The FMD and Graph FM Indices

The FMD Index

Motivation : The FM-index naturally searches in one direction (from the end of the string to the front)

To find MEMs and SMEMs, it will be useful to extend matches in both directions.

Why not two indices? This could be accomplished with 2 FM-indices, but having the search work within a single index will be more efficient.

First formal description of FMD index

BIOINFORMATICS ORIGINAL PAPER Vol. 28 no. 14 2012, pages 1838–1844
doi:10.1093/bioinformatics/bts280

Sequence analysis Advance Access publication May 7, 2012

Exploring single-sample SNP and INDEL calling with whole-genome *de novo* assembly

Heng Li

Medical Population Genetics Program, Broad Institute, 7 Cambridge Center, MA 02142, USA

Associate Editor: Michael Brudno

The FMD Index

Some notation. For pattern P and text T

$$I^l(P) = \min\{k : P \text{ is the prefix of } T_{S(k)}\}$$

$$I^u(P) = \max\{k : P \text{ is the prefix of } T_{S(k)}\}$$

Then $[I^l(P), I^u(P)]$ is the suffix array interval for P

The length of this is given by $I^s(P) = I^u(P) - I^l(P) + 1$

Some notation. For pattern P and text T

The FMD Index

Let $R_0, R_1, \ldots, R_{n-1}$ denote a series of DNA/RNA texts

Define a new text $T = R_0\overline{R}_0R_1\overline{R}_1 \ldots R_{n-1}\overline{R}_{n-1}$

Where $\overline{R}$ is the reverse complement of R

Consider *bi-intervals* of the index of the form $[I^l(P), I^l(P), I^s(P)]$

Also, recall that we can extend a “normal” interval as

$$I^l(aP) = C(a) + O(a, I^l(P) - 1)$$

$$I^u(aP) = C(a) + O(a, I^u(P)) - 1$$

The FMD Index

Assume we have the bi-interval of P, $[I^l(P), I^l(\overline{P}), I^s(P)]$

How do we compute the bi-interval of aP ?

We know that $[I^l(\overline{aP}), I^u(\overline{aP})]$ is a subinterval of

$[I^l(\overline{P}), I^u(\overline{P})]$, why?

Because P is a prefix of $\overline{aP} = \overline{P} \circ \overline{a}$

Further, because of the symmetry of T, $I^s(cP) = I^s(\overline{cP}), \forall c$

The FMD Index

Example:
W = AACG
a = G
aW = GAACG
$\overline{\text{Wa}}$ = CGTTC

Consider symmetry of T:

```
#AACG  = #CGTT
#AAACG = #CGTTT
#CAACG = #CGTTG
#GAACG = #CGTTC
#TAACG = #CGTTA
```

So, given $\overline{\text{W}}$, to extend to $\overline{\text{Wa}}$, we can simply *count!*

Algorithm 2: Backward extension

Input: Bi-interval $[k,l,s]$ of string W and a symbol a
Output: Bi-interval of string aW

Function BACKWARDEXT($[k,l,s],a$) **begin**
  for $b \leftarrow 0$ **to** 5 **do**
    $k_b \leftarrow C(b)+O(b,k-1)$
    $s_b \leftarrow O(b,k+s-1)-O(b,k-1)$
  $l_0 \leftarrow l$;
  $l_4 \leftarrow l_0+s_0$;
  for $b \leftarrow 3$ **to** 1 **do**
    $l_b \leftarrow l_{b+1}+s_{b+1}$
  $l_5 \leftarrow l_1+s_1$;
  return $[k_a,l_a,s_a]$

This is the part that requires some thought

```
$,A,C,G,T,N
0,1,2,3,4,5
```

The FMD Index

Forward extension is simply backward extension in the reverse complement!

Algorithm 3: Forward extension

Input: Bi-interval $[k, l, s]$ of string W and a symbol a
Output: Bi-interval of string Wa

Function FORWARDEXT($[k, l, s], a$) **begin**
  $[l', k', s'] \leftarrow$ BACKWARDEXT($[l, k, s], \overline{a}$);
  return $[k', l', s']$

