Imputation

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Summer Course 2025

Intended learning outcomes

1

Understand the motivation behind imputation

2

Understand the techniques used for phasing and imputation

3

Understand the use of genotype likelihoods with imputation

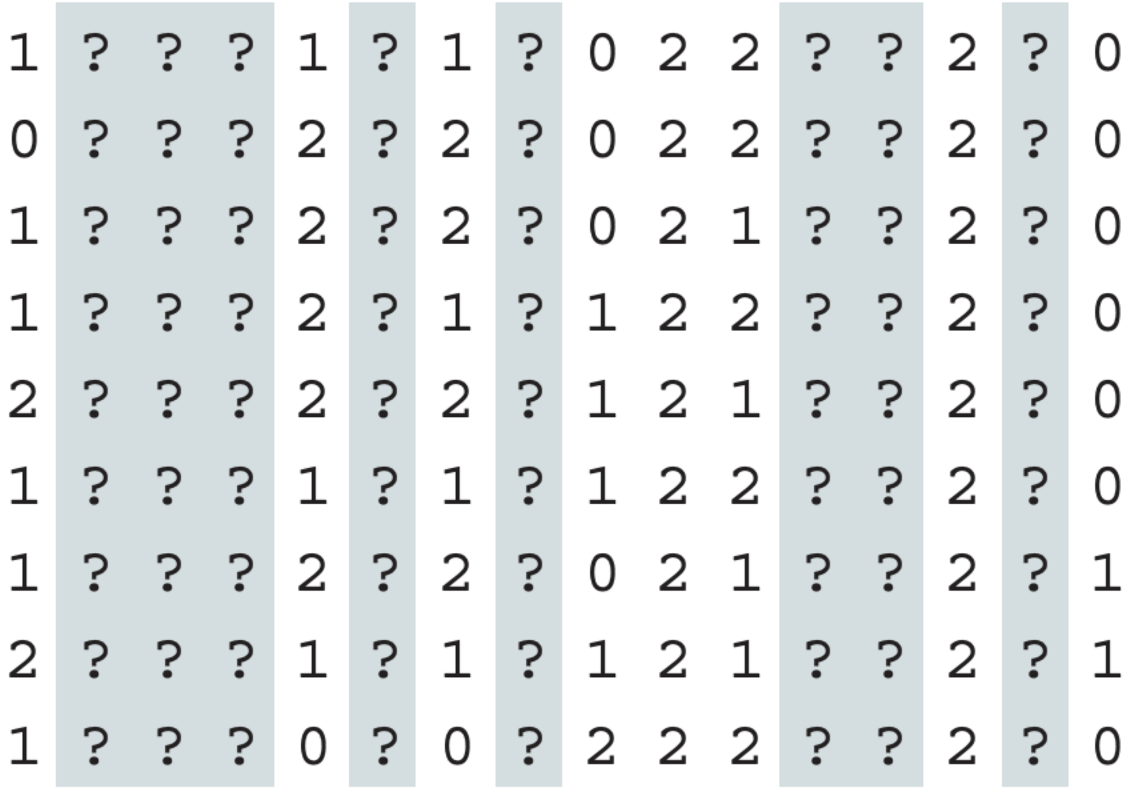
Overview for today

- Problem setting
- Motivation
- Background
- Phasing → Imputation
- Ideas behind imputation
- Exercises

Problem setting

You have sparse data for some samples at some markers – but you want to fill in the gaps.

Genotype data with missing data at untyped SNPs (grey question marks)



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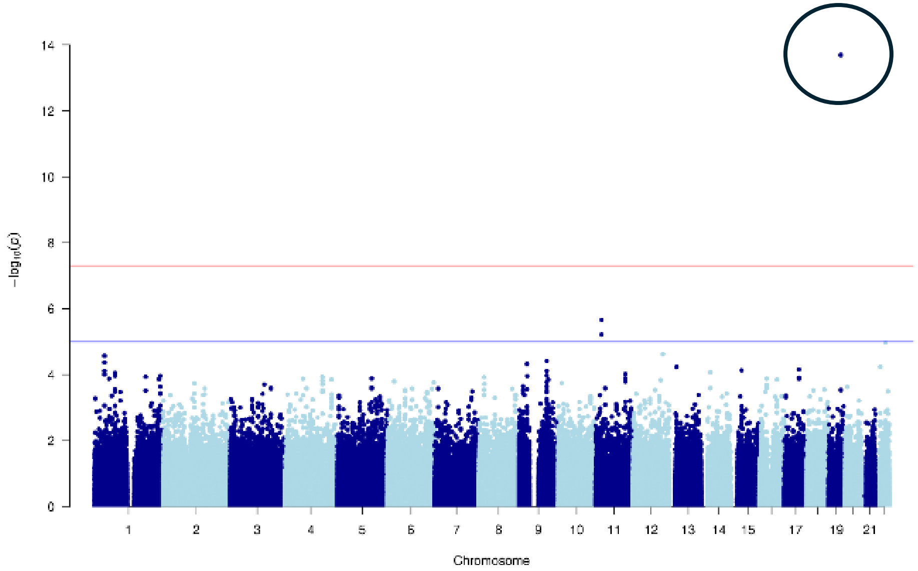
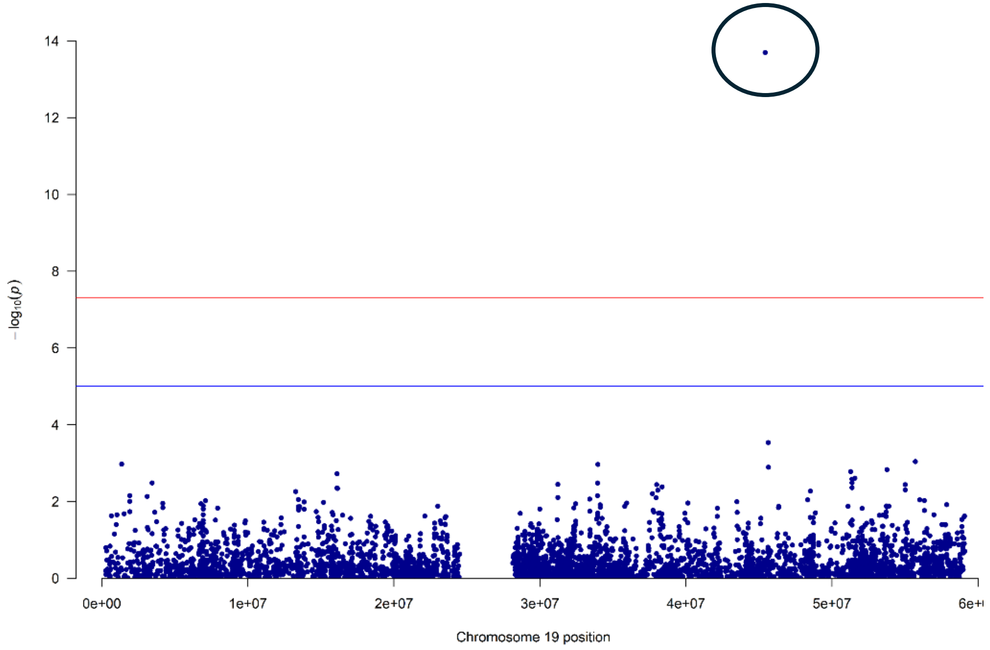
1	?	?	?	0	?	0	?	2	2	2	?	?	2	?	0

Why impute?

- Many reasons to imput
  - Meta-analysis – combining results from multiple studies
  - Fine Mapping – better location of GWAS signals
  - Combining data from different chips
- Other less common uses
  - Sporadic missing data imputation
  - Correction of genotyping errors

