DeepSV: a deep learning based variant scorer

Félix Raimundo
Department of Computer Science
École Polytechnique
Palaiseau, France
felix.raimundo@inria.fr

February 16, 2018

Abstract

In this paper, we present DeepSV, a deep learning based method for scoring the likelihood that a set of anomalous read pairs are caused by a structural variant, by opposition to mapping or sequencing errors.

We identified a region of fixed size that contains enough signal to make classification with deep learning methods, and thus allowing us to move away from the previous methods based on linear classifiers applied on few hand-crafted features.

1 Definitions

In this papers we will be using the sequencing terms as defined in [1], whose most relevant ones are copied here.

Segment A contiguous sequence or subsequence.

Read A raw sequence of DNA that comes off a sequencing machine.

Coverage Number of reads mapped at a specific location in the reference genome.

Read Pair Long sequence of DNA of which the sequencing machine reads the two extremities. Each of the extremities are reads, are associated a direction, and are separated by a distance called insert size.

Note: For the duration of this paper, we will assume that the two reads of a read pair are both directed to the center, i.e. the first read is directed from left to right, called forward, and the second right to left, called backward.

2 Properties of the data

In this paper we will be making the following two assumptions:

Assumption 1 The distance between two reads of a read pair, called insert size, follows a normal distribution when they are generated.

Assumption 2 The length of reads, called read size, follows a normal distribution.
Note: Empirical data is known not to verify theses assumptions, however they are a good approximation of reality and are used in most other variant callers (see [2], [3], [4], [5], [6]).
Note: The distance between two reads of a pair generated from a target genome can be different once the two reads are mapped on a reference genome, the analysis of that phenomenon is the basis of our study.

Simplification 1 During the rest of this document we will assume that the insert size and read size are constant when the reads are generated, indeed the two distribution have a low standard deviation relative to the mean, this approximation is thus sensible.
All the future claims stay valid without this approximation, but would make the text much less readable by introducing many confidence intervals.

Section *Dealing with reality* will describe how we deal with real data, where these assumptions are not correct.

Property 1 Because of assumptions 1 and 2, and simplification 1, it follows that the second pair of a read pair is fully contained within $[insert\_size, insert\_size + read\_size]$ of the end of the first one in the genome from which the reads are extracted.

2.1 Structural Variants

Variant We call variant, a difference between the genome of the person being sequenced and the reference genome, they are the cause of the genetic diversity in the population.

Some variants are called *structural variants*, because they are considered so large that they come from a structural difference. The limit between regular variant and structural variant does not have a proper definition, but they are usually considered to be changes affecting more than 50bp.

Structural variants are separated in two categories:

- Balanced rearrangements: which do not affect the total number of nucleotides in the genome.
- Imbalanced rearrangements: which affect the total number of nucleotides in the genome, also called Copy Number Variation (CNV).

The CNVs are themselves divided in three categories:

- Deletions: where a large portion of the genome is deleted relative to the reference.
- Tandem duplication: where a large portion of the genome is duplicated, potentially multiple times; the duplicates are directly next to each other.
- Interspersed duplication: where a large portion of the genome is duplicated, potentially multiple times; the duplicates are separated by segments of DNA.

Likewise the balanced rearrangements are divided in two categories:

- Translocation: where a large portion of DNA is moved to another location in the genome (potentially on another chromosome).
- Inversion: where a large portion of DNA has the order of its nucleotides reversed.

In our study we will only work on deletions, tandem duplications, and inversions. We however believe that our method could be extended to work on the other types of variants (see *Future Work*).

Breakpoint We call breakpoints the locations where structural rearrangements happen in the genome being sequenced, there are:

- 1 in the case of deletions.
- n for tandem duplications with n duplicates.
- n for interspersed duplications with n duplicates.
- 2 for inversions
- 2 for translocations.

2.2 Methods of detection

The current state of the art algorithms for finding structural variants are based on a mixture of the four following methods (see [7] or [8] for a deeper review):

- Assembly based (AS), does *de novo* assembly on regions suspected to contain an SV. They are rarely used as: assembly is computationally expensive and not always possible in regions with repetitive sequences.
- Read count (RC), observes the distribution of coverage in the genome. It can only detect CNVs as reads in translocations and inverted regions are properly mapped. Furthermore reads are not generated uniformly in the genome from which the reads come, it is thus not an optimal method alone.

- Split reads (SR), uses reads that fall on the breakpoint. Those reads are unmapped, as part of them is in the rearrangement. These reads are split so that they can be mapped properly. As the split reads are smaller than regular reads they cannot always be mapped unambiguously.
- Paired reads (PR), uses pairs of mapped reads that have an insert size far away from the mean insert size, or who do not have the expected orientation. This method is often used to identify regions that contain SV and followed by a finer analysis.

