SVJedi : Structural variation genotyping using long reads

Lolita Lecompte, Pierre Peterlongo, Dominique Lavenier, Claire Lemaitre

SVJedi : Structural variation genotyping using long reads

Lolita Lecompte[1], Pierre Peterlongo[1], Dominique Lavenier[1], Claire Lemaitre[1]
[1]Univ Rennes, Inria, CNRS, IRISA, F-35000 Rennes, France

Introduction

Structural variations (SVs) are DNA segments that have been moved regarding another reference genome. The number of known SVs is increasing, especially with the development of **third generation sequencing technologies**, which produce long reads data.

Discovery vs. Genotyping

SV discovery

Given a reference genome, **discover** SVs between a sequencing sample and a reference genome.

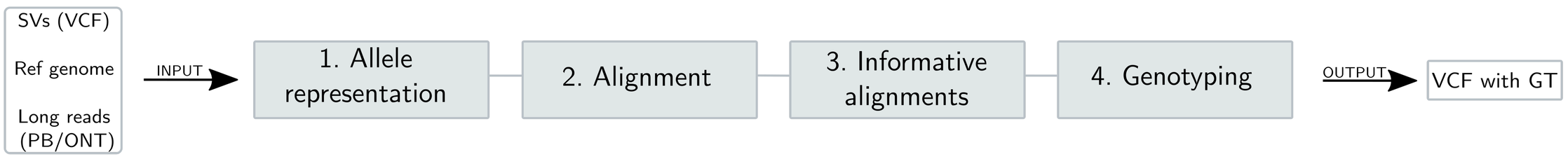
SVIM (2019), Sniffles (2018), pbsv (2018), NanoSV (2017)

SV genotyping

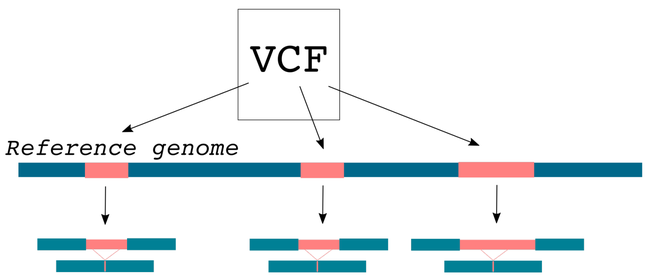
Given a set of already known variants for a species, **assess the presence or absence** of each variant in a given sequencing sample.

There is **no known method** for SV genotyping with long reads.

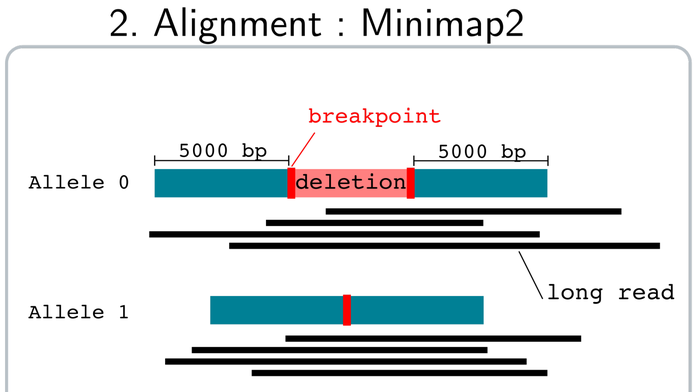
Method - SVJedi



1. Generating allele sequences



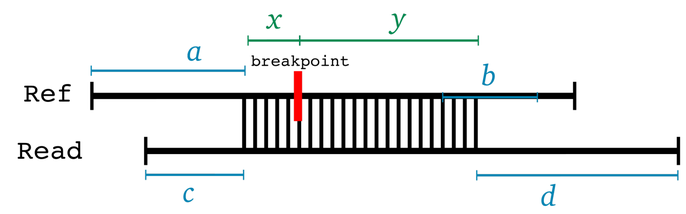
2. Alignment : Minimap2



3. Selection of informative alignments

- Breakpoint overlap

- Semi-global alignment



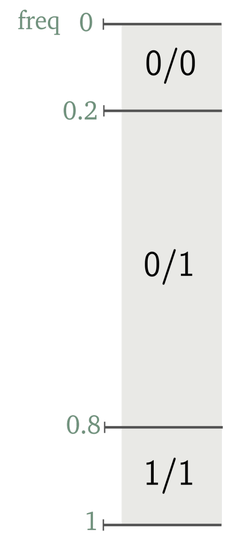
x > d_over & y > d_over

(a < d_end || c < d_end) & (b < d_end || d < d_end)

4. Genotype estimation

$$\text{freq} = \frac{\text{allele 0}}{\text{allele 0 + allele 1}}$$

- Normalization
- Minimum read number filter
- Genotype estimation



Results on a simulated dataset

Simulated dataset

- **1,000 deletions** selected on the human chromosome 1 from dbVar (50 bp - 10k bp)
- Equally distributed : 0/0, 0/1, 1/1
- Long reads simulated with SimLoRD [1] 16 % error rate, 20X sequence depth

Does *SV discovery* tools correctly estimate genotypes?

SVJedi

Truth \	0/0	0/1	1/1	./.
0/0	330	3	0	0
0/1	19	305	6	4
1/1	3	10	311	9

Precision : 95.85 %

Sniffles [2]

Truth \	0/0	0/1	1/1
0/1	3	89	0
1/1	0	254	60

Recall : 60.87 %
Precision : 36.70 %

80.9 % of 1/1 deletions are wrongly genotyped as 0/1

Results on a real dataset

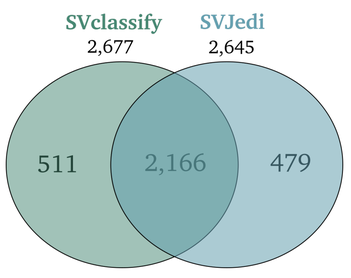
Dataset

- Sample: NA12878
- Data: Nanopore WGS consortium (37X)
- svclassify [3]: **2,677** high confidence deletions

SVJedi

svclassify \	0/0	0/1	1/1	./.
0/1	194	1,289	202	28
1/1	8	75	877	4

Identity : 81.89 %
Predicted genotypes = 98.81 %
Runtime : 2h35 (40 CPU)



Conclusion

- New method to genotype SVs using long reads data.
- Importance of dedicated genotyping methods.
- Currently only applied to deletions.
- Implementation: SVJedi

https://github.com/llecompte/SVJedi
Contact: lolita.lecompte@inria.fr

References

[1] Bianca K Stöcker, Johannes Köster, and Sven Rahmann. Simlord: simulation of long read data. *Bioinformatics*, 32(17):2704–2706, 2016.

[2] Fritz J Sedlazeck, Philipp Rescheneder, Moritz Smolka, Han Fang, Maria Nattestad, Arndt von Haeseler, and Michael C Schatz. Accurate detection of complex structural variations using single-molecule sequencing. *Nature methods*, 15(6):461, 2018.

[3] Hemang Parikh, Marghoob Mohiyuddin, Hugo YK Lam, Hariharan Iyer, Desu Chen, Mark Pratt, Gabor Bartha, Noah Spies, Wolfgang Losert, Justin M Zook, et al. svclassify: a method to establish benchmark structural variant calls. *BMC genomics*, 17(1):64, 2016.