PhD defense - Université Paris Diderot

The annotation of transposable elements through the understanding of their diversification

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PhD directors: Hadi Quesneville (INRA, URGI) and Catherine Feuillet (INRA, GDEC)

Outline

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1. Introduction on TE discovery and their impacts on genomes
   - Brief history on TEs, their function and evolution
   - Impacts of TEs and their structural classification
2. Considering TE diversification in *de novo* annotation approaches
   - Aim, approach and pitfalls
   - Comparative analysis and combined approach
   - Identification of TE families and their structural variants

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2. Considering TE diversification in *de novo* annotation approaches
   - Aim, approach and pitfalls
   - Comparative analysis and combined approach
   - Identification of TE families and their structural variants
3. Discussion and perspectives
   - Application of the tools and practical consequences
   - A new method to detect TEs and study their diversification

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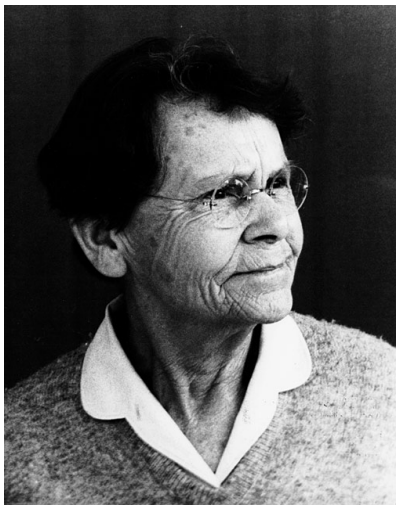
Context of the TE discovery

Barbara McClintock was a plant geneticist at Cold Spring Harbor:

- in 1944, cross of two maize lines and "genetic earthquake";
- in 1950, publication on mutable loci (Ac-Ds);
- in 1956, publication on "controlling elements".



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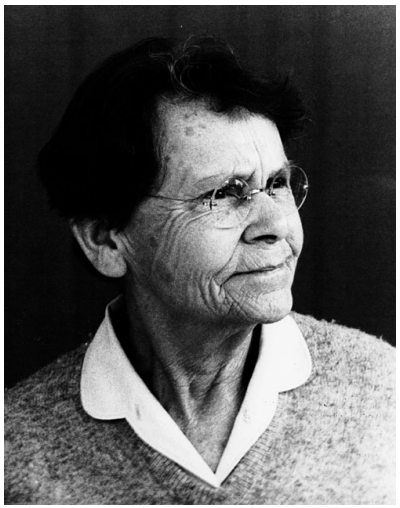

DNA was known to carry genes only since 1944, and its structure was discovered only in 1953: what to think about "jumping" genes?

TE definition, function and evolution

- TEs are mobile genetic elements (DNA sequences).
- They can multiply within genomes (non-Mendelian inheritance).
- They are present in virtually all species (horizontal transfers).

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For decades since their discovery, TE existence, amount and ubiquity were key arguments in several major debates in theoretical biology:

- archetypes of the selfish gene, seen as ultimate parasites;
- only "junk DNA" or potential exaptations;
- possible role in the regulation of gene expression.

Annotation of TE content in sequenced genomes

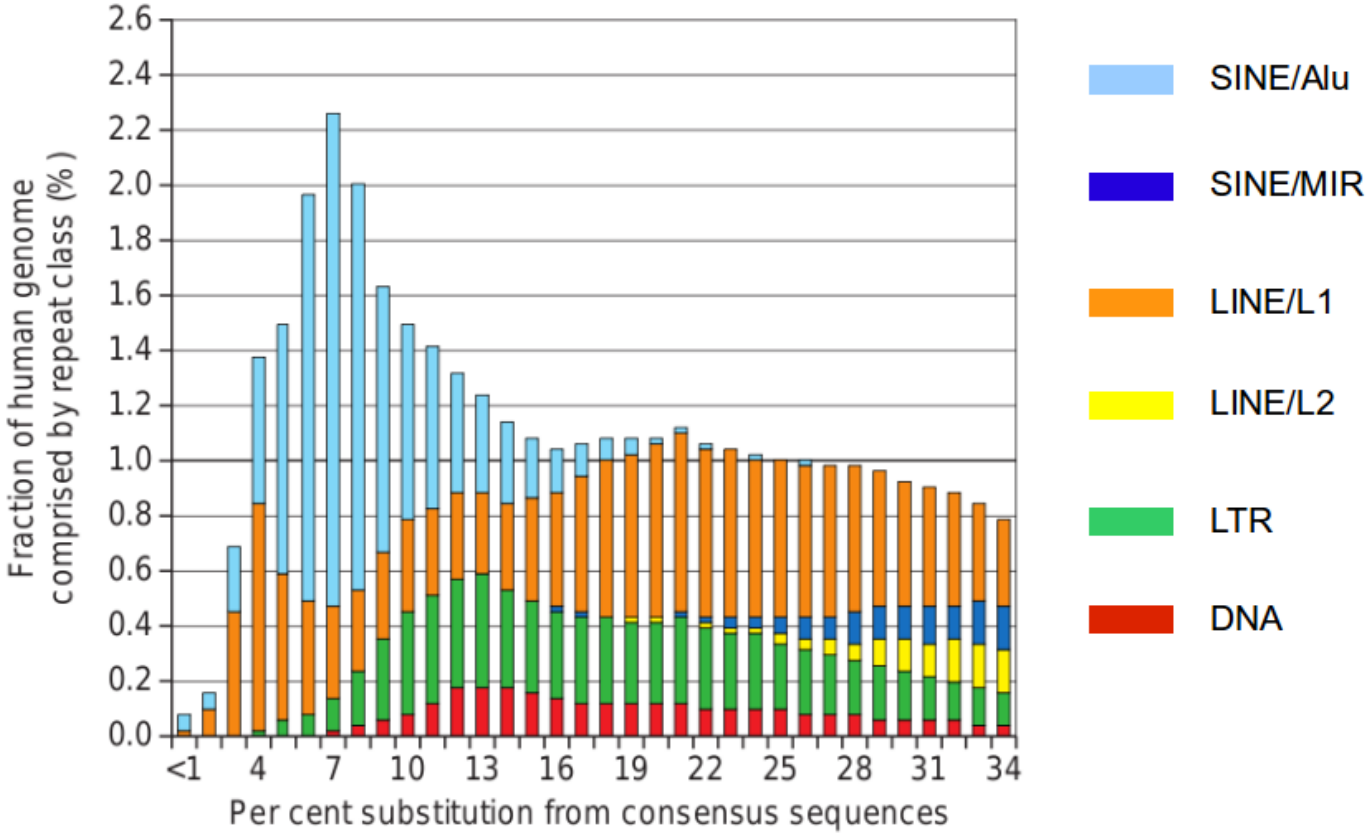

Figure: Relative age distribution of TE copies representing $\approx$ 45% of the 3-Gb human genome, annotated with known TE sequences (Lander *et al.*, 2001).

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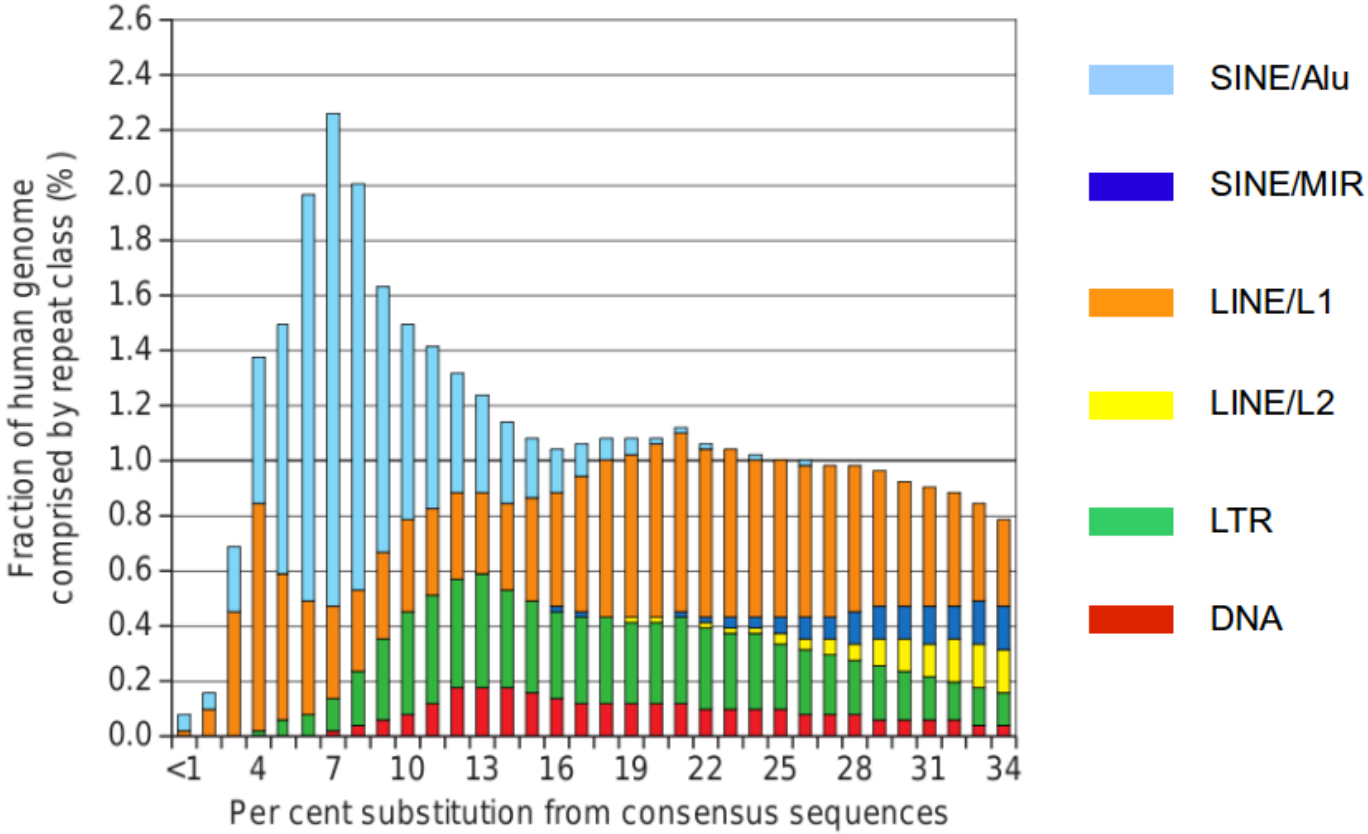

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For non-model species, *de novo* approaches are required.

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Impacts of TEs on gene expression

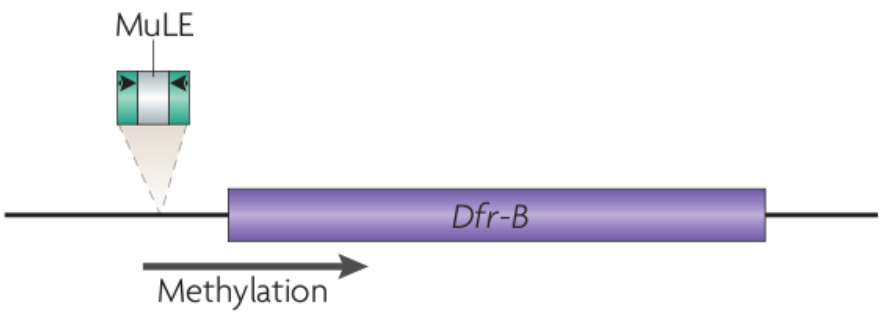

Figure: DNA methylation of a TE can spread to the promoter of a neighbouring gene, such as in morning glory flowers, causing petal-colour streaks (Slotkin and Martienssen, 2007).

Impacts of TEs on gene expression

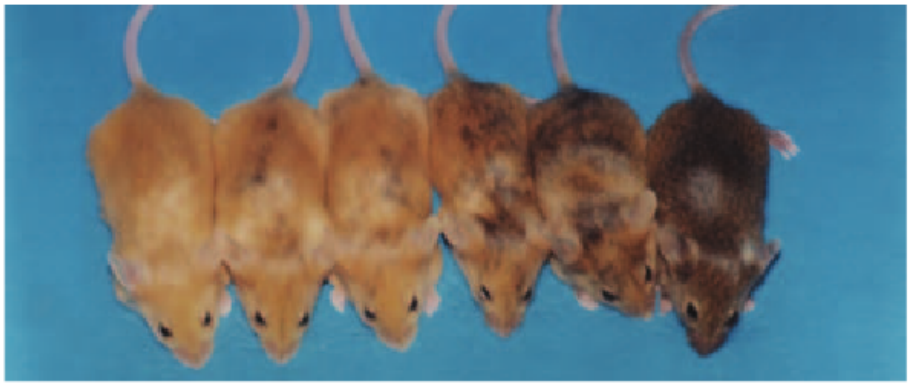

Figure: TEs can produce outward-reading transcripts that extend into neighboring genes, like here in mice where the transcription level of the *agouti* gene depends on the epigenetic status of a TE, thereby influencing coat darkness (Slotkin and Martienssen, 2007).

