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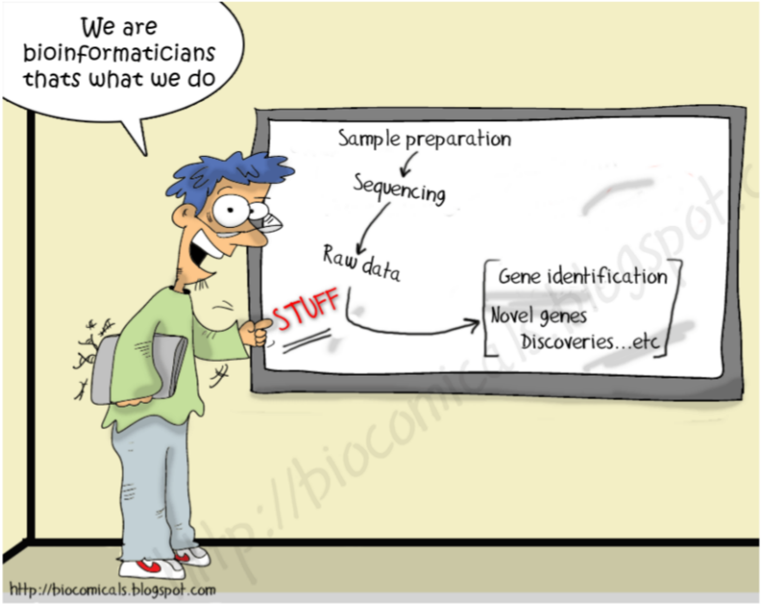
16th July 2019

Genotype and SNP calling and estimation of allele frequencies

Matteo Fumagalli


We are bioinformaticians thats what we do
Sample preparation
Sequencing
Raw data
STUFF
Gene identification
Novel genes
Discoveries...etc
http://biocomicals.blogspot.com

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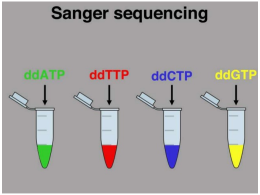
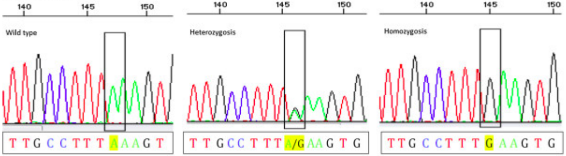
Presentation outline

Motivation

Sanger sequencing

aka first/former generation sequencing





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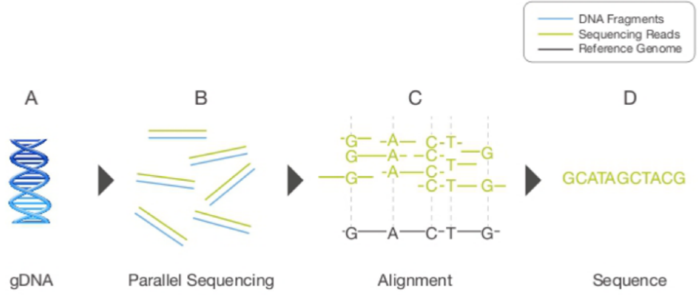
Next Generation Sequencing



A. Extracted gDNA
B. gDNA is fragmented into a library of small segments that are each sequenced in parallel.
C. Individual sequence reads are reassembled by aligning to a reference genome
D. The whole-genome sequence is derived from the consensus of aligned reads.

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From genomes to variants

Genome (FASTA)

```
>ARPM2ref|NC_000001.10|:2938046-2939467 Homo sapiens chromosome 1, GRCh37 primary
reference assembly
TGGAAGAGGCCTCAGCAGGCCCAGGCCACCTGGAGGGAGAGCAGACCTGCGGCTGAGGATGCAGGGCTCC
CGGGCACGGTGCTAGCCCTGCCTTGAGACACCCCGAGAGCTGTGGGAAGAGCTGTGGGATCCCCTATTGC
ATCACAAAGCGGCCCTGGAGGGCTGGTCTTTATTTTGATGAGGCTGAGAAGGGAAGGCTGCGGGCATGTT
TAATCCGCACGCTTTAGACTCCCCGGCTGTGATTTTTGACAATGGCTCGGGGTTCTGCAAAGCGGGCCTG
TCTGGGGAGTTTGGACCCCGGCACATGGTCAGCTCCATCGTGGGGCACCTGAAATTCCAGGCTCCCTCAG
```

