C++ Programming

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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 . . .

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

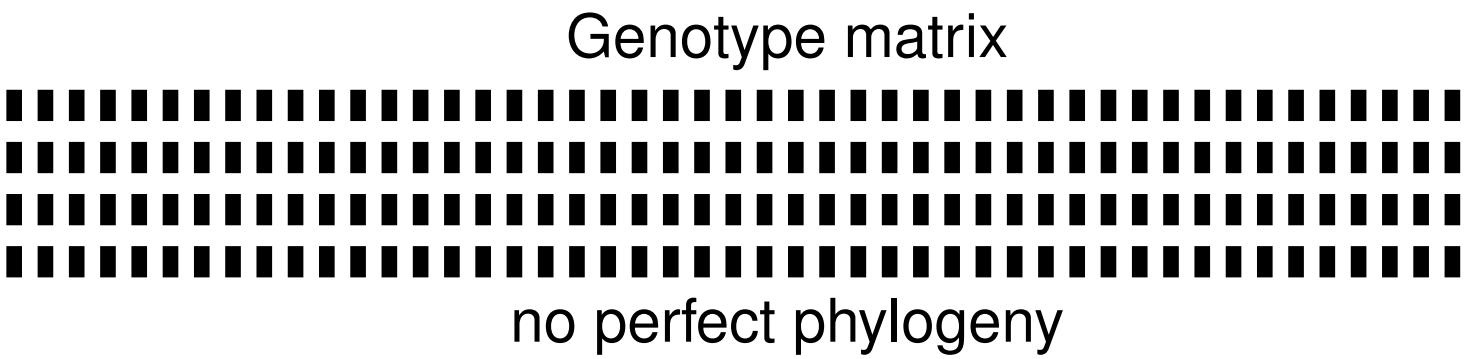
   Solutions:
   - Additional assumption like the rich data hypothesis.

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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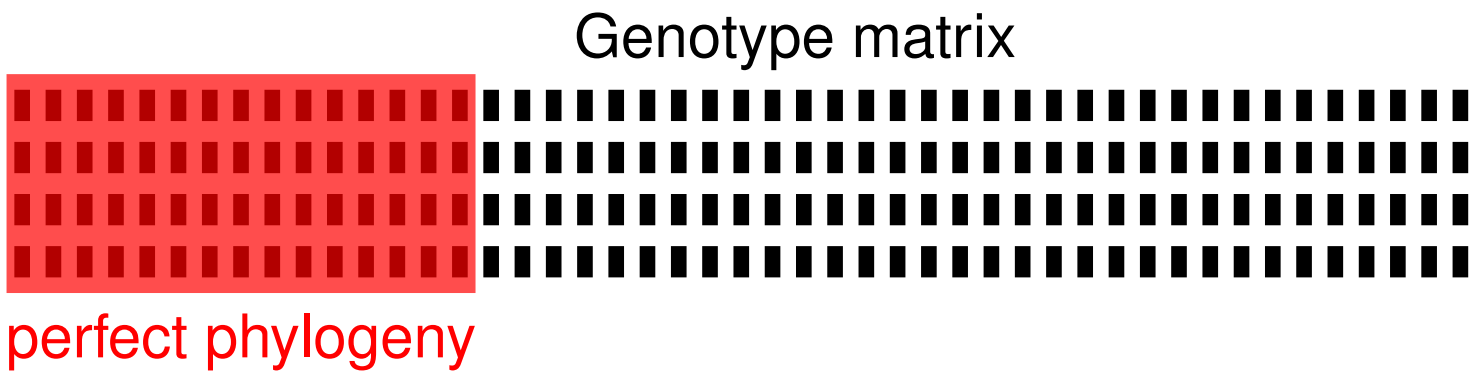