Impacts of TEs on gene expression

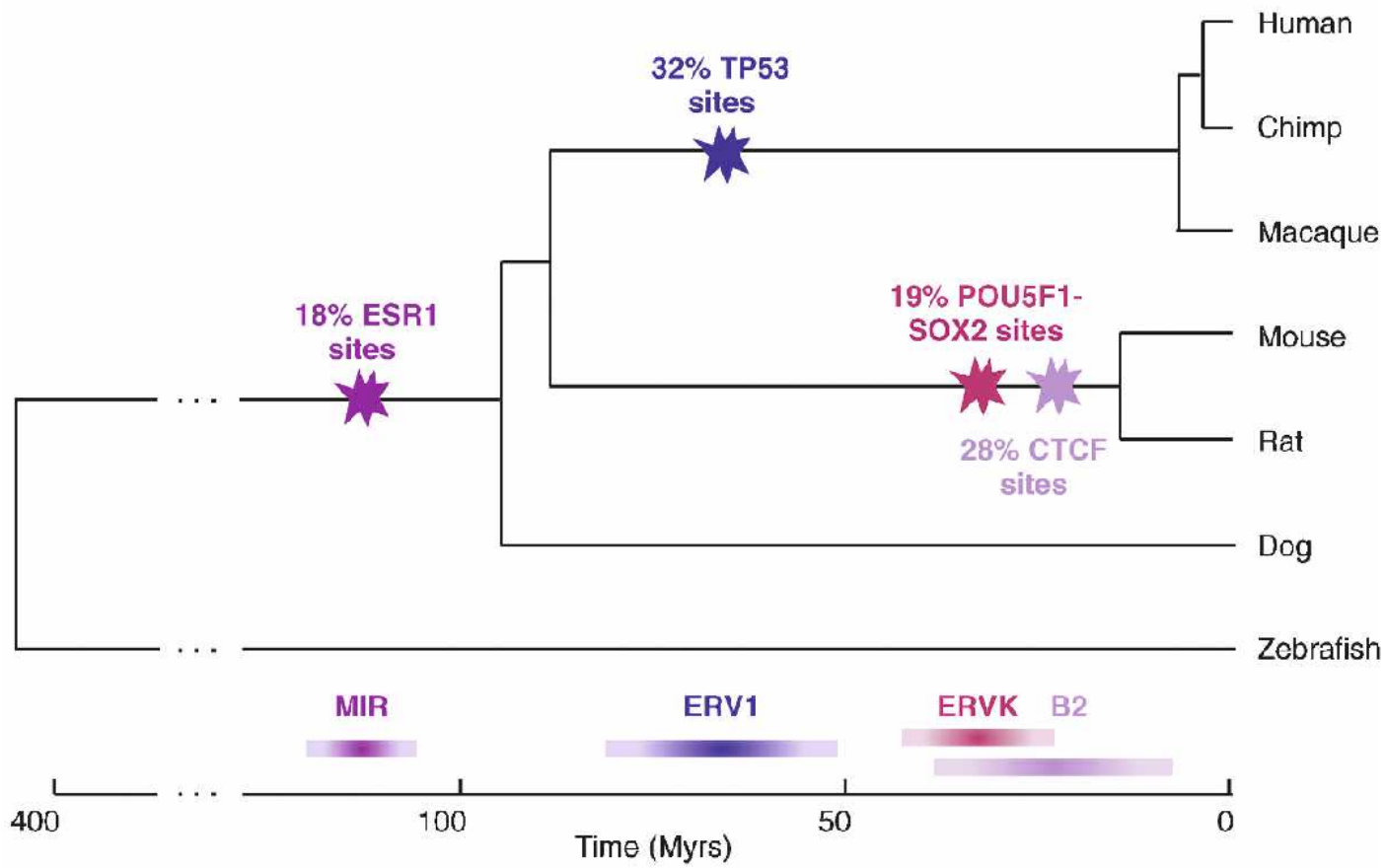

Figure: TE dynamics generate sequence diversity with potential impacts on regulatory networks, as shown here with the evolution of some mammalian transcription factor binding sites embedded within TEs (Bourque *et al.*, 2008).

Unified classification of eukaryotic TEs

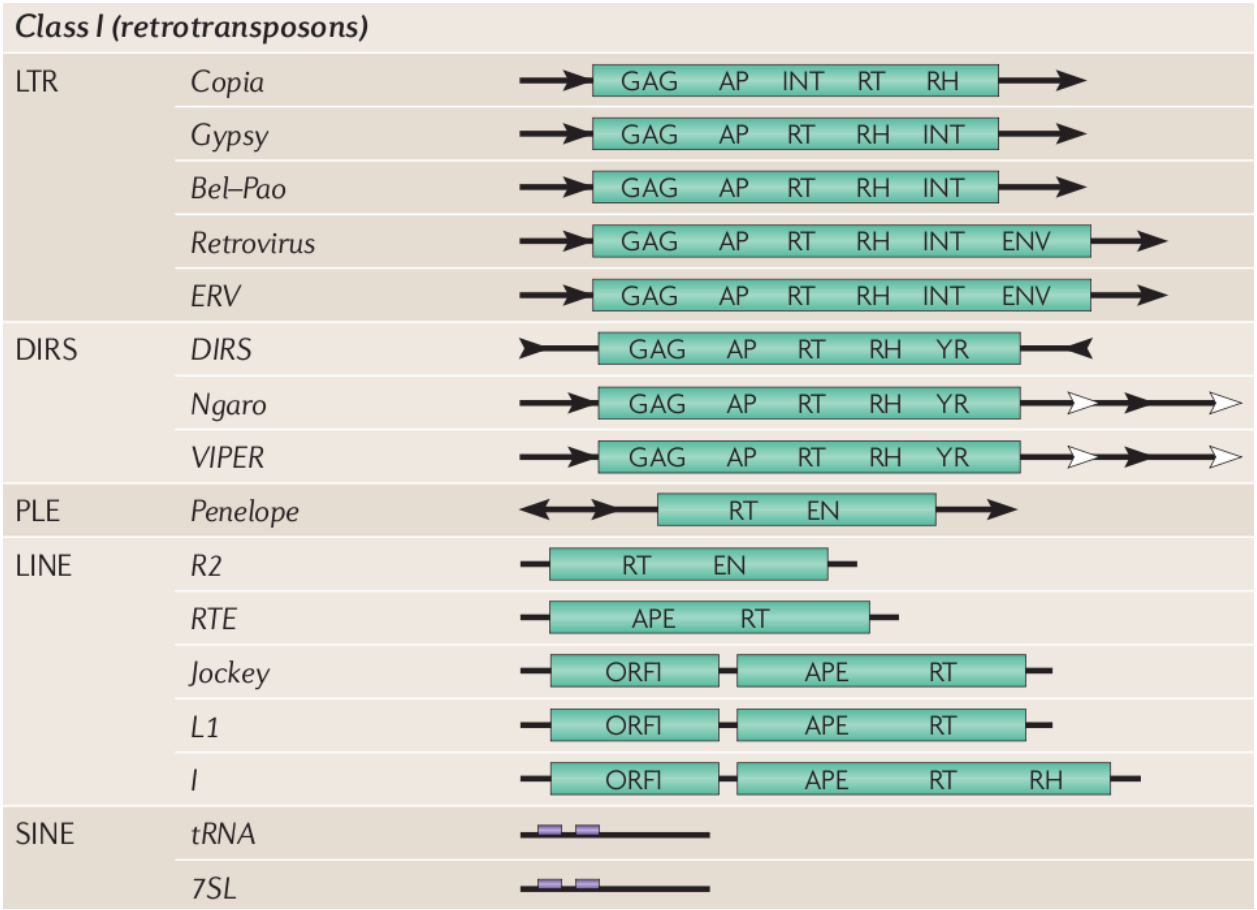

Figure: TEs from class I (Wicker *et al.*, 2007).

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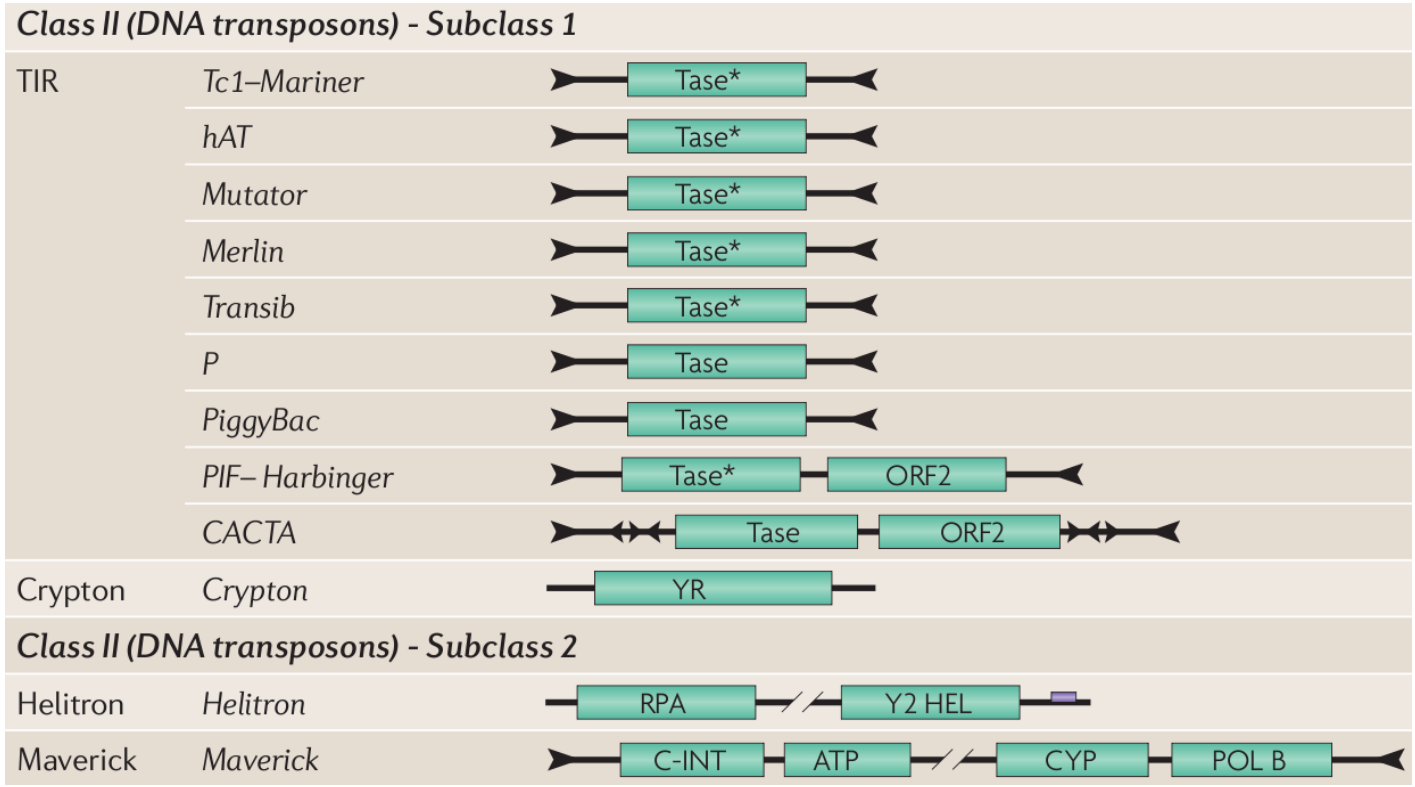

Figure: TEs from class II (Wicker *et al.*, 2007).

Presence of TE structural variants in genomes

However, several examples of TE structural variants have been found, which are not all easily accounted for by the current classification:

- non-autonomous TEs deriving from autonomous ones;
- chimeras resulting from the combination of two different TEs;
- TEs containing gene fragments from one or several genes.

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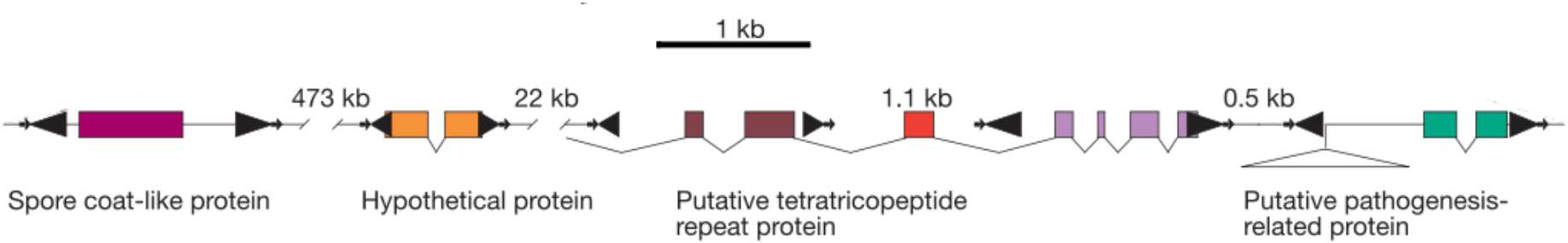

Figure: Examples of Pack-MULEs in the rice genome (Jiang *et al.*, 2004).

