Models and algorithms for genome comparison and sequence alignment

Géraldine Jean

Towards a modern analysis of omics data of the Ocean - mission Microbiome: CEODOS and AtlantEco expeditions

May 15-18th, 2023, Valparaiso-Chile

Warning

- Computer scientist in computational biology

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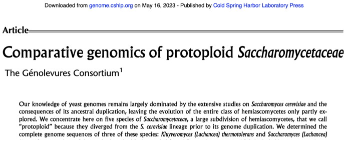

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Article

Comparative genomics of protoploid *Saccharomycetaceae*

The Génolevures Consortium[1]

Our knowledge of yeast genomes remains largely dominated by the extensive studies on *Saccharomyces cerevisiae* and the consequences of its ancestral duplication, leaving the evolution of the entire class of hemiascomycetes only partly explored. We concentrate here on five species of *Saccharomycetaceae*, a large subdivision of hemiascomycetes, that we call "protoploid" because they diverged from the *S. cerevisiae* lineage prior to its genome duplication. We determined the complete genome sequences of three of these species: *Kluyveromyces (Lachancea) thermotolerans* and *Saccharomyces (Lachancea)*

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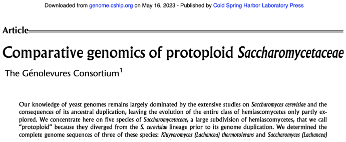

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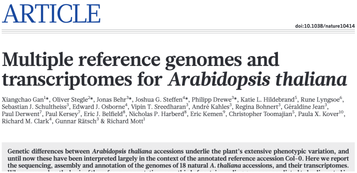

ARTICLE

doi:10.1038/nature10414

Multiple reference genomes and transcriptomes for *Arabidopsis thaliana*

Xiangchao Gan[1]*, Oliver Stegle[2]*, Jonas Behr[3]*, Joshua G. Steffen[4]*, Philipp Drewe[3]*, Katie L. Hildebrand[5], Rune Lyngsoe[6], Sebastian J. Schultheiss[3], Edward J. Osborne[4], Vipin T. Sreedharan[3], André Kahles[3], Regina Bohnert[3], Géraldine Jean[3], Paul Derwent[7], Paul Kersey[7], Eric J. Belfield[8], Nicholas P. Harberd[8], Eric Kemen[9], Christopher Toomajian[5], Paula X. Kover[10], Richard M. Clark[4], Gunnar Rätsch[3] & Richard Mott[1]

Genetic differences between *Arabidopsis thaliana* accessions underlie the plant's extensive phenotypic variation, and until now these have been interpreted largely in the context of the annotated reference accession Col-0. Here we report the sequencing, assembly and annotation of the genomes of 18 natural *A. thaliana* accessions, and their transcriptomes.

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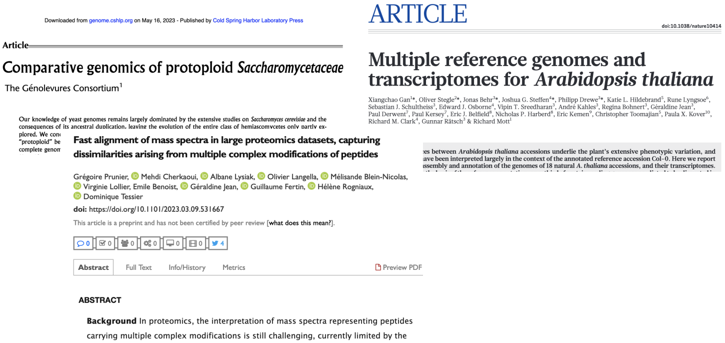

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Fast alignment of mass spectra in large proteomics datasets, capturing dissimilarities arising from multiple complex modifications of peptides

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doi: https://doi.org/10.1101/2023.03.09.531667

This article is a preprint and has not been certified by peer review [what does this mean?].

