imputeR Documentation

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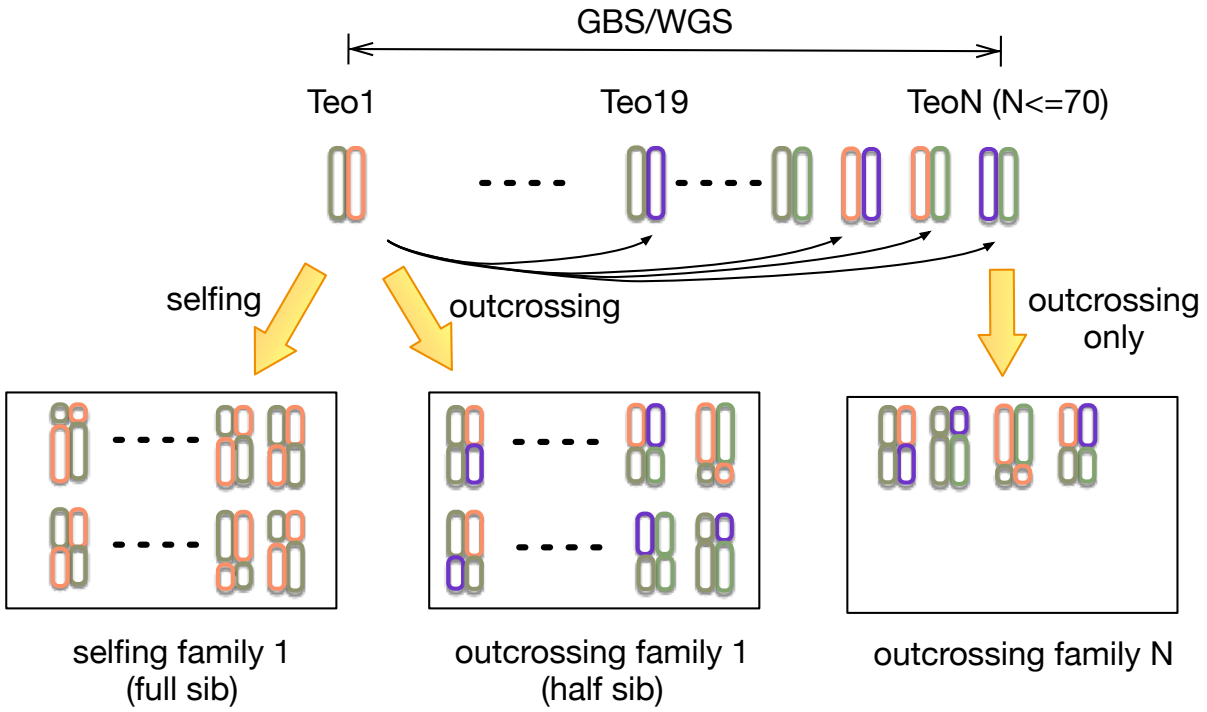
1 Introduction

1.1 Crossing Scheme and Experimental Design



In this experiment, we selfed and outcrossed a set of ~70 teosinte landraces to get a progeny array composed of 4,875 individuals. The ~70 founders and all the progeny were genotyped using GBS. We also re-sequenced 20/70 founder lines (the others will be re-sequenced soon). Because of the high error rate of the GBS data, especially problematic for calling heterozygous sites, we employed a phasing and imputation strategy to infer the expected genotypes by combining parentage and GBS information.

This file is to document the `R` package we developed to solve the problems step by step.

