Multi-generational pedigrees with Sequoia

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Pedigree reconstruction > paternity assignment

Often not all candidate parents are genotyped
$\rightarrow$ cluster siblings & assign dummy parent to each sibship

But: those sibships are unconnected to the rest of the pedigree.

- Sometimes a sibship can be matched to a non-genotyped parent using field data. If this field parent has field parents itself, it can provide a link to the rest of the pedigree
- If those field-grandparents are genotyped, they should be related to all siblings by 0.25, and so it should be possible to infer them genetically

Additionally: Colony needs to be run cohort-by-cohort; finding sibships that span multiple cohorts is a pain

Full pedigree reconstruction

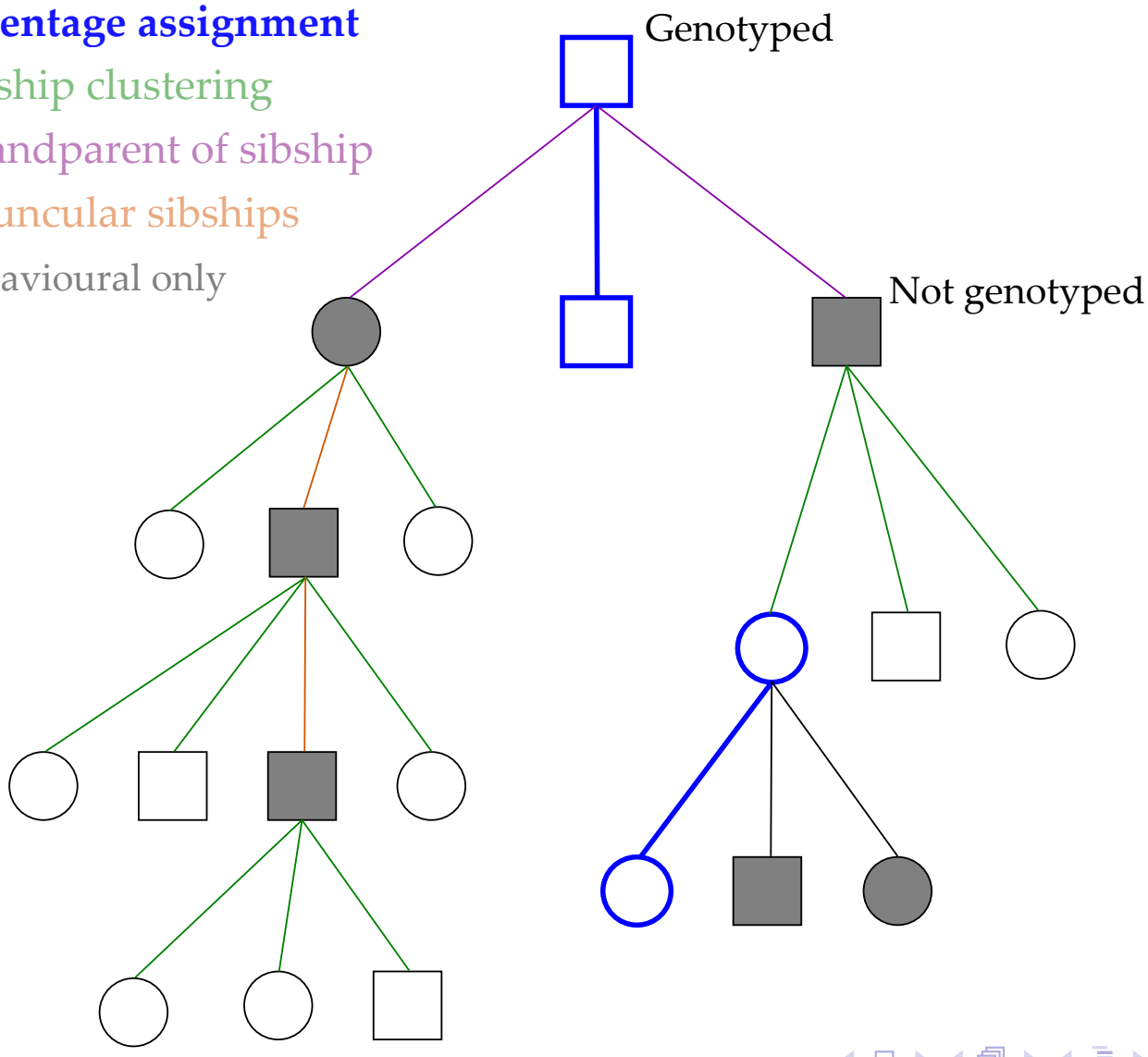
Parentage assignment

Sibship clustering

Grandparent of sibship

Avuncular sibships

Behavioural only



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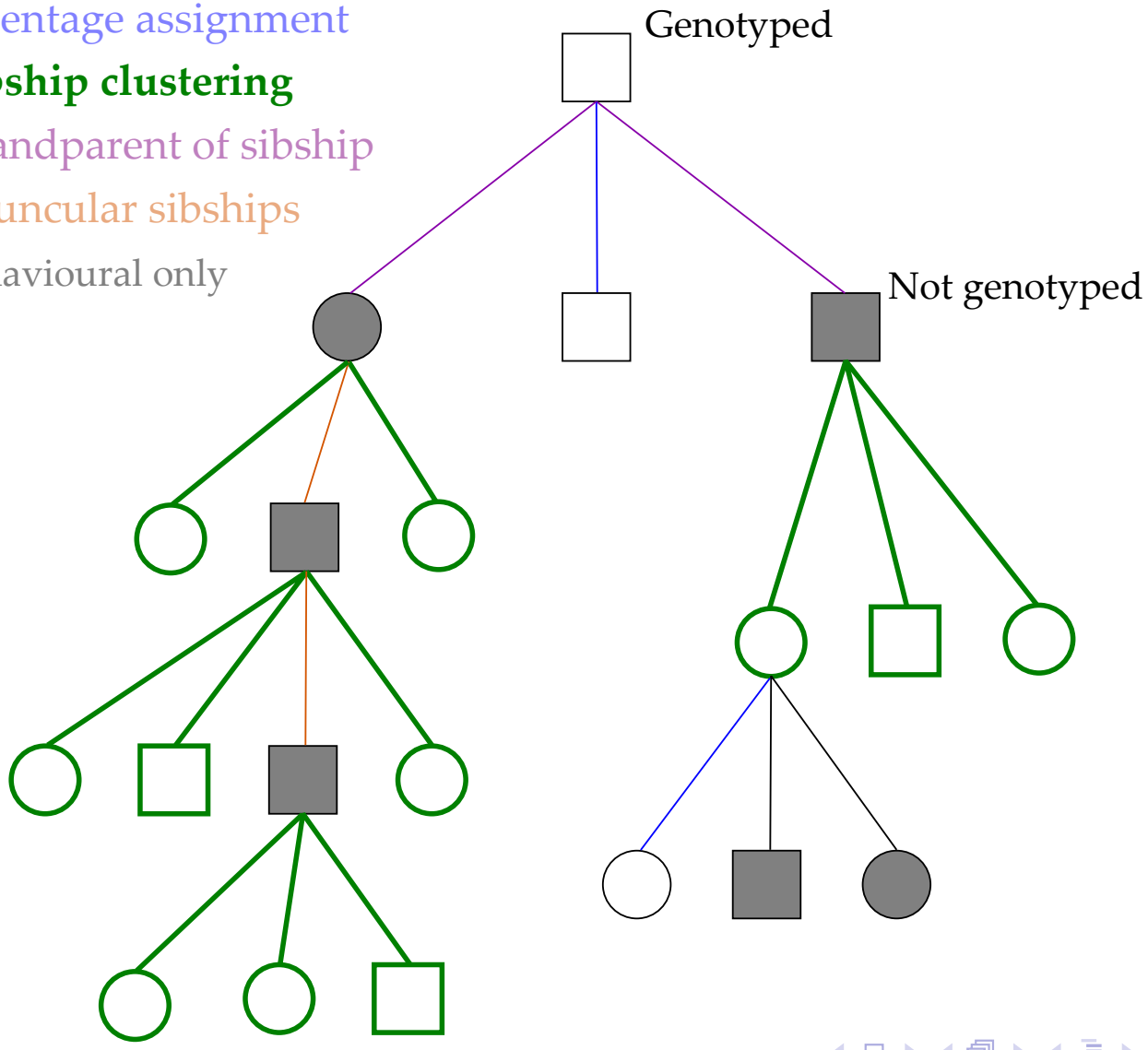

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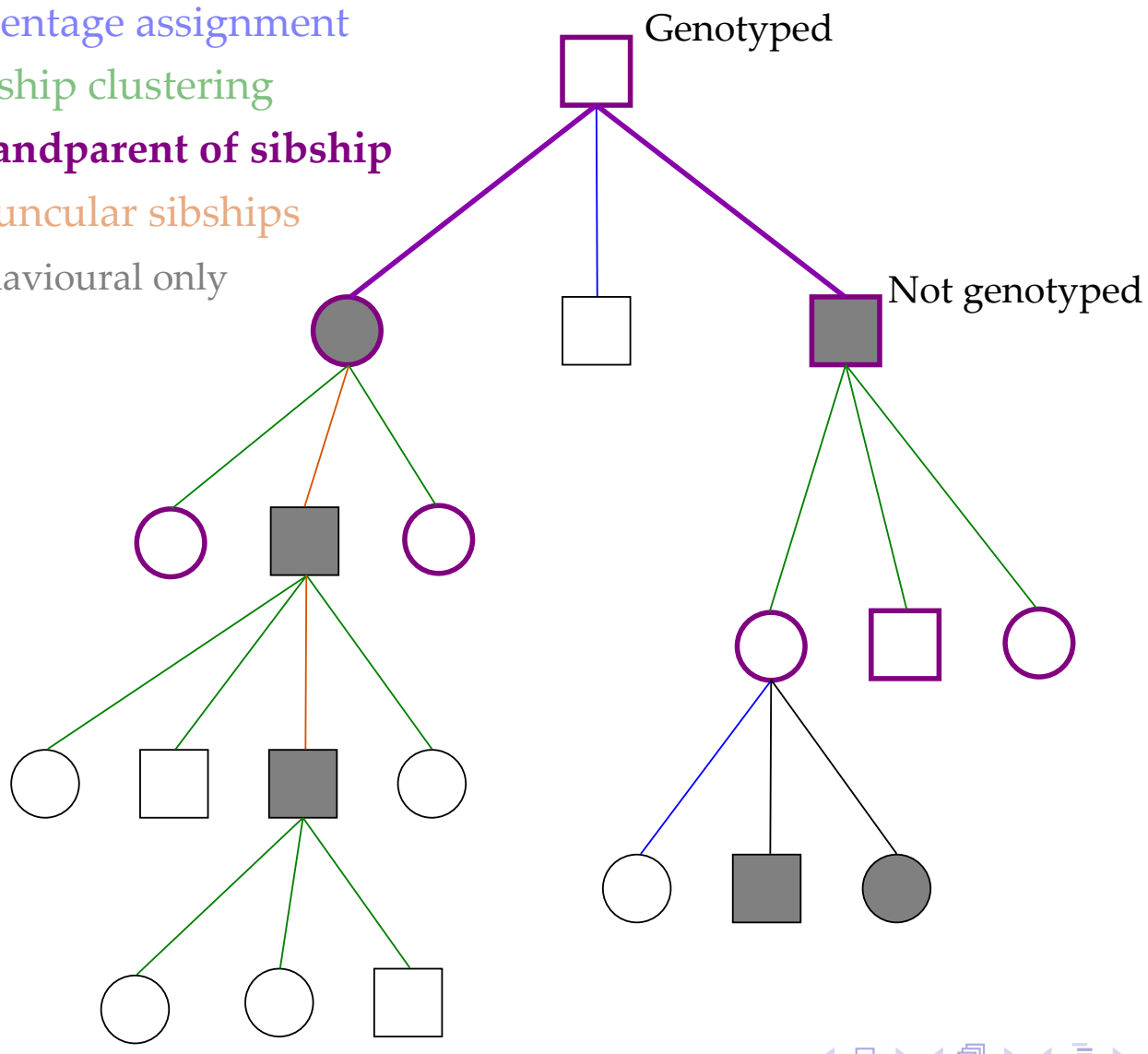