Example – imputed vs. non-imputed signal



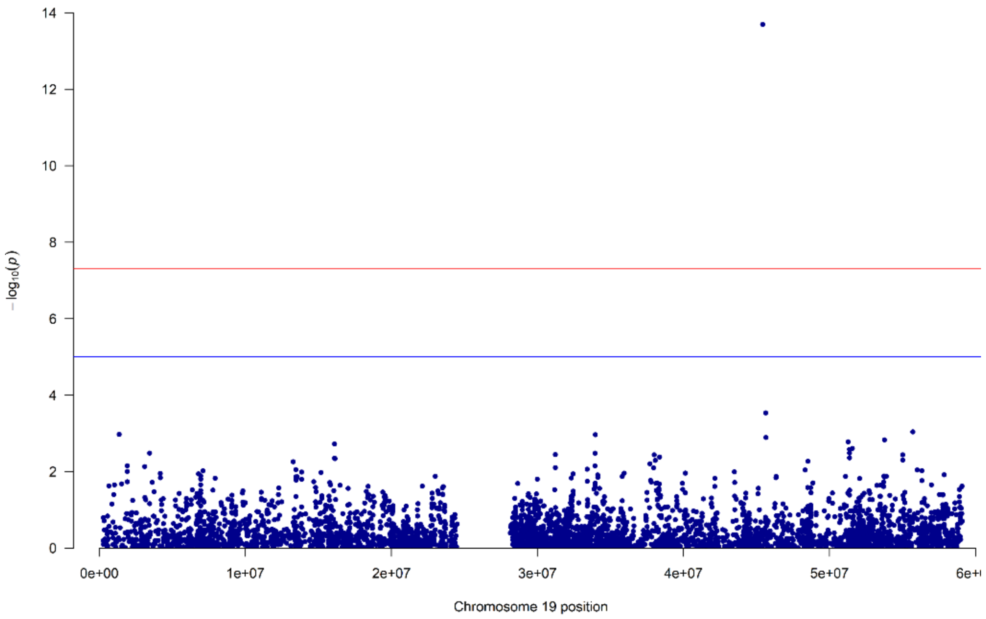


GWAS using only genotyped SNPs

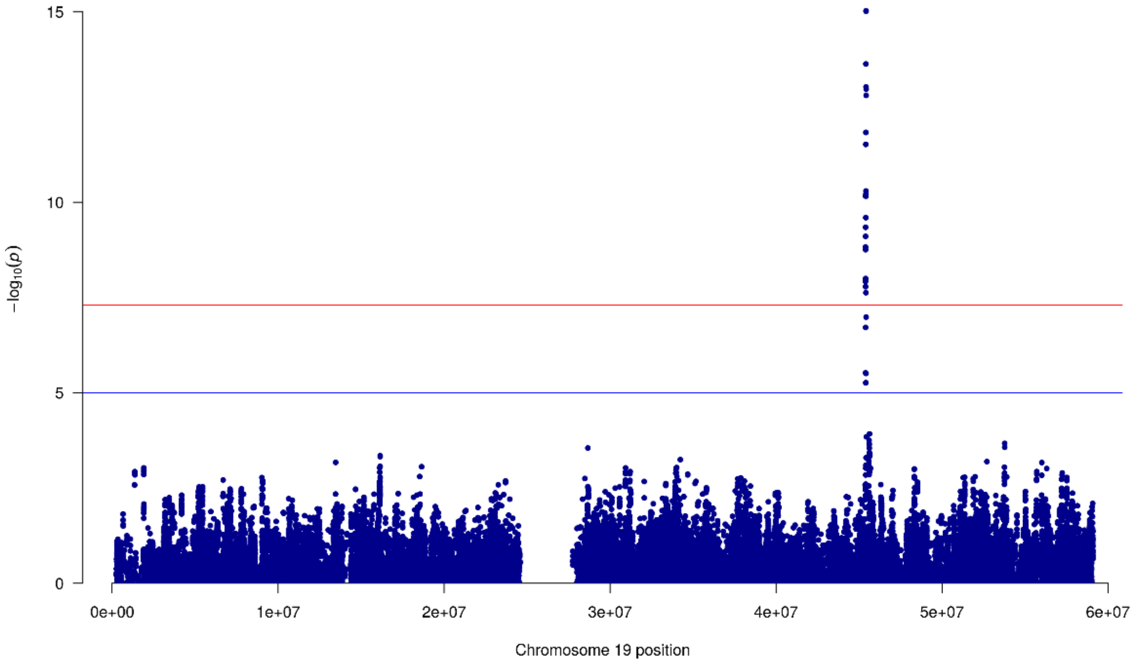
HT: Sarah Medland, QIMR

Example – imputed vs. non-imputed signal

Genotyped only



Post imputation



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Why impute?

- Samples vs. depth tradeoff in sequencing studies
  - Low pass / low coverage sequencing quite common in humans
  - Several advantages to increasing sample size

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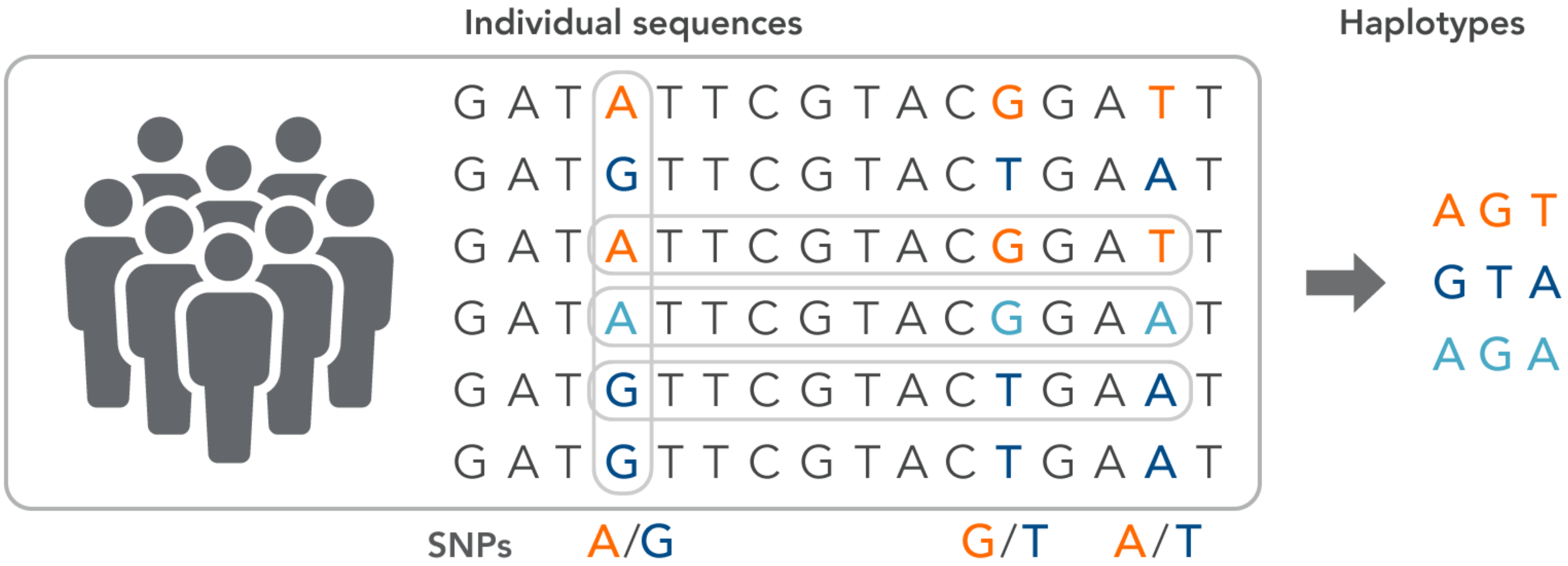
  - Low pass / low coverage sequencing quite common in humans
  - Several advantages to increasing sample size

- SNP chip data
  - Older studies
  - More focused set of markers – CVD, metabolic disorders etc.