Finding SMEMs with the FMD Index

Algorithm 5: Finding SMEMs

Input: String P and start position i_0; $P[-1]=0$
Output: Set of bi-intervals of SMEMs overlapping i_0

```
Function SuperMEM1(P, i_0) begin
    Initialize Curr, Prev and Match as empty arrays;
    [k, l, s] ← [C(P[i_0]), C(P̄[i_0]), C(P[i_0]+1) − C(P[i_0])];
    for i ← i_0 + 1 to |P| do
        if i = |P| then
            Append [k, l, s] to Curr
        else
            [k', l', s'] ← ForwardExt([k, l, s], P[i]);
            if s' ≠ s then
                Append [k, l, s] to Curr
            if s' = 0 then
                break;
            [k, l, s] ← [k', l', s']
    Swap array Curr and Prev;
    i' ← |P|;
    for i ← i_0 − 1 to −1 do
        Reset Curr to empty;
        s'' ← −1;
        for [k, l, s] in Prev do
            [k', l', s'] ← BackwardExt([k, l, s], P[i]);
            if s' = 0 or i = −1 then
                if Curr is empty and i + 1 < i' + 1 then
                    i' ← i;
                    Append [k, l, s] to Match
            if s' ≠ 0 and s' ≠ s'' then
                s'' ← s';
                Append [k, l, s] to Curr
        if Curr is empty then
            break
        Swap Curr and Prev;
    return Match
```

Extend "forward"

Extend "backward"

The Graph FM-Index & HISAT2

Graph-based genome alignment and genotyping with HISAT2 and HISAT-genotype

Daehwan Kim, Joseph M. Paggi, Chanhee Park, Christopher Bennett & Steven L. Salzberg