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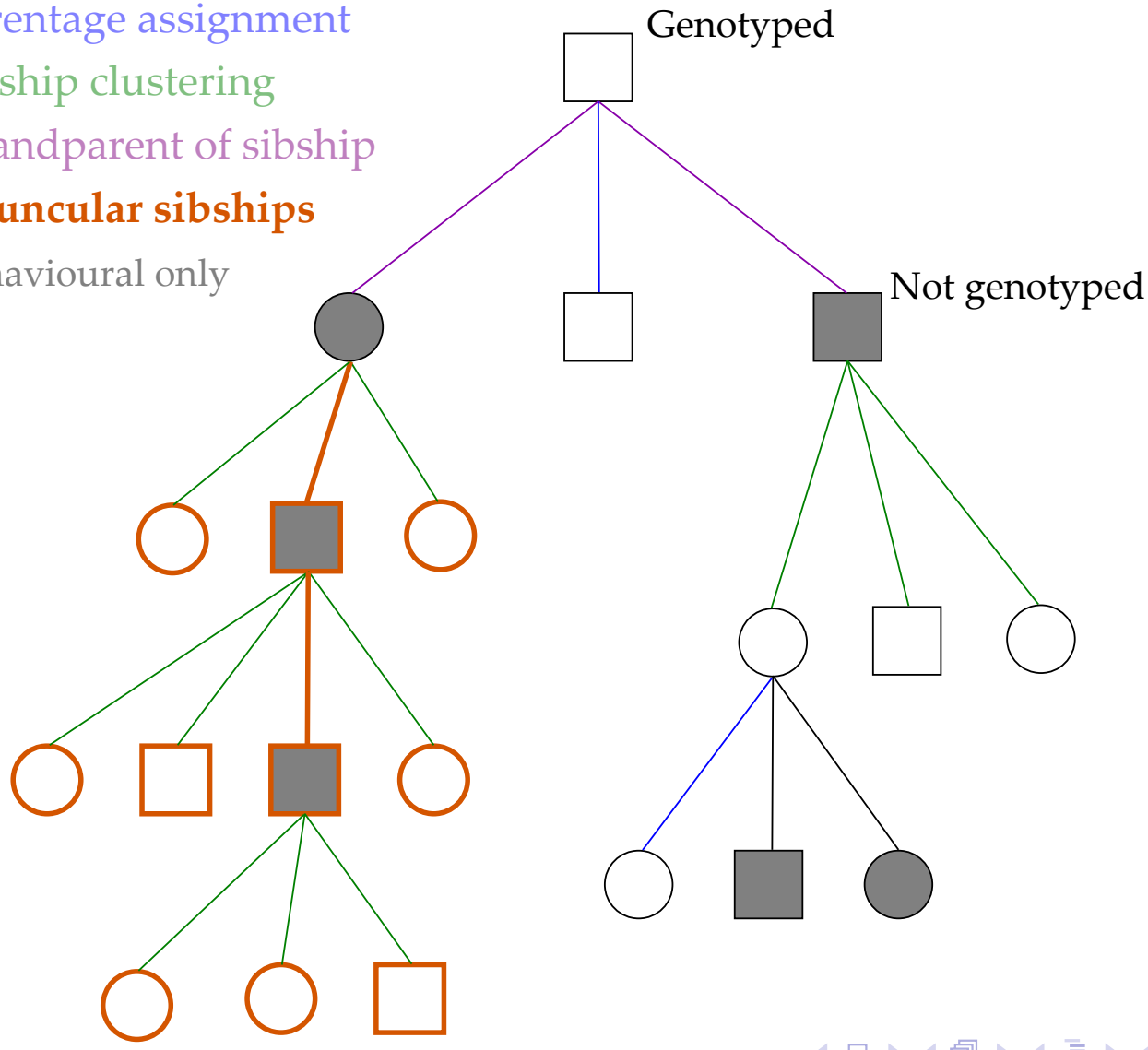

How do you make a pedigree from genomic data?

- Just exclude all impossible candidate parents (/relatives)
  - Provides no solution if > 1 candidate parent is non-excluded

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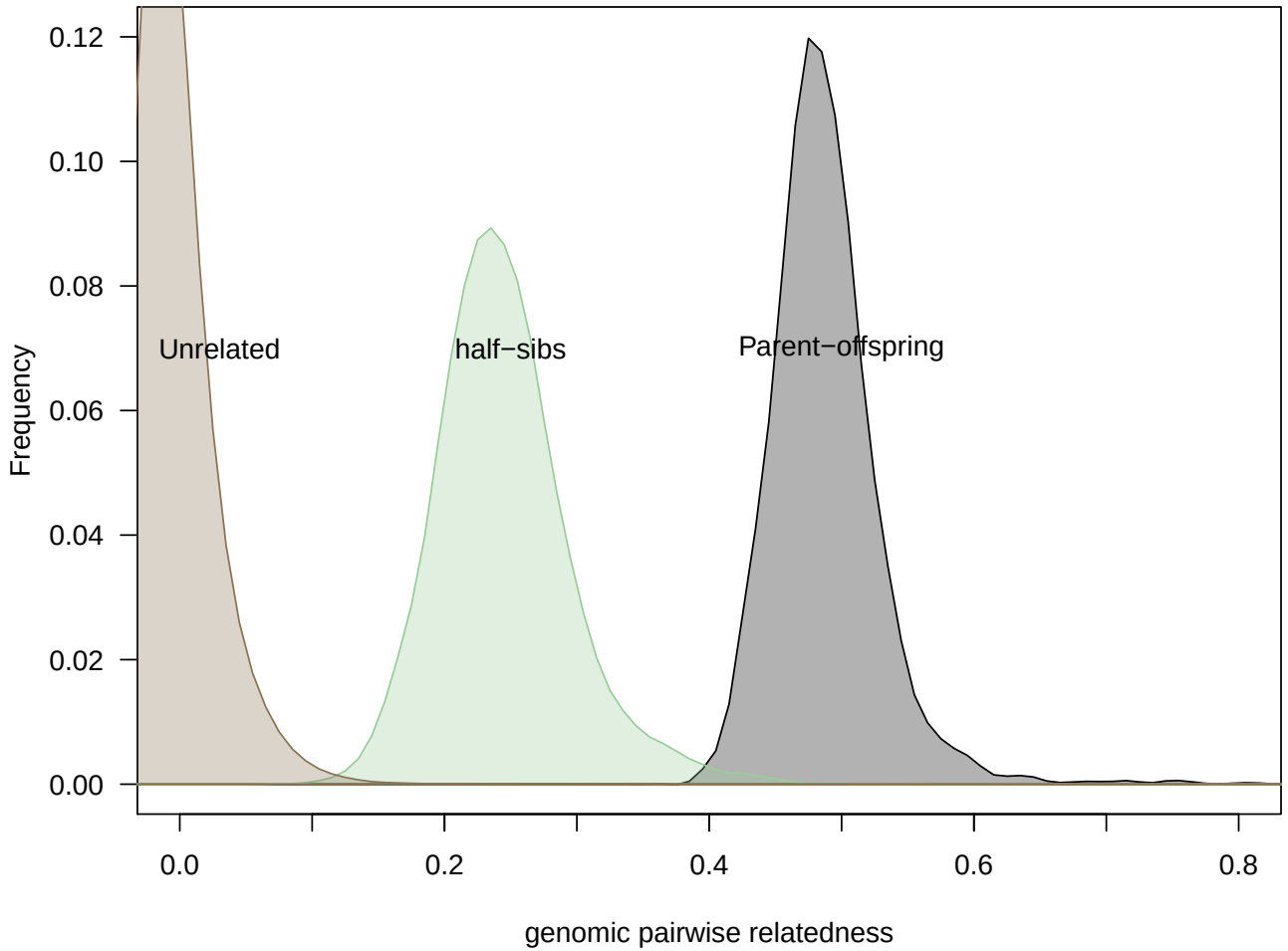

