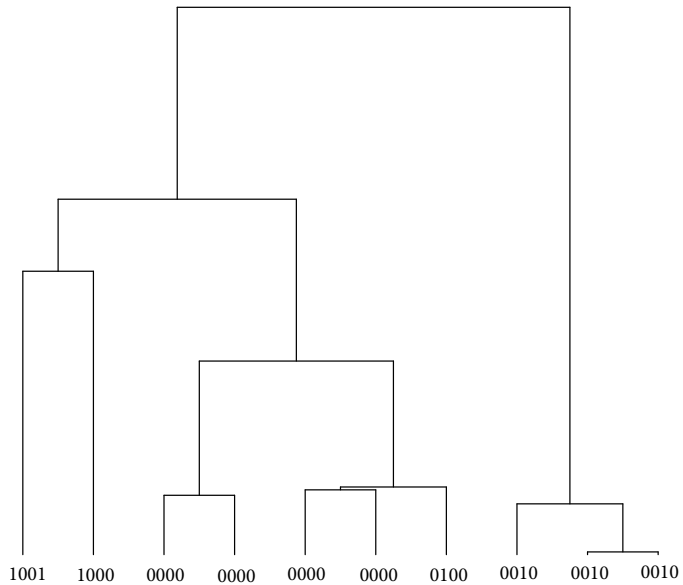
Sampling gene genealogies conditional on genotype data from trios

Kelly Burkett

August, 2018

Gene genealogy or Ancestral tree

- Tree describing the relationships among sequences sampled from unrelated individuals in a population
  - Tips of the tree correspond to the observed sequences
  - Root of the tree is common ancestor of all sequences



- Due to recombination, ancestral tree differs along a genomic sequence
  - Restrict attention to ancestry of a single focal point
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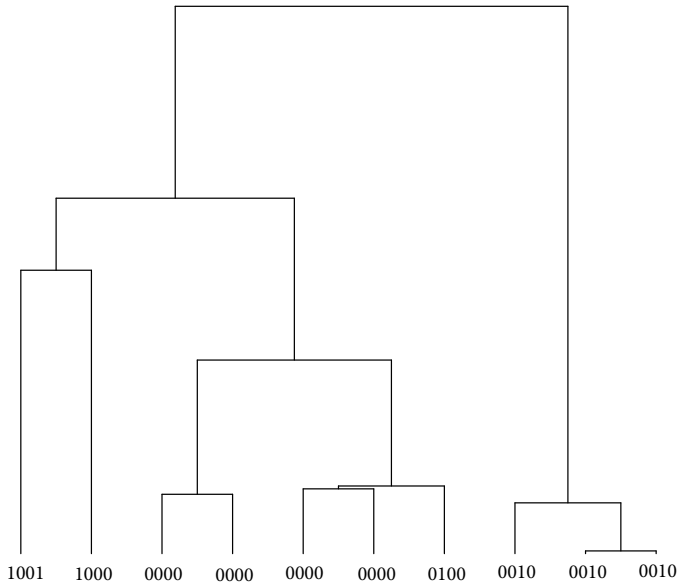

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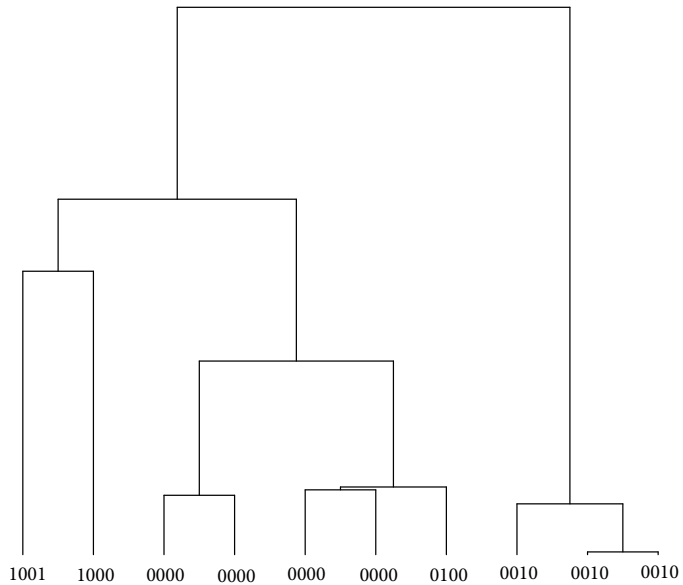

