type", "detectionMethod")]
```

```

      provider      type
1   BioGrid psi-mi:MI:0915(physical association)
2   IntAct   psi-mi:MI:0914(association)
3   IMEx     psi-mi:MI:0914(association)
4   mentha   psi-mi:MI:0914(association)
5   mentha   psi-mi:MI:0915(physical association)
6 Reactome-FIs -
      detectionMethod
1 psi-mi:MI:0004(affinity chromatography technology)
2   psi-mi:MI:0676(tandem affinity purification)
3   psi-mi:MI:0676(tandem affinity purification)
4   psi-mi:MI:0676(tandem affinity purification)
5 psi-mi:MI:0004(affinity chromatography technology)
6   psi-mi:MI:0046(experimental knowledge based)

```

These are quite heterogeneous. The well-established “tandem affinity purification” proteomics method probably warrants more weight than “predictive text mining”. Let’s focus on them:

```
> tbl[grep("affinity", tbl$detectionMethod),
+      c("type", "publicationID", "firstAuthor", "confidenceScore", "provider")]
```

```

      type      publicationID
1 psi-mi:MI:0915(physical association) pubmed:21150319
2   psi-mi:MI:0914(association) pubmed:21150319|imex:IM-16995
3   psi-mi:MI:0914(association) pubmed:21150319|imex:IM-16995
4   psi-mi:MI:0914(association) pubmed:21150319
5 psi-mi:MI:0915(physical association) pubmed:21150319
      firstAuthor confidenceScore provider
1   Agrawal P (2010) <NA> BioGrid
2 Agrawal et al. (2010) intact-miscore:0.35 IntAct
3 Agrawal et al. (2010) intact-miscore:0.35 IMEx
4 - mentha-score:0.236 mentha
5 - mentha-score:0.236 mentha

```

This result demonstrates that different providers report results from the same paper in different ways, sometimes omitting confidence scores, and sometimes using different (though related) terms from the PSI controlled vocabularies.

3 Retrieve all Myc interactions found by Agrawal et al, 2010, using tandem affinity purification

These reports of TP53/Myc interactions by detection methods variously described as “affinity chromatography technology” and “tandem affinity purification”, both accompanied by a reference to the same recent paper (“**Proteomic profiling of Myc-associated proteins**”, Agrawal et al, 2010), suggests the next task: obtain all of the interactions reported in that paper.

```
> tbl.myc <- interactions(psicquic, "MYC", species="9606", publicationID="21150319")
```

```

List of 2
 $ message: chr "Unknown SSL protocol error in connection to imex.mbi.ucla.edu:443 "
 $ call : language function (type, msg, asError = TRUE) { ...
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
character(0)
[1] "failed url: https://imex.mbi.ucla.edu/xpsq-dip-all/service/soap/currentidentifier:MYC%20AND%20species:9606%20AND%20pubid:21150319"
List of 2
 $ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
 $ call : language function (type, msg, asError = TRUE) { ...
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
character(0)
[1] "failed url: https://psicquic.curated.innatedb.com/webservices/current/search/query/identifier:MYC%20AND%20species:9606%20AND%20pubid:21150319"
List of 2
 $ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
 $ call : language function (type, msg, asError = TRUE) { ...
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
character(0)

```

```
[1] "failed url: https://irefindex.vib.be/webservices/current/search/query/identifier:MYC%20AND%20species:9606%20AND%20pubid:21150319"
List of 2
 $ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
 $ call    : language function (type, msg, asError = TRUE) { ...
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
character(0)
[1] "failed url: https://psicquic.tfact2gene.biogateway.eu/psicquic/webservices/current/search/query/identifier:MYC%20AND%20species:9606%20AND%20pubid:21150319"
```

How many were returned? From what sources? Any confidence scores reported?

```
> dim(tbl.myc)

[1] 1537  16

> table(tbl.myc$provider)

BioGrid    IMEx  IntAct  mentha
  107     452    452    526

> table(tbl.myc$confidenceScore)

intact-miscore:0.35 intact-miscore:0.53 intact-miscore:0.56 intact-miscore:0.60
           802           54           20           2
intact-miscore:0.64 intact-miscore:0.67 intact-miscore:0.69 intact-miscore:0.79
           2           10           6           2
intact-miscore:0.98 mentha-score:0.126 mentha-score:0.236 mentha-score:0.309
           6           296           166           1
mentha-score:0.332 mentha-score:0.416 mentha-score:0.454 mentha-score:0.49
           18           25           4           3
mentha-score:0.554 mentha-score:0.623 mentha-score:0.731 mentha-score:0.74
           4           1           1           1
mentha-score:0.891 mentha-score:0.967 mentha-score:1
           2           1           3
```

4 Gene symbols for input, “native” identifiers for results

PSICQUIC queries apparently expect HUGO gene symbols for input. These are translated by each provider into each provider’s native identifier type, which is nearly always a protein id of some sort. The results returned use the protein identifier native to each provider – but see notes on the use of our IDMapper class for converting these protein identifiers to gene symbols and entrez geneIDs. If you submit a protein identifier in a query, it is apparently used without translation, and the interactions returned are limited to those which use exactly the protein identifier you supplied. Thus the use of gene symbols is recommended for all of your calls to the *interactions* method.

Here is a sampling of the identifiers returned by the PSICQUIC providers:

- refseq:NP_001123512
- uniprotkb:Q16820
- string:9606.ENSP00000373992—uniprotkb:Q9UMJ4
- entrez gene/locuslink:2041—BIOGRID:108355

5 Add Entrez GeneIDs and HUGO Gene Symbols

Though informative, this heterogeneity along with the frequent absence of entrez geneIDs and gene symbols limits the immediate usefulness of these results for many prospective users. We attempt to remedy this with the IDMapper class, which uses biomaRt and some simple parsing strategies to map these lengthy identifiers into both geneID and gene symbol. At this point in the development of the PSICQUIC package, this step – which adds four columns to the results data.frame – must be done explicitly, and is currently limited to human identifiers only. Support for additional species will be added.