1.2 Install and Usage

Install devtools first, and then use devtools to install imputeR from github.

```
# install and load devtools
devtools::install_github("hadley/devtools")
library(devtools)
# install and load imputeR
install_github("yangjl/imputeR")
library(imputeR)
```

1.3 How to find help

Within "R" console, type `?impute_parent` or `help(impute_parent)` to find help information about the function.

```
?impute_parent
```

```
## No documentation for 'impute_parent' in specified packages and libraries:
## you could try '??impute_parent'
```

1.4 How to load hdf5 file

To load `hdf5` file, you need to install Vince's tasselr and ProgenyArray packages. If you fail to install them, please follow the above links and install the required dependencies.

```
# install devtools and then install the devlopmental version
# of tasselr and ProgenyArray using devtools.
devtools::install_github("hadley/devtools")
library(devtools)
install_github("vsbuffalo/tasselr")
install_github("vsbuffalo/ProgenyArray")
install_github("yangjl/imputeR")
```

Load the required packages. Note you have to specify the locations of the packages if they were not in your searching path.

```
# load packages
library(parallel)
library(devtools)
options(mc.cores=NULL)
# you need to specify the location where the packages were installed.
load_all("~/bin/tasselr")
load_all("~/bin/ProgenyArray")
load_all("~/Documents/Github/imputeR")
```

The following several lines help you to reformat the `*.h5` HDF5 file into an R object. You need to specify the path of the HDF5 file.

```
# Note: at least 100G memory will be needed to load the hdf5 file
# load h5file
teo <- initTasselHDF5("largedata/teo.h5", version="5")
teo <- loadBiallelicGenotypes(teo, verbose = TRUE)
# reformat to imputeR object
source("R/load_data.R")
ob <- imputeRob(teo)
save(file="largedata/teo.RData", list="ob")
```

2 Infer parent's genotype from GBS data

If we have parent's WGS data, this step can be skipped.

We have observed mom and observed (selfed) kids. We want to know $P(G|\theta)$, or the probability of mom's genotype given observed data θ. And according to Bayes' theorem,

$P(G|\theta) \propto P(\theta|G) \times P(G)$,

where $P(G)$ is the probability of the genotype according to the Hardy-Weinberg equilibrium estimated from the population. This consists of observed genotypes (G') of both mom and kids. So:

$$P(G|\theta) \propto \left(\prod_{i=1}^{k} P(G'_k|G) \right) \times P(G'_{mom}|G) \times P(G),$$

where $P(G'_{mom}|G)$ is the probability of mom's observed genotype given a true genotype G by considering error rates, i.e. GBS homozygote error = 0.02 and heterozygote error = 0.8.
And $P(G'_k|G)$ is the probability of the k th kid's observed genotype given genotype G by considering error rates and Mendelian segregation rate. The function `impute_mom` was implemented to compute mom's genotype probabilities.

2.1 Example: step by step

In the below toy example, we simulate a family of self and outcross progeny with 50 kids for 3 loci. We will assume 50% missing data, and 50% selfing rate.

Load the packages.

```
library(devtools)
library(imputeR)
```

First we set some parameters for simulation

```
    source("~/Documents/Github/imputeR/R/utils.R")
    source("~/Documents/Github/imputeR/R/ImputeParent.R")
    misscode = 3 # code for missing data
    numloci=3 # number of loci
    hom.error=0.02 #homozygous error rate
    het.error=0.8 #heterozygous error rate
    imiss=0.5 # % missing data
    selfing=0.5 # selfing rate
    size.array=50 # family size
    rec=0.25 # mean number of crossovers per chromosome
```

Then we make our focal parent

```
    sfs <- getsfs() # make neutral SFS
    p <- sample(sfs, numloci, replace=TRUE) # get sample of allele freqs from SFS

    ### make focal_parent using a data.frame
    sim_focal <- data.frame(hap1=ran.hap(numloci,p), hap2=ran.hap(numloci,p))
```

What is our focal parent's real genotype:

```
    sim_focal
```

```
##   hap1 hap2
## 1    0    1
## 2    0    0
## 3    0    0
```

