Ancestry Specific Allele Frequency Estimation (ASAFE)

Qian Sophia Zhang

Joint work with Dr. Sharon Browning and Dr. Brian Browning
Department of Biostatistics
University of Washington

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1. Motivation for ASAFE

2. Available Data

3. Proposed Approach

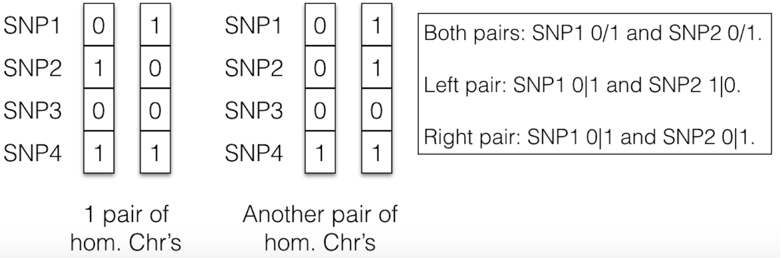
4. Data Simulation

5. Results

Genetic Terminology

Human genomes are packaged into pairs of homologous chromosomes. 2 pairs shown below. Rows are SNPs.

- "SNP" := Point along a chromosome where genomes differ. Often there are two variants or "alleles" at a SNP, labeled 0 and 1.



SNP1	0	1	SNP1	0	1
SNP2	1	0	SNP2	0	1
SNP3	0	0	SNP3	0	0
SNP4	1	1	SNP4	1	1

1 pair of hom. Chr's

Another pair of hom. Chr's

Both pairs: SNP1 0/1 and SNP2 0/1.

Left pair: SNP1 0|1 and SNP2 1|0.

Right pair: SNP1 0|1 and SNP2 0|1.

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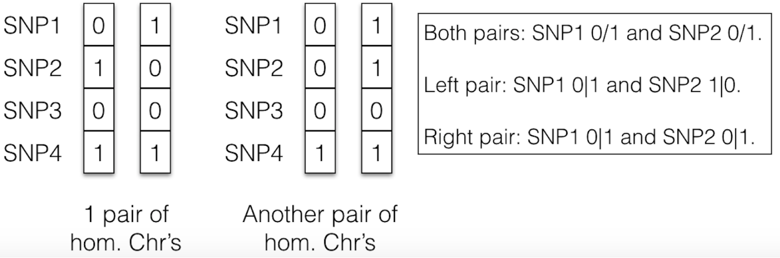
- "SNP" := Point along a chromosome where genomes differ.
  Often there are two variants or "alleles" at a SNP, labeled 0 and 1.
- "Genotype" := 2 homologous chromosomes' alleles at a SNP
  Ex: SNP1's genotype is $0/1$, or $0|1$ or $1|0$. $/$ and $|$ denote phase.



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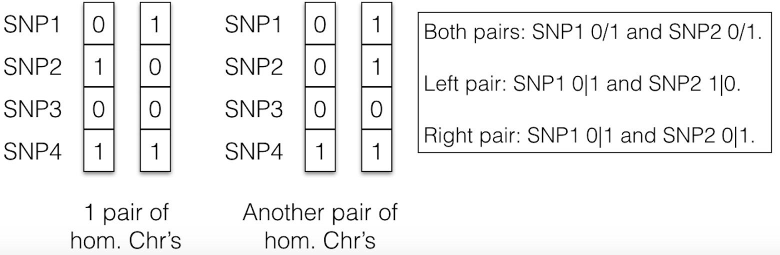

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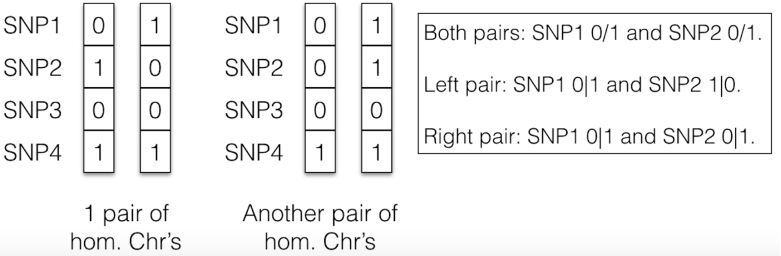

