

# Fully Dynamic de Bruijn Graphs

Alan Kuhnle , Victoria Crawford, Yuanpu Xie , Zizhao Zhang, Ke Bo

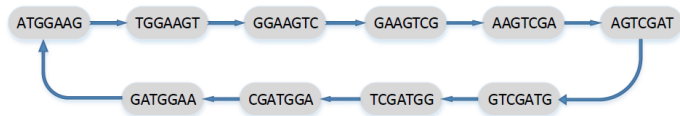
April 10, 2017

- 1 Introduction
- 2 Data Structure
- 3 Implementation
- 4 Experiments

# Genome assembly: De-Bruijn graph

De-Bruijn graph: Reconstructing a string from a set of its  $k$ -mers

- ① Data structure method on genome assembly.
- ② Consist of multiple  $K$ -mers which generated by genome sequence.
- ③ Same vertices,  $K-1$  mers are glue together in the final step.



**Fig. 1.** The de Bruijn graph constructed from string ATGGAAGTCGATGGAAG, with  $k = 7$ .

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- Next-generation sequencing (NGS) data usually comes with large volume and short size, which has large amount of repetitive regions.
- Compared to 'overlap-consensus-layout' method, De Bruijn graph-based assembly approach handles the assembly of repetitive regions better

# Application problem

- Using de Bruijn graph in practice is the high memory occupation for certain organisms
- Human genome encoded in a de Bruijn graph with a k-mer size of 27 requires 15GB to store the node sequences
- Bulges and whirls occur because of sequencing errors or repeats in the genome, so would like to be able to efficiently add and remove edges from graph

**How to efficiently update graph while maintaining memory space efficiency?**



# Fully Dynamic de Bruijn Graphs(Belazzougui et al. (2016))

## **Introduces compact, dynamic representation of De Bruijn graph**

- Nodes and edges can be inserted and deleted efficiently
- k-mers are represented by integers using a combination of Karp-Rabin hashing and minimal perfect hashing.
- A partition of the graph into a forest allows efficient membership queries with no error.

# Project

- 1 Implement the data structure from the paper.
- 2 Evaluate our data structure on graphs built from real sequencing data.
- 3 Compare our data structure with alternative approaches for De Bruijn graphs

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- De Bruijn graph and forest

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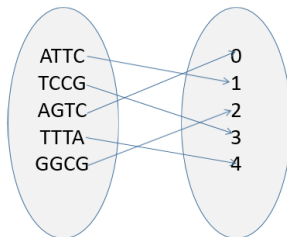
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- 2 **Karp-Rabin**: Given a prime  $P$  and base  $r$ , a Rabin-Karp hash function  $f$  is a function defined over the space of all strings of length  $k$  such that  $f(x_1 \dots x_k) = (\sum_{i=1}^n x_i r^i) \bmod P$ .

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# Hash function properties

## Lemma

*Given a static set  $N$  of  $n$   $k$ -tuples over an alphabet  $\Sigma$  of size  $\sigma$ , with high probability in  $O(kn)$  expected time we can build a function  $f: \Sigma^k \rightarrow \{0, \dots, n-1\}$  with the following properties:*

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- ③ given a  $k$ -tuple  $v$ , we can compute  $f(v)$  in  $O(k)$  time.
- ④ given  $u$  and  $v$ , such that suffix of  $u$  of length  $k-1$  is the prefix of  $v$  of length, or vice versa, we can compute  $f(v)$  in  $O(1)$  time if we already computed  $f(u)$ .

## Example of the hash function

- A string of nucleotides has an alphabet of size 4, so we can look at that string as a number written in base 4. For example, we can denote A as 0, C as 1, G as 2, and T as 3.



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- Suppose we only have two k-mers, one qualified minimal perfect hashing function  $f$  needs to ensure that  $f(\text{"ATTC"}) = 0$  and  $f(\text{"TTCG"}) = 1$   
or  
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- ③ the space bound for  $f$  is  $O(n(\log \log n + \log \log \sigma))$  bits with high probability.
- ④ insertions and deletions take  $O(k)$  amortized expected time.
- ⑤ the data structure may work incorrectly with very low probability (inverse polynomial in  $n$ ).



