

CSE 549: Efficient representation of de Bruijn Graphs



Bloom Filters & De Bruijn Graphs

Recall the Bloom Filter: how could this data structure be useful for representing a De Bruijn graph?

Say we have a bloom filter B , for all of the k -mers in our data set, and say I give you one k -mer that is truly present.

We now have a “navigational” representation of the De Bruijn graph (can return the set of neighbors of a node, but not select/iterate over nodes); why?

Detour: Bloom Filters & De Bruijn Graphs

How could this data structure be useful for representing a De Bruijn graph?



A given $(k-1)$ -mer can only have $2 * |\Sigma|$ neighbors;
 $|\Sigma|$ incoming and $|\Sigma|$ outgoing neighbors — for
genomes $|\Sigma| = 4$

To navigate in the De Bruijn graph, we can simply
query all possible successors, and see which are
actually present.

Bloom Filters & De Bruijn Graphs

But, a Bloom filter still has false-positives, right?

May return some neighbors that are not actually present.

Pell et al., PNAS 2012, use a lossy Bloom filter directly

Chikhi & Rizk, WABI 2012, present a *loss/less* datastructure
based on Bloom filters

Salikhov et al., WABI 2013 extend this work and introduce
the concept of “cascading” Bloom filters

First, some bounds

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Research Articles

On the Representation of De Bruijn Graphs

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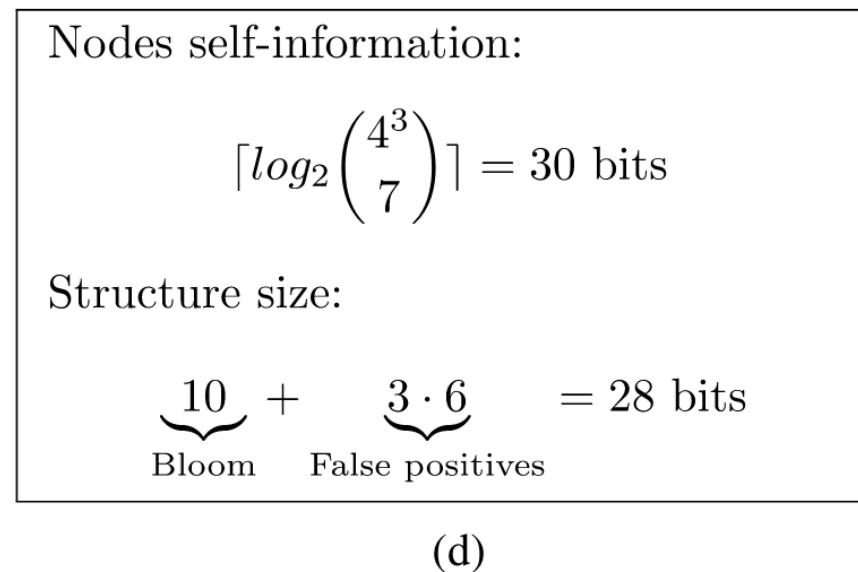
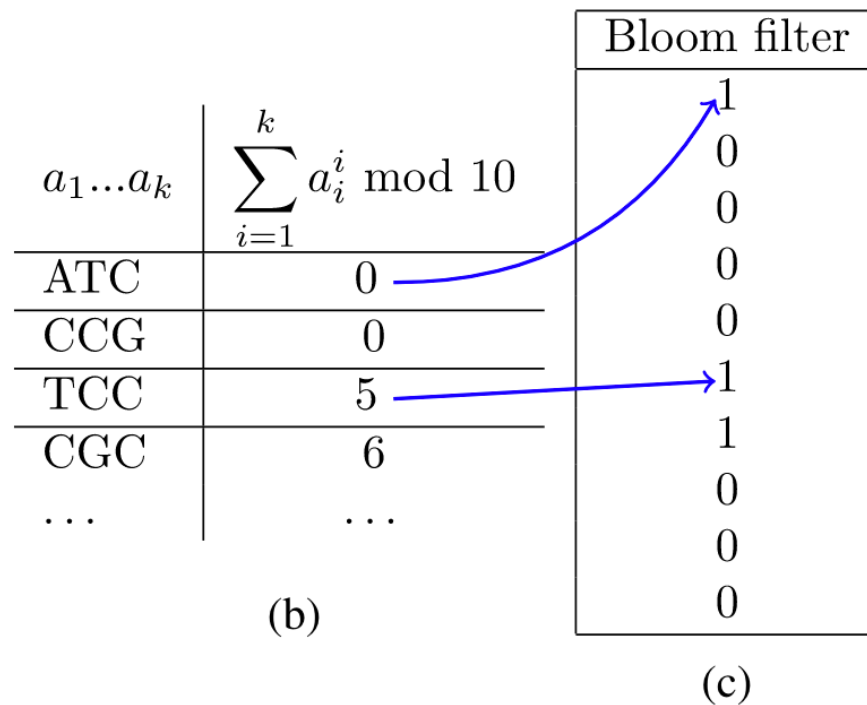
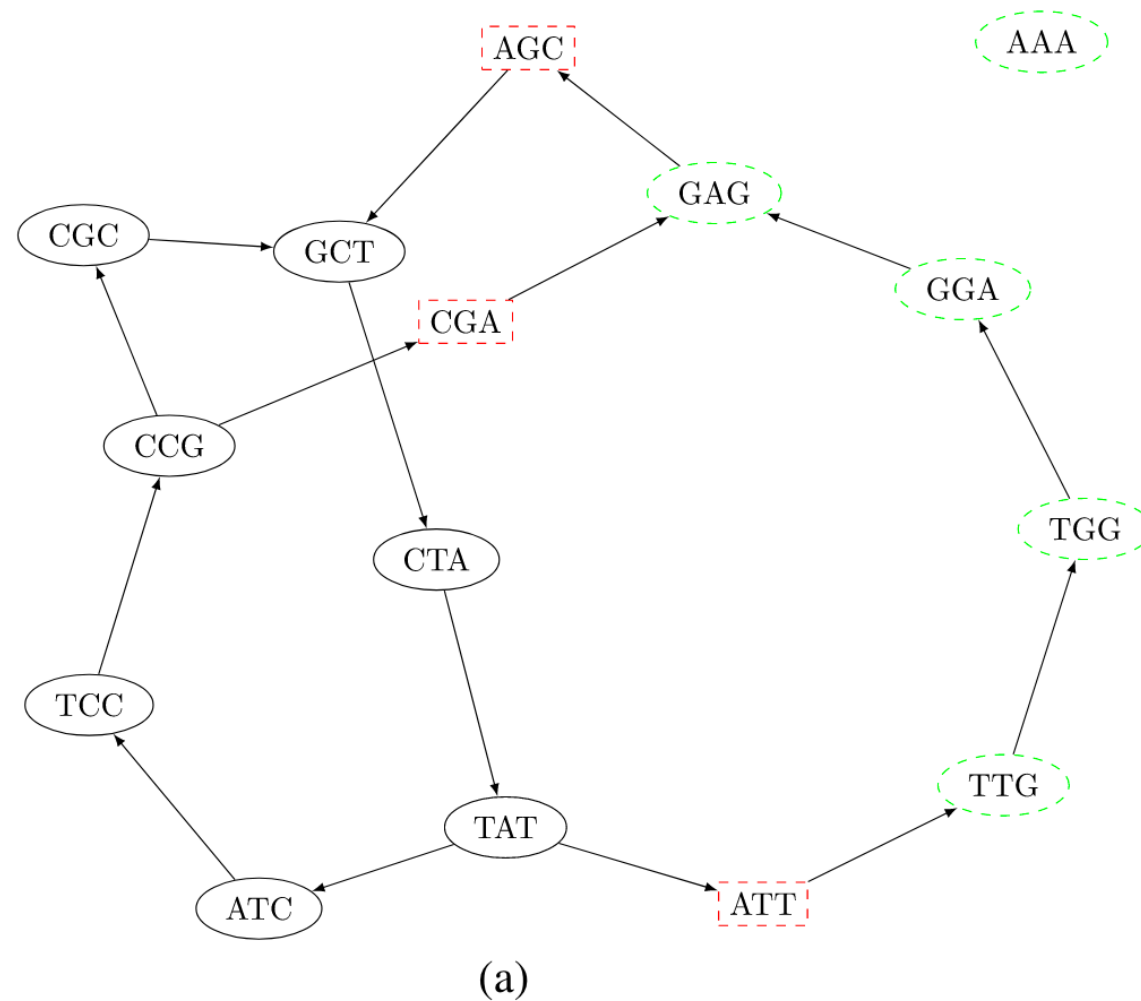
We use the term membership data structure to refer to a way of representing a dBG and answering k -mer membership queries. We can view this as a pair of algorithms: (CONST, MEMB). The CONST algorithm takes a set of k -mers S (i.e., a dBG) and outputs a bit string. We call CONST a constructor, since it constructs a representation of a dBG. The MEMB algorithm takes as input a bit string and a k -mer x and outputs true or false. Intuitively, MEMB takes a representation of a dBG created by CONST and outputs whether a given k -mer is present. Formally, we require that for all $x \in \Sigma^k$, $\text{MEMB}(\text{CONST}(S), x)$ is true if and only if $x \in S$.

