

Guide for xerxes v0.2.0.0

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1 Fstats command

Xerxes allows you to analyse genotype data across poseidon packages, including your own, as explained above by “hooking” in your own package via a `--baseDir` (or `-d`) parameter. This has the advantage that you can compute arbitrary F-Statistics across groups and individuals distributed in many packages, without the need to explicitly merge the data first. Xerxes also takes care of merging PLINK and EIGENSTRAT data on the fly. It also takes care of different genotype base sets, like Human-Origins vs. 1240K. It also flips alleles automatically across genotype files, and throws an error if the alleles in different packages are incongruent with each other. Xerxes is also smart enough to select only the packages relevant for the statistics that you need, and then streams through only those genotype data.

Here is an example command for computing several F-Statistics:

```
xerxes fstats -d ... -d ... \  
  --stat "F4(<Chimp.REF>, <Altai_published.DG>, Yoruba, French)" \  
  --stat "F3(<Chimp.REF>, <Altai_snpAD.DG>, Spanish)" \  
  --statFile fstats.txt  
  --statConfig fstats.yaml  
  -f outputfile.txt
```

First, the two options `-d ...` exemplify that you need to provide at least one base directory for poseidon packages, but can also give multiple. Second, F-Statistics can be entered in three different ways:

1. Directly via the command line using `--stat`.

34 2. Using a simple text file using `--statFile`

35 3. Using a powerful configuration file that allows more options.

36 These three input ways can be mixed and matched, and given multiple times. They are explained below.

37 Last, option `-f` can be used to write the output table into a tab-separated text file, beyond just printing a table

38 into the standard out when the program finishes. Note that there are more options, which you can view using

39 `xerxes fstats --help`:

40 Usage: `xerxes fstats (-d|--baseDir DIR) [-j|--jackknife ARG]`

41 `[-e|--excludeChroms ARG]`

42 `(--stat ARG | --statConfig ARG | --statFile ARG)`

43 `[--noTransitions] [-f|--tableOutFile ARG]`

44 `[--blockTableFile ARG]`

45

46 Compute f-statistics on groups and individuals within and across Poseidon

47 packages

48

49 Available options:

50 `-h,--help` Show this help text

51 `-d,--baseDir DIR` A base directory to search for Poseidon packages.

52 `-j,--jackknife ARG` Jackknife setting. If given an integer number, this

53 defines the block size in SNPs. Set to "CHR" if you

54 want jackknife blocks defined as entire chromosomes.

55 The default is at 5000 SNPs

56 `-e,--excludeChroms ARG` List of chromosome names to exclude chromosomes,

57 given as comma-separated list. Defaults to X, Y, MT,

58 chrX, chrY, chrMT, 23,24,90

59 `--stat ARG` Specify a summary statistic to be computed. Can be

60 given multiple times. Possible options are: F4(a, b,

61 c, d), F3(a, b, c), F3star(a, b, c), F2(a, b), PWM(a,

62 b), FST(a, b), Het(a) and some more special options

63 described at

64 <https://poseidon-framework.github.io/#/xerxes?id=fstats-command>.

65 Valid entities used in the statistics are group names

66 as specified in the *.fam, *.ind or *.janno files,

67 individual names using the syntax "<Ind_name>", so

68 enclosing them in angular brackets, and entire

69 packages like "*Package1*" using the Poseidon package

70 title. You can mix entity types, like in

71 "F4(<Ind1>,Group2,*Pac*,<Ind4>)". Group or individual

72 names are separated by commas, and a comma can be

73 followed by any number of spaces.

74 `--statConfig ARG` Specify a yaml file for the Fstatistics and group

75 configurations

76 `--statFile ARG` Specify a file with F-Statistics specified similarly

77 as specified for option `--stat`. One line per

```

78             statistics, and no new-line at the end
79  --maxSnps ARG             Stop after a maximum nr of snps has been processed.
80                             Useful for short test runs
81  --noTransitions           Skip transition SNPs and use only transversions
82  -f,--tableOutFile ARG     a file to which results are written as tab-separated
83                             file
84  --blockTableFile ARG      a file to which the per-Block results are written as
85                             tab-separated file

```

1.1 Allowed statistics

The following statistics are allowed in the `--stat`, `--statFile` and `--statConfig` options. In all of the following, symbols `a`, `b`, `c` or `d` stand for arbitrary entities allowed in Poseidon, so groups (such as `French`), individuals (such as `<MA1.SG>`) or packages (such as `*2012_PattersonGenetics*`).