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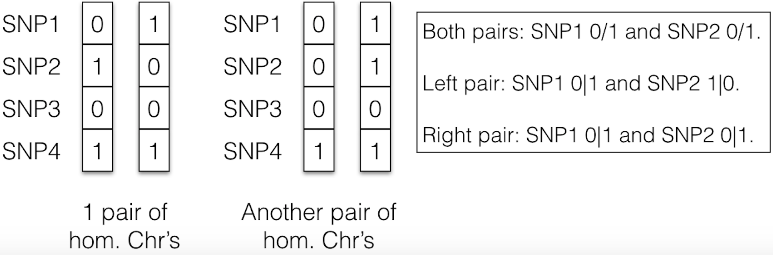
- "Unphased genotype" (/): SNP's genotype is NOT ordered with respect to another SNP's genotype
- "Phased genotype" (|): SNP's genotype IS ordered with respect to another SNP's genotype
- Alleles on the same side of | are on the same chromosome, but not necessarily for /



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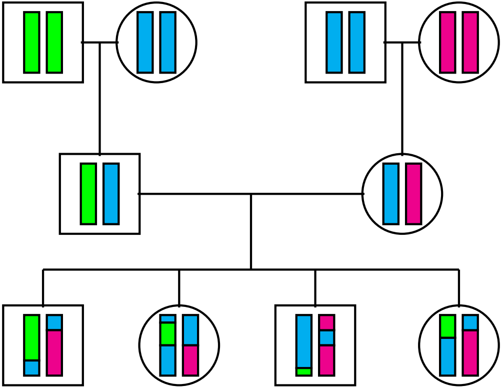
Hispanic Community Health Study (HCHS)

- Cohort study of $13,000$ US Hispanics
- Hispanics are admixed, descended from multiple ancestral populations: Africans, Europeans, and Native Americans
- In this cohort, we test each bi-allelic SNP for association with a trait, say diabetes
- If a SNP is significantly associated with a trait, we want to perform a follow-up study on new individuals to see if we can replicate the association

The Problem that ASAFE Solves

- For a significant SNP, want ancestry-specific allele frequencies := P(Allele 1 | African), P(Allele 1 | European), and P(Allele 1 | Native American), i.e. frequencies of allele 1 amongst chromosomes of African, European, or Native American origin at the SNP



- ASAFE := EM algorithm for estimating these frequencies, for a SNP

How Ancestry Specific Allele Frequencies Relate to HCHS

- These frequencies inform the design of a replication study: If allele 1 were more common amongst the African chromosomes than amongst the other two ancestries' chromosomes, then one would want to recruit a population of predominantly African descent for the replication study

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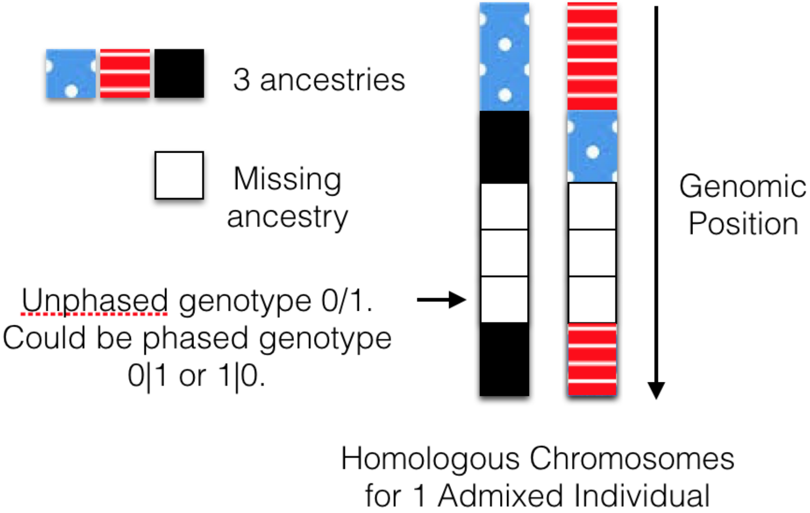
Available Data

- At some SNPs, the RFMix program takes phased genotypes as input, and outputs admixed individuals' phased ancestries
- Available data on admixed individuals
  - Phased ancestries, Phased genotypes: Some SNPs
  - No ancestry calls, Unphased genotypes: Other SNPs

Available Data



3 ancestries

Missing ancestry

Unphased genotype 0/1. Could be phased genotype 0|1 or 1|0.