An NDS is a pair of algorithms, CONST and NBR. As before, CONST takes a set of k -mers and outputs a bit string. NBR takes a bit string and a k -mer and outputs a set of k -mers. The algorithms must satisfy that for every dBG S and a k -mer $x \in S$, $\text{NBR}(\text{CONST}(S), x) = \text{ext}(x) \cap S$. Note that if $x \notin S$, then the behavior of $\text{NBR}(\text{CONST}(S), x)$ is undefined. We observe that a membership data structure immediately implies an NDS because an NBR query can be reduced to eight MEMB queries.

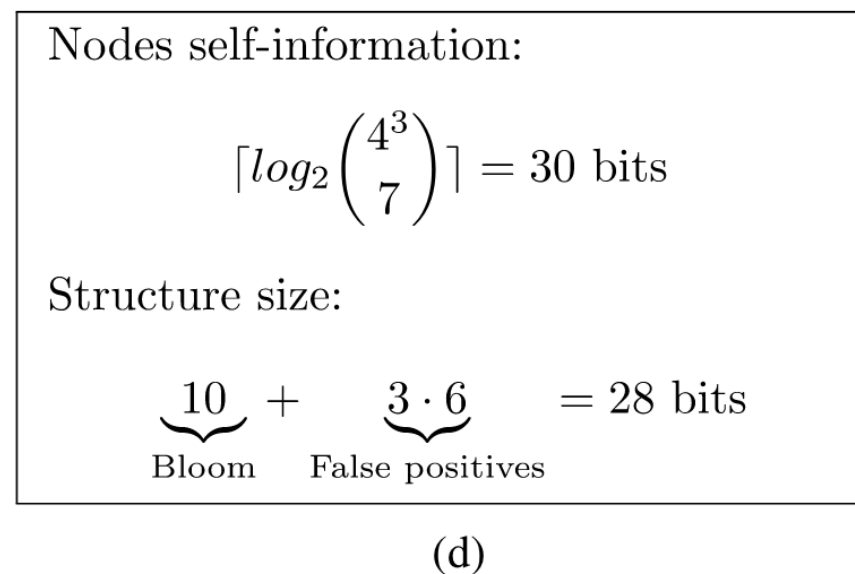
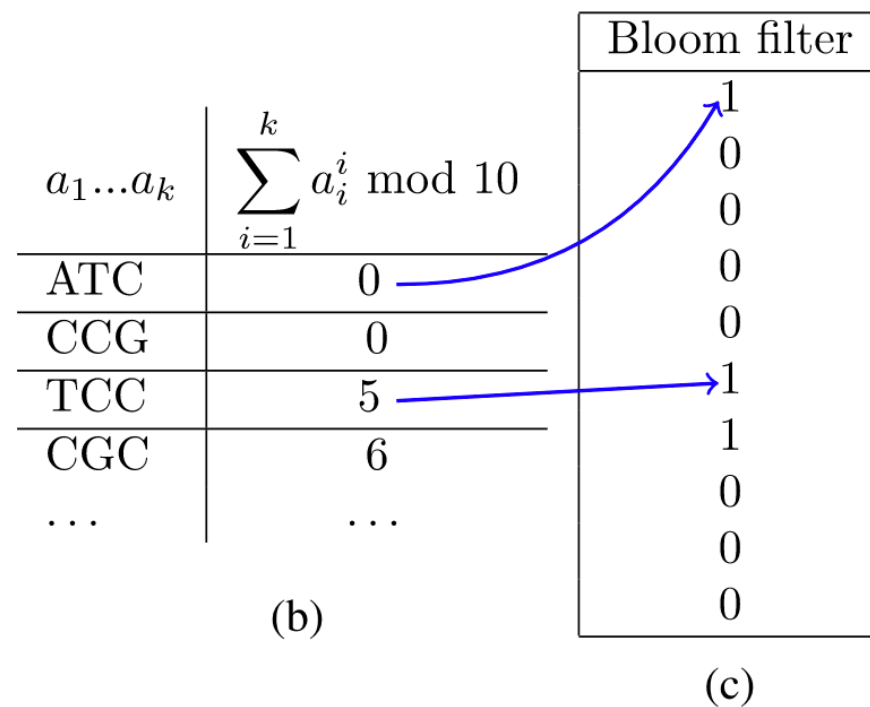
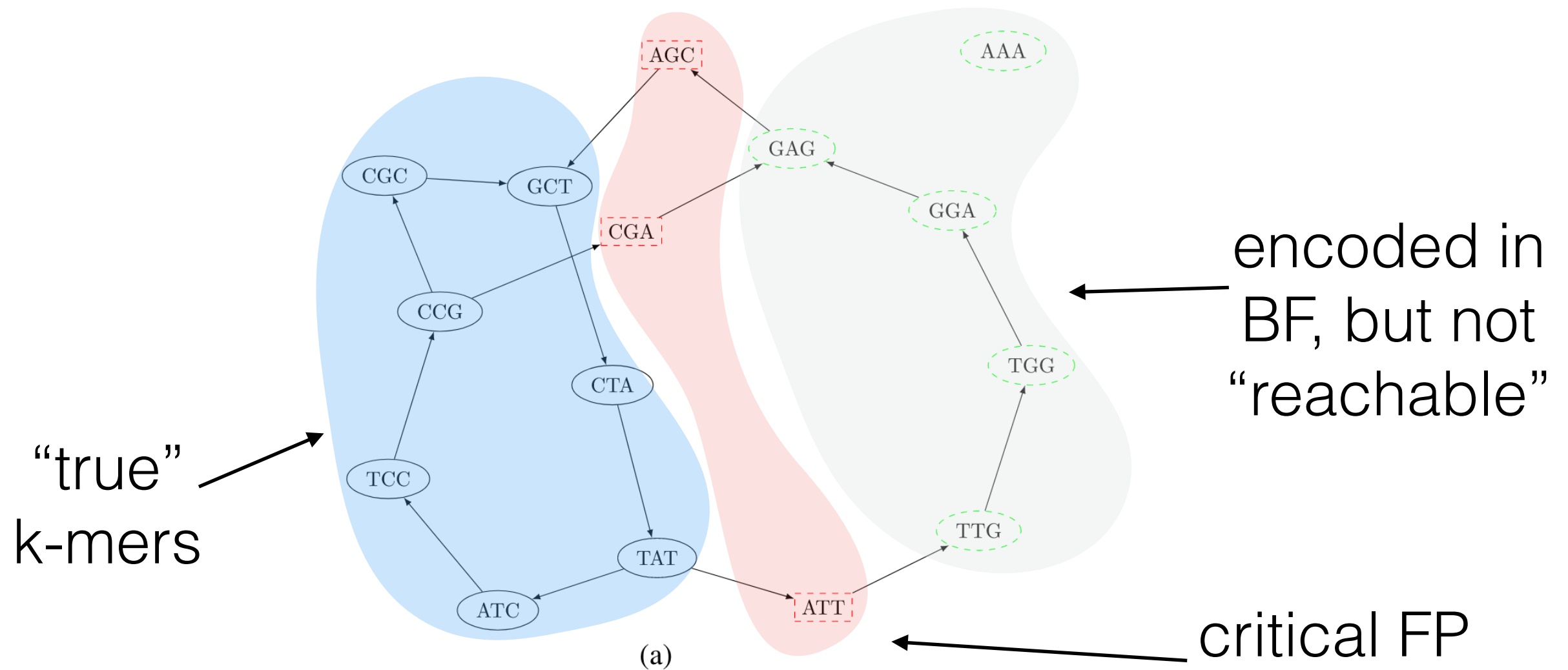
In this section, we prove that a navigational data structure on de Bruijn graphs needs at least 3.24 bits per k -mer to represent the graph:

Theorem 1. *Consider an arbitrary NDS and let CONST be its constructor. For any $0 < \epsilon < 1$, there exists a k and $x \in \Sigma^k$ such that $|\text{CONST}(x)| \geq |x| \cdot (c - \epsilon)$, where $c = 8 - 3 \lg 3 \approx 3.25$.*

Critical False Positives



Critical False Positives



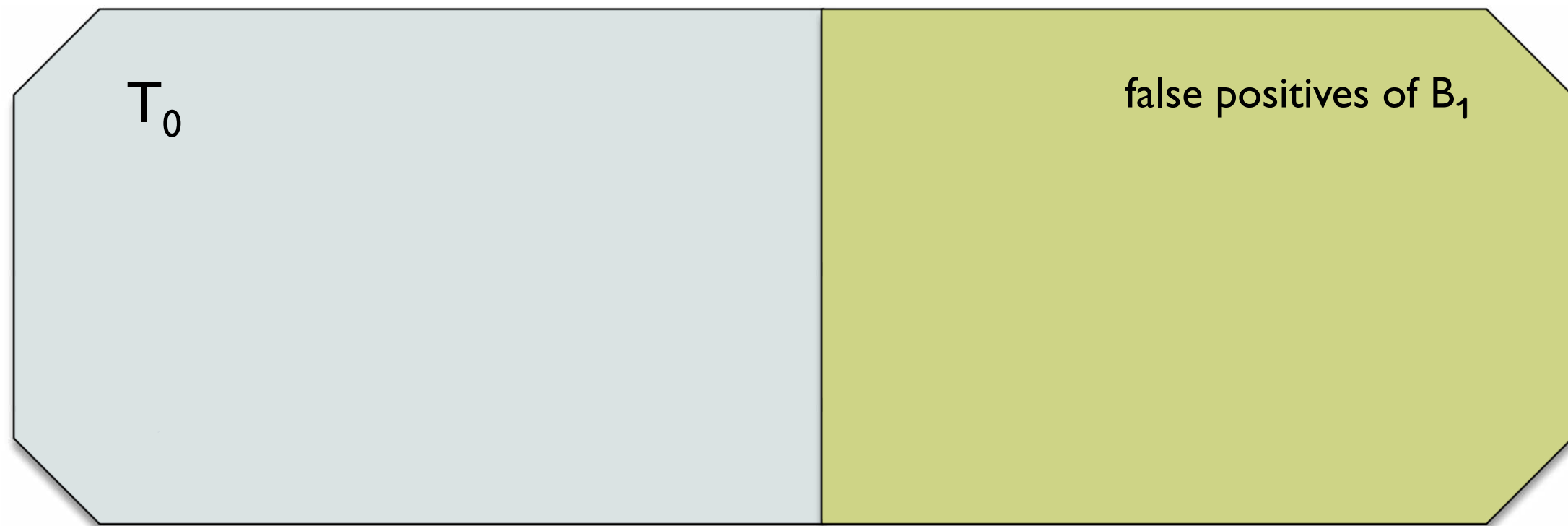
Idea of Chkhi and Rizk

Assume we want to represent specific set T_0 of k -mers with a Bloom filter B_1

Key observation: in assembly, not all k -mers can be queried, only those having $k-1$ overlap with k -mers known to be in the graph.