- `F2vanilla(a, b)`: F2-Statistics - Vanilla version. Computed using $F2vanilla(a, b) = (a-b)^2$ across the genome.
- `F2(a, b)`: F2-Statistics (bias-corrected version). Computed as $F2(a, b) = F2vanilla(a, b) - \frac{hA}{sA} - \frac{hB}{sB}$, where where `sA` is the number of non-missing alleles in entity A, and $hA = \frac{nA * nA'}{sA * (sA - 1)}$ is an estimator of half the heterozygosity (see `Het(a)`), and likewise for `sB` and `nB` etc.
- `F3vanilla(a,b,c)`: F3-Statistics - Vanilla version, recommended if used as Outgroup-F3 statistics or with group `c` being pseudo-haploid: Are computed as $F3(a, b, c) = (c-a)(c-b)$ across all SNPs.
- `F3(a,b,c)`: F3-statistics (bias-corrected version). Computed as $F3(a, b, c) = F3vanilla(a, b) - \frac{hC}{sC}$.
- `F3star(a,b,c)`: F3-Statistics as defined in Patterson et al. 2012 - normalised and bias-corrected version, recommended for Admixture-F3 tests. Are computed by i) first subtracting per SNP from the vanilla-F3 statistic a bias-correction term hC/sC , as above for F2, and ii) then normalising the genome-wide estimate by a genome-wide estimate of the heterozygosity of entity C (`Het(c)`), in order to make results comparable between different groups C (see Patterson et al., Genetics, 2012)
- `F4(a,b,c,d)`: F4 statistics. Are computed by averaging the quantity $(a-b)(c-d)$ across all SNPs. No bias correction is necessary for this statistic.
- `Het(a)`: An estimate of the heterozygosity across all SNPs, computed as $2 * hA$, with `hA` defined as above in F2
- `FST(a, b)`: An estimate of FST across the genome, following the formular from Appendix A in Patterson et al. 2012, which is a ratio of two terms, with numerator being `F2(a, b)` including bias correction, and the denominator being `F2(a, b) + hA + hB` including bias correction and `hA` and `hB` defined as above.
- `PWM(a, b)`: The pairwise mismatch rate between entities `a` and `b`, computed from allele frequencies as $\frac{a}{(1 - b) + (1 - a) b}$.

All of these equations are from Patterson, Nick, Priya Moorjani, Yontao Luo, Swapan Mallick, Nadin Rohland, Yiping Zhan, Teri Genschoreck, Teresa Webster, and David Reich. 2012. "Ancient Admixture in Human History." Genetics 192 (3): 1065–93. See also Appendix A of this paper for the unbiased estimators used above.

For each of the "slots" A, B, C or D, you can enter: * Individuals, using the syntax `<Individual_Name> *` Groups, using no special syntax `"Group_Name"` * Packages, using syntax `*Package_Name*` (This can be useful if you happen to have a homogenous set of individuals from multiple groups in one package and want to consider all of these as one group.)

1.2 Defining statistics directly via --stat

This is the simplest option to instruct the program to compute a specified statistic. Each statistic requires a separate input using --stat using this input method. Example:

```
xerxes fstats -d ... -d ... --stat "F3(French, Spanish, <Chimp.REF>) --stat "FST(French, Spanish)"
```

1.3 Defining statistics in a simple text file

You can prepare a text file, into which you write the above statistics, one statistics per line. Example:

```
F4(<Chimp.REF>, <Altai_published.DG>, Yoruba, French)
```

```
F4(<Chimp.REF>, <Altai_snpAD.DG>, Spanish, French)
```

```
F4(Mbuti,Nganasan,Saami.DG,Finnish)
```

you can then load these statistics using the option --statFile fstats.txt.

