TaFuCo: A Precise Targeted Gene Fusion Caller

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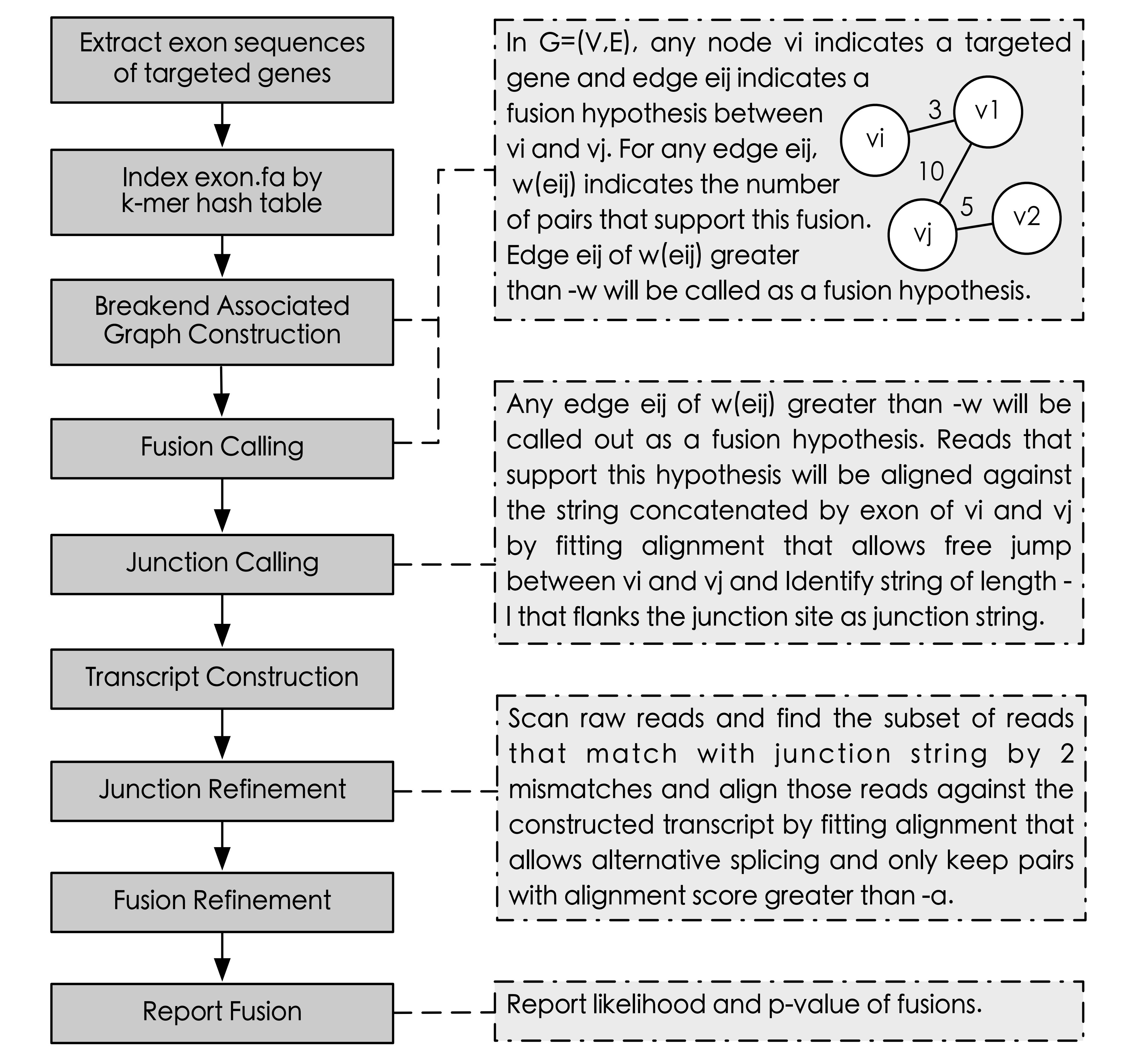
Abstract

Genomic translocation events frequently underlie cancer development through generation of gene fusions. Identification of such fusion transcripts by RNA-seq data would help to discover new potential therapeutic targets. We developed **TaFuCo** (Targeted Gene Fusion Caller) (https://github.com/r3fang/TaFuCo), a precise, user friendly, ultrafast, C-implemented and mapping-free Bioinformatics software for targeted fusion detection from RNA-seq data. We applied **TaFuCo** to simulated data and RNA-seq data of different tumor types, and find it to be very sensitive (~85%) and highly precise (~99%) in detecting gene fusion with maximum memory usage of only 2GB.

