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

- A haplotype matrix H.

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

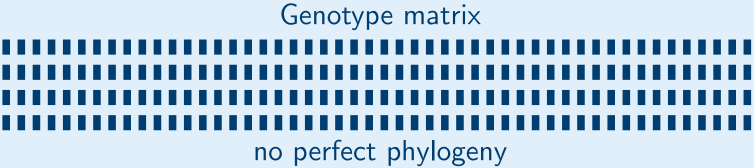
1. Data may be missing.
   - This makes the problem NP-complete . . .
   - . . . even for very restricted cases.

   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.



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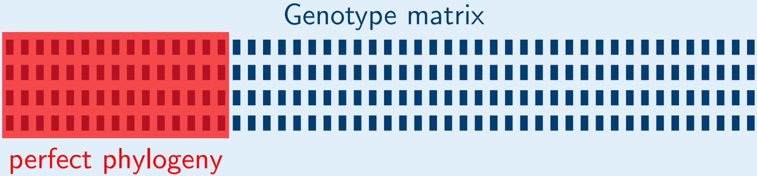

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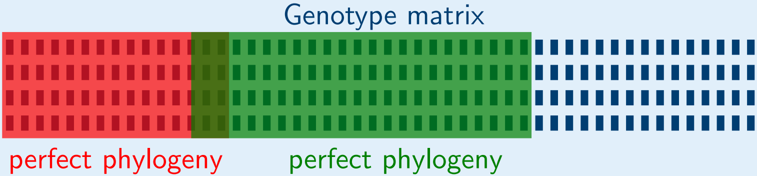

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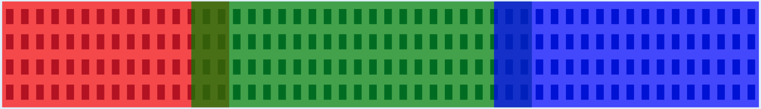
Genotype matrix

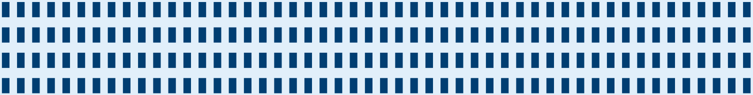


perfect phylogeny perfect phylogeny perfect phylogeny

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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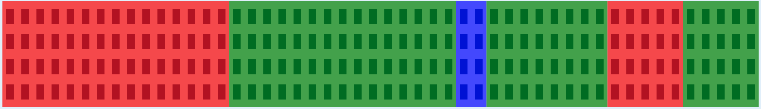

perfect phylogeny perfect phylogeny

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 $\chi_{\mathrm{PP}}(M)$?

Example

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

No perfect phylogeny is possible.

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Perfect phylogeny

Perfect phylogeny

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

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 phylogenies. □

Implications for pp-partitions of haplotype matrices.

Corollary

If $\chi_{\mathrm{PP}}(M) = 2$ *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 $\chi_{\mathrm{PP}}(M)$?

Example

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

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 $\chi_{\mathrm{PP}}(M)$?

Example

$$M: \quad \begin{array}{c|cc|c} 2 & 2 & 2 & 2 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 2 & 2 & 0 \\ 1 & 1 & 0 & 0 \end{array}$$

Perfect phylogeny

Perfect phylogeny

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

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 same perfect phylogeny. □

Implications for pp-partitions of genotype matrices.

Corollary

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

- NP-*hard,*
- *not fixed-parameter tractable, unless* $\mathrm{P} = \mathrm{NP}$,
- *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.

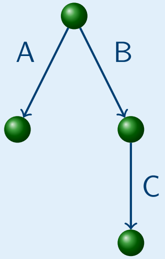
Genotype matrix

$$G: \begin{array}{ccc} A & B & C \\ \hline 2 & 2 & 2 \\ 0 & 2 & 0 \\ 2 & 0 & 0 \\ 0 & 2 & 2 \end{array}$$

Haplotype matrix

$$H: \begin{array}{ccc} A & B & C \\ \hline 1 & 0 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 1 \end{array}$$

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.