1.4 Input via a configuration file

This is the most powerful way to input F-Statistics. Here is an example:

```
groupDefs:
  CEU2: ["CEU.SG", "-<NA12889.SG>", "-<NA12890.SG>"]
  FIN2: ["FIN.SG", "-<HG00383.SG>", "-<HG00384.SG>"]
  GBR2: ["GBR.SG", "-<HG01791.SG>", "-<HG02215.SG>"]
  IBS2: ["IBS.SG", "-<HG02238.SG>", "-<HG02239.SG>"]
fstats:
- type: F2
  a: ["French", "Spanish"]
  b: ["Han", "CEU2"]
  # Ascertainment is optional
- type: F3 # This will create 3x2x1 = 6 Statistics
  a: ["French", "Spanish", "Mbuti"]
  b: ["Han", "CEU2"]
  c: ["<Chimp.REF>"]
  ascertainment:
    outgroup: "<Chimp.REF>" # ascertaining on outgroup-polarised derived allele frequency
    reference: "CEU2"
    lower: 0.05
    upper: 0.95
- type: F4 # This will create 5x5x4x1 = 100 Statistics
  a: ["<I0156.SG>", "<I0157.SG>", "<I0159.SG>", "<I0160.SG>", "<I0161.SG>"]
  b: ["<I0156.SG>", "<I0157.SG>", "<I0159.SG>", "<I0160.SG>", "<I0161.SG>"]
  c: ["CEU2", "FIN2", "GBR2", "IBS2"]
  d: ["<Chimp.REF>"]
  ascertainment:
    # A missing outgroup means: ascertain on minor allele frequency
    reference: "CEU.SG"
```

```

160     lower: 0.00
161     upper: 0.10

```

162 The top level structure of this [YAML](#) file is an object with two fields: **groupDefs** (which is optional) and **fstats**
163 (which is mandatory).

164 1.4.1 Group Definitions

165 You can specify adhoc group definitions using the syntax above. Every group consists of a name (used as object
166 key) and then a JSON- or YAML-list of signed entities, following the same syntax of **trident forge** (see
167 [trident](#)). Briefly: Individuals, Groups and Packages can be added or excluded (prefixed by a -) in order. In the
168 example above, two individuals are removed from each group.

169 Note that currently, groups can be defined only independently, so not incremental to each other. That means,
170 you cannot currently use an already defined new group name in the entity list of a following group name.

171 1.4.2 Statistic input using YAML

172 Each statistic defined in the **fstats** section of the YAML file, actually defines a loop over multiple populations
173 in each statistic. In the example above, there are 6 F3-Statistics, each using a different combination of the input
174 groups defined in each of the **a:**, **b:** and **c:** slots. There are also 100 (!) F4 statistics, following all combinations
175 of 5x5x4x1 slots defined in **a:**, **b:**, **c:** and **d:**. This makes it very convenient to loop over statistics.

176 1.4.3 Ascertainment (experimental feature)

177 In addition, every statistic section allows for a definition of an ascertainment specification, using a special
178 key **ascertainment:**, which is optional. If given, you can specify an optional **outgroup**, a **reference** group in
179 which to ascertain SNPs, and **lower** and **upper** allele frequency bounds. If specified, only SNPs for which the
180 **reference** group has an allele frequency within the given bounds are used to compute the statistic (note that
181 normalisation is still using all non-missing SNPs for that given statistic). If an **outgroup** is defined, then the
182 outgroup-polarised derived allele frequency is used. If no **outgroup** is defined, then the minor allele frequency is
183 used instead. If an outgroup is defined, any sites where the outgroup is polymorphic are treated as missing.

184 You can save this into a text file, for example named **fstats_config.yaml**, and load it via **--statConfig**
185 **fstats_config.yaml**.

186 1.5 Output

187 The final output of the **fstats** command looks like this:

```

188 .----- .----- .----- .----- .----- .----- .----- .-----
189 | Statistic |      a      |      b      |      c      |      d      | NrSites | Estimate_Total | Estimate_Jackknif
190 :===== :===== :===== :===== :===== :===== :===== :=====
191 | F3        | French      | Italian_North | Mbuti      |              | 593124 | 5.9698e-2      | 5.9698e-2
192 | F3        | French      | Han           | Mbuti      |              | 593124 | 5.0233e-2      | 5.0233e-2
193 | F3        | Sardinian   | Pima          | French     |              | 593124 | -1.2483e-3     | -1.2483e-3
194 | F4        | French      | Russian       | Han        | Mbuti      | 593124 | -1.6778e-3     | -1.6778e-3
195 | F4        | Sardinian   | French        | Pima       | Mbuti      | 593124 | -1.4384e-3     | -1.4384e-3
196 '-----' '-----' '-----' '-----' '-----' '-----' '-----' '-----

```

197 which lists each statistic, the slots a, b, c and d, the number of sites with non-missing data for that statistic,
198 Ascertainment information (outgroup, reference, lower and upper bound, if given), the genome-wide estimate, its
199 standard error and its Z-score. If you specify an output file using option `--tableOutFile` or `-f`, these results
200 are also written as tab-separated file.