Reads (FASTQ)

```
CCAATGATTTTTTTCCGTGTTTCAGAATACGGTTAA
+SRR038845.41 HWI-EAS038:6:1:0:1474 length=36
BCCBA@BB@BBBBAB@B9B@=BABA@A:@693:@B=
@SRR038845.53 HWI-EAS038:6:1:1:360 length=36
GTTCAAAAAGAACTAAATTGTGTCAATAGAAAACTC
+SRR038845.53 HWI-EAS038:6:1:1:360 length=36
```

Mapped Reads (mpileup, BAM)

```
seq1 272 T 24  ,.$.....,,.,.,...,,,.,..^+. <<<+;<<<<<<<<<<<=<;<;7<&
seq1 273 T 23  ,.....,,.,.,...,,,.,..A <<<;<<<<<<<<<3<=<<<;<<+
seq1 274 T 23  ,.$....,,.,.,...,,,.,...    7<7;<;<<<<<<<<<=<;<;<<6
seq1 275 A 23  ,$....,,.,.,...,,,.,...^l.  <+;9*<<<<<<<<<=<<:;<<<<
seq1 276 G 22  ...T,,.,.,...,,,.,....  33;+<<7=7<<7<&<<1;<<6<
seq1 277 T 22  ....,,.,.,.C.,,,.,..G.  +7<;<<<<<<<&<=<<:;<<&<
seq1 278 G 23  ....,,.,.,...,,,.,....^k.   %38*<<;<7<<7<=<<<;<<<<<
seq1 279 C 23  A..T,,.,.,...,,,.,..... ;75&<<<<<<<<<=<<<9<<:<<
```

Variants (VCF)

```
##fileformat=VCFv4.1
##fileDate=20140930
##source=23andme2vcf.pl https://github.com/arrogantrobot/23andme2vcf
##reference=file://23andme_v3_hg19_ref.txt.gz
##FORMAT=<ID=GT,Number=1,Type=String,Description="Genotype">
#CHROM  POS     ID          REF     ALT     QUAL    FILTER  INFO    FORMAT  GENOTYPE
chr1    82154   rs4477212           a       .       .       .       .       GT      0
/0
chr1    752566  rs3094315           g       A       .       .       .       GT      1
/1
chr1    752721  rs3131972           A       G       .       .       .       GT      1
/1
chr1    798959  rs11240777          g       .       .       .       .       GT      0
/0
chr1    800007  rs6681049           T       C       .       .       .       GT      1
/1
```

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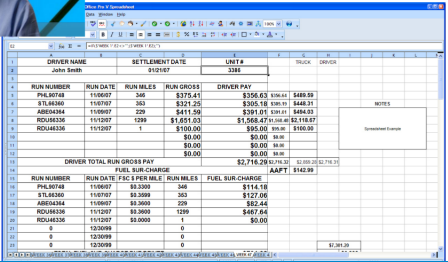
Forget about



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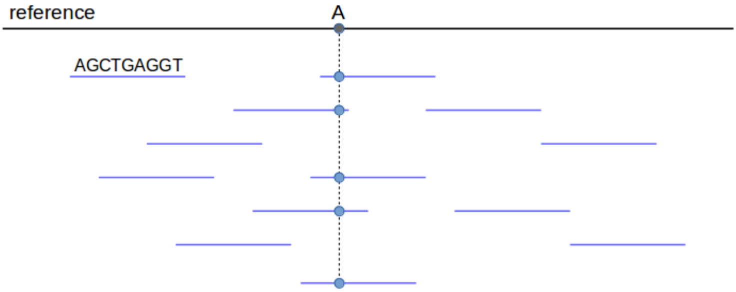
Why do we need statistics?



is a **nucleotide**/base/allele with a certain **quality** score

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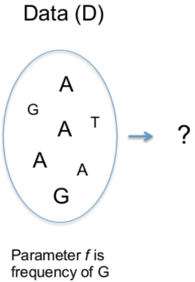
Statistical inference



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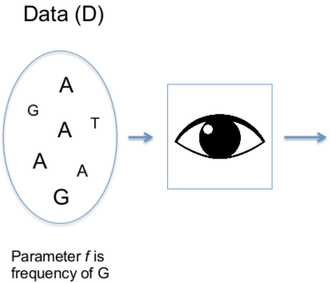
Statistical inference