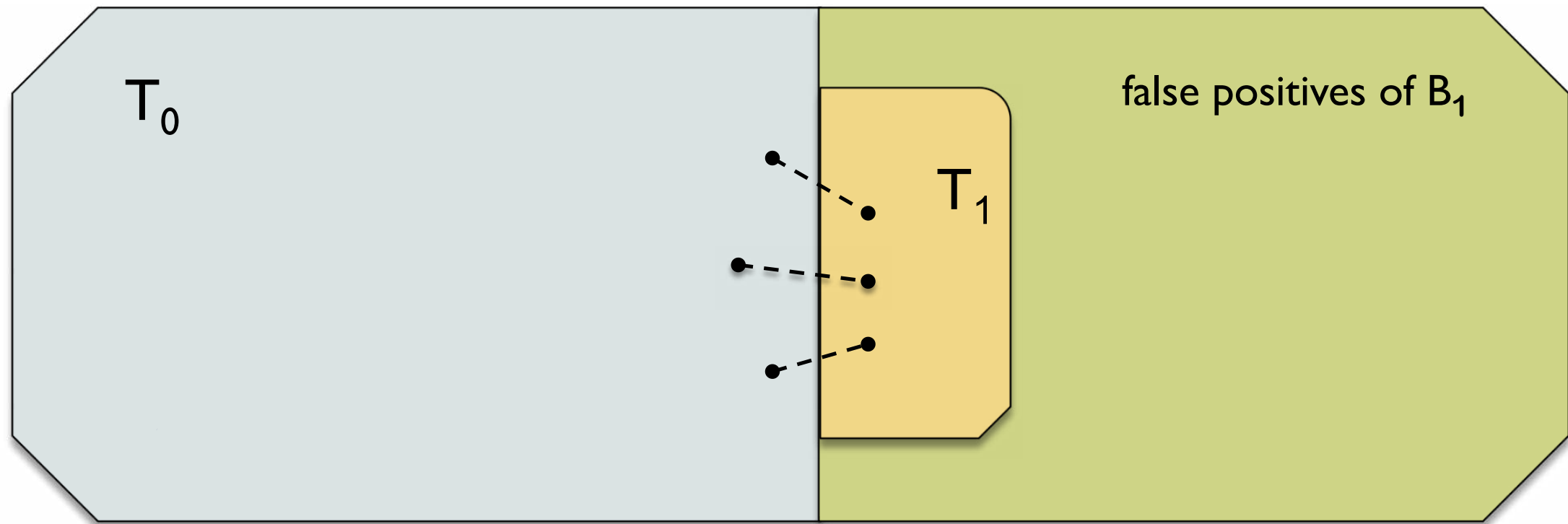
The set T_1 of “critical false positives” (false neighbors of true k -mers) is *much* smaller than the set of all false positives and can be stored explicitly

Storing B_1 and T_1 is much more space efficient than other exact methods for storing T_0 . Membership of w in T_0 is tested by first querying B_1 , and if $w \in B_1$, check that it is *not* in T_1 .



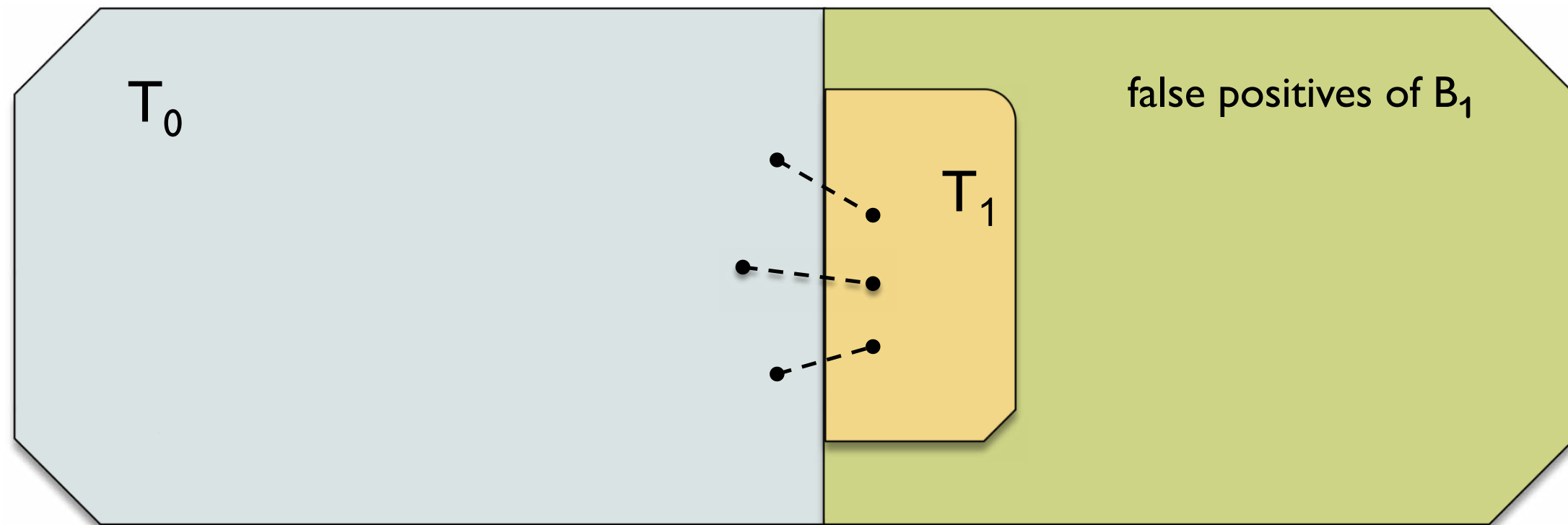
- Represent T_0 by Bloom filter B_1





- ▶ Represent T_0 by Bloom filter B_1
- ▶ Compute T_1 ('critical false positives') and represent it e.g. by a hash table




