Building Large Updatable Colored de Bruijn Graphs via Merging

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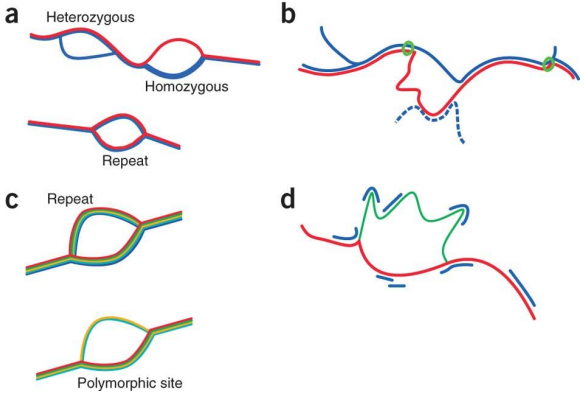
Colored de Bruijn Graphs

In 2012, Iqbal *et al.* introduced the colored de Bruijn graph with CORTEX. It can detect complex variants within a population without a reference.



Related Work

Efficient de Bruijn graphs

- ABySS
- Conway and Bromage
- Okanohara and Sadakane
- Minia
- BOSS
- MEGAHIT
- Chikhi *et al.*

Efficient colored de Bruijn graphs

- VARI
- Rainbowfish
- Bloom filter trie
- Mantis
- Almodaresi *et al.*

Efficient color representation

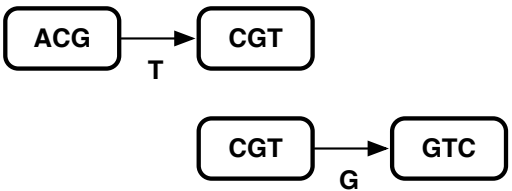
- Mustafa *et al.*
- Mutli-BRWT

Our contribution

- We developed VARI-MERGE
  - Construct succinct colored de Bruijn for sub-populations using VARI
  - New algorithm to merge succinct colored de Bruijn graphs
- Advantages
  - Compress data early $=>$ Use less and faster memory
  - Reuse previous work $=>$ Incremental update
- First to demonstrate incremental update at this scale

Background: de Bruijn Graphs

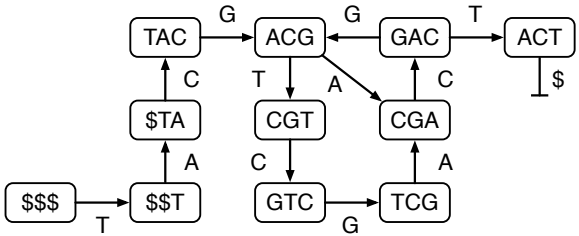
T = TACG**ACGT**CGACT



ACG
CGT

Vertex labels are redundant

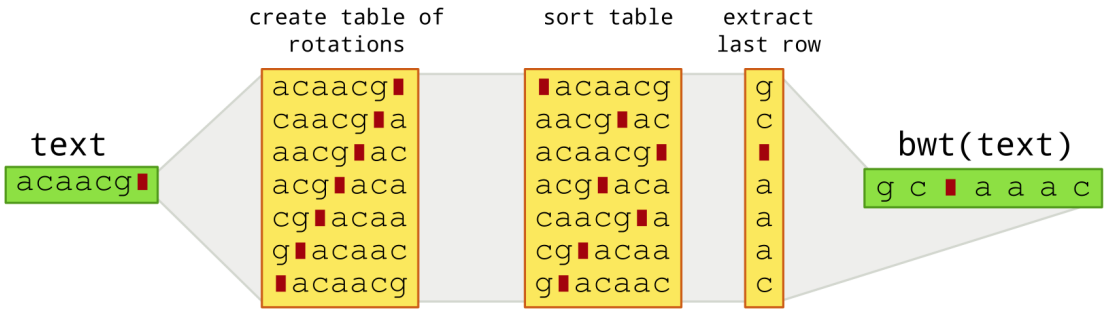
T = TACGACGTCGACT



Burrows-Wheeler Transform (BWT)

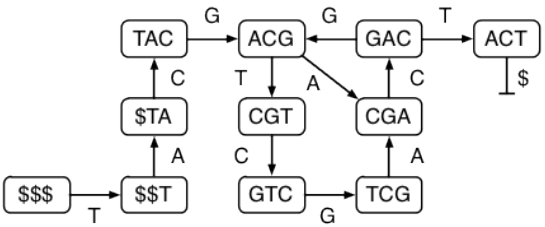
Advantages:

- Compresses repetitive strings well.
- *Self index*: Encodes original string and can provide an index of the implicit *suffix array*.
- BWT[i] $=$ X[SA[i] $-$ 1] if SA[i] $>$ 1 and \$ otherwise.