   For this, a maximal matching in a special graph needs to be computed

Summary

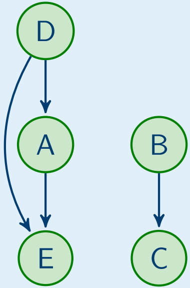
- Finding optimal pp-partitions is intractable.
- It is even intractable to find a pp-partition when just two noncontiguous blocks are known to suffice.
- For perfect path phylogenies, optimal partitions can be computed in polynomial time.

The algorithm in action.

Genotype matrix

$$G: \begin{array}{ccccc} \mathsf{A} & \mathsf{B} & \mathsf{C} & \mathsf{D} & \mathsf{E} \\ \hline 2 & 2 & 2 & 2 & 2 \\ 0 & 1 & 2 & 1 & 0 \\ 1 & 0 & 0 & 1 & 2 \\ 0 & 2 & 2 & 0 & 0 \end{array}$$

Partial order



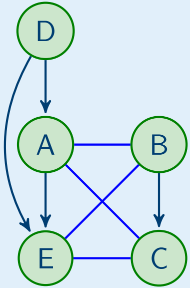
Partial order: $\longrightarrow$

The algorithm in action.

Genotype matrix

$$\begin{array}{cccccc} & A & B & C & D & E \\ \cline{2-6} & 2 & 2 & 2 & 2 & 2 \\ G: & 0 & 1 & 2 & 1 & 0 \\ & 1 & 0 & 0 & 1 & 2 \\ & 0 & 2 & 2 & 0 & 0 \end{array}$$

Partial order

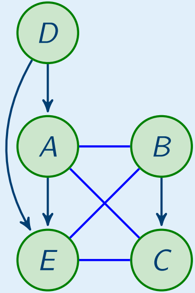


Partial order: ⟶

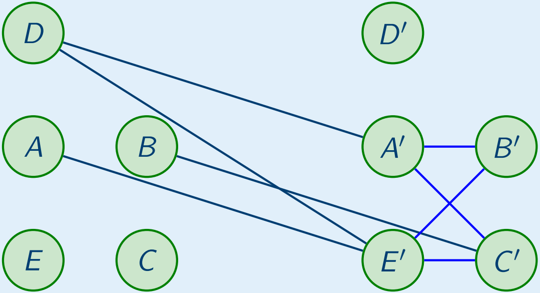
Compatible as children of root: —

The algorithm in action.

Partial order



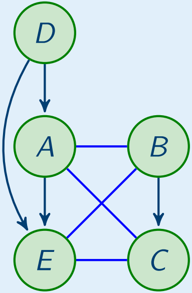
Matching graph



◂ Return

The algorithm in action.

Partial order



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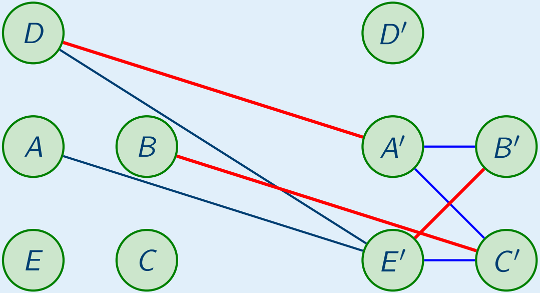

A maximal matching in the matching graph

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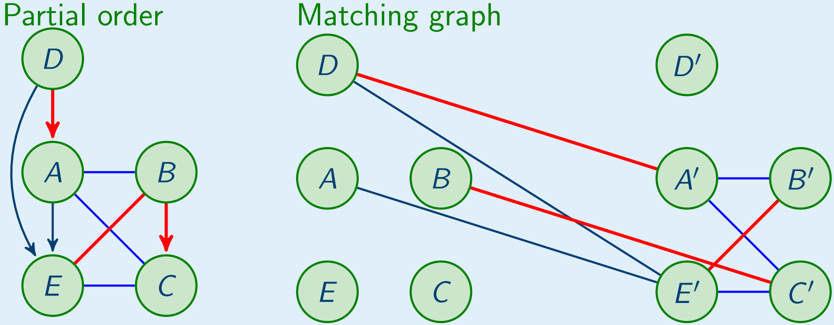
The algorithm in action.



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

◂ Return

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