Genome Assembly

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Background

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In our cells, DNA carries genetic information:

- Each DNA strand contains a sequence of A, C, G, and Ts
- The human genome is around 3 billion base pairs long

Types of DNA Variation:

- Single base variations
- Copy number variations

```
>HSBGPG
GGCAGATTCCCCCTAGACCCGCCCGCACCATGGTCAG
TGGGCACAGCCCAGAGGGTATAAACAGTGCTGGAGGC
AGTCCTGAGCAGCAGCCCAGCGCAGCCACCGAGACAC
CTCGCCCTATTGGCCCTGGCCGCACTTTGCATCGCTG
CCACCTCCCCTCAGGCCGCATTGCAGTGGGGGCTGAG
CACCTCTTCTCACCCCTTTGGCTGGCAGTCCCTTTGC
AGGCTCAATCCATTTGCCCCAGCTCTGCCCTTGCAGA
AGCTGCCCGAGACGCAGGGGAAGGAGGATGAGGGCCC
ACCAGGCTCCCTTTCCTTTGCAGGTGCGAAGCCCAGC
GTGCAGGTATGAGGATGGACCTGATGGGTTCCTGGAC
CCCTCAGTCTCATTCCCCCACTCCTGCCACCTCCTGT
GCCTGCTCCCCACCTGATCCTCCCAAACCCAGAGCCA
CTCCACAGCCTTTGTGTCCAAGCAGGAGGGCAGCGAG
GCTACCTGTATCAATGGCTGGGGTGAGAGAAAAGGCA
```

(a) FASTA file stores reference genome

```
@H3GFVCCXX150415:8:2224:9627:35467/1
GGGAATTTTAACTGGCAAAACTCAGAACTCCATCCAAAC
+
AAAFF<<FFAFAFAAAAFFFAFAAAAAAFAAAFAAFAFA
@H3GFVCCXX150415:8:2224:8957:23407/1
CATACTTGATGGTCTCAGATATGTGTGGATTTTGGAATT
+
<FAFAFFAAAA7AAFAAAAFAAAAAAFAFAFFFAAFFFF
@H3GFVCCXX150415:8:2224:8907:25745/1
GTTAATTAAAAGCCCTTTACGAATGGACTAGATGTACCT
+
AAAFFAFAF/FFAAAA<FAA7FFAAAFAFAF7FAAFAAF
@H3GFVCCXX150415:8:2224:8825:55175/1
GCACCCTGTGTCAACAACCTGAGAGTGGCCTTGAGTTGC
+
AAFAAAFAAAAAFFAFFAAFAFAAAAFAAAFFFAFAFAA
```

(b) FASTQ file stores sequenced reads

Data Source: National Center for Biotechnology Information

Mapping vs Assembly

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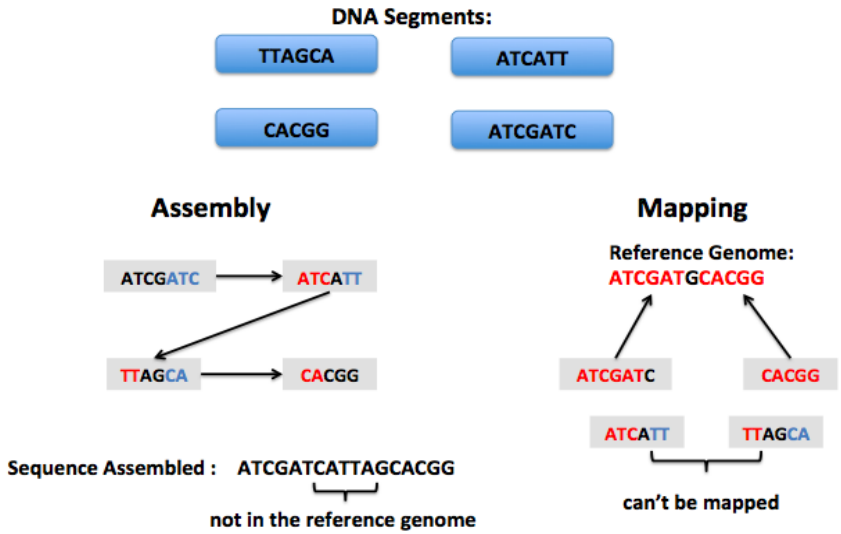
Assembly