Now we make our set of parents for each of our progeny. The first `outcrossed` parents are random, then next `size.array - outcrossed` are just the focal parent.

```
    #first outcrossed
    outcrossed=rbinom(n=1,prob=(1-selfing),size=size.array)
    out_parents <- vector("list", outcrossed)
    out_parents <- lapply(1:outcrossed, function(i) data.frame(hap1=ran.hap(numloci,p), hap2=ran.hap(nu
    #now selfed
    self_parents <- vector("list", size.array-outcrossed)
    self_parents <- lapply(1:(size.array-outcrossed), function(i) sim_focal )
    #combine
    if(outcrossed==0){
        parent_array=self_parents
    }else if (outcrossed==size.array){
        parent_array=out_parents
    }else{
        parent_array=c(out_parents,self_parents)
    }

    #now we make their diploid genotypes, we add the focal parent on to the end of the parents array
    parents<-lapply(parent_array, function(q) q[,1]+q[,2]  )
    parents[[size.array+1]]=c(sim_focal[,1]+sim_focal[,2])
    #finally, add error to make some crappy gbs_parents
    gbs_parents=lapply(parents, function(a) add_error(a,hom.error,het.error))
```

Now we make a progeny array for these parents.

```
    progeny <- vector("list", size.array)
    #use the kid function!
    #each entry in progeny list has two vectors. [[1]] is true genotype, [[2]] is observed
    progeny <- lapply(1:size.array, function(a) kid(p2=list(parent_array[[a]][,1], parent_array[[a]][,2

    #now setup observed kids
    obs_kids=list()
    for(i in 1:size.array){ obs_kids[[i]]=progeny[[i]][[2]] }
```

Now we impute the focal parent

```
    #which parent is our focal one? Here we set to end of parents array for ease
    obs_parent=size.array+1 #focal parent
    #which parents are the other parent of each offspring. These are in order since we simulated them t
    other_parents=c(1:outcrossed,rep(obs_parent,size.array-outcrossed)) #list of other parents
```

2.2 Simulation using `imputeR` package

Above simulation steps were packed into a funcion `sim.array`. This function will simulate a `GBS.array` object for the following functions to use.

```
# find help
?sim.array
# make the simulation repeatable
set.seed(1234)
GBS.array <- sim.array(size.array=50, numloci=100, hom.error = 0.02, het.error = 0.8,
  rec = 0.25, selfing = 0.5, imiss = 0.5, misscode = 3)
```

We now impute parent genotypes using `impute_parent` and extract results using `parentgeno`. In the resulting table `res`, the first three columns are the probabilities of genotype `0, 1, 2`. The 4th column is the odd ratio of the highest divided by the 2nd highest probability. `gmax` parent's genotype with the highest probability. `gor` parent's genotype with the highest probability and `OR` bigger than the specified threshold.

```
#The stuff:
inferred_geno_likes <- impute_parent(GBS.array, hom.error=0.02, het.error=0.8, imiss=0.5)
```

```
## ###>>> Loading a progeny array with [ 100 ] GBS loci
## ###>>> Of [ 50 ] kids, [ 24 ] are outcrossed and [ 26 ] are selfed
## ###>>> no allele frequencies provided. Generating random allele frequencies from a neutral SFS
```

```
res <- parentgeno(inferred_geno_likes, oddratio=0.6931472, returnall=TRUE)
res$true_parent <- GBS.array@true_parents[[50]]$hap1 + GBS.array@true_parents[[50]]$hap2
#error rates
nrow(subset(res, gmax != true_parent ))/nrow(res)
```

```
## [1] 0.01
```

```
nrow(subset(res, gor != true_parent & gor !=3 ))/nrow(res)
```

```
## [1] 0.01
```

2.3 Real Data

Then, for each parent, run `impute_parent` as in the toy example above. Note that you will need to supply a vector of allele frequencies at each locus estimated from the parents. If you do not supply this or leave `p=NULL`, a random allele frequency drawn from the neutral SFS will be used instead (this is Very Bad). Since parents are coded as 0,1, or 2 for N parents the allele frequency p at a locus can be calculated as $\frac{\sum_{i=1}^{N} p_i}{2N}$.