In the case of DeepSV we use paired reads to identify regions of interest and use a pattern recognition model on the selected regions to decide whether they contain an SV. We expect our model to use RC and PR methods for predictions. AS and SR methods can be used to locate the breakpoints with higher precision once the prediction is made.

The next sections will explain what patterns we expect to find in these regions.

2.3 Anomalous paired reads

Anomalous read pairs (ARP) are read pairs that do not have the normal orientation or insert size once mapped.

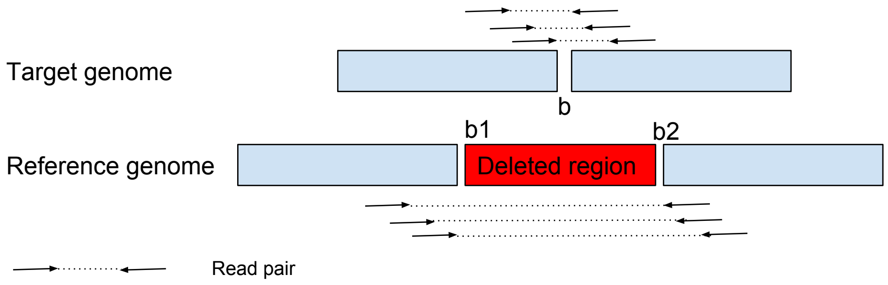
Property 2 Assuming no errors in the reads or mapping, ARPs contain a breakpoint between their two reads.

Indeed, if one read was on the breakpoint, it could not be mapped as a part of it would be on a large rearrangement.

Respectively, if both reads were the same side of a breakpoint, they would be mapped normally and would thus not be caught as anomalous.

Property 3 Because of properties 1 and 2 we can conclude that all reads in ARPs will be at most $read\_size + insert\_size$ away from the breakpoint in the genome that generated the reads.

2.3.1 Deletion



In the case of deletions there is a single breakpoint b, the deleted region is $[b1, b2]$.

Assuming no errors in the reads or mapping:

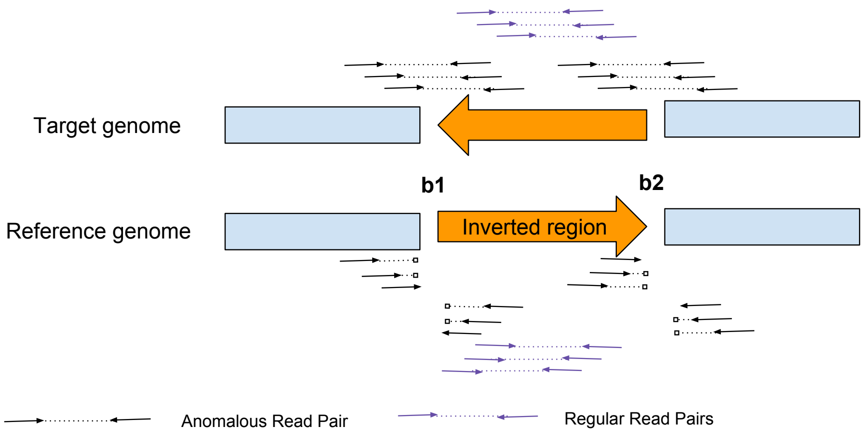
- reads originally left of $k$bp from b will be mapped at $[b1-k-read\_size, b1-k]$ instead of $[b-k-read\_size, b-k]$ and in the correct direction.
- reads originally right of $k$bp from b will be mapped at $[b2+k, b2+k+read\_size]$ instead of $[b+k, b+k+read\_size]$ and in the correct direction.
- no reads should be mapped in $[b1, b2]$.

In the case of ARPs, by using property 3, we know that $k < insert\_size$, we can thus conclude that all ARPs will be contained within $[b1 - insert\_size - read\_size, b1] \cup [b2 + insert\_size + read\_size, b2]$, these reads will have an expected distance of $insert\_size + (b2 - b1)$.

By using property 3, we can conclude that given a set of ARPs supporting a deletion, b1 will be contained within $insert\_size + read\_size$ of the leftmost read, and b2 will be contained within $insert\_size + read\_size$ of the rightmost read.

We have thus constructed two intervals containing all the ARPs and RC information, these two intervals' sizes are only dependent on the insert size and read size, not the size of the deletion.

2.3.2 Inversion



In the case of inversions there are two breakpoints b1 and b2, the inverted region is $[b1, b2]$.