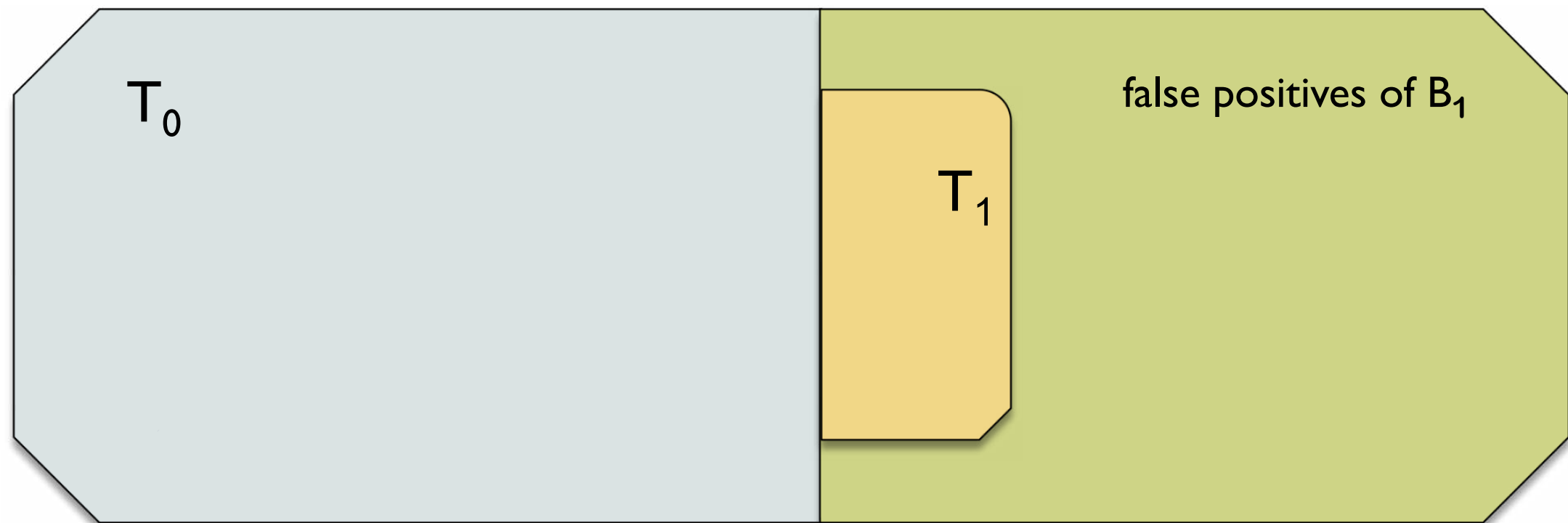


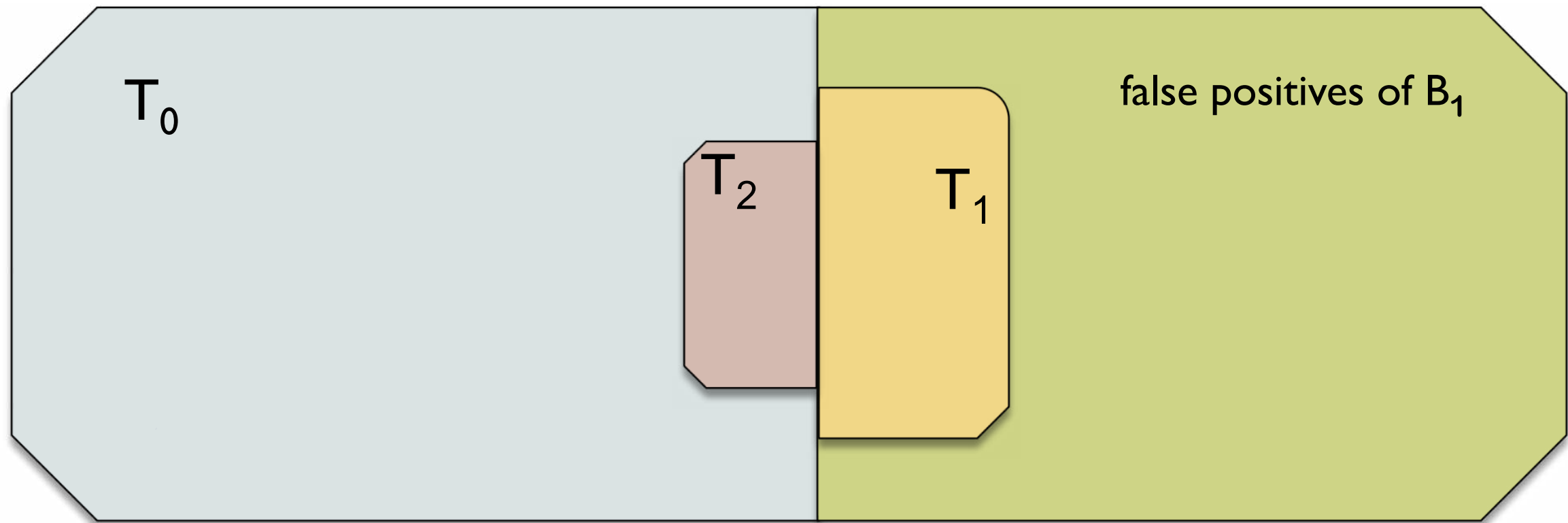
- ▶ Represent T_0 by Bloom filter B_1
- ▶ Compute T_1 ('critical false positives') and represent it e.g. by a hash table
- ▶ Result (example): 13.2 bits/node for $k=27$ (of which 11.1 bits for B_1 and 2.1 bits for T_1)