Background

Genotypes vs. haplotypes



Individual sequences

GATATTCGTACGGATT
GATGTTCGTACTGAAT
GATATTCGTACGGATT
GATATTCGTACGGAAT
GATGTTCGTACTGAAT
GATGTTCGTACTGAAT

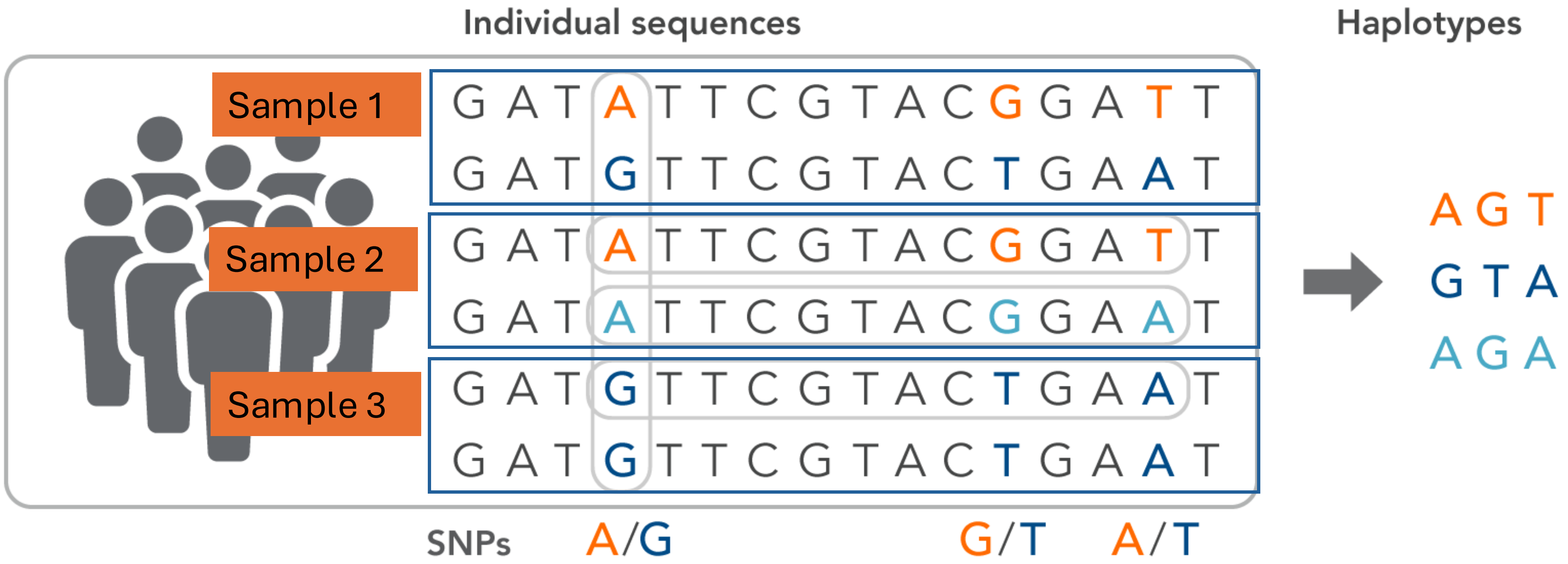
SNPs A/G G/T A/T

Haplotypes

AGT
GTA
AGA

Background

Genotypes vs. haplotypes



Individual sequences

Haplotypes

Sample 1

G A T A T T C G T A C G G A T T

G A T G T T C G T A C T G A A T

Sample 2

G A T A T T C G T A C G G A T T

G A T A T T C G T A C G G A A T

Sample 3

G A T G T T C G T A C T G A A T

G A T G T T C G T A C T G A A T

A G T

G T A

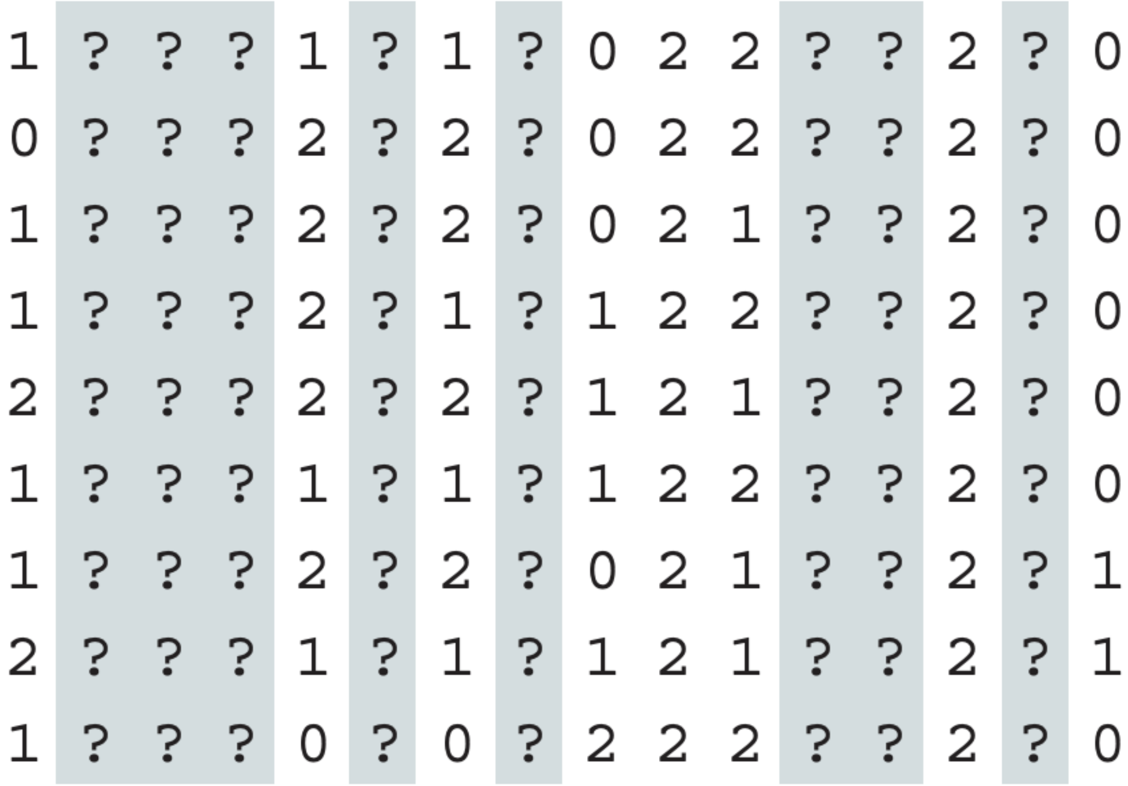
A G A

SNPs A/G G/T A/T

Genotypes			
Sample 1	A/G	G/T	A/T
Sample 2	A/A	G/G	A/T
Sample 3	G/G	T/T	A/A

Problem setting revisited

You have sparse data for some samples at some markers – but you want to fill in the gaps.



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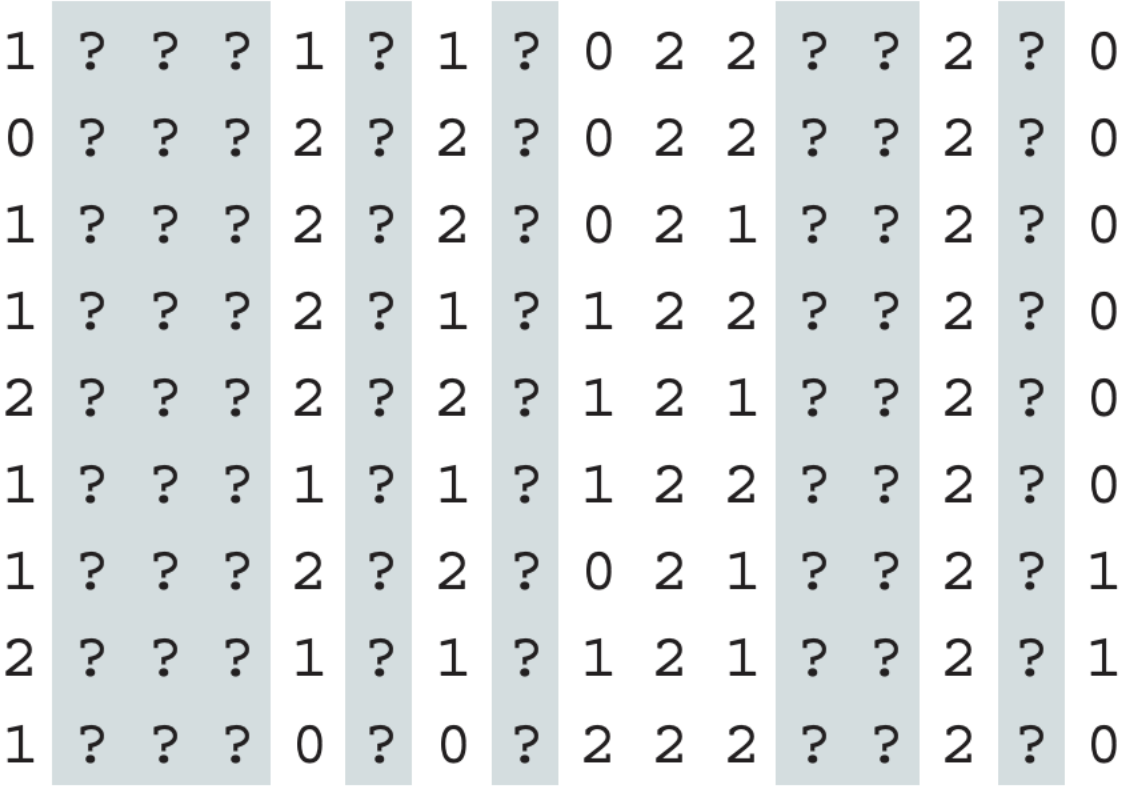
1	?	?	?	2	?	1	?	1	2	2	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	1	?	?	2	?	0
1	?	?	?	1	?	1	?	1	2	2	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	1
2	?	?	?	1	?	1	?	1	2	1	?	?	2	?	1
1	?	?	?	0	?	0	?	2	2	2	?	?	2	?	0

