Genotype imputation

The scientific art of guessing stuff

Lecturer profile

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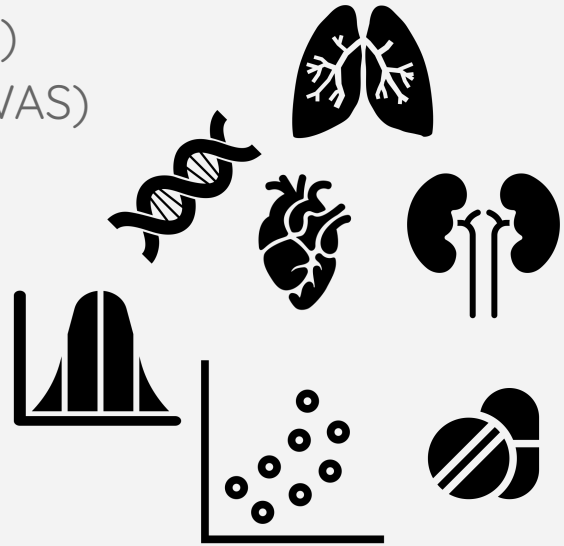
Brunak group

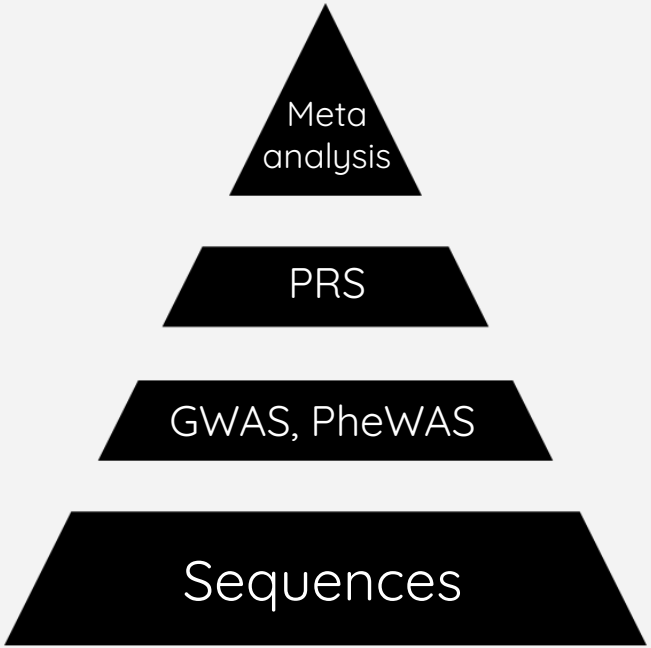
Research interests: Translational Disease Systems Biology

- Genome-wide association studies (GWAS)
- Phenome-wide association studies (PheWAS)
- Polygenic Risk Scores (PRS)
- Genotype Imputation



- Survival analysis
- Drug repositioning
- **Systems biology** & precision medicine

Basic structure



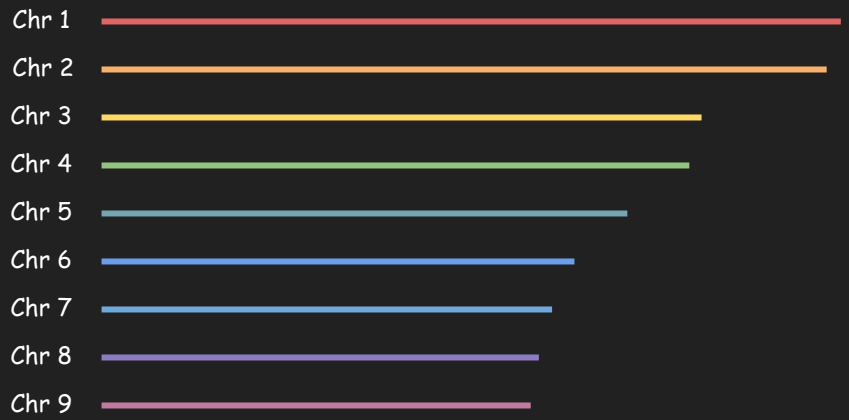
Whole Genome Sequencing vs Global Sequencing Array