```
> idMapper <- IDMapper("9606")
> tbl.myc <- addGeneInfo(idMapper, tbl.myc)
> print(head(tbl.myc$A.name))
```

```
[1] "MYC" "MYC" "MYC" "MYC" "MYC" "MYC"
```

```
> print(head(tbl.myc$B.name))
```

```
[1] "MYC"      "MAX"      "KNDC1"    "CNMD"     "MICALL2"  "MPEP"
```

6 Retrieve Interactions Among a Set of Genes

If the *id* argument to the *interactions* method contains two or more gene symbols, then all interactions among all possible pairs of those genes will be retrieved. Keep in mind that the number of unique combinations grows larger non-linearly with the number of genes supplied, and that each unique pair becomes a distinct query to each of the specified providers.

```
> tbl.3 <- interactions(psicquic, id=c("ALK", "JAK3", "SHC3"),
+                         species="9606", quiet=TRUE)
```

```
List of 2
```

```
$ message: chr "Unknown SSL protocol error in connection to imex.mbi.ucla.edu:443 "
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://imex.mbi.ucla.edu/xpsq-dip-all/service/soap/currentidentifier:%28ALK%20AND%20JAK3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "Unknown SSL protocol error in connection to imex.mbi.ucla.edu:443 "
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://imex.mbi.ucla.edu/xpsq-dip-all/service/soap/currentidentifier:%28ALK%20AND%20SHC3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "Unknown SSL protocol error in connection to imex.mbi.ucla.edu:443 "
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://imex.mbi.ucla.edu/xpsq-dip-all/service/soap/currentidentifier:%28JAK3%20AND%20SHC3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://psicquic.curated.innatedb.com/webservices/current/search/query/identifier:%28ALK%20AND%20JAK3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://psicquic.curated.innatedb.com/webservices/current/search/query/identifier:%28ALK%20AND%20SHC3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://psicquic.curated.innatedb.com/webservices/current/search/query/identifier:%28JAK3%20AND%20SHC3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://irefindex.vib.be/webservices/current/search/query/identifier:%28ALK%20AND%20JAK3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://irefindex.vib.be/webservices/current/search/query/identifier:%28ALK%20AND%20SHC3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://irefindex.vib.be/webservices/current/search/query/identifier:%28JAK3%20AND%20SHC3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
```

```
character(0)
```

```
[1] "failed url: https://psicquic.tfact2gene.biogateway.eu/psicquic/webservices/current/search/query/identifier:%28ALK%20AND%20JAK3%29%20AND%20species:9606"
```

```
List of 2
```

```
$ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
```

```
$ call : language function (type, msg, asError = TRUE) { ...
```

```

- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
character(0)
[1] "failed url: https://psicquic.tfact2gene.biogateway.eu/psicquic/webservices/current/search/query/identifier:%28ALK%20AND%20SHC3%29%20AND%20species:9606"
List of 2
 $ message: chr "error:1407742E:SSL routines:SSL23_GET_SERVER_HELLO:tlsv1 alert protocol version"
 $ call    : language function (type, msg, asError = TRUE) { ...
- attr(*, "class")= chr [1:4] "SSL_CONNECT_ERROR" "GenericCurlError" "error" "condition"
character(0)
[1] "failed url: https://psicquic.tfact2gene.biogateway.eu/psicquic/webservices/current/search/query/identifier:%28JAK3%20AND%20SHC3%29%20AND%20species:9606"

> tbl.3g <- addGeneInfo(idMapper, tbl.3)
> tbl.3gd <- with(tbl.3g, as.data.frame(table(detectionMethod, type, A.name, B.name, provider)))
> print(tbl.3gd <- subset(tbl.3gd, Freq > 0))

```

```

                                detectionMethod
15 psi-mi:MI:0004(affinity chromatography technology)
27 psi-mi:MI:0004(affinity chromatography technology)
42      psi-mi:MI:0046(experimental knowledge based)
46      psi-mi:MI:0046(experimental knowledge based)
87 psi-mi:MI:0004(affinity chromatography technology)
99 psi-mi:MI:0004(affinity chromatography technology)
                                type A.name B.name      provider Freq
15 psi-mi:MI:0915(physical association)   ALK   JAK3      BioGrid    2
27 psi-mi:MI:0915(physical association)   ALK   SHC3      BioGrid    1
42      - JAK3   ALK Reactome-FIs    1
46      - SHC3   ALK Reactome-FIs    1
87 psi-mi:MI:0915(physical association)   ALK   JAK3      mentha    2
99 psi-mi:MI:0915(physical association)   ALK   SHC3      mentha    1

```

7 References

- Aranda, Bruno, Hagen Blankenburg, Samuel Kerrien, Fiona SL Brinkman, Arnaud Ceol, Emilie Chautard, Jose M. Dana et al. "PSICQUIC and PSISCORE: accessing and scoring molecular interactions." *Nature methods* 8, no. 7 (2011): 528-529.
- Agrawal, Pooja, Keping Yu, Arthur R. Salomon, and John M. Sedivy. "Proteomic profiling of Myc-associated proteins." *Cell Cycle* 9, no. 24 (2010): 4908-4921.