

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

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Workshop on Algorithms in Bioinformatics, 2006

## Outline

### 1 Introduction

- The Model and the Problem
- The Integrated Approach

### 2 Bad News: Hardness Results

- Hardness of PP-Partitioning of Haplotype Matrices
- Hardness of PP-Partitioning of Genotype Matrices

### 3 Good News: Tractability Results

- Perfect Path Phylogenies
- Tractability of PPP-Partitioning of Genotype Matrices

The Model and the Problem

## What is haplotyping and why is it important?

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

## The Model and the Problem

# 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.

## The Model and the Problem

# 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  $H$ .
- Pairs of rows in  $H$  explain the rows of  $G$ .
- The haplotypes in  $H$  form a perfect phylogeny.

## The Model and the Problem

# 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:

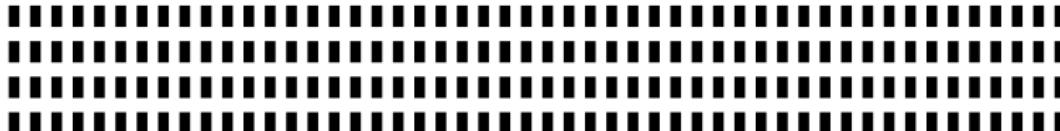
- Look for phylogenetic networks.
- Correct data.
- Find blocks where a perfect phylogeny is possible.

## The Integrated Approach

## 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



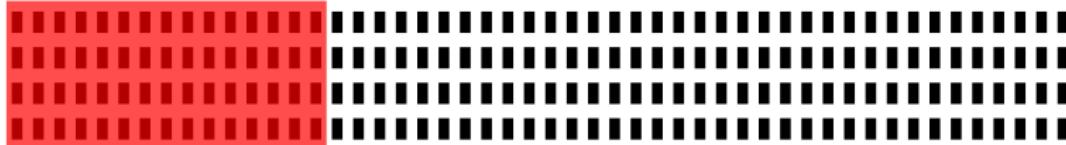
no perfect phylogeny

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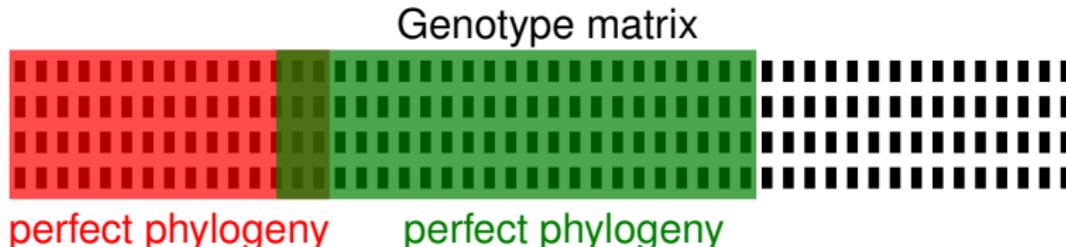


perfect phylogeny

## The Integrated Approach

## How blocks help in perfect phylogeny haplotyping.

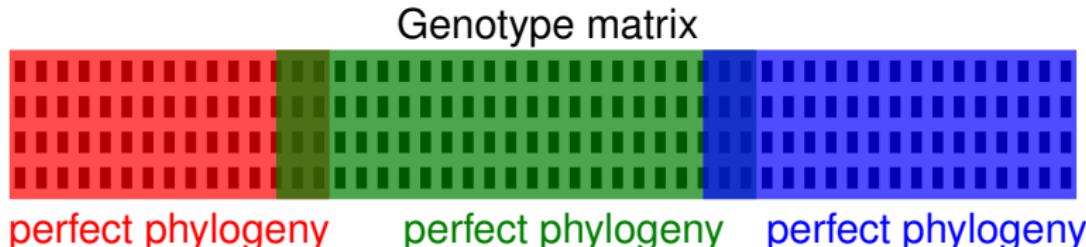
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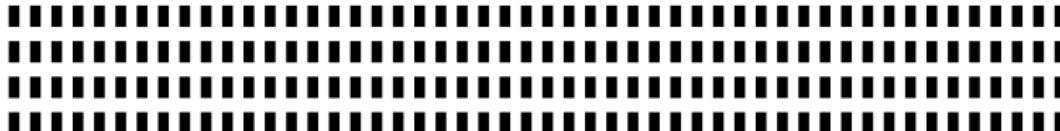


