PIntron: a fast method for gene-structure prediction

Paola Bonizzoni

Gianluca Della Vedova

Yuri Pirola

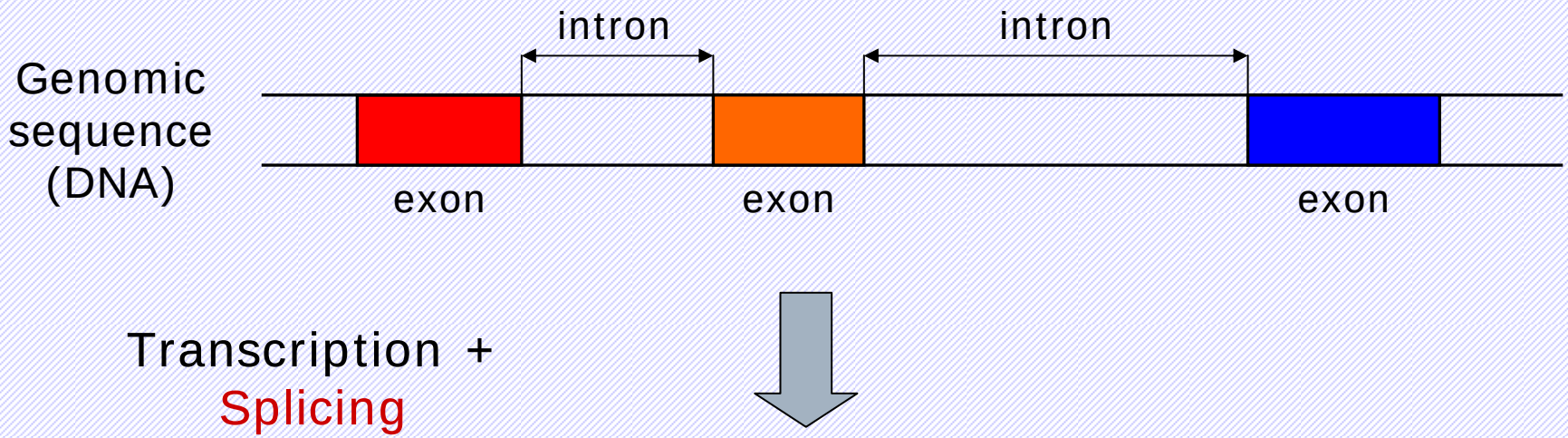
Raffaella Rizzi

Università degli Studi di Milano-Bicocca, Italy

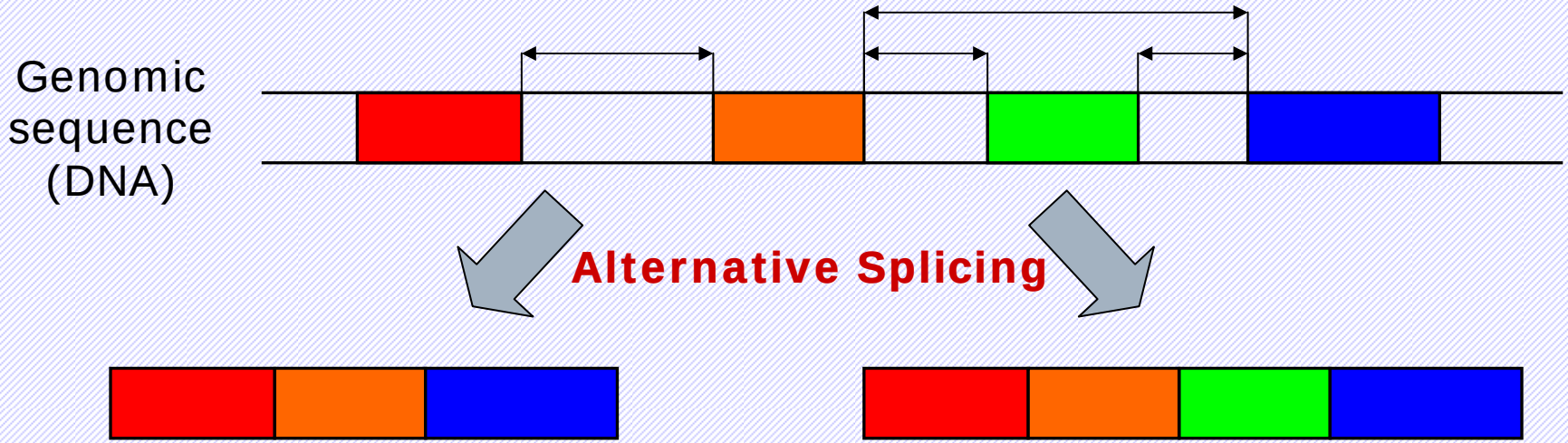
Outline

- The computational problem
- Prior work
- Our pipeline
- Experimental comparison