Theory vs Real world

Uses and applications

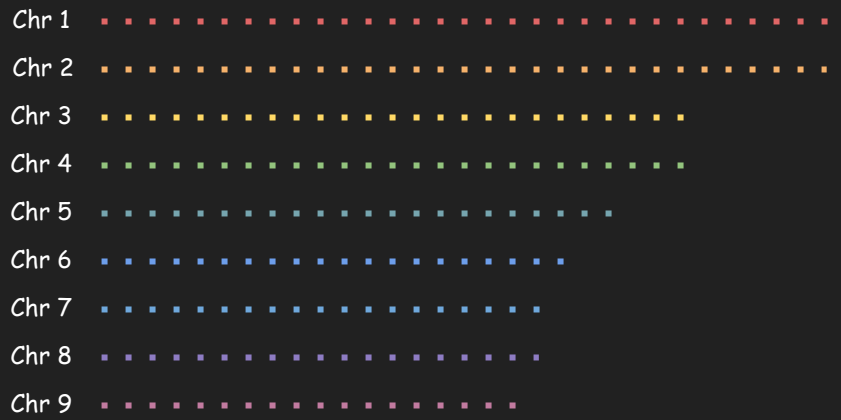
Whole Genome Sequencing (WGS)

The process of determining the entirety of an individual's genome sequence.

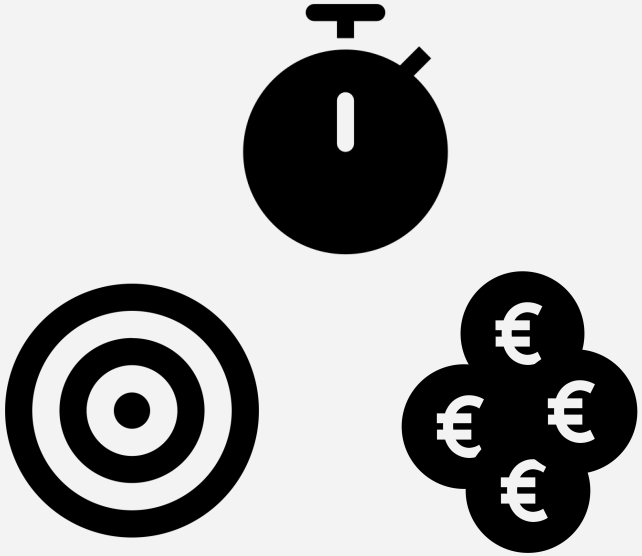


Global Sequencing Array (GSA)

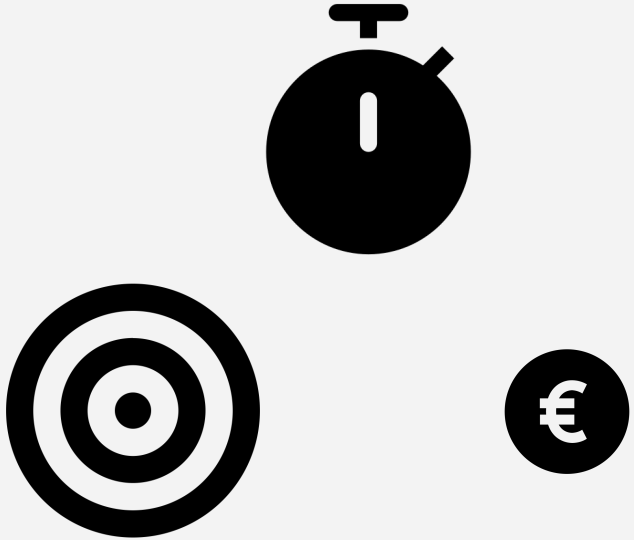
Array genotyping a (known) part of an individual's genome. *Specific SNPs*



Whole Genome Sequencing (WGS)

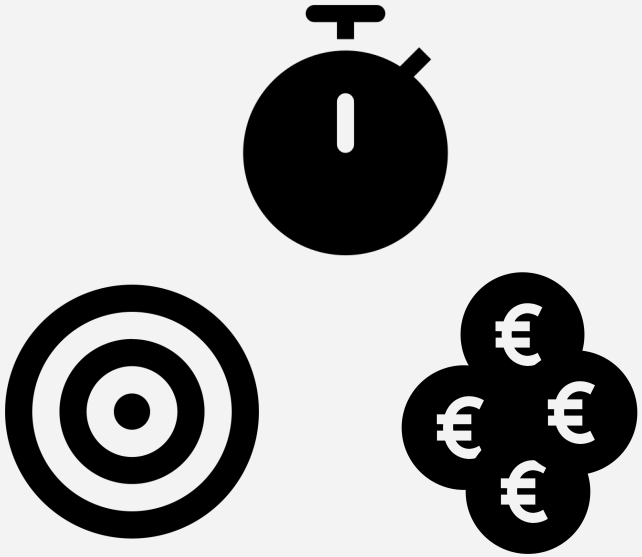


Global Sequencing Array (GSA)