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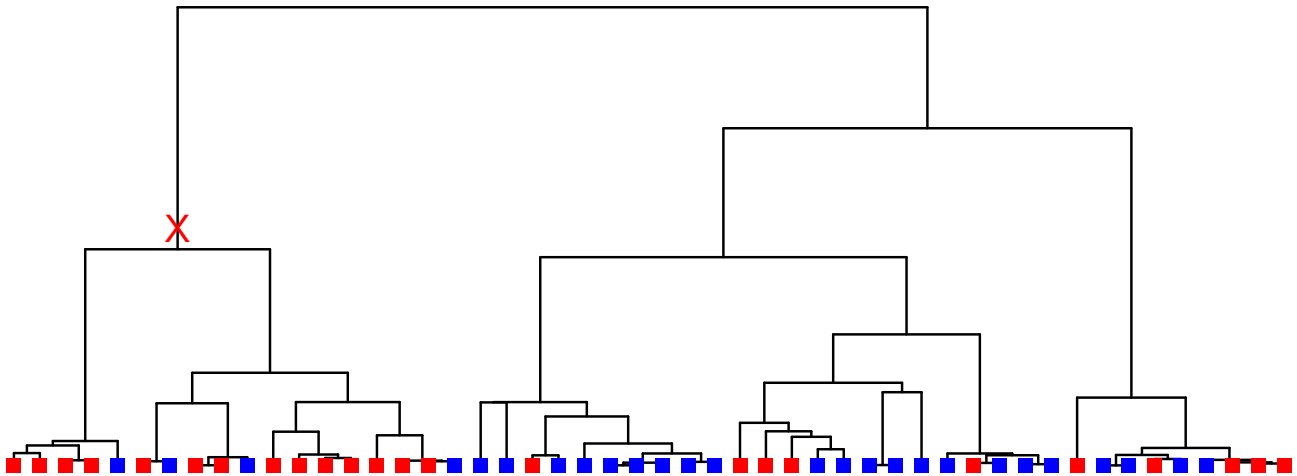
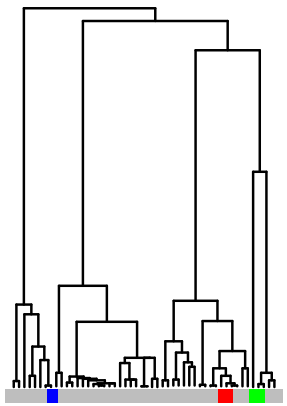
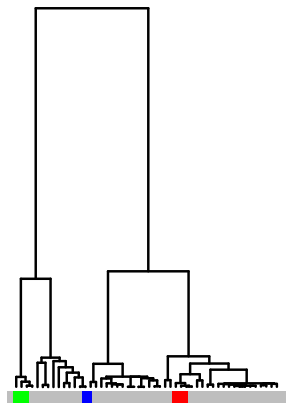
Disease mutations on the ancestral tree

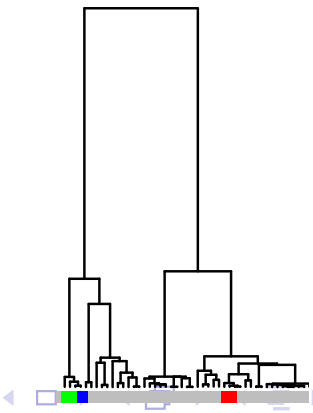
Common variant:



Rare variants:

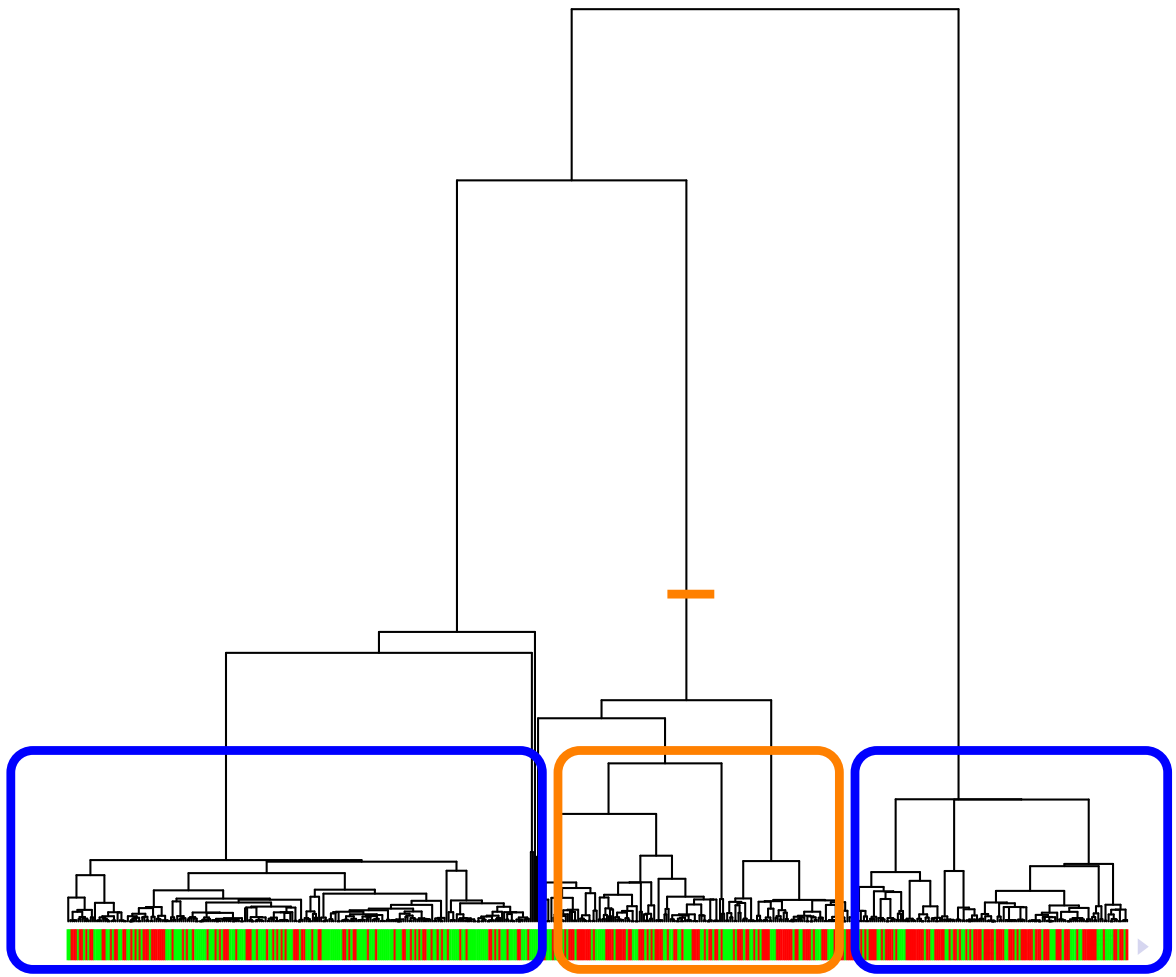






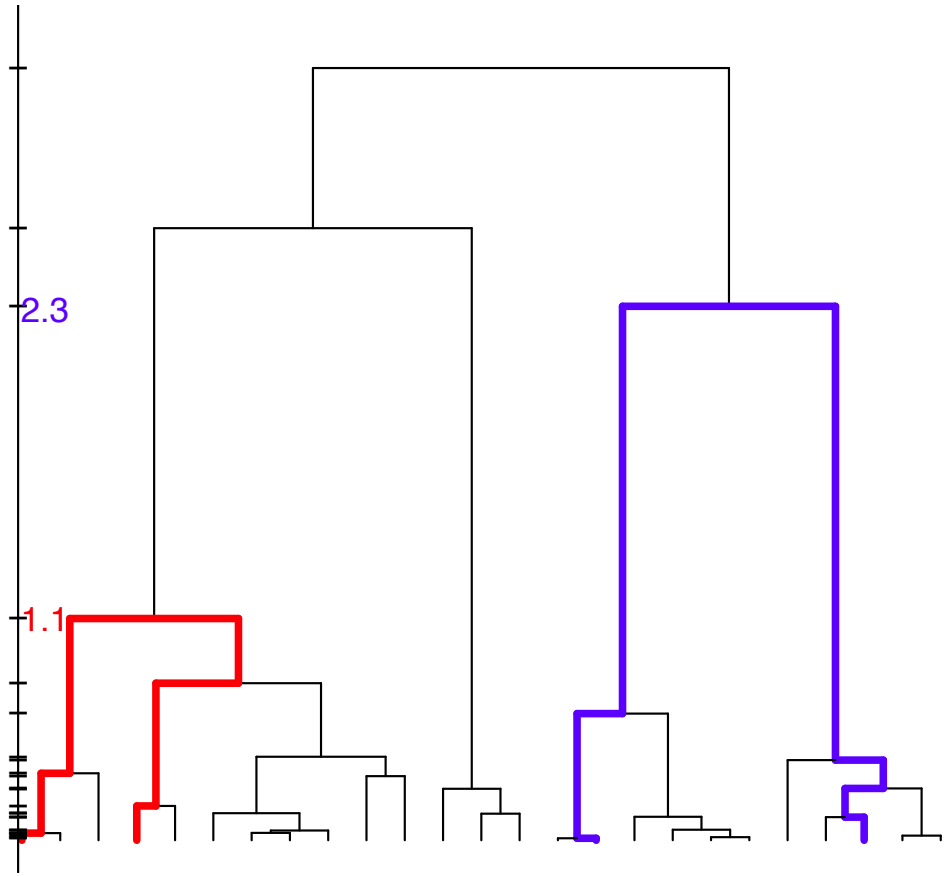
Bipartition clustering (e.g. Minichiello and Durbin, 2006)

- Each internal branch partitions tips into two groups
- Tree defines a factor with two levels



Using the tree as a measure of similarity/distance

$$d_{ij}(T) = f(\text{time to first common ancestor})$$



-Correlate tree distance with distance in phenotype using Mantel test (see Burkett KM, McNeney B, Graham J, Greenwood CMT, 2014.)

Handling uncertainty of the ancestral tree

- True gene genealogy not known; genetic data contains information about the unknown tree.

- Use statistical/phylogenetic methods to reconstruct a tree
  - Hierarchical clustering, minimal trees, ...
  - Reconstructing a single tree doesn't account for tree uncertainty.

- Alternatively, sample multiple trees from distribution that depends on observed data
  - Incorporate population genetic models
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Sampling trees conditional on haplotype data

- **T** is the tree topology and node times; **H** vector of observed haplotypes:

Haplotype	Count
10000110000101000100010001001	15
10000110000101000100010000000	3
10000110010101011100011000000	1
⋮	⋮
00011000100010100011100110110	3
00111000100010100011100100000	4