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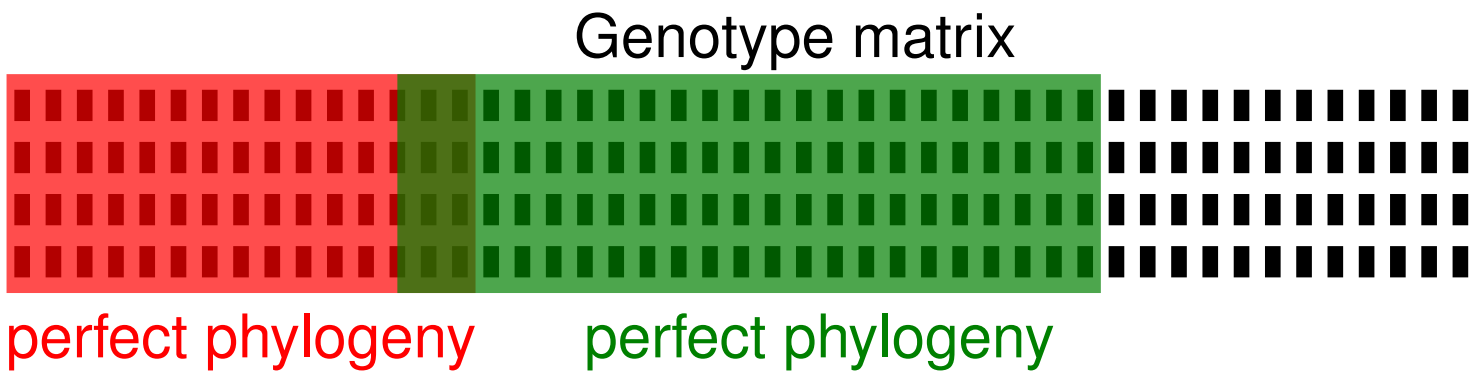

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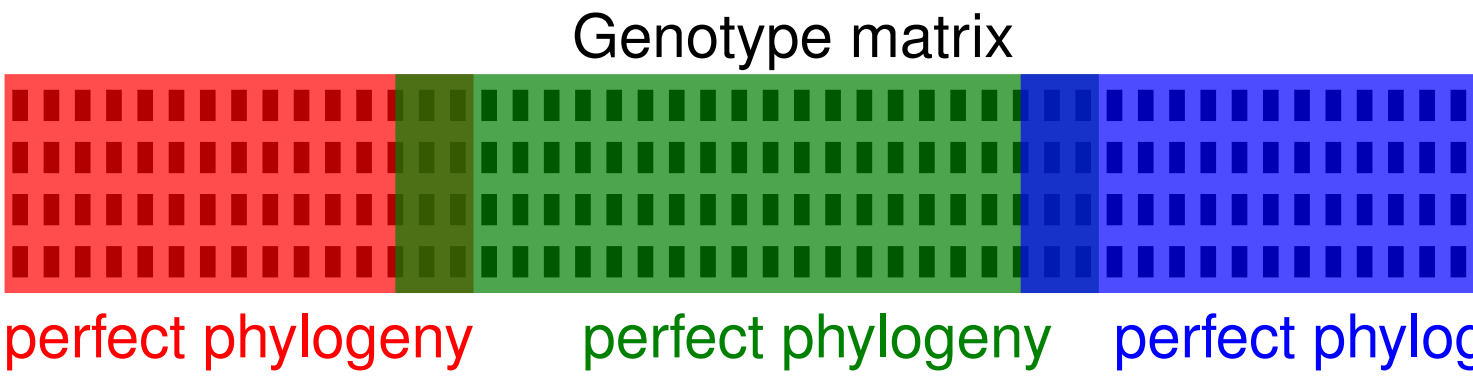
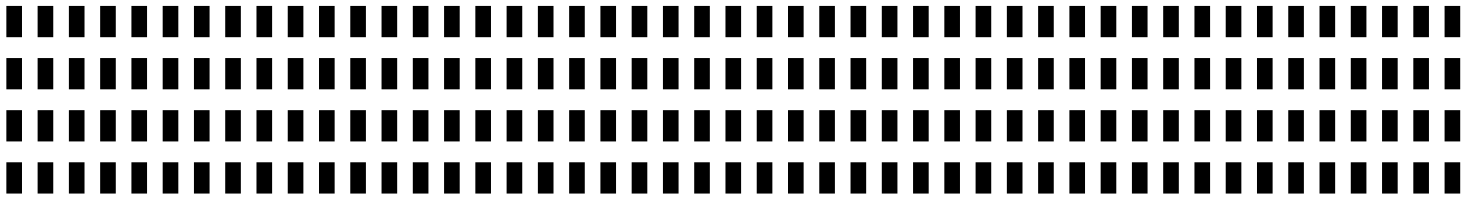