Eukaryotic Gene Structure



Alternative Splicing

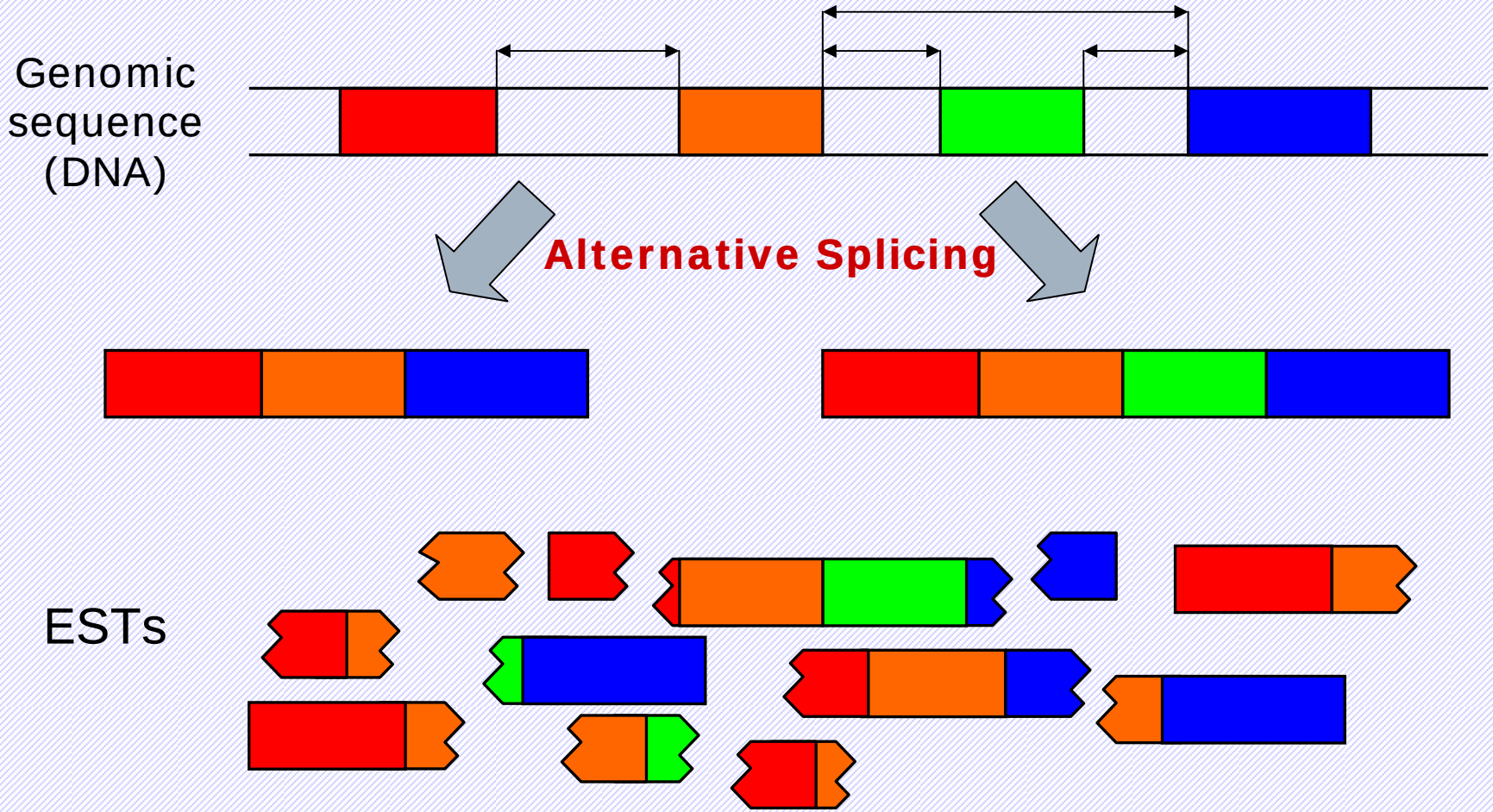


2 distinct mRNAs/full-length isoforms → 2 distinct proteins

- AS is widespread (95% of human genes)
- Aberrant AS events → diseases

(Pan et al., Nat Gen, 2008) and (Matlin et al., Nat Rev, 2005)

