Day 1
Basics: DNA variation, Phenotypes, & Lottery

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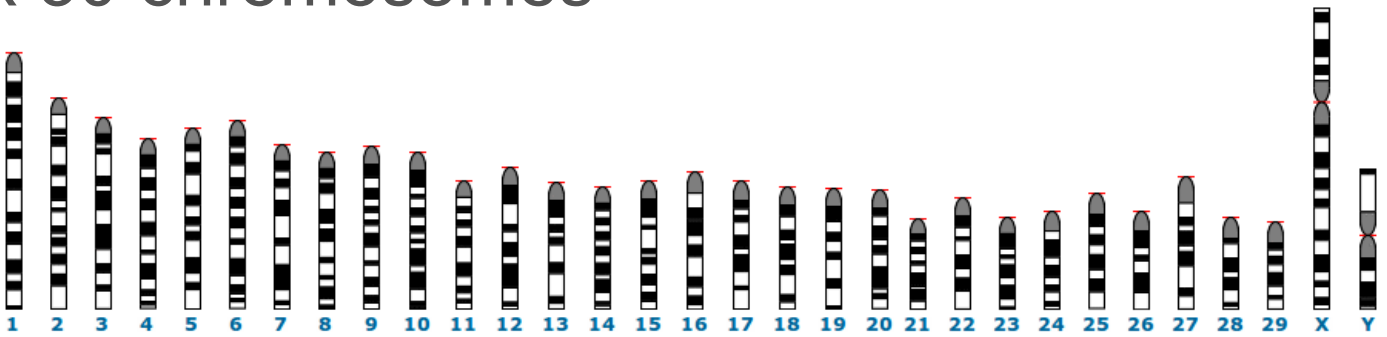
2024-02-05

Learning objectives

- Encoding DNA variation
- Simulate DNA & phenotypes in AlphaSimR
- Simulate inheritance in AlphaSimR

Genome (cattle example)