Objective of the integrated approach.

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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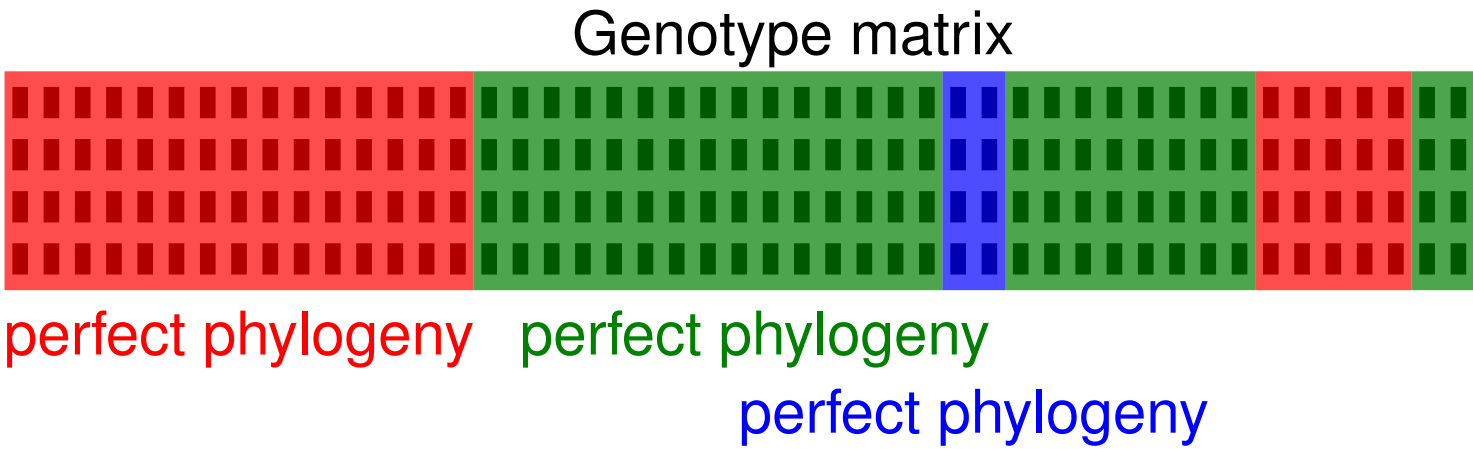

The formal computational problem.

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:

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	0	0
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1	1	0
0	0	1
1	0	0

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 $\chi_{\mathsf{PP}}(M) = 2$ 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* $\mathsf{P} = \mathsf{NP}$*,*
- *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:

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

Example

M:

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

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

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:

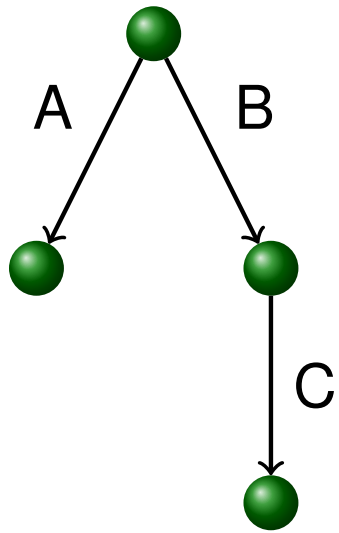
A	B	C
2	2	2
0	2	0
2	0	0
0	2	2

Haplotype matrix

H:

A	B	C
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



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- It gets genotype matrices as input.
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(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.