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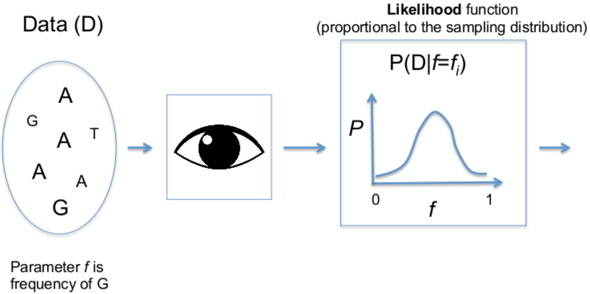
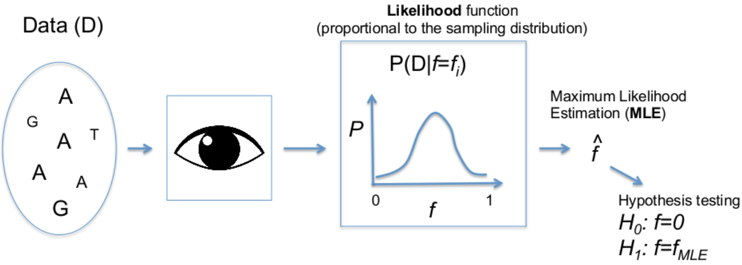
Statistical inference



Statistical inference



Likelihood approach:

- All the information on the parameter is in the likelihood function (we use all the data!).
- More data leads to less bias and less variance.
- Suitable for hypothesis testing.

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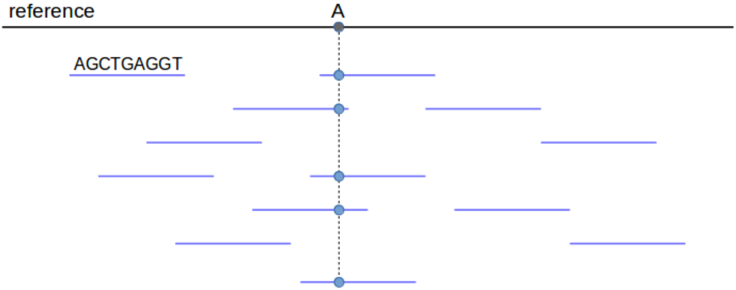
That is why we need statistics!



- is a **nucleotide**/base/allele with a certain **quality** score

Genotype likelihoods

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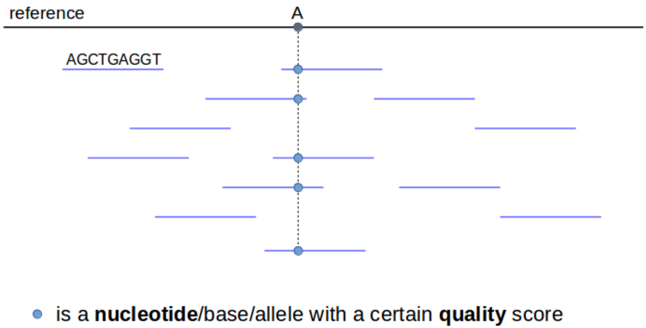
Given a possible genotype, what is the probability of observing this NGS data?



Genotype likelihoods - equation

Likelihood

$P(D|G = \{A_1, A_2, ..., A_n\})$
with
$A_i \in \{A, C, G, T\}$ and n being the ploidy level

Genotype likelihoods - equation

Likelihood

$P(D|G = \{A_1, A_2, ..., A_n\})$
with
$A_i \in \{A, C, G, T\}$ and n being the ploidy level

How many genotypes likelihoods do we need to calculate for each each diploid individual at each site?