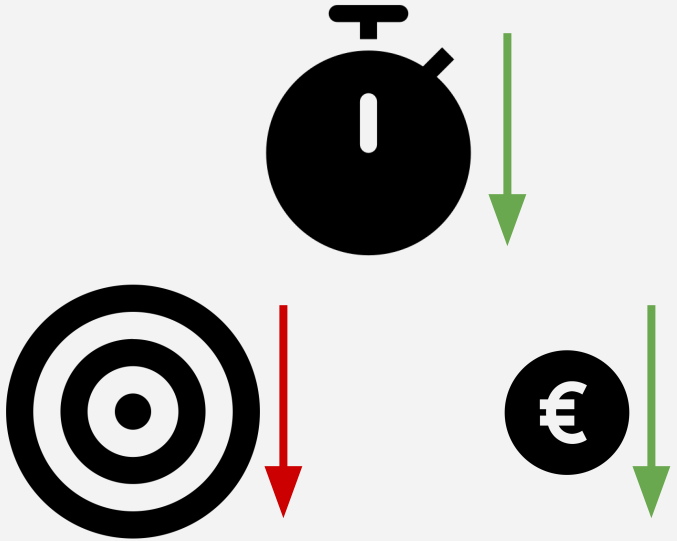


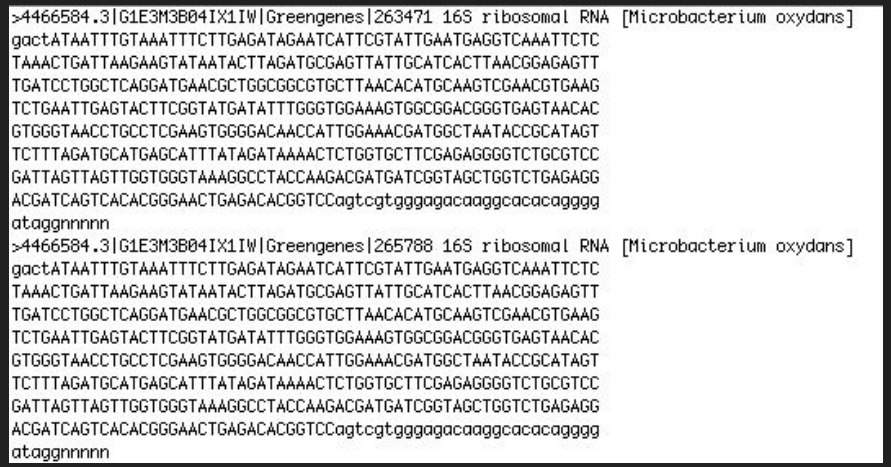
Uses and applications

Whole Genome Sequencing (WGS)



Global Sequencing Array (GSA)

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Fasta files

Variant Call Format

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Variant Call Format

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0/1 heterozygous
1/1 alt. homozygous
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BED/BIM/FAM

BED

It is a BINARY file format.

0	0	1	2
1	2	0	1
0	0	1	1
0	2	1	2

BIM

Basically a tsv file for variants.

1. Chromosome code (either an integer, or 'X'/'Y'/'XY'/'MT'; '0' indicates unknown) or name
2. Variant identifier
3. Position in morgans or centimorgans (safe to use dummy value of '0')
4. Base-pair coordinate (1-based; limited to 2^{31}-2)
5. Allele 1 (corresponding to clear bits in .bed; usually minor)
6. Allele 2 (corresponding to set bits in .bed; usually major)

FAM

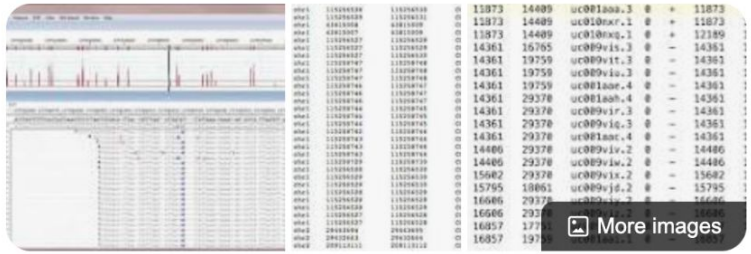
Basically a tsv file for individual info.

