Finding Common Motifs in DNA Sequences

A survey

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Outline

- Some biology
- The problem
- An early graph-based approach: WINNOWER
- Avoiding the explicit search for cliques: PRUNER
- An approach based on suffix-trees: SMILE
- Merging WINNOWER and SMILE: MITRA
- Conclusions

Some Biology

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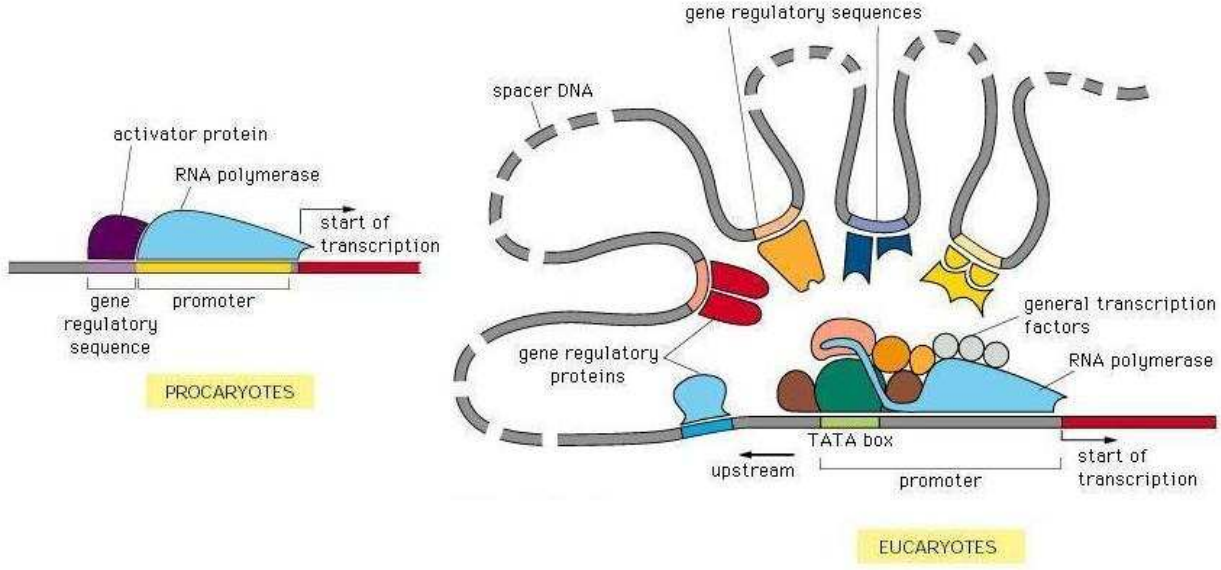
  - Directed by proteins which specifically bind to motifs present in regulatory regions



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$l = 5 \qquad e = 1 \qquad q = t = 3$

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should find CATAA | CATAT | CATAG | CATAC

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Note that CATAT never occurs exactly

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- Sometimes it is useful to search for *composite motifs*
  - combined simple motifs co-occurring in non-overlapping positions in various input sequences at a certain distance from one another
    - Easier to find, especially if one of the components is poorly conserved across the input sequences
    - The added distance restriction avoids the extraction of too many motifs

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- Finally,

$$N = \sum_{i=1}^{t} n_i$$

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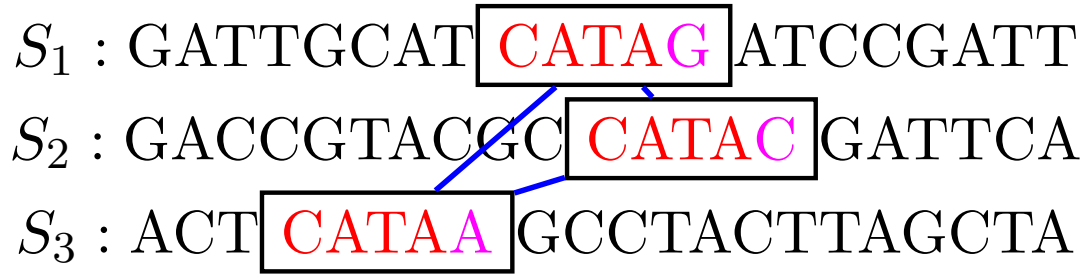
- Example:

  $\mathrm{ATAT} \qquad \mathrm{GTGT} \qquad \mathrm{TTTT}$

  are at a distance no larger than 2 from one another, but there is no pattern at a distance of 1 from all of them

WINNOWER

- Example of a 3-clique where all edges of G participate on the clique



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- Finding a maximal k-clique in a graph for $k > 2$ is NP-Complete
- WINNOWER adopts a winnowing strategy to try to remove all edges which cannot be part of a q-clique in hope that after the iterative process only q-cliques remain

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$\rightarrow$ The algorithm will remove all spurious edges for increasing values of k

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- For $k = 2$
  - A vertex u is a neighbour of an edge (v, w) if $\{v, w, u\}$ is a triangle in G
  - We need to remove every edge which does not have at least $q - 2$ neighbours in different partitions

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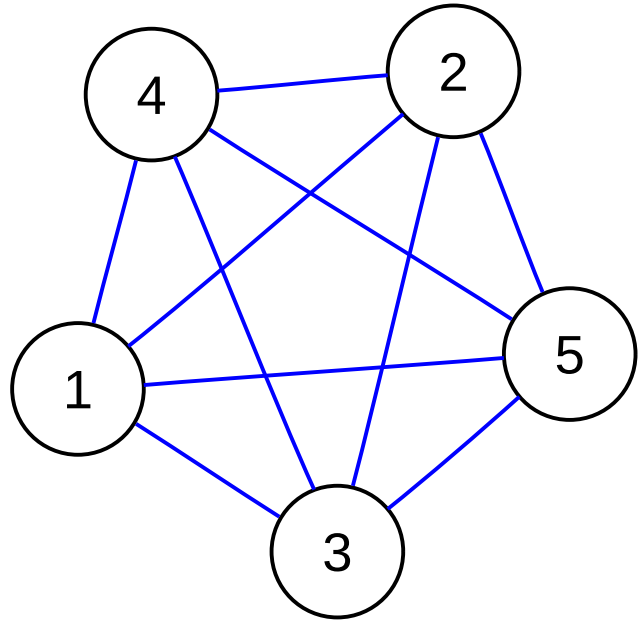
  - Thus, every edge on a q-clique belongs to at least $\binom{q-2}{k-2}$ extendable clique of size k
  - WINNOWER works up to $k = 3$, in which case, all edges not belonging to at least $q - 2$ extendable cliques are deemed inconsistent and removed

WINNOWER



A maximal 5-clique. All edges must participate in 3 different triangles.

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- It does not consider composite motifs directly
- Assumes that a motif will not repeat in the same sequence

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- Treats edges differently according to the degree of similarity between its connecting vertices
- The price to pay is incompleteness

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- Uses the notion of set of *consistent patterns* of two l-mers m_1 and m_2, denoted $\rho(m_1, m_2)$

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- Note that, regardless of the value of e, if $\delta(m_1, m_2) > 2e$ then $\rho(m_1, m_2) = \emptyset$

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In particular,

- For any m_1,$m_2 \in \Sigma^l$ such that $e < \delta(m_1, m_2) \leq 2e$ we have $|\rho(m_1, m_2)| \in O(l^{\frac{e}{2}} |\Sigma|^{\frac{e}{2}})$ and its size is maximal for $\delta(m_1, m_2) = e + 1$

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- Whereas, if $\delta(m_1, m_2) \leq e$, then $|\rho(m_1, m_2)| \in O(l^e|\Sigma|^e)$

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- In many cases the algorithm can report or discard a pattern without looking into edges in E_2

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- PRUNER starts by building a graph G identical to the one built by WINNOWER
- It proceeds to delete all vertices m such that $\gamma(m) < q - 1$, just like WINNOWER for $k = 1$

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- $\eta(i)$ is scanned and for each pattern p a partition count $c(p)$ is computed

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- If $q - 1 \leq c(p) + R < q - 1$ then we have to compare p with every other vertex which is still connected to m_i to check whether $\delta(p, m_j) \leq e$

  After computing the new partition count

  - If it is still less than $q - 1$, p is discarded
  - Otherwise, p is reported

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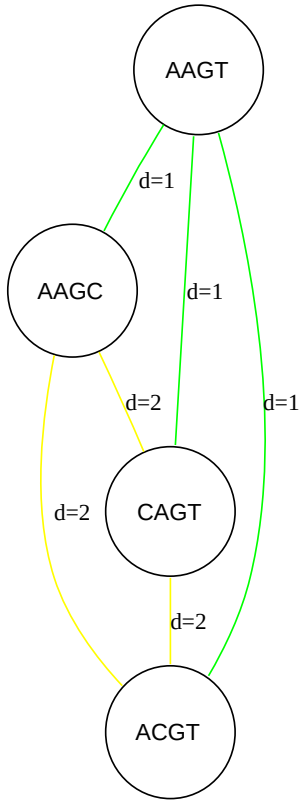
- The remaining vertices, if any, are guaranteed to have a partition degree larger than q
- The associated l-mers are, thus, valid patterns and are reported
- However, consistent patterns for each pair of vertices are not computed at this stage of the algorithm which may cause some valid patterns not to be reported

PRUNER

Consider the following graph, where each vertex corresponds to a different partition
Edges in E_1 are in yellow and edges in E_2 are in green



$q = 4$

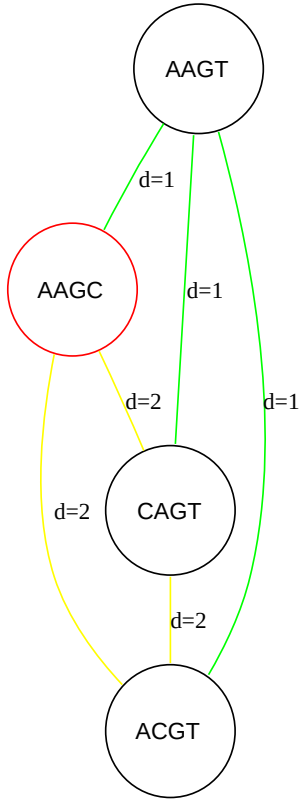
$e = 1$

For every edge $m_i \in E$

$\gamma(m_i) \geq q - 1 = 3$

No vertex is removed at this stage

PRUNER



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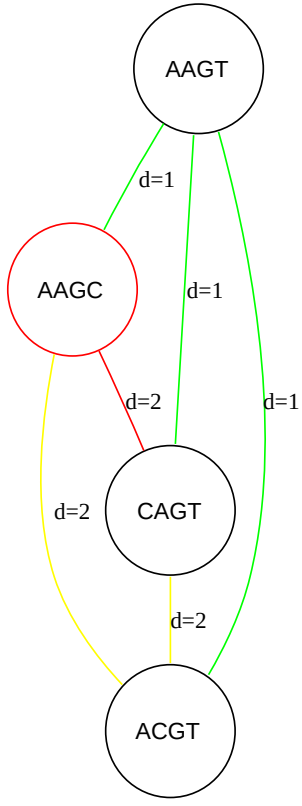
Consider vertex AAGC

PRUNER



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$$\rho(\mathrm{AAGC}, \mathrm{CAGT}) = \{\mathrm{CAGC}, \mathrm{AAGT}\}$$

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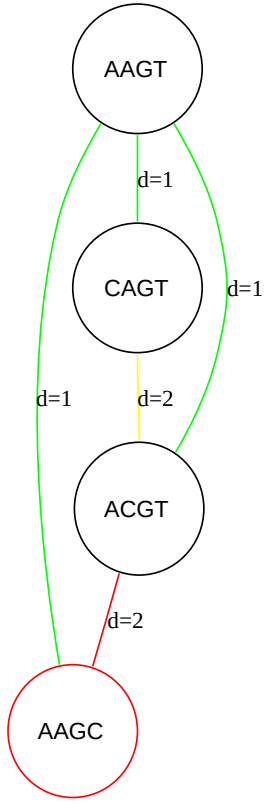

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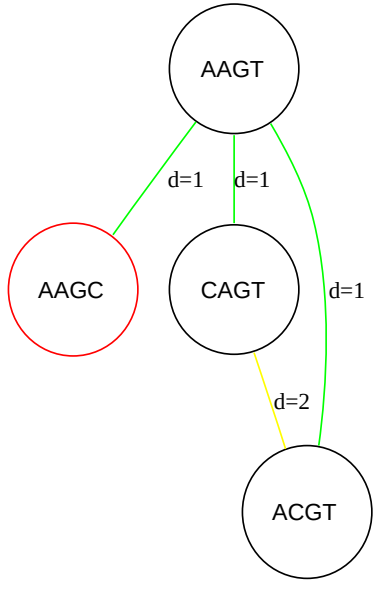
$$\eta(\mathrm{AAGC}) = \{\mathrm{CAGC}, \mathrm{AAGT}, \mathrm{AAGT}, \mathrm{ACGC}\}$$