- Reconstructs genome from sequenced reads
- Particularly useful to detect large genetic variants. (i.e. free from bias towards reference genome)
- Slow, memory-intensive, and hard to implement

Mapping

- Match to reference genome to locate variation
- Fast, easy to understand
- Cannot handle sequenced reads containing complex variation



Constructing De Bruijn Graph of Reference Genome

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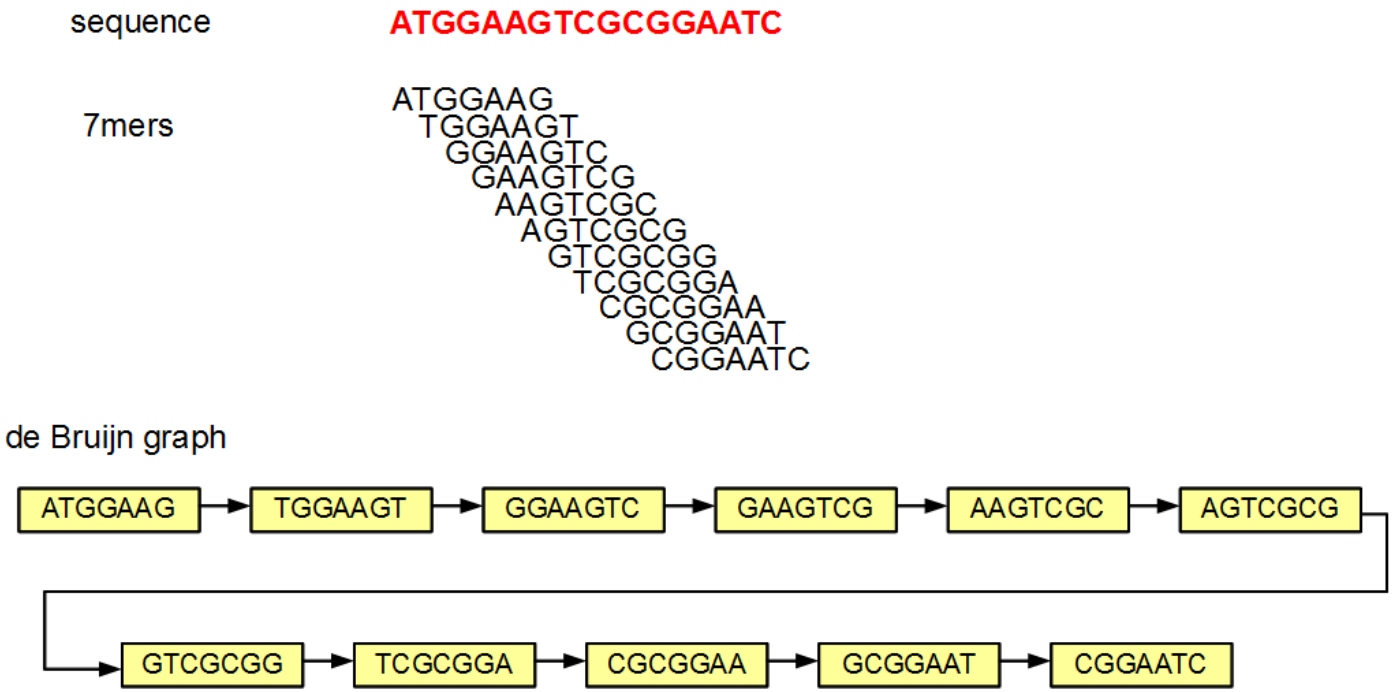
Create process to store and reassemble a reference genome
Method: Break DNA string into 'kmers' and store in a De Bruijn Graph



