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On the Complexity of SNP Block Partitioning Under the Perfect Phylogeny Model

An appropriate subtitle

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Outline

Introduction

- The Model and the Problem

- The Integrated Approach

Bad News: Hardness Results

- Hardness of PP-Partitioning of Haplotype Matrices

- Hardness of PP-Partitioning of Genotype Matrices

Good News: Tractability Results

- Perfect Path Phylogenies

- Tractability of PPP-Partitioning of Genotype Matrices



What is haplotyping and why is it important?

You hopefully know this after the previous three talks. . .



General formalization of haplotyping.

Inputs

- ▶ A genotype matrix G .
- ▶ The rows of the matrix are taxa / individuals.
- ▶ The columns of the matrix are SNP sites / characters.

Outputs

- ▶ A haplotype matrix H .
- ▶ Pairs of rows in H explain the rows of G .
- ▶ The haplotypes in H are biologically plausible.



Our formalization of haplotyping.

Inputs

- ▶ A genotype matrix G .
- ▶ The rows of the matrix are individuals / taxa.
- ▶ The columns of the matrix are SNP sites / characters.
- ▶ The problem is directed: one haplotype is known.
- ▶ The input is biallelic: there are only two homozygous states (0 and 1) and one heterozygous state (2).

Outputs



We can do perfect phylogeny haplotyping efficiently, but ...

1. Data may be missing.

- ▶ This makes the problem NP-complete ...
- ▶ ... even for very restricted cases.

Solutions:

- ▶ Additional assumption like the rich data hypothesis.

2. No perfect phylogeny is possible.

- ▶ This can be caused by chromosomal crossing-over effects.
- ▶ This can be caused by incorrect data.
- ▶ This can be caused by multiple mutations at the same sites.

Solutions:

- ▶ Look for phylogenetic networks.
- ▶ Correct data.
- ▶ Find blocks where a perfect phylogeny is possible.



How blocks help in perfect phylogeny haplotyping.

1. Partition the site set into overlapping contiguous blocks.
2. Compute a perfect phylogeny for each block and combine them.
3. Use dynamic programming for finding the partition.

Genotype matrix



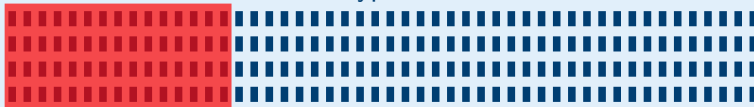
no perfect phylogeny



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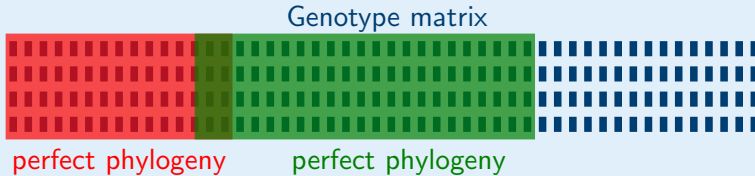


perfect phylogeny



How blocks help in perfect phylogeny haplotyping.

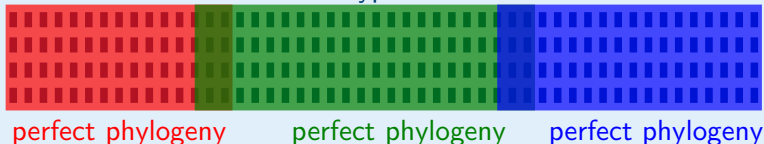
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Genotype matrix



Objective of the integrated approach.

1. Partition the site set into **noncontiguous** blocks.
2. Compute a perfect phylogeny for each block and combine them.
3. Compute partition while computing perfect phylogenies.

Genotype matrix



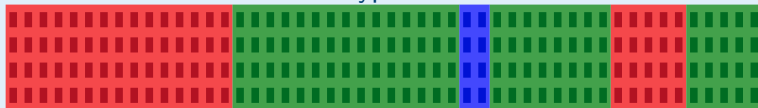
no perfect phylogeny



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Genotype matrix



perfect phylogeny

perfect phylogeny

perfect phylogeny



The formal computational problem.

We are interested in the computational complexity of the function χ_{PP} :

- ▶ It gets genotype matrices as input.
- ▶ It maps them to a number k .
- ▶ This number is minimal such that the sites can be covered by k sets, each admitting a perfect phylogeny.
(We call this a **pp-partition**.)