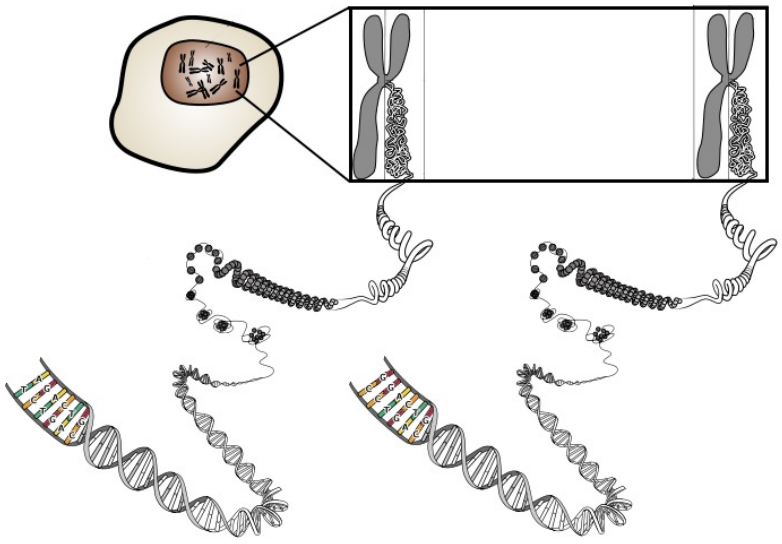
- 2 x 30 chromosomes



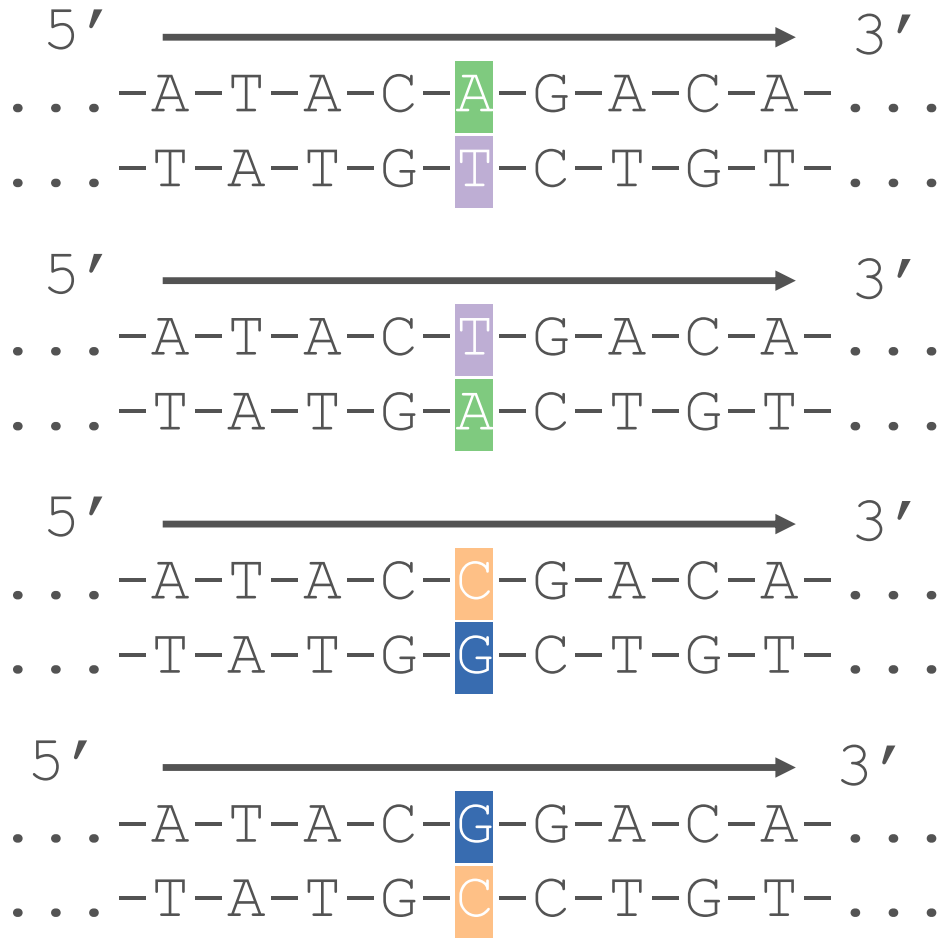
- DNA, 2 x 3 billion (10^9) base pairs

Adenine
Thymine
A
T

Cytosine
Guanine
C
G



Single Nucleotide Polymorphism



How many SNPs and other variants?

The sequences of 150,119 genomes in the UK biobank

www.biorxiv.org/content/10.1101/2021.11.16.468246v2

"… This constitutes a set of high quality variants, including 585,040,410 SNPs, representing 7.0% of all possible human SNPs, and 58,707,036 indels."

→ ~600M SNPs

→ ~60M indels

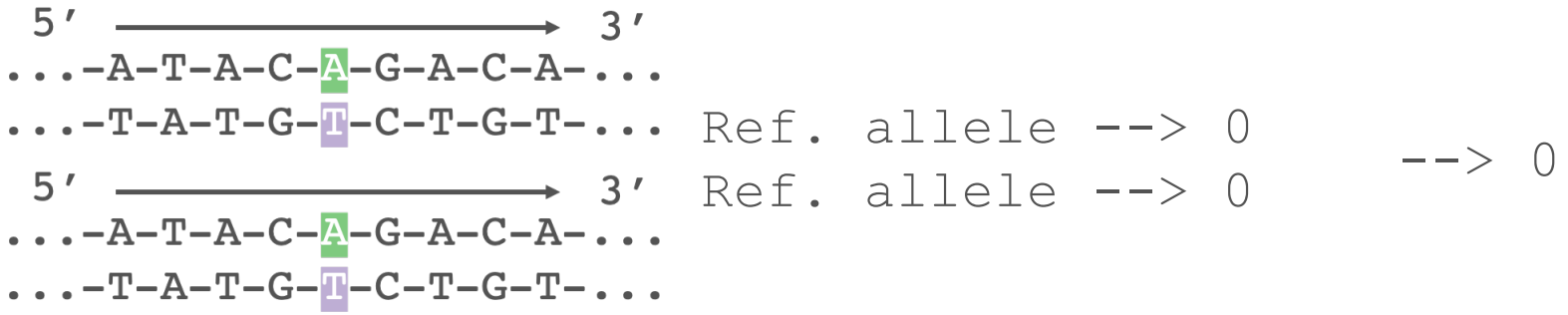
"... We identified 895,055 structural variants and 2,536,688 microsatellites, groups of variants typically excluded from large scale WGS studies.

→ ~1M structural variants!!!

→ ~3M microsatellites!!!

MEGA-SCALE DATA!!!

Bi-allelic SNP alleles, genotypes, & dosages



Bi-allelic SNP alleles, genotypes, & dosages

Genome-wide haplotypes & genotype

Haplotype 1	0	1	1	0	0	1
Haplotype 2	1	1	1	1	0	0
Genotype	1	2	2	1	0	1

For practicals

- Work through

  - `Day_1_Intro_AlphaSimR`
    - `01Practical_DNA`
      - `01a_Simulating_DNA.html`
      - `01b_Simulating_DNA.Rmd`
      - `01c_Simulating_DNA_exercise.Rmd (PRACTICAL)`