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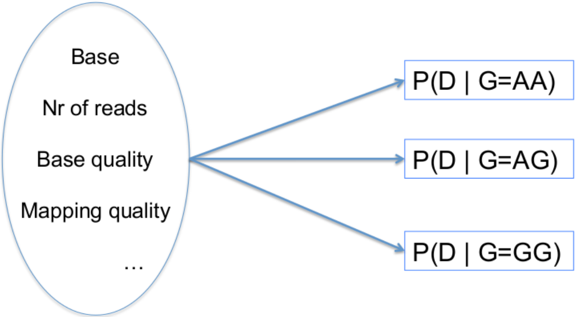
Genotype likelihoods - rationale

Chrom1   272   A   24   AAAAAGGAGAGGTAAG   <<<+;<<<<<<<<<<<<=<;<;7<&

Base quality in Phred scale



Genotype likelihoods - calculation

Likelihood function

$$P(D|G = \{A_1, A_2, ..., A_N\}) = \prod_{i=1}^{R} \sum_{j=1}^{N} \frac{L_{A_j,i}}{N}$$

- $L_{A_j,i} = P(D|A_G = A_j)$
- $A_i \in \{A, C, G, T\}$
- R is the depth (nr. of reads)
- N is the ploidy level (nr. of chromosomal copies)

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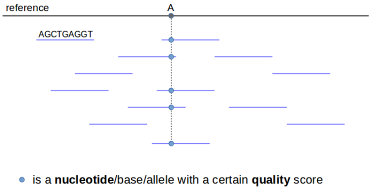
Genotype likelihoods - example



A

A

A

G

with all with quality scores equal to 20 (in phred score)

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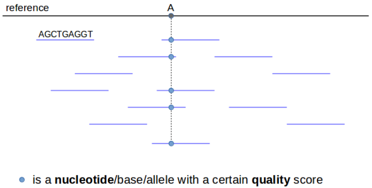
Genotype likelihoods - example



A
A
A
G
with all with quality scores equal to 20 (in phred score)

What is $P(D|G = AC) =?$

Genotype likelihoods - example

Likelihood function

$$P(D|G = \{A_1, A_2, ..., A_N\}) = \prod_{i=1}^{R} \sum_{j=1}^{N} \frac{L_{A_j,i}}{N}$$

A
A
A
G
& Q=20

$$P(D|G = \{A, C\}) = ...$$

Genotype likelihoods - example

Likelihood function

$$P(D|G=\{A_1,A_2,...,A_N\}) = \prod_{i=1}^{R}\sum_{j=1}^{N}\frac{L_{A_j,i}}{N}$$

A
A
A
G
& Q=20
$N=2; i=1; A_1=A; A_2=C$

$$P(D|G=\{A,C\}) = (\frac{L_{A,1}}{2}+\frac{L_{C,1}}{2})\times ...$$

What are $L_{A,1}$ and $L_{C,1}$?

Genotype likelihoods - example

Likelihood function

$$P(D|G = \{A_1, A_2, ..., A_N\}) = \prod_{i=1}^{R} \sum_{j=1}^{N} \frac{L_{A_j,i}}{N}$$

A
A
A
G

$$L_{C,1} =$$

Genotype likelihoods - example

Likelihood function

$$P(D|G = \{A_1, A_2, ..., A_N\}) = \prod_{i=1}^{R} \sum_{j=1}^{N} \frac{L_{A_j,i}}{N}$$

A
A
A
G

$$L_{C,1} = \frac{\epsilon}{3}$$

$$L_{A,1} =$$

Genotype likelihoods - example

Likelihood function

$$P(D|G=\{A_1,A_2,...,A_N\})=\prod_{i=1}^{R}\sum_{j=1}^{N}\frac{L_{A_j,i}}{N}$$

A
A
A
G

$$L_{C,1}=\frac{\epsilon}{3}$$

$$L_{A,1}=1-\epsilon$$

$$P(D|G=\{A,C\})=(\frac{1-\epsilon}{2}+\frac{\epsilon}{6})\times\ldots$$

Genotype likelihoods - example

Likelihood function

$$P(D|G = \{A_1, A_2, ..., A_N\}) = \prod_{i=1}^{R} \sum_{j=1}^{N} \frac{L_{A_j,i}}{N}$$

A
A
A
G

$$L_{C,4} =$$

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Genotype likelihoods - example

Likelihood function

$$P(D|G=\{A_1,A_2,...,A_N\})=\prod_{i=1}^{R}\sum_{j=1}^{N}\frac{L_{A_j,i}}{N}$$

A
A
A
G

$$L_{C,4}=\frac{\epsilon}{3}$$

$$L_{A,4}=$$

Genotype likelihoods - example

Likelihood function

$$P(D|G=\{A_1,A_2,...,A_N\})=\prod_{i=1}^{R}\sum_{j=1}^{N}\frac{L_{A_j,i}}{N}$$

A
A
A
G

$$L_{C,4}=\frac{\epsilon}{3}$$

$$L_{A,4}=\frac{\epsilon}{3}$$

$$P(D|G=\{A,C\})=(\frac{1-\epsilon}{2}+\frac{\epsilon}{6})^3\times\frac{\epsilon}{3}$$

What is ϵ?