Nature Biotechnology **37**, 907–915 (2019) | Download Citation

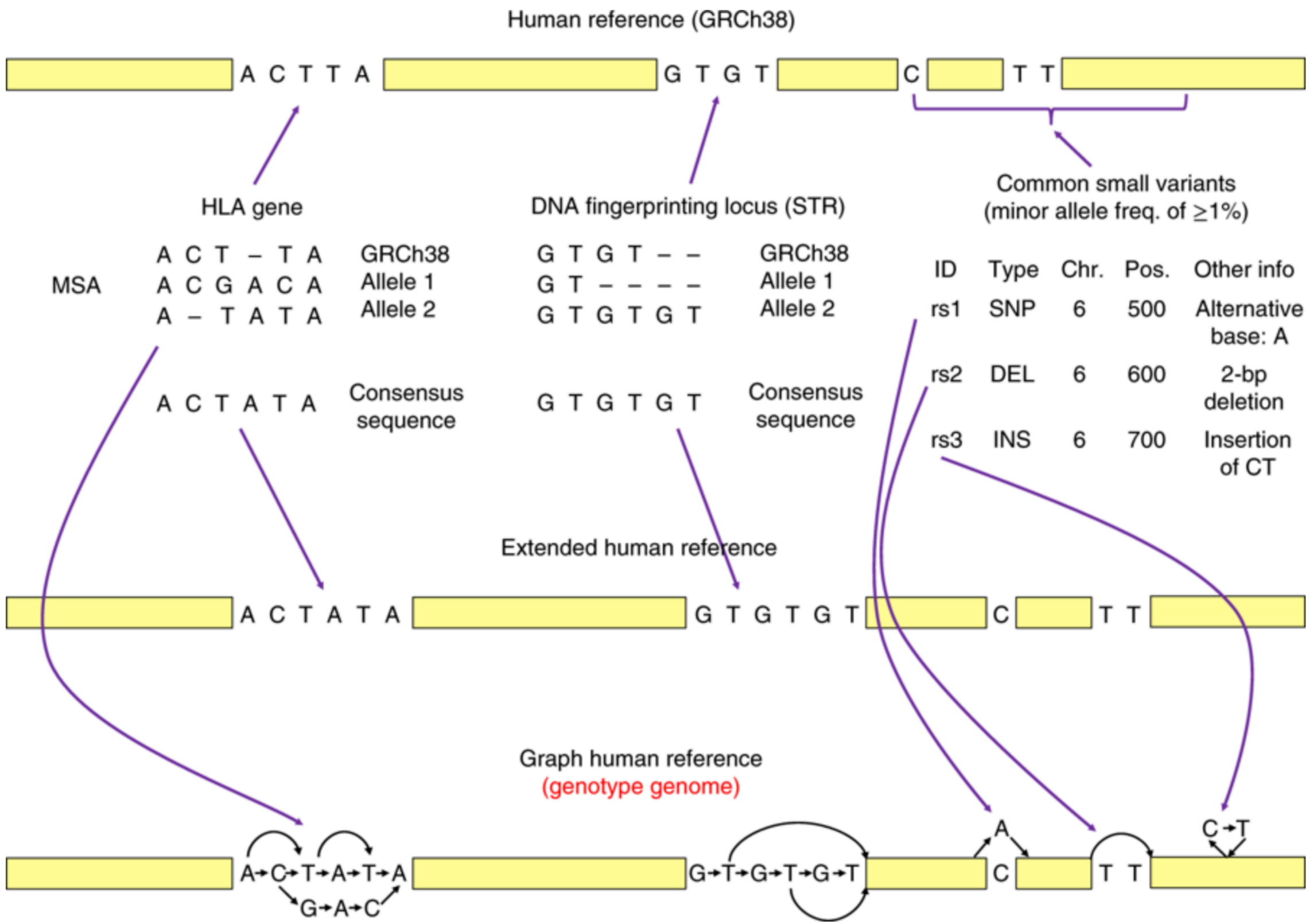
The Graph FM-Index

Idea / motivation : **No sample is the reference**

We have spent a lot of effort characterizing major human variants, yet most aligners simply map against a single human reference genome that doesn't even have the most likely variant at each locus.

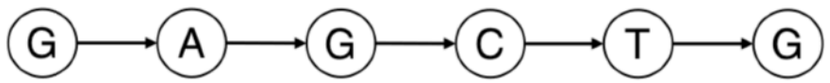
HISAT2 is one of a new breed of "graph" aligners, that views the genome as a graph rather than a simple string. This framework allows encoding variants as alternative "paths" through the genome.

The Graph FM-Index



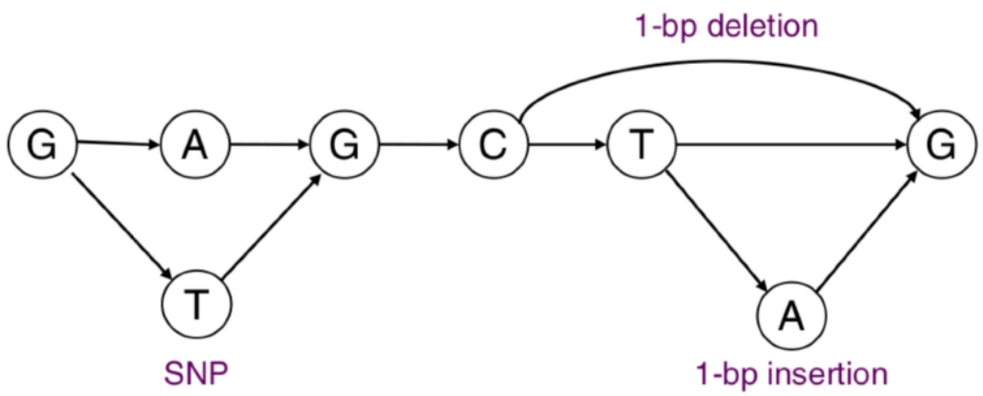
The Graph FM-Index

1. Reference sequence (6 bp long)



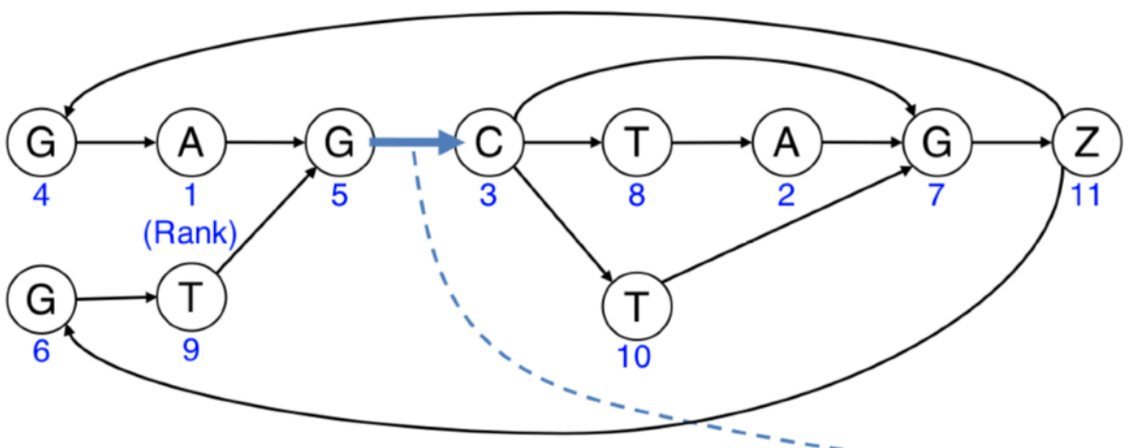
single-nucleotide variant (A/T), a 1-bp deletion (T) and a 1-bp insertion (A)

