atlasqtl: an R package for variable selection in sparse regression with hierarchically-related outcomes

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Statistical problems in the high-dimensional setting multiply, prompted by the proliferation of technologies capable of measuring large volumes of information, whether on health and lifestyle parameters, molecular entities or even galaxies. As well as growing in dimension, the datasets collected are also growing in complexity, which calls for elaborate and flexible modelling approaches. When coupled with robust and efficient inference, Bayesian hierarchical modelling is a powerful framework for describing intricate dependencies at the scale required by current applications, while conveying uncertainty in a coherent fashion. In this note, we present the R package `atlasqtl`, which implements a scalable hierarchical framework for variable selection in regression problems with high-dimensional predictor and response spaces.

Model and inference

The model consists of series of hierarchically-related spike-and-slab regressions that permit borrowing information across large numbers of responses. A graphical representation is provided in Figure 1, and the full model and inference algorithm are detailed in Ruffieux et al. (2020). Each pair of predictor X_s and response y_t has its corresponding regression coefficient β_{st} and spike-and-slab binary latent variable γ_{st}, from which posterior probabilities of association are conveniently obtained, $\text{pr}(\gamma_{st} = 1 \mid y)$, and employed to implement Bayesian false discovery rate control. The model is also tailored to the detection of *hotspots*, namely, predictors associated with several responses: the top-level hierarchy entails a probit submodel which involves a response-specific contribution to the spike-and-slab probability of association, via ζ_t, and a predictor-specific modulation of this contribution, via θ_s. The latter parameter also acts as the propensity of predictor X_s to be a hotspot and is assigned a horseshoe prior, which adapts to the overall problem sparsity (via the global scale σ_0), while flexibly capturing hotspot effects (via the Cauchy tail of the local scale λ_s). Joint inference requires special attention as the binary latent matrix $\Gamma = \{\gamma_{st}\}$ creates a discrete search space of dimension $2^{p \times q}$. To overcome this complication, `atlasqtl` implements a variational inference algorithm based on a structured mean-field factorisation and efficient batch updates. The algorithm is augmented with a simulated annealing scheme that improves the exploration of highly multimodal spaces by introducing so-called "temperature" parameters controlling the degree of separation of the modes of a series of "heated" distributions (Ruffieux et al. (2020)).

`atlasqtl` can be employed in any sparse multiple-response regression setting. Hereafter we discuss a use case in the context of expression quantitative trait locus (eQTL) analysis, in which *hotspot genetic variants*, controlling many molecular traits at once, may be responsible for important functional mechanisms underlying specific disease endpoints — such studies aim to clarify the genetic architecture of diseases by estimating associations between up to a few million candidate predictors (genetic variants) and several thousand responses (molecular traits, such as genomic, proteomic, metabolomic levels).

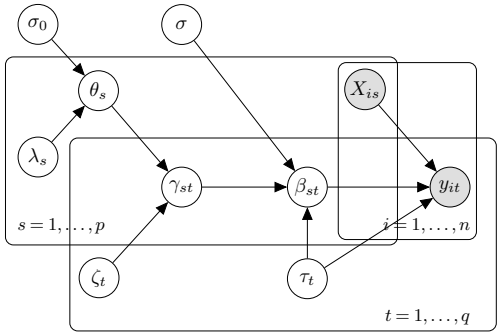


Figure 1: Graphical representation of the model. The shaded nodes are observed, the others are inferred.

Installation

The `atlasqtl` package is written in R with C++ subroutines. It can be installed following the instructions provided at https://github.com/hruffieux/atlasqtl#installation. Note that the GSL library must be installed prior to installing the package.

Data and reproducibility

The material used in this example is available at https://github.com/hruffieux/software_corner_ibs_bulletin for replication purposes. It involves synthetic genotyping data generated using our in-house R package `echoseq` (https://github.com/hruffieux/echoseq); these data emulate real genotypes (single nucleotide polymorphisms,

"SNPs") in the *LYZ* gene region, which cannot be shared without data access agreement. The expression data consist of monocyte levels before and after immune stimulation (resting, IFNg, LPS2h, LPS24h), as well as B-cell levels. To each of these transcriptomic datasets corresponds a separate eQTL problem.

Analysis

We illustrate the main package functionalities on the five eQTL problems (corresponding datasets stored in the list `list_data`). `atlasqtl` requires the specification of just two hyperparameters via the elicitation of a prior mean `mu_t` and variance `v_t` for the number of predictors associated with each response. The sensitivity of inference to these choices should be evaluated on a case-by-case basis; it is however very limited when a permutation-based FDR threshold is employed, where the "null-case" permutation runs use the same hyperparameter specifications. The remaining model parameters are inferred by variational inference. In particular, the horseshoe prior on the hotspot propensity circumvents ad-hoc choices of top-level variances (for which inference is prone to spurious effects). This specification also has desirable multiplicity adjustment properties for dealing with the large-response case, see Ruffieux et al. (2020).