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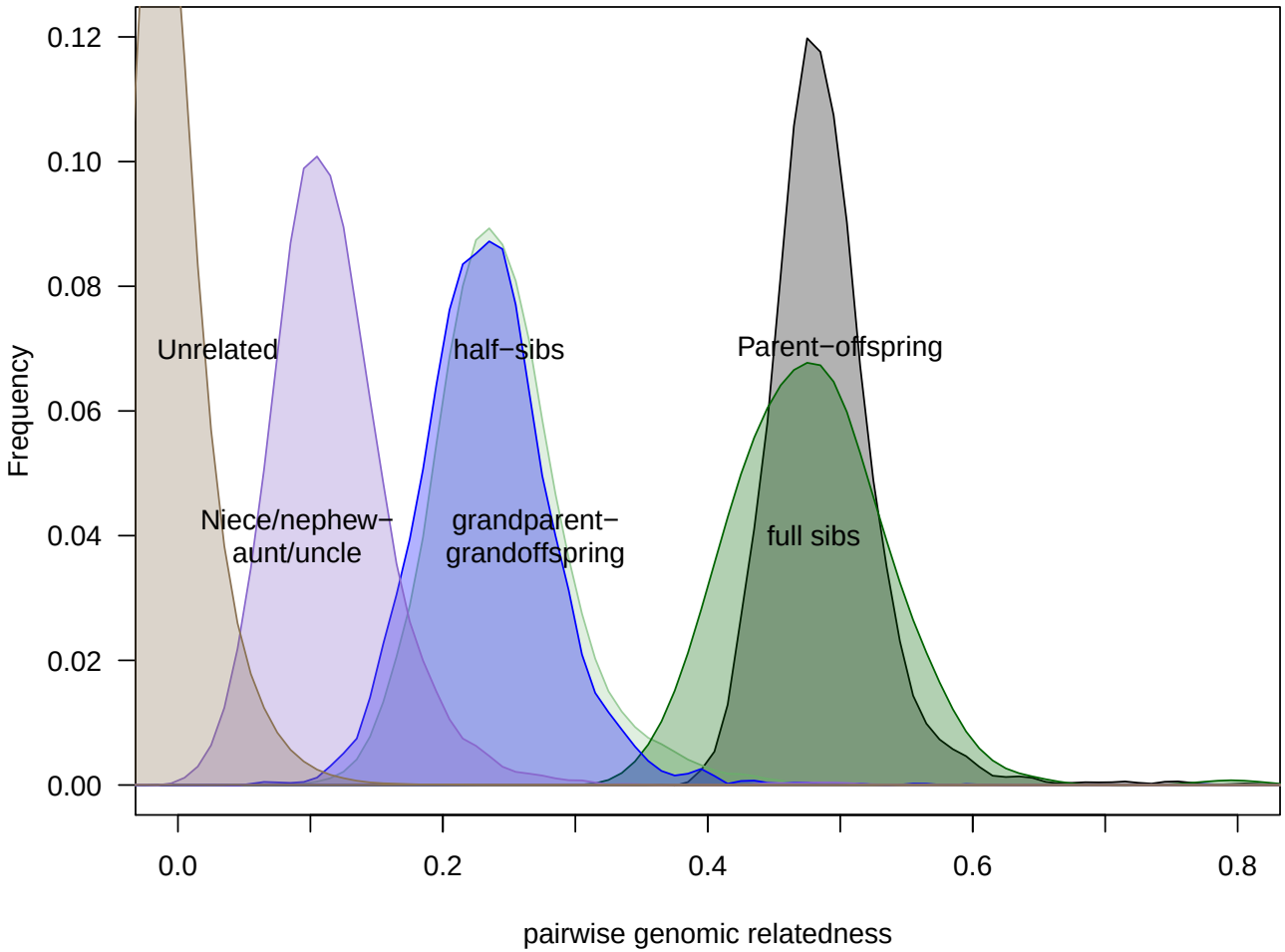

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- Likelihood approach

Likelihood approach

Likelihood of a pedigree = probability of observing the genotypes, given that pedigree

- The probability that you have observed genotyped G, given that you have actual genotype Z ($1 - \epsilon$ etc.)
- Probability that you inherited genotype Z, given that your parents have genotype X and Y (0, 1/2, 1/4, or 1)
- Probability that parent P has actual genotype X given its observed genotype, or allele frequency + HWE, or your siblings's genotypes

Sum over all (3*3*3) possible values of X, Y and Z

(microsat w 10 alleles $\rightarrow$ 10 homs + 9*10 hets, 166 375 possible combo's)