2. Graphical representation (original graph)



Prefix doubling and pruning

3. Prefix-sorted graph



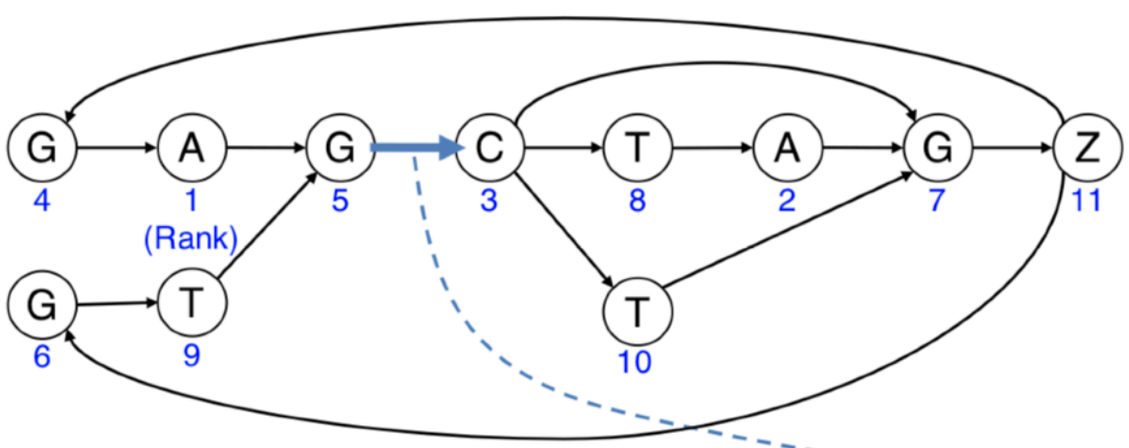
4. Tabular representation of the prefix-sorted graph

Outgoing edge(s)		Incoming edge(s)	
Node rank	First	Last	Node rank
1	A	G	1
2	A	T	2
3	C C C	G Z A T	3 4 5
4	G		
5	G	Z	6
6	G	A C T	7
7	G		
8	T		
9	T	C	8
10	T	G	9
11	Z Z	C G	10 11

Siren, J., Valimaki, N. & Makinen, V. Indexing graphs for path queries with applications in genome research. *IEEE-ACM Trans. Comput. Biol. Bioinform.* **11**, 375–388 (2014).

(the transformation from 2 -> 3 is crucial to allow indexing)

The Graph FM-Index



Outgoing edge(s)			Incoming edge(s)	
Node rank	First		Last	Node rank
1	A		G	1
2	A		T	2
3	C C C		G Z A	3 4 5
4	G		T	
5	G		Z	6
6	G		A	7
7	G		C	
8	T		T	
9	T		C	8
10	T		G	9
11	Z Z		C G	10 11