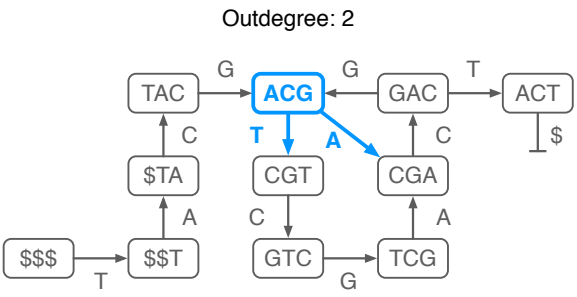
Succinct de Bruijn graphs sort origin labels colex.

Succinct de Bruijn Graphs represent edges as last-to-first mappings in the Burrows-Wheeler transform.



Node	*W*
$ $ $	T
C G A	C
$ T A	C
G A C	G
G A C	T
T A C	G-
G T C	G
A C G	A
A C G	T
T C G	A-
$ $ T	A
A C T	$
C G T	C

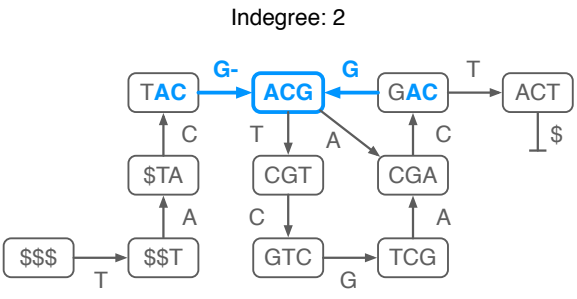
Encoding common origin vertices



F	
$	0
A	1
C	3
G	7
T	10

v	i	L	*Node*			W
0	0	1	$	$	$	T
1	1	1	C	G	A	C
2	2	1	$	T	A	C
3	3	0	G	A	C	G
	4	1	G	A	C	T
4	5	1	T	A	C	G-
5	6	1	G	T	C	G
6	7	0	A	C	G	A
	8	1	A	C	G	T
7	9	1	T	C	G	A-
8	10	1	$	$	T	A
9	11	1	A	C	T	$
10	12	1	C	G	T	C

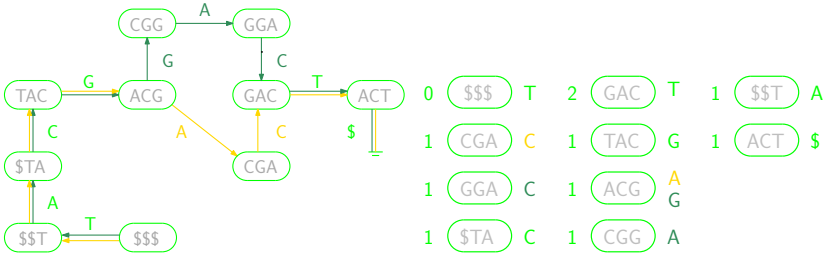
Encoding common destination vertices



F	
$	0
A	1
C	3
G	7
T	10

v	i	L	*Node*			W
0	0	1	$	$	$	T
1	1	1	C	G	A	C
2	2	1	$	T	A	C
3	3	0	G	A	C	G
	4	1	G	A	C	T
4	5	1	T	A	C	G-
5	6	1	G	T	C	G
6	7	0	A	C	G	A
	8	1	A	C	G	T
7	9	1	T	C	G	A-
8	10	1	$	$	T	A
9	11	1	A	C	T	$
10	12	1	C	G	T	C