$\rightarrow$ can be extended to many individuals, not just pairs

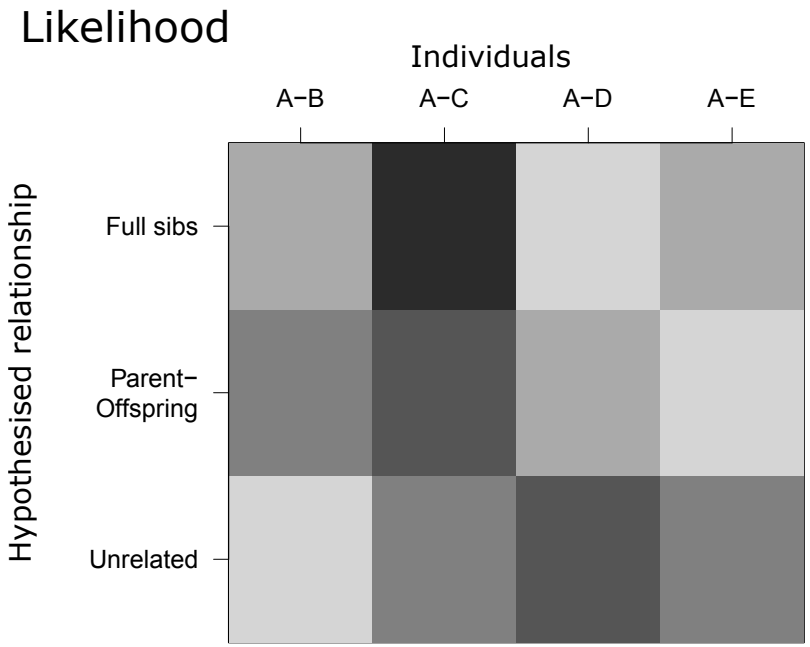
Problems with likelihoods - 1

- the likelihood that A is the parent of B, is identical to the likelihood of B being the parent of A
  - need info on who of the two is the eldest (or candidate parent lists)
  - possible to find 'complementary' parent pairs even w/o age info
- the likelihoods of all 2nd degree relationships (half sib, grandparental, full avuncular) are identical
  - age info can help a lot
  - if both have a parent assigned, the likelihoods do differ (does work with dummy parents too)

Problems with likelihoods - 2

"Although comparison of alternative genealogical relationships between a specified set of individuals is an entirely consistent statistical procedure,

comparison of alternative individuals for a given genealogical relationship is not." (Thompson, 1987)



Darker = higher pairwise likelihood

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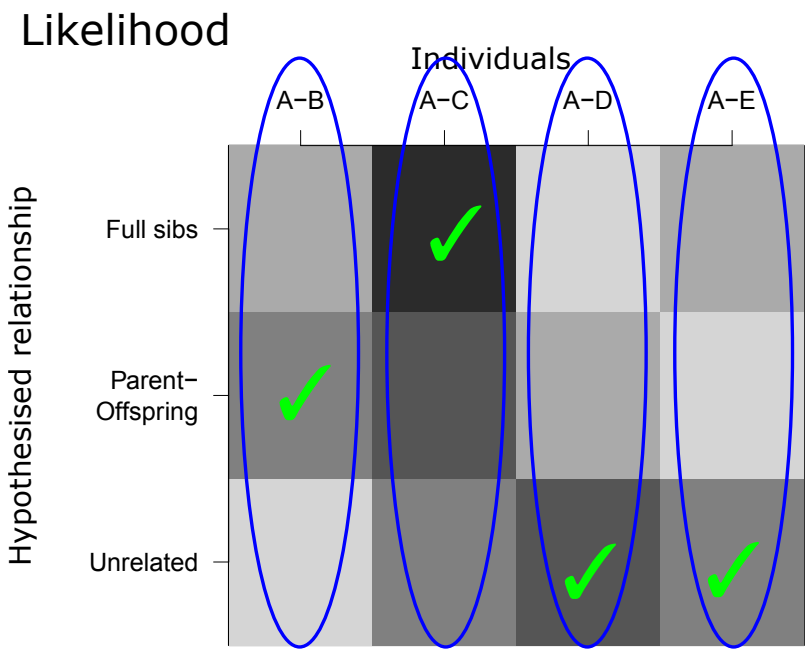
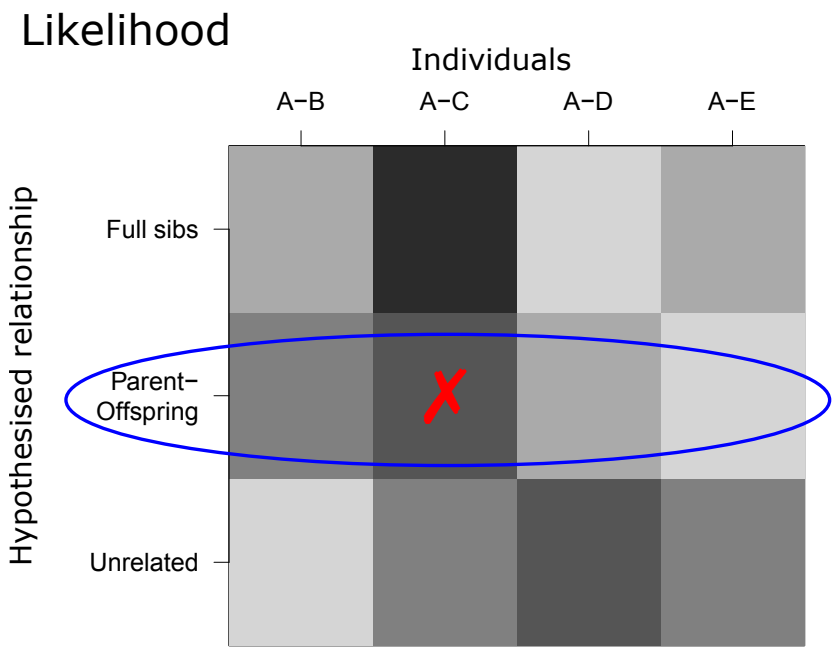