PRUNER



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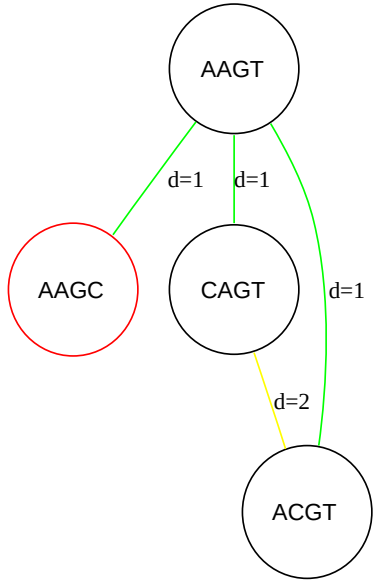
Finished processing vertex AAGC

Sorting and scanning $\eta(\mathrm{AAGC})$

$\eta(\mathrm{AAGC}) = \{\mathrm{CAGC}, \mathrm{AAGT}, \mathrm{AAGT}, \mathrm{ACGC}\}$

PRUNER



$q = 4$

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Finished processing vertex AAGC

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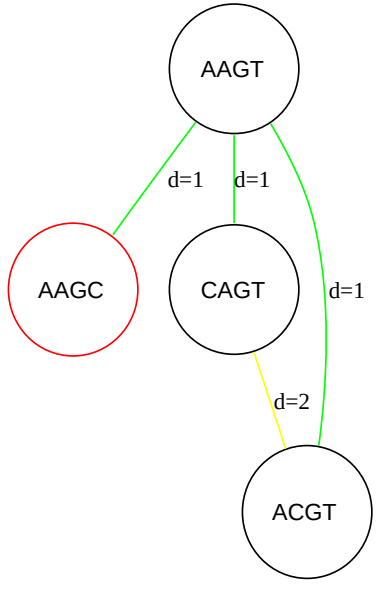

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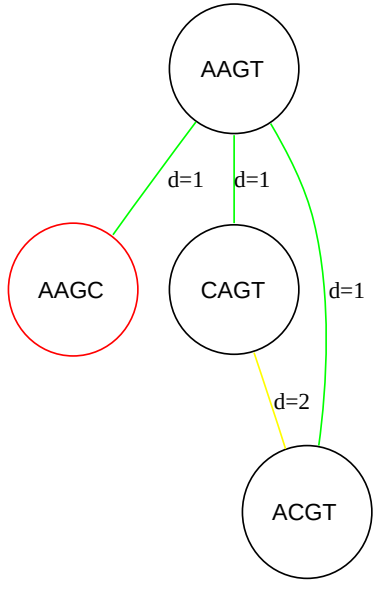

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$\eta(\mathrm{AAGC}) = \{\overline{\mathrm{ACGC}}^{\sharp 1}, \overline{\mathrm{AAGT}, \mathrm{AAGT}}^{\sharp 2}, \overline{\mathrm{CAGC}}^{\sharp 1}\}$

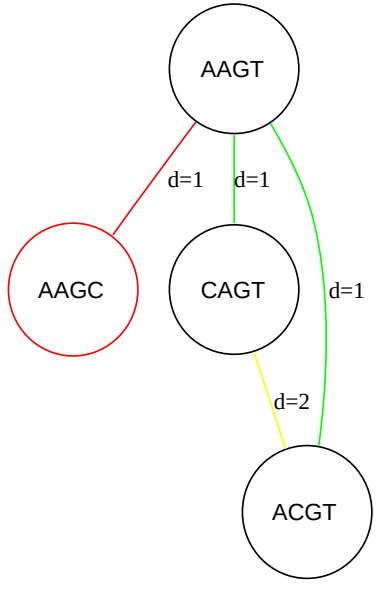
$c(\mathrm{ACGC}) + R < q - 1 \Leftrightarrow 1 + 1 < 3$ DISCARD

$c(\mathrm{CAGC}) + R < q - 1 \Leftrightarrow 1 + 1 < 3$ DISCARD

$q - 1 \leq c(\mathrm{AAGT}) + R < q - 1 + R \Leftrightarrow$

$\Leftrightarrow 3 \leq 3 < 4$ CHECK E_2 edges

PRUNER



$q = 4$

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$\delta(\mathrm{AAGT}, \mathrm{AAGT}) = 0 < e$

The new partition count is increased

$c(\mathrm{AAGT}) = 3 \geq q - 1$ REPORT

PRUNER would now process the remaining vertices . . .

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- To facilitate the discussion we will think of $\mathcal{T}$ as if it were a trie

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- The traversal stops if there are no more valid paths or if the paths do not represent occurrences in at least $q \leq t$ sequences, in which case, the sub-trie below the current node in $\mathcal{M}$ is pruned

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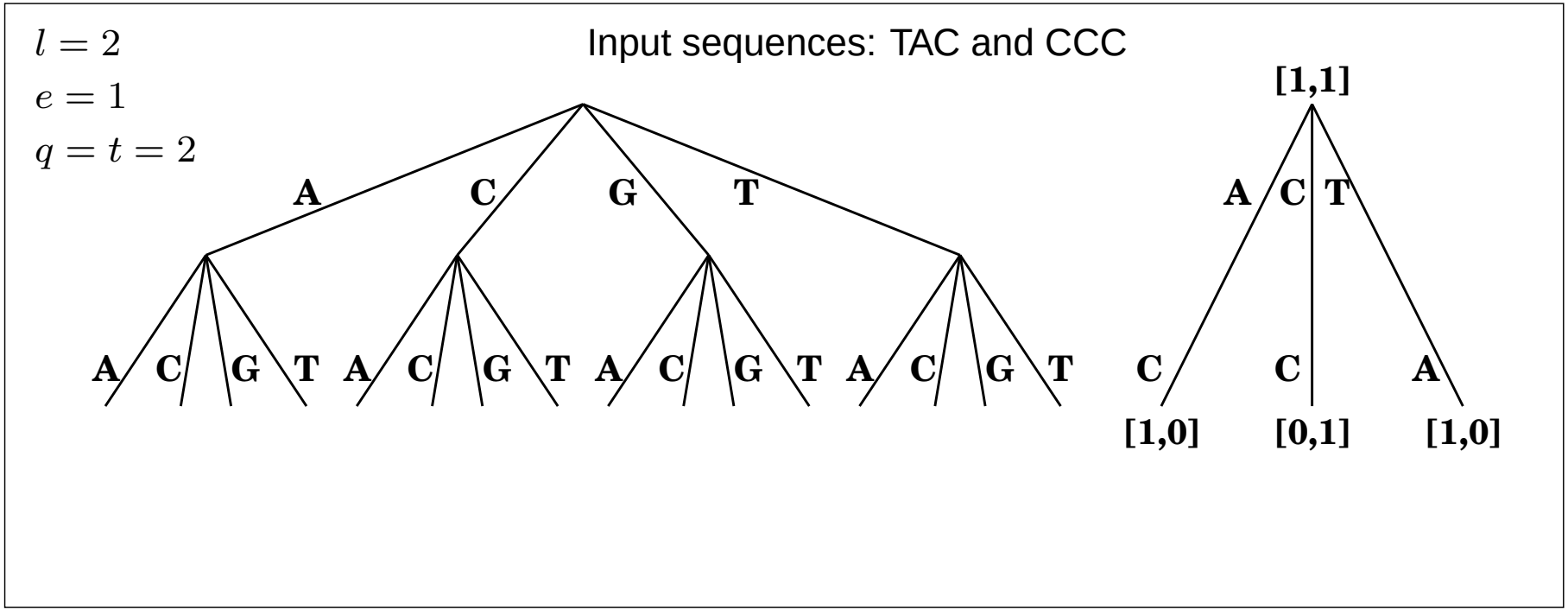
- If we are able to reach a node v in $\mathcal{M}$ at depth l and still have valid paths in $\mathcal{T}$ we report the path-label of v as a valid pattern
- Note that the algorithm can easily not only extract motifs of length l but also motifs within any range of lengths $l_{\min}, \ldots, l_{\max}$
  - Continue the traversal of $\mathcal{M}$ as far as depth $l_{\max}$
  - Report any pattern with at least $l_{\min}$ characters that respects the extraction requirements

SMILE

Extraction of Simple Motifs



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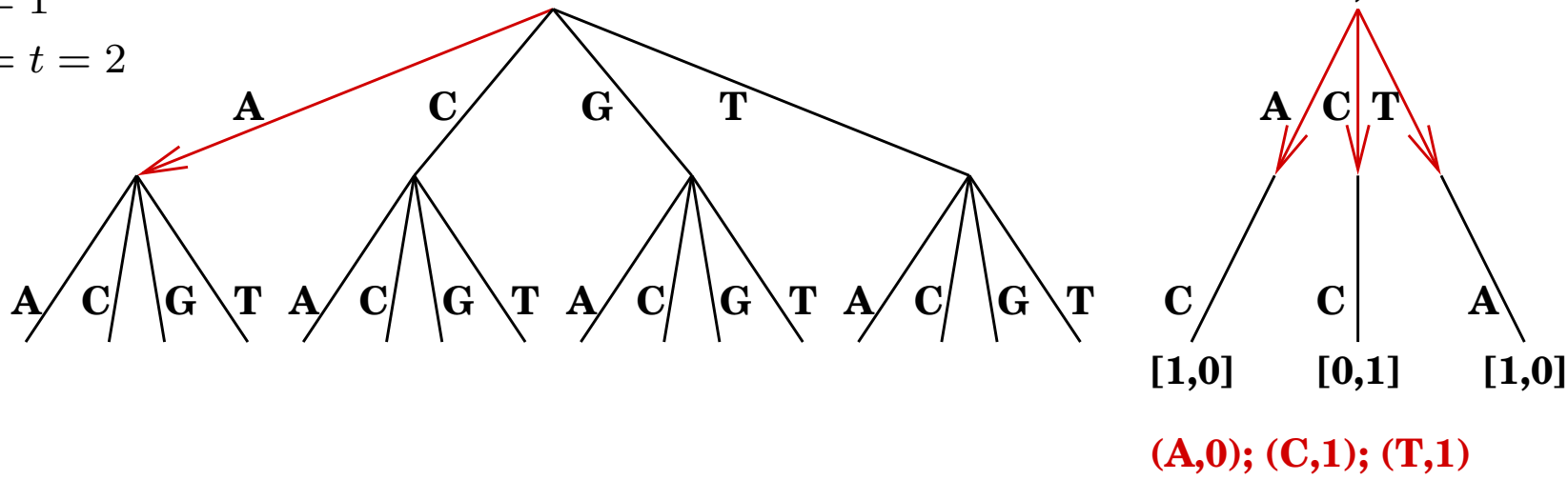

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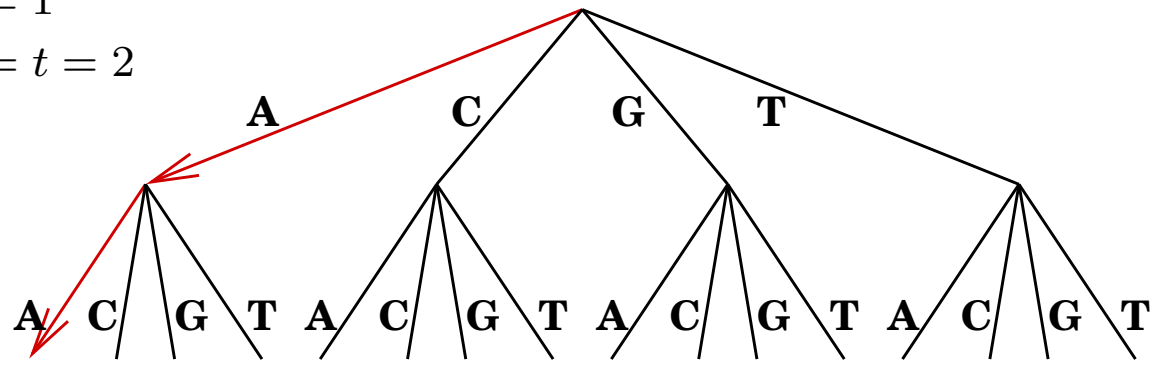

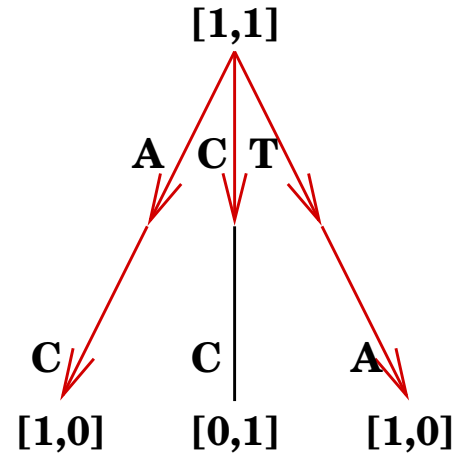

(A,0); (C,1); (T,1)

(AC,1); (TA,1)