- `sampletrees` (Burkett, McNeney, Graham 2013a,b and 2016) builds on an approach outlined in Zöllner and Pritchard (2005) to sample from $f(\mathbf{T}|\mathbf{H})$
  - Include latent variables for states of internal nodes: recombination variables, **R**, and sequence at internal nodes, **S**.
  - Sample from the augmented distribution, $f(\mathbf{T}, \mathbf{R}, \mathbf{S}|\mathbf{H})$; interested mainly in **T**.

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`sampletrees`: Sampling conditional on haplotypes

- $f(\mathbf{T}, \mathbf{R}, \mathbf{S}|\mathbf{H}) \propto f(\mathbf{H}, \mathbf{S}|\mathbf{R}, \mathbf{T}, \theta) f(\mathbf{R}|\mathbf{T}, \rho) f(\mathbf{T}) f(\theta) f(\rho)$ modelled using population genetic models:
  - $f(\mathbf{T})$: coalescent model
  - $f(\mathbf{H}, \mathbf{S}|\mathbf{R}, \mathbf{T}, \theta)$ and $f(\mathbf{R}|\mathbf{T}, \rho)$: Mutation/recombination events on the branches of the tree assumed Poisson distributed with rates θ and ρ

- MCMC sampling requires proposal distributions to update components of $\mathbf{T}, \mathbf{R}, \mathbf{S}$.
  - Five proposal distributions to update state of internal nodes, topology, rate parameters.
  - At a step, a random choice is made to determine which proposal distribution is used.
  - Update is either accepted or rejected with probability determined by Metropolis-Hastings acceptance ratio.