Genomic Position

Homologous Chromosomes for 1 Admixed Individual

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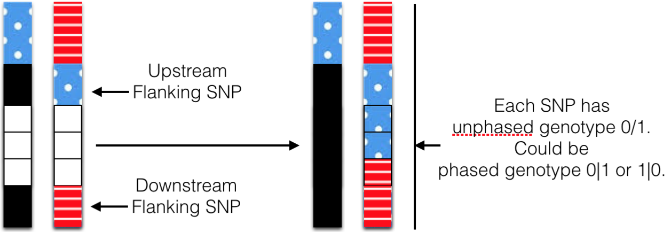
Proposed Approach: Fill in Ancestries

Consider a block of SNPs that have been genotyped in the admixed sample, but that do not have ancestries called. For any SNP in this block:

- Call the SNP's ancestry the nearest flanking ancestry

Then we know all SNPs' unphased genotypes and local ancestry pairs.



Proposed Approach: EM Algorithm to Deal with Unknown Phase of Genotype Relative to Ancestry Pair (ASAFE)

Consider an ancestry-specific allele (allele, ancestry) = (g,a):

- Allele g = 0 or 1
- Ancestry a = African (A), European (E), Native American (N)

There are 6 possibles (g,a) alleles, so 21 values for unordered (g,a)/(g,a) genotype. We call these values unordered (g,a)-genotype categories.

1 complete observation = The (g,a)-genotype category that an individual belongs to at a SNP.

Complete, Unobserved Data Categories

Entry C_i is the name of the i-th complete, unobserved category.

Table: Complete Data Unordered (g,a)-genotype Categories.

(g,a)\(g',a')	(0, A)	(0, E)	(0,N)	(1, A)	(1, E)	(1, N)
(0, A)	C_1					
(0, E)	C_2	C_4				
(0, N)	C_3	C_5	C_6			
(1, A)	C_7	C_9	C_{11}	C_{16}		
(1, E)	C_8	C_{12}	C_{14}	C_{17}	C_{19}	
(1, N)	C_{10}	C_{13}	C_{15}	C_{18}	C_{20}	C_{21}

Hardy-Weinberg Equilibrium assumed in the admixed population to get probability p_j of an individual falling into the j-th complete data category:

$$p_j = \begin{cases} p_{ga}p_{g'a'}, & \text{if } (g,a) = (g',a') \\ 2p_{ga}p_{g'a'}, & \text{otherwise} \end{cases}$$

Incomplete, Observed Data Categories

Entry O_i is the name of the i-th incomplete, observed category. Colored entries are observed data categories that map to multiple complete data categories.

Table: Incomplete, Observed Data Categories.

(g,a)\(g',a')	(0, A)	(0, E)	(0,N)	(1, A)	(1, E)	(1, N)
(0, A)	O_1					
(0, E)	O_2	O_4				
(0, N)	O_3	O_5	O_6			
(1, A)	O_7	O_8	O_9	O_{13}		
(1, E)	O_8	O_{10}	O_{11}	O_{14}	O_{16}	
(1, N)	O_9	O_{11}	O_{12}	O_{15}	O_{17}	O_{18}

Overlaying complete and observed categories gives their correspondence. This correspondence allows us to express the probability p'_j of an individual being in observed data category $j', j' \in \{1, ..., 18\}$ in terms of complete data category probabilities $p_j, j \in \{1, ..., 21\}$.

Outline Approach to Estimating Ancestry-Specific Allele Frequencies

Because of the connection

- Between p'_j and p_j, and
- Between p_j and (g,a)-allele probabilities $\vec{p} = [p_{ga} : g \in \{0,1\}, a \in \{A, E, N\}]$,

maximizing the observed data log likelihood (e.g. via EM algorithm ASAFE)

$$log(P(\vec{o} = [o_1, ..., o_n])|\vec{p}' = [p'_1, ..., p'_{18}]) = \sum_{j'=1}^{18} m'_{j'} log(p'_{j'})$$

where o_i = Observed category of the i-th individual, and $m'_{j'}$ = Number of individuals in observed category j'

gives us a maximum likelihood estimate (MLE) $\hat{\vec{p}} = [\hat{p}_{0A}, \hat{p}_{0E}, \hat{p}_{0N}, \hat{p}_{1A}, \hat{p}_{1E}, \hat{p}_{1N}]$ of $\vec{p}$, from which we obtain ancestry-specific allele frequency estimates:
$\hat{p}_{1|a} = \hat{p}_{1a}/\hat{p}_a = \hat{p}_{1a}/(\hat{p}_{1a} + \hat{p}_{0a}), a \in \{A, E, N\} \leftarrow \text{THE GOAL!}$