Questions

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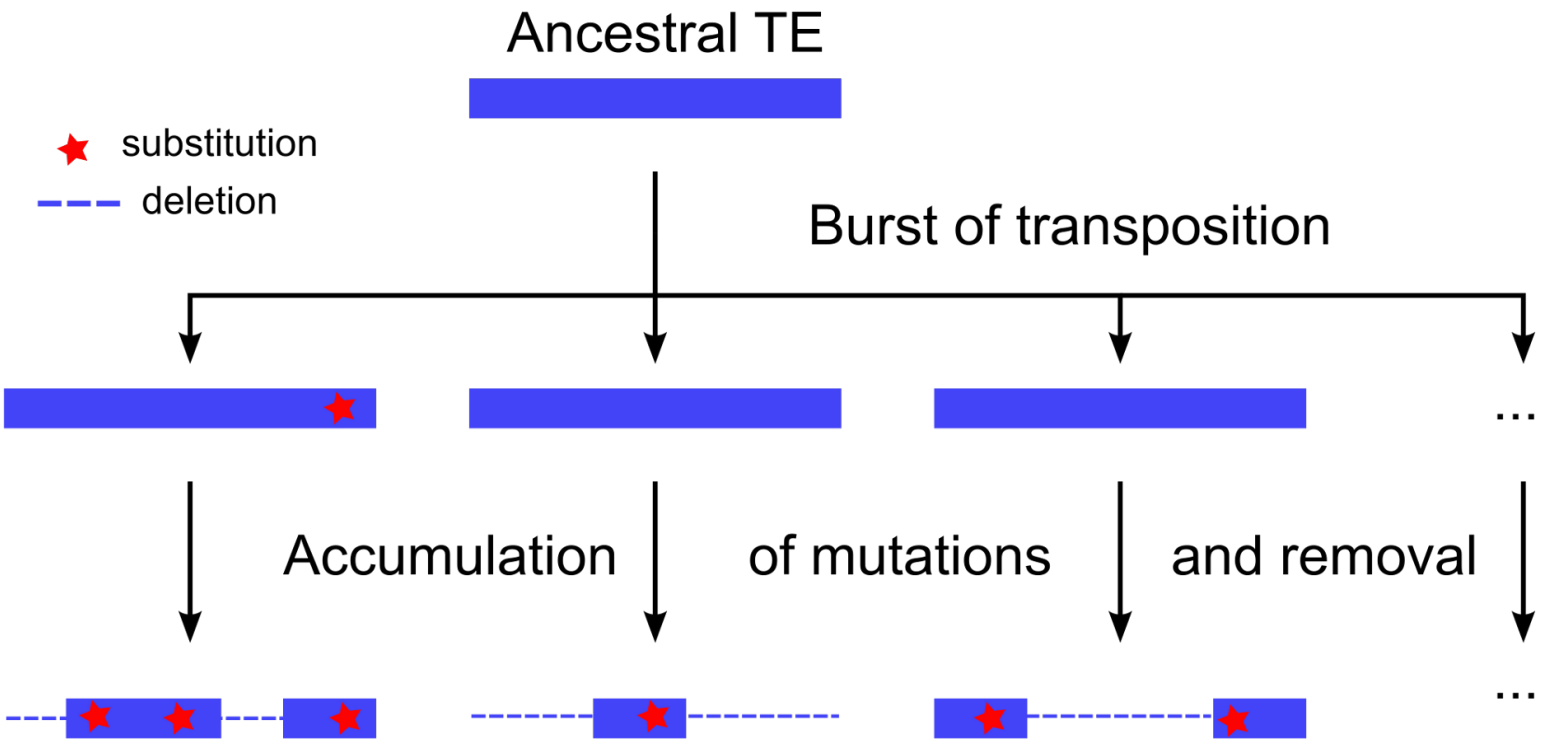
- What are the basic evolutionary principles from which the existing *de novo* programs were built?
- How reliable are their predictions? How is their quality assessed?
- Are they able to recover and distinguish structural variants belonging to the same TE family?
- How can we extend their scope and implement a robust tool to automatically annotate the TE content of newly sequenced genomes?
- What can we learn on TEs and genome biology in general using a *de novo* approach for TE detection?

Outline

Usual model of TE dynamics



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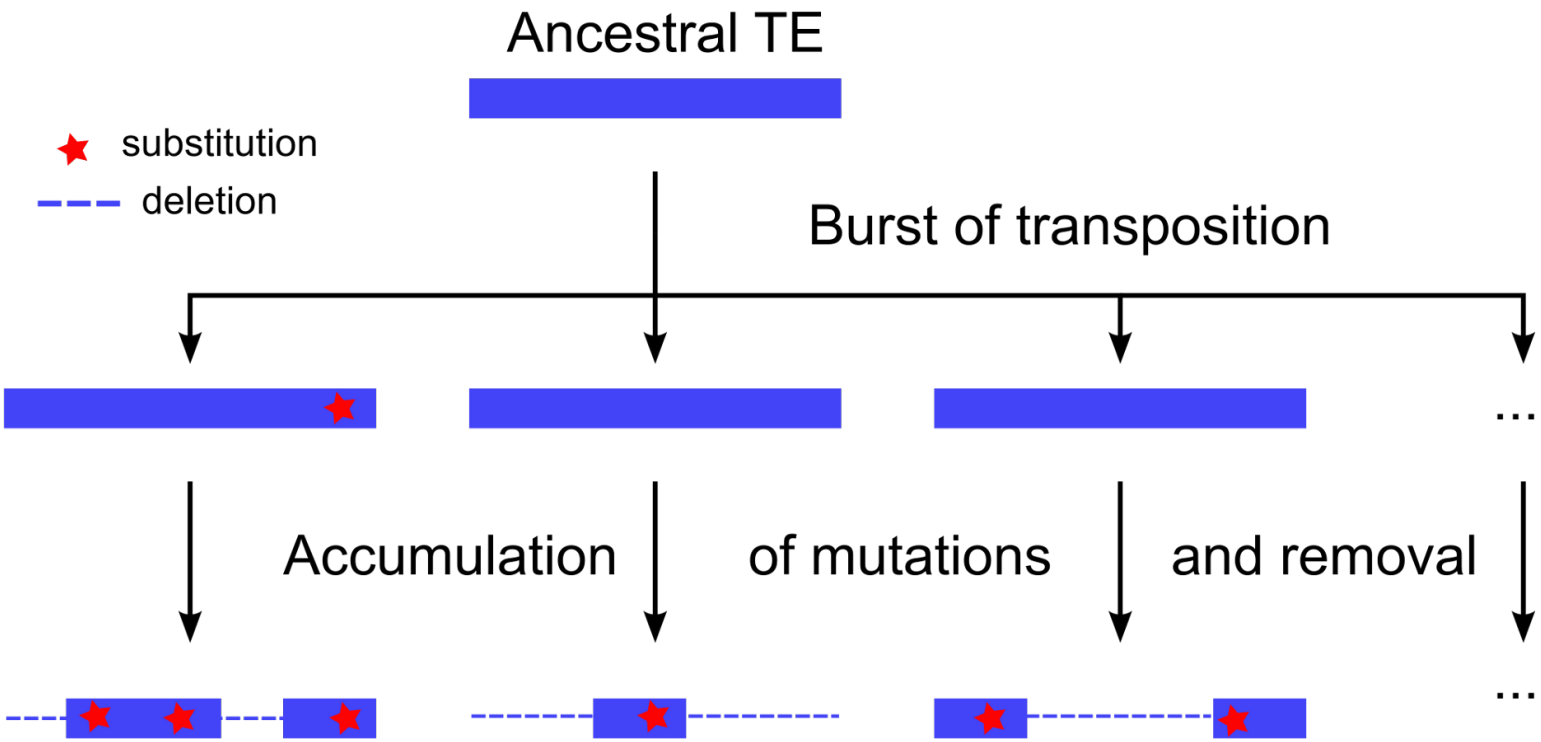


In this model of a TE family, the aim is to automatically recover the full ancestral TE as one consensus sequence.

Build *de novo* TE consensus

Raw genomic sequences
(pseudomolecules,
BACs, contigs, ...)

↓

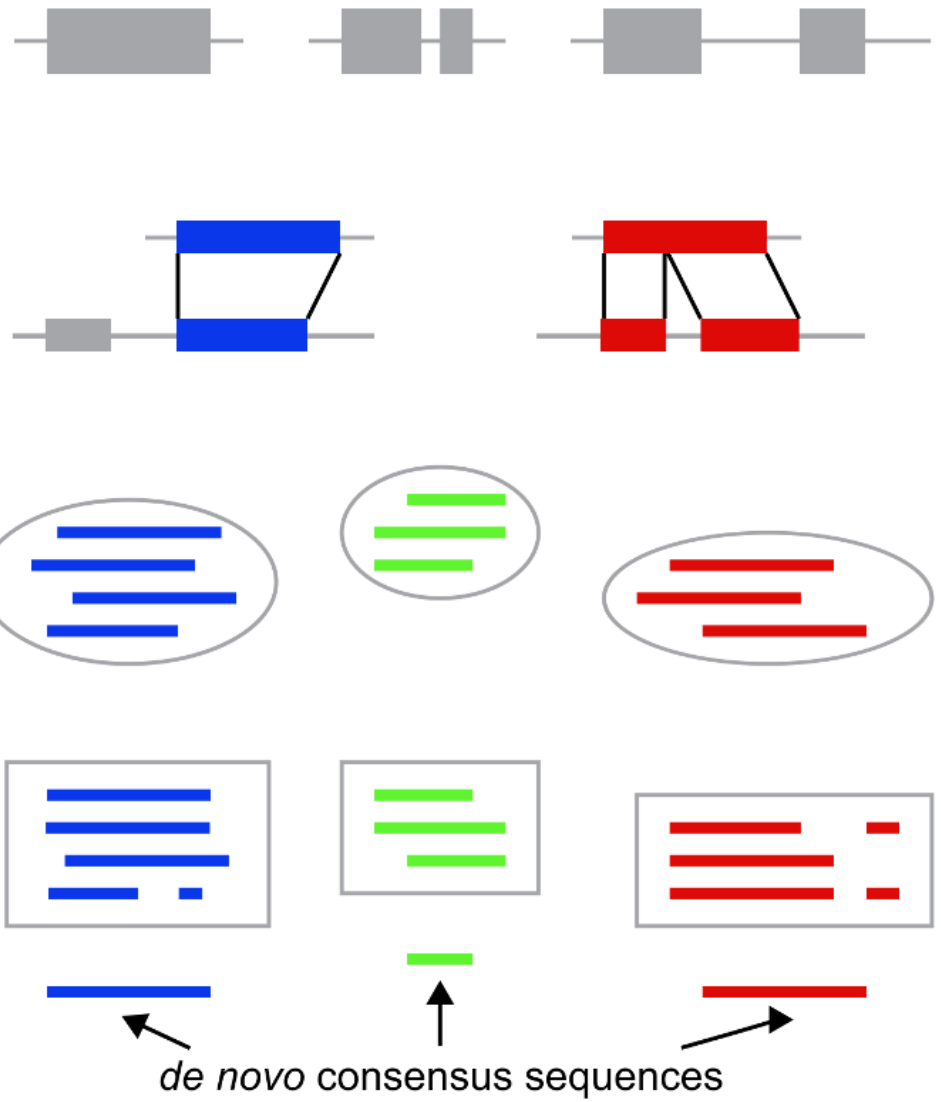
Self-alignment
(BLASTER or PALS)

↓

Clustering
(GROUPER, RECON
or PILER)

↓

Multiple alignment
(MAP, MAFFT, MUSCLE,
PRANK or CLUSTAL-W)



Material and datasets

We chose 2 well-known, small genomes to perform the analysis:

- *D. melanogaster*, release 4, 129 Mb (mainly euchromatin)
- *A. thaliana*, release 9, 119 Mb

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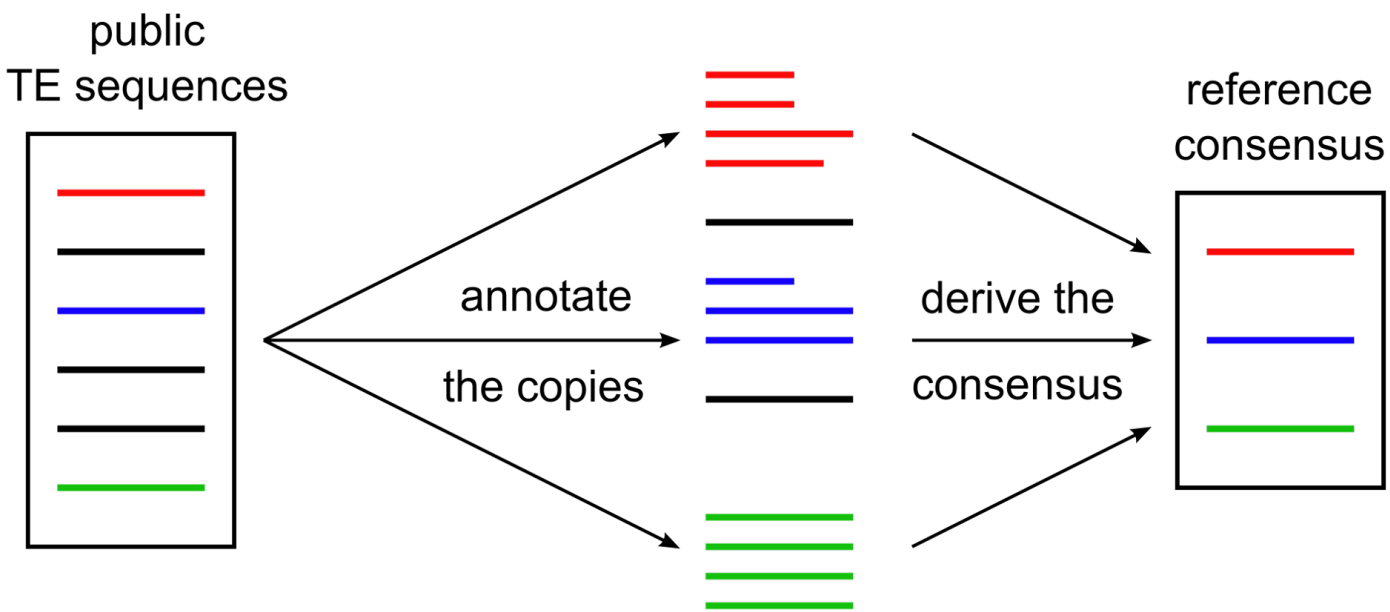
Moreover, known TE sequences are publicly available for these genomes:

- Berkeley Drosophila Genome Project: 126 sequences
- Repbase for *A. thaliana*: 318 sequences.