1. Family ID ('FID')
2. Within-family ID ('IID'; cannot be '0')
3. Within-family ID of father ('0' if father isn't in dataset)
4. Within-family ID of mother ('0' if mother isn't in dataset)
5. Sex code ('1' = male, '2' = female, '0' = unknown)
6. Phenotype value ('1' = control, '2' = case, '-9'/'0'/non-numeric = missing data if case/control)

Beware!

BED files

A BED file (. bed) is a tab-delimited text file that defines a feature track. It can have any file extension, but . bed is recommended. The BED file format is described on the UCSC Genome Bioinformatics web site: http://genome.ucsc.edu/FAQ/FAQformat.



Broad Institute
https://software.broadinstitute.org › software › igv › B...

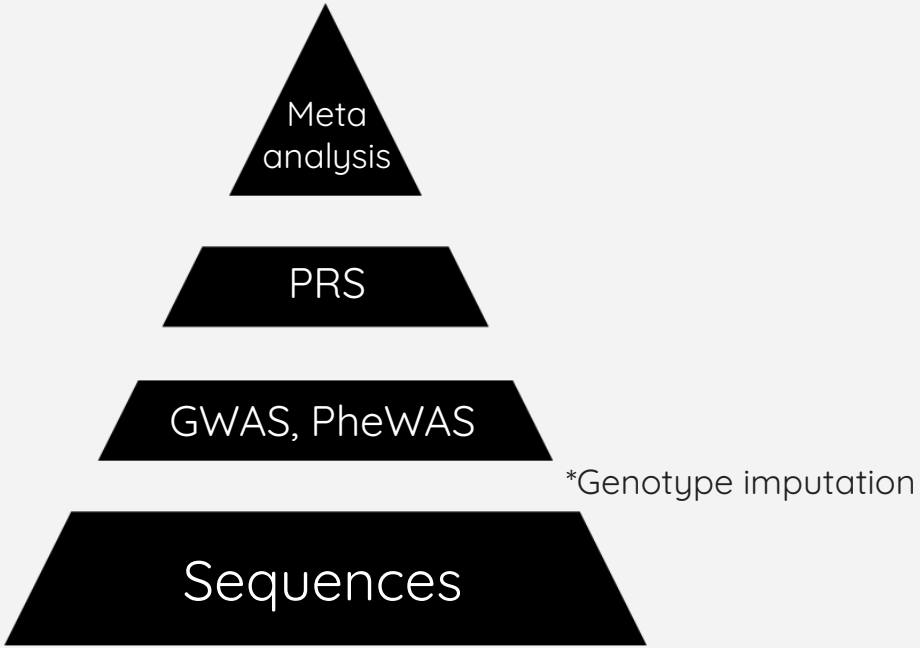
BED | Integrative Genomics Viewer - Broad Institute

Exercise 1

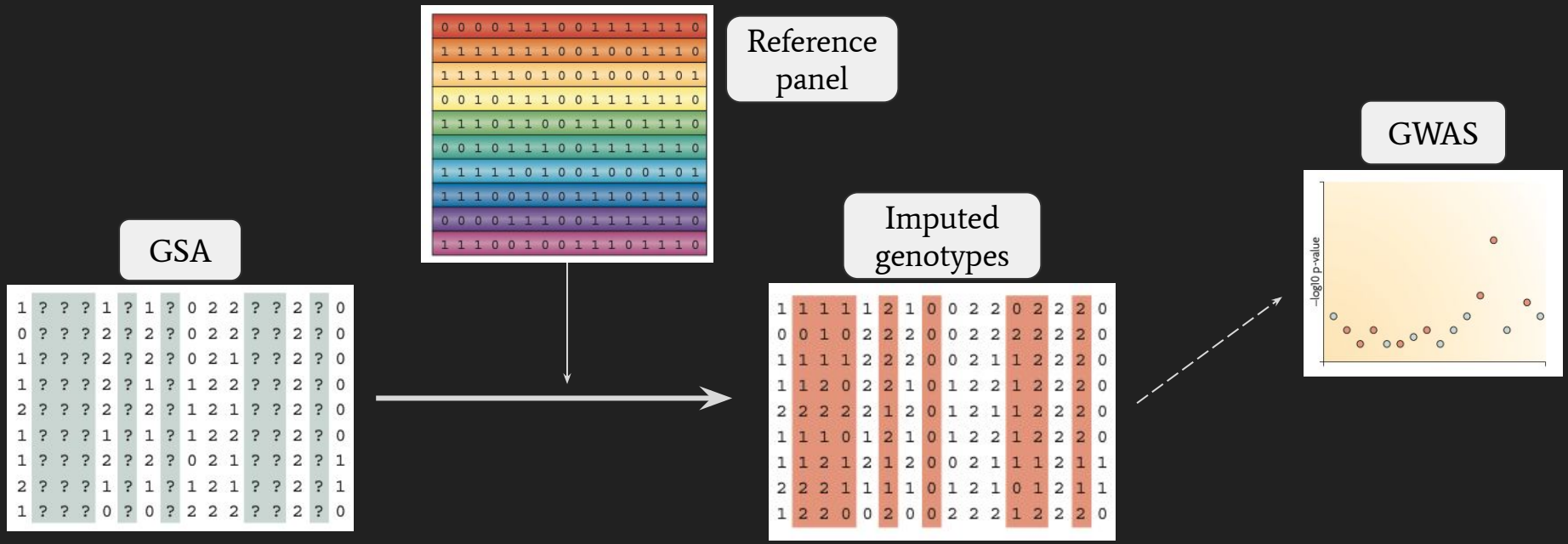
Set-up and data exploration.

