Minimum Factorization Agreement of Spliced ESTs

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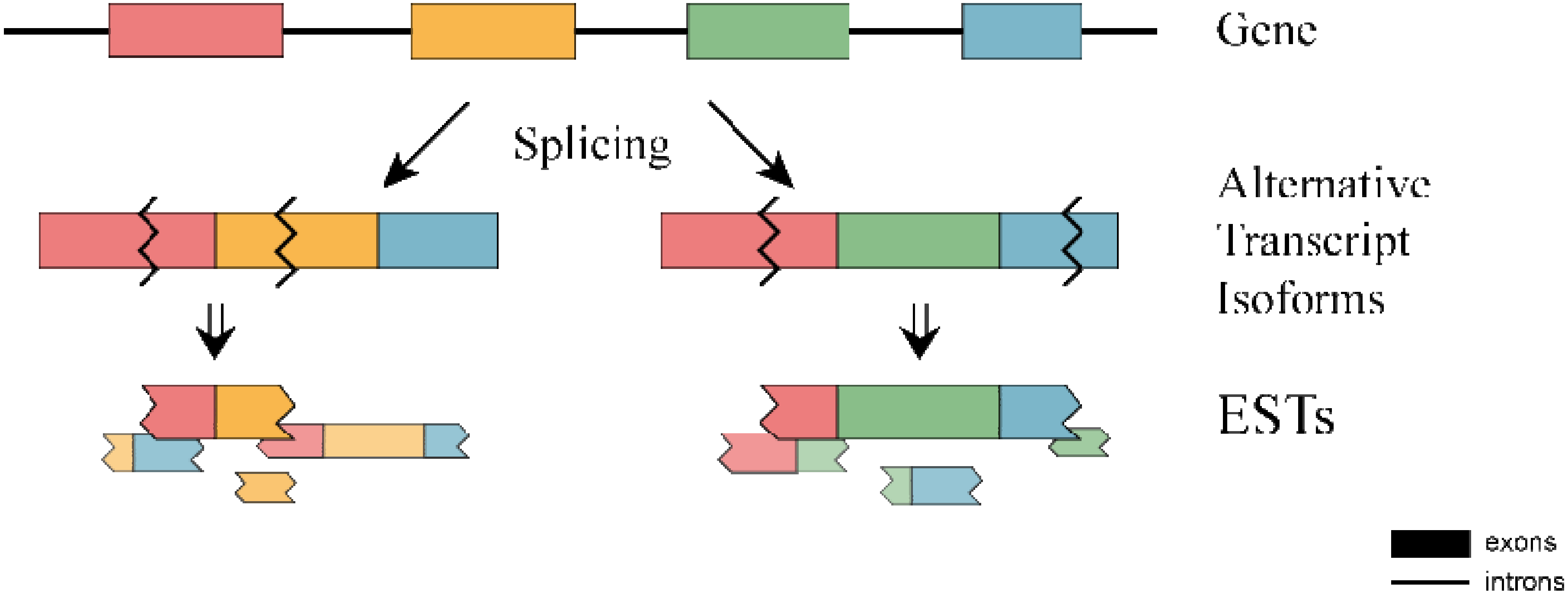
Outline

- Introduction and Motivations
- The Minimum Factorization Agreement Problem
- The Algorithmic Solution
- Experimental Results
- Conclusions