201 Additionally, an option `--blockOutFile` can be specified, to which then a table with estimates per Jackknife
202 block is written.

203 1.6 Whitepaper

204 The repository comes with a [detailed whitepaper](#) that describes some more mathematica details of the methods
205 implemented here.

206 2 RAS (in development)

207 The RAS command computes pairwise RAS statistics between a collection of “left” entities, and a collection of
208 “right” entities. Every Entity is either a group name or an individual, with the similar syntax as in F-statistics
209 above, so `French` is a group, and `<IND001>` is an individual.

210 The input of left-pops and right-pops uses a YAML file via `--popConfigFile`. Here is an example:

```
211 groupDefs:  
212   group1: a,b,-c,-<d>  
213   group2: e,f,-<g>  
214 popLefts:  
215 - <I13721>  
216 - <I14000>  
217 - <I13722>  
218 - <Iceman.SG>  
219 popRights:  
220 - Mbuti  
221 - Mixe  
222 - Spanish  
223 outgroup: <Chimp.REF>
```

224 In this case, two groups are defined on the fly: `group1` comprises groups `a` and `b`, but excludes group `c` and
225 individual `d`. Note that inclusions and exclusions are executed in order. `group2` comprises of group `e` and group
226 `f`, but excludes individual `<g>`.

227 As in [RAScalculator](#), the allele frequency ascertainment is done across right populations only.

228 There are a couple of options, as specified in the CLI help (`xerxes ras --help`):

```
229 Usage: xerxes ras (-d|--baseDir DIR) [-j|--jackknife ARG]  
230               [-e|--excludeChroms ARG] --popConfigFile ARG  
231               [-k|--maxAlleleCount ARG] [-m|--maxMissingness ARG]  
232               (-f|--tableOutFile ARG)  
233 Compute RAS statistics on groups and individuals within and across Poseidon  
234 packages
```

235

236 Available options:

237 -h,--help Show this help text
238 -d,--baseDir DIR a base directory to search for Poseidon Packages
239 (could be a Poseidon repository)
240 -j,--jackknife ARG Jackknife setting. If given an integer number, this
241 defines the block size in SNPs. Set to "CHR" if you
242 want jackknife blocks defined as entire chromosomes.
243 The default is at 5000 SNPs
244 -e,--excludeChroms ARG List of chromosome names to exclude chromosomes,
245 given as comma-separated list. Defaults to X, Y, MT,
246 chrX, chrY, chrMT, 23,24,90
247 --popConfigFile ARG a file containing the population configuration
248 -k,--maxAlleleCount ARG define a maximal allele-count cutoff for the RAS
249 statistics. (default: 10)
250 -m,--maxMissingness ARG define a maximal missingness for the right
251 populations in the RAS statistics. (default: 0.1)
252 -f,--tableOutFile ARG the file to which results are written as
253 tab-separated file

254 The output gives both cumulative (up to allele-count k) and and per-allele-frequency RAS (for allele count k) for
255 every pair of left and rights. The standard out contains a pretty-printed table, and in addition, a tab-separated
256 file is written to the file specified using option -f.

257 **xerxes ras** makes a few important assumptions: 1) It assumes that the Right Populations are “nearly” completely
258 non-missing. Any allele that is actually missing from the rights is in fact treated as homozygous-reference! A
259 different approach would be to compute the actual frequencies on the non-missing right alleles, but then we
260 cannot anymore nicely accumulate over different ascertainment allele counts. 2) If no outgroup is specified, the
261 ascertainment operates on minor-allele frequency (as in fstats) 3) If an outgroup is specified and missing from a
262 SNP, or if the SNP is polymorphic, the SNP is skipped as missing