ABSTRACT

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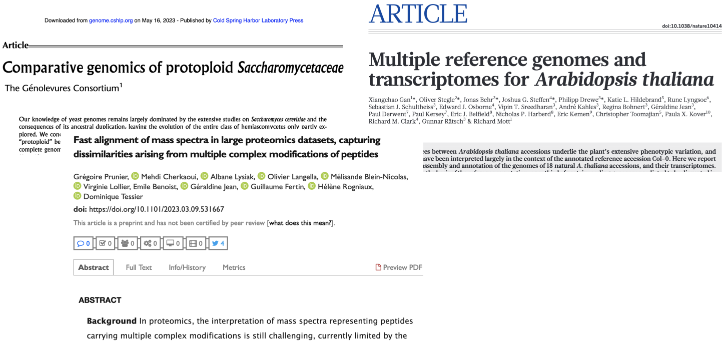

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ABSTRACT

Background In proteomics, the interpretation of mass spectra representing peptides carrying multiple complex modifications is still challenging, currently limited by the

- Not working with environmental data (yet) ;)

General Interests

Using methods from **algorithms on strings** and **graph theory** to study...

Comparative Genomics

- Rearrangement scenario/distance
- Sequence alignment

Next-Generation Sequencing Problems

- Sequence alignment
- De novo assembly of repeats

Mass spectrometry

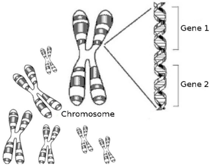
- De novo analysis of the spectrum for identification of unknown metabolite
- Peptide identification and protein inference

Scientific Context

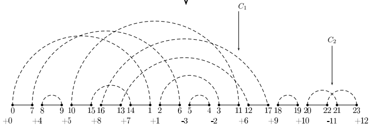
1. Biological objects
   genomes, genes, RNA sequences, spectrum...

2. Combinatorial objects
   string, tree, graph, permutation...

3. Algorithmics tools
   3.1 Computational complexity analysis
   3.2 algorithm development: approximation algorithms, FPT algorithms, heuristics...



genome A = +4 +5 + 8 +7 +1 -3 -2 +6 +9 +10 -11
genome B = +1 +2 +3 +4 +5 +6 +7 +8 +9 +10 +11

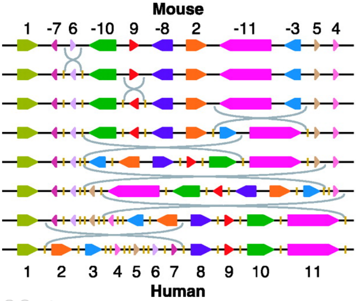


Focus

- Evolution through Genome Rearrangements
  - Is it interesting (and possible) to have such distances between MAGs?
  - Can we compare these distances to other types of distance?
- RNA-seq read alignments with PALMapper
  - Does the sequence I use exist in the database? is it certified?
  - How can we align considering SNPs?

Definition

- Genome = **ordered sequence** of genes
- GR = large-scale (=gene level) evolutionary events modifying the genome (thus the genes order)
- Studying evolution through GR:
  - take **2 species** (=2 genomes)
  - infer **minimum number** of GR between them (=distance)

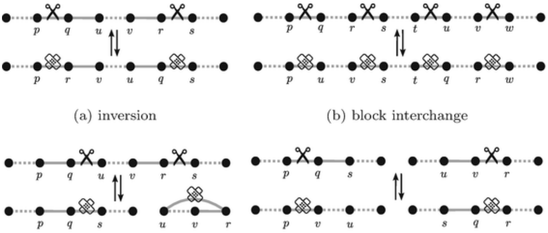


Source: https://www.pnas.org/content/100/13/7672

Definition

Heavily studied problems [FLR^{+}09] from 90's:

- different genomes: linear, circular, multichromosomal, with or without gene duplications, strand information or not...
- different genome models: (signed) permutations, (signed) strings, paths and cycles in graphs...
- different GR: inversion, transposition, double cut and join (DCJ)...