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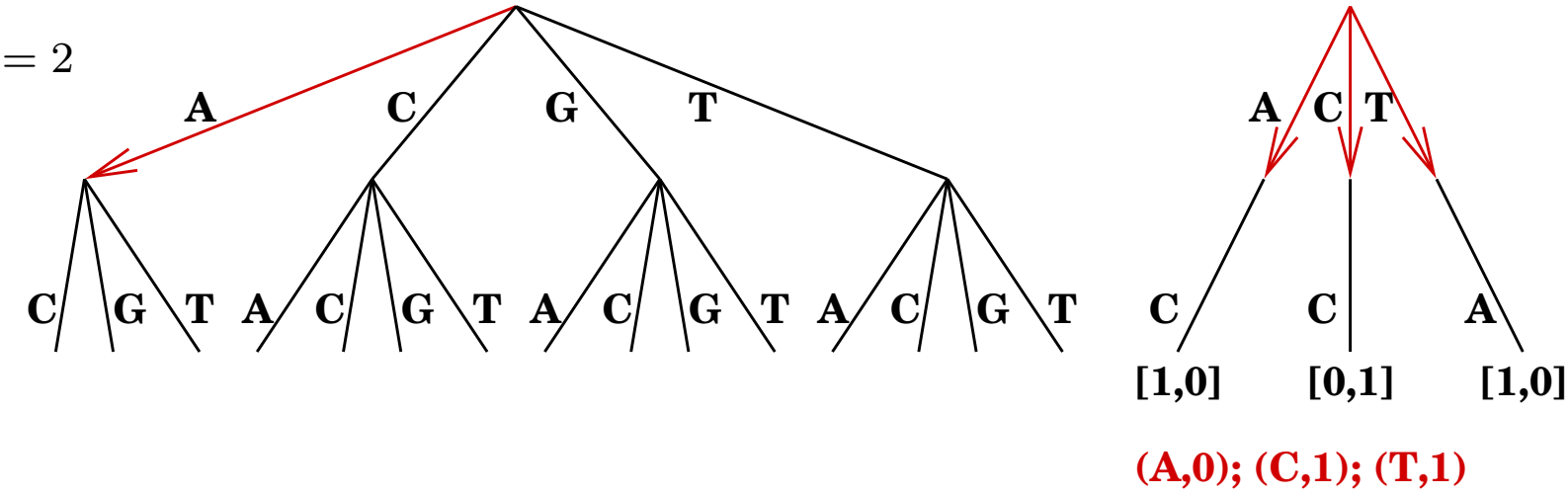

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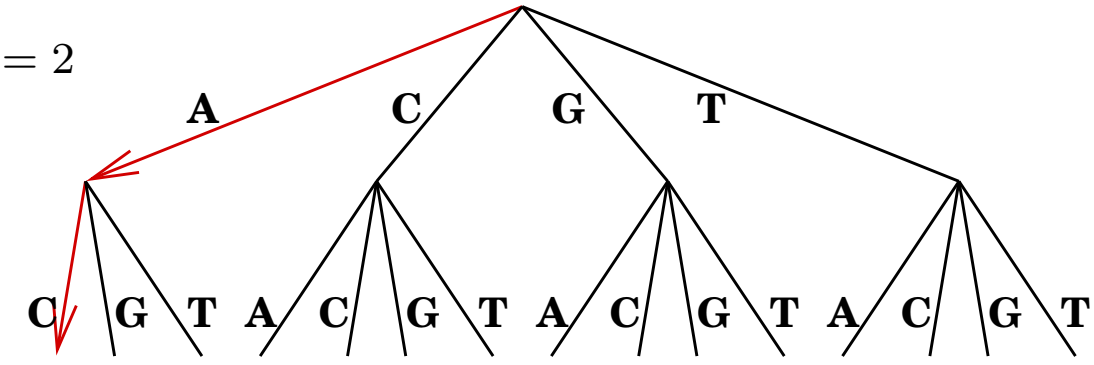

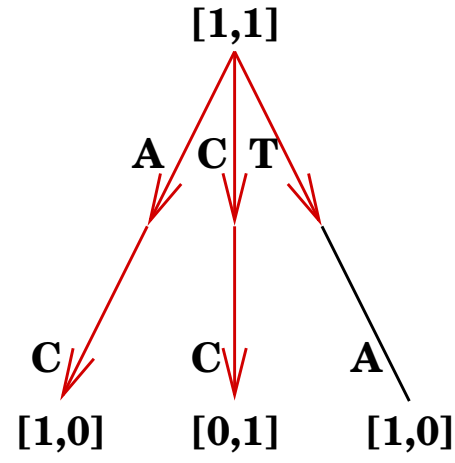

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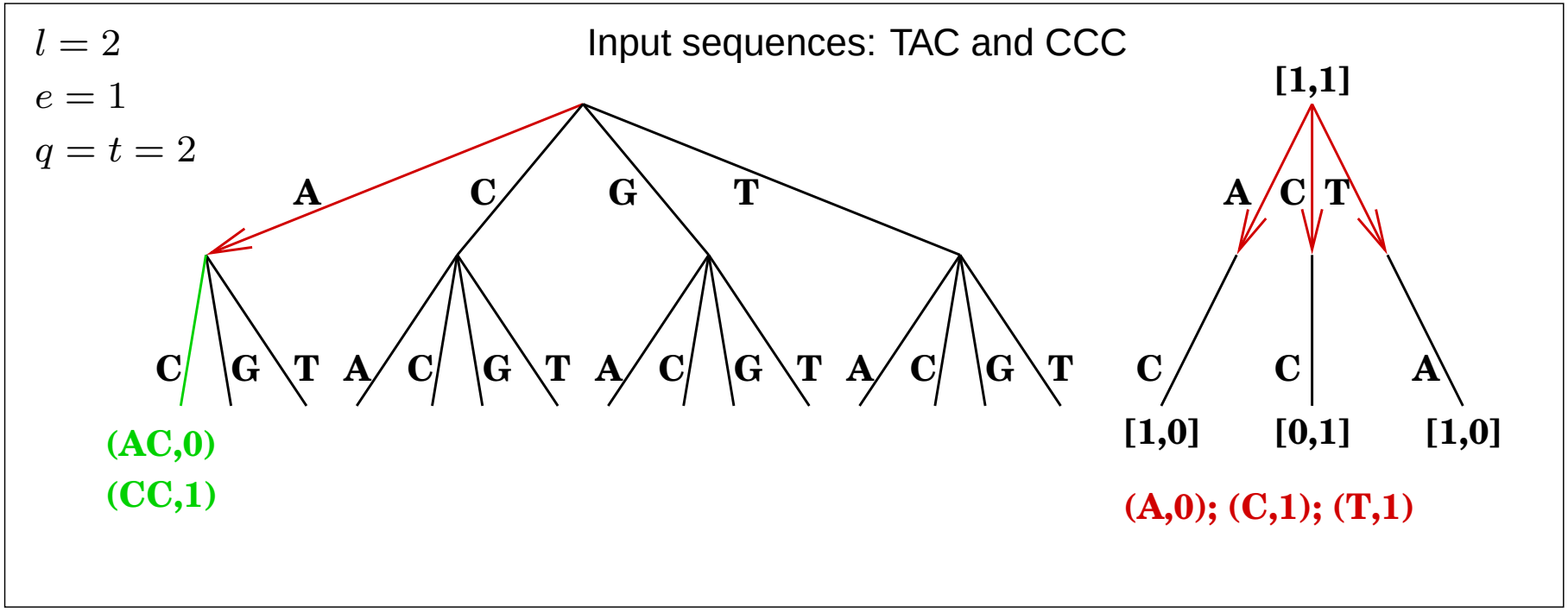

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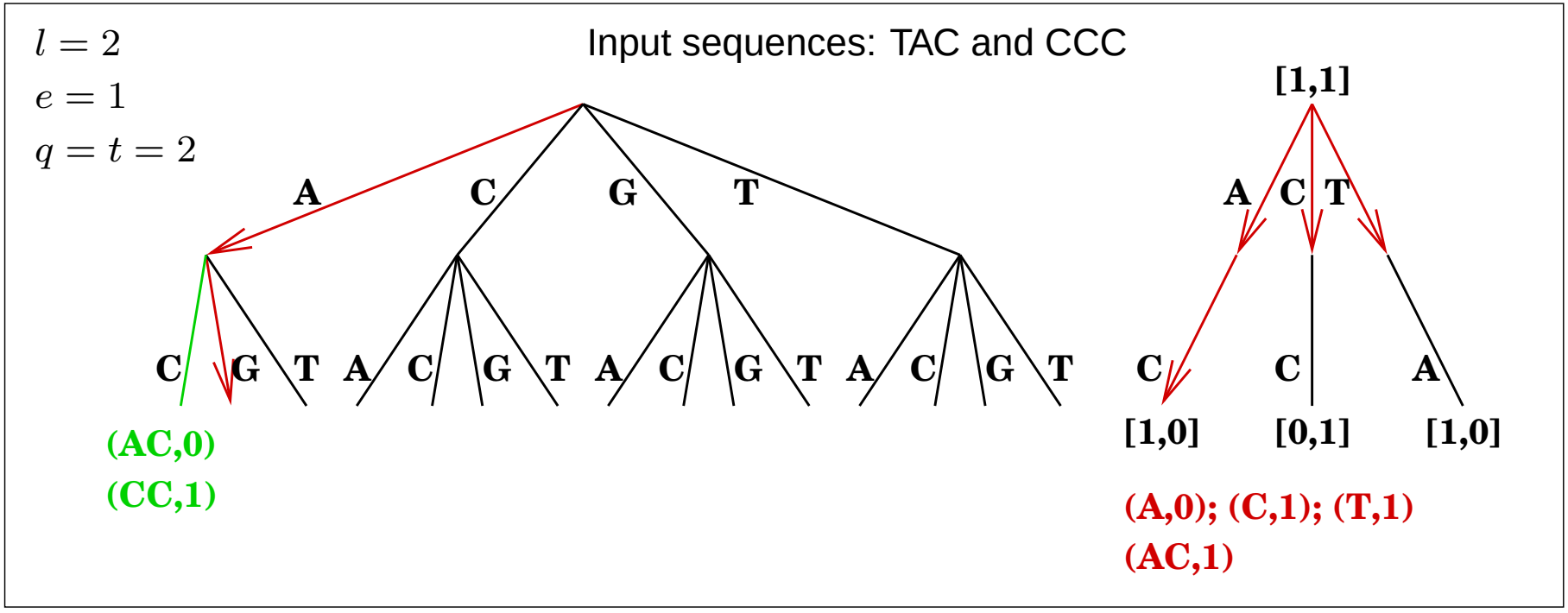

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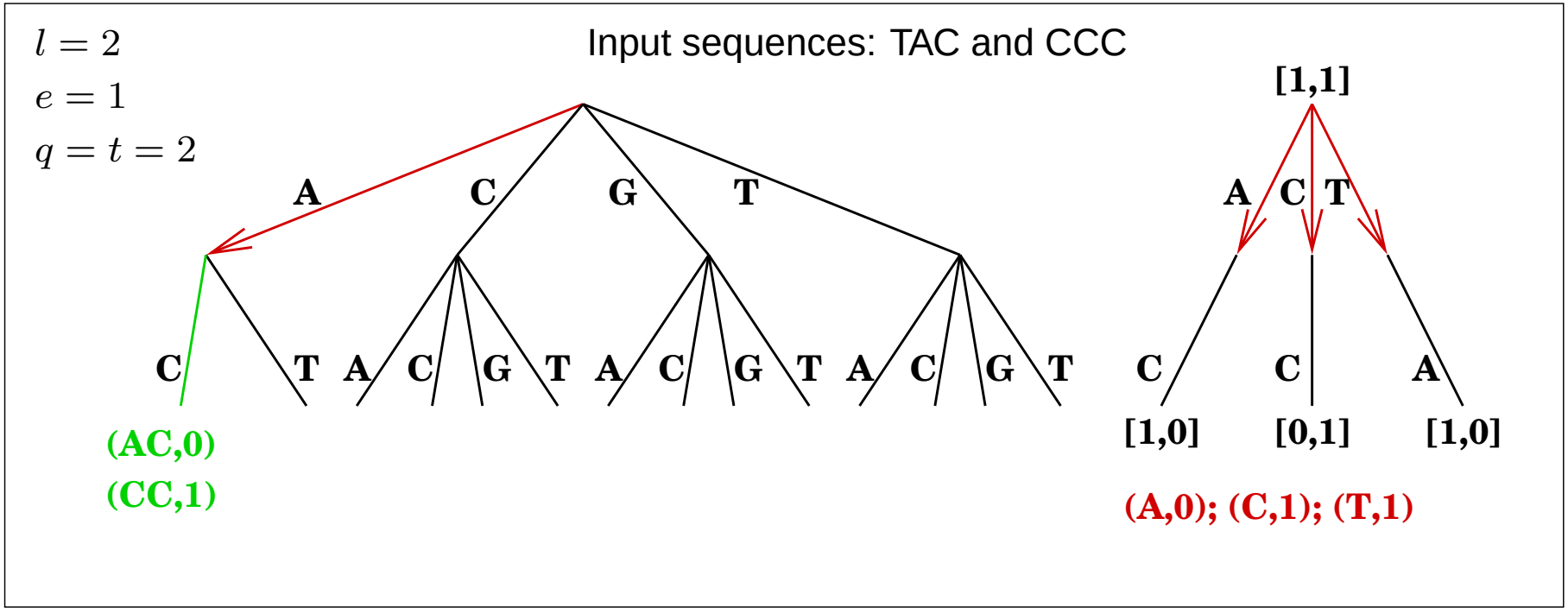