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Example: Applying sampler to 'haplotype' data

Data: Trios with Crohn's disease; 103 markers in 5q31 (Rioux et al. 2001; gap R package)

Procedure:

1. Impute haplotype data based on family relationships and genotypes (Beagle; Browning and Browning, 2009)
2. For each of $K = 100$ focal points, sample M trees $\{\mathbf{T}_{k,1}, \ldots \mathbf{T}_{k,M}\}$ from $f(\mathbf{T}_k|\mathbf{H})$ using `sampletrees`
3. Compute a tree-based statistic, $S(\mathbf{T}, D)$, on each tree to get $S(\mathbf{T}_{k,1}, D), \ldots, S(\mathbf{T}_{k,M}, D)$
   - D - Haplotype is transmitted or not.
   - $S(\cdot)$ - measures whether transmitted haplotypes are more closely related. E.g correlation between transmission status and clusters defined on the tree.
4. For each focal point, summarize the distribution of $\mathbf{S}_k$

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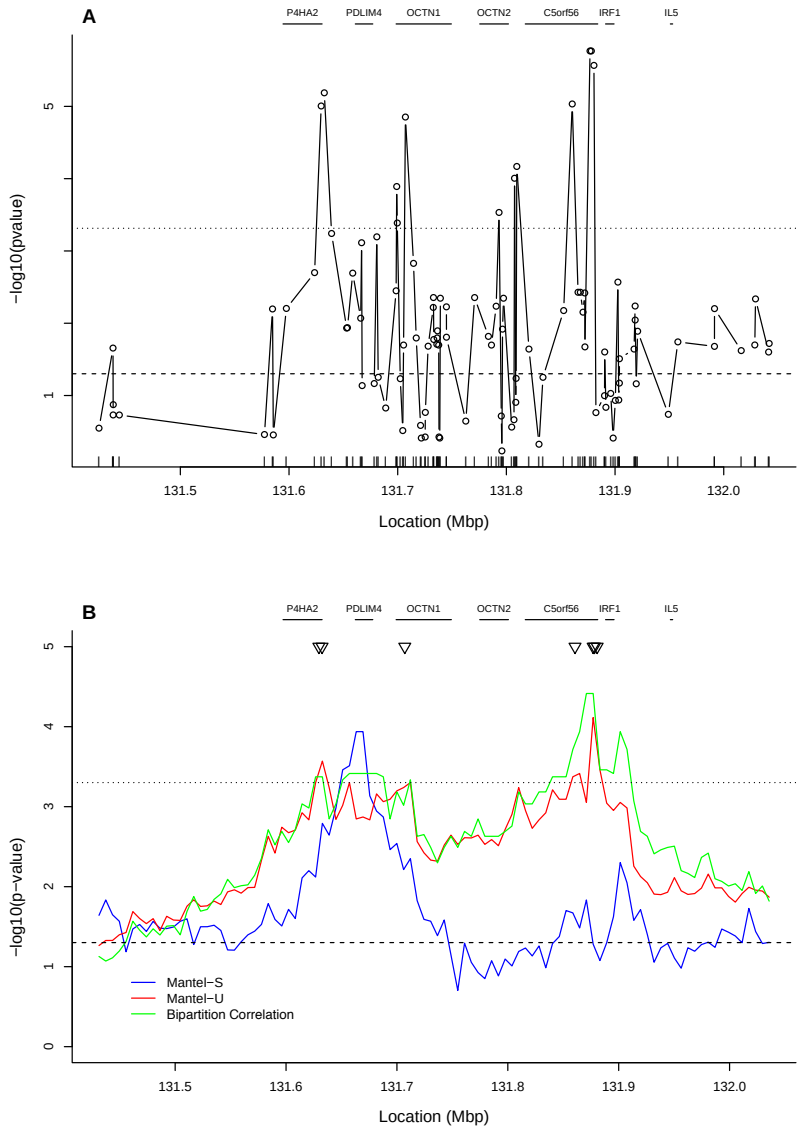

(green - Burkett KM, Greenwood CMT, McNeney B, Graham J, 2013c).