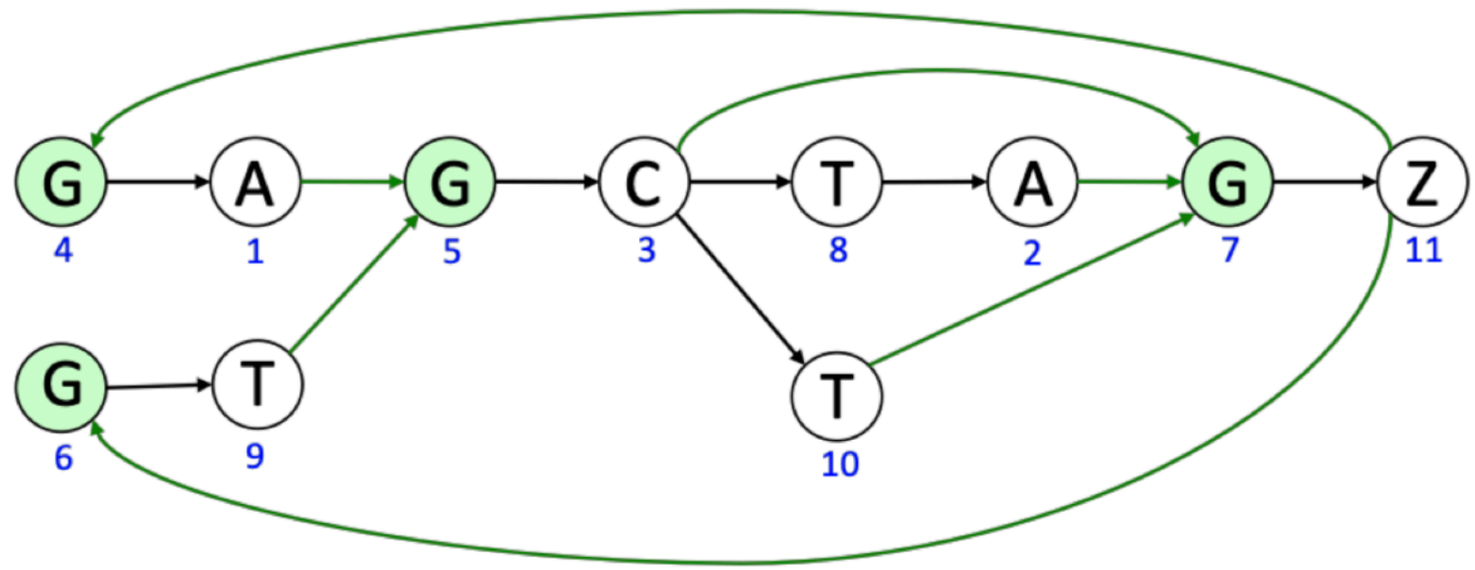
The Graph FM-Index

Outgoing edge(s)		Incoming edge(s)	
Node ID	First	Last	Node ID
1	A	G	1
2	A	T	2
3	C C C	G Z A T	3 4 5
4	G	Z	6
5	G	A C T	7
6	G		
7	G		
8	T	C	8
9	T	G	9
10	T	C	10
11	Z Z	G	11

Searching the Graph FM-Index

Outgoing edge(s)			Incoming edge(s)	
Node ID	First		Last	Node ID
1	A		G	1
2	A		T	2
3	C C C		G	3
			Z	4
			A T	5
4	G	1		
5	G		Z	6
6	G		A C T	7
7	G			
8	T			
9	T		C	8
10	T		G	9
11	Z Z		C	10
			G	11