▸ The algorithm in action

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.

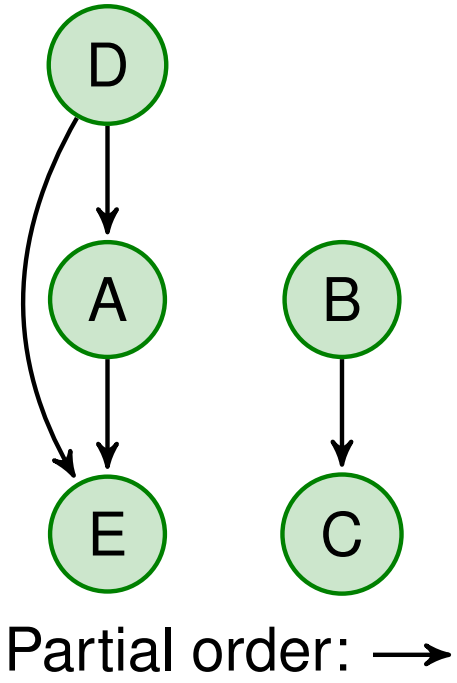
Computation of the partial order.

Genotype matrix

G:

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

Partial order



The algorithm in action.

Computation of the partial order.

Genotype matrix

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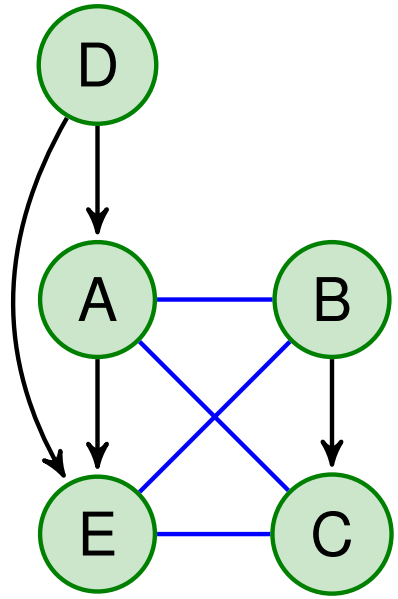
Partial order



Partial order: $\longrightarrow$

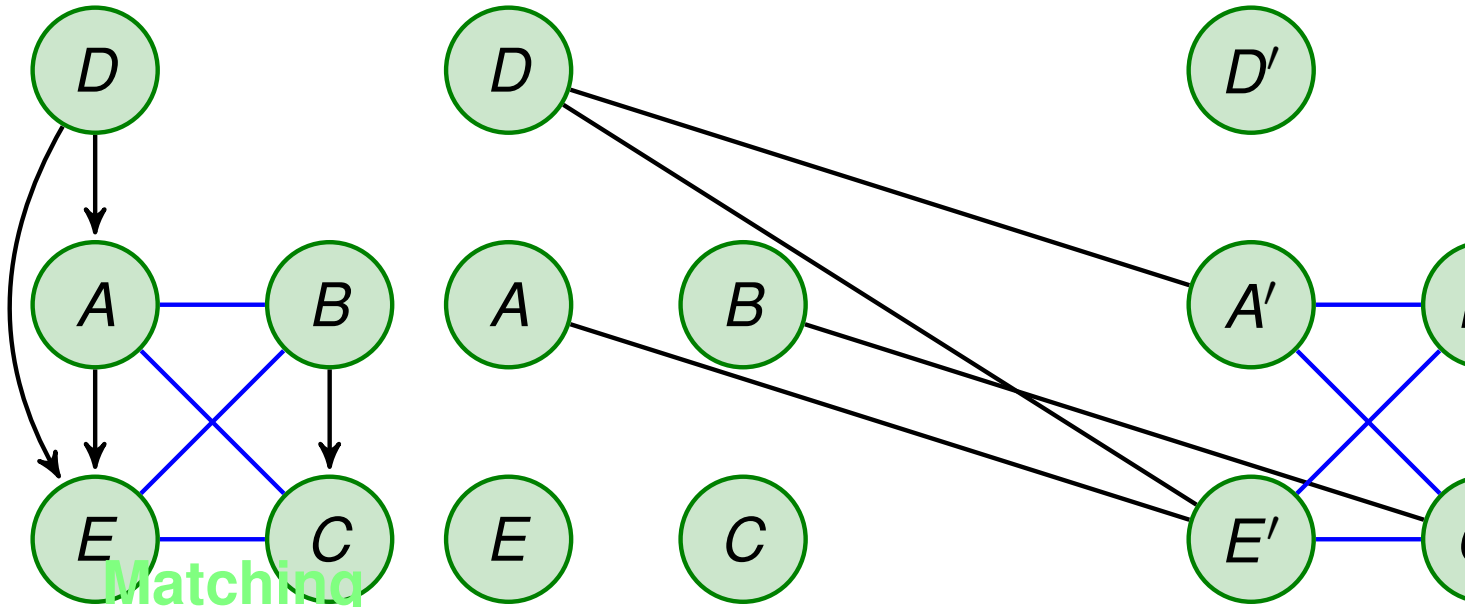
Compatible as children of root:

—

The algorithm in action.

The matching in the special graph.

Partial order

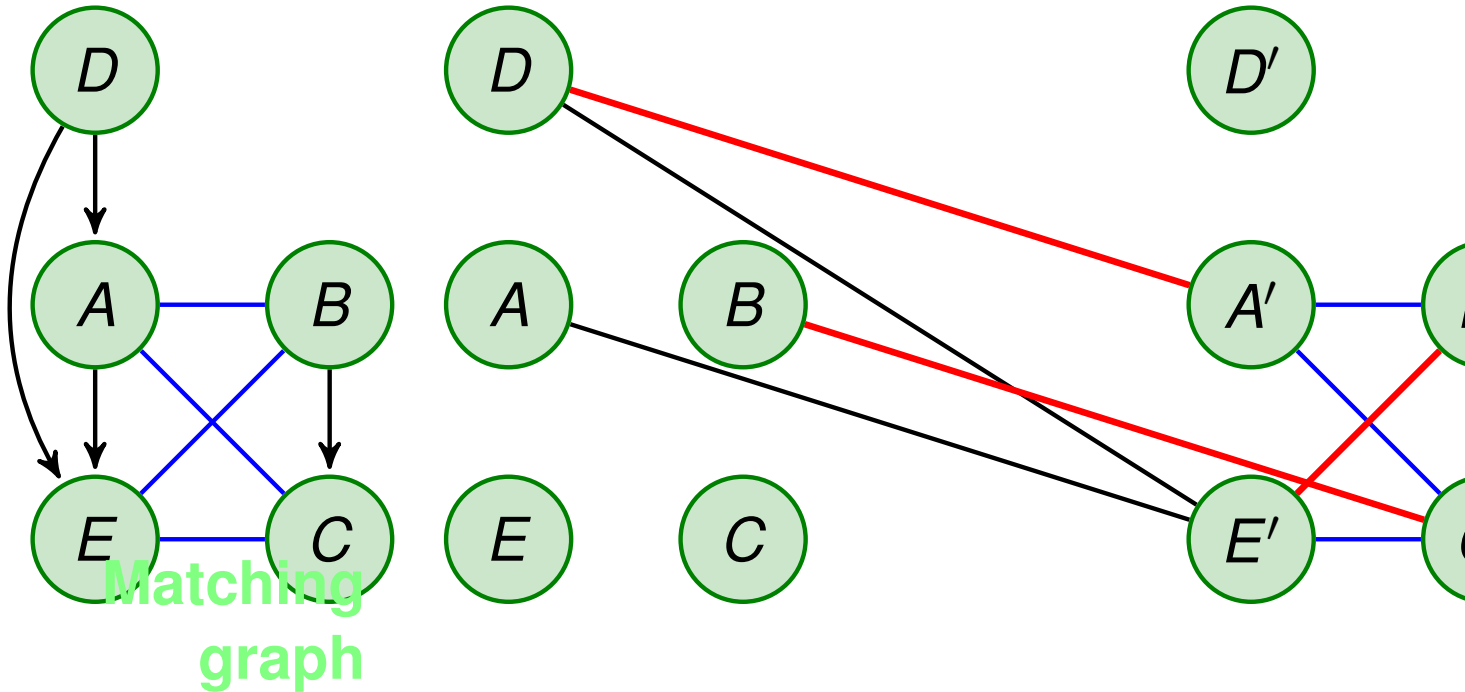


Return

The algorithm in action.

The matching in the special graph.

Partial order