## The Integrated Approach

## 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

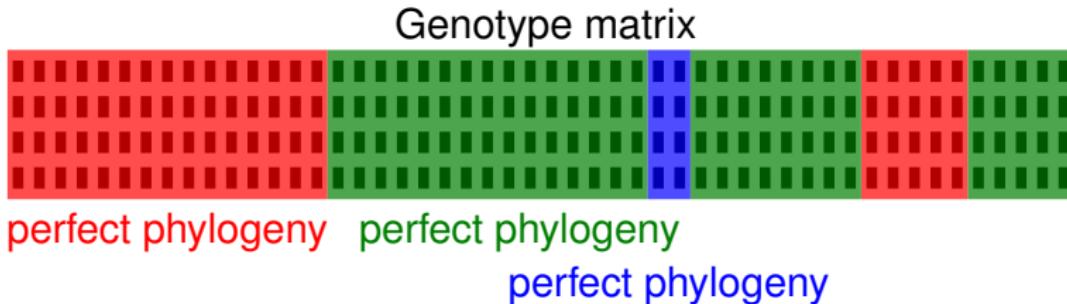


no perfect phylogeny

## The Integrated Approach

# 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.



## The Integrated Approach

## The formal computational problem.

We are interested in the computational complexity of the function  $\chi_{\text{PP}}$ :

- 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**.)

## Hardness of PP-Partitioning of Haplotype Matrices

## 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  $\chi_{\text{PP}}(M)$ ?

### 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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- The inputs  $M$  do not allow a perfect phylogeny.
- What is  $\chi_{\text{PP}}(M)$ ?

## 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

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

## Hardness of PP-Partitioning of Haplotype Matrices

# 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. □

## Hardness of PP-Partitioning of Haplotype Matrices

# Implications for pp-partitions of haplotype matrices.

## Corollary

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

## Corollary

*Computing  $\chi_{\text{PP}}$  for haplotype matrices is*

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

## Hardness of PP-Partitioning of Genotype Matrices

## 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  $\chi_{\text{PP}}(M)$ ?

### Example

$M:$	$\begin{matrix} 2 & 2 & 2 & 2 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 2 & 2 & 0 \\ 1 & 1 & 0 & 0 \end{matrix}$	No perfect phylogeny is possible.
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## Hardness of PP-Partitioning of Genotype Matrices

## 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  $\chi_{\text{PP}}(M)$ ?

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

## Hardness of PP-Partitioning of Genotype Matrices

# 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. □

## Hardness of PP-Partitioning of Genotype Matrices

# Implications for pp-partitions of genotype matrices.

## Corollary

*Even if we know  $\chi_{\text{PP}}(M) = 2$  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.

## Perfect Path Phylogenies

## 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.

Perfect Path Phylogenies

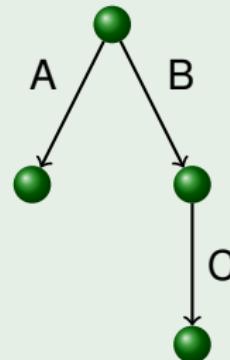
## Example of a perfect path phylogeny.

**Genotype matrix**

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

**Haplotype matrix**

	A	B	C
G:	1	0	0
H:	0	1	1
	0	0	0
	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  $\chi_{\text{PPP}}$ :

- 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.)

Tractability of PPP-Partitioning of Genotype Matrices

## 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.

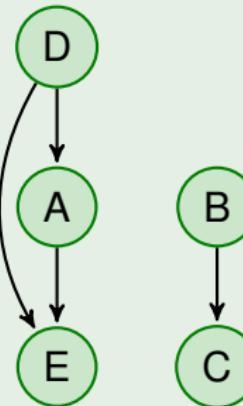
## Summary

- 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. Computation of the partial order.