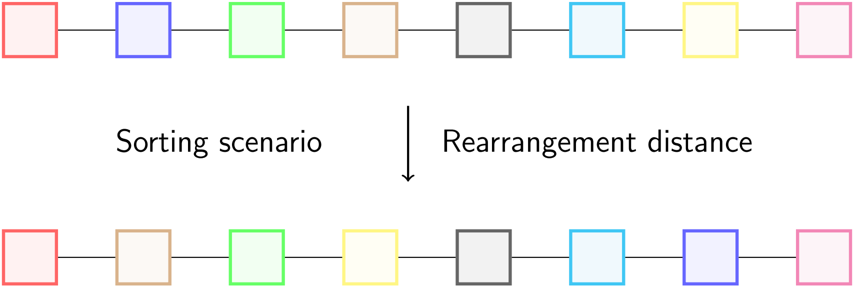
(a) inversion (b) block interchange

(c) fusion/fission (d) translocation

Source: [HMB18]

GR on both gene order and intergenic regions

- Standard models not realistic enough [BKBT16, BGKT16]
- Systematic underestimate of the distance

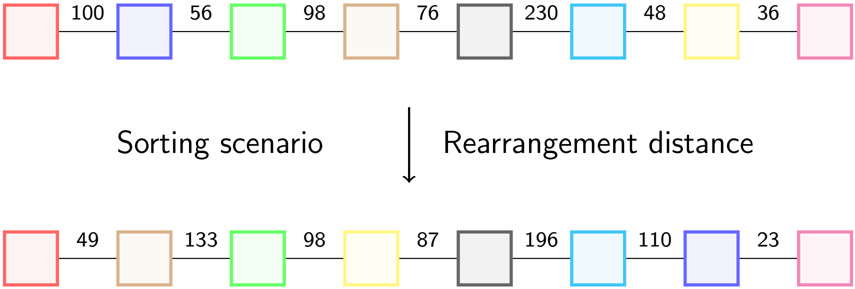


Sorting scenario

Rearrangement distance

GR on both gene order and intergenic regions

- Standard models not realistic enough [BKBT16, BGKT16]
- Systematic underestimate of the distance
- Genes separated by intergenic regions of different sizes
- Intergenic regions should be considered for computing rearrangement distances



Results

- Original paper [FJT17]
  - Same content of genes without duplication and unique operation (DCJ)
  - Already "difficult" even for this simplistic model

- Extended work (collaboration U. Campinas - Brazil) [OJF+21, BJF+20, OJF+20b, BJF+19, OJF+20a]
  - different gene contents
  - unbalanced intergenic sizes
  - different sets of operations

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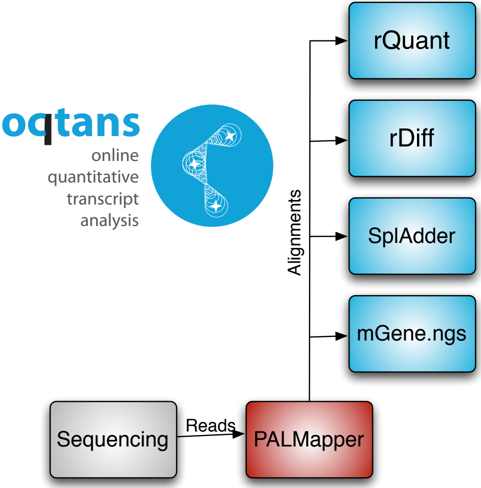
PALMapper in oqtans



Isoform quantitation & bias modeling [BR10]

Tests for differential isoform expression [Stegle et al. 2010, 2012 i.p.]

Graph construction & sampling [Behr et al. 2012 i.p.]

Gene finding with RNA-seq evidence [Behr et al., 2010, 2012 i.p.]

Accurate spliced alignments [De Bona et al., 2008, Jean et al. 2010, 2012 i.p.]

Accuracy of downstream analysis drastically depends on accuracy of read mapping

Motivations

- Improve alignments by using more information:
  - Accurate splice site models
  - Intron length model
  - Quality scores model

  Idea: Use a machine learning method to infer an optimal scoring function

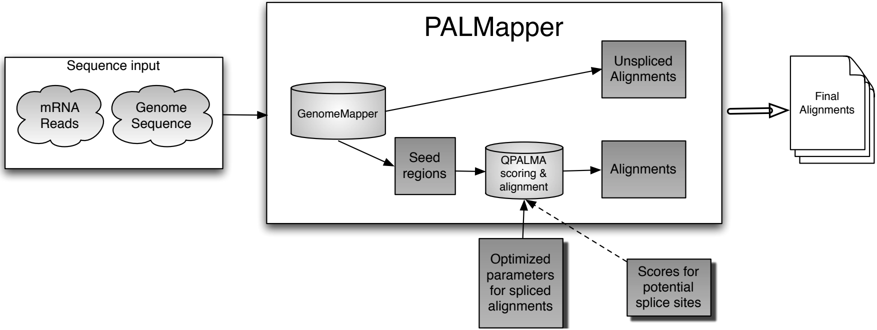
- Align reads efficiently:
  - Use a genomic mapper to find seed regions
  - Restrict the length of the genome to align against