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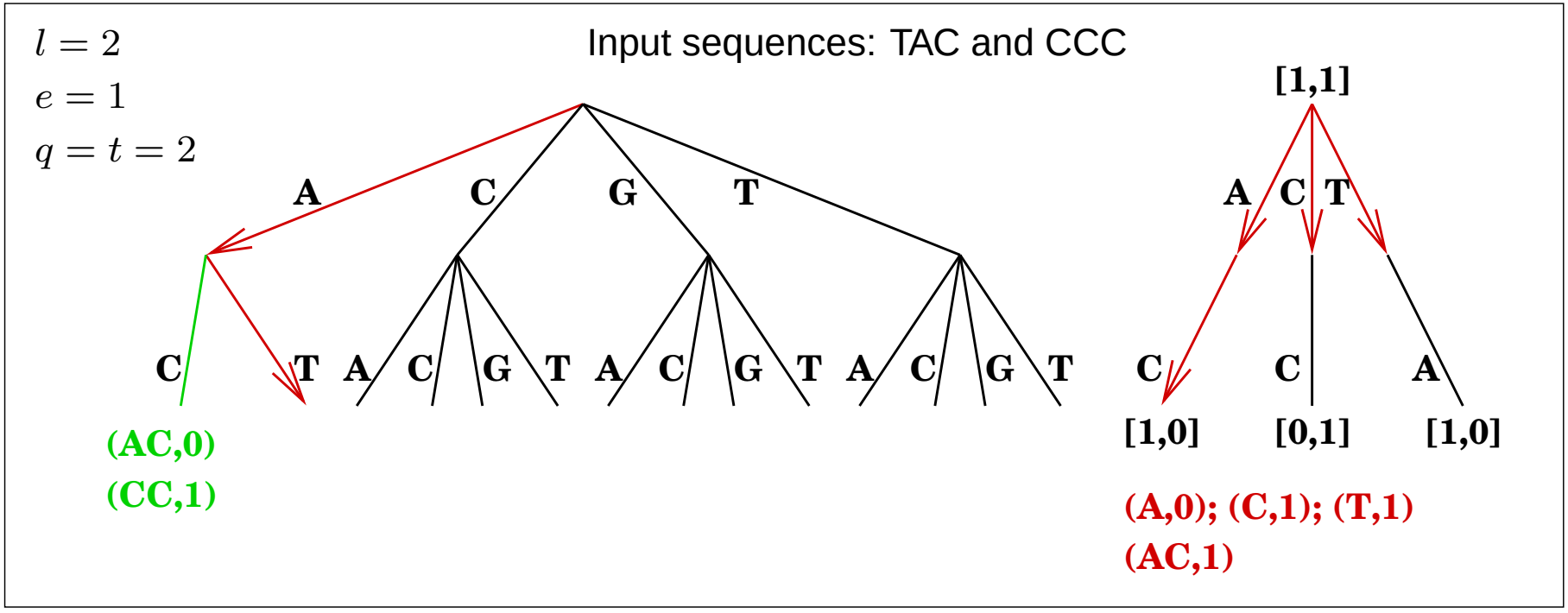

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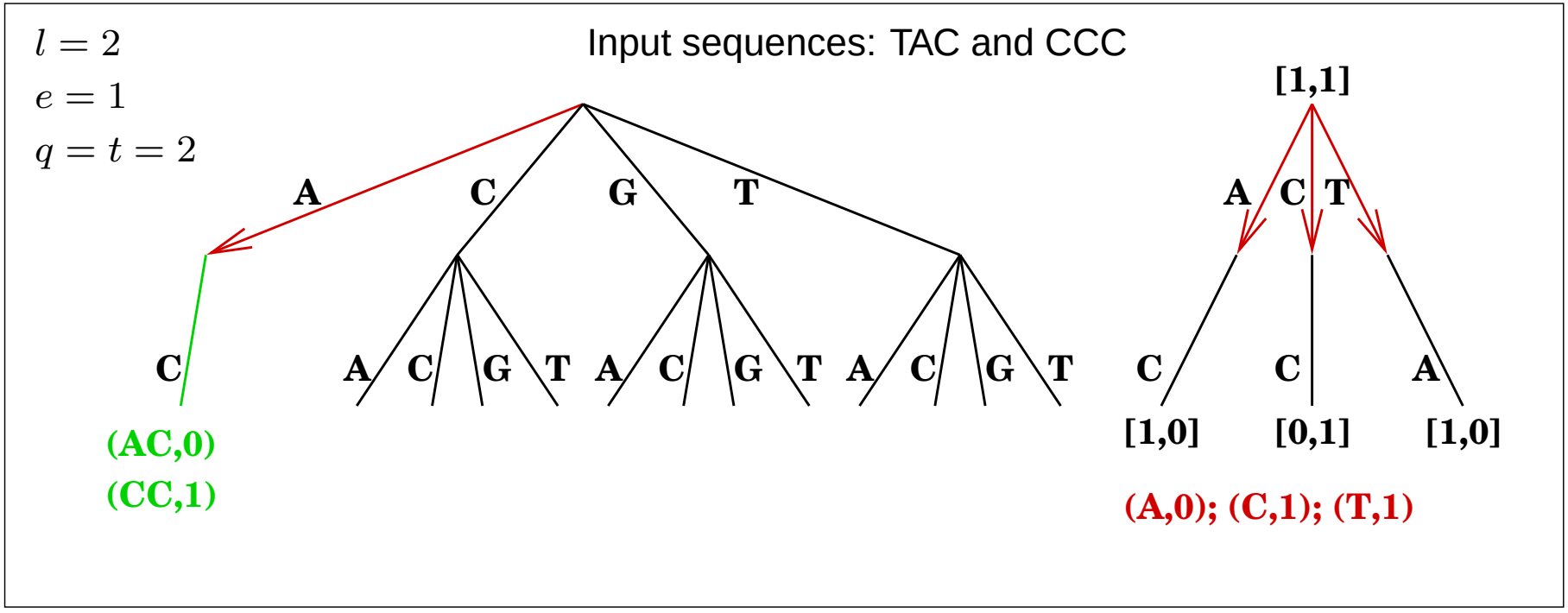

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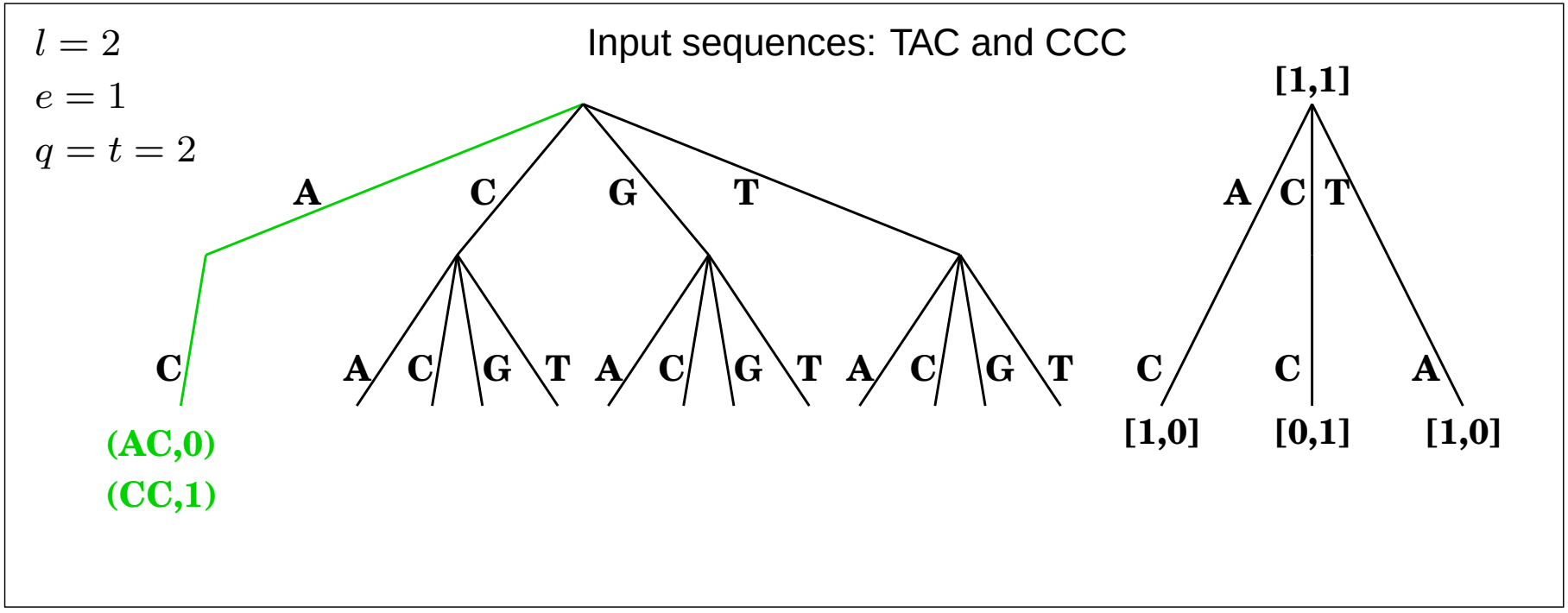

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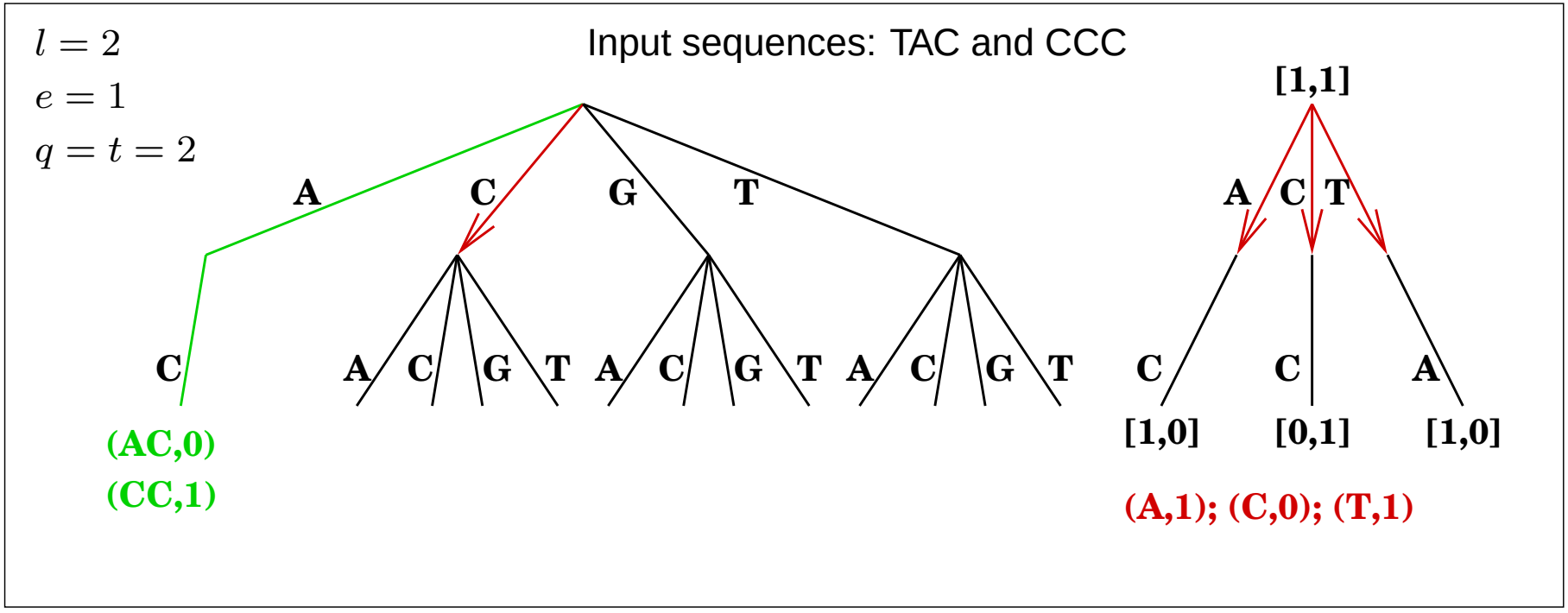