Problem setting revisited – easy version



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1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	0
1	?	?	?	2	?	1	?	1	2	2	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	1	?	?	2	?	0
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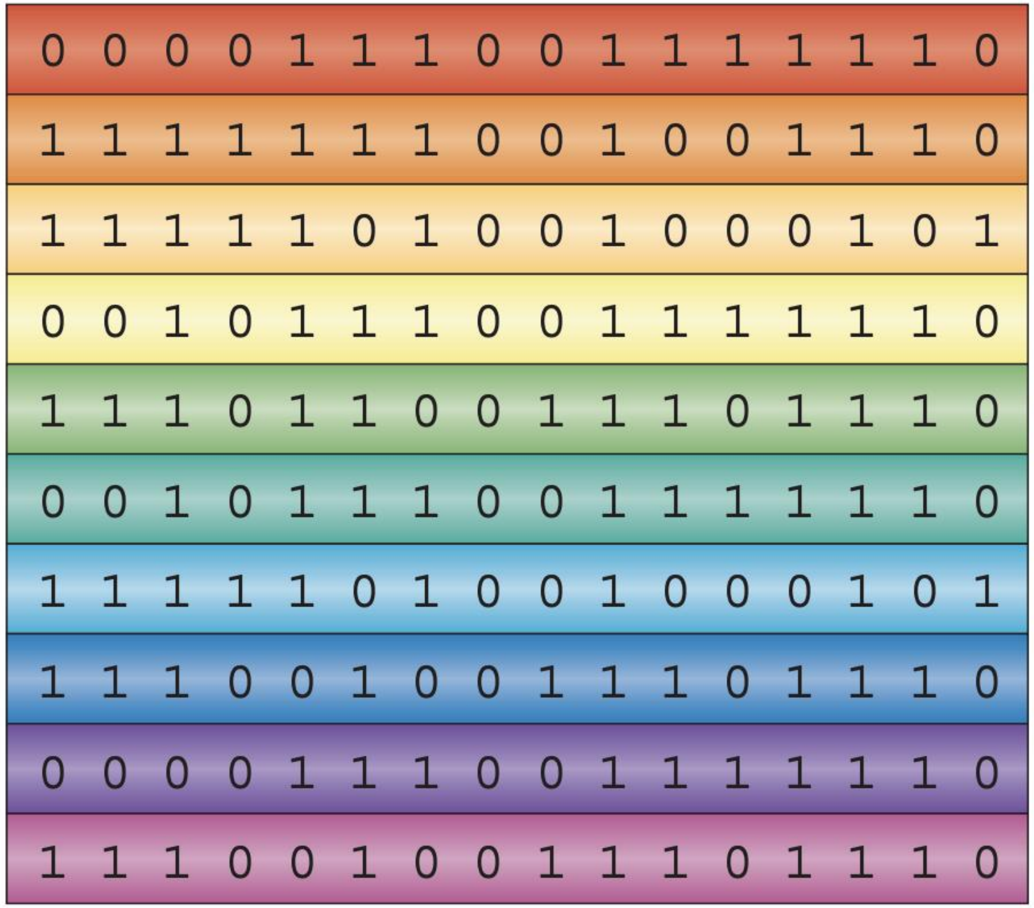
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	1
2	?	?	?	1	?	1	?	1	2	1	?	?	2	?	1
1	?	?	?	0	?	0	?	2	2	2	?	?	2	?	0

Reference set of haplotypes, for example, HapMap



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1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0

Group discussion

Take 10 minutes to discuss how you would impute the missing genoyptes in the sample, given the reference haplotypes.

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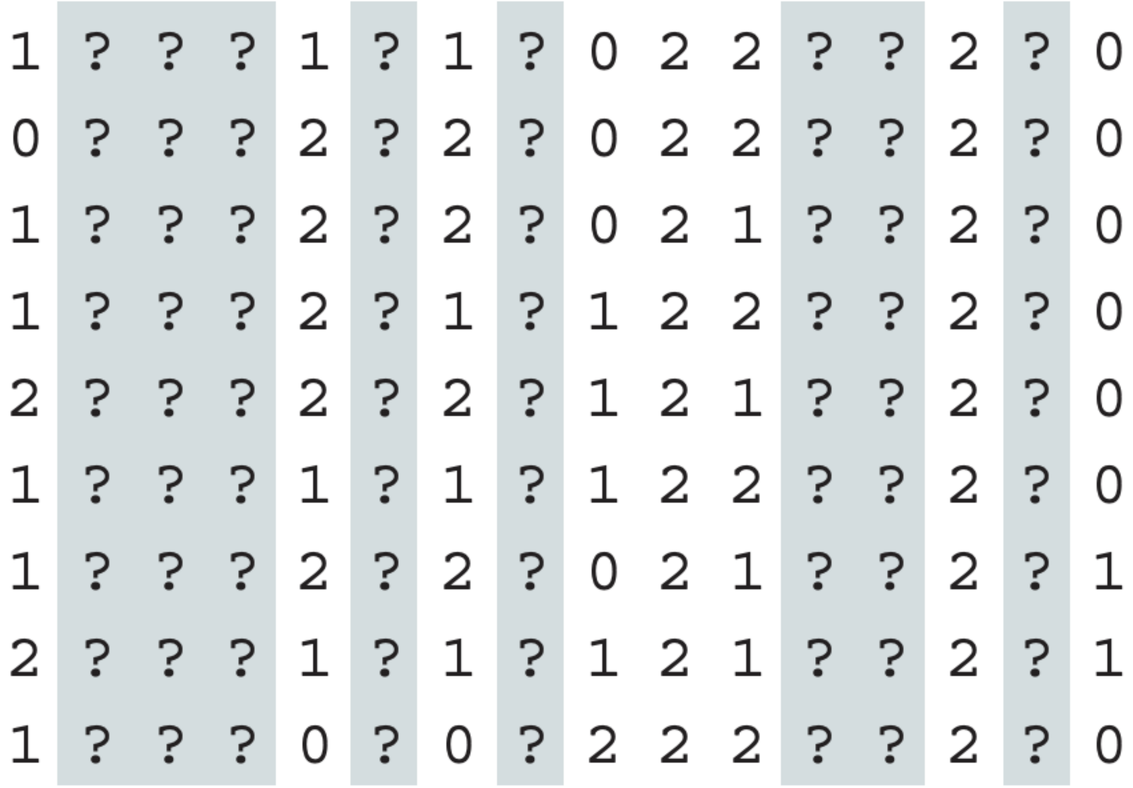
- Consider how you would get the missing genotypes?
- Is there intermediate information that would make the problem easier to solve?
  - What information – if you knew about the target samples – would make imputation easier?
- How do things like mutation and recombination play a role?

Discuss solutions

Imputation – changing the problem definition



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2	?	?	?	1	?	1	?	1	2	1	?	?	2	?	1
1	?	?	?	0	?	0	?	2	2	2	?	?	2	?	0

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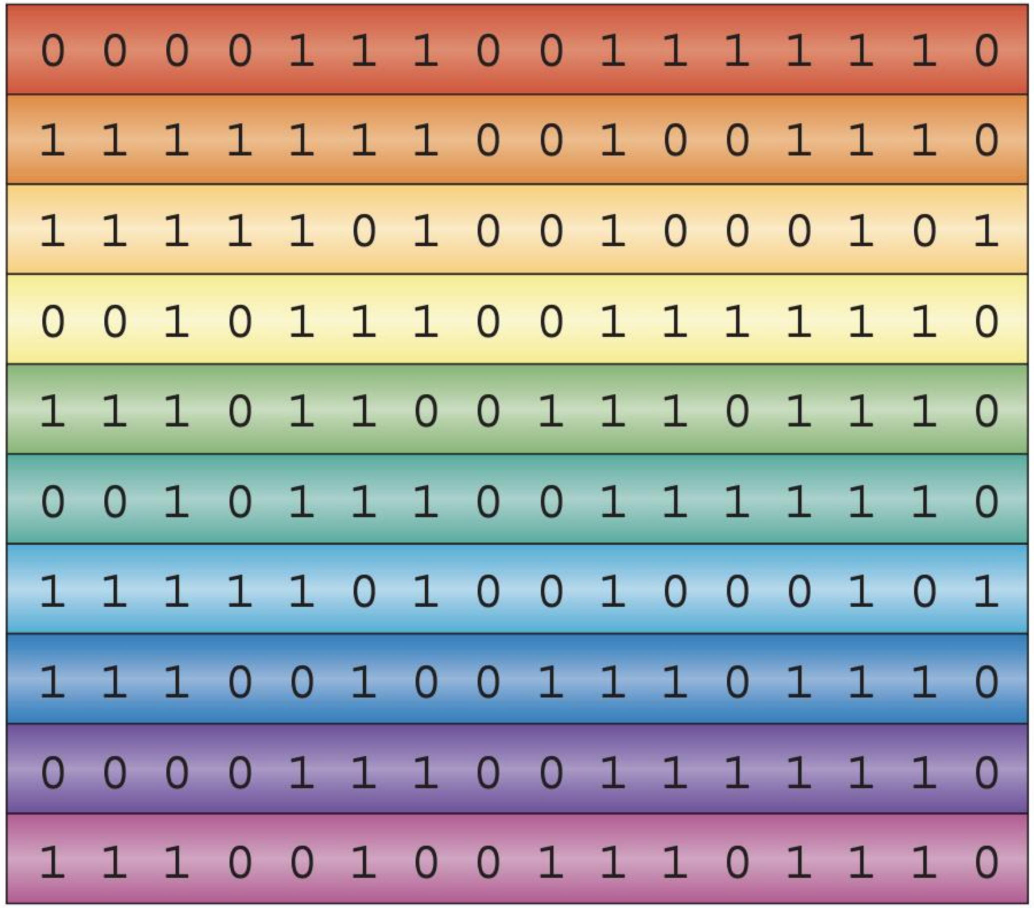