3 Phasing focal parent's haplotype

According to Bayes' theorem, we got:

$$P(H_f|\theta) \propto P(\theta|H_f) \times P(H_f)$$

- Where θ denotes observed data.
- $P(H_f)$ is the probability of our focal parent's haplotypes for a given window size of n.

Our prior assumption for $P(H_f)$ is that all possible haplotypes are equally likely. So,

$$P(H_f|\theta) \propto P(\theta|H_f)$$

We assume H_i as the haplotype of the other parent for the ith kid. Because all possible haplotypes (H_i, p ranged from 1 to k) inherited from other parents constitute a partition of the sample space, which includes k kids reproduced by the focal parent (H_f). The hapoltypes (H_i) are pairwise mutually exclusive. Therefore,

$$P(H_f|\theta) \propto \sum_{i=1}^{k} P(\theta|H_f, H_i)$$

It can be further expressed by:

$$P(H_f|\theta) \propto \sum_{i=1}^{k} P(K_i'|H_f, H_i)$$

$$P(H_f|\theta) \propto \sum_{i=1}^{k} \prod_{l=1}^{n} P(G_{i,l}'|H_1, H_2)$$

- $P(K_i'|H_f, H_i)$ is the probability of ith kid's haplotype given parents' haplotype of H_f and H_i.
- $P(G_{i,l}'|H_f, H_i)$ is the probability of ith kid's genotype at locus l given parents' haplotype of H_f and H_i.

3.1 Simulated data

We implemented a function `phase_parent` to do the phasing work. It was conducted in two steps by two major functions `phase_chunk` and `join_chunks`. First, we get the most likely focal parent's haplotype in a window. We then extend the window by one bp each time into a larger chromosomal chunk until the new haplotype in a window conflict with the existing chunk. In the conflict case, a new chromosomal chunk will be created. Second, we compute the possibilities of the haplotypes of two neighboring chunks. The most likely joined haplotype chunks will be returned by the function `join_chunks`.

```
# to make the random events repeatable
set.seed(1234)
# simulate a GBS.array object
GBS.array <- sim.array(size.array=50, numloci=100, hom.error = 0.02, het.error = 0.8,
                       rec = 0.25, selfing = 0.5, imiss = 0.5, misscode = 3)
# get perfect parent genotype
GBS.array <- get_true_GBS(GBS.array)
# get probability matrices
probs <- error_mx(hom.error=0.02, het.error=0.8, imiss=0.5)
# phasing
res <- phase_parent(GBS.array, win_length=10, join_length=10, verbose=FALSE)
```

```r
# compute error rate
phase_error_rate(GBS.array, phase=res)
```

```
## ###>>> phasing error rate [ 0 ] for [ 16 ] heterozygote sites.
```

3.2 Real data

4 Imputing and Phasing Kids

$$P(H_k|\theta) \propto P(\theta|H_k) \times P(H_k)$$
$$P(H_k|\theta) \propto \left(\prod_{i=k} P(H'_k|H_k)\right) \times P(H_k)$$
$$P(H_k|\theta) \propto \left(\prod_{i=k} \prod_{l=1}^{n} P(G'_{i,l}|H_k)\right) \times P(H_k)$$

- Where θ denotes observed data.
- $P(H)$ is the probability of the haplotype for a given window size of n.
- $P(G'_{i,l}|H)$ is the probability of kid i at locus l for a given haplotype H.
- The prior $P(H)$ is that all possible haplotypes of a given window size are equally likely.

```
phase <- read.csv("../data/sim_phasing_res.csv")

hist(phase$er, breaks=30, main="Simulation (N=100)",col="#faebd7", xlab="Phasing Error Rate")
abline(v=mean(phase$er), col="red", lwd=2)
abline(v=median(phase$er), col="darkblue", lwd=2)
```