Solutions to problem 2

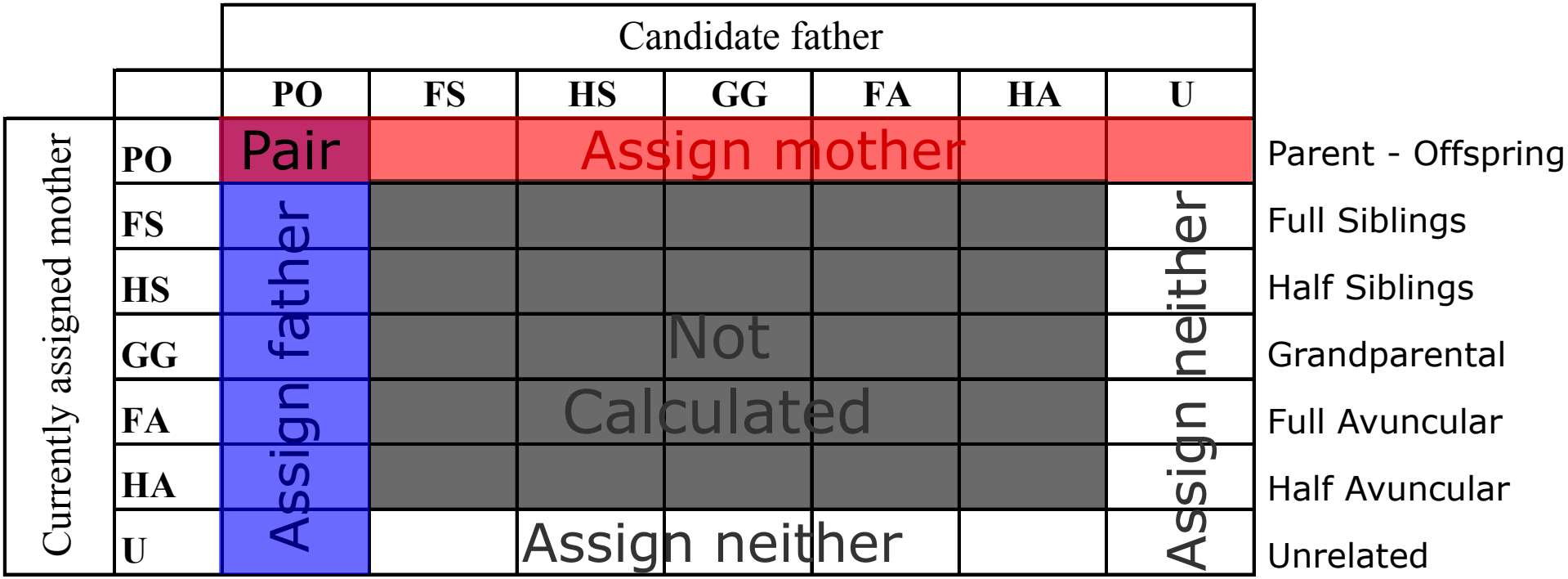
Colony, MasterBayes (?): optimise likelihood over all individuals, rather than each pair

Sequoia - For each pair of candidate relatives, calculate the likelihood of observing their genotypes if they were . . .

1. parent and offspring
2. full siblings
3. half siblings
4. grandparent and grandoffspring
5. full avuncular (aunt/uncle - niece/nephew)
6. 3rd degree relatives (half avuncular, cousins, great-grandparent)
7. unrelated

And assign only if the focal relationship is more likely than all others.

Parent pairs



Calculate the 7 likelihoods conditional on the opposite-sex candidate parent being a parent, and on it being unrelated (including inbred variations)

Repeat for all possible pairs among those that passed filtering (more likely parents will 'take over')

Inbreeding & 'double' relationships

Big disadvantage of this approach: Requires explicit consideration of all possible configurations for best results.

For example, these are easily mistaken for full siblings:

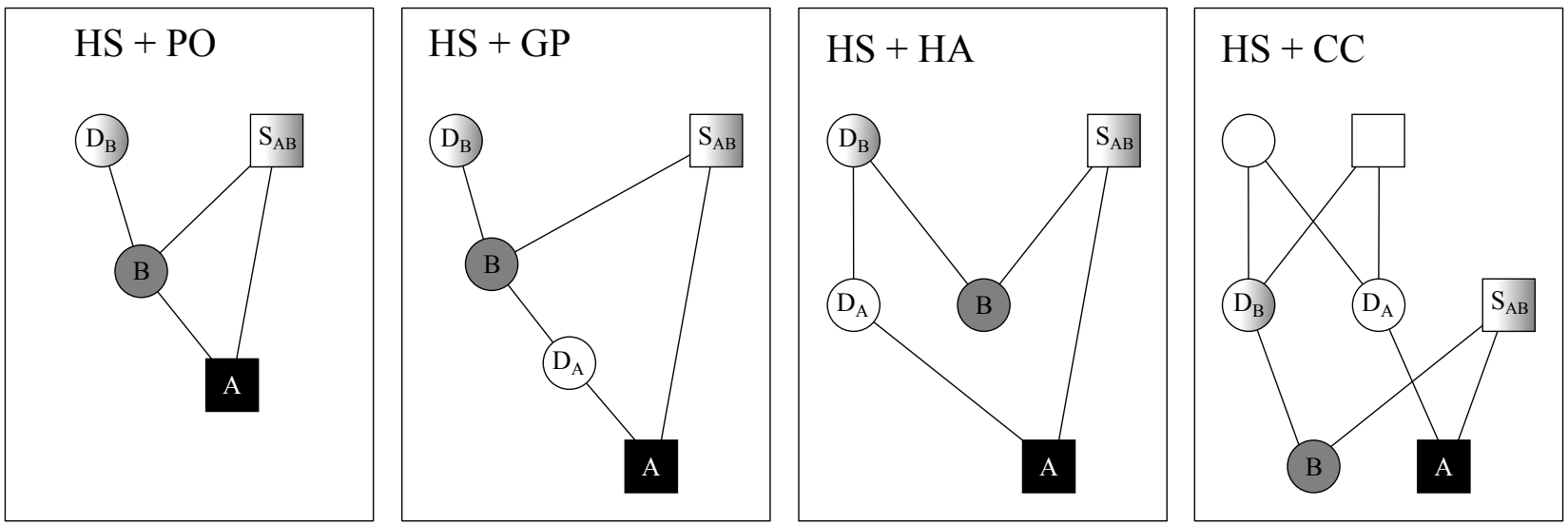


Figure: Examples of double relationships between genotyped individuals A and B, where D_B and S_{AB} may or may not be genotyped, and D_A is not genotyped.