VARI method: e.g. a two colored de Bruijn graph and its representation



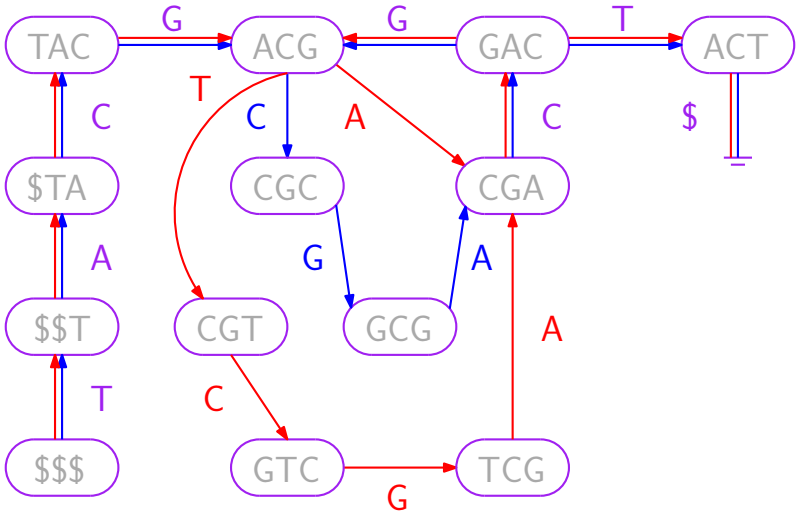
$$\text{EBWT}(G) = \texttt{TCCCTGAGAA\$}$$

$$C^{\text{T}} = \begin{matrix}\texttt{11011110011}\\ \texttt{10111101111}\end{matrix}$$

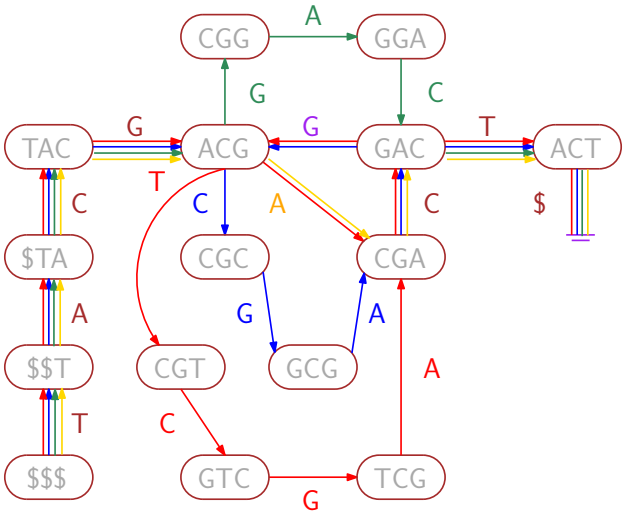
VARI-MERGE: Main Algorithm

1. Consider the final population as a collection of sub-populations
2. Run VARI on each sub-population
3. Run our new algorithm, MERGE on the succinct de Bruijn graphs

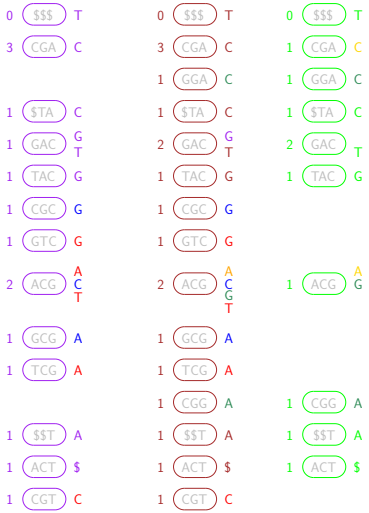
Another two colored de Bruijn graph



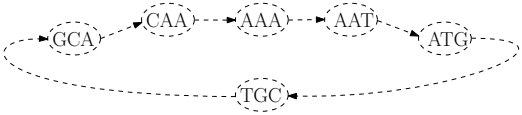
A four colored merged de Bruijn graph



Merging edge labels requires origin vertex label



Two succinct de Bruijn graphs, ignoring color

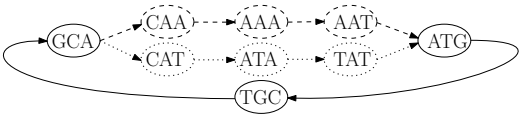


	MSD			LSD
Edge k-mer 1	A	A	A	T
	C	A	A	A
	G	C	A	A
	T	G	C	A
	A	T	G	C
Edge k-mer 6	A	A	T	G

	G	C	A	T
	A	T	A	T
	T	G	C	A
	A	T	G	C
	C	A	T	A
	T	A	T	G

The merged graph

Can we generate the merged succinct graph without reconstructing full vertex k-mers?