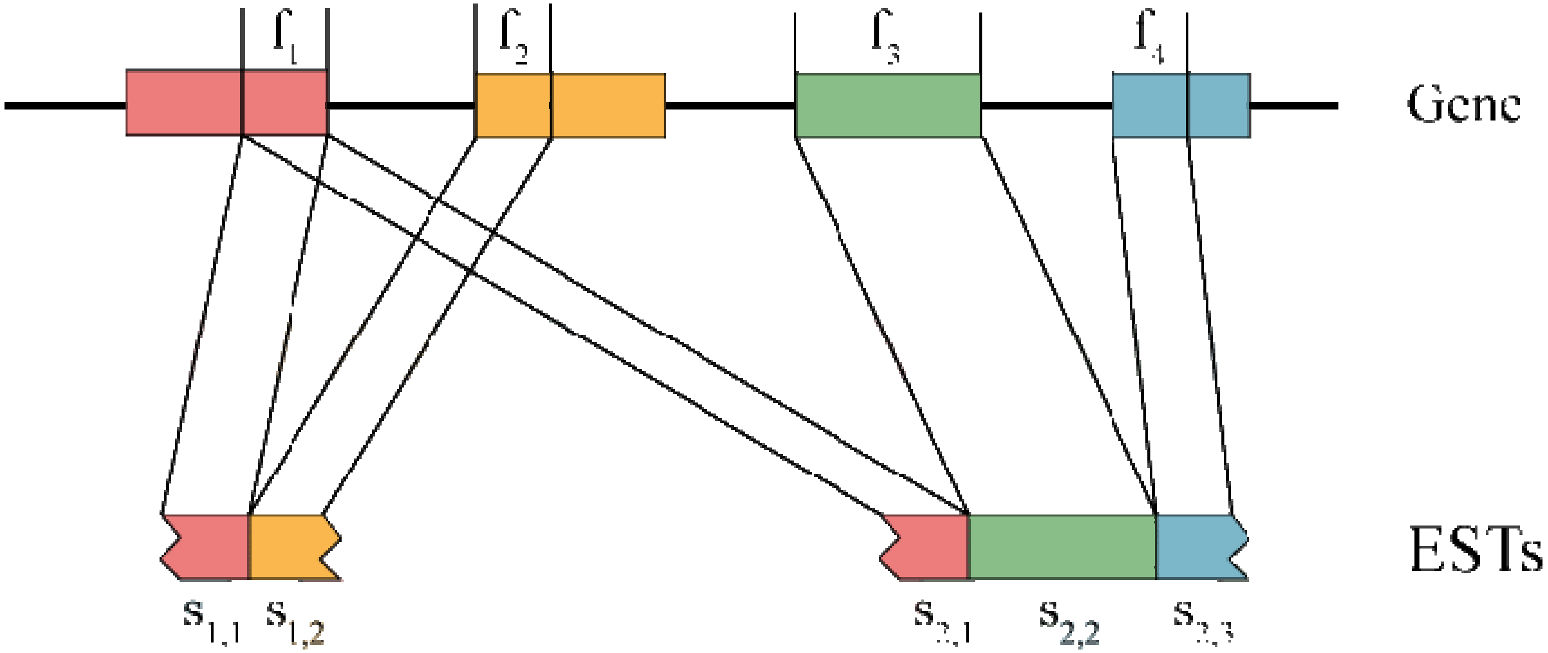
What is an EST?

- **E**xpressed **S**equence **T**ag (**EST**) =
  short fragment of a transcript
- But: Alternative Splicing → 1 gene = *n* transcripts



What is an EST?

f_1, f_2, f_3, and f_4 = **factors**



composition of EST_i = f_1, f_2

spliced EST of EST_i = $\{(s_{1,1}, f_1), (s_{1,2}, f_2)\}$

Why ESTs are used?

- Considerations:
  - ESTs are cheap to obtain
  - ESTs provide some information about transcripts
- Common idea:

  Combining several ESTs to predict:

    - *alternative splicing events*
    - *intron-exon structure*
    - *alternative transcripts*
    - *…*