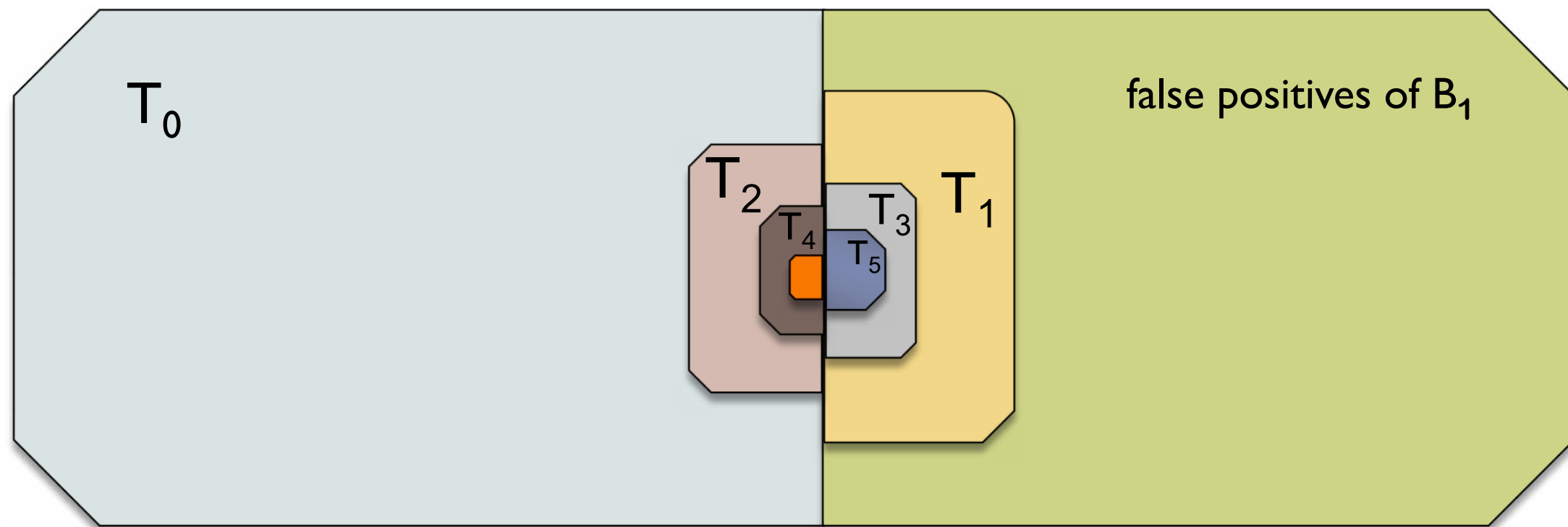
Improving on Chikhi and Rizk's method

- ▶ *Main idea*: iteratively apply the same construction to T_1 i.e. encode T_1 by a Bloom filter B_2 and set of 'false-false positives' T_2 , then apply this to T_2 etc.
- ▶  *cascading Bloom filters*

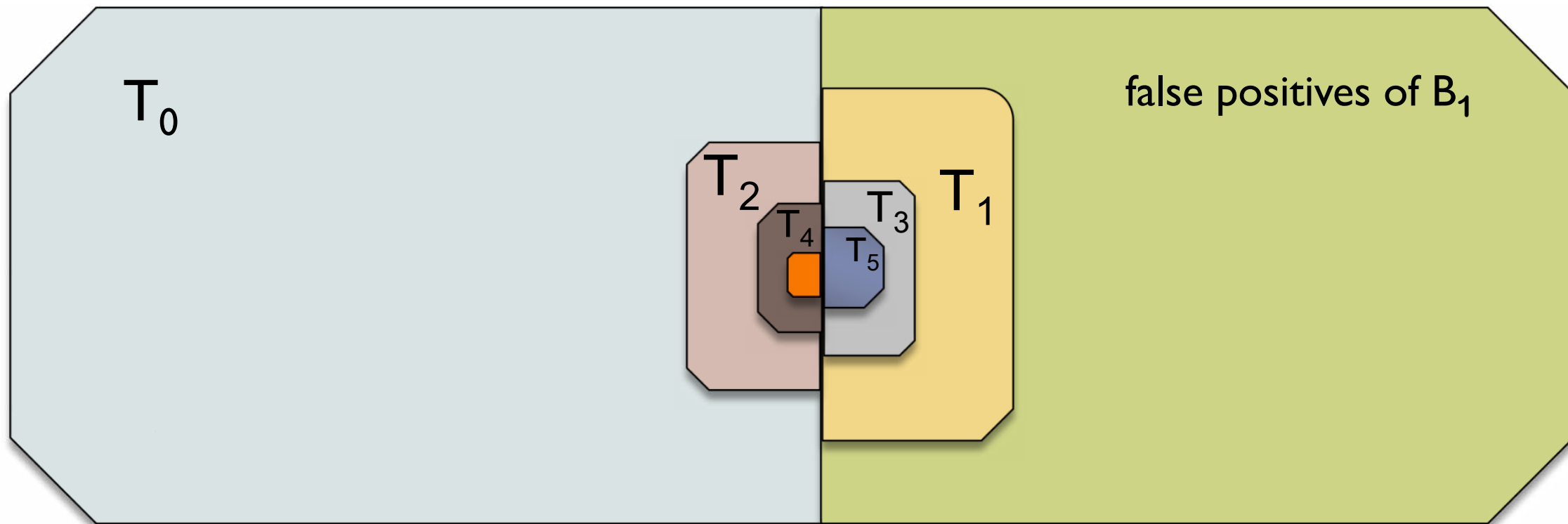




- ▶ further encode T_1 via a Bloom filter B_2 and set T_2 , where $T_2 \subseteq T_0$ is the set of k -mers stored in B_2 by mistake ('false² positives')



- ▶ further encode T_1 via a Bloom filter B_2 and set T_2 , where $T_2 \subseteq T_0$ is the set of k -mers stored in B_2 by mistake ('false² positives')
- ▶ iterate the construction on T_2
- ▶ we obtain a sequence of sets $T_0, T_1, T_2, T_3, \dots$ encode by Bloom filters $B_1, B_2, B_3, B_4, \dots$ respectively
- ▶ $T_0 \supseteq T_2 \supseteq T_4 \supseteq \dots, T_1 \supseteq T_3 \supseteq T_5 \supseteq$



Lemma [correctness]: For a k -mer w , consider the smallest i such that $w \notin B_{i+1}$. Then $w \in T_0$ if i is odd and $w \notin T_0$ if i is even.