  Idea: Adapt dynamic programming algorithm to RNA-seq specificities

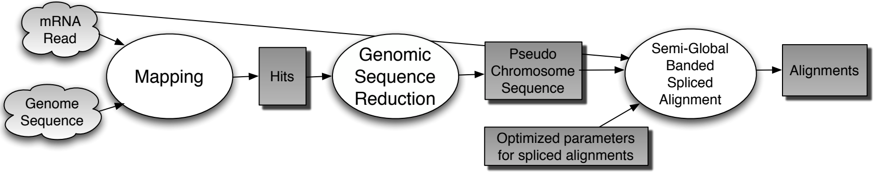
RNA-seq Read Alignments with PALMapper

PALMapper pipeline [JKS+10]

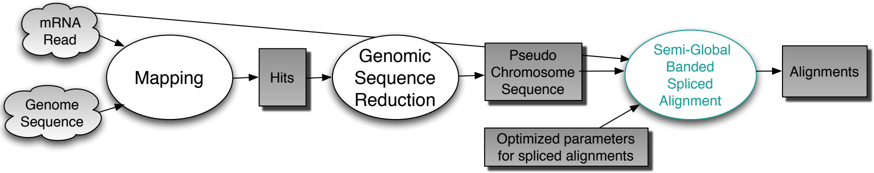
- **GenomeMapper** identifies unspliced alignments and *seed regions* for spliced reads [SHO+09]
- **QPALMA** infers spliced alignments from *seed regions* [DBOSR08]



Spliced alignments with PALMapper


mRNA Read
Genome Sequence
Mapping
Hits
Genomic Sequence Reduction
Pseudo Chromosome Sequence
Semi-Global Banded Spliced Alignment
Alignments
Optimized parameters for spliced alignments

Dynamic Programming Algorithm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Alignments

The *seed position* inferred from the seed region guides a dynamic-programming-based alignment algorithm:

Semi-Global

Align the whole read with a portion of the pseudo chromosome sequence

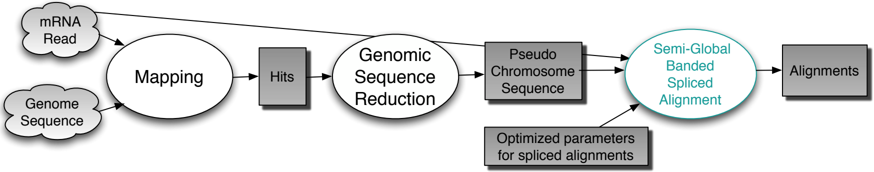
Banded

Limit the number of gaps from the perfect alignment

Spliced

Allow long gaps corresponding to introns

Dynamic Programming Algorithm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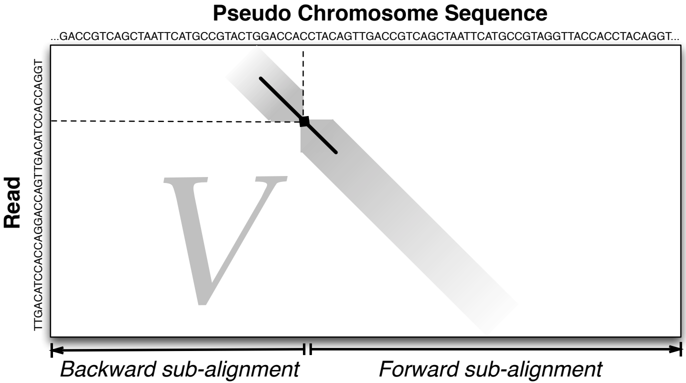
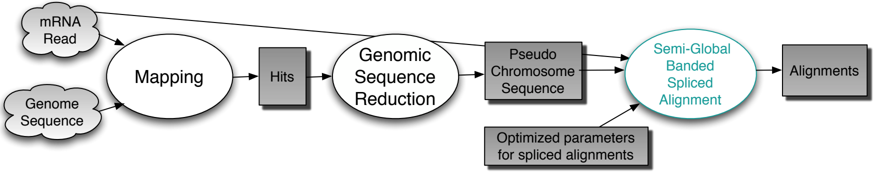