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Simulated Genetic Data

- Used MaCS [Chen et al. (2009)] to simulate Hispanic individuals' sequence data
- For each of the $56,003$ SNPs in the sequence data, ran ASAFE with inputs: Unphased admixed genotypes (ignoring known phase) and phased admixed ancestries
- Got ancestry-specific allele 1 frequencies for each ancestry (African, European, Native American), at each SNP
- For each SNP, calculated
  error $=$ Estimated $p_{1|a}$ - True $p_{1|a}$, $a \in \{A, E, N\}$

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Low Error on Simulated Data

Mean and SD of errors $\{\hat{p}_{1|a} - p_{1|a} : a \in \{A, E, N\}\}$, grouped by:

- True allele frequency bin that $p_{1|a}$ falls into: Columns
- Ancestry $a \in \{A, E, N\}$: Rows

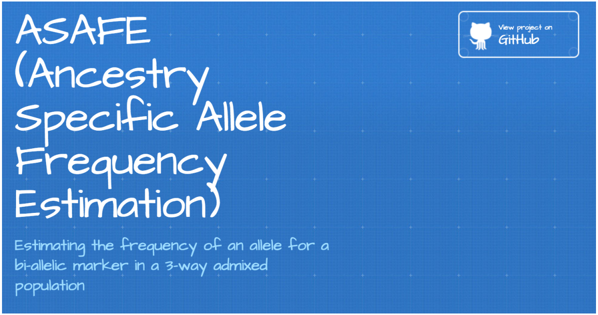
		True Allele 1 Frequency Bins				
Ancestry	Statistic	(0-0.2]	(0.2-0.4]	(0.4-0.6]	(0.6-0.8]	(0.8-1]
African	Mean	-0.0011	-0.0003	-0.0004	0.0004	-0.0004
African	SD	0.0065	0.0185	0.0233	0.0186	0.0118
European	Mean	-0.0015	-0.0004	-0.0007	-0.0010	<0.0001
European	SD	0.0077	0.0209	0.0249	0.0220	0.0122
Nat. Am.	Mean	-0.0004	-0.0017	0.0021	0.0048	0.0007
Nat. Am.	SD	0.0083	0.0235	0.0238	0.0257	0.0118

Regardless of true ancestry-specific allele frequency $p_{1|a}$ bin, errors are low: Largest $|\text{Mean}| = 0.005$. Largest SD $= 0.03$.

More Results in paper supplement.

More Info: Paper and Code

- Qian S. Zhang, Brian L. Browning, and Sharon R. Browning. Asafe: ancestry-specific allele frequency estimation. Bioinformatics, 32(14):2227 2229, 2016.
- Package "ASAFE” on Bioconductor
- Code to reproduce analysis at http://biostatqian.github.io/ASAFE/



ASAFE (Ancestry Specific Allele Frequency Estimation)

Estimating the frequency of an allele for a bi-allelic marker in a 3-way admixed population

6 Appendix: Extra Slides

Available Data

- Unphased bi-allelic SNP genotypes from three reference panels proxying ancestral Africans, Europeans, and Native Americans. Unphased admixed sample genotypes.
  → Phase all SNP genotypes
  → Program RFMix [Maples et al. (2013)] takes phased SNP genotypes, internally re-phases admixed genotypes, and outputs ancestry calls for each admixed person's chromosomes only at SNPs typed in all 3 reference panels
- Using a program called RFMix, we obtain admixed individuals' phased ancestries at some SNPs
- Available data on admixed individuals
  - Phased ancestries, Unphased genotypes: For SNPs that RFMix did not output re-phased genotypes for
  - No ancestry calls, Unphased genotypes: For SNPs that RFMix could NOT make ancestry calls for (e.g. not typed in a reference panel)

Inadequate Alternative Approaches

Goal: Estimate ancestry-specific allele frequencies, for each marker typed in the admixed sample, with available data.