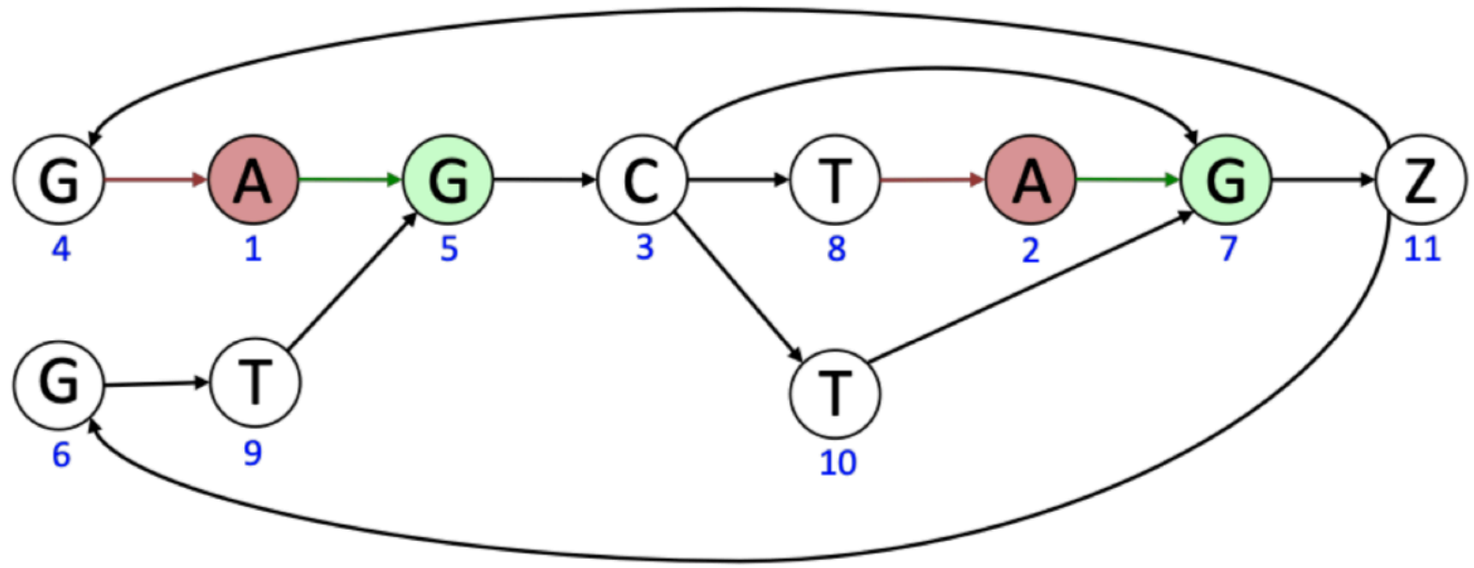
Query : TAG



Searching the Graph FM-Index

Outgoing edge(s)			Incoming edge(s)	
Node ID	First		Last	Node ID
1	A		G	1
2	A		T	2
3	C C C	2	G	3
			Z	4
			A T	5
4	G	1		
5	G		Z	6
6	G		A C T	7
7	G			
8	T			
9	T		C	8
10	T		G	9
11	Z Z		C	10
			G	11

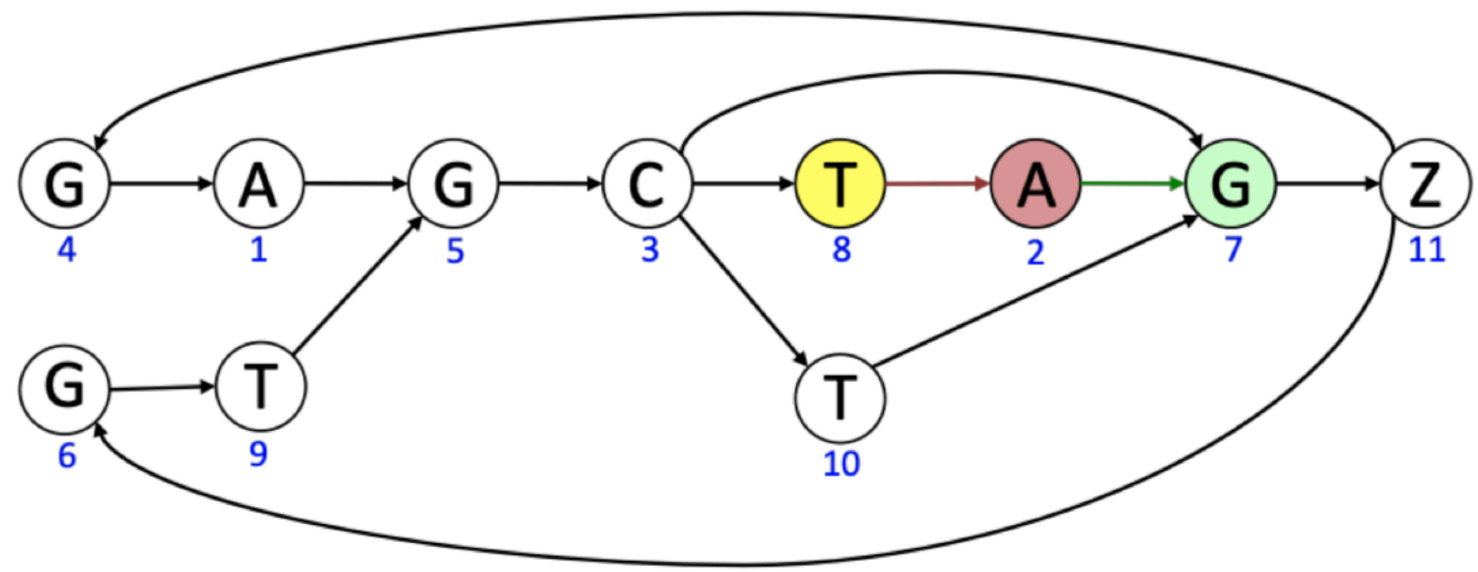
Query : TAG



Searching the Graph FM-Index

Outgoing edge(s)			Incoming edge(s)	
Node ID	First		Last	Node ID
1	A	3 →	G	1
2	A		T	2
3	C C C	2 ↖	G	3
			Z	4
			A T	5
4	G	1 ↗	Z	6
5	G			
6	G		A C T	7
7	G			
8	T			
9	T		C	8
10	T		G	9
11	Z Z		C	10
			G	11