Genotype imputation

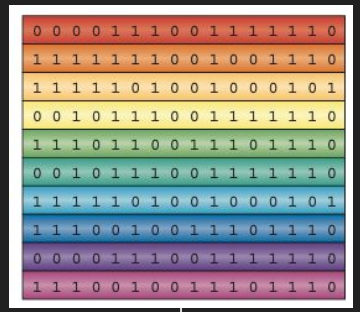
Basic structure



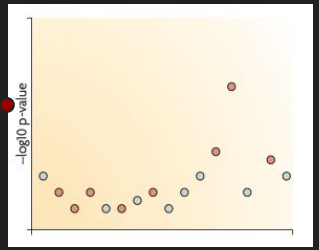
How does “genotype imputation” work?



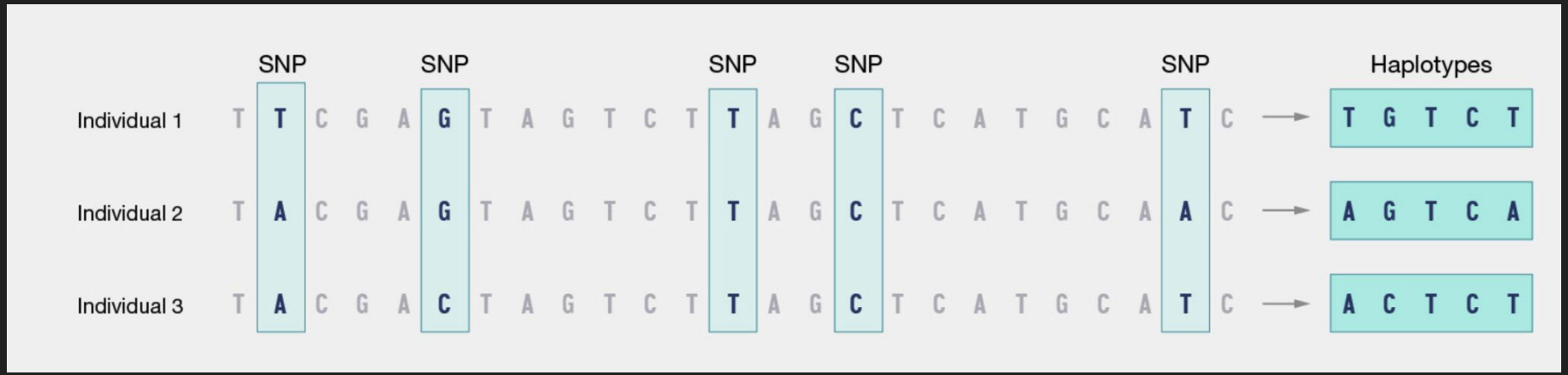
How does “genotype imputation” work?