Genotype likelihoods - example

Genotype	Likelihood (log10)
AA	-2.49
AC	**-3.38**
AG	-1.22
AT	-3.38
CC	-9.91
CG	-7.74
CT	-9.91
GG	-7.44
GT	-7.74
TT	-9.91

A
A
A
G
$\epsilon = 0.01$

Genotype calling

Genotype calling

Genotype	Likelihood (log10)
AA	-2.49
AC	-3.38
AG	-1.22
AT	-3.38
CC	-9.91
CG	-7.74
CT	-9.91
GG	-7.44
GT	-7.74
TT	-9.91

AAAG & $\epsilon = 0.01$

What is the genotype here?

Genotype calling

Genotype	Likelihood (log10)
AA	-2.49
AC	-3.38
AG	**-1.22**
AT	-3.38
CC	-9.91
CG	-7.74
CT	-9.91
GG	-7.44
GT	-7.74
TT	-9.91

AAAG & $\epsilon = 0.01$
What is the genotype?
AG.

Maximum Likelihood

The simplest genotype caller: choose the genotype with the highest likelihood.

Major and minor alleles

Likelihood function

$$\log P(D|G = A) = \sum_{i=1}^{R} \log L_{A_j,i}$$

AAAG & $\epsilon = 0.01$

Allele	Likelihood
A	**-2.49**
C	-3.38
G	**-1.22**
T	-3.38

We can reduce the genotype space to 3 entries (from 10, for diploids).

Genotype calling

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood
AA	-5.73
AG	-2.80
GG	-17.12

At what extent is the data affecting the called genotype and its **confidence**?

Open jupyter-notebook.

Genotype likelihood ratio

$$\log_{10} \frac{L_{G(1)}}{L_{G(2)}} > t$$

i.e. $t = 1$ meaning that the most likely genotype is 10 times more likely than the second most likely one

Pros and cons?

- Yes:

Genotype likelihood ratio

$$\log_{10} \frac{L_{G(1)}}{L_{G(2)}} > t$$

i.e. $t = 1$ meaning that the most likely genotype is 10 times more likely than the second most likely one

Pros and cons?

- Yes: genotype are called with higher **confidence**
- No:

Genotype likelihood ratio

$$\log_{10} \frac{L_{G(1)}}{L_{G(2)}} > t$$

i.e. $t = 1$ meaning that the most likely genotype is 10 times more likely than the second most likely one

Pros and cons?

- Yes: genotype are called with higher **confidence**
- No: more **missing** data

Practical: genotype likelihoods and (basic) genotype calling
`https://github.com/mfumagalli/Copenhagen`

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The monster dilemma

Figure 1: Nessie, the Loch Ness Monster. True or fake news?

The monster dilemma - likelihood

Let's denote D (data) as the set of observations specifying whether I tell you that I saw Nessie ($D = 1$) or not ($D = 0$).
D is our sample space, the set of all possible outcomes of the experiment, and $D = \{0, 1\}$.
We want to make some inferences on the probability that Nessie exists, or that it is true that I saw it (her?). Let's denote this probability as N.

- $D = \{0, 1\}$, whether I tell you I saw Nessie or not.
- $N = \{0, 1\}$, whether Nessie exists or not.

The monster dilemma - likelihood

Questions

- What are $p(D = 1|N = 1)$ and $p(D = 1|N = 0)$?
- What is a Maximum Likelihood Estimate of N?
- What is a statistical test for $N = 1$?

The monster dilemma - likelihood

Let's assume that $p(D = 1|N = 0) = 0.01$ and $p(D = 1|N = 1) = 0.90$ are valid for each observer l, with $l = 3$. Then the log-likelihood of $N = 0$ is given by $\sum_{l=1}^{3} log(p(D = 1|N = 0)) = -6.91$ while the log-likelihood of $N = 1$ is given by $\sum_{l=1}^{3} log(p(D = 1|N = 1)) = -0.32$. With 3 observations of $D = 1$ we obtained a likelihood ratio (LR, of $N = 1$ vs $N = 0$) of 6.59.

