The qpgraph package
Network inference and eQTL mapping

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Brief overview of the qpgraph package

- Entered BioC release cycle on april 2009 providing functionality to infer molecular regulatory networks from gene expression microarray data.
- It relies on graphical model theory and it is therefore similar to some of the packages in `http://cran.r-project.org/web/views/gR.html`.
- Its methodology is published in two papers (Castelo & Roverato, 2006, 2009) accumulating together 95 citations in Google Scholar. The BioC site reports an average of 4 downloads a day from distinct IPs.
- Most citations come from other methodological papers, but some independent groups have successfully used it in their analysis of microarray data, such as:

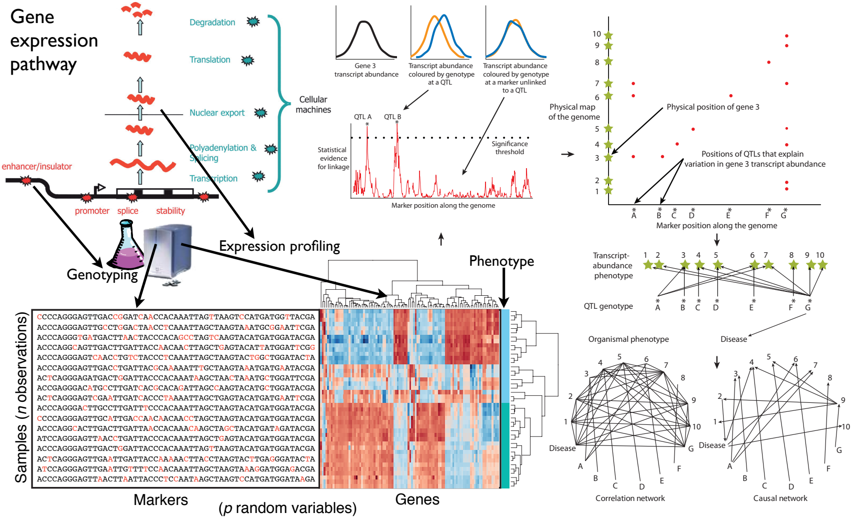
  Pietiläinen et al. Association of lipidome remodeling in the adipocyte membrane with acquired obesity in humans. PLoS Biology, 9(6):e1000623, 2011.

  Oresic et al. Metabolome in schizophrenia and other psychotic disorders: a general population-based study. Genome Medicine, 3:19, 2011.

Brief overview of the qpgraph package

- Network inference by conditional (in)dependence: `qpCItest()`, `qpAllCItests()`, `qpNrr()`, `qpAvgNrr()`.
- Inference from multiple data sets: `qpGenNrr()`.
- Model-based estimation of partial correlations: `qpPAC()`
- Adjustment for fixed and confounding effects via `fix.Q` argument.
- Missing data treated via complete-case analysis and EM algorithm.
- Assessment of network quality: `qpPrecisionRecall()`, `qpFunctionalCoherence()`.
- Exploration of results: `qpClique()`, `qpGraphDensity()`, `qpGraph()`, `qpTopPairs()`, `qpPlotNetwork()`.
- Simulation of data from synthetic networks: `qpRndGraph()`, `qpG2Sigma()`, `rmvnorm()` from *mvtnorm*.
- Parallelization with progress reporting via snow-like MPI clusters.

Long-term goal of the qpgraph package


Gene expression pathway
Degradation
Translation
Nuclear export
Polyadenylation & Splicing
Transcription
Cellular machines
enhancer/insulator
promoter
splice
stability
Genotyping
Expression profiling
Gene 3 transcript abundance
Transcript abundance coloured by genotype at a QTL
Transcript abundance coloured by genotype at a marker unlinked to a QTL
QTL A
QTL B
Statistical evidence for linkage
Significance threshold
Marker position along the genome
Physical map of the genome
Physical position of gene 3
Positions of QTLs that explain variation in gene 3 transcript abundance
10
9
8
7
6
5
4
3
2
1
A
B
C
D
E
F
G
Marker position along the genome
Phenotype
Transcript-abundance phenotype
QTL genotype
Organismal phenotype
Disease
Correlation network
Causal network
Samples (n observations)
Markers
Genes
(p random variables)

```
CCCCAGGGAGTTGACCGGATCAACCACAAATTAGTTAAGTCCATGATGGTTACGA
ACCCAGGGAGTTGCCTGGACTAACCTCAAATTAGCTAAGTAAATGCGGAATTCGA
ACCCAGGGTGATGACTTAACTACCCACAGCCTAGTCAAGTACATGATGGATACGA
ACCCAGGCAGTTGACTTGATTACCAACAACTTAGCTGAGTACATTATGGATTCGG
ACCCAGGGAGTCAACCTGTCTACCCTCAAATTAGCTAAGTACTGGCTGGATACTA
ACCCAGGGAGTTGACCTGATTACGCAAAAATTTGCTAAGTAAATGATGAATACGA
ACTCAGGGAGATGACTGGATTACCCACAAATAAGCTAACTAAATGCTGGATTCGA
ACCGAGGGACATGCCTTGATCACGCACAGATTAGCCAAGTACATGCTGGATACGA
ACTCAGGGAGTCGAATTGATCACCCTAAAATTAGCTGAGTACATGATGAATTCGA
ACCCAGGGACTTGCCTTGATTTCCCACAAATTAGCTAAGTACATGATGGATACGA
CCCCAGGGAGTTGCATTGACCAACAACAACCTAGCTAAGTACATGATGGATACGA
ACCCAGGCACTTGACTTGATTAACCACAAACAAGCTAGCTACATGATAGATACGA
ATCCAGGGAGTTAACCTGATTACCCACAAATTAGCTGAGTACATGATGGATACGA
ACCCAGGGAGTTGACTGGATTACCCACAAATTAGTTAAGTACATGATGGATACGA
ACTCAGGGAGTTGAATTGATTACCAAAAACTTACCTAAGTACTTGAGGGATACTA
ATCCAGGGAGTTGAATTGTTTTCCAACAAATTAGCTAAGTAAAGGATGGAGACGA
ACCCAGGGAGTTAACTTAATTACCCTCCAATAAGCTAAGTCCATGATGGATAAGA
```