The code below runs the five `atlasqtl` analyses in parallel. The annealing schedule (initial temperature, grid size and type of spacing) can be supplied via the argument `anneal` — here we use a default geometric schedule on the inverse temperature, with initial temperature of 2 and grid size 10. The argument `add_collinear_back` is a boolean indicating whether or not to include the final posterior summaries for all possible collinear variables in X (which are removed during the run to ensure the stability of inference). A number of additional settings (e.g., tolerance, maximum number of iterations, checkpointing, etc.) can be chosen by the user and are detailed on the help page of the function, which can be displayed by running `?atlasqtl`. Note that the parallel execution relies on the R package `parallel` which has already been installed as part of the `atlasqtl` installation.

```
require(atlasqtl)

mu_t <- 1
v_t <- 4

vec_type <- names(list_data) # names of the eQTL problems
                             # (resting, IFNg, LPS2h,
                             # LPS24h monocytes and B-cells).

n_cpus <- 4 # nb of CPUs for parallel execution - please
            # change this number according to your setup.

list_out <- parallel::mclapply(vec_type, function(type) {

  snps <- list_data[[type]]$snps
  expr <- list_data[[type]]$expr

  atlasqtl(Y = expr, X = snps,
           p0 = c(mu_t, v_t),
           add_collinear_back = TRUE)

}, mc.cores = n_cpus)

names(list_out) <- vec_type
```

The object returned by `atlasqtl` contains a range of useful posterior quantities, which can be employed to assess:

- the pairwise associations between each pair of SNP and trait: using the variational posterior probabilities (PPIs) stored in `gam_vb` ($p \times q$ matrix) and the variational posterior means of the regression estimates stored in `beta_vb` ($p \times q$ matrix);
- the hotspot propensities: using the variational posterior mean of θ_s stored in `theta_vb` (vector of length p).

It also contains diagnostic values on the final status of convergence and number of iterations used for the coordinate ascent variational algorithm.

The custom `print.atlasqtl` and `summary.atlasqtl` function provide information about the run and a summary of the above posterior quantities; e.g., for the unstimulated-monocyte eQTL analysis:

```
print_atlasqtl(list_out$bcells, anneal, maxit, tol) # replace by list_o
```

```
## *** Successful convergence after 81 iterations, using an
##  absolute tolerance of 0.1 on the absolute changes in the
##  ELBO (default) ***
##
## Geometric annealing on the inverse temperature was
## applied for the first 10 iterations, with initial
## temperature of 2 (default).
```

```
summary(list_out$bcells)
```

```
##      Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
## 0.0003006 0.0004040 0.0005374 0.0041631 0.0011154 1.0000000
##       Min.    1st Qu.     Median       Mean    3rd Qu.       Max.
## -0.4288846 -0.0000070  0.0000000 -0.0000225  0.0000070  0.5296392
##       Min.    1st Qu.     Median       Mean    3rd Qu.       Max.
## -0.0003095 -0.0002730 -0.0002464  0.0409836 -0.0001878  1.6264974
```

Finally, we display a Manhattan-type plot which indicates the position of the hotspots, as estimated in the five different eQTL analyses.

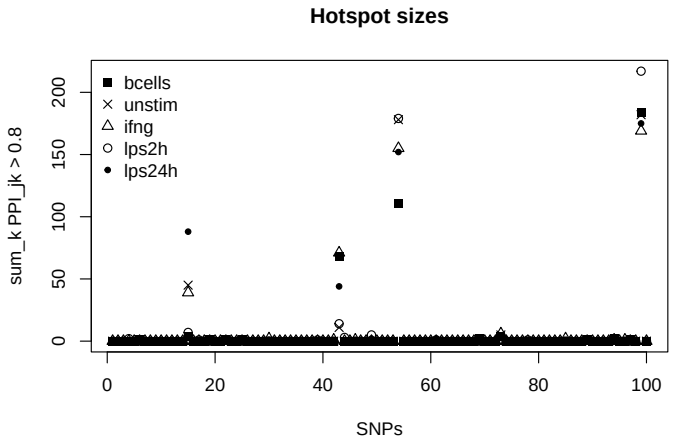
Also note that permutation analyses can be run to compute calibrated Bayesian FDR thresholds on the PPIs; we don't implement this for computational economy and use an arbitrary threshold instead. The procedure to derive these permutation-based FDR threshold is described in details in Ruffieux et al. (2017) and Ruffieux et al. (2020).

```
thres <- 0.8
list_rs_thres <- lapply(list_out,
                        function(ll_type)
                          rowSums(ll_type$gam_vb>thres))

vec_pch <- c(15, 4, 2, 21, 20)

plot(list_rs_thres[[1]], pch = vec_pch[1],
     ylim = c(0, max(unlist(list_rs_thres))),
     main = "Hotspot sizes",
     xlab = "SNPs",
     ylab = paste0("sum_k PPI_jk > ", thres))
```

```
for (type_id in 2:5) {
  points(list_rs_thres[[type_id]], pch = vec_pch[type_id])
}
legend("topleft", legend = vec_type, pch = vec_pch,
       bty = "n")
```



References

Ruffieux, H., A. C. Davison, J. Hager, J. Inshaw, B. Fairfax, S. Richardson, and L. Bottolo. 2020. "A Global-Local Approach for Detecting Hotspots in Multiple Response Regression." *The Annals of Applied Statistics* 14: 905–28.

Ruffieux, H., A. C. Davison, J. Hager, and I. Irincheeva. 2017. "Efficient Inference for Genetic Association Studies with Multiple Outcomes." *Biostatistics* 18: 618–36.