Take home message no. 1

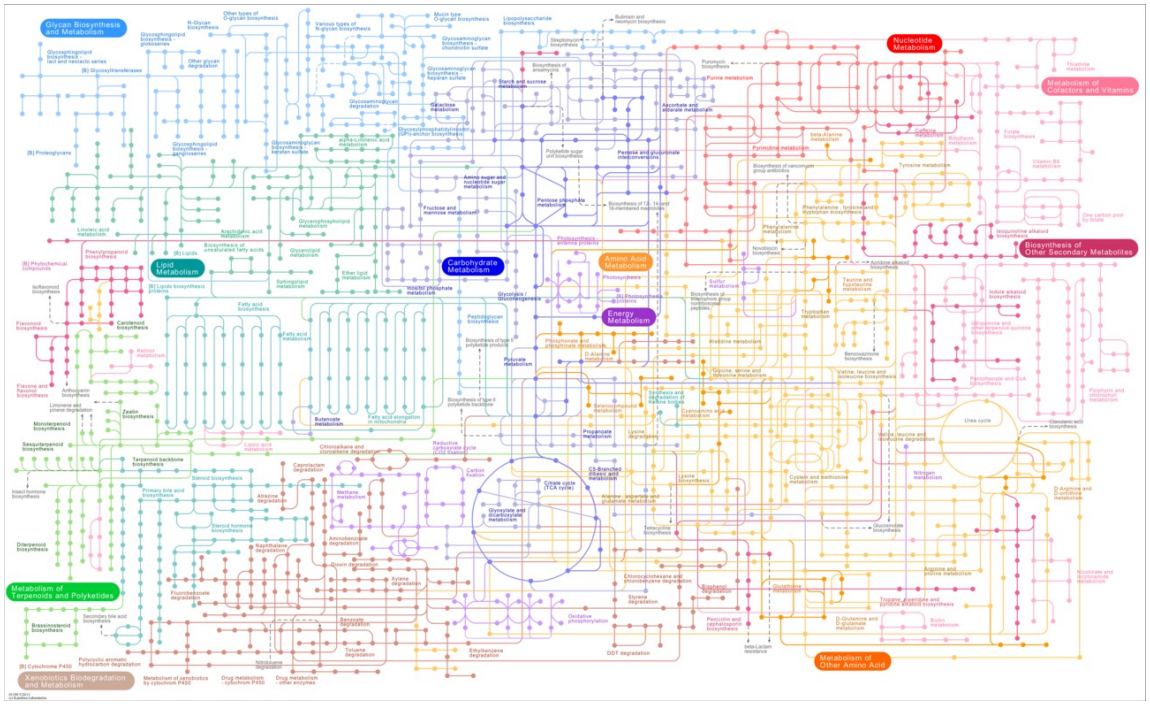
Encoding haplotypes as a series of 0 & 1

Encoding genotypes as a series of 0, 1, & 2

From genomes to phenotypes?

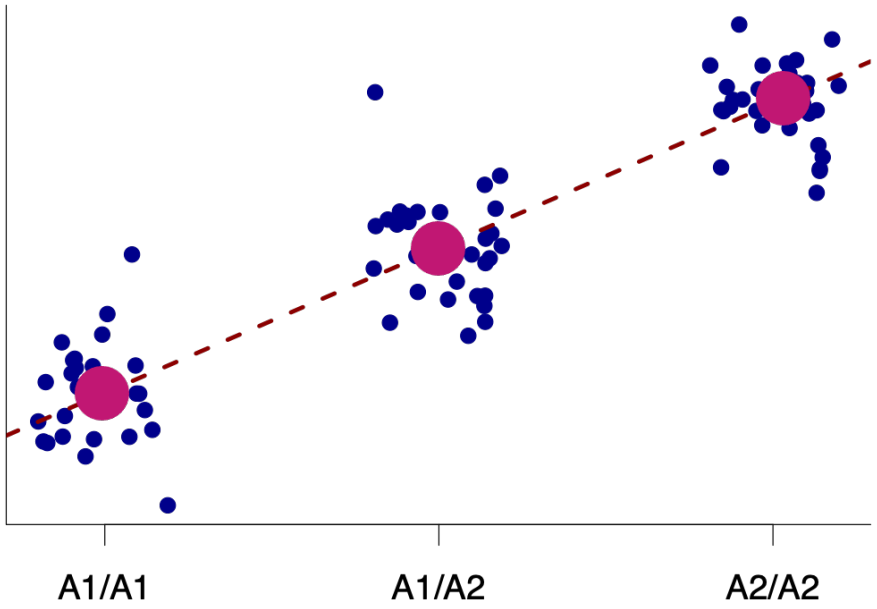
Phenotype = Function(Genomes, Environment)

But what is The Function?