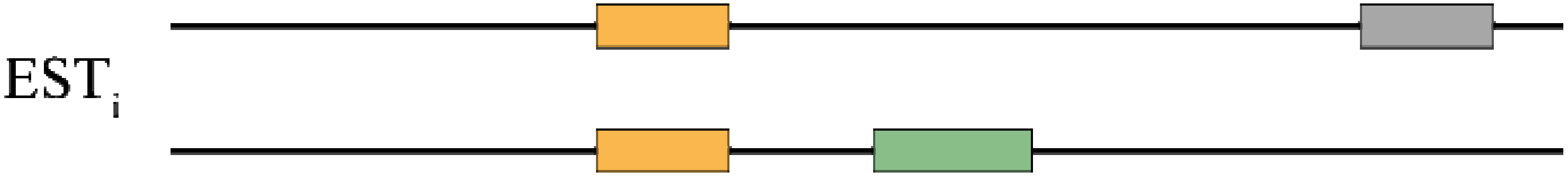
Basic ingredient:
spliced ESTs

Problems

Using ESTs poses several problems due to…

- Sequencing errors
  - especially along the terminal factors
  - near the splice junctions
- Terminal EST factors may be short (10-30bp)
- Genomic sequences may present **repeated substrings**

An Example

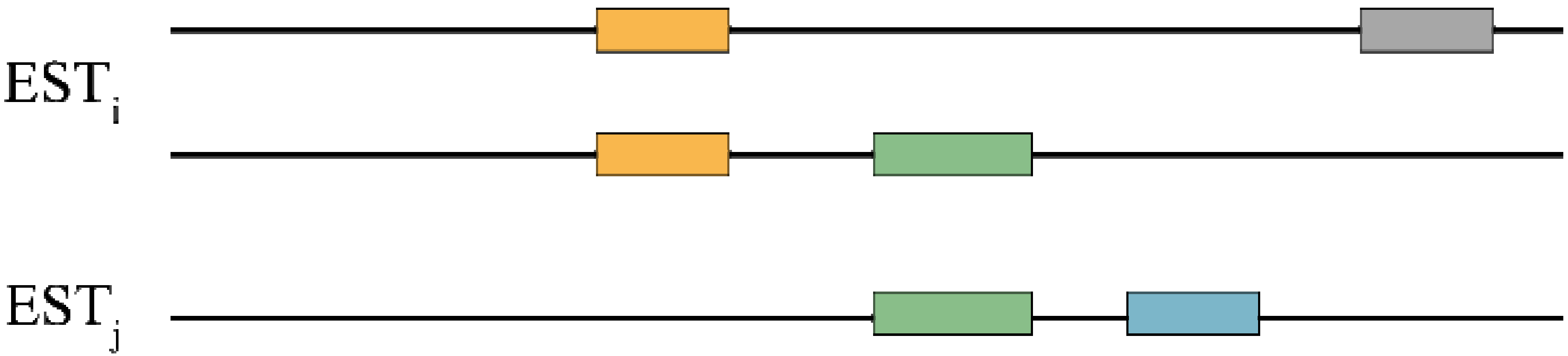


Two possible compositions…

How to choose the “correct” one?

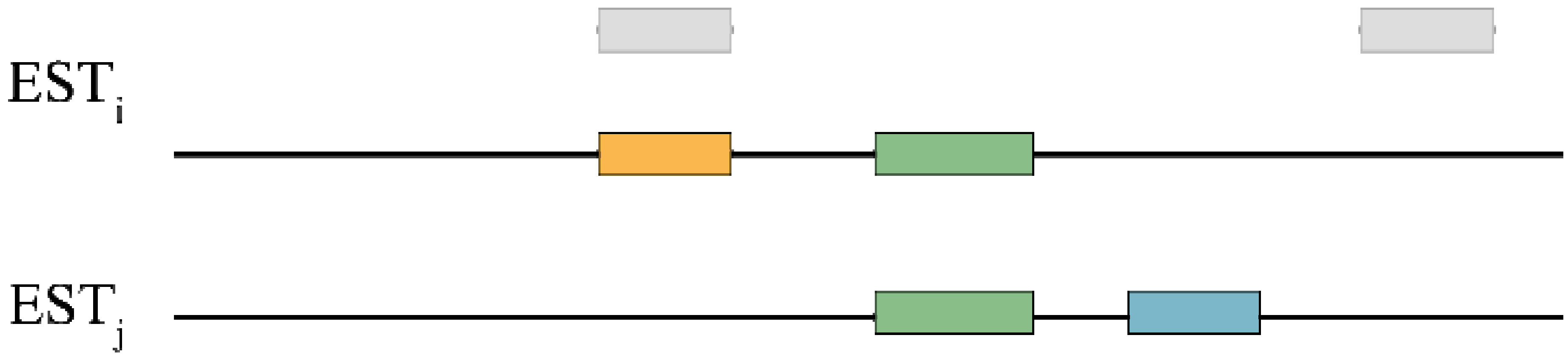
Popular tools (GMap, EST_GENOME, Spidey, …) often report one “best alignment”