**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

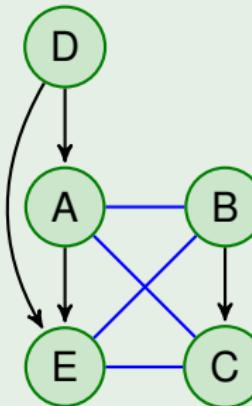
**Partial order**

Partial order: →

## The algorithm in action. Computation of the partial order.

**Genotype matrix**

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

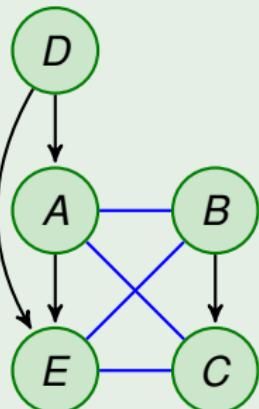
**Partial order**

Partial order: →

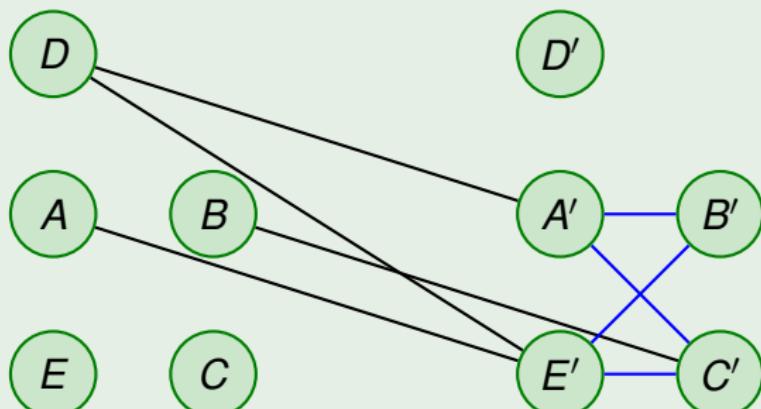
Compatible as children of root: —

## The algorithm in action. The matching in the special graph.

Partial order

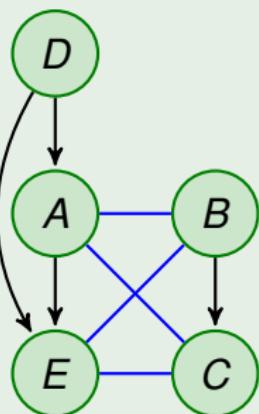


Matching graph

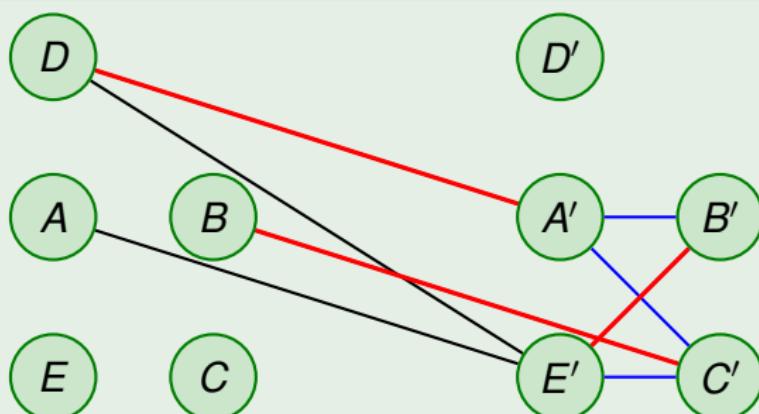


## The algorithm in action. The matching in the special graph.

Partial order



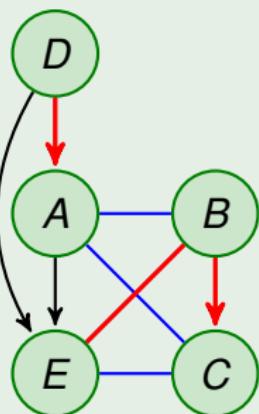
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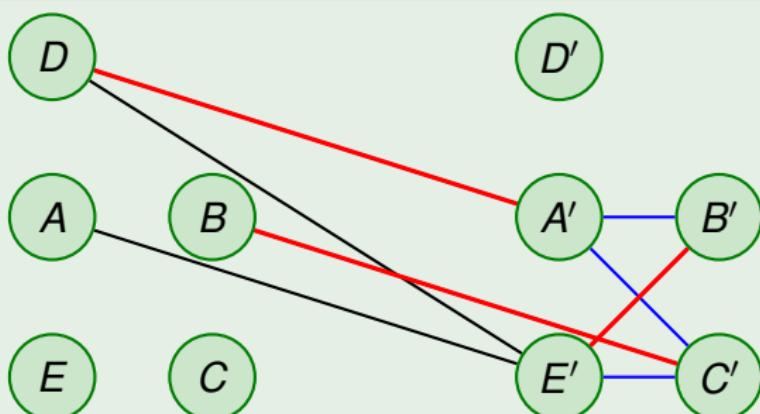
A maximal matching in the matching graph

## The algorithm in action. The matching in the special graph.

Partial order



Matching graph



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