Pseudo Chromosome Sequence
...GACCGTCAGCTAATTCATGCCGTACTGGACCACCTACAGTTGACCGTCAGCTAATTCATGCCGTAGGTTACCACCTACAGGT...
Read
TTGACATCCACCAGGACCAGTTGACATCCACCAGGT
V
Backward sub-alignment
Forward sub-alignment

Dynamic Programming Algorithm



mRNA Read

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Mapping

Hits

Genomic Sequence Reduction

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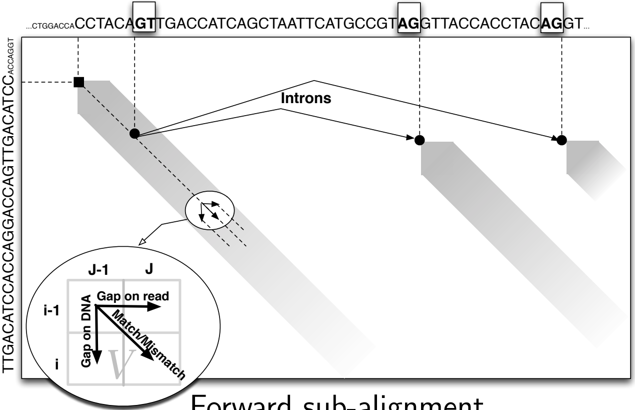
Semi-Global Banded Spliced Alignment

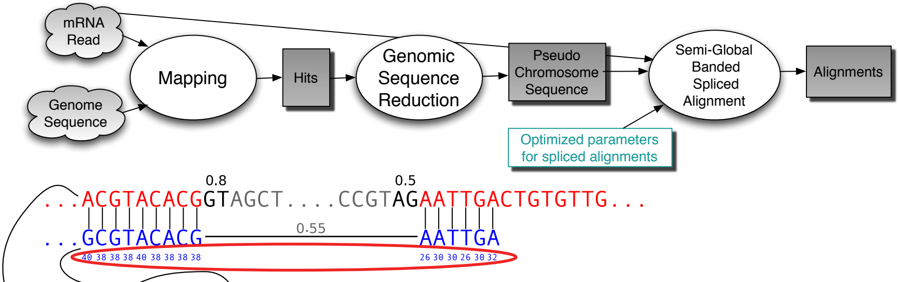
Optimized parameters for spliced alignments

Alignments


...CTGGACCACCTACAGTTGACCATCAGCTAATTCATGCCGTAGGTTACCACCTACAGGT...
TTGACATCCACCAGGACCAGTTGACATCCACCAGGT
Introns
J-1
J
i-1
i
Gap on read
Gap on DNA
Match/Mismatch
V

Forward sub-alignment

QPALMA extended scoring model


mRNA Read
Genome Sequence
Mapping
Hits
Genomic Sequence Reduction
Pseudo Chromosome Sequence
Semi-Global Banded Spliced Alignment
Alignments
Optimized parameters for spliced alignments
0.8
0.5
...ACGTACACGGTAGCT....CCGTAGAATTGACTGTGTTG...
...GCGTACACG
0.55
AATTGA
40 38 38 38 40 38 38 38 38
26 30 30 26 30 32

	gap	A	C	G	T	N
gap	0.33	$f_{-A}(\cdot)$	$f_{-C}(\cdot)$	$f_{-G}(\cdot)$	$f_{-T}(\cdot)$	$f_{-N}(\cdot)$
A	0.31	$f_{AA}(\cdot)$	$f_{AC}(\cdot)$	$f_{AG}(\cdot)$	$f_{AT}(\cdot)$	$f_{AN}(\cdot)$
C	0.44	$f_{CA}(\cdot)$	$f_{CC}(\cdot)$	$f_{CG}(\cdot)$	$f_{CT}(\cdot)$	$f_{CN}(\cdot)$
G	0.13	$f_{GA}(\cdot)$	$f_{GC}(\cdot)$	$f_{GG}(\cdot)$	$f_{GT}(\cdot)$	$f_{GN}(\cdot)$
T	0.55	$f_{TA}(\cdot)$	$f_{TC}(\cdot)$	$f_{TG}(\cdot)$	$f_{TT}(\cdot)$	$f_{TN}(\cdot)$
N	0.12	$f_{NA}(\cdot)$	$f_{NC}(\cdot)$	$f_{NG}(\cdot)$	$f_{NT}(\cdot)$	$f_{NN}(\cdot)$