Prior BWT merge methods

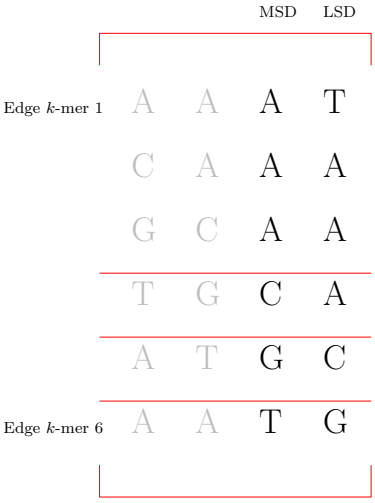
- Holt and McMillan
- Sirén

Generate Most Significant Digit (MSD) column

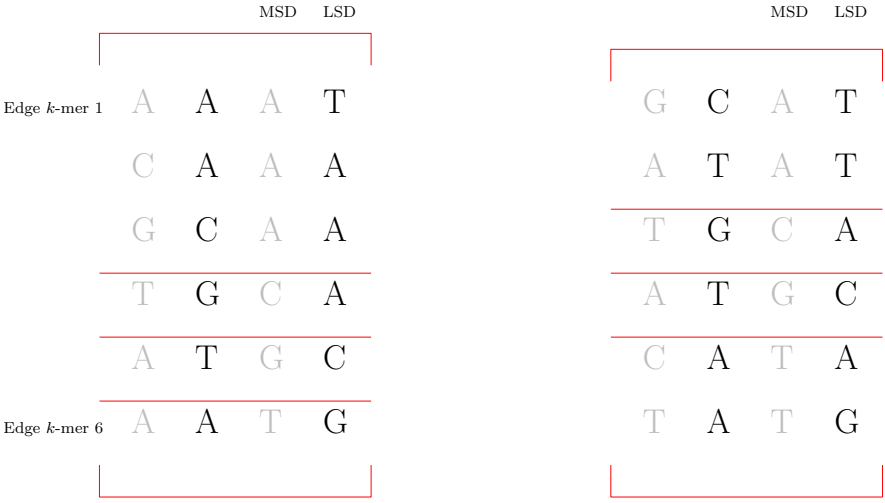
			MSD	LSD
Edge k-mer 1	A	A	A	T
	C	A	A	A
	G	C	A	A
	T	G	C	A
	A	T	G	C
Edge k-mer 6	A	A	T	G

			MSD	LSD
	G	C	A	T
	A	T	A	T
	T	G	C	A
	A	T	G	C
	C	A	T	A
	T	A	T	G

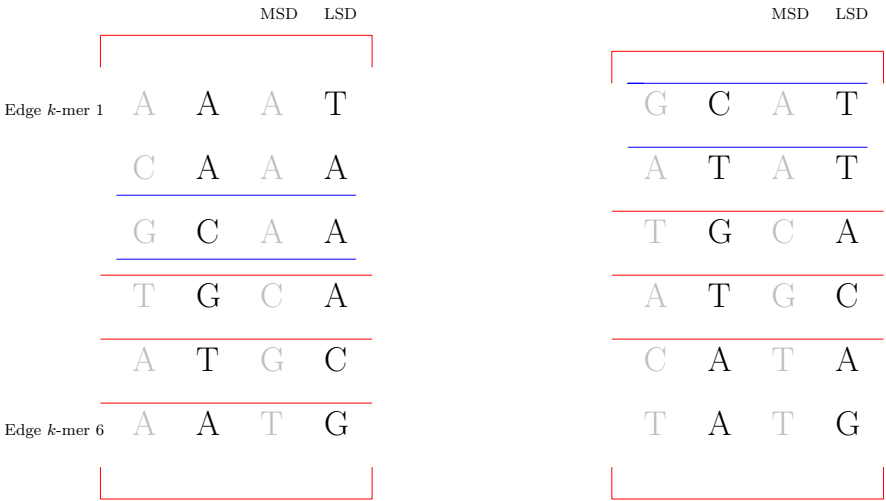
Generate common suffix groups for vertex labels



Generate next most significant digit column



Recursively subdivide existing groups using new column



Constructing 8,000 Salmonella sample graph via merging

Program	Time	External Memory	RAM
VARI	37 h 27 min	4.6 TB	271 GB
VARIMERGE	26 h 30 min	1.5 TB	137 GB

Incremental update performance

Program	Time	External Memory	RAM
VARI(16000)	69 h 8 min	2.34 TB	254 GB
VARI(1)	7 s	460 MB	2.3 GB
MERGE(16000, 1)	7 h 9 min	0	254 GB

Comparison of space-efficient colored graph construction methods

Dataset	No. of k-mers	Program	Output Size	Time	RAM(RSS)
16,000	5.8 Billion	VARI / Rainbowfish	N/A	N/A	N/A
		Bloom Filter Trie	N/A	N/A	N/A
		Multi-BRWT	N/A	N/A	N/A
		Mantis / Method of Almodaresi et al.	256 GB	36 h 12 m	316 GB
		VARIMERGE	233 GB	69 h 8 m	254 GB

Conclusion

- Uncompressed work in small chunk reduces external memory
- Reusing previous computational work lets us build an updated version
- Radix based method satisfies metadata consistency and has no random access

Future work

- What is the optimal sub-population size for initial succinct colored de Bruijn graphs?
- VARIMERGE is radix based, would a trie based merge like bwt-merge be superior under some circumstances?