Likelihood optimisation

Calculating all these likelihoods makes checking each potential assignment computationally intensive

- MCMC with tens of thousands of iterations probably would take months
  - $\rightarrow$ no per-individual posterior probability
- Use a conservative hill-climbing algorithm
  - Build upon already made assignments ($\rightarrow$ some pre-set assignment threshold needed)
  - Asymptotes usually in < 10 iterations
  - LLR(Parent / most likely not-parent relationship) in final pedigree provides indication of assignment confidence
- Don't do all calculations for all pairs

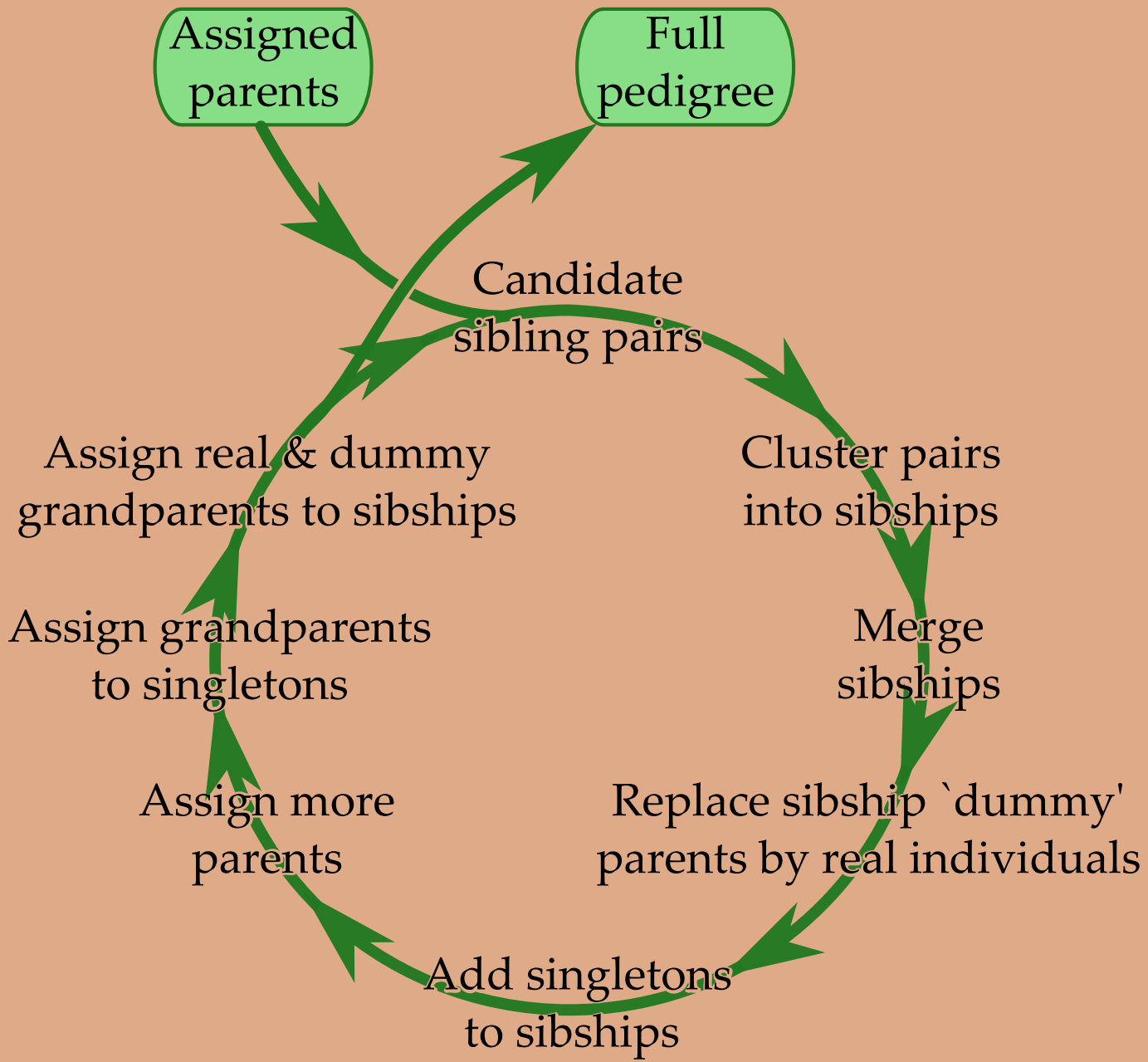
Speeding things up

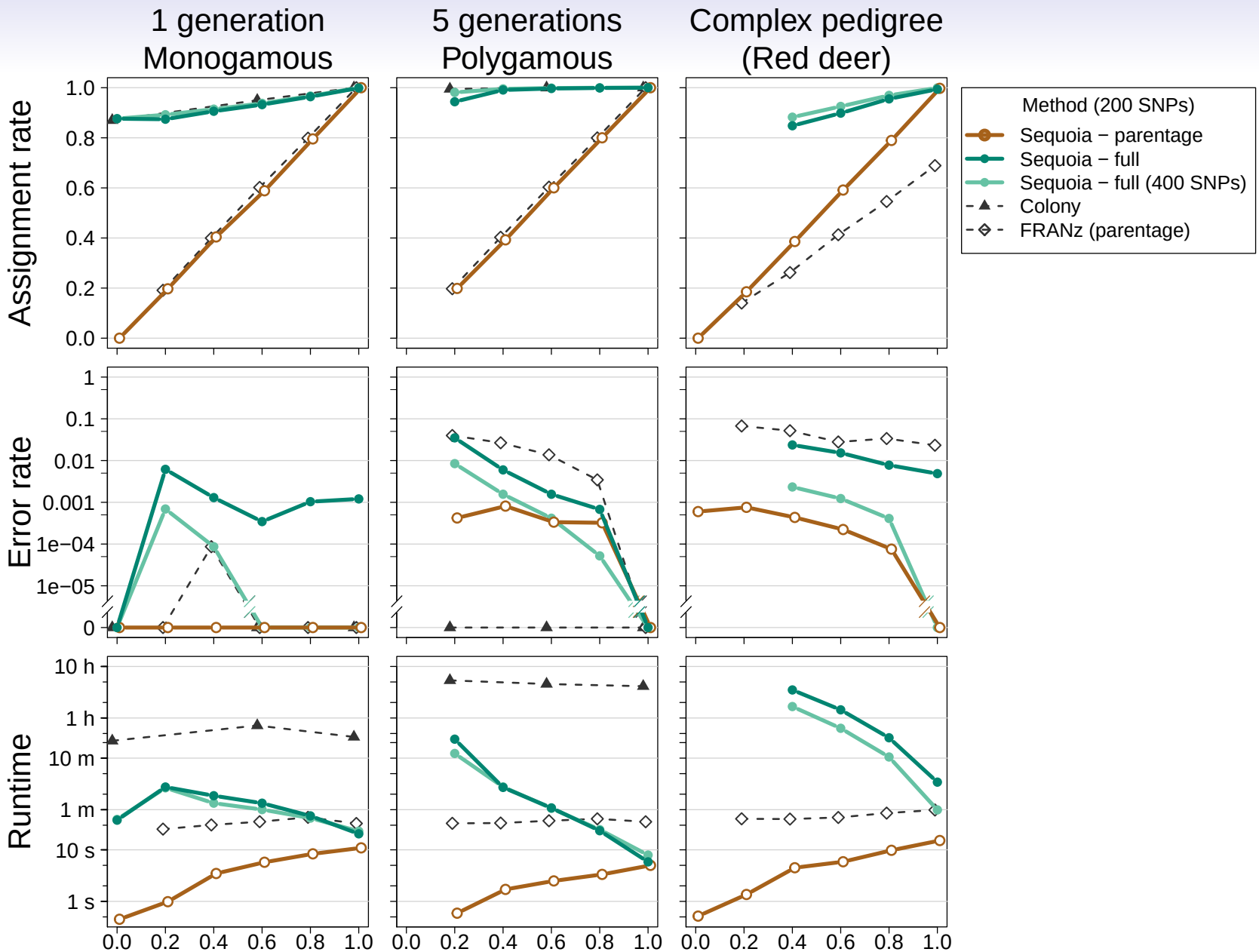
Everybody is a potential candidate parent for everybody else $\rightarrow$ drop all candidates through a series of filters with decreasing 'mesh size' before doing all likelihood computations