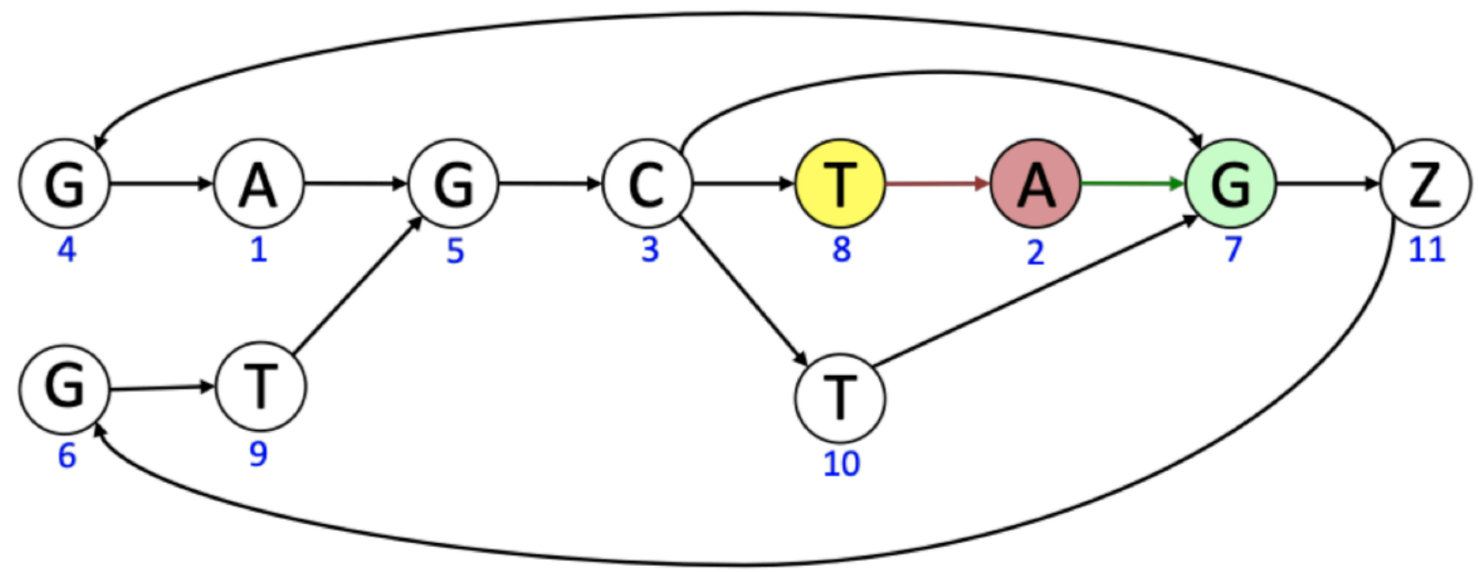
Query : TAG



Searching the Graph FM-Index

Outgoing edge(s)			Incoming edge(s)	
Node ID	First		Last	Node ID
1	A	3	G	1
2	A		T	2
3	C C C	2	G	3
			Z	4
			A	5
4	G	1	T	4
5	G		Z	6
6	G		A	7
7	G		C	
8	T		T	
9	T		C	8
10	T		G	9
11	Z Z		C	10
			G	11