Dependent on reference



Reference panel



Reference panel

Ancestry

General reference panels available at the moment:

- HapMap3
- 1000Genomes

Reference panel

Ancestry

Populations

The following population samples were studied:

ASW	African ancestry in Southwest USA
CEU	Utah residents with Northern and Western European ancestry from the CEPH collection
CHB	Han Chinese in Beijing, China
CHD	Chinese in Metropolitan Denver, Colorado
GIH	Gujarati Indians in Houston, Texas
JPT	Japanese in Tokyo, Japan
LWK	Luhya in Webuye, Kenya
MXL	Mexican ancestry in Los Angeles, California
MKK	Maasai in Kinyawa, Kenya
TSI	Toscani in Italia
YRI	Yoruba in Ibadan, Nigeria

From theory to practice

Data preparation

Tools: plink

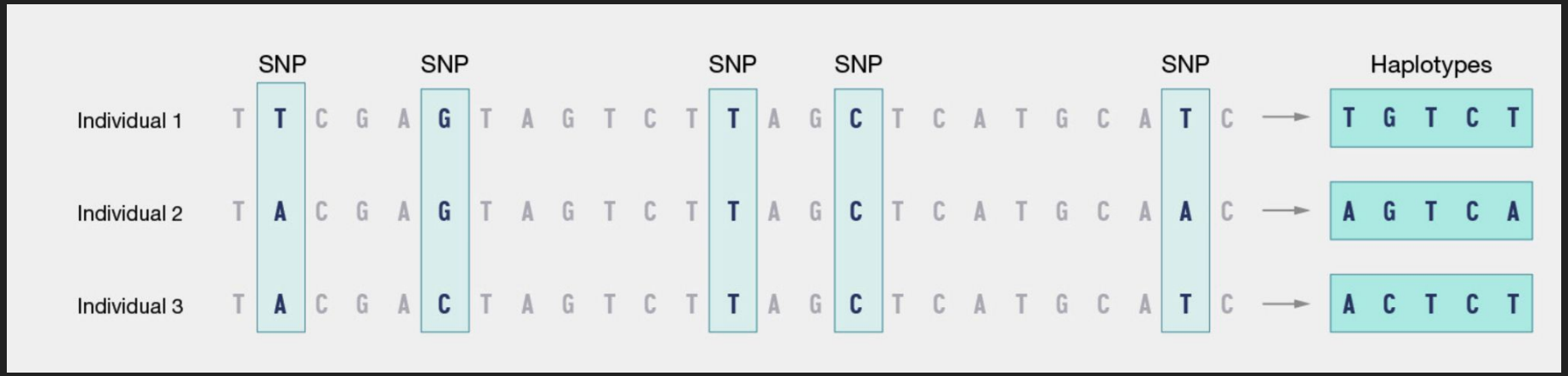
1. Correct input strand
2. Sort bcf
3. **SNP quality control (maf, geno)**
4. **Individual quality control (mind)**
5. Chromosome split
6. Remove duplicate variants

Exercise 2

Data preparation - Some basic filtering.

Phasing / Haplotype estimation

- Shapeit4



State-of-the-art

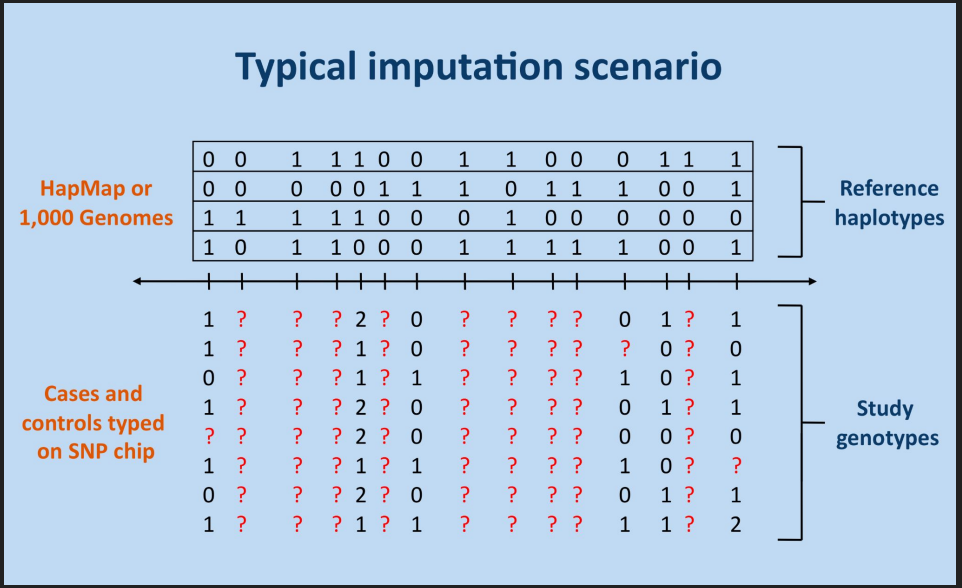
Imputation:

1. Impute5
2. Minimac4
3. BEAGLE

State-of-the-art

Imputation:

1. **Impute5**
2. Minimac4
3. BEAGLE



Exercise 3

Let’s impute some genotypes.