# Representation of edges in de Bruijn graph

- 1 The edges ( $E$ ) of  $G$  are stored in two binary matrices,  $IN$  and  $OUT$ , each of size  $n \times |\Sigma|$ .
- 2 These two matrices are used to maintain the  $IN$  and  $OUT$  edge of each vertex. We can move each vertex forward and backward using this information.

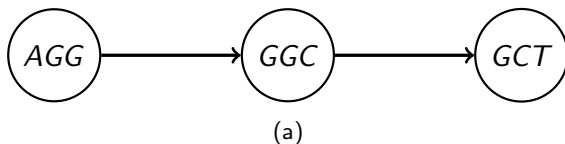
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- 3 The  $IN$  and  $OUT$  matrices can be constructed as:

$$(u = ba_1 \dots a_{k-1}, v = a_1 a_2 \dots a_{k-1} c) \in E \\ \iff OUT(f(u), c) = 1, IN(f(v), b) = 1.$$

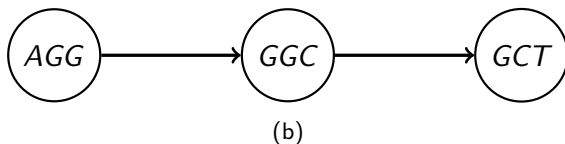
## Example of *IN* and *OUT* matrices

Here is a simple de bruijn graph:



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Suppose  $f(AGG) = 0, f(GGC) = 1, f(GCT) = 2$ , the *IN* and *OUT* matrices can be initialized as:

## Example of *IN* and *OUT* matrices

IN	A	G	C	T
0(AGG)	0	0	0	0
1(GGC)	1	0	0	0
2(GCT)	0	1	0	0

OUT	A	G	C	T
0(AGG)	0	0	1	0
1(GGC)	0	0	0	1
2(GCT)	0	0	0	0

(a)

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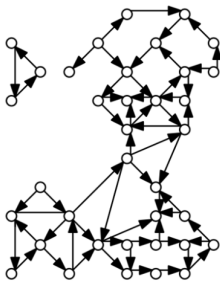
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- 4 Given a start point, we can move forward and backward using *IN* and *OUT* matrices. Once we reached the root, we can check if the resulting k-mer matches with root k-mer.

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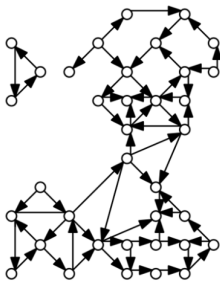
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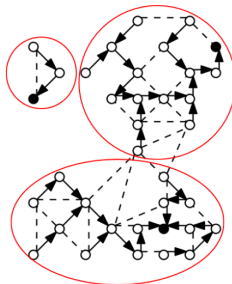
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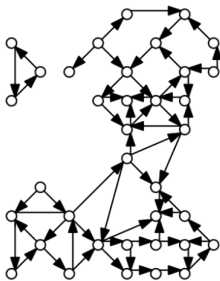
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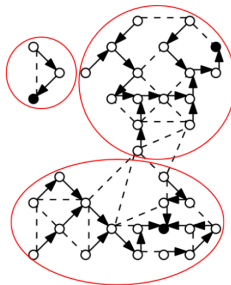
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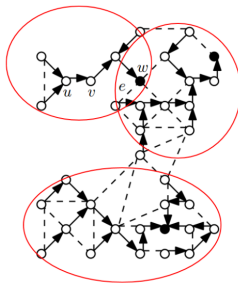
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Adding an edge

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- 3 listing the edges incident to a node we are visiting takes  $O(\sigma)$  time, and crossing an edge takes  $O(1)$  time.



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- $K$ -mer representation
- Hash function implementation
- the BitArray class
- IN, OUT, and forest implementation
- Forest construction procedure
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- “Semi-dynamic De Bruijn Graph”

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- Example:

$$\overbrace{0000 \dots}^{\text{Zeros}} \overbrace{11100100}^{2K \text{ bits}} = TGCA$$

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- How do we construct the Karp-Rabin hash function?

## Building the Karp-Rabin Hash Function

- For the prime  $P$ , pick the smallest prime greater than  $Kn^2$ .

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- For  $K = 27$  on *E. coli*, lower bound for prime is

16584693176107222092.

Max value in unsigned 64-bit integer:

18446744073709551615.