Does the Loch ness monster exist?

"Eyes" thinking

What's "wrong"?

Our inference on N, our parameter, is driven solely by our observations, given by our likelihood function.

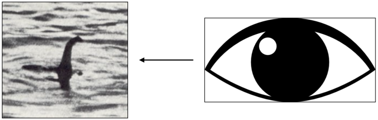


Figure 2: The eye: a "likelihood" organ.

"Blind Brain" thinking

In real life we take many decisions based not only on what we observe but also on some believes of ours*.

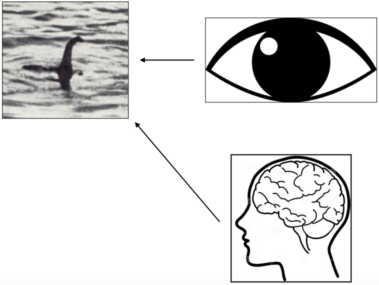


Figure 3: The brain: a "non-likelihood" organ.

* unfortunately in many cases

Eyes+Brain thinking

- with "eyes only" our intuition is that $p(N|D) \approx p(D|N)$
- with "the brain" our intuition is that $p(N|D) \approx p(D|N)p(N)$

Our "belief" expresses the probability $p(N)$ **unconditional** of the data.

Question

How can we define $p(N)$?

"Eyes + Blind Brain" thinking

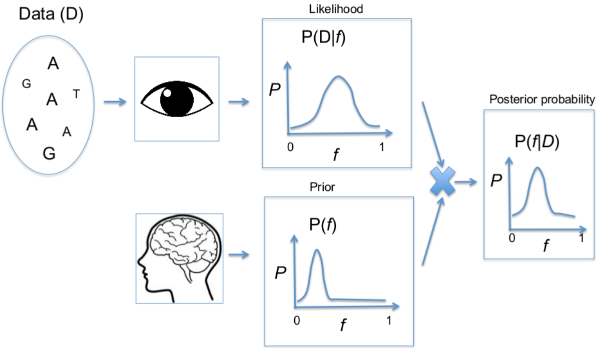
The "belief" function $p(N)$ is called **prior probability** and the joint product of the likelihood $p(D|N)$ and the prior is proportional to the **posterior probability** $p(N|D)$.

The use of posterior probabilities for inferences is called Bayesian statistics.

Bayesian *vs.* Likelihoodist

- we derive "proper" probability distributions of our parameters rather than deriving a point estimate;
- a probability is assigned to a hypothesis rather than a hypothesis is tested;
- we can "accept" the null hypothesis rather than "fail to reject" it;
- parsimony imposed in model choice rather than correcting for multiple tests.

Bayesian inference



Bayes' Theorem

$$p(G|D) = \frac{f(D|G)\pi(G)}{\int f(D|G)\pi(G)dG}$$

- G is not a fixed parameter but a random quantity with prior distribution $\pi(G)$
- $p(G|D)$ is the posterior probability distribution of G
- $\int p(G|D)dG = 1$

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Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	1/3	

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	1/3	0.05
AG	-2.80		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	1/3	0.05
AG	-2.80	1/3	0.95
GG	-17.12		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	1/3	0.05
AG	-2.80	1/3	0.95
GG	-17.12	1/3	0

What is the called genotype? What's its confidence?

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	1/3	0.05
AG	-2.80	1/3	0.95
GG	-17.12	1/3	0

What is the called genotype? What's its confidence?
Only call genotypes if the largest probability is above a certain threshold (e.g. 0.95).

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & **A is the reference allele**

$P(AA) > P(AG) > P(GG)$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & **A is the reference allele**
$P(AA) > P(AG) > P(GG)$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.80	0.22
AG	-2.80		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & **A is the reference allele**
$P(AA) > P(AG) > P(GG)$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.80	0.22
AG	-2.80	0.15	0.78
GG	-17.12		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & **A is the reference allele**
$P(AA) > P(AG) > P(GG)$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.80	0.22
AG	-2.80	0.15	0.78
GG	-17.12	0.05	0

Warning: the reference allele is just one of the possible alleles, often chosen arbitrarily: why so much weight???