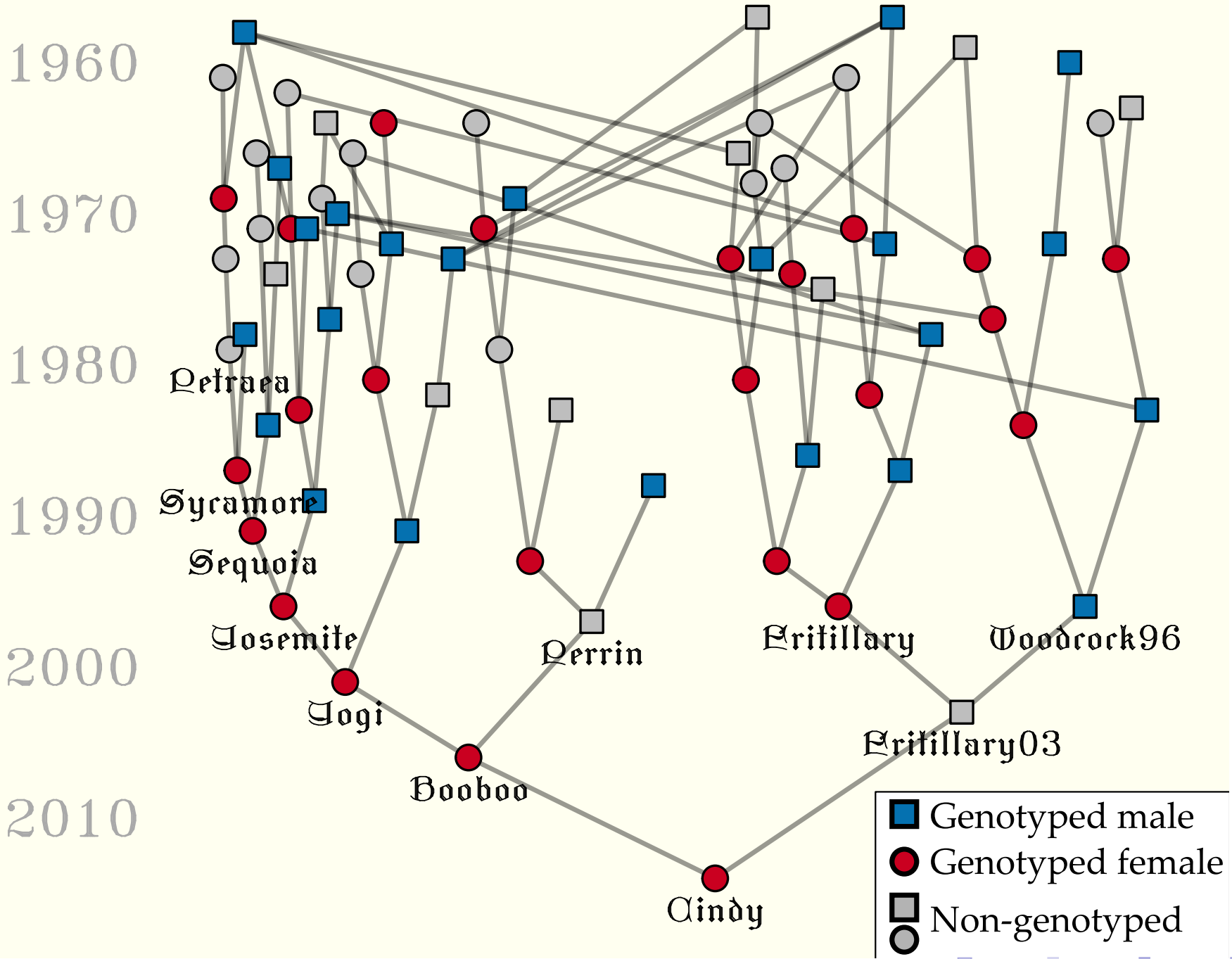
- Exclude any with many opposing homozygous loci
- Exclude any which are younger
- Calculate the approximate LLR(parent/unrelated), without considering any possibly already assigned parents, and exclude if this LLR is lower than T_{filter} (user-set, default -2)

and only then

- calculate the likelihoods of all possible relationships, and assign if parent-offspring is more likely than the next-most-likely by a margin T_{assign} (user-set, default $+0.5$)


Assigned parents
Full pedigree
Candidate sibling pairs
Cluster pairs into sibships
Merge sibships
Replace sibship `dummy' parents by real individuals
Add singletons to sibships
Assign more parents
Assign grandparents to singletons
Assign real & dummy grandparents to sibships


1 generation
Monogamous
5 generations
Polygamous
Complex pedigree
(Red deer)
Assignment rate
Error rate
Runtime
Prop. genotyped parents
Method (200 SNPs)
Sequoia − parentage
Sequoia − full
Sequoia − full (400 SNPs)
Colony
FRANz (parentage)


1960
1970
1980
1990
2000
2010
Petraea
Sycamore
Sequoia
Yosemite
Yogi
Booboo
Perrin
Cindy
Eritillary
Woodcock96
Eritillary03
Genotyped male
Genotyped female
Non-genotyped