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- Note that the hash function can hash any kmer, but is bijective when restricted to kmers that actually exist in our De Bruijn graph.

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## Building the Hash Function

- Recall: A minimal perfect hash function on a set  $A$  of size  $n$  is a hash function that maps elements of  $A$  injectively to the set  $\{0, \dots, n - 1\}$ .
- We use the BBHash<sup>3</sup> library to build a minimal perfect hash function on the image of our kmers under the Karp-Rabin hash.
- We store our base  $r$ , the prime  $P$ , and our MPHF object from BBHash, and we can now hash any kmer to  $\{0, \dots, n - 1\}$ .
- Note that the hash function can hash any kmer, but is bijective when restricted to kmers that actually exist in our De Bruijn graph.
- That completes the generation of the hash function.

---

<sup>3</sup><https://github.com/rizkg/BBHash>

## Construction of Hash function

---

```
1: procedure GENERATEHASH
   Input  $S$ , a set of  $n$   $k$ -tuples over an alphabet  $\Sigma$  of size  $\sigma$ 
2:    $R = \max(\sigma, kn^2)$ 
3:    $P = \text{getPrime}(R)$ 
4:    $r = \text{randomNumber}(0, P - 1)$ 
5:    $f = \text{rabinHash}(r, P)$ 
6:   while  $\text{isInjective}(f, S)$  is FALSE do
7:      $r = \text{randomNumber}(0, P - 1)$ 
8:      $f = \text{rabinHash}(r, P)$ 
9:   end while
10:   $g = \text{minimalPerfectHash}(f(S))$  ;
11:  return  $g \circ f$  ;
12: end procedure
```

---

## Updating a Karp-Rabin value

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- What is the problem with naively implementing this update?

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- Add  $(4P - \text{first} \cdot r)$  to  $f(m)$ , as this will always be nonnegative.



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- This will slow data access down since multiple operations are required for each access, but much more memory efficient.

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010...101...

int 0                  int 1



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- With this class, only waste at most 31 bits in memory per instance of the class.

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- To construct, simply read through edge  $k + 1$ -mers and set the correct index of each of IN, OUT.

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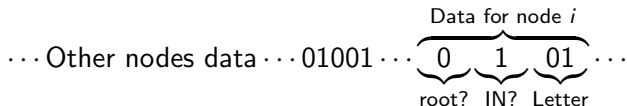
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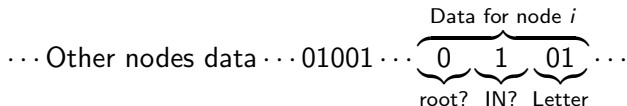
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- This is how we will do membership queries (explained more later).

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- We break the graph up into trees in the desired height range as we go along.

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- Add its hash and kmer to the map.

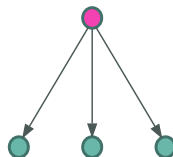




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## De Bruijn breadth first search

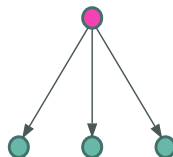
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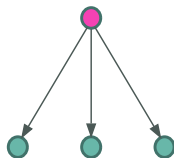
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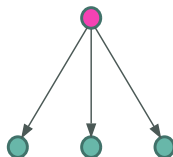
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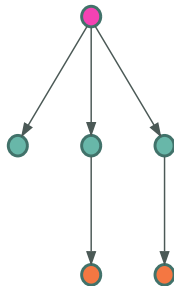
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- Set the root bit to false, and don't store these kmers.