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Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & $f(A) = 0.7$ from a reference panel

$P(AA) =?$
$P(AG) =?$
$P(GG) =?$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & $f(A) = 0.7$ from a reference panel

$P(AA) = ?$

$P(AG) = ?$

$P(GG) = ?$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.49	0.06
AG	-2.80		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & $f(A) = 0.7$ from a reference panel

$P(AA) = ?$

$P(AG) = ?$

$P(GG) = ?$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.49	0.06
AG	-2.80	0.42	0.94
GG	-17.12		

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & $f(A) = 0.7$ from a reference panel

$P(AA) = ?$
$P(AG) = ?$
$P(GG) = ?$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.49	0.06
AG	-2.80	0.42	0.94
GG	-17.12	0.09	0

If the assumption of Hardy Weinberg Equilibrium can be reasonably met.

What happens if that's not the case?

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & $f(A) = 0.7$ from a reference panel

$P(AA) =?$
$P(AG) =?$
$P(GG) =?$

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.49	0.06
AG	-2.80	0.42	0.94
GG	-17.12	0.09	0

If the assumption of Hardy Weinberg Equilibrium can be reasonably met.

What happens if that's not the case?

Inbreeding can be incorporated: $f_{AA} = (1-f)^2 + (1-f)fF$ ...

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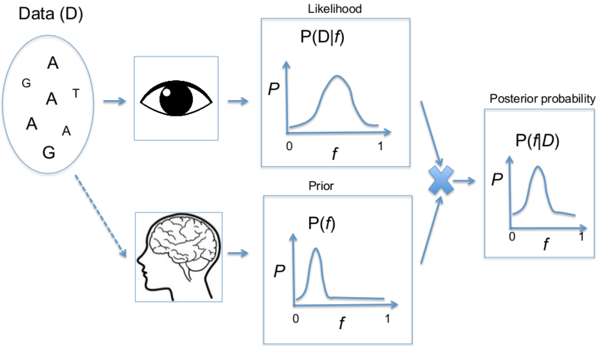
"Eyes + non-Blind Brain" inference



Empirical Bayesian

Genotype posterior probability

AAAG & $\epsilon = 0.01$ & A,G alleles & $f(A) = 0.7$ from the data itself

Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73		

Genotype posterior probability

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Genotype	Likelihood (log)	Prior	Posterior
AA	-5.73	0.49	0.04
AG	-2.80	0.42	0.96
GG	-17.12	0.09	0

- if the assumption of HWE(+-F) can be met (no population structure)
- if enough samples to have a robust estimate of the allele frequencies

Practical: (advanced) genotype calling

`https://github.com/mfumagalli/Copenhagen`

Genotype posterior probability

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How can we estimate allele frequencies from NGS data?

SNP calling

Estimating allele frequencies

Assuming 2 alleles (A,G) with true allele frequency of 0.50

Sample	True genotype	Reads allele A	Read allele G
1	AA	7	0
2	AA	25	1
3	AG	5	3
4	AG	4	4
5	GG	0	2
6	GG	0	4

What is the simplest estimator of allele frequencies?

Estimating allele frequencies

Assuming 2 alleles (A,G) with true allele frequency of 0.50

Sample	True genotype	Reads allele A	Read allele G
1	AA	7	0
2	AA	25	1
3	AG	5	3
4	AG	4	4
5	GG	0	2
6	GG	0	4
Total		41	14

$$\hat{f} = \frac{\sum_{i=1}^{N} n_{A,i}}{\sum_{i=1}^{N}(n_{A,i} + n_{G,i})}$$

$\hat{f} = 0.75$

What is wrong with this estimator?

Estimating allele frequencies

Assuming 2 alleles (A,G) with true allele frequency of 0.50

Sample	True genotype	Reads allele A	Read allele G
1	AA	7	0
2	AA	25	1
3	AG	5	3
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6	GG	0	4
Total		41	14

$$\hat{n_A} = \sum_{i=1}^{N} (1-\epsilon) n_{A,i} + \epsilon n_{G,i} - \epsilon n_{A,i} - (1-\epsilon) n_{G,i}$$

$\hat{f} = 0.77$

Estimating allele frequencies

Maximum Likelihood estimator

$$P(D|f) = \prod_{i=1}^{N} \sum_{g \in \{0,1,2\}} P(D|G=g)P(G=g|f)$$

Estimating allele frequencies

Maximum Likelihood estimator

$$P(D|f) = \prod_{i=1}^{N} \sum_{g \in \{0,1,2\}} P(D|G=g)P(G=g|f)$$

$P(D|G=g)$ is the genotype likelihood and $P(G=g|f)$ is given by HWE (for instance).