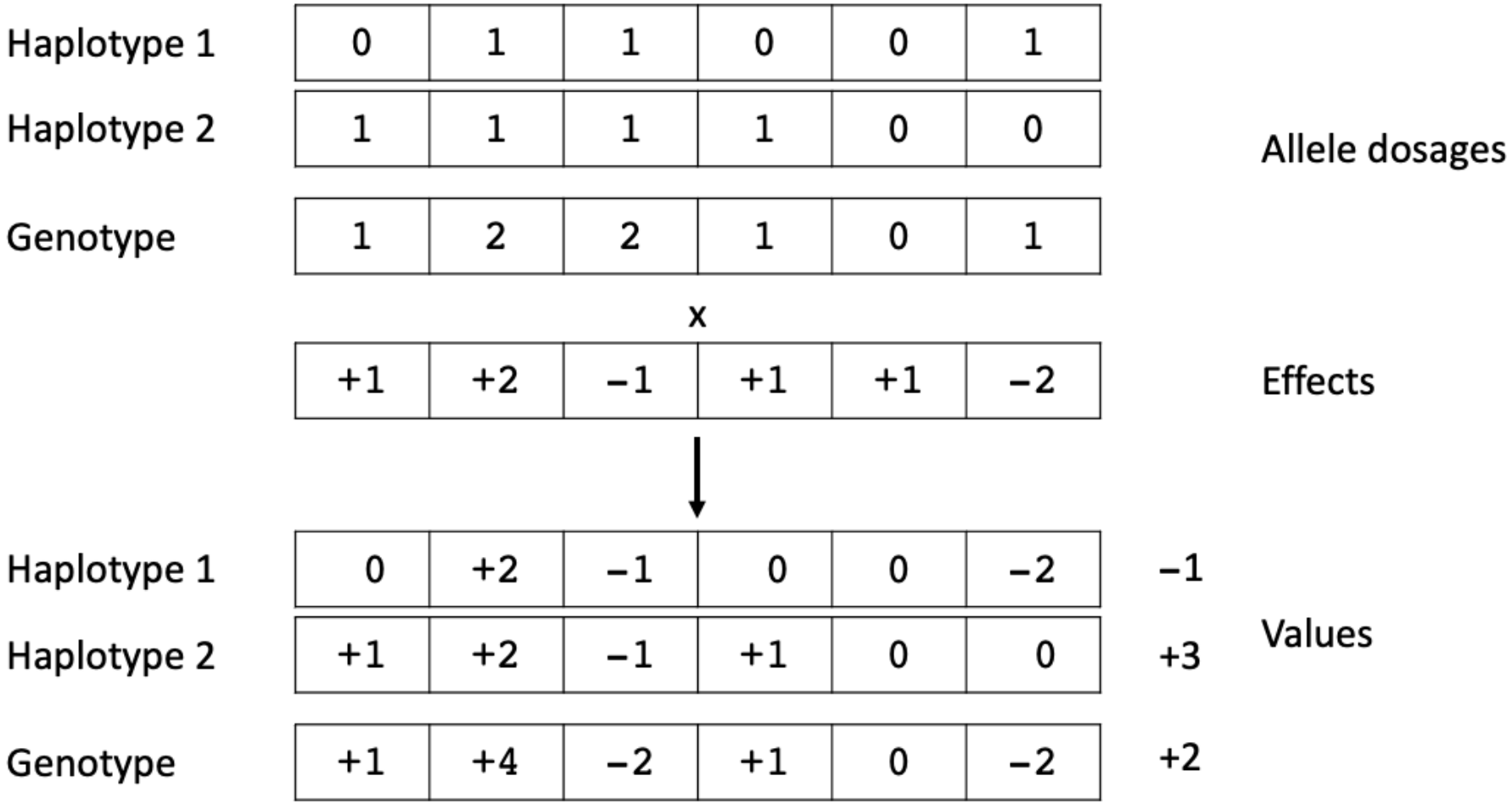
Assume an additive function

- Simple 1st order approximation of The Function
- With additive effects and no environment interaction (more later!)