An Example



Idea: redundancy can help to choose the “right” one

An Example



Idea: redundancy can help to choose the "right" one

Minimum Agreement Factorization problem

Minimum Agreement Factorization problem (MAF)

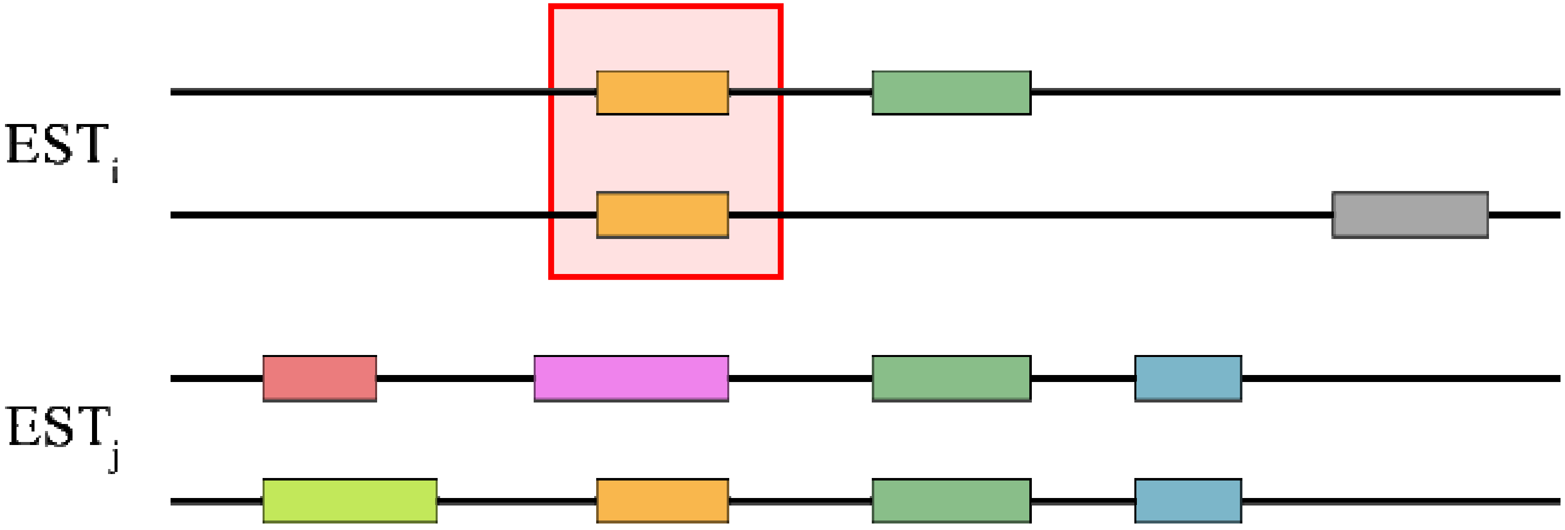
- **Input:**
  The set of compositions C(S) of a family S of EST sequences (over the set of factors F)
- **Output:**
  A minimum-cardinality set F' of factors such that for each EST of S, there exists a composition that uses only factors in F' (F' is a factorization agreement set).