Sampling trees conditional on trio data (joint work with Marie-Hélène Roy-Gagnon)

Motivation:

1. With trio data, child's genotypes provide information about the phase of the parental haplotypes
   - In example shown, we imputed haplotype phase and treated it as known when sampling genealogies.
   - Conditioning on the child's genotypes would be a better use of the data.

2. Does inclusion of additional phase information from other sources improve sampling when phase is not known?
   - Sampling conditional on unphased genotypes performs poorly.
   - The child's genotype limits the parental phase configurations
   - In theory, could improve sampling when phase is not known.

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Gene genealogy of parental sequences

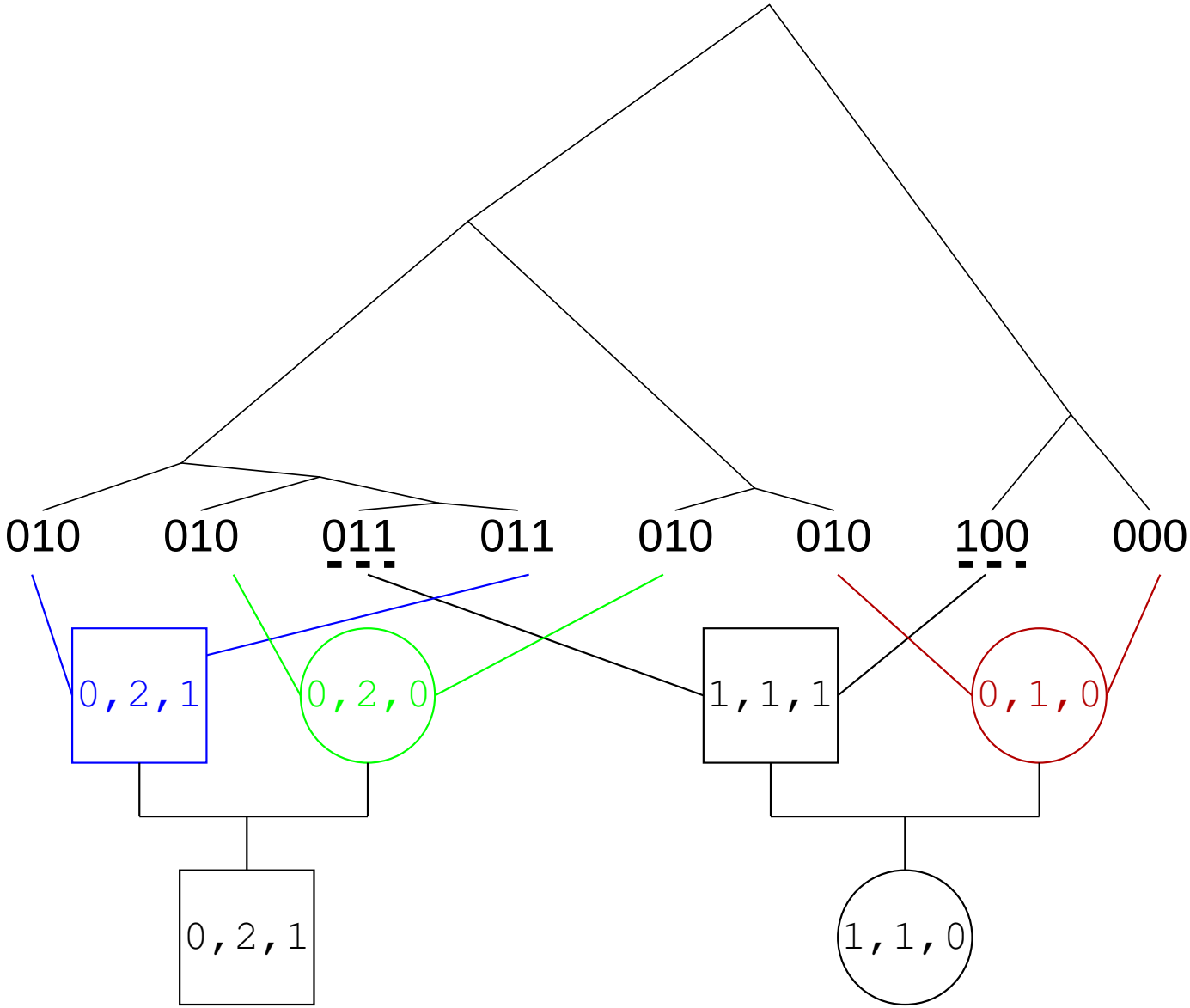

Table of possible genotype values for a trio

Mother	Father 0	Father 1	Father 2
0	0 (0/0)	0 (0/0) 1 (0/1)	1 (0/1)
1	0 (0/0) 1 (1/0)	0 (0/0) 1 2 (1/1)	1 (0/1) 2 (1/1)
2	1 (1/0)	1 (1/0) 2 (1/1)	2 (1/1)

- Each internal cell of the table contains the child's possible genotype.
- Brackets denotes the maternally inherited allele on the left and paternally inherited allele on the right.

Genotypes/haplotypes at 14 loci for an example trio

Genotype data

Individual	1	2	3	4	5	6	7	8	9	10	11	12	13	14
m	1	1	0	1	1	0	1	0	1	0	1	1	1	0
f	1	1	1	1	1	0	1	0	2	0	1	1	1	0
c	1	0	0	1	1	0	1	0	1	0	1	0	1	0

Haplotype data

Sequence	1	2	3	4	5	6	7	8	9	10	11	12	13	14
m_t	?	0	0	?	?	0	?	0	0	0	?	0	?	0
m_u	?	1	0	?	?	0	?	0	1	0	?	1	?	0
f_t	?	0	0	?	?	0	?	0	1	0	?	0	?	0
f_u	?	1	1	?	?	0	?	0	1	0	?	1	?	0

- m=Mother, f=Father, c=Child
- m_t, m_u = Mother's transmitted and untransmitted haplotypes, respectively
- f_t, f_u = Father's transmitted and untransmitted haplotypes, respectively
- '?' if alleles transmitted from the parents are not known

Extending model for genotype data on trios

- Now assume that **H** are set of (unknown) parental sequences. **G** are the observed genotypes for the trio.