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0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0

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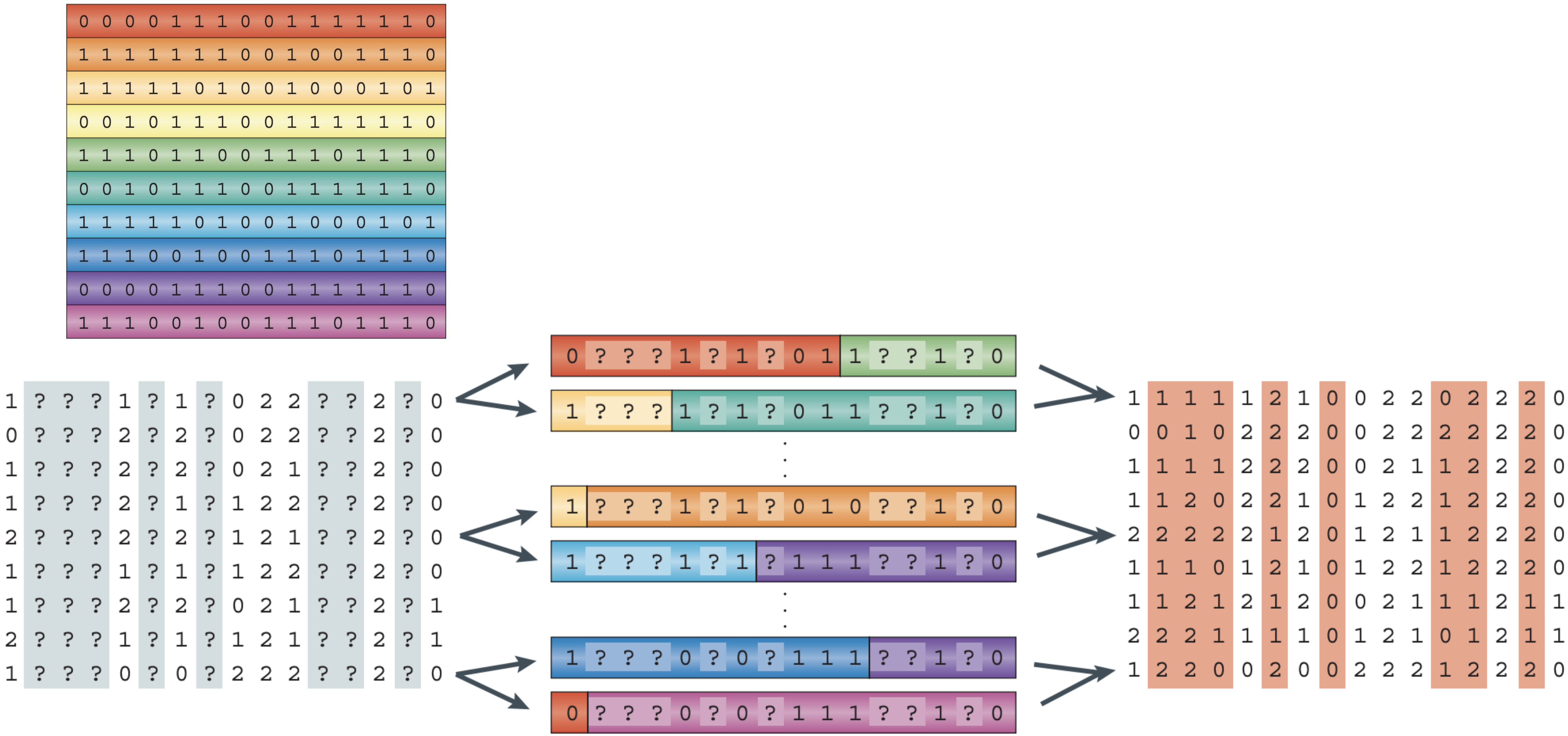

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1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0

1	?	?	?	1	?	1	?	0	2	2	?	?	2	?	0
0	?	?	?	2	?	2	?	0	2	2	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	0
1	?	?	?	2	?	1	?	1	2	2	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	1	?	?	2	?	0
1	?	?	?	1	?	1	?	1	2	2	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	1
2	?	?	?	1	?	1	?	1	2	1	?	?	2	?	1
1	?	?	?	0	?	0	?	2	2	2	?	?	2	?	0

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

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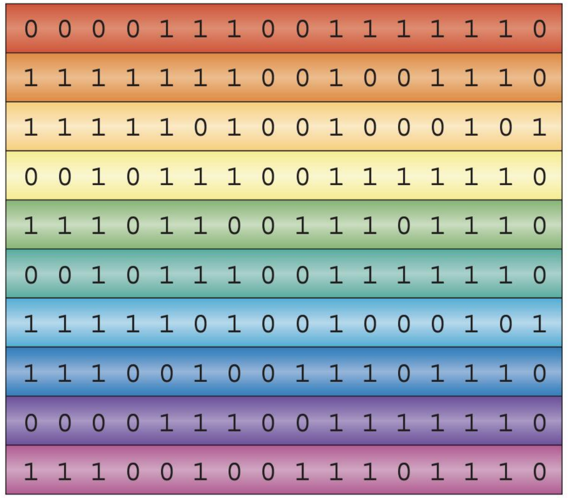

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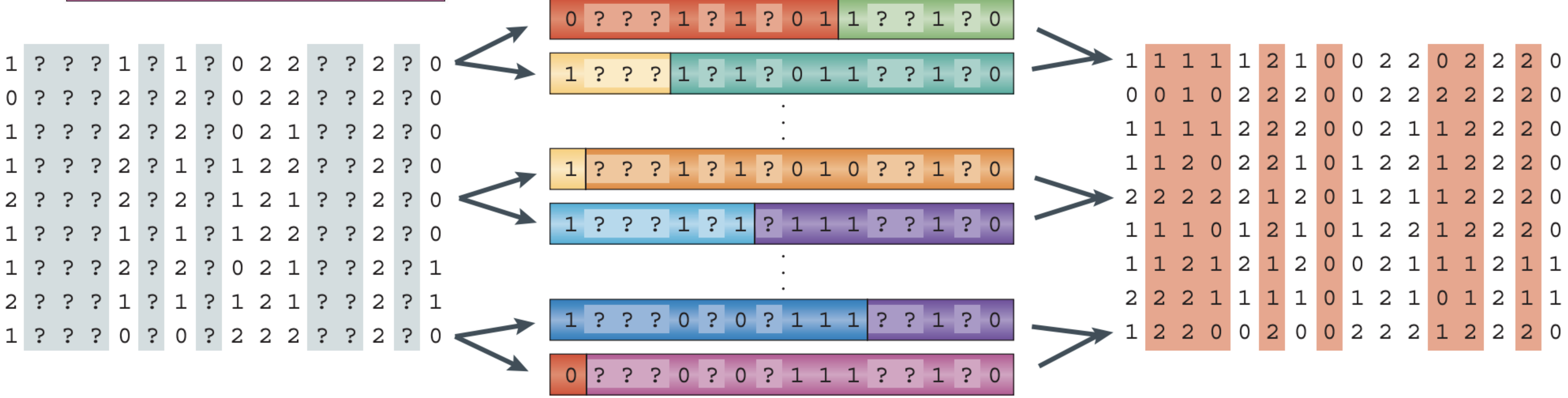
1	1	1	1	1	0	1	0	0	1	0	0	0	1	0	1
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0
0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0

Problem now changed from imputation (filling missing genotypes) to phasing (finding haplotypes given genotypes)



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1	?	?	?	2	?	1	?	1	2	2	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	1	?	?	2	?	0
1	?	?	?	1	?	1	?	1	2	2	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	1
2	?	?	?	1	?	1	?	1	2	1	?	?	2	?	1
1	?	?	?	0	?	0	?	2	2	2	?	?	2	?	0

0	?	?	?	1	?	1	?	0	1	1	?	?	1	?	0
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1	2	2	0	0	2	0	0	2	2	2	1	2	2	2	0

Phasing – from genotypes to haplotypes

Given a set of reference haplotypes H, we need to sample a mosaic of haplotypes that are consistent with the observed genoytpes G.