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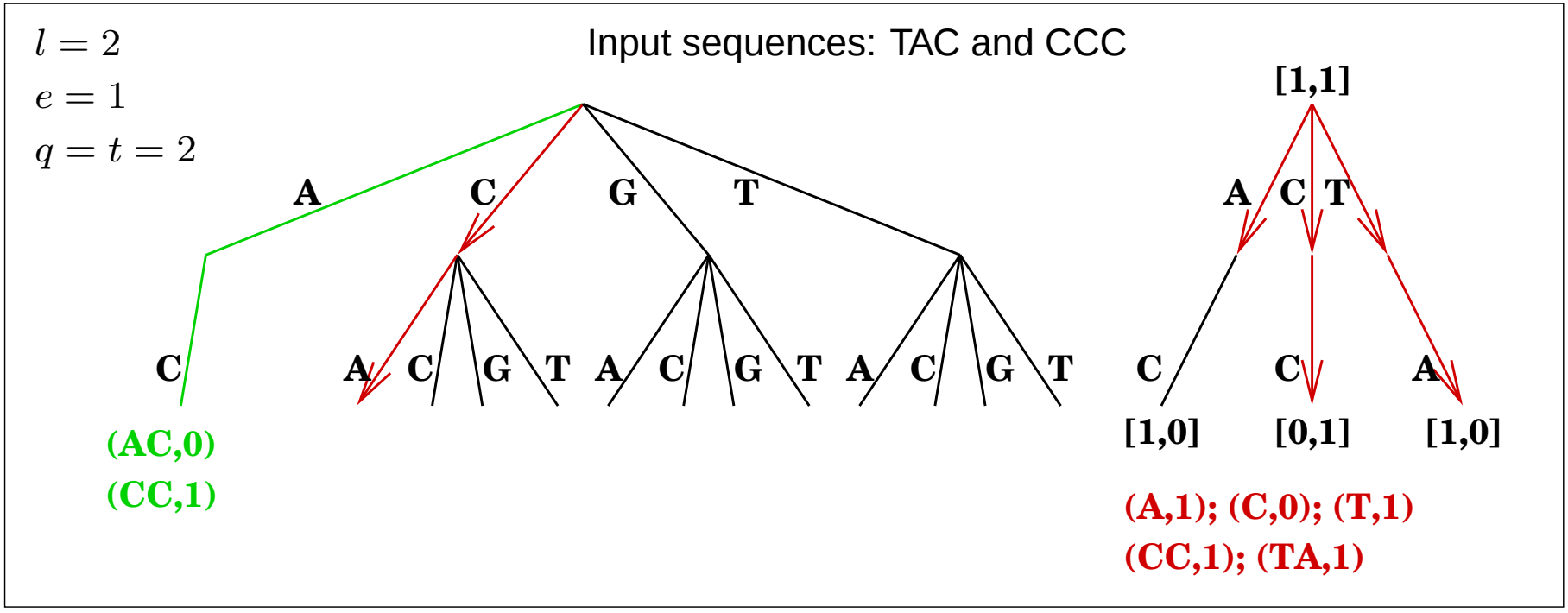

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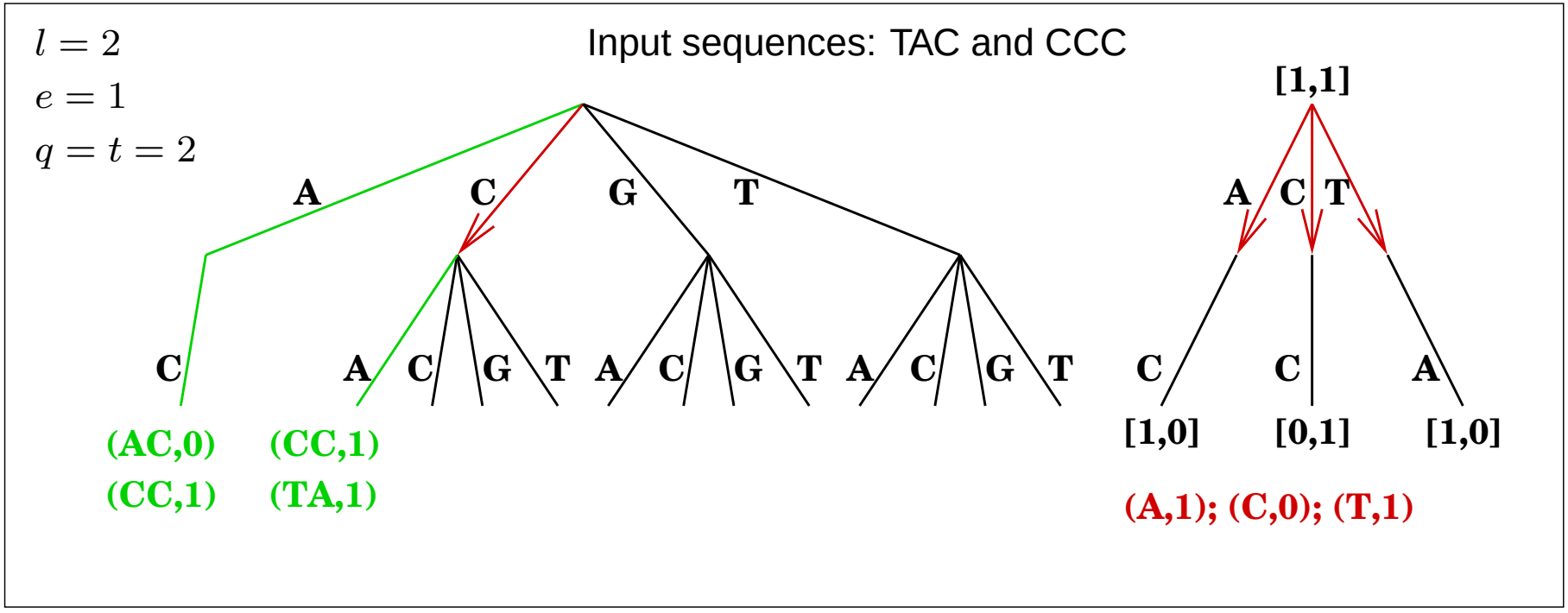

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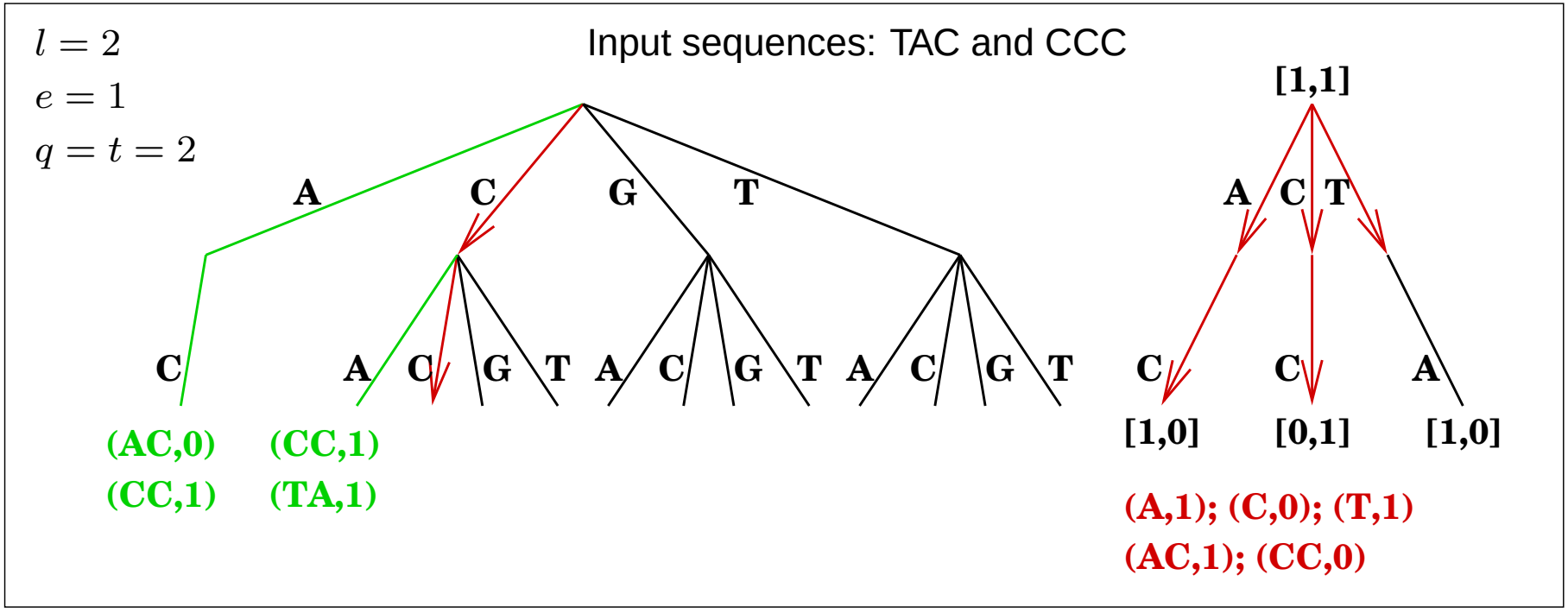

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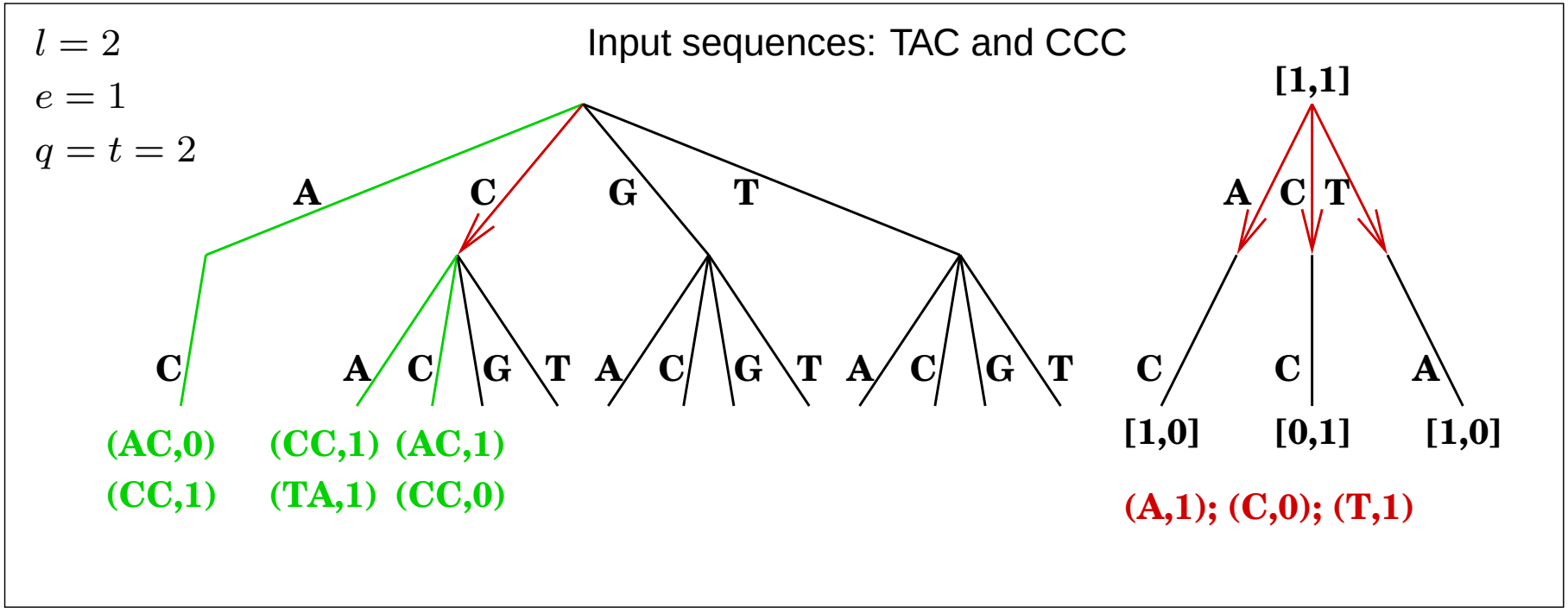

