



# Redes Generativas Adversarias Para La Segmentación De Nervios Periféricos

Director: Hernán Felipe Arias García, PhD.

Andrés Jiménez García<sup>1</sup>    Wilson A. Rodríguez Mosquera<sup>2</sup>

<sup>1</sup>Universidad del Quindío, Armenia(Q)

<sup>2</sup>Universidad del Quindío, Armenia(Q)

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- Hardness of PP-Partitioning of Genotype Matrices

Good News: Tractability Results

- Perfect Path Phylogenies

# 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  $G$ .

# 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.

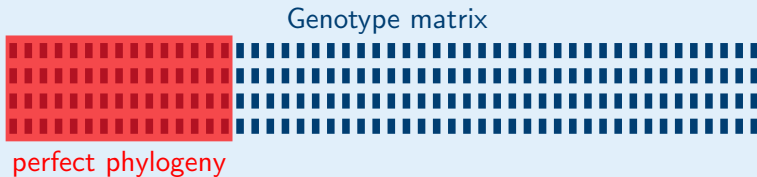
Genotype matrix



no perfect phylogeny

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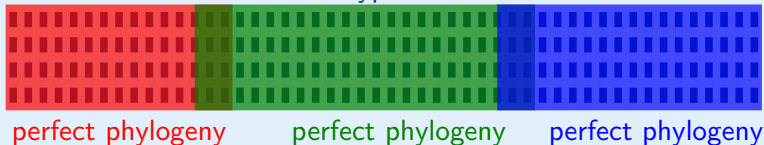
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## Objective of the integrated approach.

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

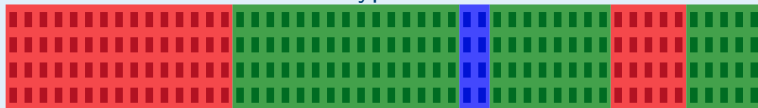


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## Objective of the integrated approach.

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Genotype matrix



perfect phylogeny

perfect phylogeny

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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  $\chi_{PP}(M)$ ?

## 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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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 phylogenies. □



# 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.

# 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

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
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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 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.

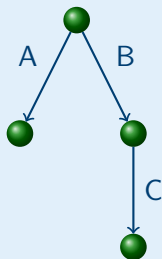
Genotype matrix

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

Haplotype matrix

	A	B	C
$H:$	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

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

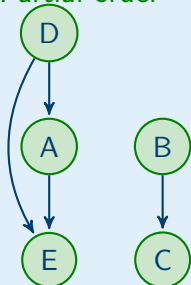
- ▶ Finding optimal pp-partitions is **intractable**.
- ▶ It is even intractable to find a pp-partition when **just two noncontiguous blocks** are known to suffice.
- ▶ For perfect **path** phylogenies, optimal partitions can be computed in polynomial time.

## The algorithm in action.

### Genotype matrix

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

### Partial order



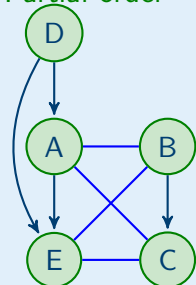
Partial order: →

## 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
	0	2	2	0	0

### Partial order

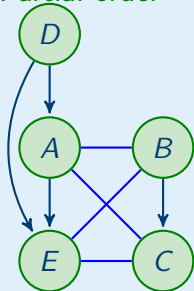


Partial order: →

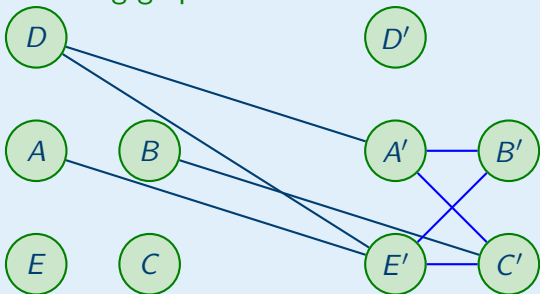
Compatible as children of root: —

## The algorithm in action.

Partial order

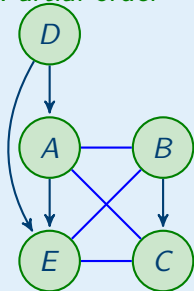


Matching graph

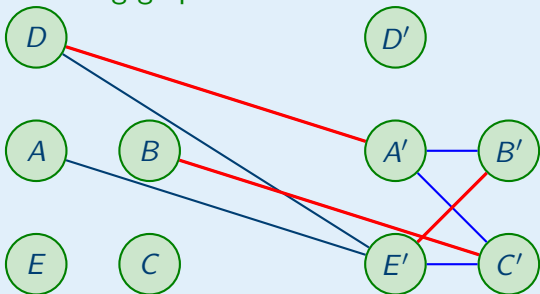


## The algorithm in action.

Partial order



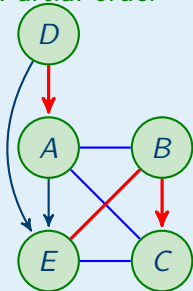
Matching graph



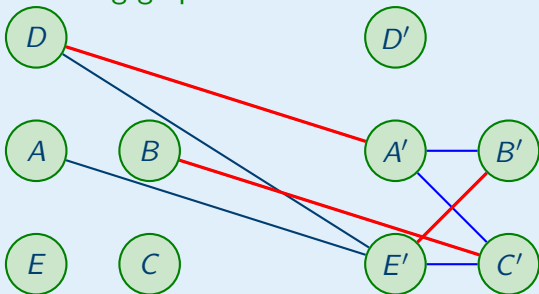
A maximal matching in the matching graph

## The algorithm in action.

Partial order



Matching graph



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

◀ Return