http://www.homolog.us/Tutorials/Tut-Img/Set1/fig5.png

Impact of K on complexity of De Bruijn Graph

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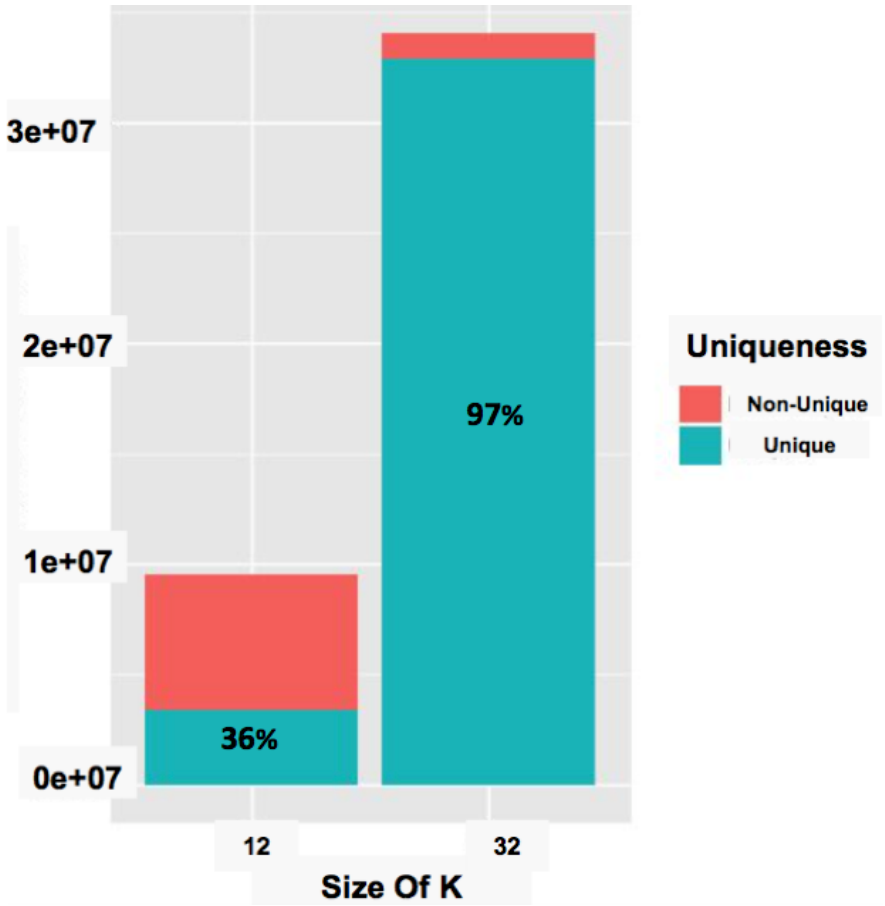

Methodology: Functions

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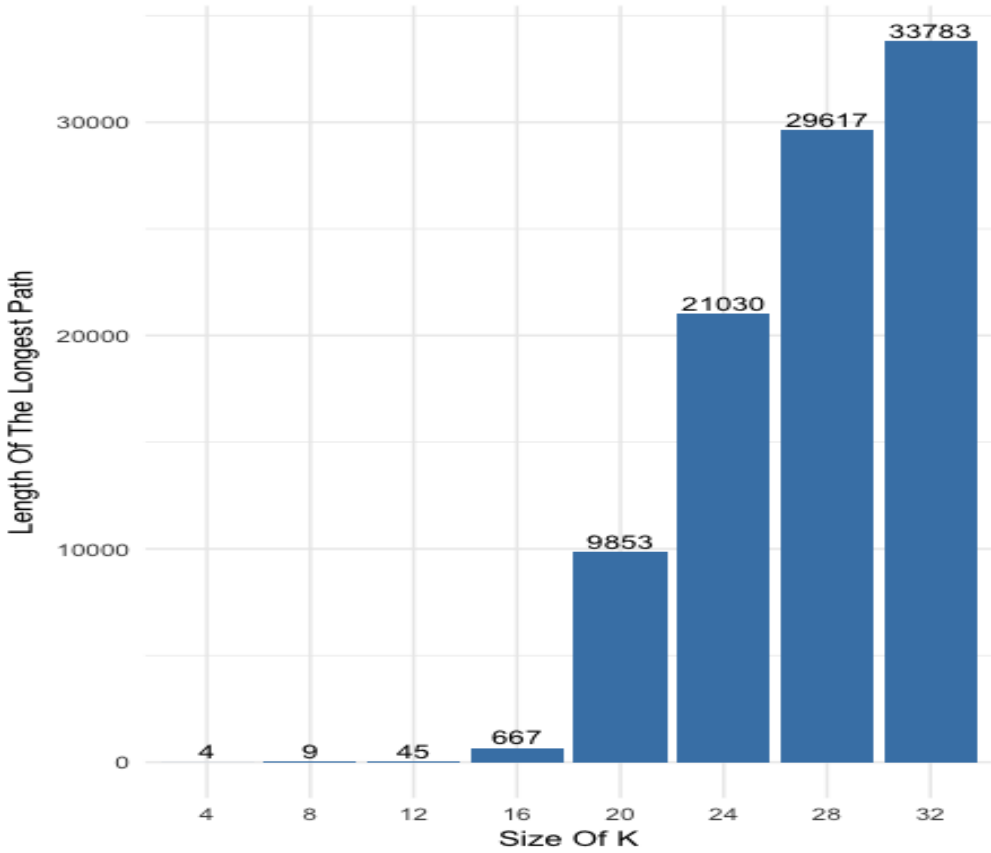