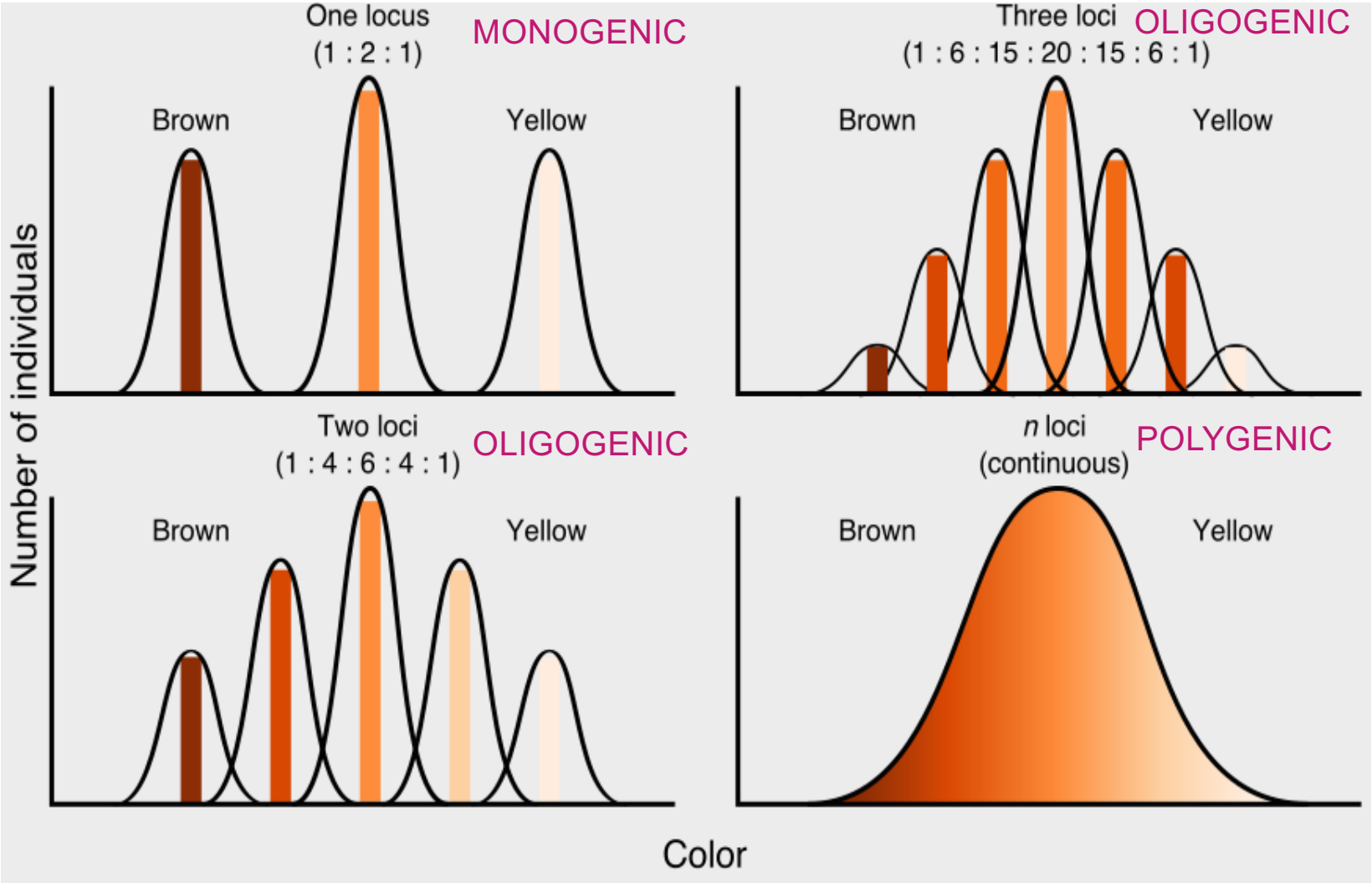


$$\text{Phenotype} = \text{Dosage}_1 * \text{Effect}_1 + \text{Dosage}_2 * \text{Effect}_2 + \ldots + \text{Dosage}_n * \text{Effect}_n + \text{Noise}$$

Genome-wide haplotype & genotype values



Hypothetical architecture for cattle coat color



QTLs & SNPs

- Defined in simulation parameters
  - See ?SimParam_addTrait
  - See ?SimParam_addSnpChip
- SNP chip overlap with QTL can be controlled
  - See ?SimParam_restrSegSites
- No genotyping error

For practicals

- Work through

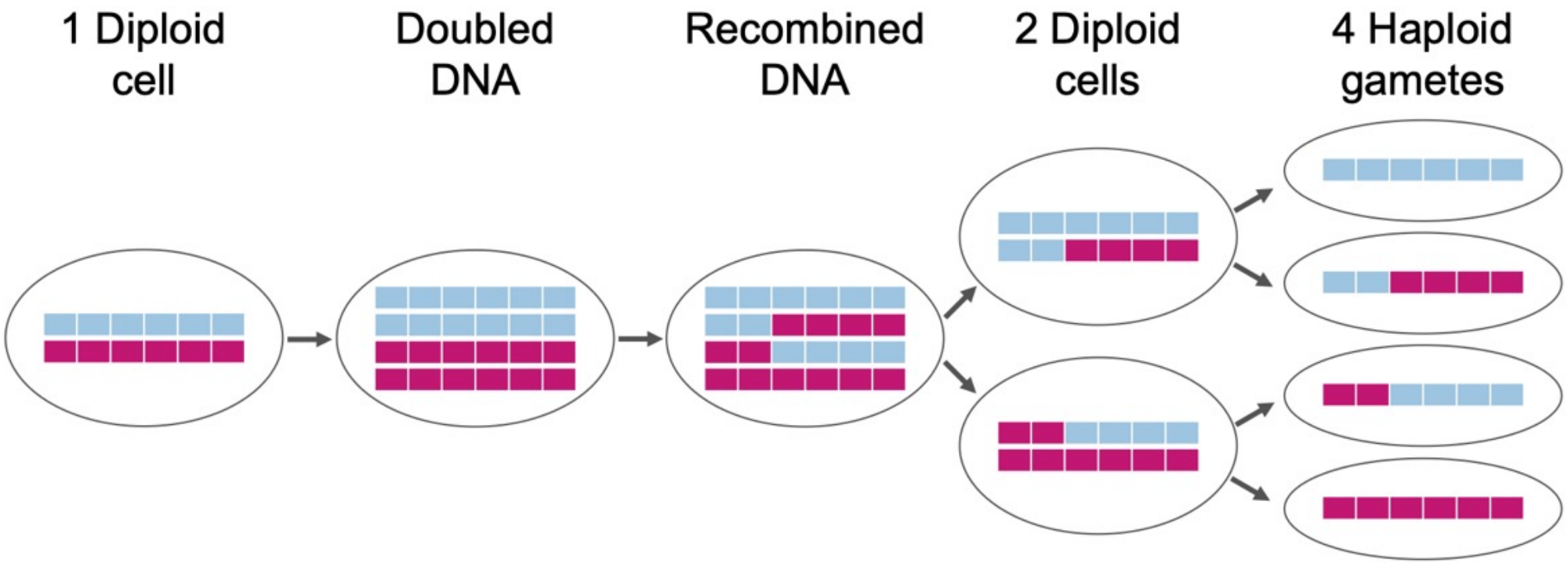
  - Day_1_Intro_AlphaSimR
    - 01Practical_DNA
      - 02a_Simulating_traits.html
      - 02b_Simulating_traits.Rmd
      - 02c_Simulating_traits_exercise.Rmd (PRACTICAL)

      - 03_Simulating_DNA_and_traits_independent_exercise.Rmd (HOMEWORK)

Take home message no. 2

Simple DNA → Phenotype models give rise to plenty of variation!

Meiosis – Recombination & Segregation



Some numbers …

- ~1 recombination per chromosome
  - recombination rate ~$1x10^{-8}$
  - 1 Morgan (=100 cM) chromosome
  - r ~ Poisson(l = 1) with Haldane mapping function
  - r ~ Gamma-sparkling(l, v) general mapping function
- ~1 to 2 mutations per chromosome
  - mutation rate ~$1x10^{-8}$ - ~$2x10^{-8}$
  - In human ~$2.5x10^{-8}$ → 23x2x2 = ~100 de-novo mutations
  - ~100 new + 2x50 old + 4x25 old-old + …
  - ~1 new mutation has an effect?