ARPs will be read pairs with one read to the left of b1 and the other in the inverted region, or read pairs with one read to the right of b2 and the other in the inverted region.

Assuming no errors in the reads or mapping:

- reads originally right of $k$bp from b1 will be mapped at $[b2-k-read\_size, b2-k]$ instead of $[b1+k, b1+k+read\_size]$ and in the opposite direction.

- reads originally left of $k$bp from b2 will be mapped at $[b1+k, b1+k+read\_size]$ instead of $[b2-k-read\_size, b2-k]$ and in the opposite direction.

- there is no variation in coverage, except at the breakpoints were the reads will not be mapped.

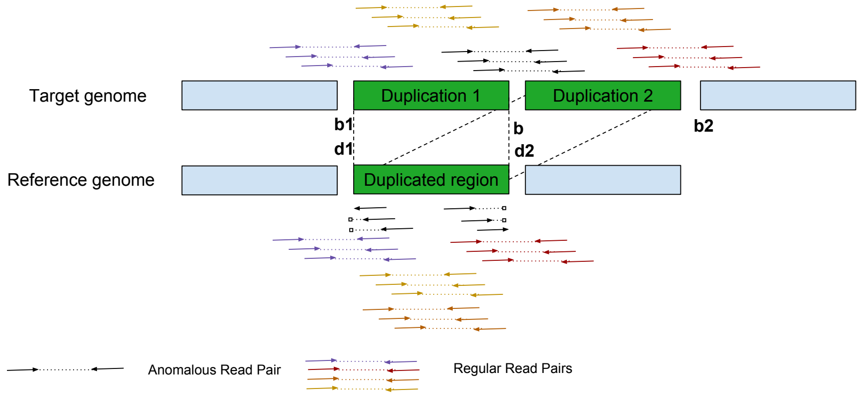
In the case of ARPs, by using property 3, we know that $k < insert\_size$, we can thus conclude that all ARPs will be contained within $[b1 - insert\_size - read\_size, b1 + insert\_size + read\_size] \cup [b2 - insert\_size - read\_size, b2 + insert\_size + read\_size]$

By using property 3, we can conclude that given a set of ARPs supporting an inversion, b1 will be contained within $insert\_size + read\_size$ of the leftmost read, and b2 will be contained within $insert\_size + read\_size$ of the rightmost read.

We have thus constructed two intervals containing all the ARPs and RC information, these two intervals' sizes are only dependent on the insert size and read size, not the size of the inversion.

Note: This only works for inversions larger than $insert\_size + read\_size$.

2.3.3 Tandem Duplication



In the case of a tandem duplication with n duplicates, there are n breakpoints b^1,...,b^n, the duplicated region is $[d1, d2]$. The breakpoints are at the junction between duplicates.

Note: For the sake of clarity there is only one duplicate in the figure.

In the case of tandem duplications, the ARPs are read pairs with, with $i \in [1, n]$, have one read left of b^i and one read right of b^i.

Assuming no errors in the reads or mapping:

- reads originally left of $k$bp from b^i will be mapped at $[d2-k-read\_size, d2-k]$ instead of $[b^i - k - read\_size, b^i - k]$ and in the correct direction.
- reads originally right of $k$bp from b^i will be mapped at $[d1 + k, d1 + k + read\_size]$ instead of $[d^i + k, d^i + k + read\_size]$ and in the correct direction.
- ARPs will thus have the order of their reads reversed, both reads will thus have opposite direction relative to normal read pairs.
- coverage in $[d1, d2]$ is expected to be $1 + n$ times higher than in non duplicated areas.

In the case of ARPs, by using property 3, we know that $k < insert\_size$, we can thus conclude that all ARPs will be contained within $[d1, d1 + insert\_size + read\_size] \cup [d2, d2 + insert\_size + read\_size]$, coverage in that region will be $1 + n$ times higher than in non duplicated areas.

By using property 3, we can conclude that given a set of ARPs supporting a tandem duplication, d1 will be contained within $insert\_size$ of the leftmost read, and d2 will be contained within $insert\_size$ of the rightmost read.

We have thus constructed two intervals containing all the ARPs and RC information, these two intervals' sizes are only dependent on the insert size and read size, not the size of the duplicated area northe number of duplicated.

Note: This only works for duplicates larger than $insert\_size + read\_size$.

2.4 Conclusion

We have shown that, given a variant and its breakpoints, we can construct two windows of size $2 \times (insert\_size + read_size)$ each, centered on the two boundaries in the reference genome, that contains all the ARPs that support it.

We have also shown that given a type of variant and ARPs supporting it, we can locate two intervals containing the boundaries, and from there two windows containing all the ARPs that would support that variant.