Finding pp-partitions of haplotype matrices.

We start with a special case:

- ▶ The inputs M are already haplotype matrices.
- ▶ The inputs M do not allow a perfect phylogeny.
- ▶ What is $\chi_{PP}(M)$?

Example

M :	0	0	0	1
	0	1	0	0
	1	0	0	0
	0	1	0	0
	1	0	0	0
	0	1	0	1
	1	1	0	0
	0	0	1	0
	1	0	1	0

No perfect phylogeny is possible.



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

Perfect phylogeny

Perfect phylogeny

$$\chi_{PP}(M) = 2.$$



Bad news about pp-partitions of haplotype matrices.

Theorem

Finding optimal pp-partition of haplotype matrices is equivalent to finding optimal graph colorings.

Proof sketch for first direction.

1. Let G be a graph.
2. Build a matrix with a column for each vertex of G .
3. For each edge of G add four rows inducing the submatrix $\begin{pmatrix} 0 & 0 \\ 0 & 1 \\ 1 & 0 \\ 1 & 1 \end{pmatrix}$.
4. The submatrix enforces that the columns lie in different perfect



Implications for pp-partitions of haplotype matrices.

Corollary

If $\chi_{PP}(M) = 2$ for a haplotype matrix M , we can find an optimal pp-partition in polynomial time.

Corollary

Computing χ_{PP} for haplotype matrices is

- ▶ NP-hard,
- ▶ not fixed-parameter tractable, unless $P = NP$,
- ▶ very hard to approximate.



Finding pp-partitions of genotype matrices.

Now comes the general case:

- ▶ The inputs M are genotype matrices.
- ▶ The inputs M do not allow a perfect phylogeny.
- ▶ What is $\chi_{PP}(M)$?

Example

$$M: \begin{array}{cccc} 2 & 2 & 2 & 2 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 2 & 2 & 0 \\ 1 & 1 & 0 & 0 \end{array}$$

No perfect phylogeny is possible.



Finding pp-partitions of genotype matrices.

Now comes the general case:

- ▶ The inputs M are genotype matrices.
- ▶ The inputs M do not allow a perfect phylogeny.
- ▶ What is $\chi_{PP}(M)$?

Example

M :

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

Perfect phylogeny

Perfect phylogeny

$$\chi_{PP}(M) = 2.$$



Bad news about pp-partitions of haplotype matrices.

Theorem

Finding optimal pp-partition of genotype matrices is at least as hard as finding optimal colorings of 3-uniform hypergraphs.

Proof sketch.

1. Let G be a 3-uniform hypergraph.
2. Build a matrix with a column for each vertex of G .
3. For each hyperedge of G add four rows inducing the submatrix $\begin{pmatrix} 2 & 2 & 2 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$.
4. The submatrix enforces that the three columns do not all lie in the



Implications for pp-partitions of genotype matrices.

Corollary

Even if we know $\chi_{PP}(M) = 2$ for a genotype matrix M , finding a pp-partition of any fixed size is still

- ▶ NP-hard,
- ▶ not fixed-parameter tractable, unless $P = NP$,
- ▶ very hard to approximate.



Automatic optimal pp-partitioning is hopeless, but...

- ▶ The hardness results are **worst-case** results for **highly artificial inputs**.
- ▶ **Real biological data** might have special properties that make the problem **tractable**.
- ▶ One such property is that perfect phylogenies are often **perfect path** phylogenies:
In HapMap data, in 70% of the blocks where a perfect phylogeny is possible a perfect path phylogeny is also possible.



Example of a perfect path phylogeny.

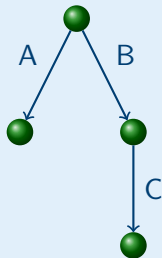
Genotype matrix

	A	B	C
	2	2	2
G:	0	2	0
	2	0	0
	0	2	2

Haplotype matrix

	A	B	C
	1	0	0
	0	1	1
	0	0	0
H:	0	1	0
	0	0	0
	1	0	0
	0	0	0
	0	1	1

Perfect path phylogeny



The modified formal computational problem.