Source of information

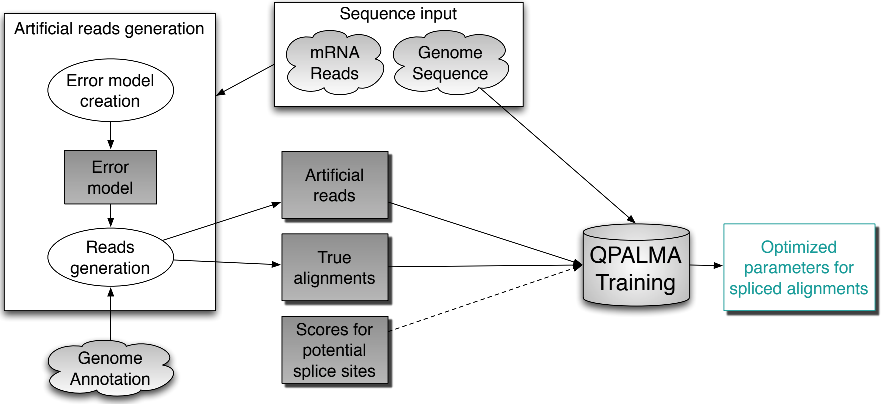
- Sequence matches
- Computational splice site predictions
- Intron length model
- Read quality information

Quality scoring $M : (\Sigma \times \mathbb{R}) \times \Sigma \to \mathbb{R}$

[DBOSR08]

QPALMA extended scoring model

Estimation of QPALMA scoring model via a large margin approach similar to SVMs



Results

Significant Speed Gain: QPalma *vs.* Palmapper

- Full sequencing run of *C. elegans* RNA-Seq data of 24 × 10^6 reads of 36-nucleotide length
- Evaluation of predicted introns

	TopHat	TopHat sen.	**QPALMA**	**PALMapper**
Recall	0.39	0.62	**0.65**	**0.65**
Precision	0.86	0.76	**0.88**	**0.88**
Running Time (min)	216	544	12000[1]	**186**

TopHat [TPS09]. [1] The running time for QPALMA was extrapolated.

Variant-Aware alignments

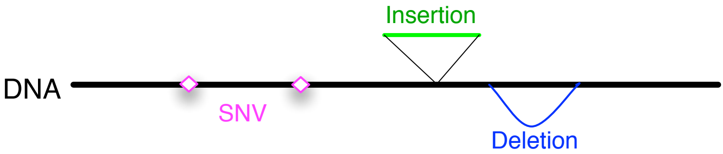
Motivation:

- Many reads may not have an alignment (errors, polymorphisms, RNA-editing)
  idea: Detect commonly occuring RNA/DNA differences and use during the alignment
- Genome of interest is unknown but a close relative is available
- Aligning against several close genomes is needed
  idea: Get variants between the genomes and use them during the alignment

Variant-Aware alignments

PALMapper strategy:

- Construct *super-sequence graph* containing all variants
- Use dynamic programming to align against all possible paths



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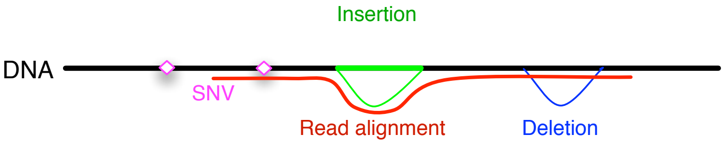

- Strategy used in paper [DZM+14] about DNA methylation in *A. thaliana*

Conclusion

Thank you ! Gracias ! Merci !

El Morado January 2019

El Morado May 2023

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