Query : TAG



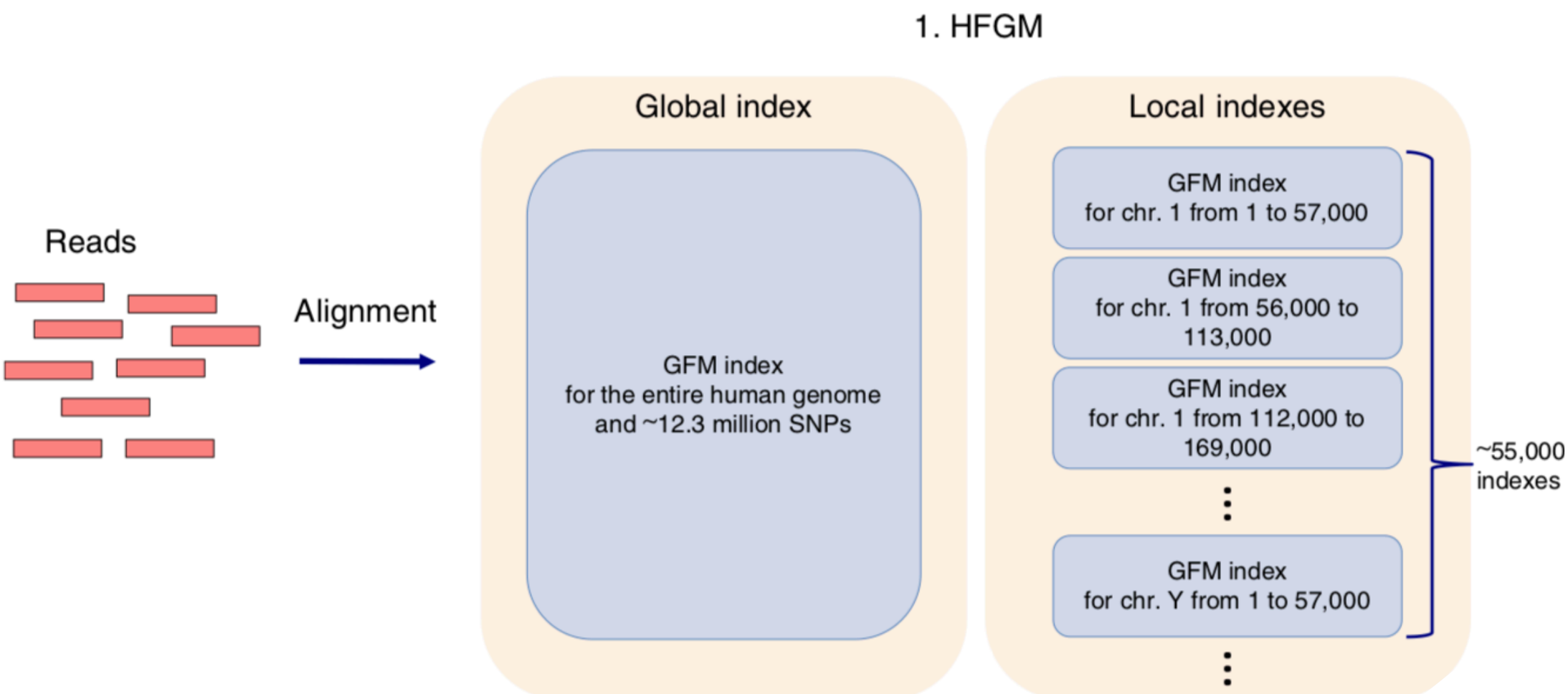
How to store the GFM efficiently

Outgoing edge(s)		Incoming edge(s)	
Node rank	First	Last	Node rank
1	A	G	1
2	A	T	2
3	C C C	G Z A T	3 4 5
4	G	Z	6
5	G	A C T	7
6	G	C	8
7	G	G	9
8	T	C	10
9	T	G	11
10	T		
11	Z Z		

Outgoing edge(s)	Incoming edge(s)	
Node rank	Last	Node rank
1	10	1
1	11	1
1	10	1
0	00	1
0	00	1
1	11	0
1	00	1
1	00	1
1	01	0
1	11	0
1	01	1
1	10	1
1	01	1
0	10	1

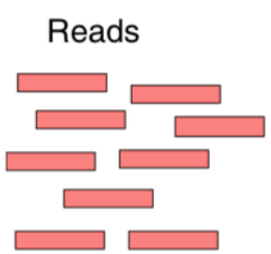
First	
A	2
C	3
G	4
T	3
Z	2

Uses same idea as HISAT to make GFM Cache-efficient



Uses same idea as HISAT to make GFM Cache-efficient

Special handling of repetitive sequences



Alignment

1. HFGM

Global index

GFM index
for the entire human genome
and ~12.3 million SNPs

Local indexes

GFM index
for chr. 1 from 1 to 57,000

GFM index
for chr. 1 from 56,000 to 113,000

GFM index
for chr. 1 from 112,000 to 169,000

⋮

GFM index
for chr. Y from 1 to 57,000

⋮

~55,000 indexes

Reads potentially mapped to ≥5 locations

2. Repeat index

FM index
for repeat sequences

Minimizer table
for repeat sequences

Reads mapped to <5 locations

3. Alignment information

Read ID	Chromosome or repeat	Position
Read 1	Chromosome 10	76,822,302
Read 2	Chromosome 17	69,091,764
Read 3	Repeat	14,916,723
Read 4	Repeat	1,780,959

Expanding repeat alignments via APIs (C++, Python and Java)

4. Alignment information (expanded when needed)

Read ID	Chromosome	Position
Read 1	Chromosome 10	76,822,302
Read 2	Chromosome 17	69,091,764
Read 3	Chromosome 4	122,942,920
Read 3	Chromosome 4	123,001,589
Read 3	Chromosome 4	127,862,299
Read 3	Chromosome 9	89,130,544
Read 3	Chromosome 20	16,910,713
Read 4	Chromosome 1	102,931,088
Read 4	Chromosome 2	105,208,801
Read 4	Chromosome 3	174,262,680
Read 4	Chromosome 4	15,844,480
	. . .	
Read 4	Chromosome X	69,679,816
Read 4	Chromosome Y	22,342,611