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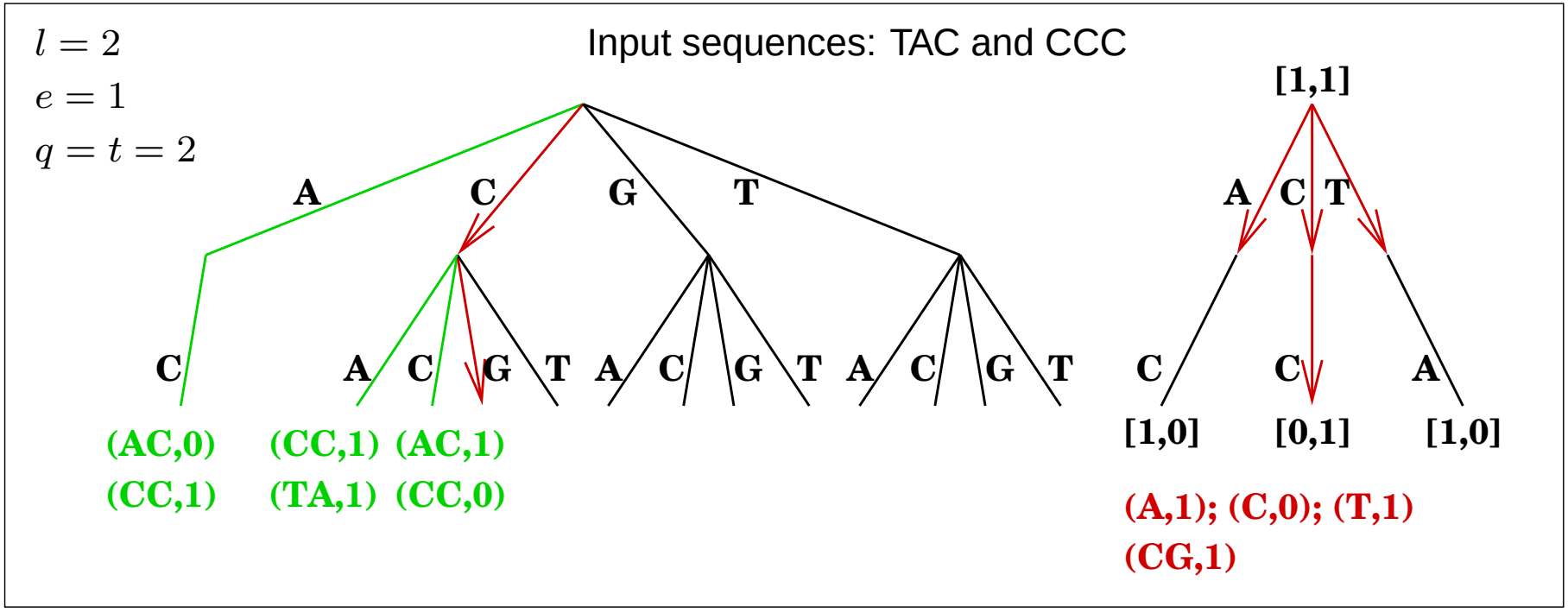

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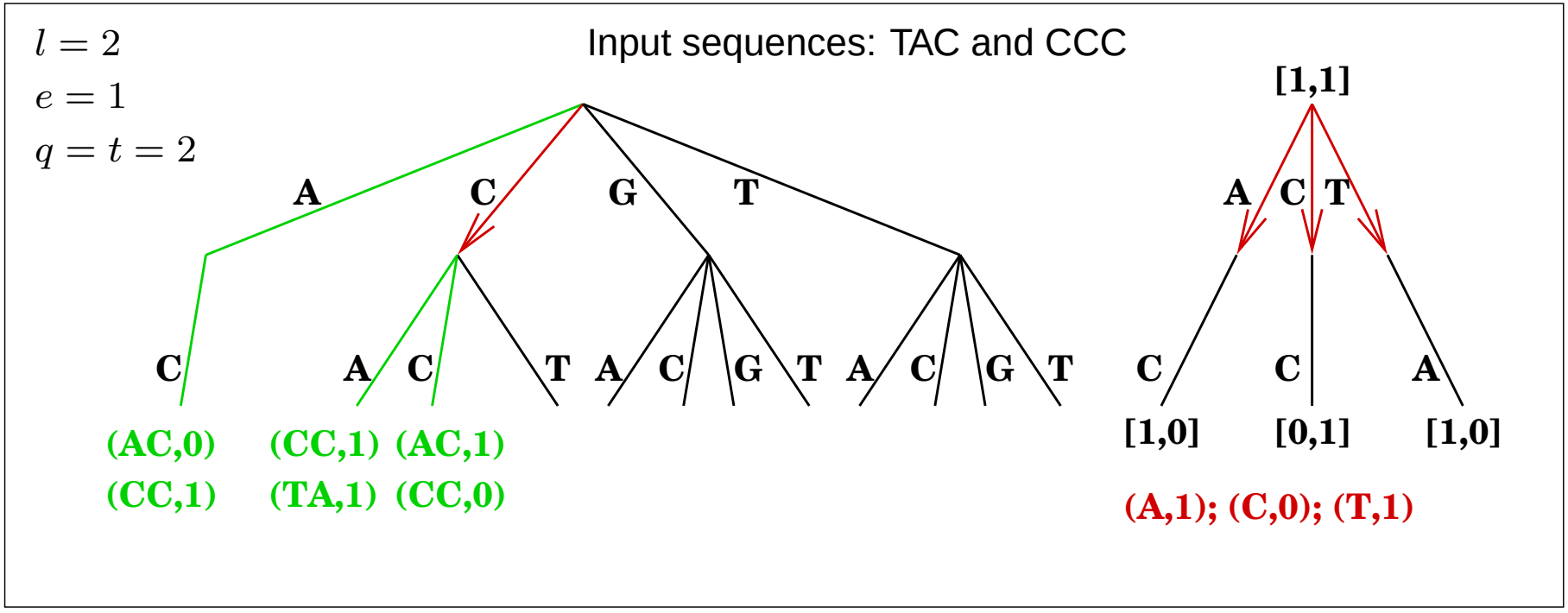

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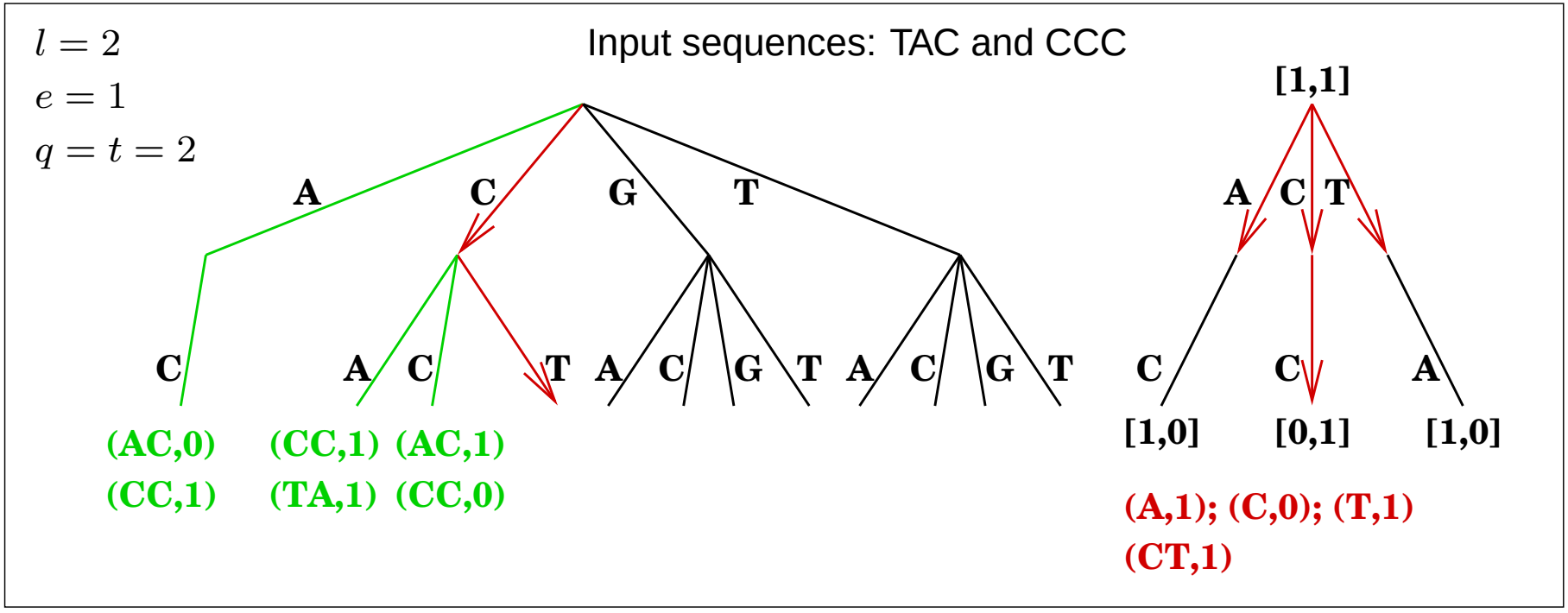

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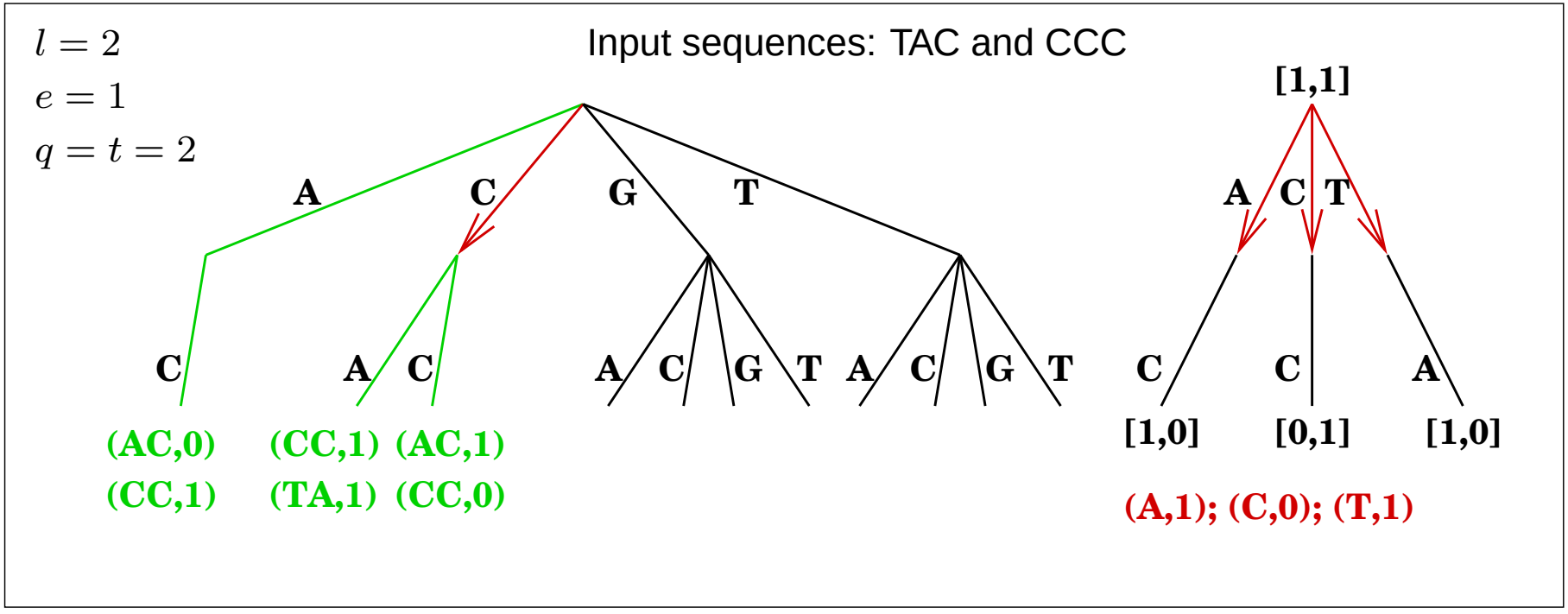

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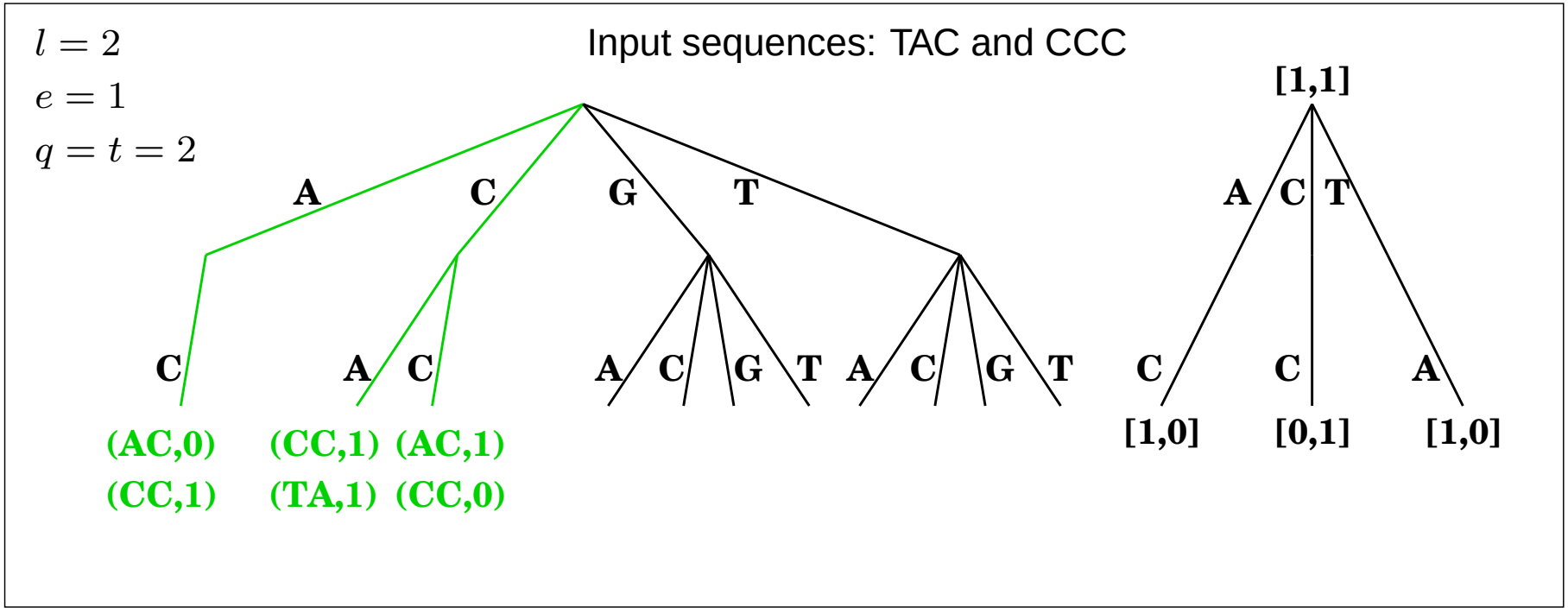