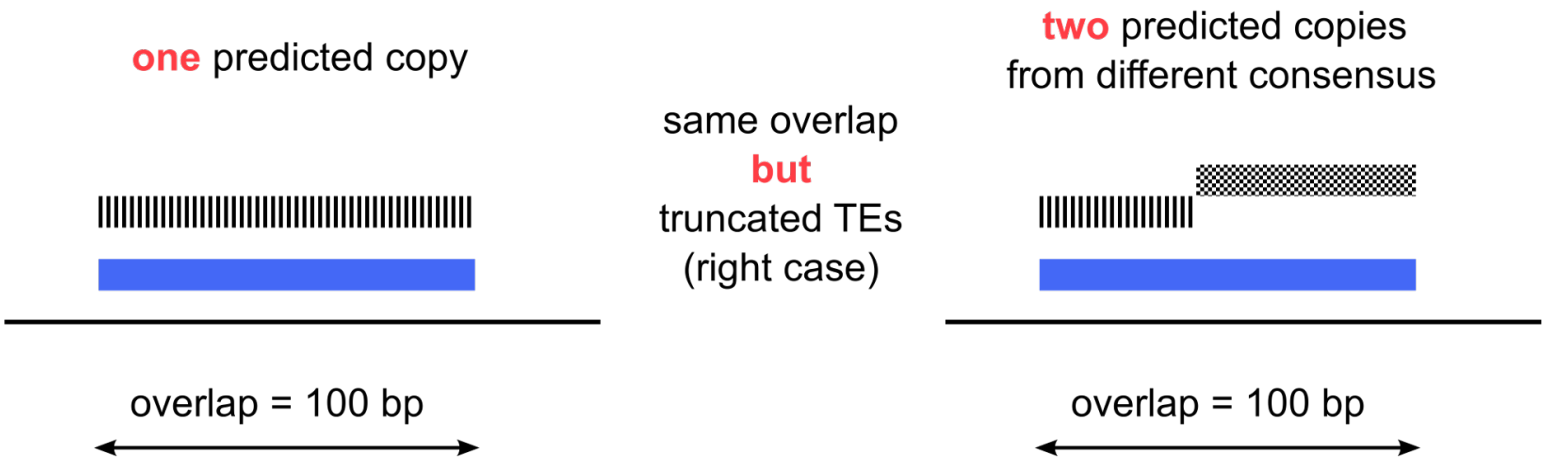
Build appropriate reference datasets

To prevent building *de novo* consensus not corresponding to TEs (e.g. duplications), only TEs with 3 copies are considered. Therefore, I built appropriate reference databanks (*ref*) for both model genomes.



Improve the test protocol of the *de novo* approach

Usually, to check the quality of a *de novo* approach, one computes the nucleotide overlap between predicted copies and known copies:



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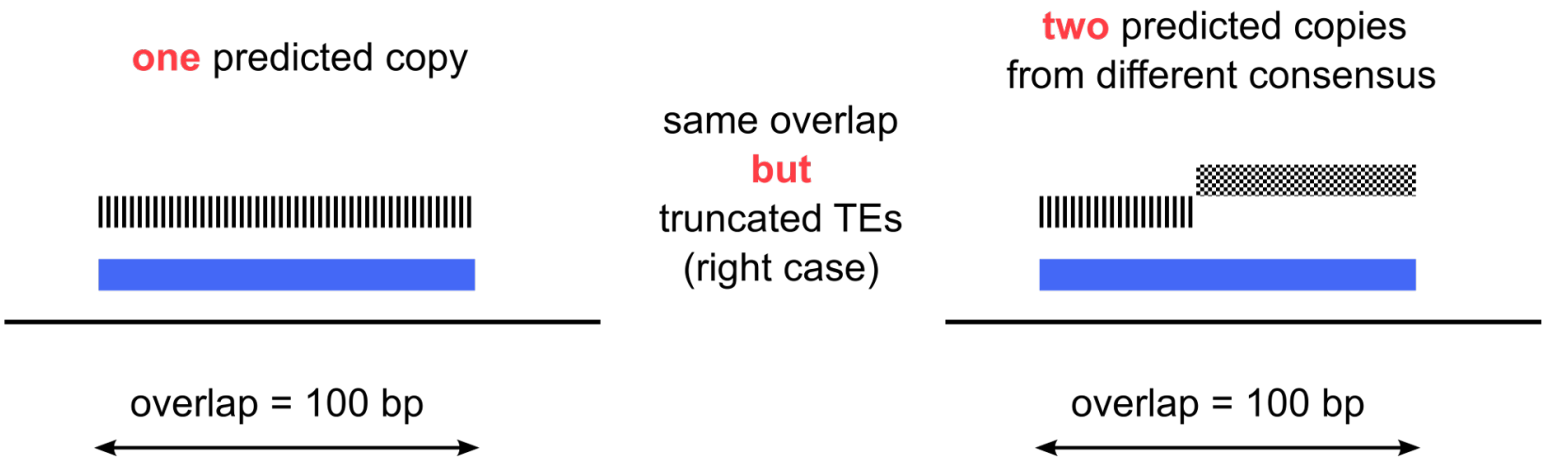

Here, need also to align the *de novo* consensus with the *ref* consensus:

- S'_n: proportion of *ref* consensus matching *de novo* consensus;
- S'_p: proportion of *de novo* consensus matching *ref* consensus;
- R_{CC}: close to 1 $\rightarrow$ many *ref* consensus are fully recovered.

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Self-alignment of the genomic sequences

- Align the whole genome with itself using stringent parameters:
  - BLASTER (Quesneville *et al.*, 2003): BLAST wrapper, heuristic
  - PALS (Rasmussen *et al.*, 2006): find all local alignments over a given length with an error rate lower than a given threshold, exact algorithm

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A. tha.	BLASTER	103,728	13.48%
	PALS	51,023	10.53%

Clustering of the all-by-all matches

- Launch clustering programs specific of interspersed repeats:
  - GROUPER (Quesneville *et al.*, 2003): chain the matches, then single-link clustering (95% coverage)
  - RECON (Bao and Eddy, 2002): single-link clustering (50% coverage) and handle segmental duplications, then single-link clustering (90% coverage) and handle related TE families
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Genome	all-by-all	GROUPER	RECON	PILER	Reference consensus
D. mel.	BLASTER	730	451	120	117
A. tha.	BLASTER	1428	1021	300	305

Multiple sequence alignment for each cluster

- Launch progressive multiple alignment programs:
  - MAP (Huang, 1994): no penalty for gaps beyond a given length
  - CLUSTAL-W (Thompson *et al.*, 1994): first to propose position-specific gap penalties
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Genome	all-by-all	clustering	MSA	R_{CC}
D. mel.	BLASTER	RECON	MAP	66.2%
			CLUSTAL-W	20.6%
			MAFFT	54.4%
			PRANK	61.8%

Results and comparison with RepeatScout

Genome	Program	Consensus	$S_n^{'}$	$S_p^{'}$	R_{CC}
D. mel.	GROUPER	730	80%	86%	66%
	RECON	451	92%	73%	66%
	PILER	120	62%	84%	51%

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	RECON	1021	74%	62%	43%
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Moreover they appear to be complementary.

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Moreover they appear to be complementary.

Genome	Program	Consensus	$S_n^{'}$	$S_p^{'}$	R_{CC}
D. mel.	RepeatScout	1770	95%	58%	25%
A. tha.	RepeatScout	3417	83%	40%	13%

Combined approach in the TEdenovo pipeline

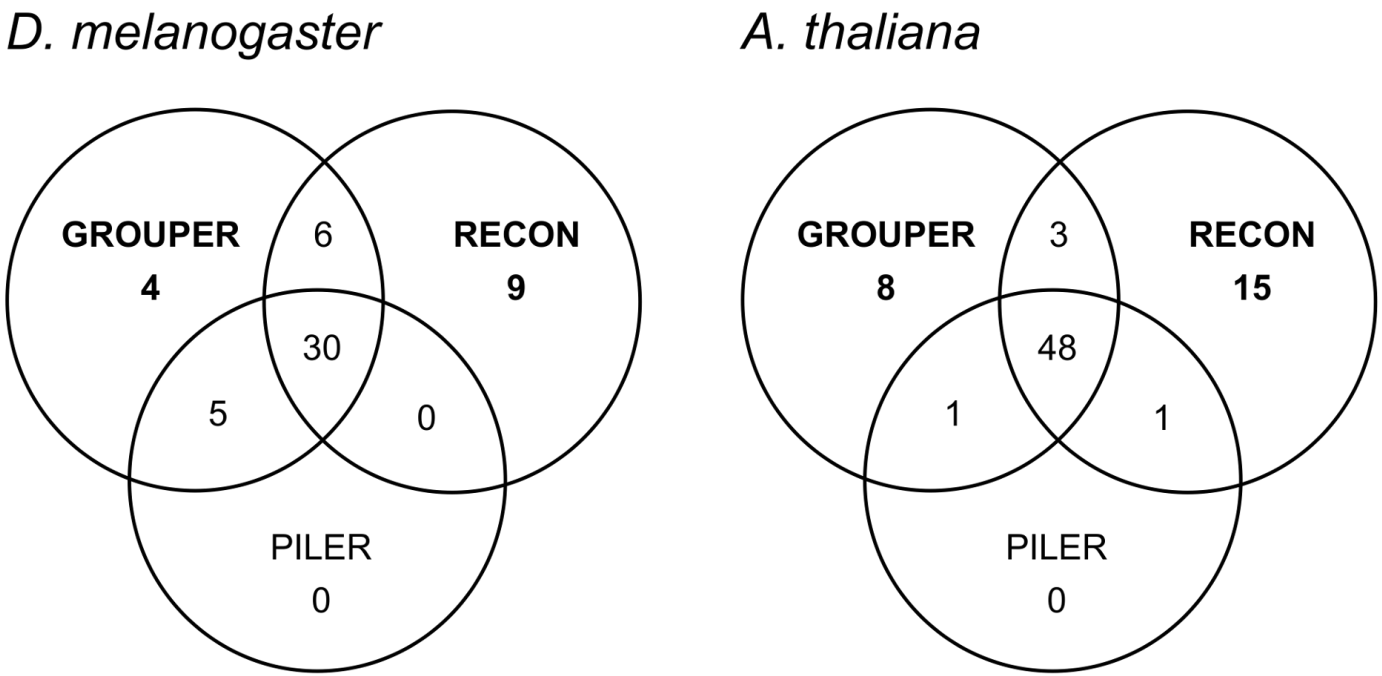

Figure: Number of TE reference sequences fully recovered by a *de novo* consensus.

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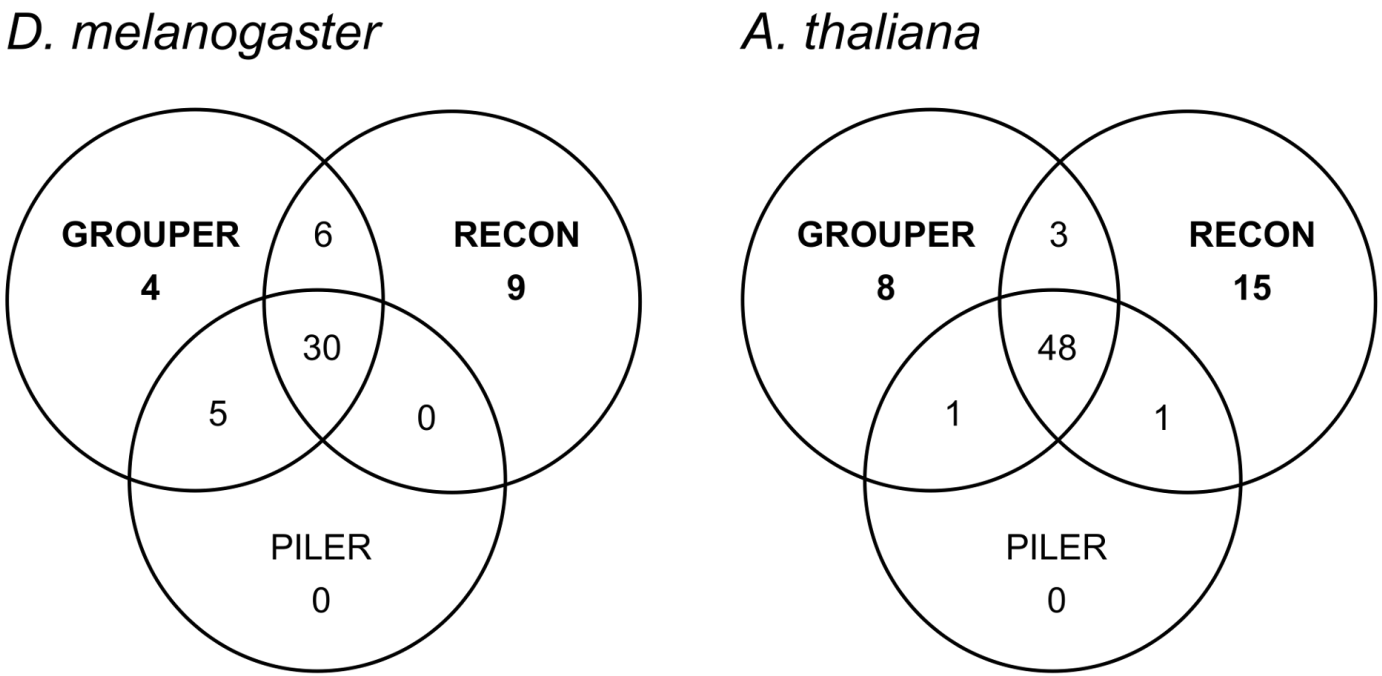

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Combining several clustering programs enables to recover more full-length TE reference sequences.