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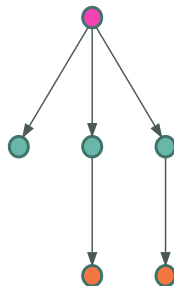
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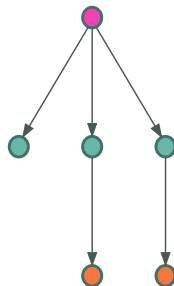
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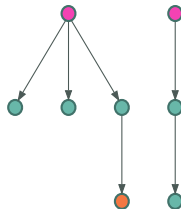
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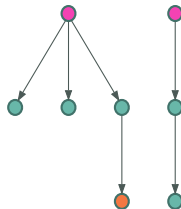
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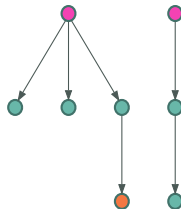
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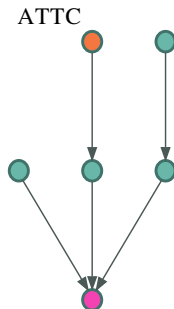
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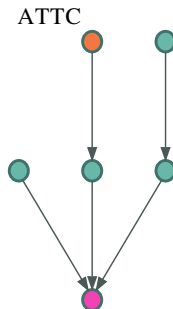
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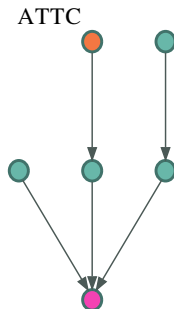
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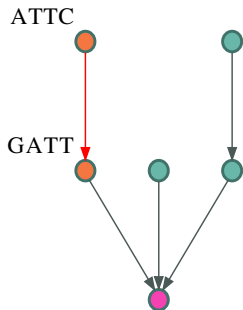
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- Note:  
Even if the kmer is not in our De Bruijn graph, we can still hash it and get a place in the forest.



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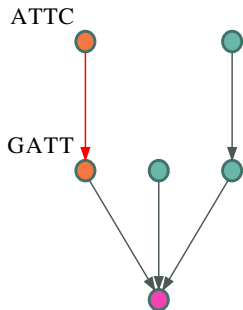




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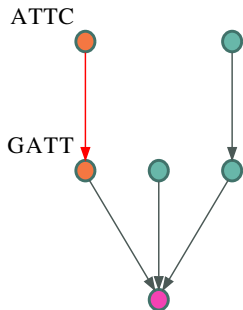
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- Check IN and OUT whether such an edge exists. Return false if it doesn't.



# Membership Query

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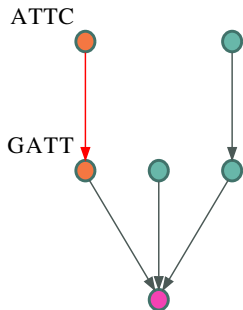
- Use the forest data and "ATTC" to do a hash update and find the parent in the forest.
- Check IN and OUT whether such an edge exists. Return false if it doesn't.
- Why would that possibly return false?



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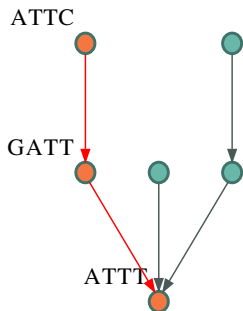
- Use the forest data and "ATTC" to do a hash update and find the parent in the forest.
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- Why would that possibly return false?
- It's possible that the hash for "GATT" doesn't have an OUT edge for "C", therefore "ATTC" can't possibly be an actual kmer.



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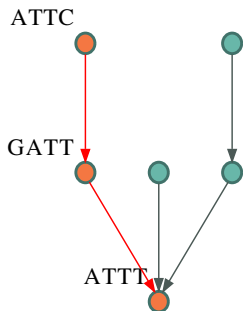
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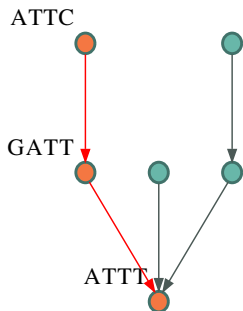
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- The root has its kmer stored



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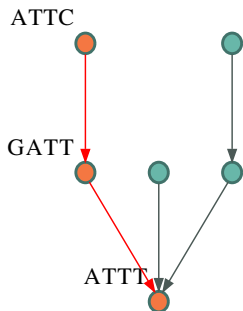
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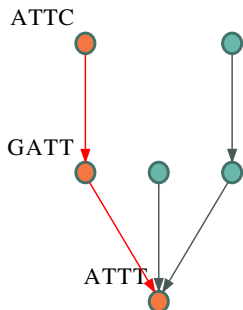
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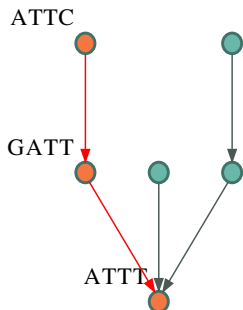




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- We have not implemented node addition and removal. The primary difficulty is having a dynamic hash function.
- We rely on the library BBHash for our minimal perfect hash function, but we need a dynamic perfect hash function.