- APX-hard *(by L-reduction from Min Set Cover)*

Real Instances

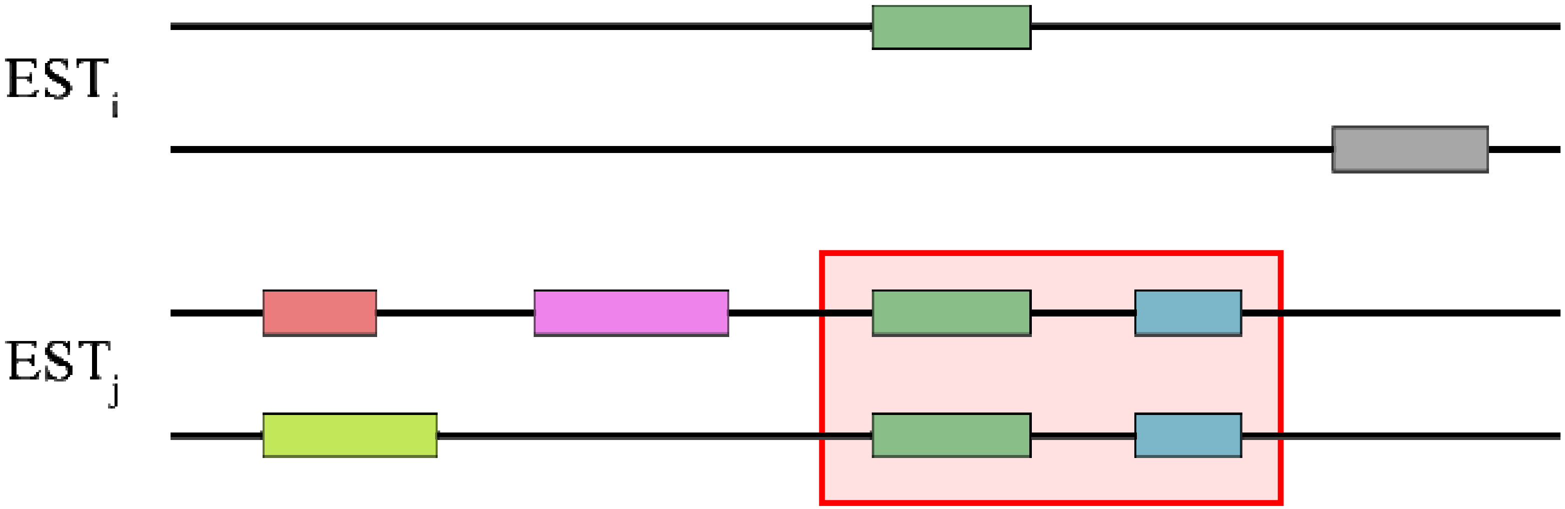
- On real data, several factors that must belong to every optimal solution can be (easily) identified (**necessary factors**)
- *Idea:* identify and remove necessary factors
  - Five rules
  - Efficient (polynomial-time)