Classification of consensus sequences

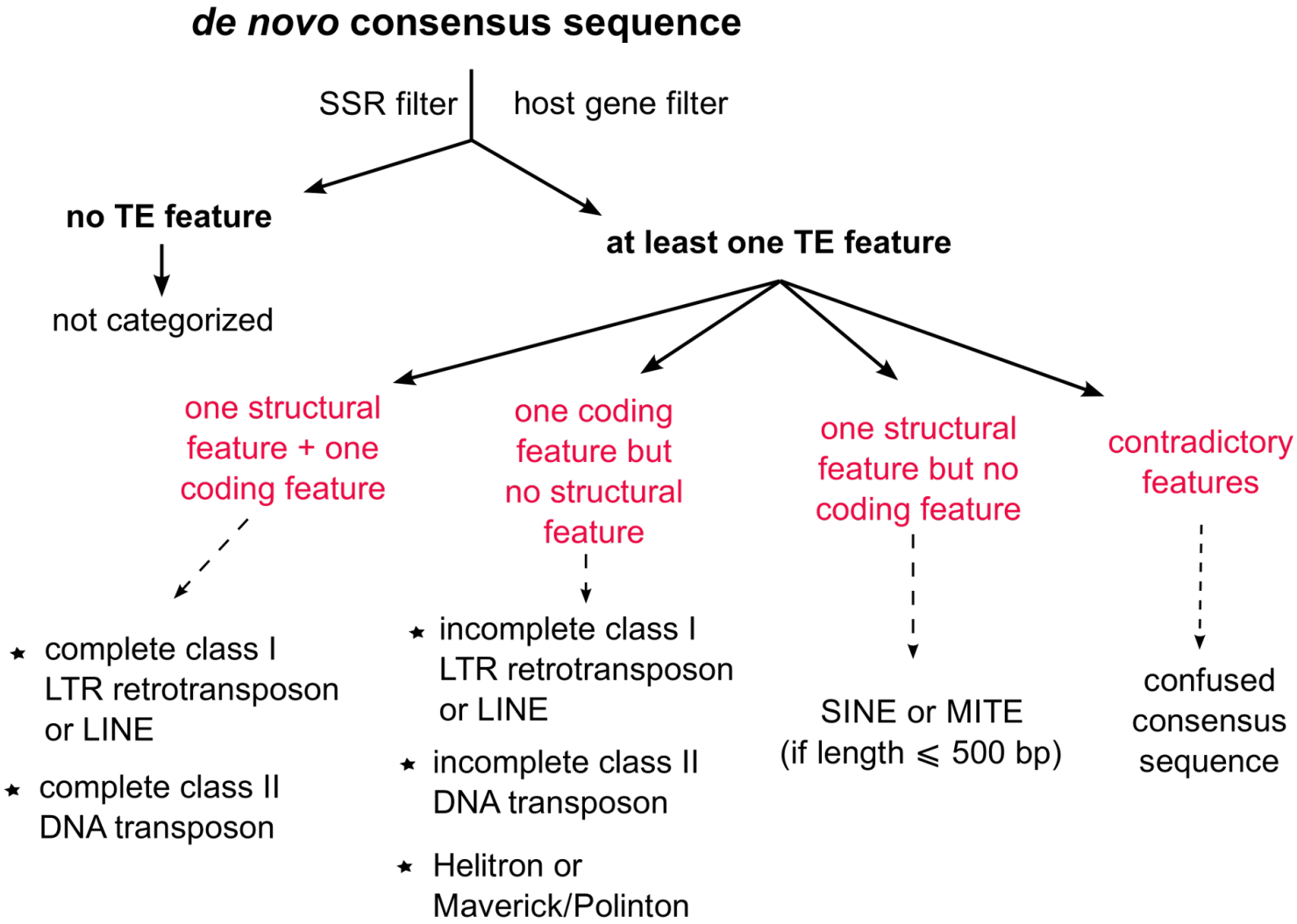

Figure: Simplified decision tree implemented in the TE classifier

Redundancy removal and validation

For instance, an "incomplete" LTR retrotransposon is removed when included over 98% of its length into a "complete" LTR retrotransposon with an identity over 95%.

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	95-98	593	92%	75%	78%
A. tha.	no	2749	74%	72%	49%
	95-98	1275	74%	67%	49%

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At the end of the TEdenovo pipeline, a databank of TE *de novo* consensus sequences is generated, of high quality and low redundancy.

TE copy annotation with TEannot

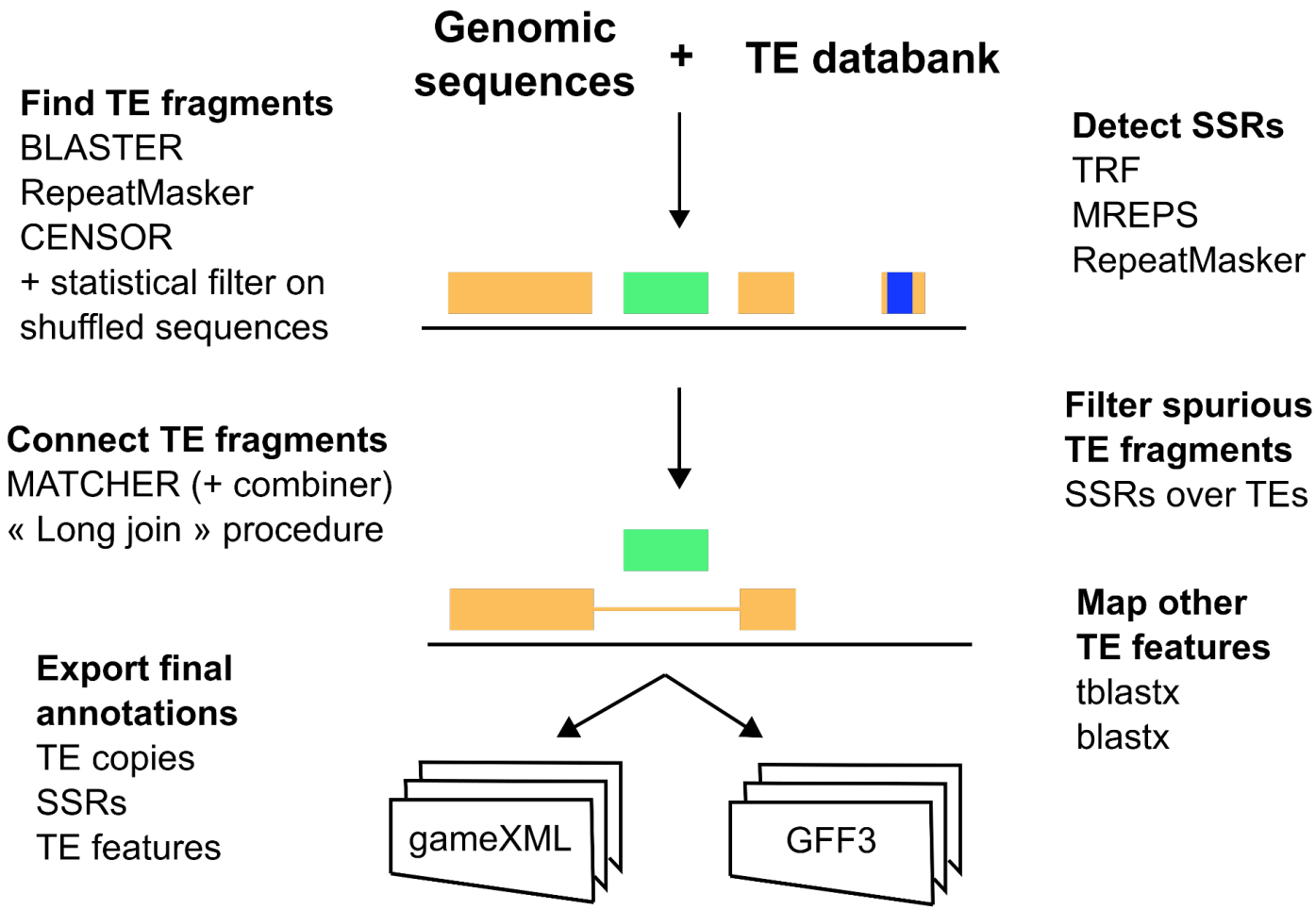
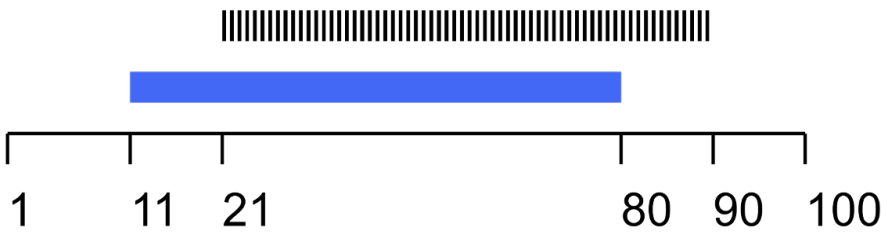


Figure: Flow chart of the TEannot pipeline (Quesneville *et al.*, 2005) on which I improved several steps to better handle the databanks of *de novo* consensus.

Validation of TE annotation with *de novo* consensus



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Sn = 60 / (60 + 10) = 86%

Specificity = TN / (TN + FP)
Sp = 20 / (20 + 10) = 67%

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D. mel.	BDGP	125	11%	na	na
	TEdenovo	568	12%	91%	97%
A. tha.	Repbase	318	19%	na	na
	TEdenovo	1232	23%	87%	92%

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Using TEdenovo and TEannot enables to automatically annotate the TE content of newly sequenced genomes with good results.

Outline

Extensive structural variation within TE families

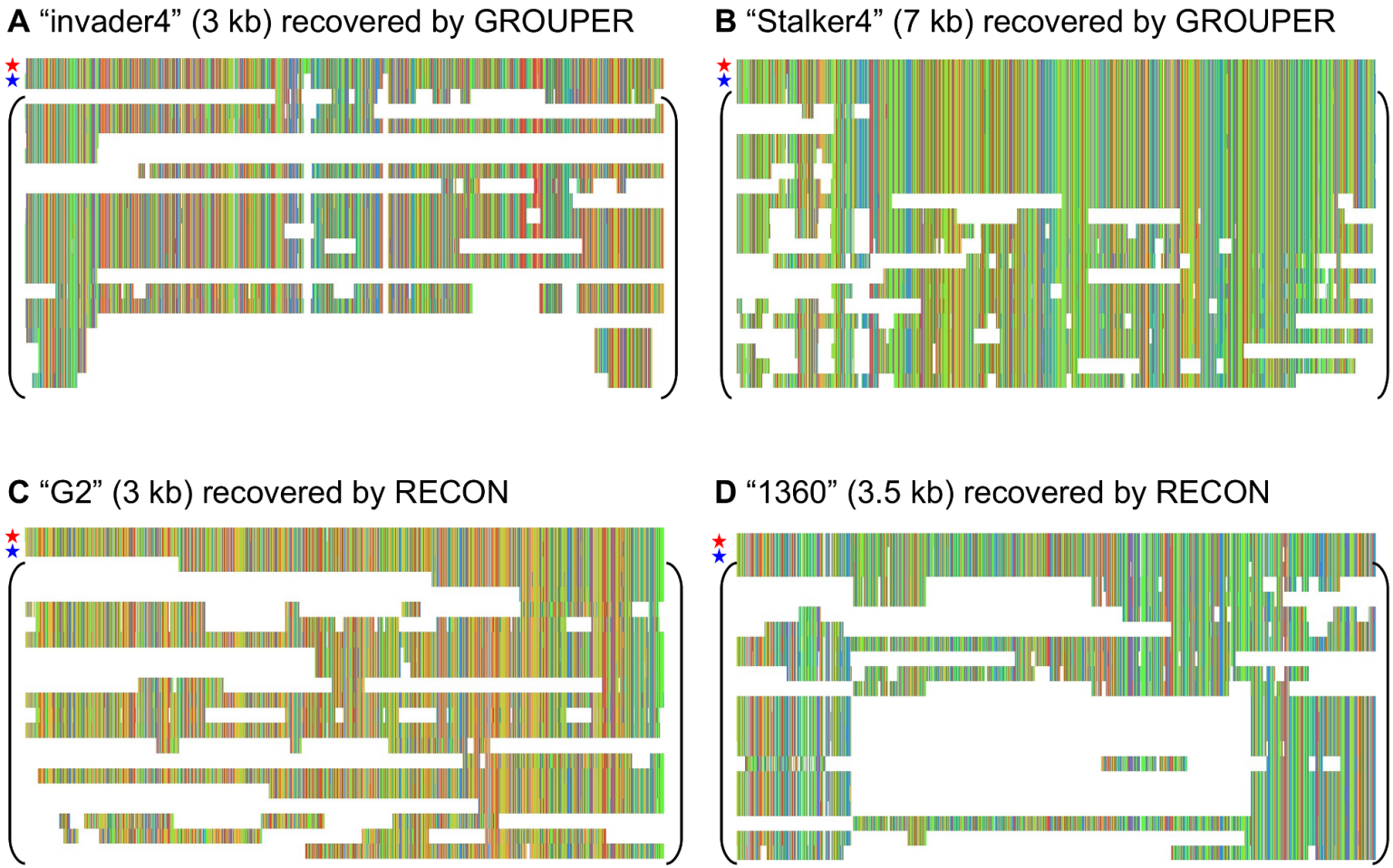

Figure: TE families for which only one clustering method fully recovered the reference sequence (red star: the reference sequence; blue star: the *de novo* consensus; in brackets: the genomic copies; one color per nucleotide).

Interpreting the diversification of a TE family?

