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

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# Outline

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

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

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

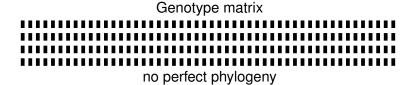
#### Solutions:

- Additional assumption like the rich data hypothesis.
- 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.

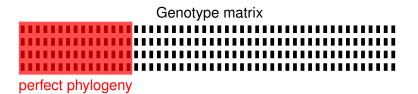
#### Solutions:

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

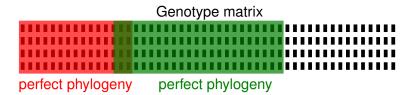
- Partition the site set into overlapping contiguous blocks.
- Compute a perfect phylogeny for each block and combine them.
- Use dynamic programming for finding the partition.



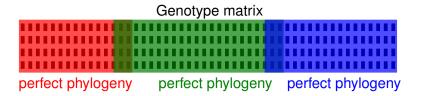
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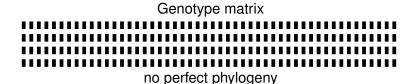


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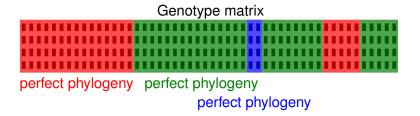
# Objective of the integrated approach.

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



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# The formal computational problem.

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

- 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:

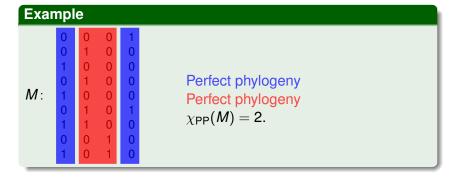
- The inputs M are already haplotype matrices.
- The inputs M do not allow a perfect phylogeny.
- What is  $\chi_{PP}(M)$ ?

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# Finding pp-partitions of haplotype matrices.

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# 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.
- Build a matrix with a column for each vertex of G.
- The submatrix  $\begin{pmatrix} 0 & 0 \\ 0 & 1 \\ 1 & 0 \end{pmatrix}$ .
- The submatrix enforces that the columns lie in different perfect phylogenies.

# 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  $\chi_{PP}$  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**

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

M: 0 0 0 1 0 0 2 2 0

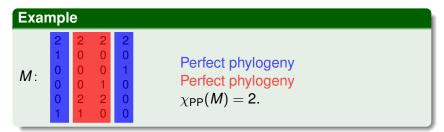
1 1 0 0

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  $\chi_{PP}(M)$ ?



# 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.

- Let G be a 3-uniform hypergraph.
- Build a matrix with a column for each vertex of G.
- The submatrix  $\begin{pmatrix} 2 & 2 & 2 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}$ .
- 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  $\chi_{PP}(M) = 2$  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**

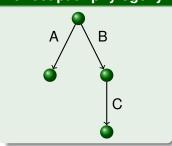
В

	2	2	2
<b>3</b> :	0	2	0
	2	Ω	Ω

# Haplotype matrix

	Α	В	С	
Н:	1	0	0	
	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.)

# Good news about ppp-partitions of genotype matrices.

#### **Theorem**

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

# **Algorithm**

- 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?
- Over 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**

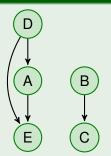
- Finding optimal pp-partitions is intractable.
- It is even intractable to find a pp-partition when just two noncontiguous blocks are known to suffice.
- For perfect path phylogenies, optimal partitions can be computed in polynomial time.

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

# Genotype matrix

	Α	В	С	D	Ε	
	2	2	2	2	2	
G:	0	1	2		0	
	1	0	0	1	2	
	0	2	2	0	0	

# **Partial order**



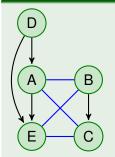
Partial order: →

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

# **Genotype matrix**

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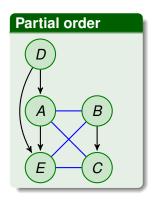
# Partial order

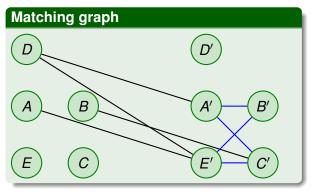


Partial order: →

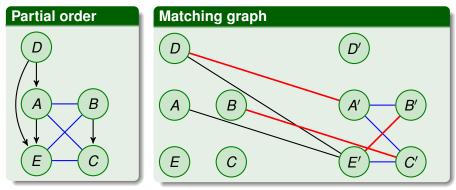
Compatible as children of root: —

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



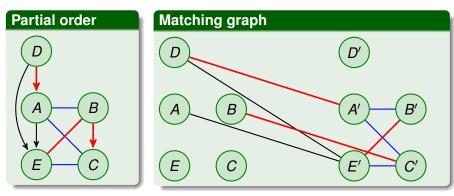


# The algorithm in action. The matching in the special graph.



A maximal matching in the matching graph

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



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