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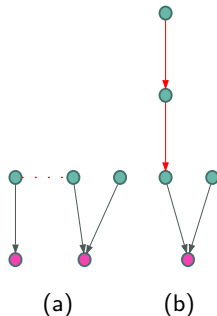
# Dynamic Edges

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- Do we do anything to the forest?
- This would affect the forest if the edge is between two graph components where at least one was not big enough to have a tree above the minimum height.
- We may be able to combine the trees so that we have trees with heights in the desired range.

# Dynamic Edges

## Adding an Edge

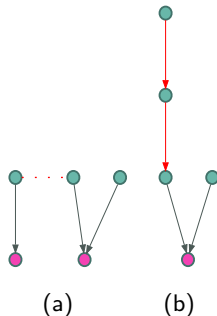
- Suppose that the edge (dotted) is between two trees in the forest below the minimum height, shown in (a).



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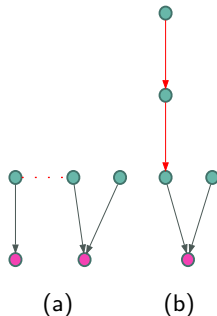
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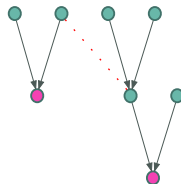
- Suppose that the edge (dotted) is between two trees in the forest below the minimum height, shown in (a).
- We can combine the trees into one tree of height less than the maximum.
- You have to add another edge to the forest, reverse the direction of some forest edges, then get rid of one of the tree's roots.



# Dynamic Edges

## Adding an Edge

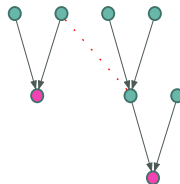
- Now suppose that only one of the trees are below the desired minimum height and we add an edge (dotted).



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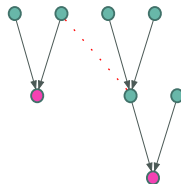
- Now suppose that only one of the trees are below the desired minimum height and we add an edge (dotted).
- What we do depends on the height of the node in the edge from the taller tree.



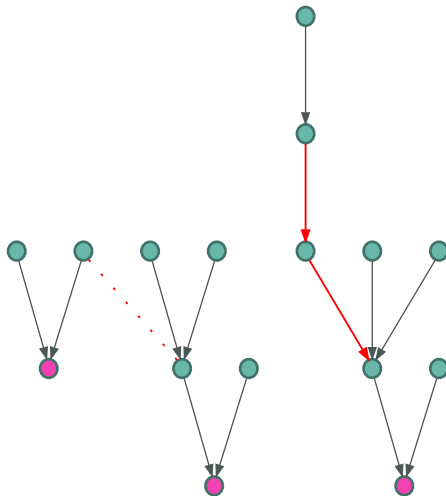
# Dynamic Edges

## Adding an Edge

- Now suppose that only one of the trees are below the desired minimum height and we add an edge (dotted).
- What we do depends on the height of the node in the edge from the taller tree.
- If the height is less than  $\alpha$ , we can change the trees similar to before.



# Adding Edges



(a) Height  $< \alpha$

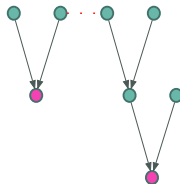
(b)



# Dynamic Edges

## Adding an Edge

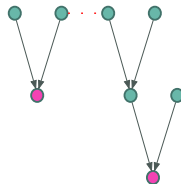
- Now suppose that the height is greater than or equal to  $\alpha$



# Dynamic Edges

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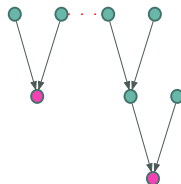
- Now suppose that the height is greater than or equal to  $\alpha$
- We can't necessarily just combine the trees like before, we could end up with a tree greater than the maximum height.