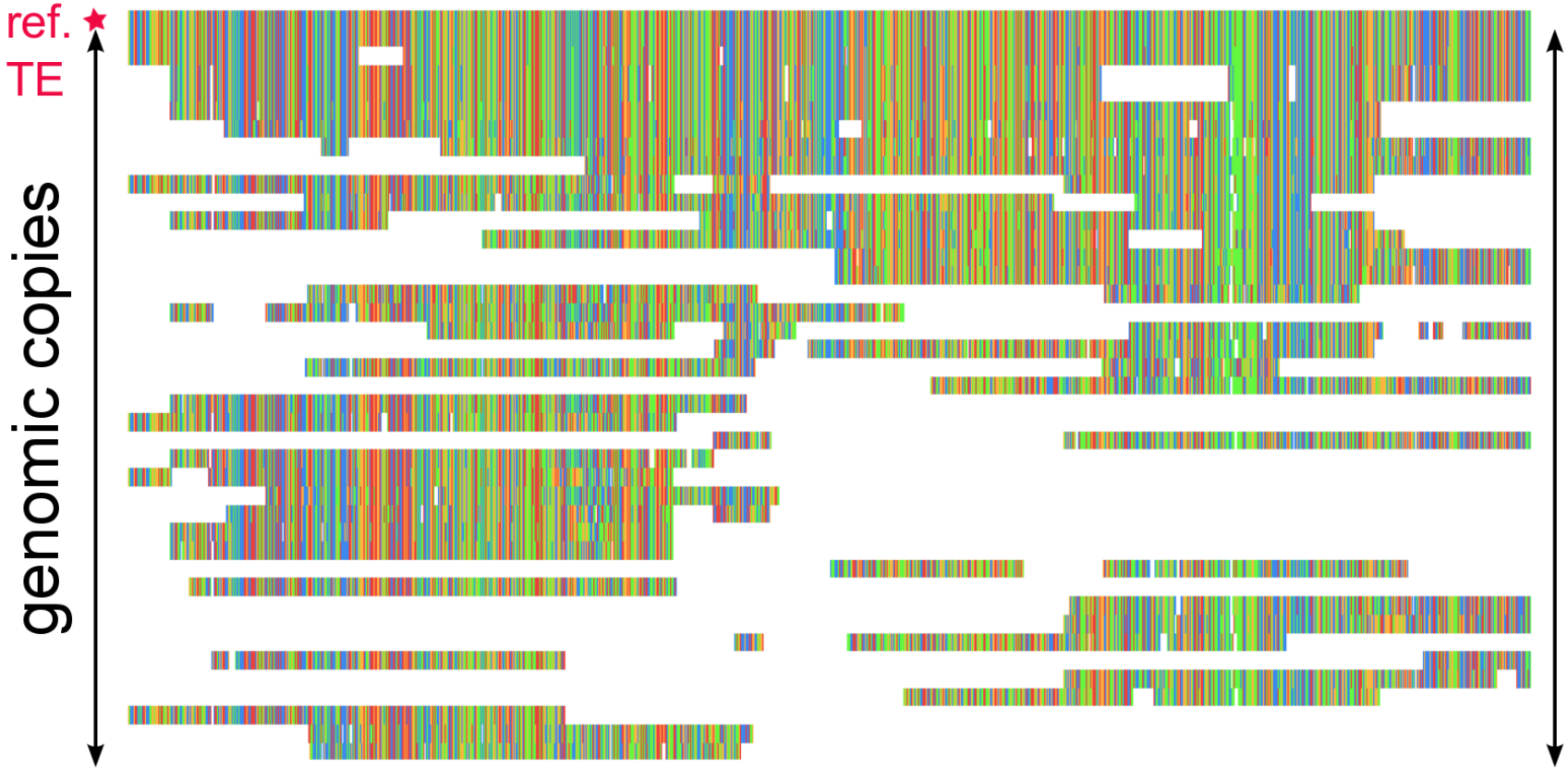

Figure: Multiple alignment of the "Athila" reference sequence (red star) with some of its longest genomic copies (black arrows).

Recovering several *de novo* consensus per TE family

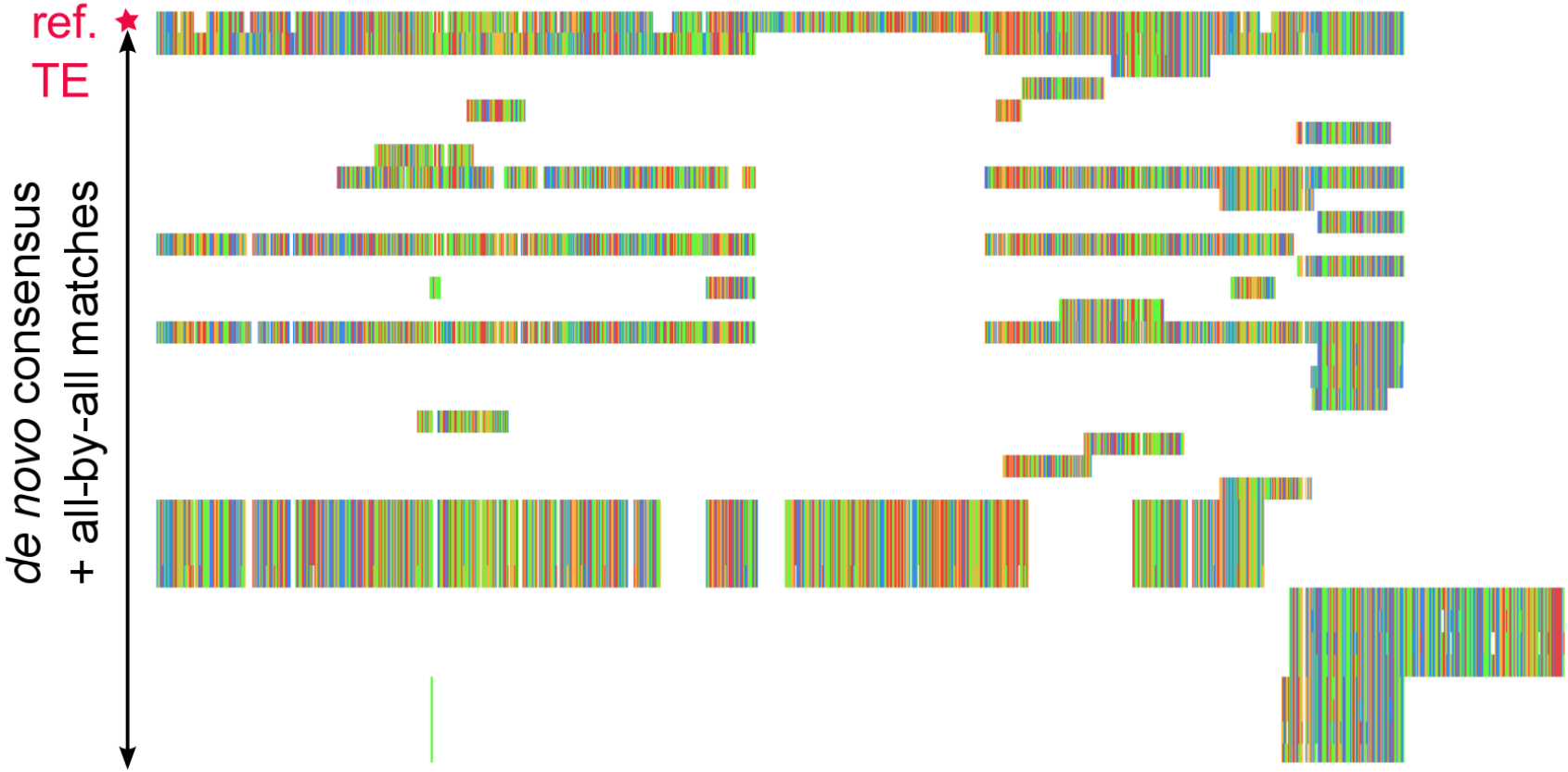

Figure: Multiple alignment of the "Athila" reference sequence (red star) and its 4 *de novo* consensus sequences, to which are added the all-by-all matches from which they were derived.

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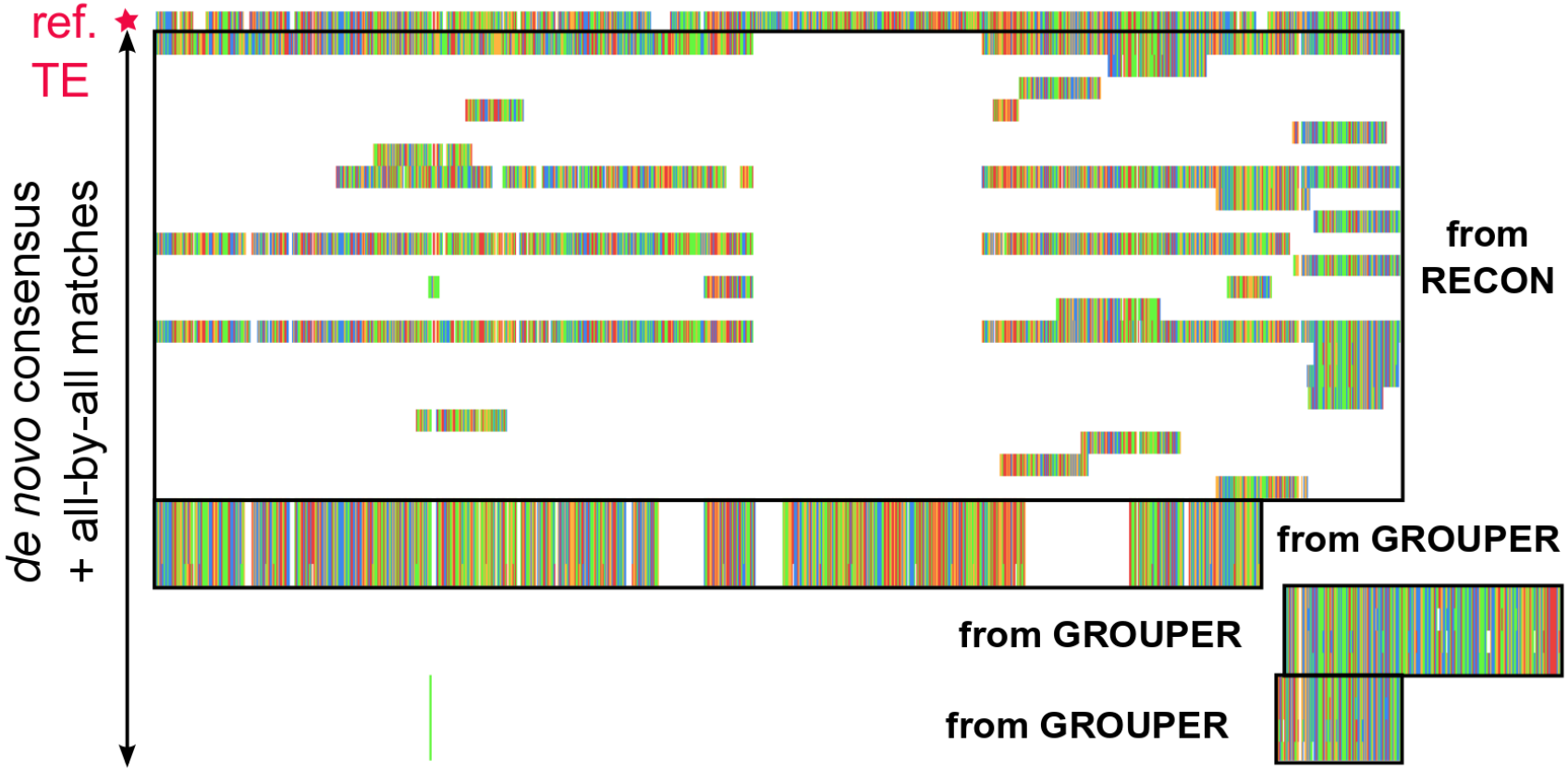

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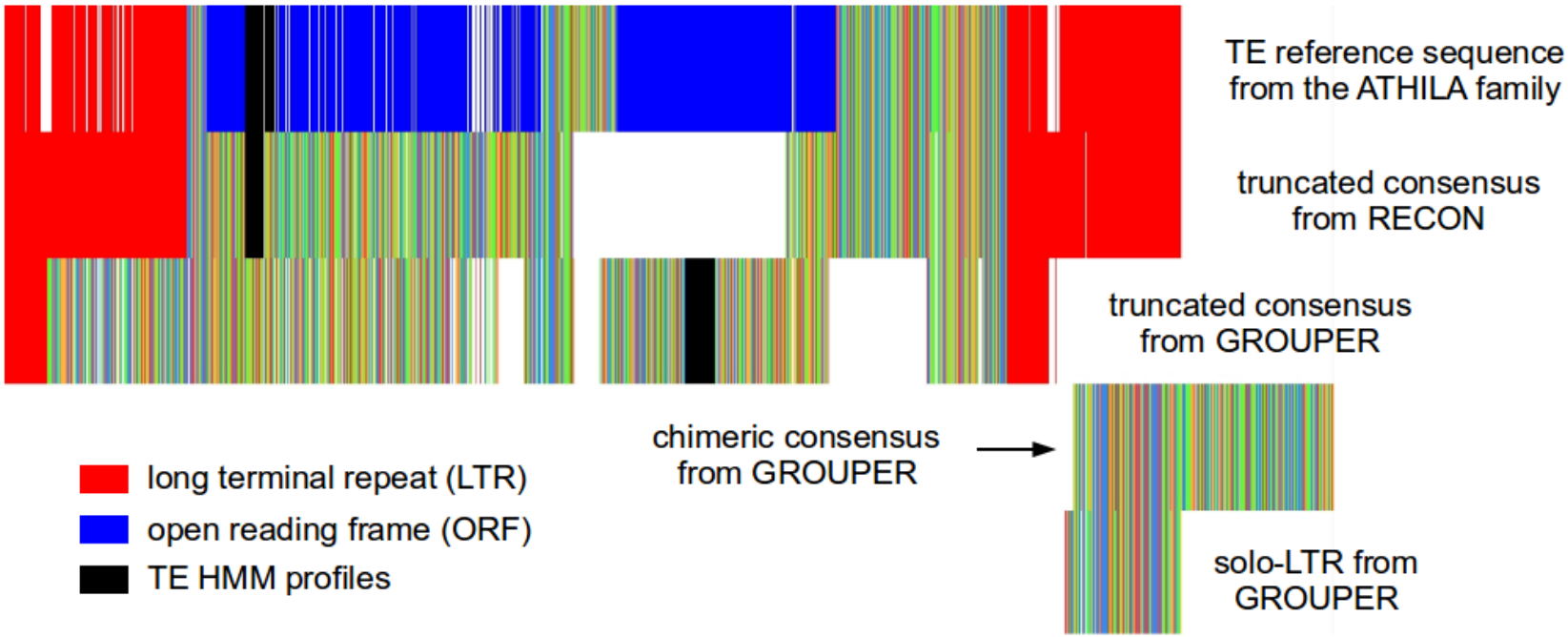
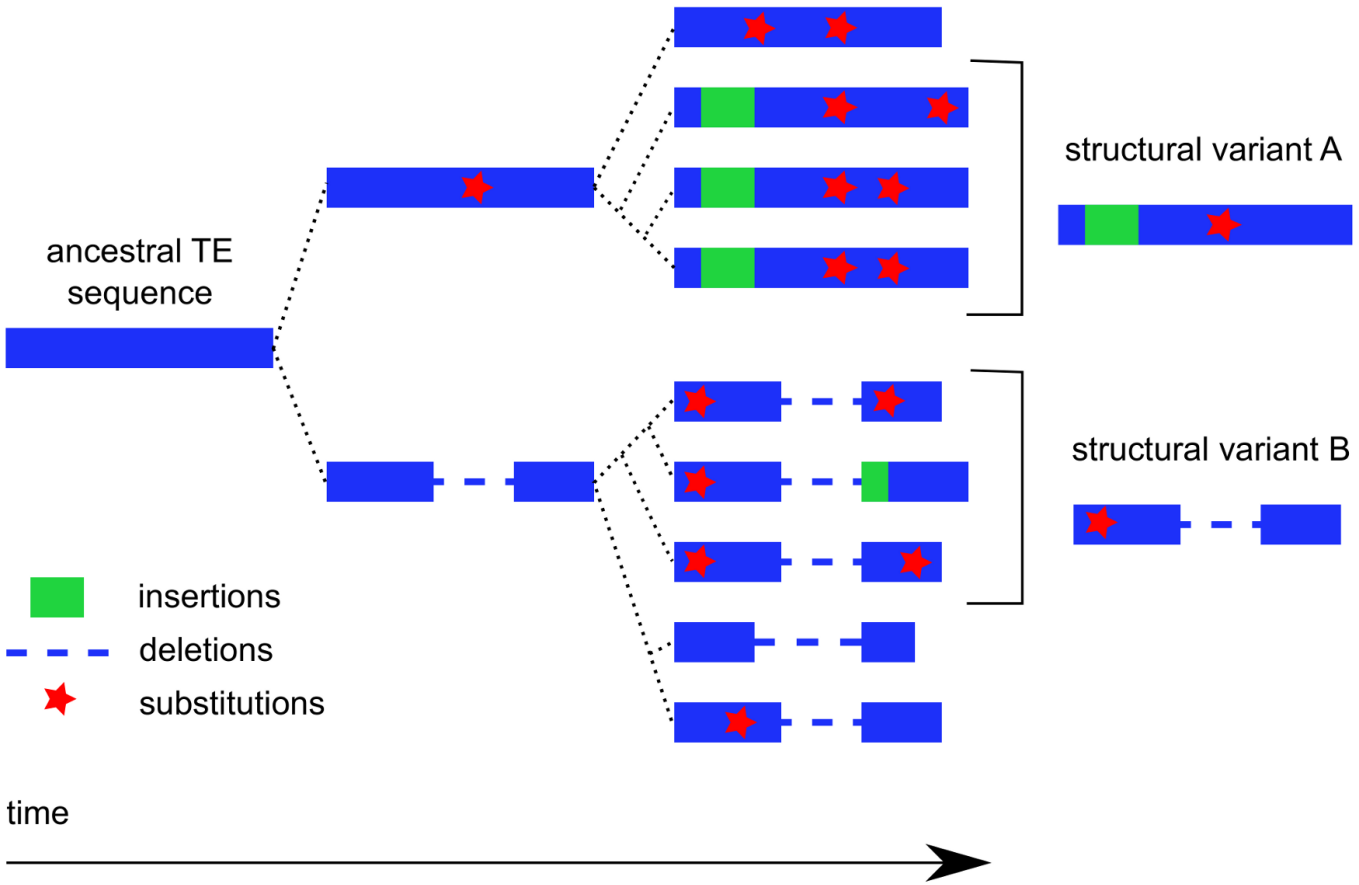
Advantage of this *de novo* approach