Workflow



Extract exon sequences of targeted genes

Index exon.fa by k-mer hash table

Breakend Associated Graph Construction

Fusion Calling

Junction Calling

Transcript Construction

Junction Refinement

Fusion Refinement

Report Fusion

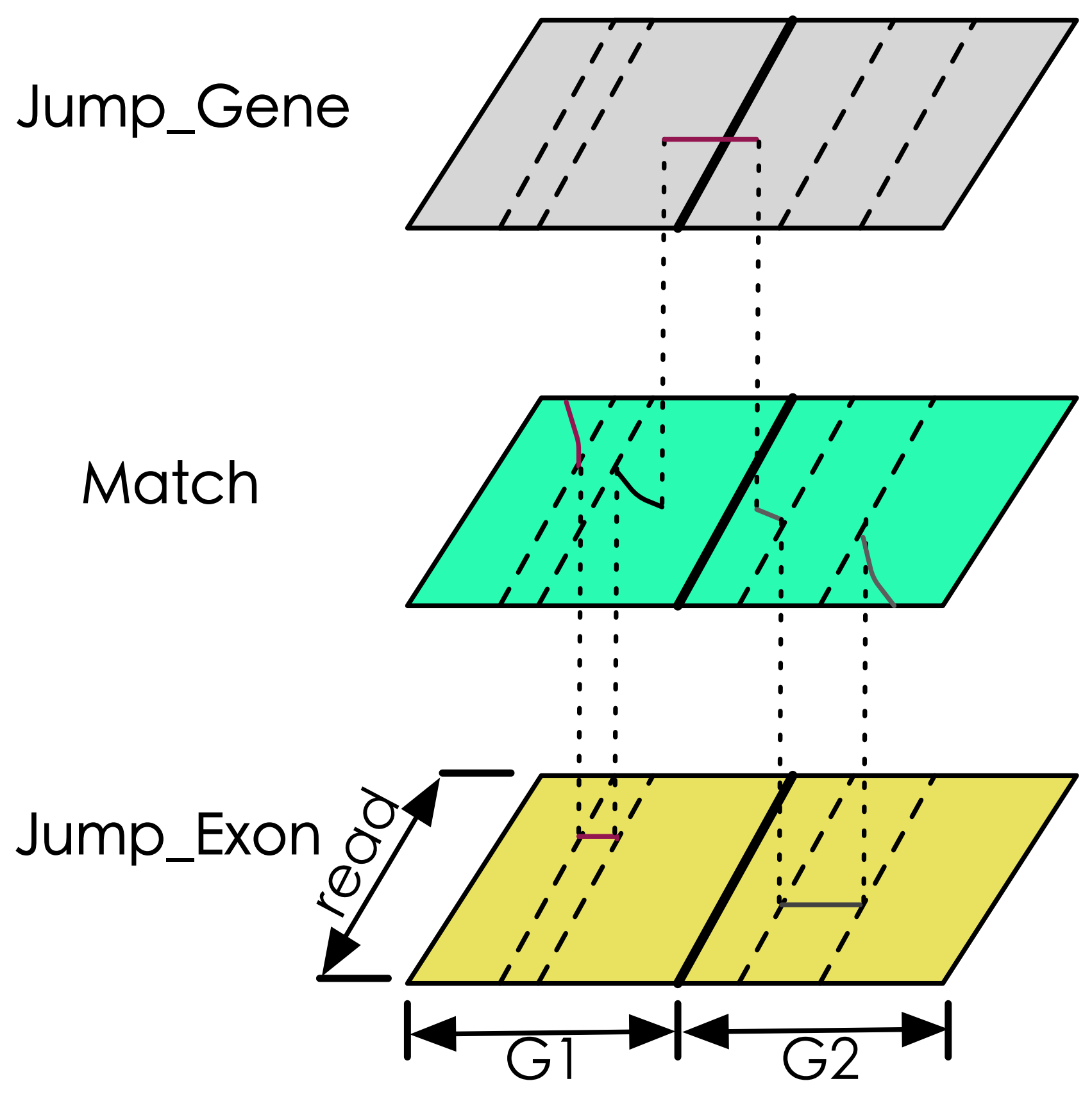
In G=(V,E), any node vi indicates a targeted gene and edge eij indicates a fusion hypothesis between vi and vj. For any edge eij, w(eij) indicates the number of pairs that support this fusion. Edge eij of w(eij) greater than -w will be called as a fusion hypothesis.