The size of these windows are only dependent on the $insert\_size$ and $read\_size$, not on the size of the structural rearrangements.

It is noteworthy that both $insert\_size$ and $read\_size$ will be extremely close between individuals provided they are sequenced using the same protocol. Our method will thus be able to predict variants on all future individuals sequenced using the same protocol. TODO CITATION.

By taking the largest intervals of the three sub sections above, we can have a single model that will deal with all variants (except for translocations and interspersed duplications).

2.5 Future works

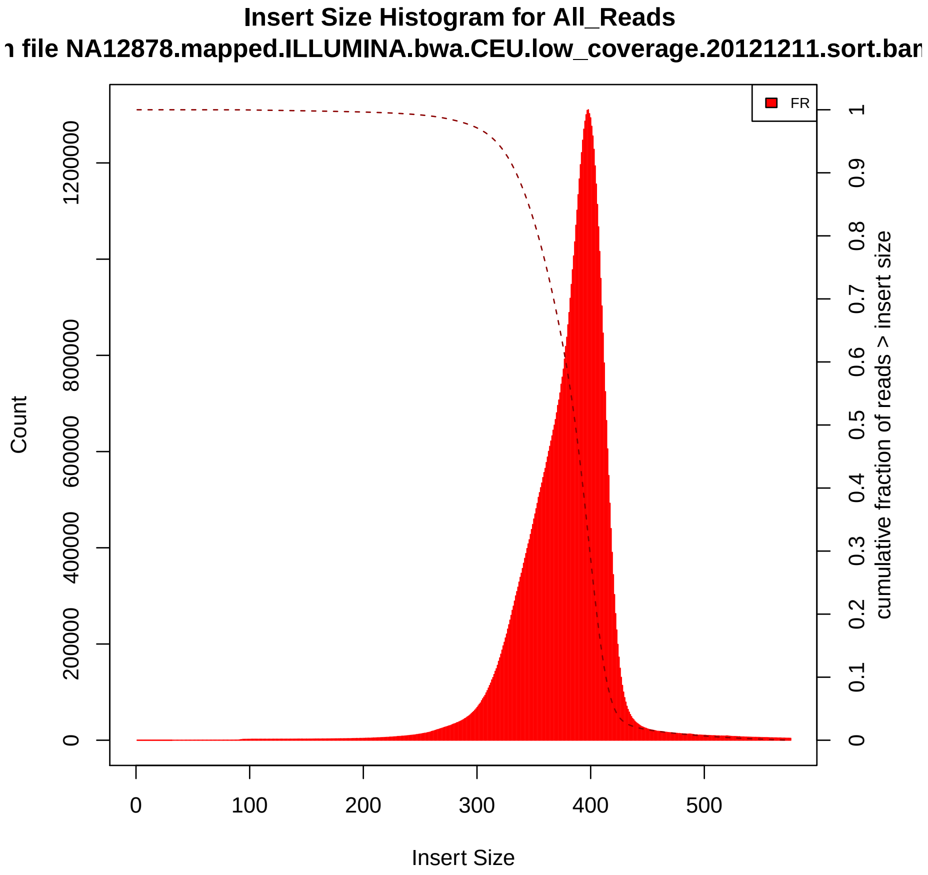
In this work we presented an algorithm for scoring the likelihood that a region contains a structural variant, by extracting a intervals independent on the size

of the variants and using pattern matching models from the deep learning community.
However this algorithm is not sufficient for finding variants from raw reads, we plan on integrating this algorithm in a full variant discovery pipeline that would emit the candidates variants as well as refining the location of the breakpoints.This full pipeline will be released with an open source license in the months following the publication of this paper.

We chose not to deal with translocations and interspersed duplications in this work is because they would require to consider twice as much intervals and we have not found an elegant way to use the same model for them. However we could very well have a model for [deletion, tandem duplication, inversion] and a model for [translocation, interspersed duplication].

3 Dealing with real data

As said before, the empirical insert size does not follow a normal distribution. We can see that it is skewed towards lower values. However, we can see that the distribution is well centered on its mean: 400 bp.



Listing 1: Picard command

```
#!/bin/bash
java -jar picard.jar CollectInsertSizeMetrics \
    I=input.bam \
    O=insert_size_metrics.txt \
    H=insert_size_histogram.pdf \
    M=0.5
```

We are aware of two reasons that could cause such a skew:

- Mobile element insertions of ALUs.
- Poor mapping in ambiguous regions.

Picard tells us that a width of 165 centered on the median, 386bp, will catch 95% of the reads, which will be considered a sufficient approximation. In consequence when building our window we will consider an insert size of 467bp.