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$$
\begin{aligned}
P(G|H) &= \prod_i P(G_i|H) \\
P(G_i|H) &= \sum_{h_1}\sum_{h_2} P(G_i|H=\{h_1,h_2\})P(H=\{h_1,h_2\}))
\end{aligned}
$$

Phasing – from genotypes to haplotypes

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Extending to sequencing data D – including genotype likelihoods

$$\begin{aligned} P(D|H) &= \prod_i P(D_i|H) \\ P(D_i|H) &= \sum_{h_1}\sum_{h_2} P(D_i|G_i)P(G_i|H=\{h_1,h_2\})P(H=\{h_1,h_2\})) \end{aligned}$$

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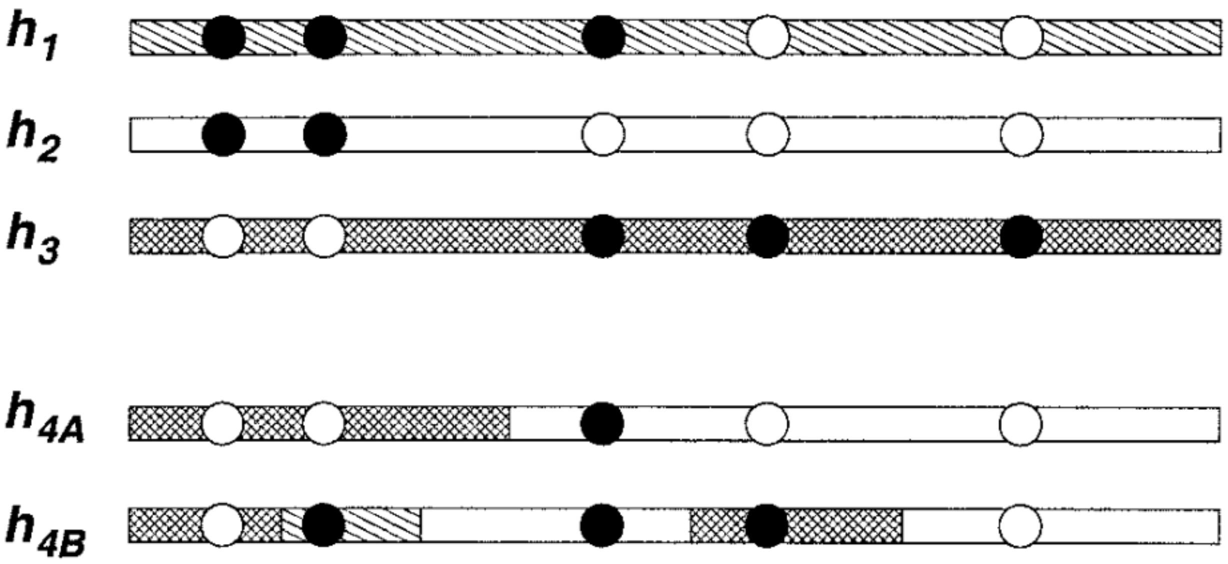
Constructing new haplotypes: Li and Stephens copying model

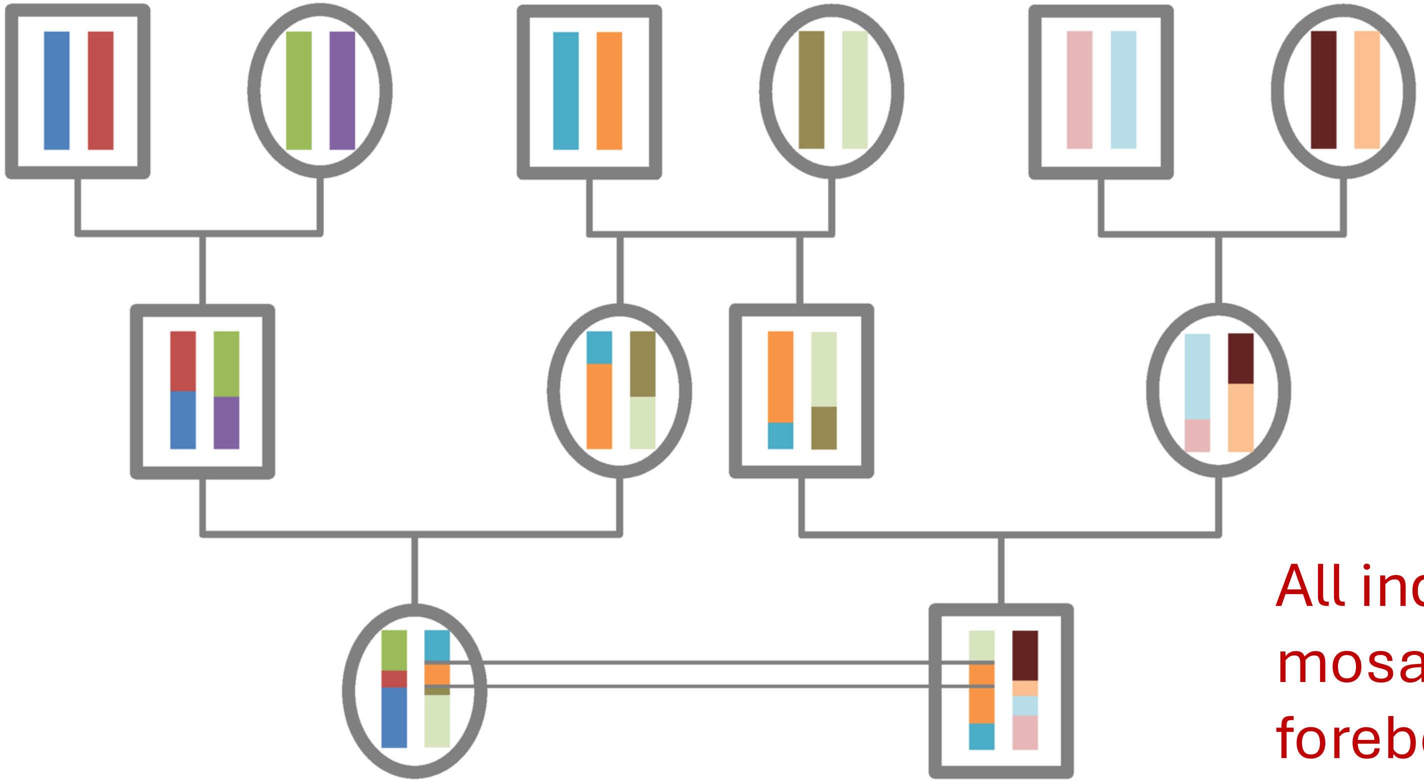


A new haplotype is made by copying from existing ones

- an imperfect mosaic of existing haplotypes

$P(h_k \mid h_1, \ldots, h_n, \Theta)$ is the probability of seeing a new haplotype h_k given haplotypes $h_1, \ldots, h_n$ and parameter Θ for the imperfect copying.

Why would this work? Some intuition



All individuals are made up by a mosaic of haplotypes from all their forebears.

Computational complexity

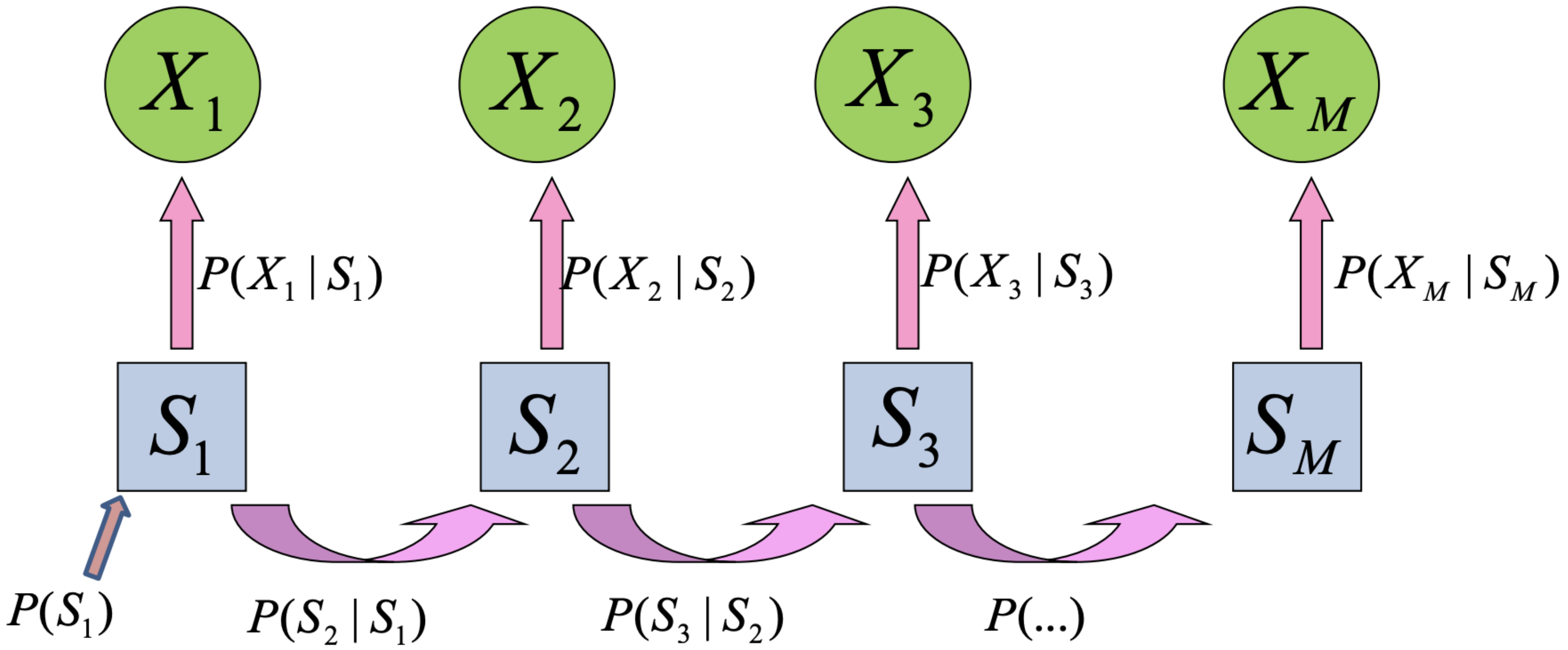
- Number of haplotypes
  - Explodes exponentially with number of markers