Enabling the interpretation of TE diversification, and building hypotheses concerning the mechanisms behind the emergence of structural variants.

Taking TE structural variations into account



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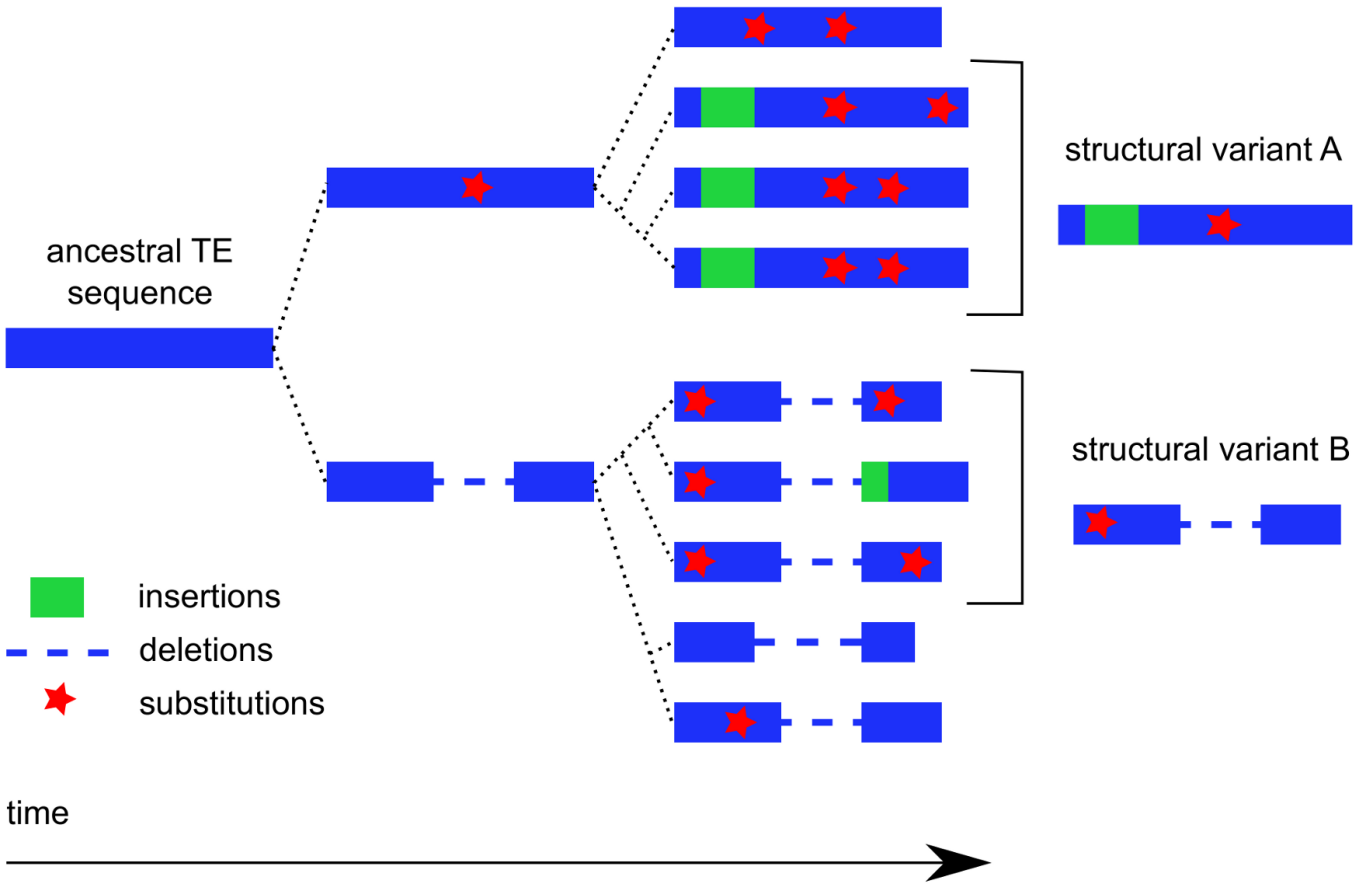

This work, from the comparative analysis to the results on TE diversification, was recently submitted (currently under review).

Outline

From TE annotation to biological questions

- TE annotation of the *M. incognita* genome
  - co-author, published in Nature Biotechnology (2008)
  - asexual plant-parasitic nematode
  - small genome (86 Mb) but high TE content (35%)
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- Correlation between TEs and synteny breaks in holocentric genomes
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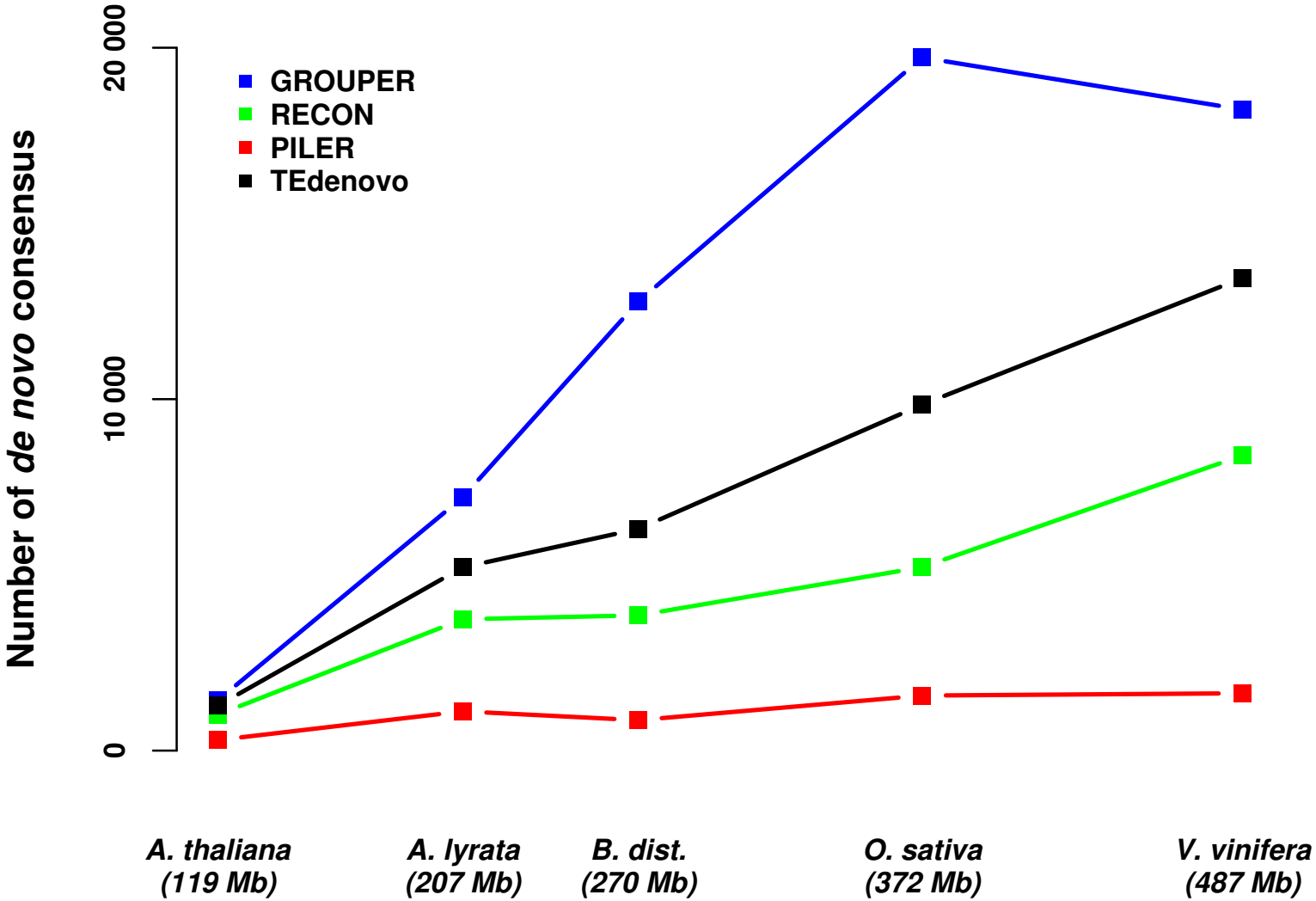
  - TE annotation in 15 syntenic BACs of Lepidopterans
  - correlation with synteny breaks which occurrence rate is 4x higher than in Drosophilidae, itself 2x higher than in mammals

Differential TE diversification in plant genomes



(Analysis on *V. vinifera*: with N. Choisne; for GROUPER, only clusters with 4 members were kept)

Projects benefiting from the pipelines

- TriAnnot, the web interface to annotate Triticeae BACs, with P. Leroy, F. Giacomoni and A. Bernard from GDEC (is underway);

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- Population genetics of TEs in Drosophilidae genomes, with A-S. Fiston-Lavier and D. Petrov from Stanford (is underway).

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Preliminary analysis for future improvements

- Unification of TE clustering algorithms:
  - new algorithm combining the advantages of GROUPER and RECON
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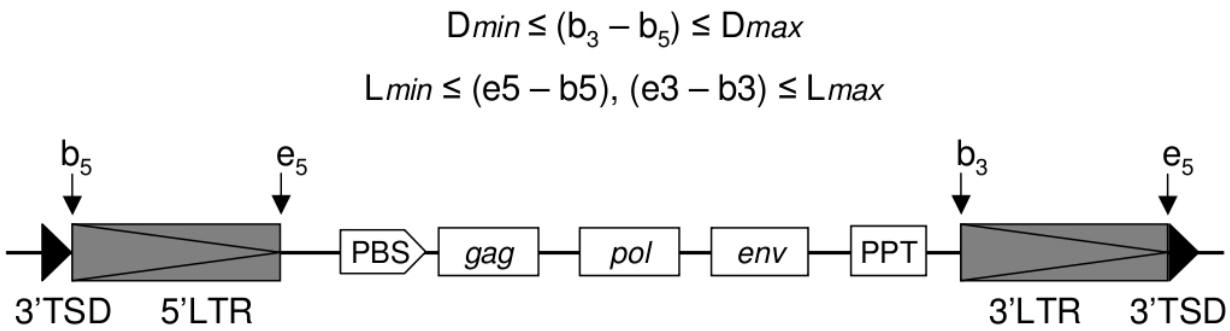

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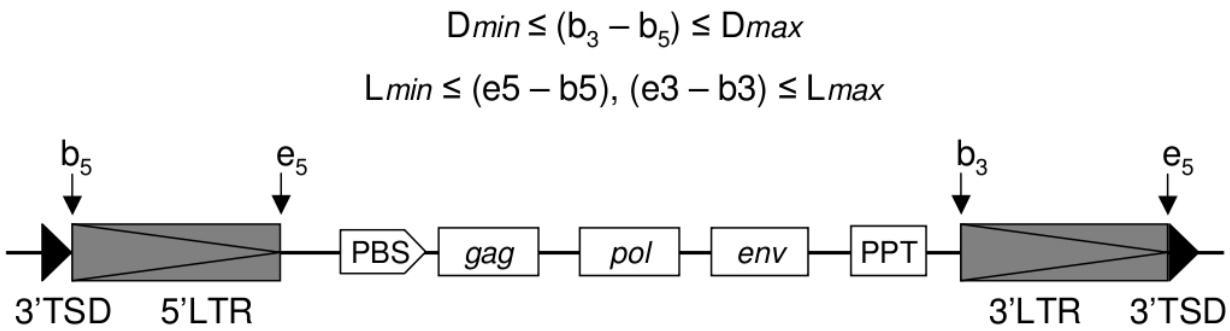

- Strategies to annotate large genomes:
  - "light" TEannot and "iterative splicing"
  - TE detection quality on genomes sequenced with NGS

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Main obstacle: in computational biology, how to test a *de novo* approach when no experiment can directly confirm or invalidate the predictions?