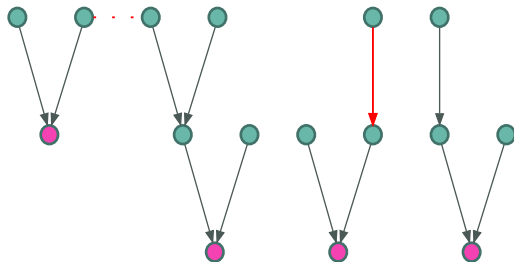
# Dynamic Edges

## Adding an Edge

- Now suppose that the height is greater than or equal to  $\alpha$
- We can't necessarily just combine the trees like before, we could end up with a tree greater than the maximum height.
- We break off some part of the bigger tree into the smaller.



# Adding Edges



(a)  $\text{Height} \geq \alpha$

(b)

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- If the edge is in our tree, then removing it breaks up a tree.
- We need to find a new root for one of the trees
- If a tree is too short, use similar techniques to above to produce a taller tree.

# Experiments

## Datasets:


Dataset	Chromosomes	Read count	Read length	Size
S288C <sup>4</sup>	17	-	-	12M
<i>E. coli</i>	1	$27 \cdot 10^6$	101	3.3G

## Platform:

- Intel(R) Xeon(R) CPU E5-2697 v4 @ 2.30GHz (18 cores) with 396 GB RAM

The results are tested by one run, which could be affected by computational resource conflicts.

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<sup>4</sup><http://www.yeastgenome.org/strain/S288C/overview> 

# Live Demo

- 1 We have developed a web-based demo to allow users do multiple types of comparisons, which makes the evaluation easier.
- 2 The link is here: <http://128.227.162.189:9999/>. Visit and play with it!

### Fully Dynamic de Bruijn Graph Running Demo

This demo runs some examples and compare results.

**K value:**

  
**# of queries:**  
**Dataset:**  

Go »View »

# Comparative Algorithms

- ❶ **Bloom Filter:** Standard Bloom filter
- ❷ **KBF1:** One-sided Bloom filter improves false positive rate three fold without using any additional storage.
- ❸ **KBF2:** Two-sided Bloom filter improves FPR by an order of magnitude while using very little additional memory<sup>5</sup>.

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<sup>5</sup><https://github.com/Kingsford-Group/kbf>

# Query $k$ -mer Generation

- 1 We generate query  $k$ -mers with three different number of queries:

-	1	2	3
number of queries (million)	0.5	1	10

- 2 We use two random ways to generate query  $k$ -mers
  - Muting one base of randomly extracted from the input  $k$ -mers
  - ~~Purely random  $k$ -mer generation.~~ However, it does not result in obvious difference compared with the first one.

## FDBG Data Structure Information

Table : The FDBG data structure information on E coli.

$k$	$k$ -mers	RAM (MB)	Trees	Avg. height
20	770,956,037	1,485	5,492,320	48.14
24	784,990,222	1,519	6,412,386	50.45
27	783,739,686	1,517	6,532,142	47.28
30	776,321,600	1,505	6,752,622	48.46

- RAM = IN and OUT matrices + forest + minimal perfect hashing
- An example when

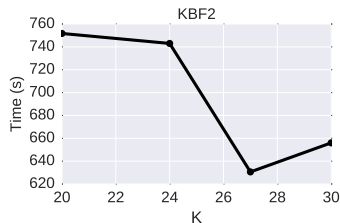
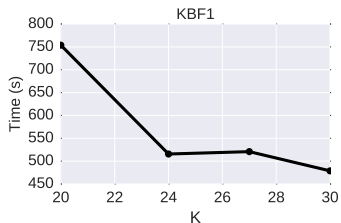
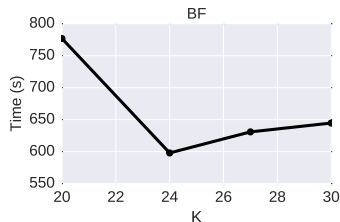
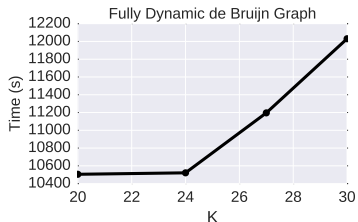
$$k = 20, N = 770956037, R = 5492320, \sigma = 4 :$$