- Solutions
  - Markov model for process
  - Work in blocks, assume blocks are independent

Markov model for phasing and imputation

Observed data: genoytpes or reads

Hidden state: haplotype pair



Markov model for phasing and imputation

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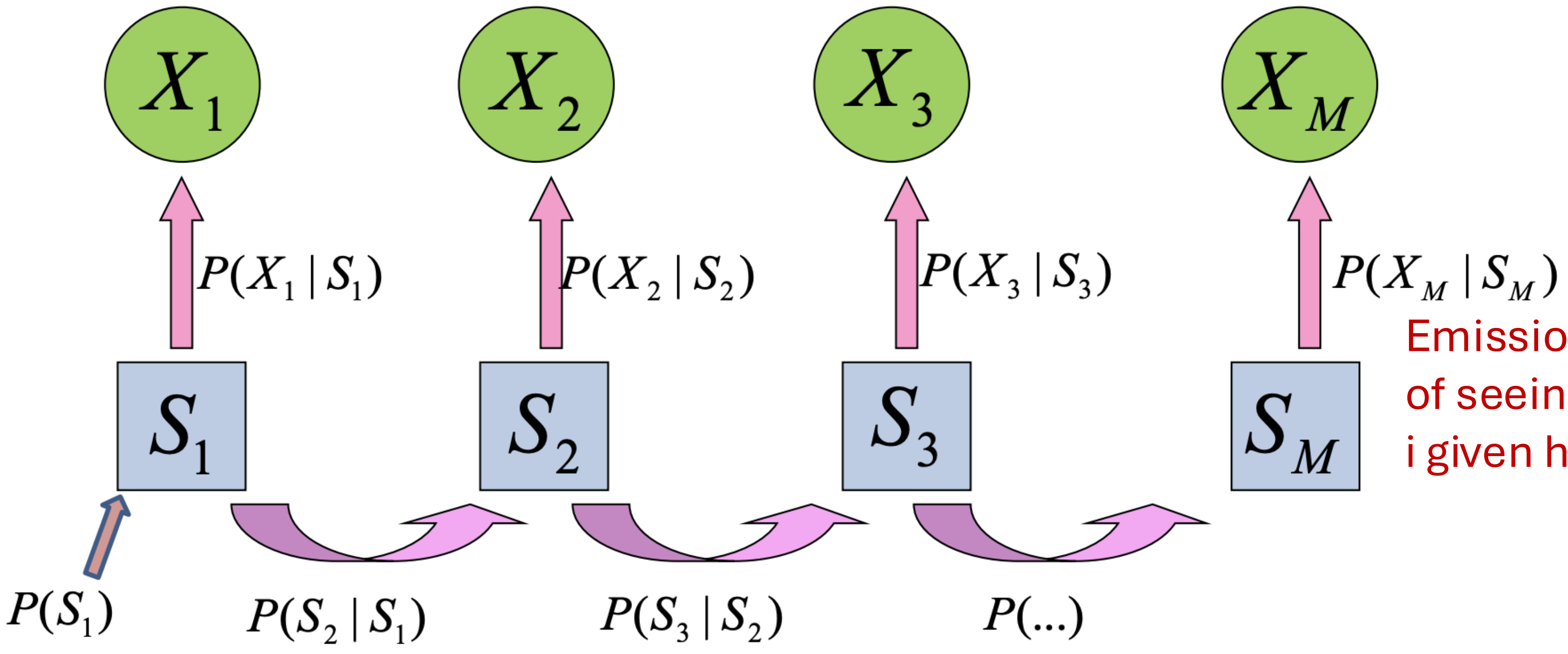

Emission probability: Probability of seeing genotype or reads at site i given haplotype pair at site i

Transition probability: Probability of haplotype pair at site i+1 when we know haplotype pair at site i

Markov model details

- Transition probability
  - What would transitions depend on?
- Emission probability
  - How do we go from haplotype pair to genotypes or reads?

No reference panel?

- Can we still impute when we have no reference panel?
  - Yes! Here we also need to figure out the haplotypes on the fly, and the haplotype frequencies.

$$
\begin{aligned}
P(G|f) &= \prod_i P(G_i|f) \\
P(G_i|f) &= \sum_{h_1} \sum_{h_2} P(G_i|H = \{h_1, h_2\}) P(H = \{h_1, h_2\}|f)) \\
P(H = \{h_1, h_2\}|f) &= f_{h_1} f_{h_2}
\end{aligned}
$$

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\begin{aligned}
P(G|f) &= \prod_i P(G_i|f) \\
P(G_i|f) &= \sum_{h_1} \sum_{h_2} P(G_i|H = \{h_1, h_2\}) P(H = \{h_1, h_2\}|f)) \\
P(H = \{h_1, h_2\}|f) &= f_{h_1} f_{h_2}
\end{aligned}
$$

$$\hat{f} = argmax_f P(G|f)$$

Computational shortcuts

- Number of haplotypes – super high
    - Keep track of only haplotypes with “high” frequency.
    - Limit number of haplotypes being tracked.
    - Work on haplotype blocks at a time.

Phasing and Imputation

To get the phase probability

$$p(h_1, h_2 | G_i, \hat{f}\,) = \frac{p(G_i|h_1,h_2)p(h_1,h_2|\hat{f}\,)}{p(G_i|\hat{f}\,)}$$

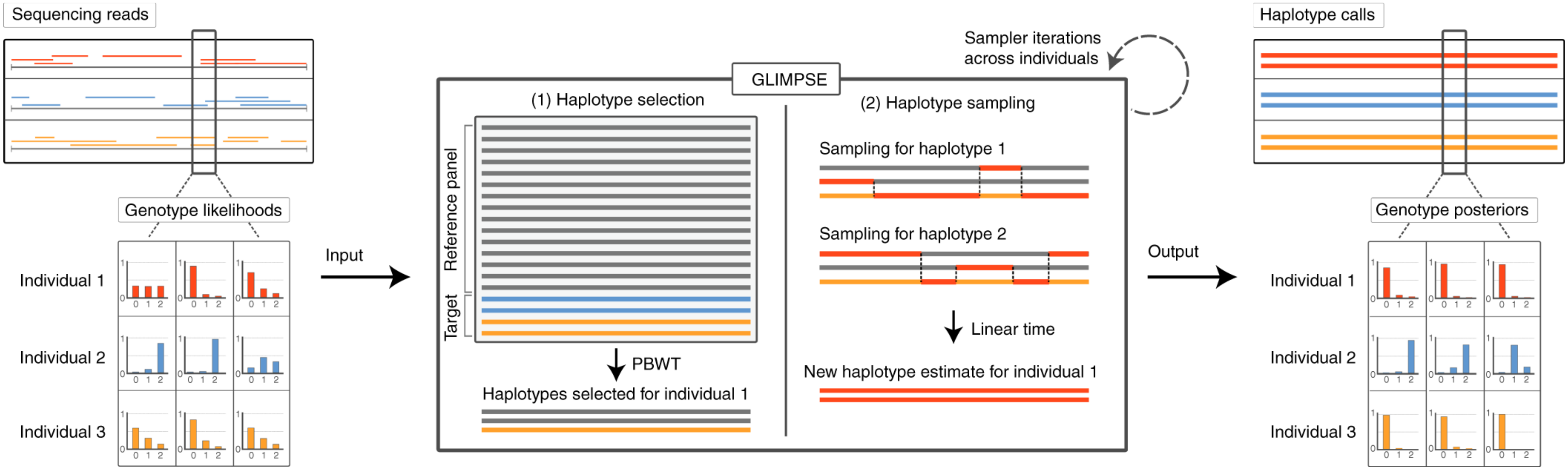
For imputation

$$p(G_{ij}|\hat{f}\,, G_{i,-j}) = \sum_{h_1}\sum_{h_2} p(G_{ij}|h_1, h_2)p(h_1, h_2|\hat{f}\,, G_{i-j})$$