References

References

[1] Heng Li, Bob Handsaker, Alec Wysoker, Tim Fennell, Jue Ruan, Nils Homer, Gabor Marth, Goncalo Abecasis, and Richard Durbin. The Sequence Alignment/Map format and SAMtools. *Bioinformatics*, 25(16):2078–2079, August 2009.

[2] Tobias Rausch, Thomas Zichner, Andreas Schlattl, Adrian M. Stütz, Vladimir Benes, and Jan O. Korbel. DELLY: structural variant discovery by integrated paired-end and split-read analysis. *Bioinformatics (Oxford, England)*, 28(18):i333–i339, September 2012.

[3] Kai Ye, Marcel H. Schulz, Quan Long, Rolf Apweiler, and Zemin Ning. Pindel: a pattern growth approach to detect break points of large deletions and medium sized insertions from paired-end short reads. *Bioinformatics (Oxford, England)*, 25(21):2865–2871, November 2009.

[4] Xiaoyu Chen, Ole Schulz-Trieglaff, Richard Shaw, Bret Barnes, Felix Schlesinger, Morten Källberg, Anthony J. Cox, Semyon Kruglyak, and Christopher T. Saunders. Manta: rapid detection of structural variants and indels for germline and cancer sequencing applications. *Bioinformatics*, 32(8):1220–1222, April 2016.

[5] Robert E. Handsaker, Vanessa Van Doren, Jennifer R. Berman, Giulio Genovese, Seva Kashin, Linda M. Boettger, and Steven A. McCarroll. Large multi-allelic copy number variations in humans. *Nature genetics*, 47(3):296–303, March 2015.

[6] Ken Chen, John W. Wallis, Michael D. McLellan, David E. Larson, Joelle M. Kalicki, Craig S. Pohl, Sean D. McGrath, Michael C. Wendl, Qunyuan Zhang, Devin P. Locke, Xiaoqi Shi, Robert S. Fulton, Timothy J. Ley, Richard K. Wilson, Li Ding, and Elaine R. Mardis. BreakDancer: An algorithm for high resolution mapping of genomic structural variation. *Nature methods*, 6(9):677–681, September 2009.

[7] Ke Lin, Sandra Smit, Guusje Bonnema, Gabino Sanchez-Perez, and Dick de Ridder. Making the difference: integrating structural variation detection tools. *Briefings in Bioinformatics*, 16(5):852–864, September 2015.

[8] Peter H. Sudmant, Tobias Rausch, Eugene J. Gardner, Robert E. Handsaker, Alexej Abyzov, John Huddleston, Yan Zhang, Kai Ye, Goo Jun, Markus Hsi-Yang Fritz, Miriam K. Konkel, Ankit Malhotra, Adrian M. Stütz, Xinghua Shi, Francesco Paolo Casale, Jieming Chen, Fereydoun Hormozdiari, Gargi Dayama, Ken Chen, Maika Malig, Mark J. P. Chaisson, Klaudia Walter, Sascha Meiers, Seva Kashin, Erik Garrison, Adam Auton, Hugo Y. K. Lam, Xinmeng Jasmine Mu, Can Alkan, Danny Antaki, Taejeong Bae, Eliza

Cerveira, Peter Chines, Zechen Chong, Laura Clarke, Elif Dal, Li Ding, Sarah Emery, Xian Fan, Madhusudan Gujral, Fatma Kahveci, Jeffrey M. Kidd, Yu Kong, Eric-Wubbo Lameijer, Shane McCarthy, Paul Flicek, Richard A. Gibbs, Gabor Marth, Christopher E. Mason, Androniki Menelaou, Donna M. Muzny, Bradley J. Nelson, Amina Noor, Nicholas F. Parrish, Matthew Pendleton, Andrew Quitadamo, Benjamin Raeder, Eric E. Schadt, Mallory Romanovitch, Andreas Schlattl, Robert Sebra, Andrey A. Shabalin, Andreas Untergasser, Jerilyn A. Walker, Min Wang, Fuli Yu, Chengsheng Zhang, Jing Zhang, Xiangqun Zheng-Bradley, Wanding Zhou, Thomas Zichner, Jonathan Sebat, Mark A. Batzer, Steven A. McCarroll, 1000 Genomes Project Consortium, Ryan E. Mills, Mark B. Gerstein, Ali Bashir, Oliver Stegle, Scott E. Devine, Charles Lee, Evan E. Eichler, and Jan O. Korbel. An integrated map of structural variation in 2,504 human genomes. *Nature*, 526(7571):75–81, October 2015.