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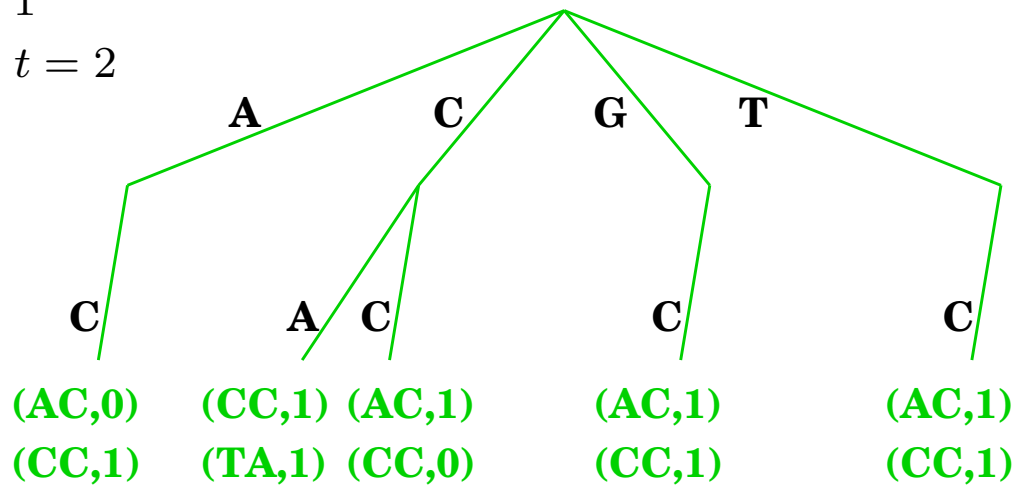

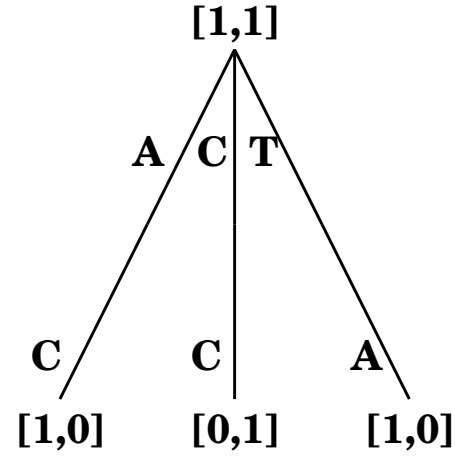

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SMILE

Extraction of composite motifs

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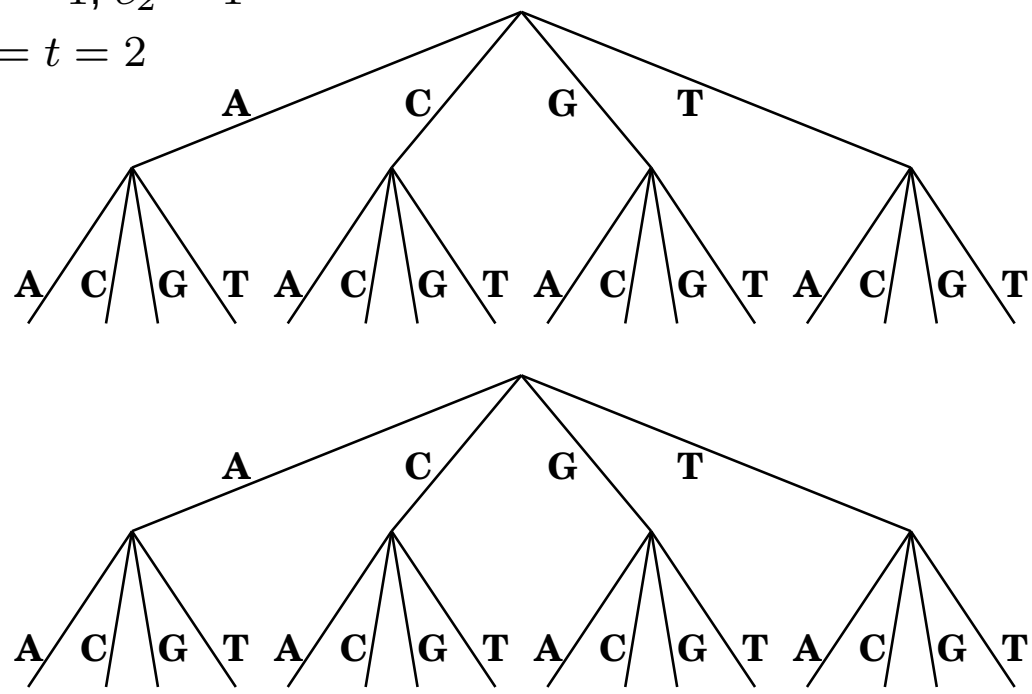

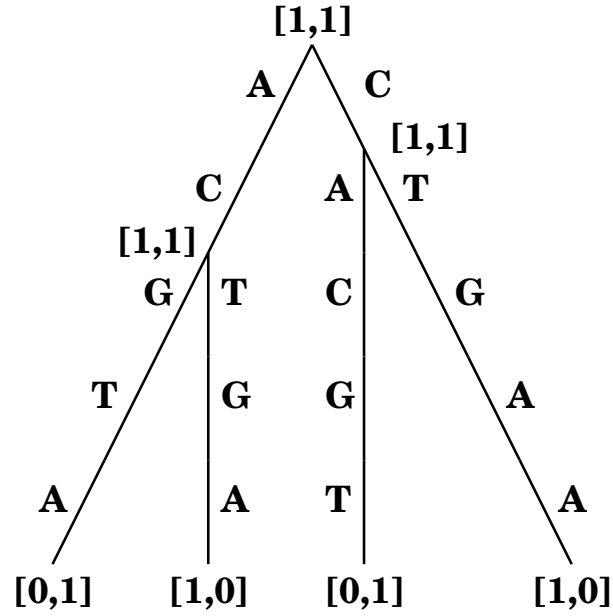

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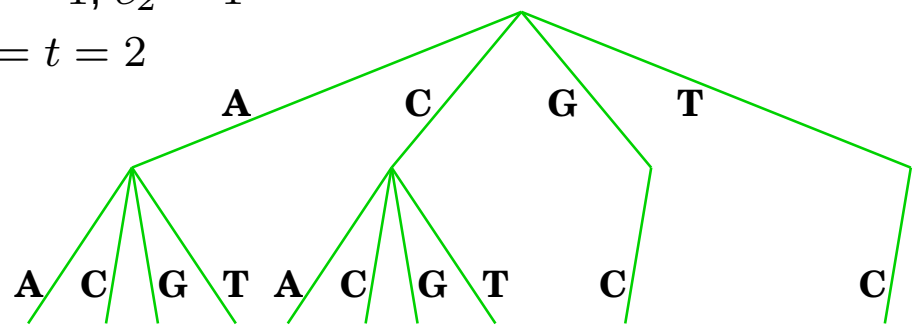

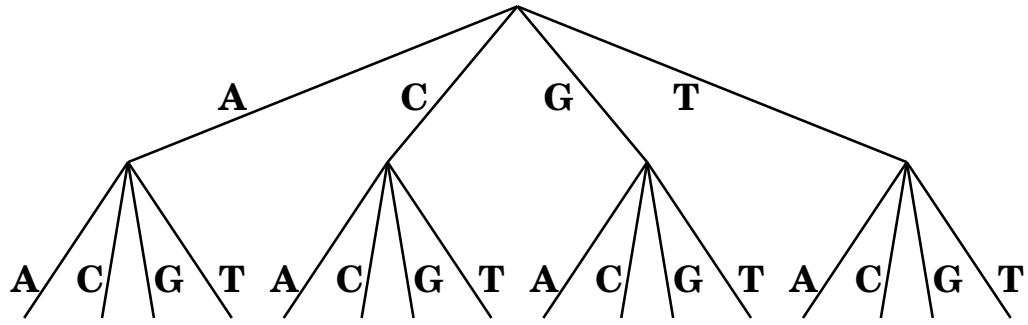

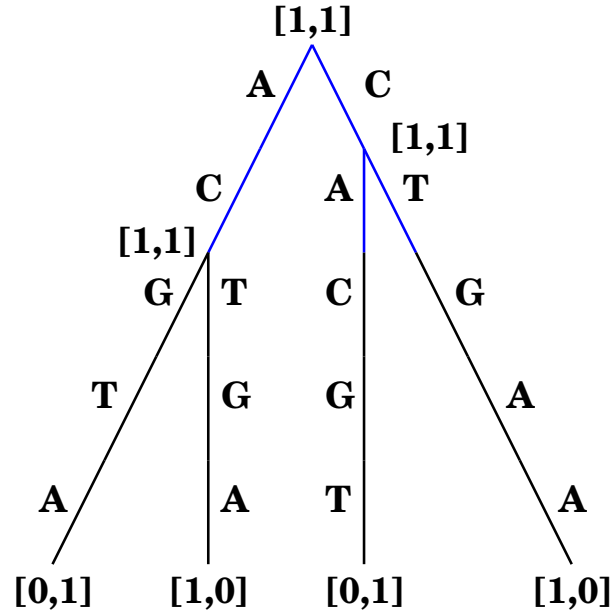

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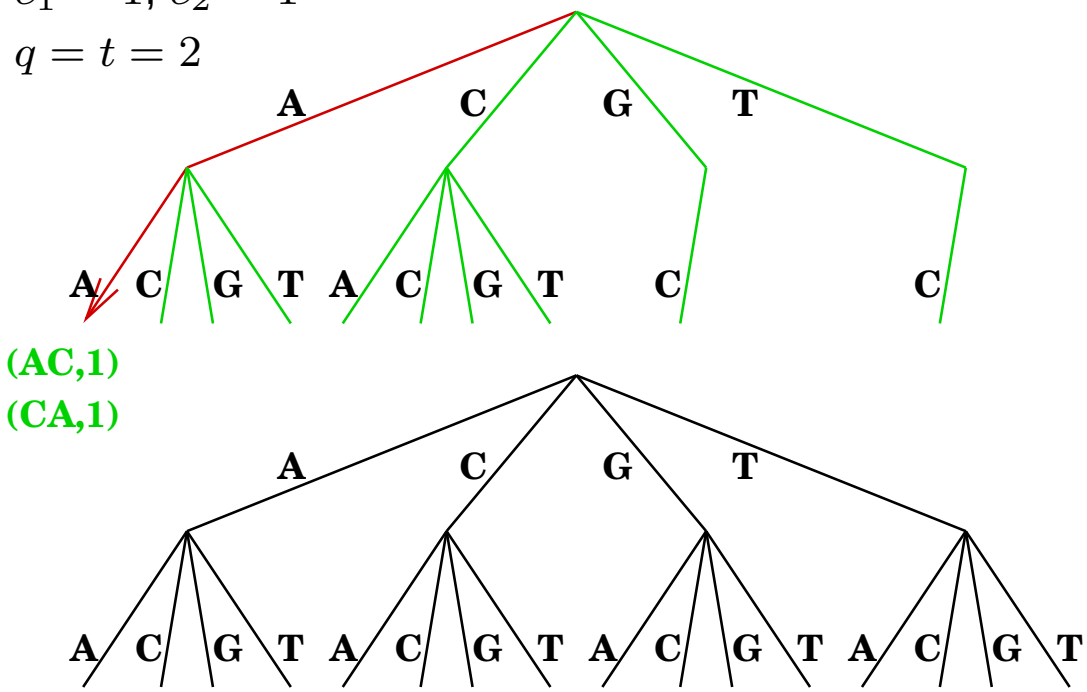