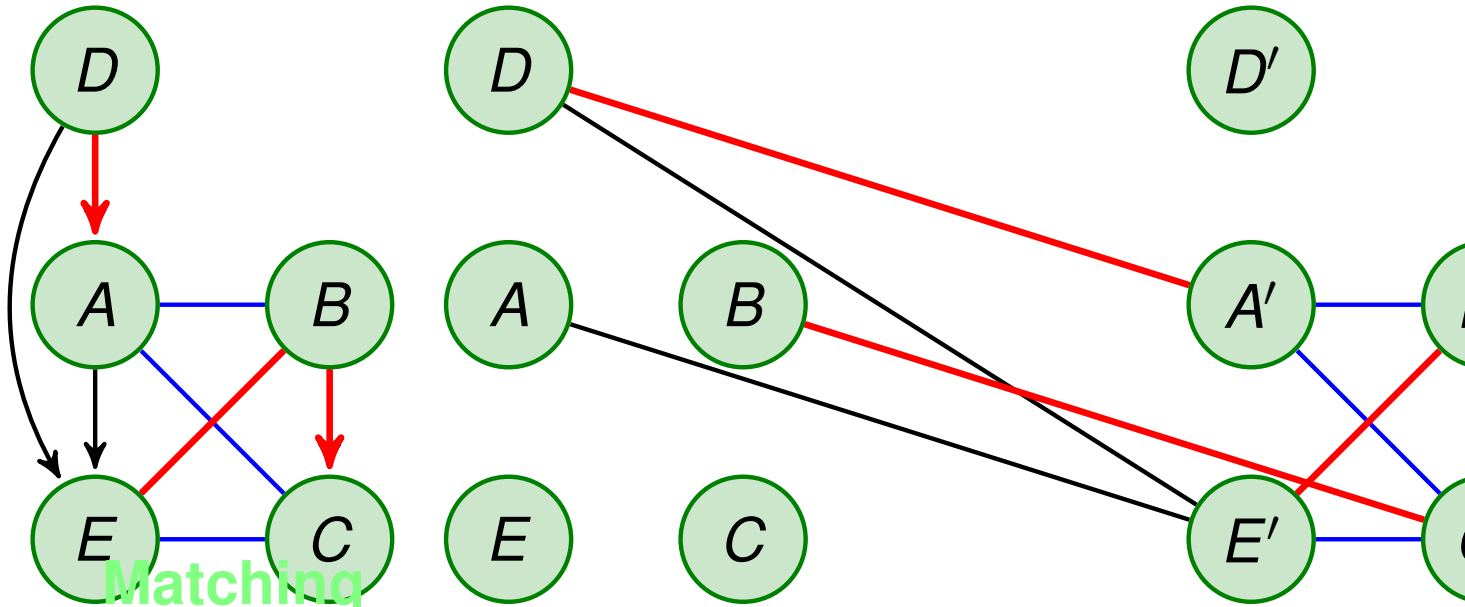


A maximal matching in the matching graph

Return

The algorithm in action.

The matching in the special graph.



Matching graph

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

Partial order

Return