In our previous example, $\hat{f} = 0.46$ which is much closer to the true value than previous estimators.

SNP calling

Challenges

- If high levels of missing data, then genotypes can be lost.
- Rare variants are hard to detect.
- Trade off between false positive and false negative rates.

How to call SNPs?

- If at least one heterozygous genotype has been called.
- If the estimated allele frequency is above a certain threshold.

SNP calling

Call a SNP if

$$\hat{f} \geq t$$

where t can be the minimum sample allele frequency detectable (e.g. $t = 1/2N$ with N diploids).

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Likelihood Ratio Test

A Likelihood Ratio Test (LRT) compares the goodness of fit between the null and the alternative model:

- Null model: $f = 0$
- Alternative model: $f \neq 0$

$$T = -2 \log \frac{L(f = 0)}{L(f = \hat{f}_{MLE})}$$

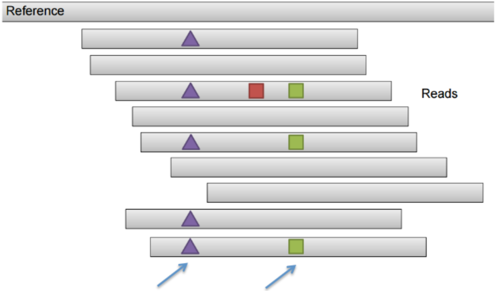
where T is χ^2 distributed with 1 degree of freedom.

Practical: allele frequencies and SNP calling
`https://github.com/mfumagalli/Copenhagen`

Imperial College London

SNP calling procedures

- Alignment-based caller



We completely rely on how reads have been mapped

Figure from Erik Garrison

Imperial College
London

SNP calling procedures

- Assembly-based caller (as in GATK)

Local re-alignment around putative variants; better resolution for INDELs detection.

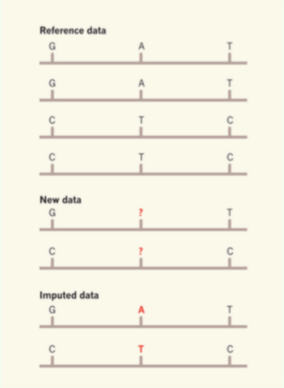
- Haplotype-based caller (as in freebayes)

Figure from Erik Garrison

Imputation

Haplotype imputation

Haplotype imputation - simplified



Reference

- 1000 Genomes
- Phased using family structures

new data

- partial information

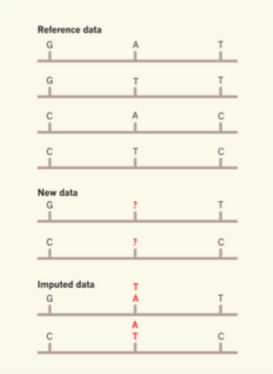
Imputed data

- Probabilistic approach
- The results retains the uncertainty of both the genotype and the haplotypes

Anders Albrechtsen

Haplotype imputation

Haplotype imputation - simplified



Reference

- 1000 Genomes
- Phased using family structures

new data

- Data with known and unknown genotypes

Imputed data

$p(? = T) =$
$p(? = A) =$

Anders Albrechtsen

Haplotype imputation

Haplotype imputation - simplified

Reference

- haplotype frequencies

new data

- Data with known and unknown genotypes

first haplotype

$$p(? = T) = \frac{0.56}{0.56+0.03} = 0.95$$
$$p(? = A) = \frac{0.03}{0.56+0.03} = 0.05$$

second haplotype

$$p(? = T) = \frac{0.21}{0.21+0.2} = 0.51$$
$$p(? = A) = \frac{0.2}{0.21+0.2} = 0.49$$

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Haplotype imputation

Haplotype imputation - simplified

Bayes formula

$$p(H = h|f, G) = \frac{P(G|H{=}h)P(H{=}h|f)}{\sum_{h'} P(G|H{=}h')P(H{=}h'|f)}$$

$P(G|H = h)$

1 if consistent

0 otherwise

first haplotype

$$p(? = T) = \frac{0.56}{0.56+0.03} = 0.95$$
$$p(? = A) = \frac{0.03}{0.56+0.03} = 0.05$$

Anders Albrechtsen