Alternative Splicing

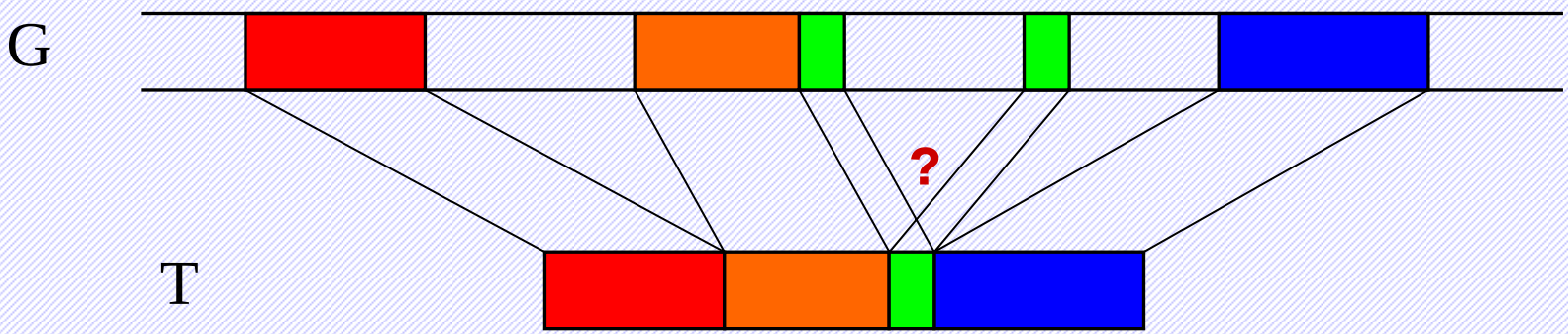


Gene structure prediction: prior work

- Three strategies:
  - ab-initio: “statistical” recognition
    - GENEZILLA, NSCAN
  - expression-based:
    alignments of ESTs, mRNAs, or proteins
    to the genomic sequence
    - Exogean, ASPic, PIntron
  - (ab-initio + expression-based) methods
    - AUGUSTUS, JIGSAW

Spliced-alignment problem

- **Problem:**
  Align a transcript T to the genomic sequence G while admitting introns
- Different alignments exist



PIntron: our pipeline

Input: a *cluster of transcripts* and a *genomic sequence*

1. For each transcript:
   a. Represent all its possible spliced-alignments
   b. Extract its biologically-meaningful alignments
2. Compute a raw consensus gene-structure
3. Refine the raw gene-structure

The Pipeline: Step 1.a

Task: represents all the spliced-alignments

How?

Embedding Graph of G and T

- *Vertices* V: maximal common substrings of G and T
- *Edges* E: connect two common substrings that could be consecutive in a spliced-alignment

– Can be built efficiently:

$$O(|G|) + O(|T|+|V|) + O(|V|^2)$$

The Pipeline: Step 1.b

Input: an embedding graph (for each transcript)

Task: extraction of "relevant" spliced-alignments

Output: some biologically-meaningful spliced-alignments (for each transcript)

How?

1. Embedding graph visit +
2. Spliced-alignment reconstruction

The Pipeline: Step 1.b (cont'd)

1. Embedding graph visit
   - computes *representative* embeddings (i.e. embeddings which induce distinct spliced-alignments)
2. Spliced-alignment reconstruction
   - computes putative exons and raw intron boundaries
   - discards low-quality alignments

The Pipeline: Step 2

Input: all the spliced-alignments of all the transcripts

Task: computation of a raw consensus gene-structure

Output: a minimal gene-structure that “explains” a single spliced-alignment of each transcript

Min Factorization Agreement

(Bonizzoni et al., WABI 2009)

Bad news: NP_hard

Good news: efficient heuristic

The Pipeline: Step 3

Input: a *raw* gene-structure

Task: refine intron boundaries and discard possible errors

Output: a *final* gene-structure

How?

- classify introns (U2, U12, BSS)
- collapse highly-similar introns unless supported by high-quality alignments
- other heuristic criteria

PIntron evaluation

- **Method:** (Guigò et al., Genom Biol, 2006)
  - Sensitivity (Sn) = TP / (TP + FN)
  - Specificity (Sp) = TP / (TP + FP)
- **Data:** 112 genes on 13 ENCODE regions
- **Gold standard:** GENCODE annotations
- For this prelim. work:

  gene structure ≡ set of introns

Evaluation Results

- Overall *Sensitivity* = **0.9780**
- Overall *Specificity* = **0.6846**
- Why *Specificity* is low?
  - our method “over-predicts”, or
  - GENCODE annotation could be “biased”
- If we keep only “canonical” introns
  - *Sensitivity* = **0.9764**
  - *Specificity* = **0.9147**

Compared with... ASPicDB

- ASPicDB (Castrignano et al., Bioinf, 2008)
  - accurate isoform-prediction method (Bonizzoni et al., JCB, 2009)
  - 101 (over 112) also in ASPicDB

	Sn	Sp	Time
ASPic	0.9631	0.7070	> 100 h
PIntron	**0.9727**	**0.7363**	**72 min**

Conclusions

- **PIntron:**
  fast and accurate pipeline for gene-structure prediction based on transcripts
- **Ongoing/future work:**
  - Comparison with other tools
  - Polishing implementation (open-source)
    (**www.algolab.eu/PIntron**)
  - Extensions to RNA-Seq

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Thanks!

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