- Let $\mathcal{F}$ denote the familial relationships present amongst members of the n trios. We are now interested in sampling from $f(\mathbf{T}|\mathbf{G}, \mathcal{F})$
- As before, model by augmenting the data with latent variables and sequentially conditioning on parental nodes:

$$f(\mathbf{T}, \mathbf{R}, \mathbf{S}, \mathbf{H}|\mathbf{G}, \mathcal{F}) \propto f(\mathbf{T}, \mathbf{R}, \mathbf{S}, \mathbf{H}, \mathbf{G}, |\mathcal{F}) = f(\mathbf{G}|\mathbf{H}, \mathcal{F}) f(\mathbf{T}, \mathbf{R}, \mathbf{S}, \mathbf{H}).$$

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Implementing trio-based tree sampler

1. Determine as much of the phase as possible from the trio genotypes alone
   - For any loci with missing transmission, we know that:

$$(m_t, m_u, f_t, f_u) = (1, 0, 0, 1) \text{ or } (0, 1, 1, 0)$$

2. Choose initial values for loci with missing transmission
   - Sample from the two configurations above; condition on surrounding loci

3. Proposal distribution to propose new transmission of alleles at the loci with missing information.
   - Allele swap
   - Similar to proposal distribution used in our genotype-based sampler
   - Randomly sample a locus with uncertain phase. Assume the chosen locus is the l^{th} for trio i.
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uOttawa

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Example: Application to the trio data

- Ran the sampler on the Crohn's dataset
  - Couldn't run all focal points; first 20 only.
  - 9-10 million iterations per focal point. Need longer run lengths.
- Acceptance rate for new proposal distribution is very low (average of 0.1%)
  - Expected based on my experience with sampling conditional on genotypes. Need longer run lengths.
- Average mutation rate/recombination rate estimates are similar whether haplotypes are imputed or not:

	Mutation Rate		Recombination Rate	
Focal Point	Trio-based	Imputed	Trio-based	Imputed
2	2.66	2.58	0.00017	0.00014
5	2.55	2.55	0.00019	0.00015
7	3.03	2.71	0.00020	0.00015
16	3.20	3.01	0.00035	0.00022
20	2.96	2.79	0.00084	0.00073