Rockman, MV. Reverse engineering the genotype-phenotype map with natural genetic variation. *Nature*, 456:738-744, 2008.

Long-term goal of the qpgraph package

- Network models aim at exploring a combinatorial number of interactions: gene-gene, gene-phenotype, SV-gene, SV-phenotype:

```
> sv <- 1e7 ## number of structural variants
> ng <- 25000 ## number of genes
> ph <- 100 ## number of phenotypes
> nl <- sv * (ng + ph) + choose(ng + ph, 2) ## number of links to explore
> nl

[1] 2.51315e+11

> sv <- 1e5 ## number of structural variants
> ng <- 6000 ## number of genes
> nl <- sv * (ng + ph) + choose(ng + ph, 2) ## number of links to explore
> nl

[1] 628601950
```

- Gene expression is a high-dimensional multivariate phenotype vector.

- When inferring a SV-gene relationship, one wants to adjust for confounding factors and, ideally, the expression of every other gene.

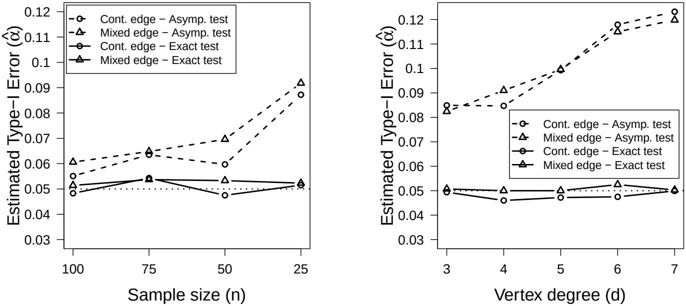
Network approach in qpgraph: limited-order correlations

- *qpgraph* approaches network inference by testing **repeatedly** (e.g., 100 times) for limited-order correlations of order $q < (n - 2)$:

```
> library(qpgraph)
> suppressMessages(library(GGdata))
> c20 <- getSS("GGdata", "20", renameChrs="chr20")
> sym2id <- revmap(illuminaHumanv1SYMBOL)
> qpCItest(c20, i=sym2id[["PTEN"]], j="rs17093026")

Conditional independence test for homogeneous mixed data using an
exact likelihood ratio test

data:  GI_38505204-S and rs17093026 given {}
Lambda = 0.9172, a = 41.5, b = 1.0, n = 86.0, p-value = 0.02769
alternative hypothesis: true Lambda is less than 1

> qpCItest(c20, i=sym2id[["PTEN"]], j="rs17093026", Q=sym2id[["CPNE1"]])

Conditional independence test for homogeneous mixed data using an
exact likelihood ratio test

data:  GI_38505204-S and rs17093026 given {GI_23397697-A}
Lambda = 0.937, a = 41, b = 1, n = 86, p-value = 0.06939
alternative hypothesis: true Lambda is less than 1
```

Network approach in qpgraph: limited-order correlations

- *qpgraph* performs *exact* likelihood ratio tests, instead of one degree of freedom chi-squared tests:



- Their computational cost grows *linearly* in the size of the conditioning sets Q.

Biological constraints can provide a major speed-up

- Computations between links are independent and can thus be performed in parallel.

- Not all associations make biological sense. We can restrict calculations to explore the space *cis*SV-gene, tf-gene, RNAbinding-gene, etc.

- *qpgraph* currently enable this in a rudimentary way via de `pairup.i` and `pairup.j` arguments:

```
> qpAllCItests(exprs(c20)[1:5000, ], estimateTime=TRUE)

   days    hours minutes seconds
      0        7      59      10

> qpAllCItests(exprs(c20)[1:5000, ], pairup.i=1:100, pairup.j=1:5000,
+              estimateTime=TRUE)

   days    hours minutes seconds
      0        0      18      15
```

Future plans

- A more friendly interface that can rely on functional terms annotated to features.

```
> nrr <- qpNrr(smlset, ~ TF*gene + hormone_receptor*gene + cisSV*gene + sex + batch,
+              q=20)
```

- The idea would be to identify whether a term refers to a function and then blow it into the set of features annotated to that function.

- This can be enabled via the `featureData` slot in *ExpressionSet* objects using binary vectors of membership to functional classes.

- Should functional names (TFs, RNAbinding, cisSV) belong to some **standard** controlled vocabulary? (e.g., *Homo.sapiens*, `http://www.sequenceontology.org`, ..)

Future plans

- Work with more efficient data structures and a representation in disk that avoids large memory footprints.

- Multicore support for parallelism, via parallel/BiocParallel (need abstraction for reporting progress).

Comments & Bugfixes

`robert.castelo@upf.edu`
`@robertclab #qpgraph`

(what about a Tweeter feed `#biocbugfix` at the BioC site?)

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