Figure: Comparison of The Lengths Of The Longest Paths

DNA Variation in a De Bruijn Graph

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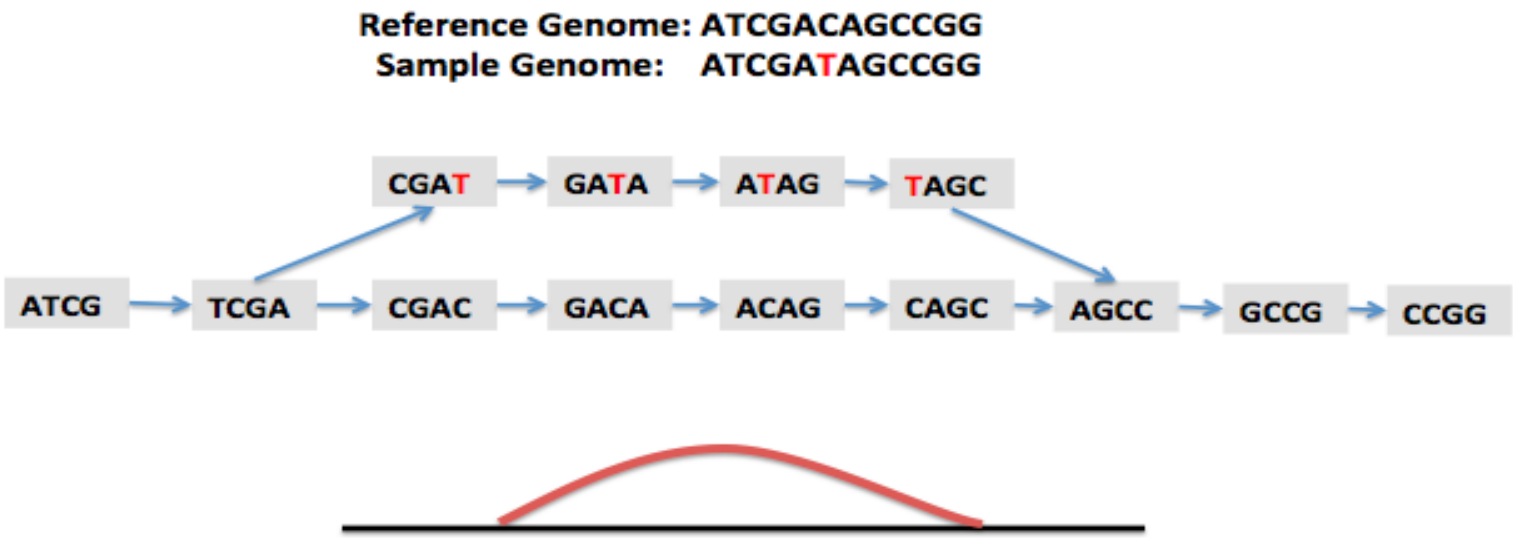