Approaches:

- (1) Find the allele 1 frequency in each reference panel
- (2) Find allele 1 frequencies in populations sequenced by the 1000 Genomes project [Via García et al. (2012)]
- (3) ADMIXTURE, STRUCTURE

Weaknesses of Approaches:

- (1), (2), (3): If a marker is not typed in a reference panel or sequenced by the 1000 Genomes project, these approaches cannot be taken
- (3) assume linkage equilibrium (independence amongst SNPs), e.g. do not make use of linkage disequilibrium from local ancestry calls

ASAFE EM Algorithm

We approximate the MLE $\hat{\vec{p}}$ using an EM algorithm:

(0) Start with an initial estimate of

$\vec{p} = \vec{p}_0 = [p_{0,ga}, g \in \{0,1\}, a \in \{A,E,N\}] = [1/6, 1/6, 1/6, 1/6, 1/6, 1/6]$

Iterate E-M steps (1 E-M = 1 iteration) until $||\vec{p}_{k+1} - \vec{p}_k||_2 < \epsilon = 10^{-8}$, where $\vec{p}_{k+1}$ is the latest estimate of $\vec{p}$ and $\vec{p}_k$ is the 2nd to latest estimate.

(1) E-Step : Evaluate

$E_{\vec{c}}(log(P(\vec{c}|\vec{p}))|\vec{o}, \vec{p}_k) = E_{\vec{c}}(\sum_{j=1}^{21}[m_j log(p_j)]|\vec{o}, \vec{p}_k) =$
$\sum_{j=1}^{21}[E_{\vec{c}}(m_j|\vec{p}, \vec{p}_k) log(p_j)]$

(2) M-Step: Set

$\vec{p}_{k+1} = \mathrm{argmax}_{\vec{p}} E_{\vec{c}}(log(P(\vec{c}|\vec{p})|\vec{o}, \vec{p}_k))$

E-Step in More Detail

On the k-th iteration of the algorithm, let the expected value of the number m_j of individuals in complete category j be denoted

$$m_{k,j} = E_{\vec{c}}(m_j | \vec{o}, \vec{p}_k) = \sum_{i=1}^{m'_{j'}} \frac{P(c_i = j | \vec{p}_k)}{P(c_i = \text{Any j that is consistent with } o_i = j' | \vec{p}_k)}$$

where

- $\vec{c} = [c_1, ..., c_n]$ are complete categories for n admixed individuals
- $\vec{o} = [o_1, ..., o_n]$ are observed categories for n admixed individuals
- $\vec{p}_k = [p_{k,0A}, p_{k,0E}, p_{k,0N}, p_{k,1A}, p_{k,1E}, p_{k,1N}]$ is the k-th estimate for the $\vec{p}$ that maximizes the observed data log likelihood
- $m'_{j'}$ is the number of individuals in observed category j' that is consistent with complete category j

M-Step in More Detail

$\hat{\vec{p}}_{k+1} = [\hat{p}_{k+1,0A}, \hat{p}_{k+1,0E}, \hat{p}_{k+1,0N}, \hat{p}_{k+1,1A}, \hat{p}_{k+1,1E}, \hat{p}_{k+1,1N}]$, where

$$\hat{p}_{k+1,0A} = \frac{2m_{k,1} + m_{k,2} + m_{k,3} + m_{k,7} + m_{k,8} + m_{k,10}}{2n}$$
$$\hat{p}_{k+1,0E} = \frac{m_{k,2} + 2m_{k,4} + m_{k,5} + m_{k,9} + m_{k,12} + m_{k,13}}{2n}$$
$$\hat{p}_{k+1,0N} = \frac{m_{k,3} + m_{k,5} + 2m_{k,6} + m_{k,11} + m_{k,14} + m_{k,15}}{2n}$$
$$\hat{p}_{k+1,1A} = \frac{m_{k,7} + m_{k,9} + m_{k,11} + 2m_{k,16} + m_{k,17} + m_{k,18}}{2n}$$
$$\hat{p}_{k+1,1E} = \frac{m_{k,8} + m_{k,12} + m_{k,14} + m_{k,17} + 2m_{k,19} + m_{k,20}}{2n}$$
$$\hat{p}_{k+1,1N} = \frac{m_{k,10} + m_{k,13} + m_{k,15} + m_{k,18} + m_{k,20} + 2m_{k,21}}{2n}$$

where $n =$ Number of individuals.

Chen, G. K., Marjoram, P., and Wall, J. D. (2009). Fast and flexible simulation of dna sequence data. *Genome research*, 19(1):136–142.

Maples, B. K., Gravel, S., Kenny, E. E., and Bustamante, C. D. (2013). Rfmix: a discriminative modeling approach for rapid and robust local-ancestry inference. *The American Journal of Human Genetics*, 93(2):278–288.

Via García, M., Consortium, . G. P., et al. (2012). An integrated map of genetic variation from 1,092 human genomes. *Nature, 2012, vol. 491, p. 56-65*.