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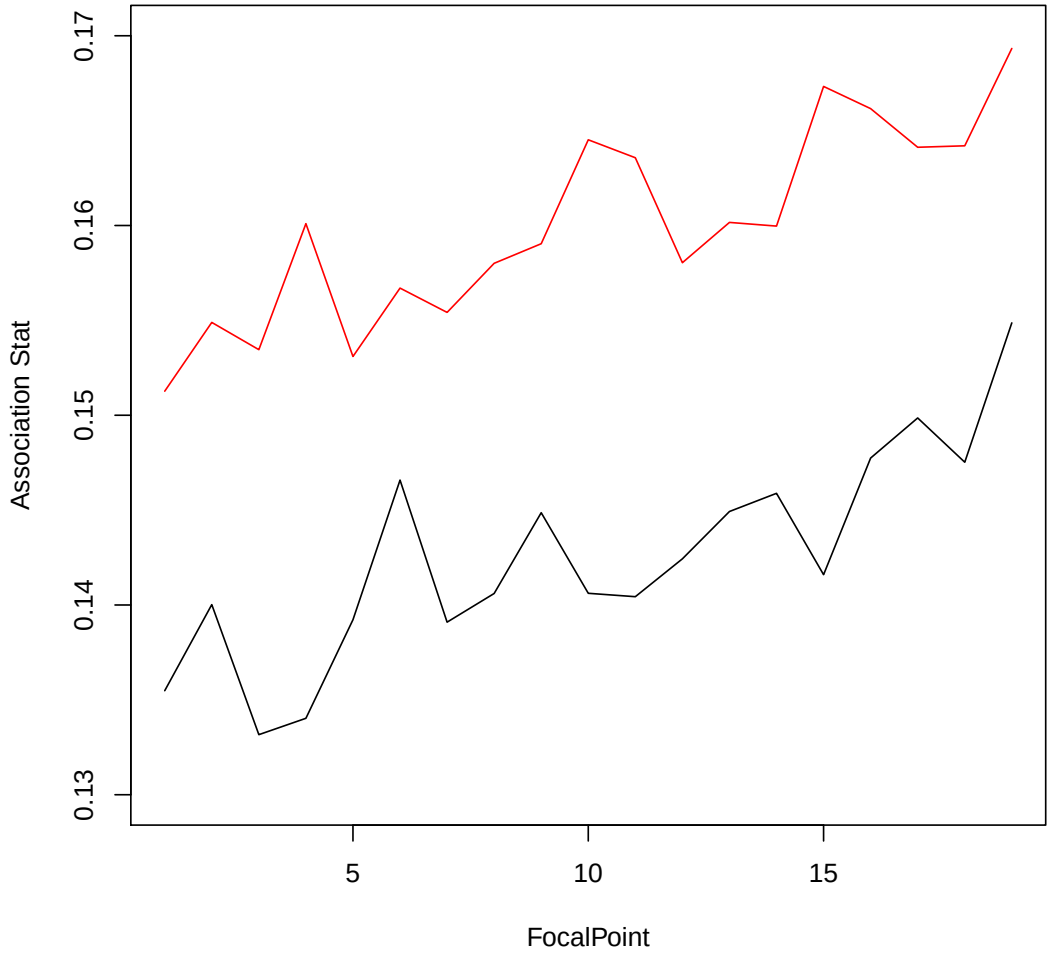

Red - Imputed data; Black - Trio data

Summary

Some thoughts based on my experiences with trio data:

- Conceptually ‘easy’ to extend previous work to trios.
  - Tips of the genealogy are the parents haplotypes.
  - Don’t need to model the history within the families.
- Need to improve the sampling at loci with missing transmission
  1. Better initialization of tip sequences
  2. Add topology change after a swap.
- Missing data
- Bigger families

Acknowledgements and References

Thanks to Bryan Paget for programming help

Some of the work presented was joint work with Jinko Graham, Brad McNeney, Celia Greenwood:

Burkett KM, McNeney B, Graham J. Sampletrees and Rsampletrees: sampling gene genealogies conditional on SNP genotype data. Bioinformatics, 32:1580-2, 2016.

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