Post-imputation

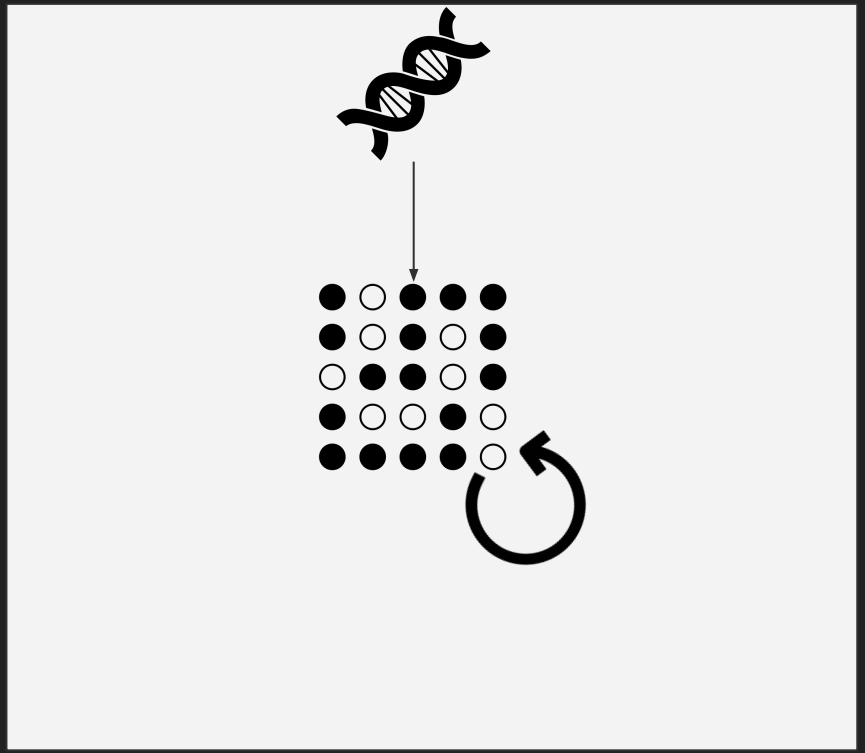
Quality control of imputed SNPs:

INFO SCORE -> range [0, 1]

Higher is better.

Deep Learning

Imputator



Rapid, Reference-Free human genotype imputation with denoising autoencoders

Raquel Dias[1,2,3], Doug Evans[1,2], Shang-Fu Chen[1,2], Kai-Yu Chen[1,2], Salvatore Loguercio[1,2], Leslie Chan[1,2], Ali Torkamani[1,2]*

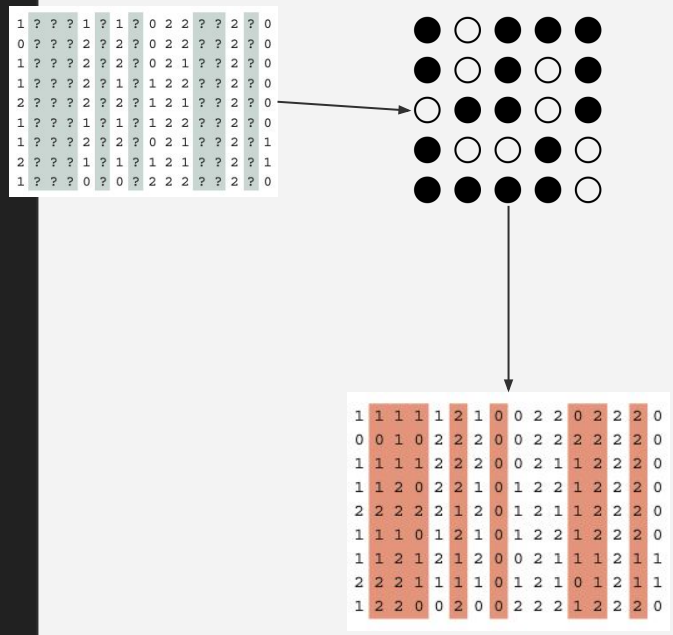
[1]Scripps Research Translational Institute, Scripps Research Institute, La Jolla, United States; [2]Department of Integrative Structural and Computational Biology, Scripps Research, La Jolla, United States; [3]Department of Microbiology and Cell Science, University of Florida, Gainesville, United States