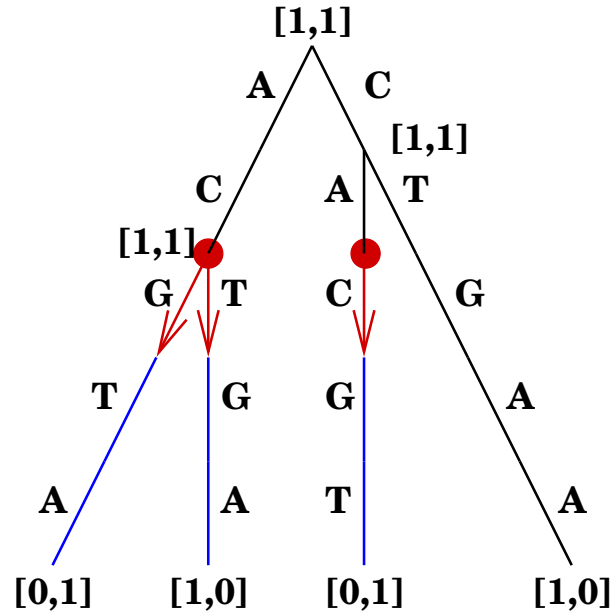

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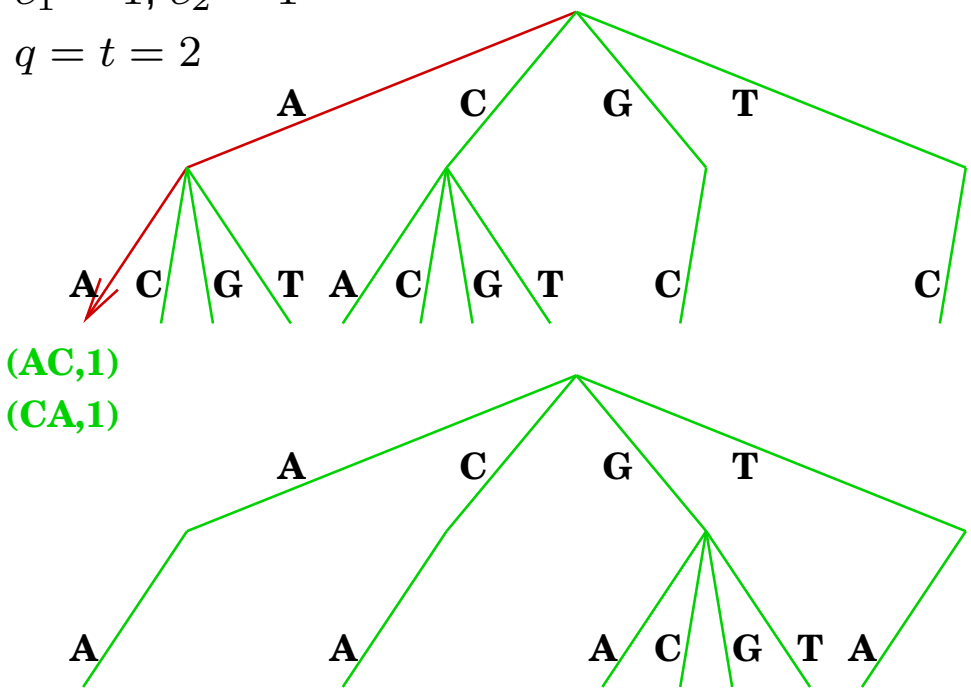

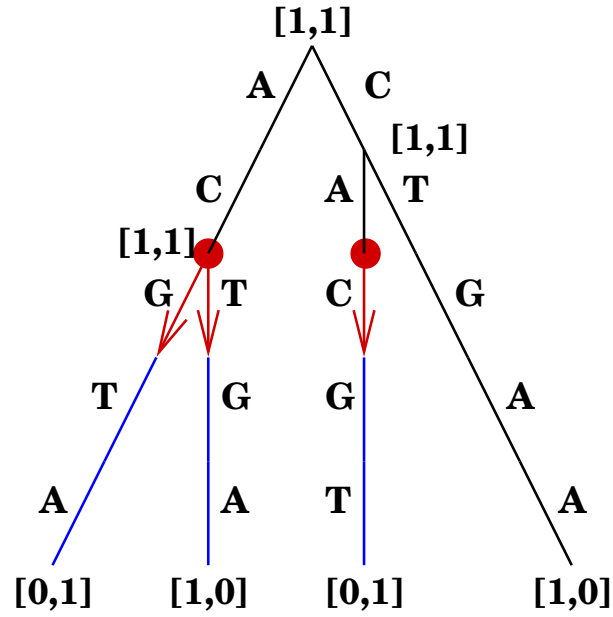

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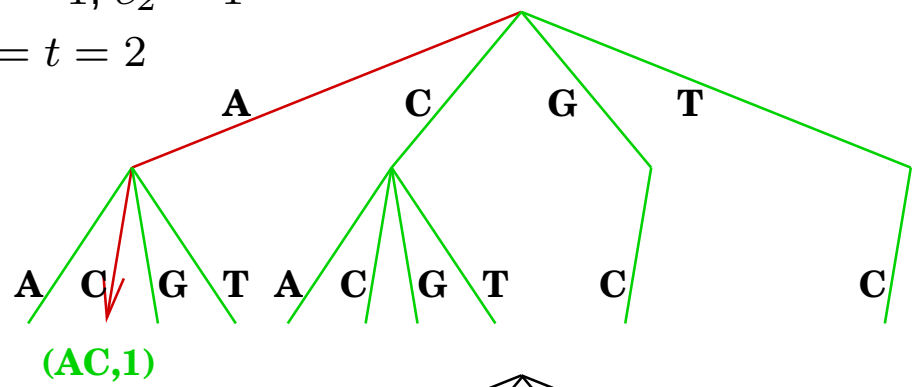

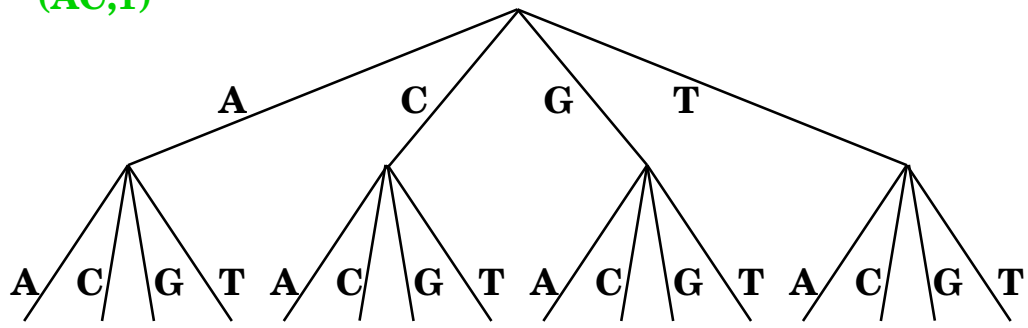

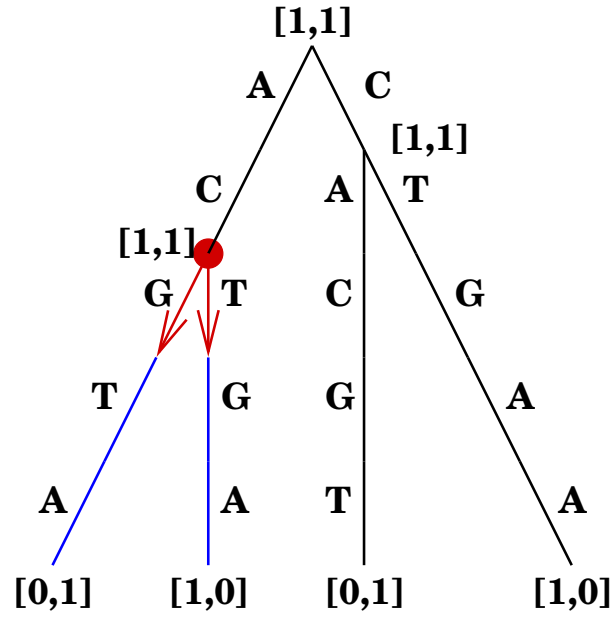

SMILE

Extraction of composite motifs

$p = 2$

$l_1 = 2, d = 1, l_2 = 2$

$e_1 = 1, e_2 = 1$

$q = t = 2$

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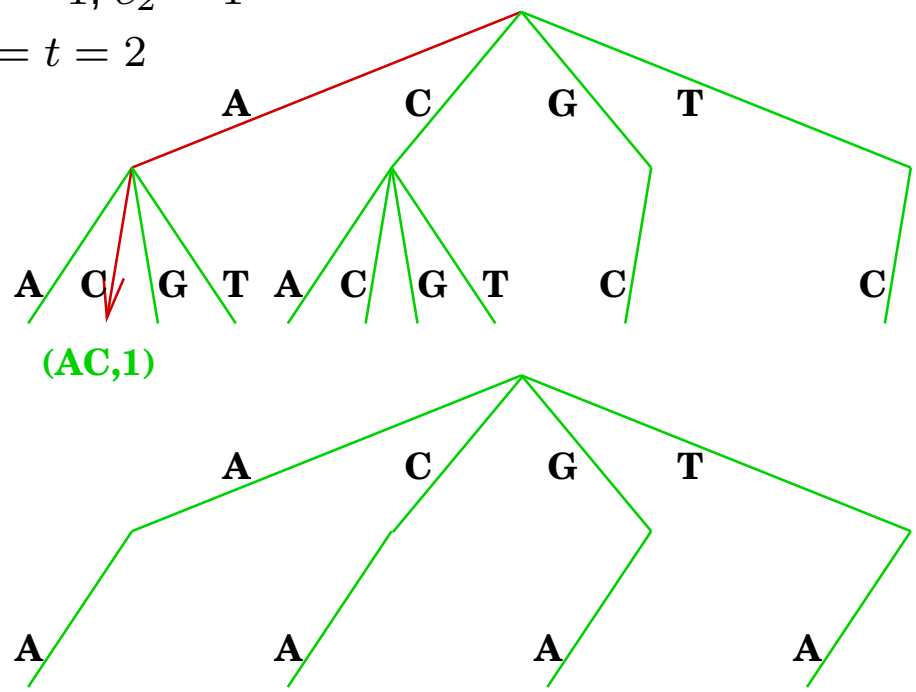

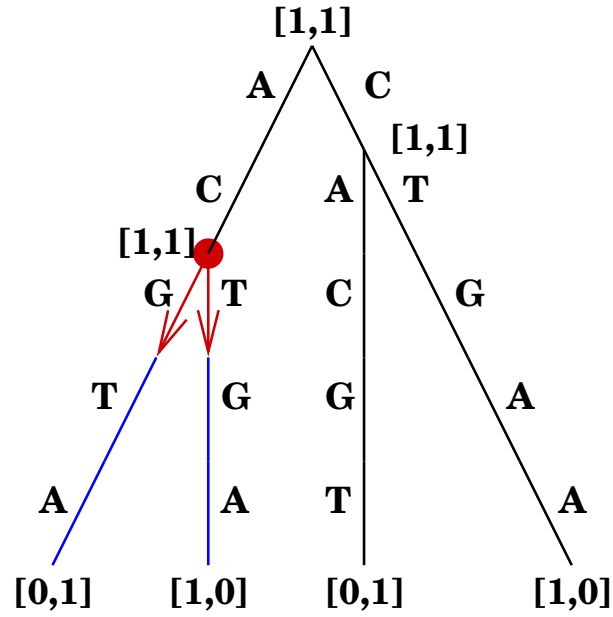

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- The extraction of simple motifs takes $O(t^2 N \mathcal{V}(e,l))$ time and $O(t^2 N)$ space, where

$$\mathcal{V}(e,l) = \sum_{i=0}^{e} \binom{l}{i} (|\Sigma| - 1)^i \leq l^e |\Sigma|^e$$

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- Combines the tree-like view of SMILE with information about pairwise similarities from the graph built by WINNOWER
- Relies on a mismatch tree data structure $\mathcal{M}$
  - Similar to a trie
  - Splits the space of all possible motifs into disjoint spaces
  - Each subspace represents motifs with the same prefix

MITRA

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- The maximum depth of $\mathcal{M}$ is l
- Each node v corresponds to the subspace of motifs $\mathcal{P}$ with a fixed prefix defined by the path-label of v and contains a reference to all l-mers in $\mathcal{S}$ which are within e mismatches of a pattern $p \in \mathcal{P}$

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- We can, then, efficiently generate the set of valid l-mers of a node at the expense of the computed information about its parent

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- If we have a match, the l-mer is still valid for the child
- Otherwise the mismatch count increases and
  - If the threshold e is surpassed the l-mer in not included in the list of v
  - If not, the l-mer remains valid, albeit with a greater mismatch count

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- The authors present two alternatives
  - Counting the number of different sequences contributing to the list of valid l-mers referred by v (MITRA-COUNT), which is tantamount to the operation of SMILE when extracting simple motifs
  - Building a graph for the node v (MITRA-GRAPH)

MITRA-GRAPH

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- Like WINNOWER, MITRA-GRAPH adopts a winnowing strategy, but only to remove vertices (and respective incident edges) with a partition degree less than $q - 1$
- If the remaining edges are insufficient to form a q-clique we can rule out its existence, otherwise the subspace will be further divided

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- (m_1, m_2) is an edge of the graph of v iff $e_1 \leq e$, $e_2 \leq e$ and $e_1 + e_2 + \varepsilon \leq 2e$
- Note that for the root node, where $e_1 = e_2 = l - d = 0$, the condition is $\varepsilon = \delta(m_1, m_2) \leq 2e$ which is precisely the graph built by WINNOWER

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- SMILE is unique in its approach to composite motifs
- MITRA-GRAPH has the virtue of combining different contributions of SMILE and WINNOWER to avoid unnecessary explorations of the search space

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- Most implementations are not publicly available

Thank you

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