Any edge eij of w(eij) greater than -w will be called out as a fusion hypothesis. Reads that support this hypothesis will be aligned against the string concatenated by exon of vi and vj by fitting alignment that allows free jump between vi and vj and Identify string of length -l that flanks the junction site as junction string.

Scan raw reads and find the subset of reads that match with junction string by 2 mismatches and align those reads against the constructed transcript by fitting alignment that allows alternative splicing and only keep pairs with alignment score greater than -a.

Report likelihood and p-value of fusions.

Affine-Gap Alignment With Jump State



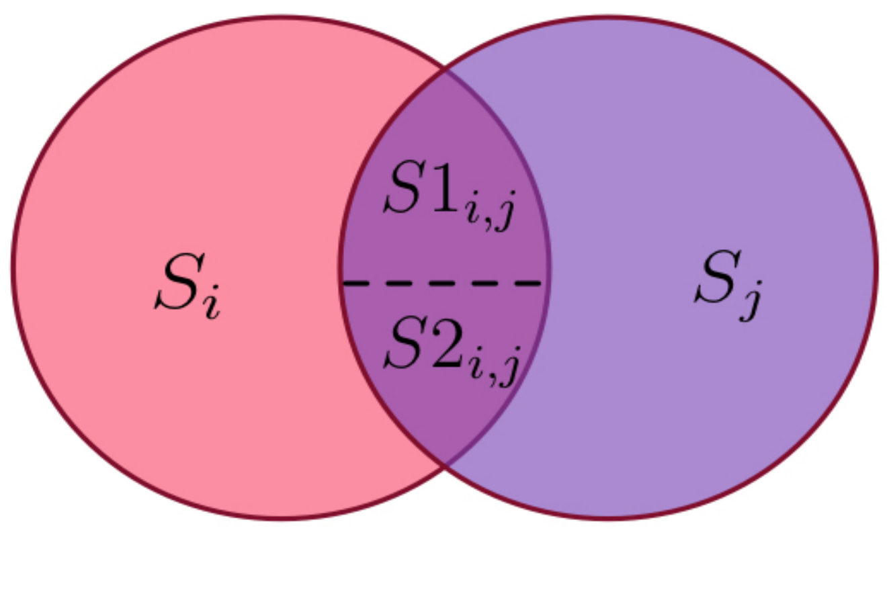
$$J(i,j) = max \begin{cases} \begin{cases} M(i,j-1)+\gamma & j<x \\ -\infty & otherwise \end{cases} \\ J(i,j-1) \end{cases}$$

$$M(i,j) = max \begin{cases} L(i-1,j-1)+\delta \\ M(i-1,j-1)+\delta \\ U(i-1,j-1)+\delta \\ \begin{cases} J(i-1,j-1)+\delta & j<x \\ -\infty & otherwise \end{cases} \\ \begin{cases} G1(i-1,j-1)+\delta & j \in S1 \\ -\infty & otherwise \end{cases} \\ \begin{cases} G2(i-1,j-1)+\delta & j \in S2 \\ -\infty & otherwise \end{cases} \end{cases}$$

$$G1(i,j) = max \begin{cases} \begin{cases} M(i,j-1)+\tau & j \in S1 \\ -\infty & otherwise \end{cases} \\ G1(i,j-1) \end{cases}$$

$$G2(i,j) = max \begin{cases} \begin{cases} M(i,j-1)+\tau & j \in S2 \\ -\infty & otherwise \end{cases} \\ G2(i,j-1) \end{cases}$$

Fusion Scoring



$$L_{i,j} = \frac{-\alpha \sum_s^{S1_{i,j}} log(1-f(s)) - \beta \sum_s^{S2_{i,j}} log(1-f(s))}{|S_i|+|S_j|}$$

in which $f(s)$ *is alignment probability,* $\alpha = 3$ *and* $\beta = 1$.

P-value

We extracted normal transcripts of targeted genes and simulated pair-end reads from the normal transcripts. Then run TaFuCo against the simulated data and calculate the score (defined above) for every gene pair. Repeat this for 200 hundred times and get the background distribution. P-value is calculated based on the background.

FAQ

Q: How precise is TaFuCo?

A: ~0.85 (Se) and ~0.99 (Sp).

Q: How fast is TaFuCo?

A: ~5min per million read pairs using a single x86_64 32-bit 2000 MHz GenuineIntel processor.

Q: How about memory use of TaFuCo?

A: 1GB would be enough for predicting against 500 genes

Q: Where can I get TaFuCo?

A: Find it on github searching TaFuCo (or scan QR code on the leftmost corner) or search TaFuCo on BaseSpace.

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