Acknowledgements

This work was supported by

- National Science Foundation (NSF) IIS Grant No. 1618814
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Questions

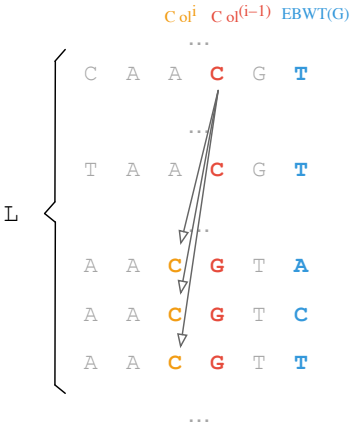
Questions?

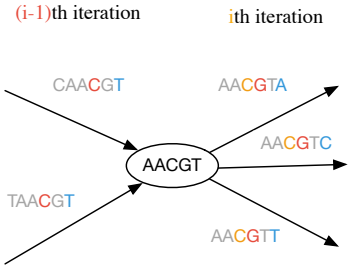
Validation

1. Build succinct colored de Bruijn graphs for *E. coli* genome datasets A and B independently using VARI
2. Merge them using VARIMERGE
3. Build a succinct colored de Bruijn graph for all the data in A and B using VARI
4. Compare merged graph from step 2 with directly constructed graph from step 3

Result: bit-for-bit identical files on disk

Efficiently computing one column at a time





Constructing 8,000 color graph via merging

	Input Stats		de Bruijn Graph			Color Matrix			Combined Requirements			
Program and Dataset	***k*-mers**	**Colors**	**RAM**	**Time**	**Size**	**RAM**	**Time**	**Size**	**RAM**	**Ext. Mem.**	**Time**	**Size**
VARI(4A)	1.1 B	4,000	136 GB	8 h 46 m	0.31 GB	52 GB	1 h 39 m	51.2 GB	136 GB	1 TB	10 h 25 m	51 GB
VARI(4B)	1.5 B	4,000	137 GB	10 h 40 m	0.52 GB	54 GB	2 h 22 m	52.5 GB	137 GB	1.5 TB	13 h 2 m	53 GB
MERGE(4A, 4B)	2.4 B	8,000	10 GB	2 h 1 m	0.63 GB	117 GB	1 h 2 m	106 GB	117 GB	0 TB	3 h 3 m	106 GB
VARIMERGE	2.4	8,000	137 GB	21 h 27 m	0.63 GB	117 GB	5 h 3 m	117 GB	137 GB	1.5 TB	26 h 30 m	106 GB

Constructing 16,000 color graph via merging

	Input Stats		de Bruijn Graph			Color Matrix			Combined Requirements			
Program and Dataset	***k*-mers**	**Colors**	**RAM**	**Time**	**Size**	**RAM**	**Time**	**Size**	**RAM**	**Ext. Mem.**	**Time**	**Size**
VARI(4C)	1.7 B	4,000	135 GB	10 h 53 m	0.46 GB	53 GB	2 h 34 m	51.8 GB	135 GB	1.6 TB	13 h 27 m	52 GB
VARI(4D)	2.4 B	4,000	137 GB	14 h 35 m	0.67 GB	59 GB	3 h 37 m	57.9 GB	137 GB	2.34 TB	18 h 12 m	59 GB
MERGE(4C, 4D)	3.8 B	8,000	17 GB	2 h 59 m	1.00 GB	118 GB	57 m	107 GB	118 GB	0 TB	3 h 56 m	108 GB
MERGE(8AB, 8CD)	5.8 B	16,000	25 GB	4 h 53 m	1.60 GB	254 GB	2 h 10 m	232 GB	254 GB	0 TB	7 h 3 m	233 GB
VARIMERGE	5.8 B	16,000	137 GB	54 h 47 m	1.60 GB	254 GB	14 h 21 m	232 GB	254 GB	2.34 TB	69 h 8 m	233 GB

FM-Index and Backward Search

Advantages:

- Exact search in O(n).
- Compressed Suffix Array (CSA)