Decoding germline *de novo* point mutations

Anne Goriely

NATURE GENETICS | VOLUME 48 | NUMBER 8 | AUGUST 2016

Analysis of a large whole-genome sequencing data set of 36,441 high-quality *de novo* mutations (DNMs) that arose in 816 family trios provides an unprecedented view into the landscape of DNMs in the germ line. This work both refines and challenges some of the views previously held on the nature and origin of DNMs.

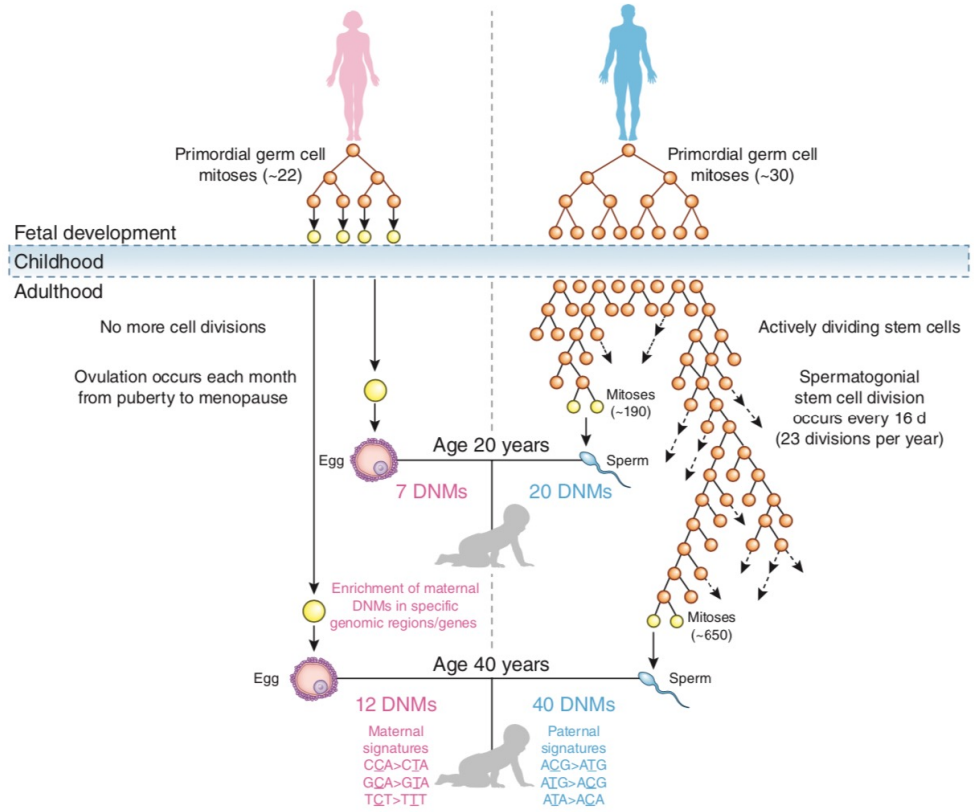


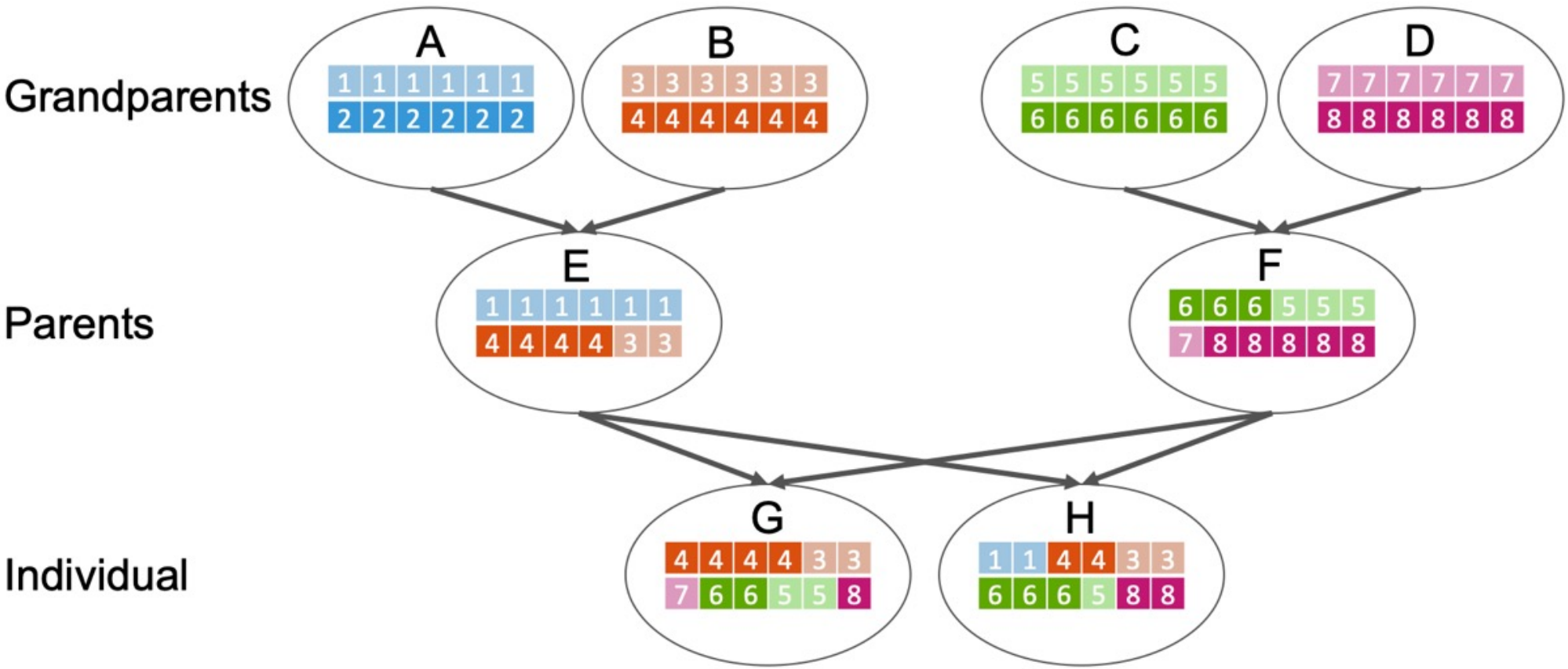
Figure 1 Gametogenesis differs in females and males. The sperm produced by a 20-year-old male has gone through ~190 cell divisions (mitoses), and this number increases to ~650 by the age of 40 years. In contrast, eggs do not replicate after birth. These sex-specific differences in germline biology are likely to explain the 3:1 excess of paternally derived DNMs observed in the progeny. However, maternal and paternal DNMs increase in number with parental age and show sex-specific mutational patterns. Orange cells, actively dividing stem cells; yellow cells, differentiating gametes undergoing meiosis.