Abstract Genotype imputation is a foundational tool for population genetics. Standard statistical imputation approaches rely on the co-location of large whole-genome sequencing-based reference panels, powerful computing environments, and potentially sensitive genetic study data. This results in computational resource and privacy-risk barriers to access to cutting-edge imputation techniques. Moreover, the accuracy of current statistical approaches is known to degrade in regions of low and complex linkage disequilibrium. Artificial neural network-based imputation approaches may overcome these limitations by encoding complex genotype relationships in easily portable inference models. Here, we demonstrate an autoencoder-based approach for genotype imputation, using a large, commonly used reference panel, and spanning the entirety of human chromosome 22. Our autoencoder-based genotype imputation strategy achieved superior imputation accuracy across the allele-frequency spectrum and across genomes of diverse ancestry, while delivering at least fourfold faster inference run time relative to standard imputation tools.

Editor's evaluation

The paper describes a novel neural-network-based strategy for imputing unmeasured genotypes, which is a standard part of most association testing pipelines. The method is computationally intensive to train, but once training is complete the imputation is fast and accurate and does not require further access to a reference panel. It has the potential to be a practically-appealing alternative to existing methods. although further work (eg training of models) is required before this new approach can be applied genome-wide.

Imputator



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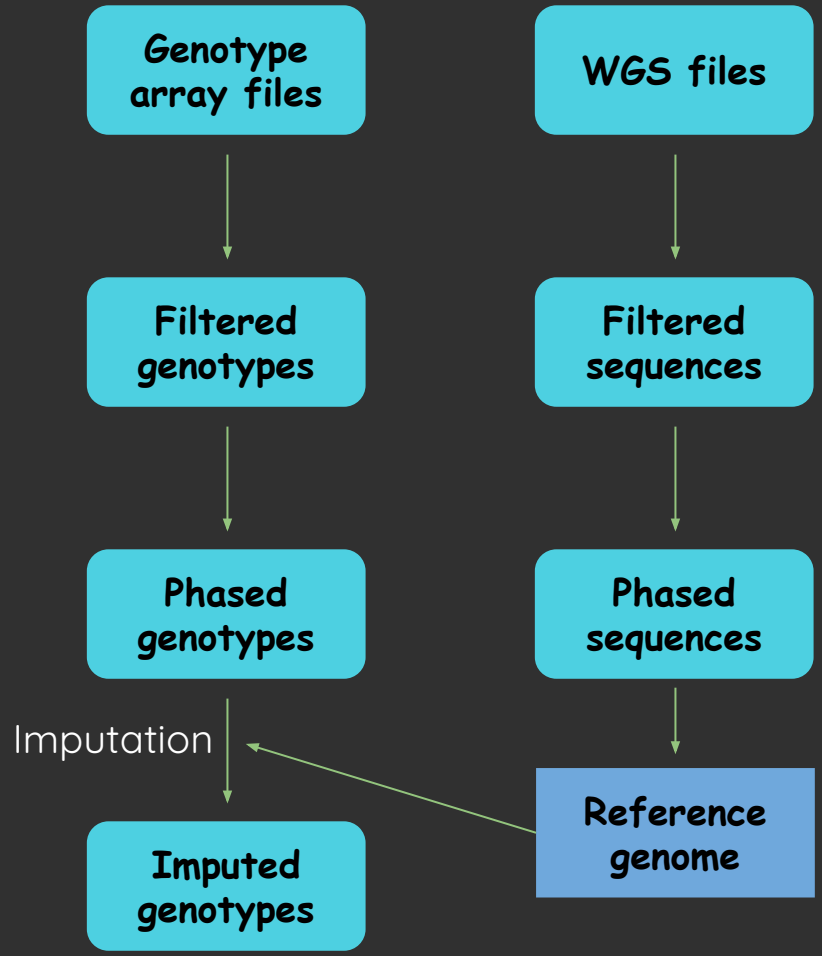
Lecture overview



Thank you