We are interested in the computational complexity of the function χ_{PPP} :

- ▶ It gets genotype matrices as input.
- ▶ It maps them to a number k .
- ▶ This number is minimal such that the sites can be covered by k sets, each admitting a perfect **path** phylogeny.
(We call this a ppp-partition.)



Good news about ppp-partitions of genotype matrices.

Theorem

Optimal ppp-partitions of genotype matrices can be computed in polynomial time.

Algorithm

1. Build the following partial order:
 - ▶ Can one column be above the other in a phylogeny?
 - ▶ Can the columns be the two children of the root of a perfect path phylogeny?
2. Cover the partial order with as few compatible chain pairs as possible.



Summary

- ▶ Finding optimal pp-partitions is intractable.
- ▶ It is even intractable to find a pp-partition when just two noncontiguous blocks are known to suffice.
- ▶ For perfect path phylogenies, optimal partitions can be computed in polynomial time.

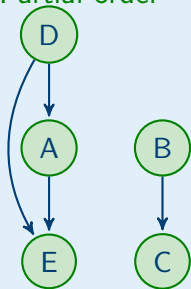


The algorithm in action.

Genotype matrix

	A	B	C	D	E
G:	2	2	2	2	2
	0	1	2	1	0
	1	0	0	1	2
	0	2	2	0	0

Partial order



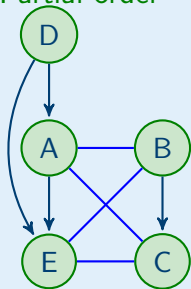
Partial order: →

The algorithm in action.

Genotype matrix

	A	B	C	D	E
G:	2	2	2	2	2
	0	1	2	1	0
	1	0	0	1	2
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Partial order



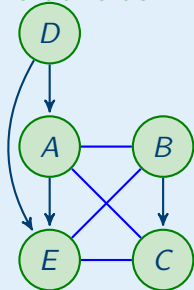
Partial order: →

Compatible as children of root: —

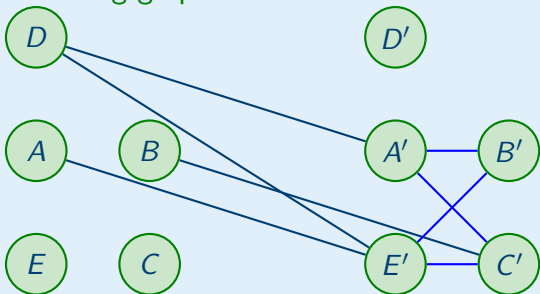


The algorithm in action.

Partial order

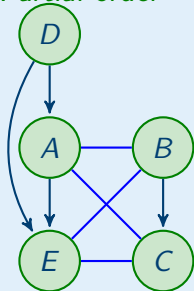


Matching graph

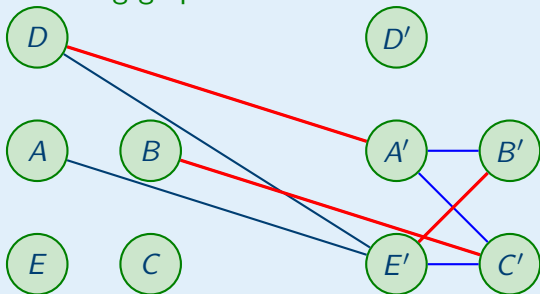


The algorithm in action.

Partial order



Matching graph

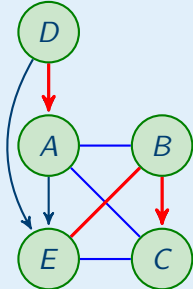


A maximal matching in the matching graph

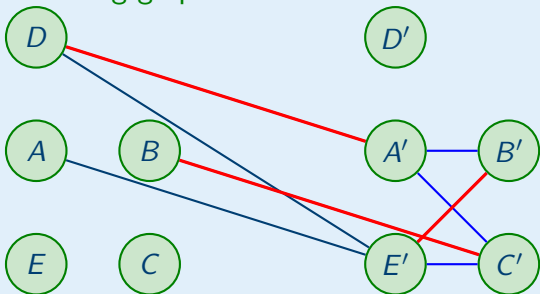


The algorithm in action.

Partial order



Matching graph



A maximal matching in the matching graph induces perfect path phylogenies.