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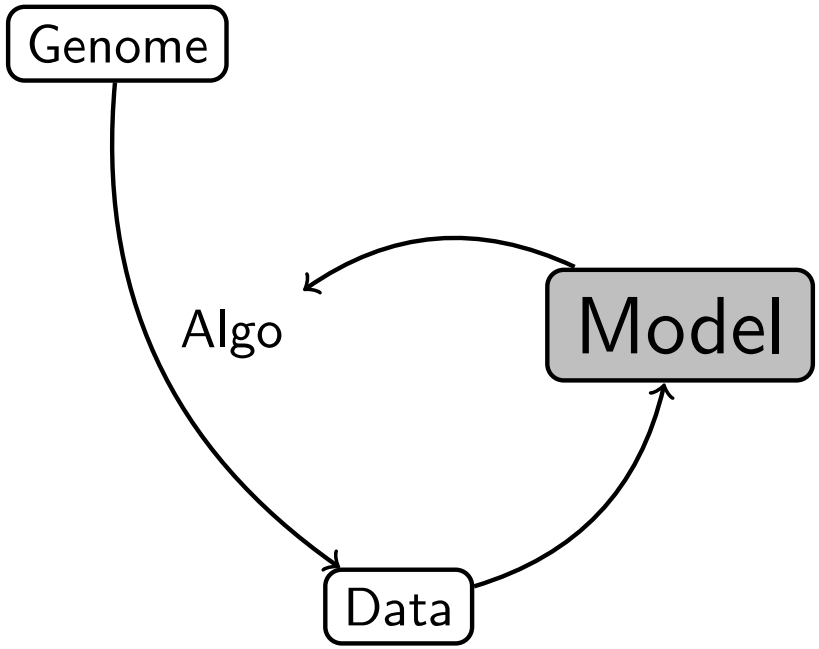
Need for pragmatic simulation, not as an end, but as a means.

Interplay between detection and simulation algorithms



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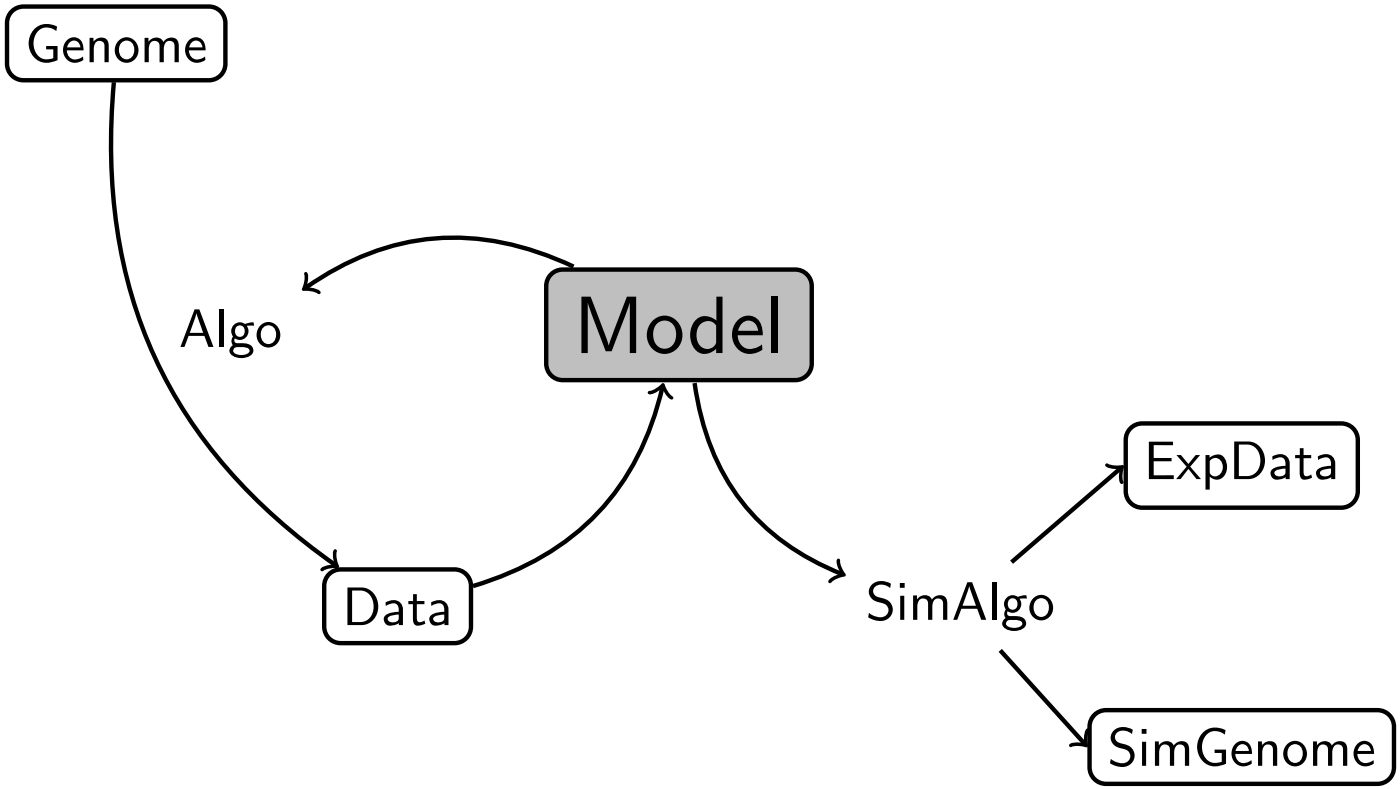

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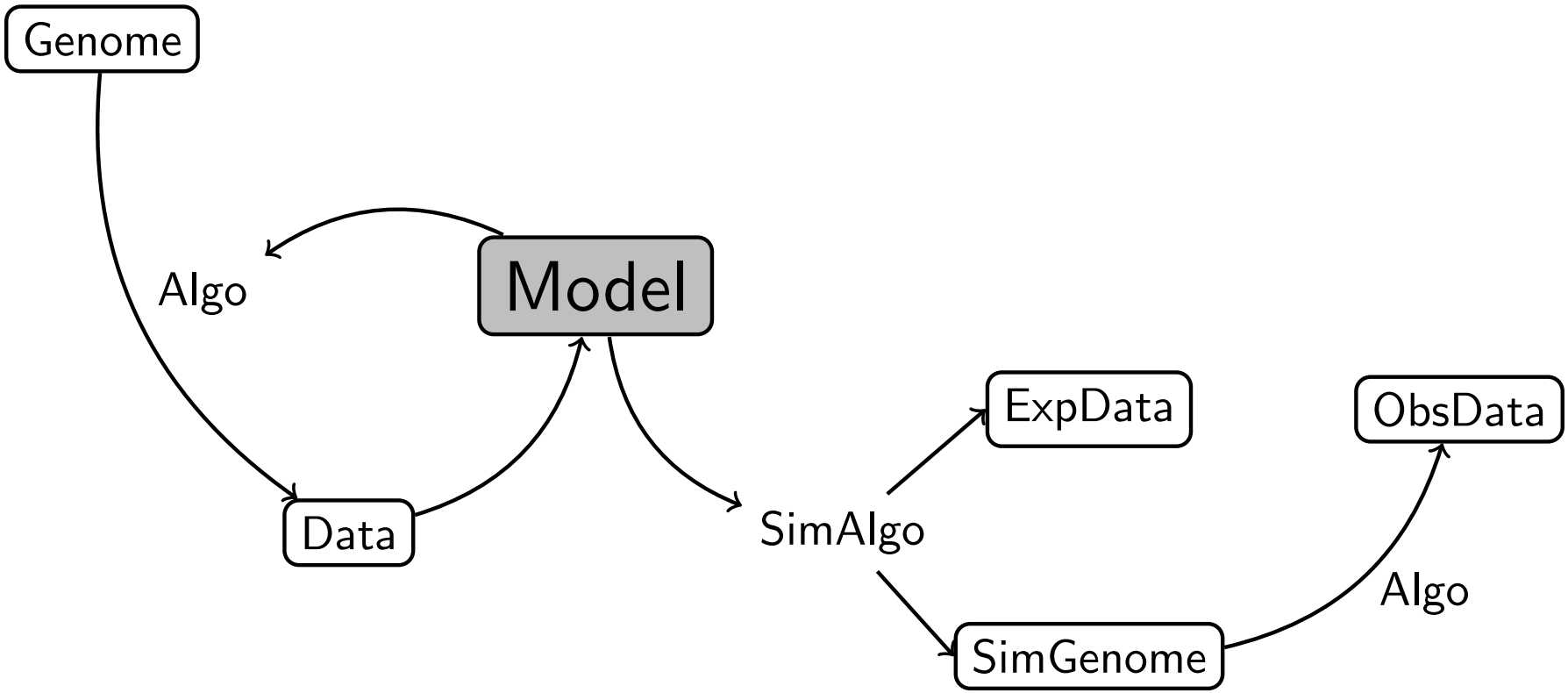

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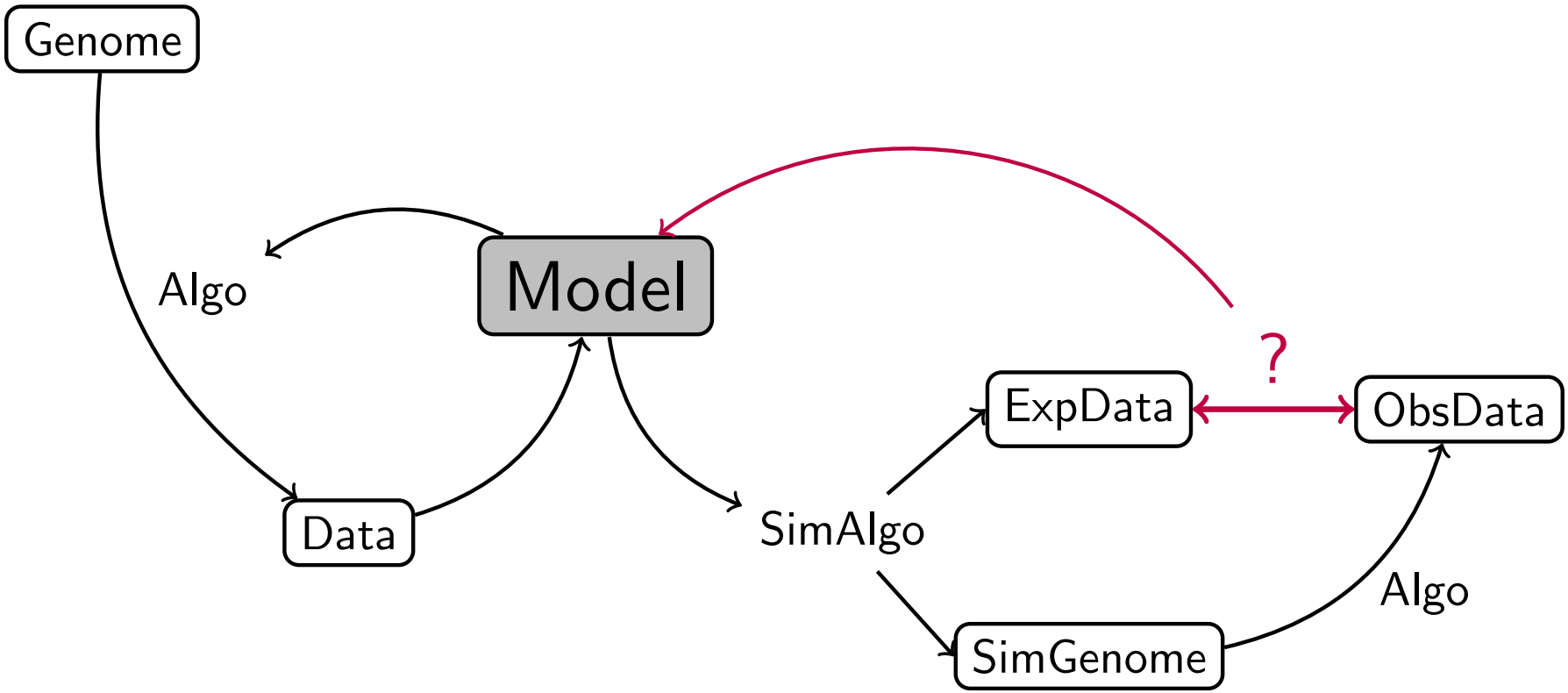

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Designing an algorithm to detect TE structural variants and identify their family is not only an improvement in terms of TE annotation, but more importantly, it is a first step towards a better understanding of TE biology.

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- The tools I developed have been applied since on various, newly sequenced genomes, confirming the importance of TE structural variants.
- Finally, I propose a methodology based on simulation to improve detection algorithms of the *de novo* approach and, through this, increase our understanding of TE diversification.

Outline

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Institutions

- my research institute: INRA
- my graduate school: Frontières du Vivant
- my university: Université Paris Diderot

Thank you for your attention!