Given an individual's sequenced DNA, we want to locate where their genome varies from the reference

Method: Create De Bruijn graph for sequenced reads to store only variations in genome

Storage Structure

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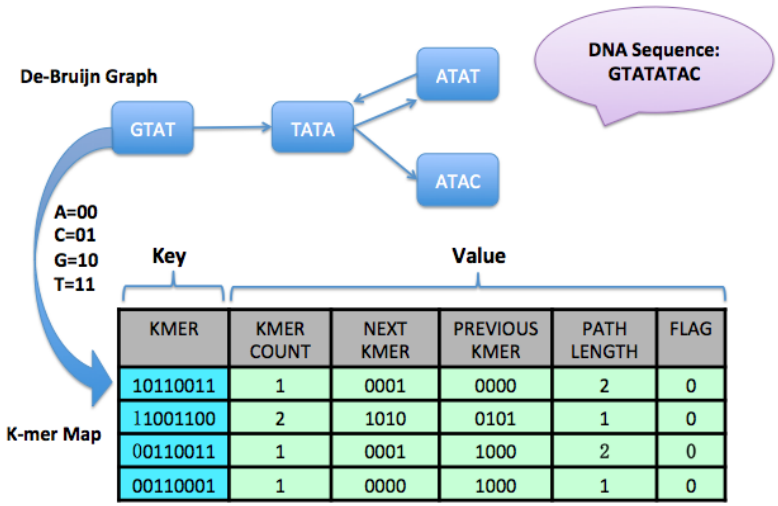
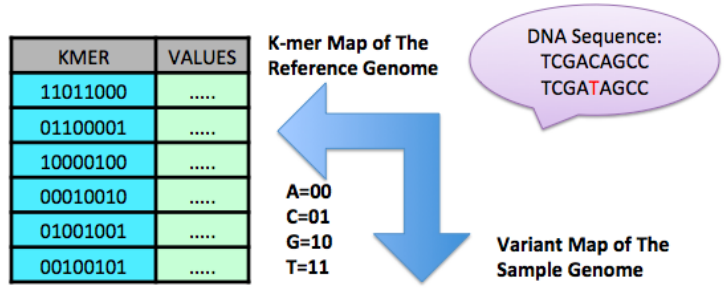


KMER	KMER COUNT	NEXT KMER	PREVIOUS KMER	PATH LENGTH	FLAG
10110011	1	0001	0000	2	0
11001100	2	1010	0101	1	0
00110011	1	0001	1000	2	0
00110001	1	0000	1000	1	0

(a) Kmer Graph Structure



KMER	VALUES
11011000	.....
01100001	.....
10000100	.....
00010010	.....
01001001	.....
00100101	.....

KMER	NEXT KMER COUNT OF A	NEXT KMER COUNT OF C	NEXT KMER COUNT OF G	NEXT KMER COUNT OF T
01100011	1	0	0	0
10001100	0	0	1	0
00110010	0	1	0	0
11001001	0	1	0	0

(b) Variant Graph Structure

Figure: Data Structures Of The Graphs

Implemented in C++

Future Plans

Cleaning/Pruning Variant Graph

- More accurate and usable
- Reduces storage size

FM indexing

- Allows compression of input text while still permitting fast substring queries

References

For Images:

- Iqbal, Zamin, Mario Caccamo, Isaac Turner, Paul Flicek, and McVean Gil. "De Novo Assembly and Genotyping of Variants Using Colored De Bruijn Graphs." Nature Genetics (2012): Nature Publishing Group. Web.

For information on sequencing and assembly methods

- Paolo Ferragina and Giovanni Manzini (2000). "Opportunistic Data Structures with Applications". Proceedings of the 41st Annual Symposium on Foundations of Computer Science. p.390.
- `http://genome.cshlp.org/content/18/5/821.long#sec-17`
- `http://cortexassembler.sourceforge.net/index_cortex_var.html`
- Umich Biostats lectures

Acknowledgments

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