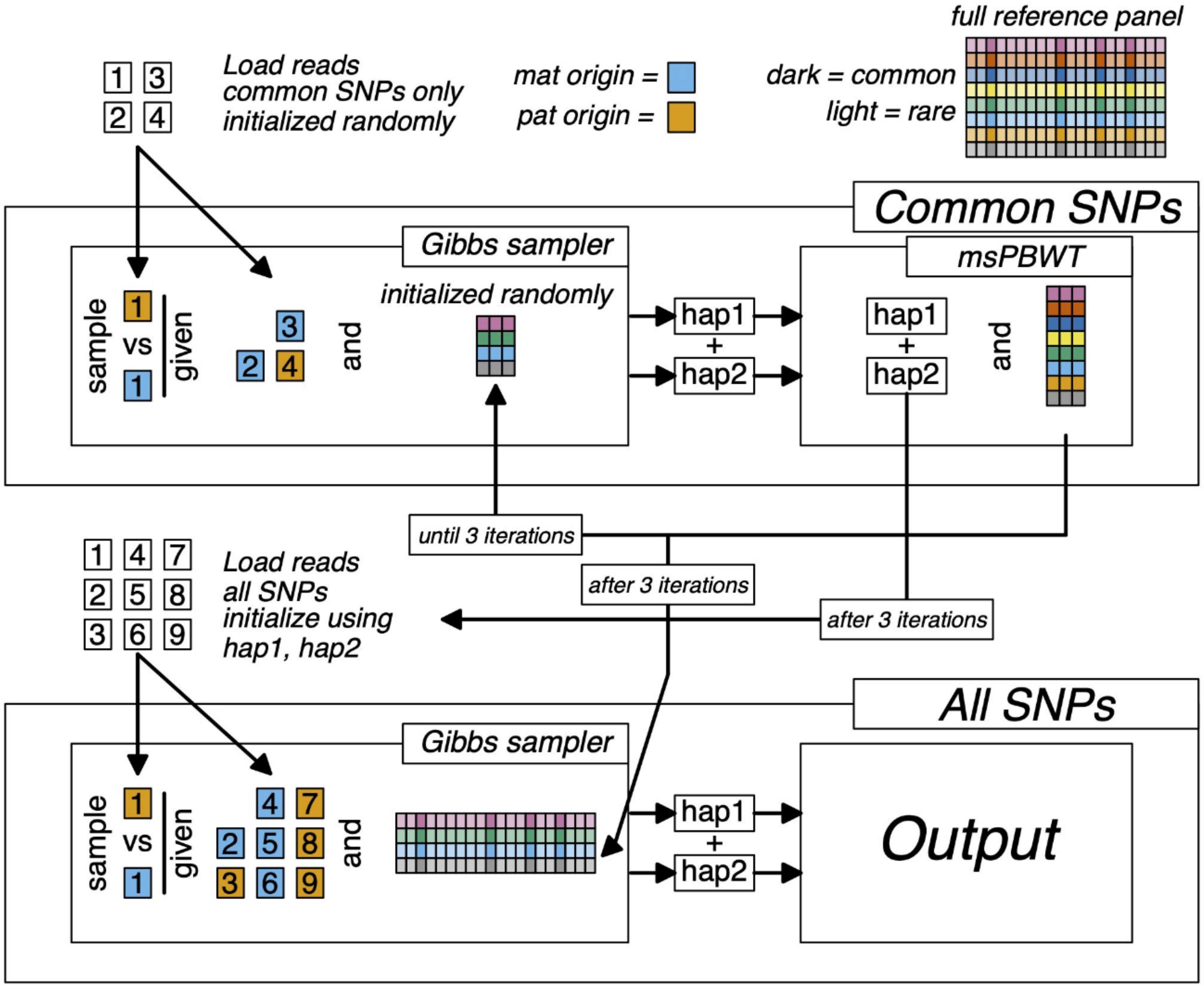
Imputation approaches

- Genotype calls + reference panels
  - Beagle 5
  - Eagle
  - Shapeit2 + impute2
- Low coverage sequencing + reference panel
  - QUILT2
  - GLIMPSE2
- Low coverage sequencing + no reference panel
  - Beagle 3 or 4
  - impute2

GLIMPSE 2

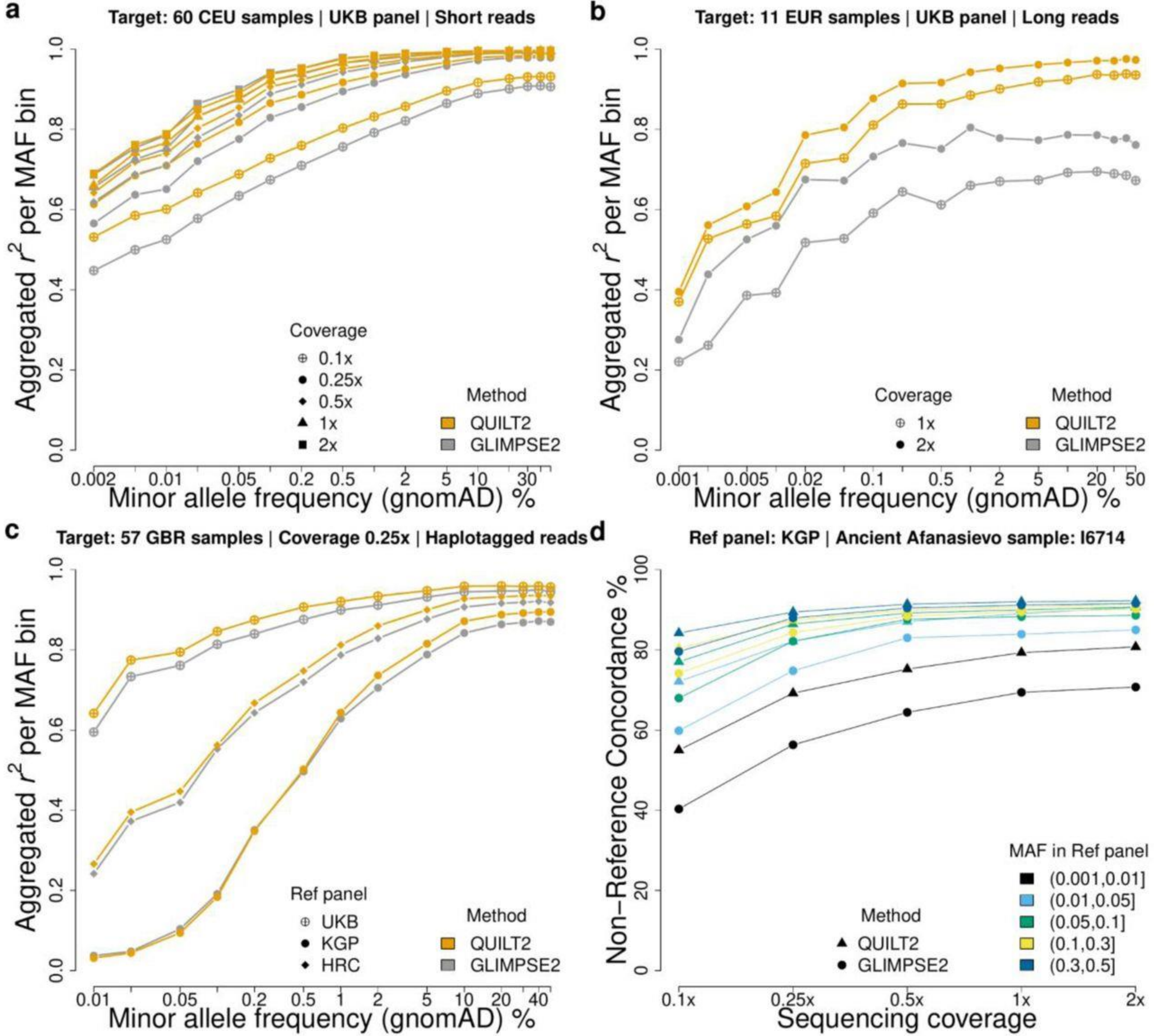

Sequencing reads
Genotype likelihoods
Individual 1
Individual 2
Individual 3
0 1 2
Input
GLIMPSE
(1) Haplotype selection
Reference panel
Target
PBWT
Haplotypes selected for individual 1
(2) Haplotype sampling
Sampling for haplotype 1
Sampling for haplotype 2
Linear time
New haplotype estimate for individual 1
Sampler iterations across individuals
Output
Haplotype calls
Genotype posteriors
Individual 1
Individual 2
Individual 3

QUILT2



full reference panel
1 3
2 4
Load reads
common SNPs only
initialized randomly
mat origin =
pat origin =
dark = common
light = rare
Common SNPs
Gibbs sampler
msPBWT
sample
1
vs
1
given
3
2
4
and
initialized randomly
hap1
+
hap2
hap1
+
hap2
and
until 3 iterations
after 3 iterations
after 3 iterations
1 4 7
2 5 8
3 6 9
Load reads
all SNPs
initialize using
hap1, hap2
All SNPs
Gibbs sampler
sample
1
vs
1
given
4 7
2 5 8
3 6 9
and
hap1
+
hap2
Output

Performance comparison



Conclusions

- Imputation – great tool for saving money and increasing power
- Different methods perform differently on different types of data
- Works best for well represented variants (common variants)