$$N \times \sigma \times 2 + (N \times 4 + R * 64) + \text{mph}$$

$$= (735 + (367 + 335) + 48) \text{MB} \times (\text{bit}/\text{MB})$$

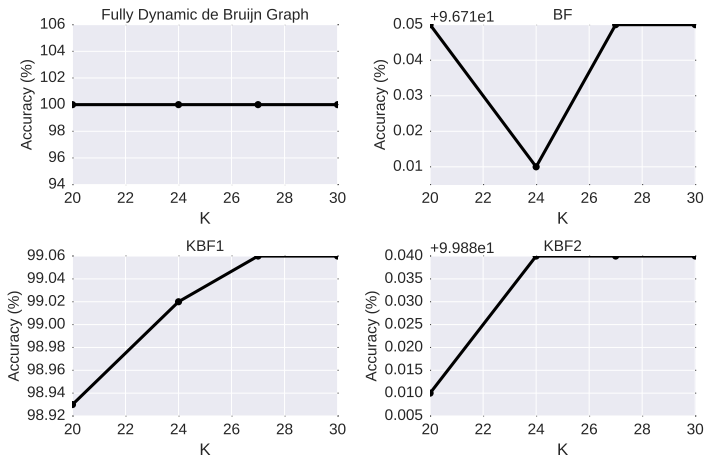
# Populate Time w.r.t $k$

Populate time



# Query Accuracy w.r.t $k$

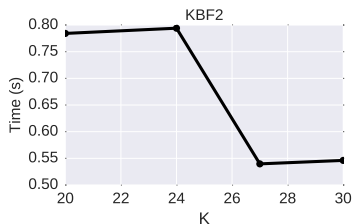
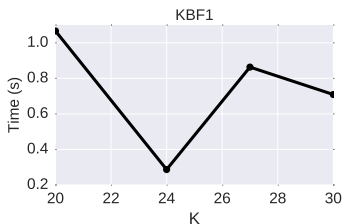
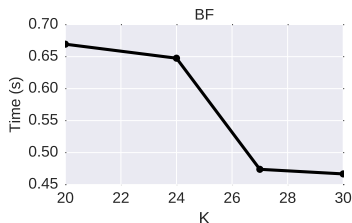
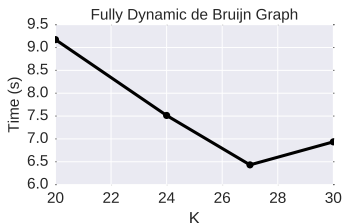
## Query Accuracy





# Query Time w.r.t $k$

Query time



# Query Time w.r.t Tree Height

Table : Query time w.r.t the tree height.

$k$	Avg. height	Query time (s)
20	48.14	6.69 <sup>6</sup>
24	50.45	7.51
27	47.28	6.43
30	48.46	6.93

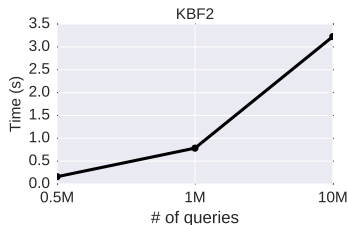
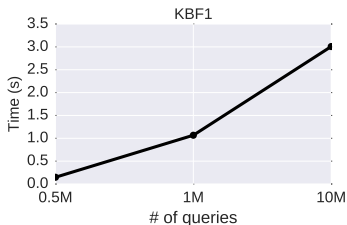
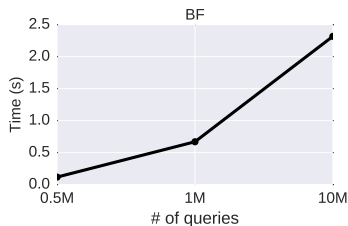
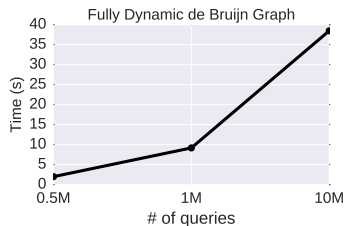
Lower tree height gives rise to lower query time, because it needs fewer steps to trace the tree.

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<sup>6</sup>Averaged by two runs.

# Query Time w.r.t Number of Queries

Query time



# Conclusion

- 1 Have implemented static De Bruijn graph data structure and will complete edge insertion and deletion.
- 2 We have tested the algorithms on two gene datasets. Compared with all Bloom filter based methods, ours has exactly 100% accuracy.
- 3 We have compared with three different methods.
- 4 We have made a website and a live demo.

# End

Thanks and Questions?