Size-reduction *(by example)*

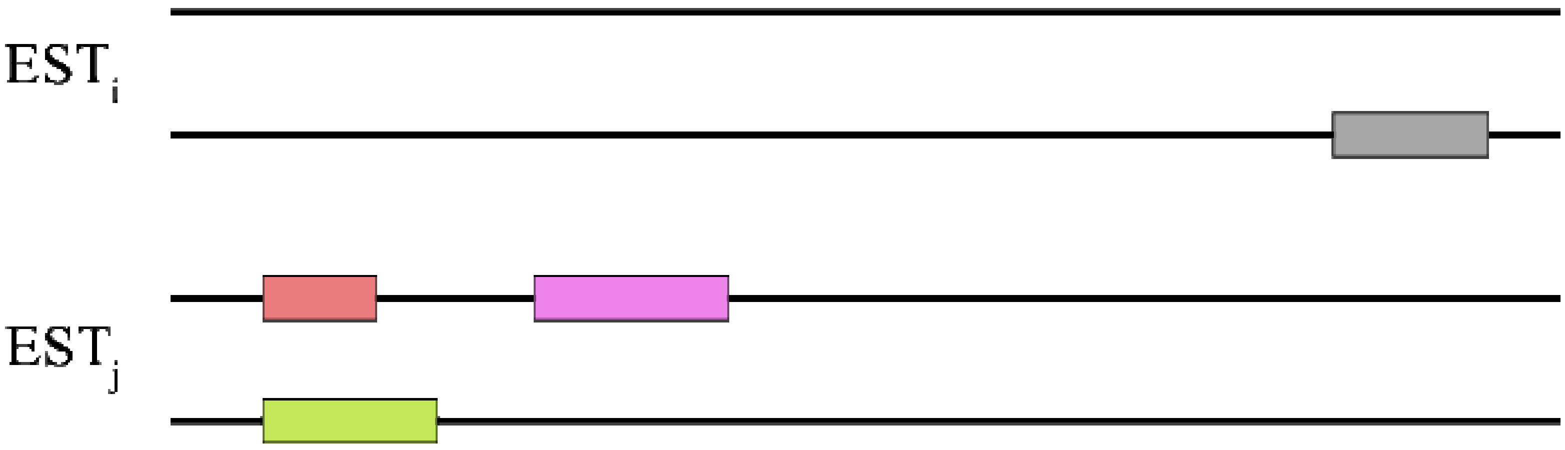


Two ESTs, Four Compositions/spliced ESTs

Size-reduction *(by example)*

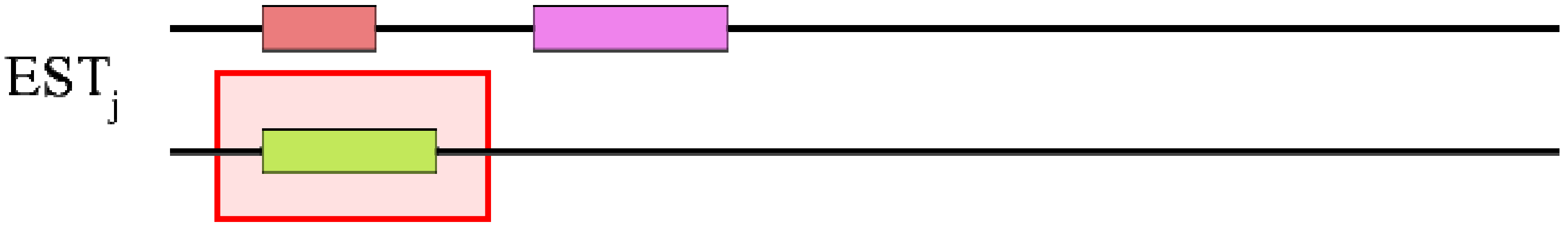


Size-reduction *(by example)*



EST_i can be removed since one of its compositions is empty.

Size-reduction *(by example)*



No more reduction rules can be applied…

…but the problem is easier.

The Algorithmic Solution

- Two-step algorithm:
  1. **Size-reduction**
     (identification of necessary factors)
  2. (Exponential-time) **Exact algorithm**
     (on the remaining factors)

Exact Algorithm

- Exact algorithm: (naïve version)
  - Enumeration of all subsets of factors in non-decreasing order
  - Checking if the subset is a factorization agreement set
  - Exponential-time in $|F|$: $O(2^{|F|} |F| |C(S)|)$

- Usually $|F|$ much smaller than $|C(S)|$

Exact Algorithm

- Naïve version: efficient implementation
  - Bit-parallelism
  - Data locality
- Refined versions may:
  - Discard part of the search space
  - Storing previously computed values
- Refined versions require (often):
  - Extra space
  - Complex implementations

Preliminary Experimentation

- *Data (given a gene):*
  - its genomic sequence
  - its UniGene EST cluster
  - a set of spliced ESTs (compositions) based on the longest common substrings between genomic and EST sequence
- *Results (on 4 genes):*
  - Size-reduction step finds an optimal solution (the exponential algorithm is not needed)
  - The solutions are similar to the ones obtained from another well-known tool (GMap)

Conclusions

- **Conclusions:**
  - A method which exploits redundancy to resolve ambiguity in spliced ESTs
  - Theoretical computational complexity ≠ practical feasibility

- **Future works:**
  - In-depth experimentation *(ongoing)*
  - Associating different meanings to the concept of “factor” (e.g. splice sites, introns, …)

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