Somatic mutations

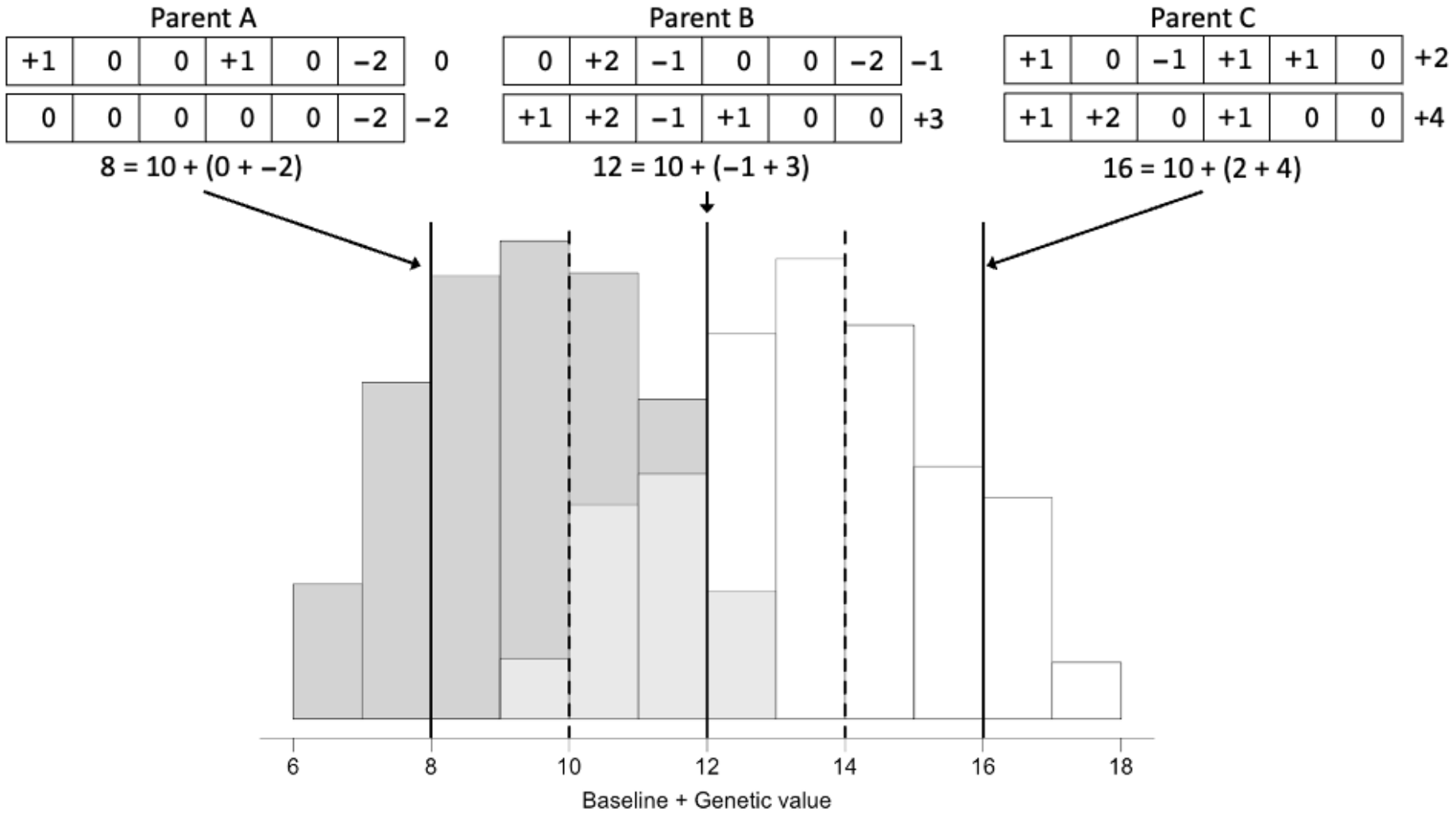
- ~$3x10^{-7}$ --> ~10x more common than germline!
- A somatic cell can then have 1000+ mutations!
  100 from germline x 10+ = 1000+
- ~$10^{12 \text{ to } 13}$ cells in the body
- ~$10^{(12 \text{ to } 13)+3}$ = ~$1x10^{15\text{-}16}$ mutations in an adult with most nucleotides mutated in thousands of cells

Lynch (2016) https://doi.org/10.1534/genetics.115.180471

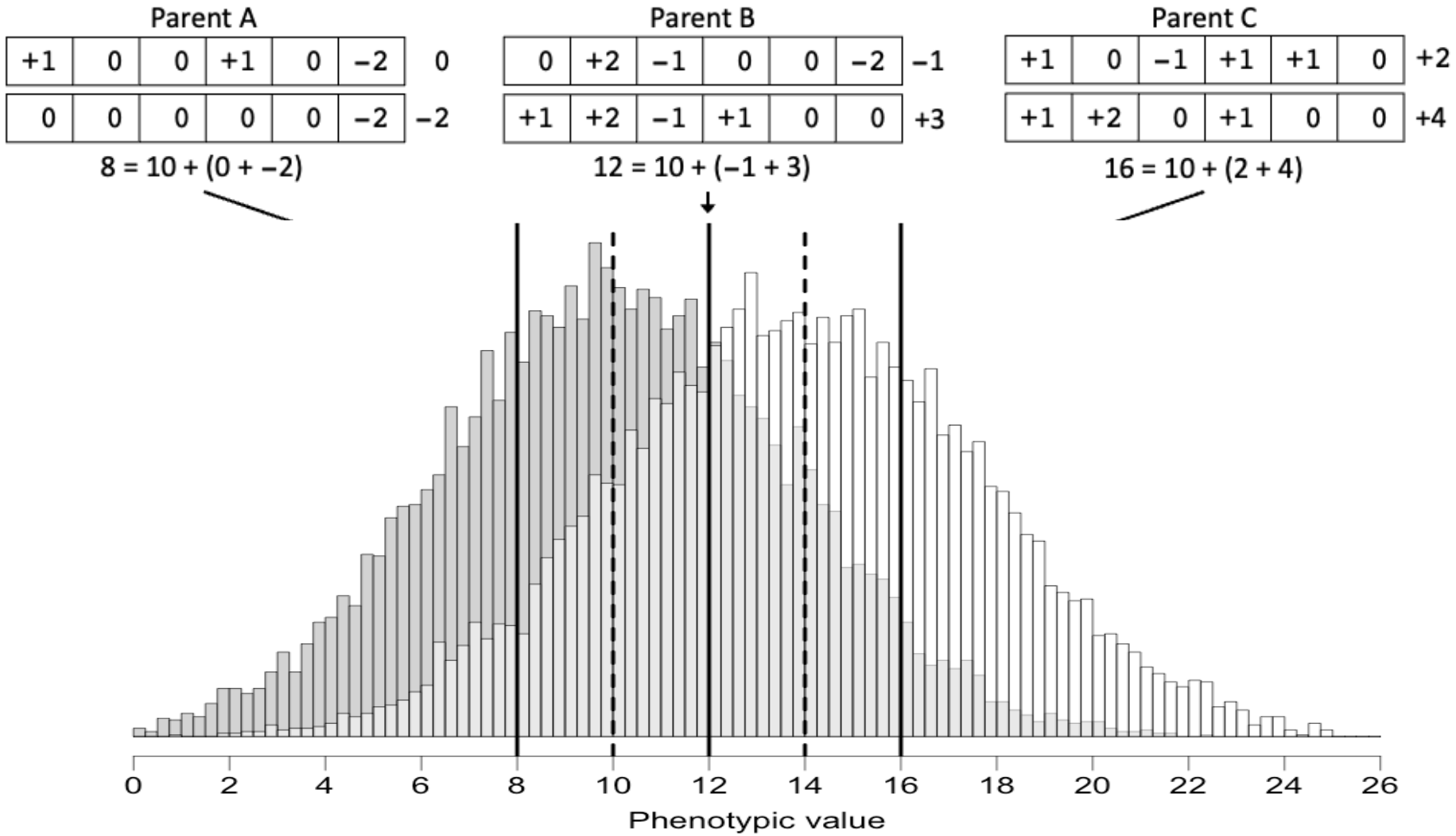
Meiosis in the context of a pedigree



Between and within family genetic variation



Between and within family phenotypic variation



For practicals

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      - 04a_DNA_lottery_genome.html
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      - 04c_DNA_lottery_genome_exercise.Rmd (PRACTICAL)

      - 04a_DNA_lottery_trait.html
      - 04b_DNA_lottery_trait.Rmd
      - 04c_DNA_lottery_trait_exercise.Rmd (PRACTICAL)

Take home message no. 3

Variation between & within families is substantial and driven by meiosis!

Takeaways

- Learning objectives
  - Encoding DNA variation
  - Simulate DNA & phenotypes in AlphaSimR
  - Simulate inheritance in AlphaSimR

- Take home messages
  - Encoding haplotypes (genotypes) as a series of 0 & 1 (0, 1, & 2)
  - Simple DNA → Phenotype models give rise to plenty of variation
  - Variation between & within families is substantial and driven by meiosis!

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