- ▶ if $w \notin B_1$ then $w \notin T_0$
- ▶ if $w \in B_1$, but $w \notin B_2$ then $w \in T_0$
- ▶ if $w \in B_1$, $w \in B_2$, but $w \notin B_3$ then $w \notin T_0$
- ▶ etc.

Assuming infinite number of filters

Let $N=|T_0|$ and $r=m_i/n_i$ is the same for every B_i . Then the total size is

$$\underbrace{rN}_{|B_1|} + \underbrace{6rNc^r}_{|B_2|} + \underbrace{rNc^r}_{|B_3|} + \underbrace{6rNc^{2r}}_{|B_4|} + \underbrace{rNc^{2r}}_{|B_5|} + \dots = N(1+6c^r) \frac{r}{1-c^r}$$

The minimum is achieved for $r=5.464$, which yields the memory consumption of **8.45** bits/node

Infinity difficult to deal with ;)

- In practice we will store only a small finite number of filters B_1, B_2, \dots, B_t together with the set T_t stored explicitly
- $t=1 \Rightarrow$ Chkhi&Rizk's method
- The estimation should be adjusted, optimal value of r has to be updated, example for $t=4$

| k | optimal r | bits per k -mer |
|-----|-------------|-------------------|
| 16 | 5.776737 | 8.555654 |
| 32 | 6.048557 | 8.664086 |
| 64 | 6.398529 | 8.824496 |
| 128 | 6.819496 | 9.045435 |

Table: Estimations for $t=4$. Optimal r and corresponding memory consumption

Compared to Chikhi&Rizk's method

| k | “Optimal” (infinite) Cascading Bloom Filter | Cascading Bloom Filter with $t = 4$ | Data structure of Chikhi & Rizk |
|-----|--|--|------------------------------------|
| 16 | 8.45 | 8.555654 | 12.0785 |
| 32 | 8.45 | 8.664086 | 13.5185 |
| 64 | 8.45 | 8.824496 | 14.9585 |
| 128 | 8.45 | 9.045435 | 16.3985 |

Table: Space (bits/node) compared to Chikhi&Rizk
for $t=4$ and different values of k .

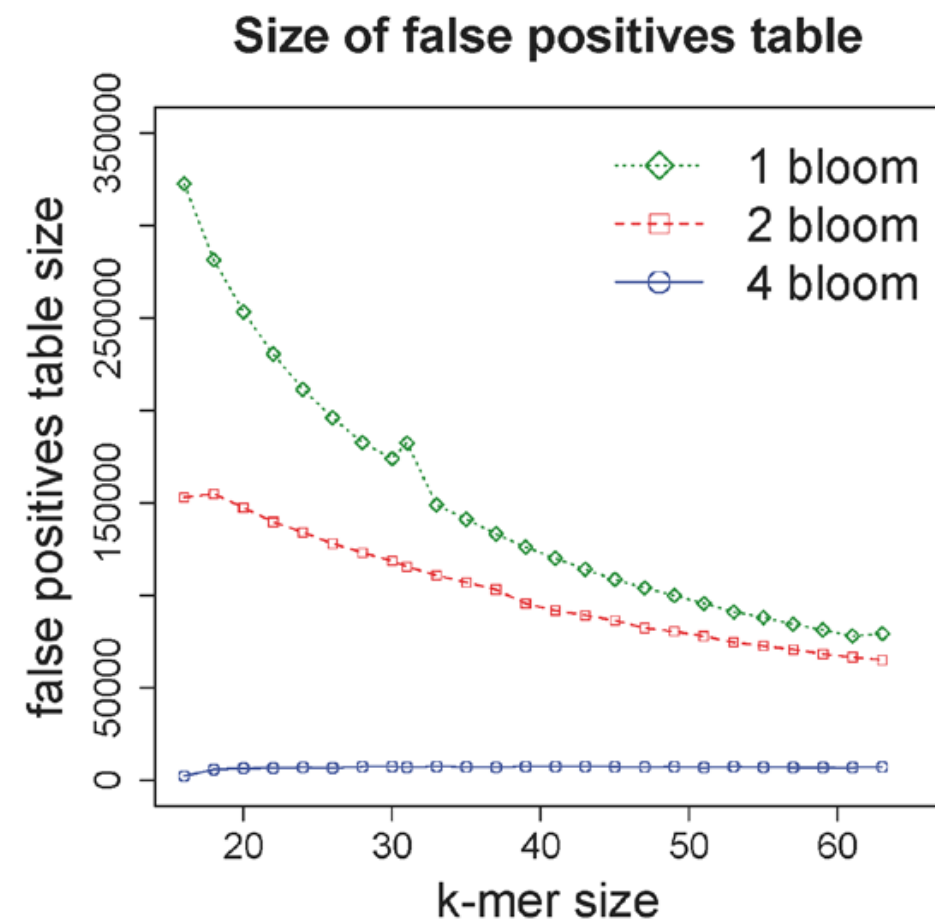
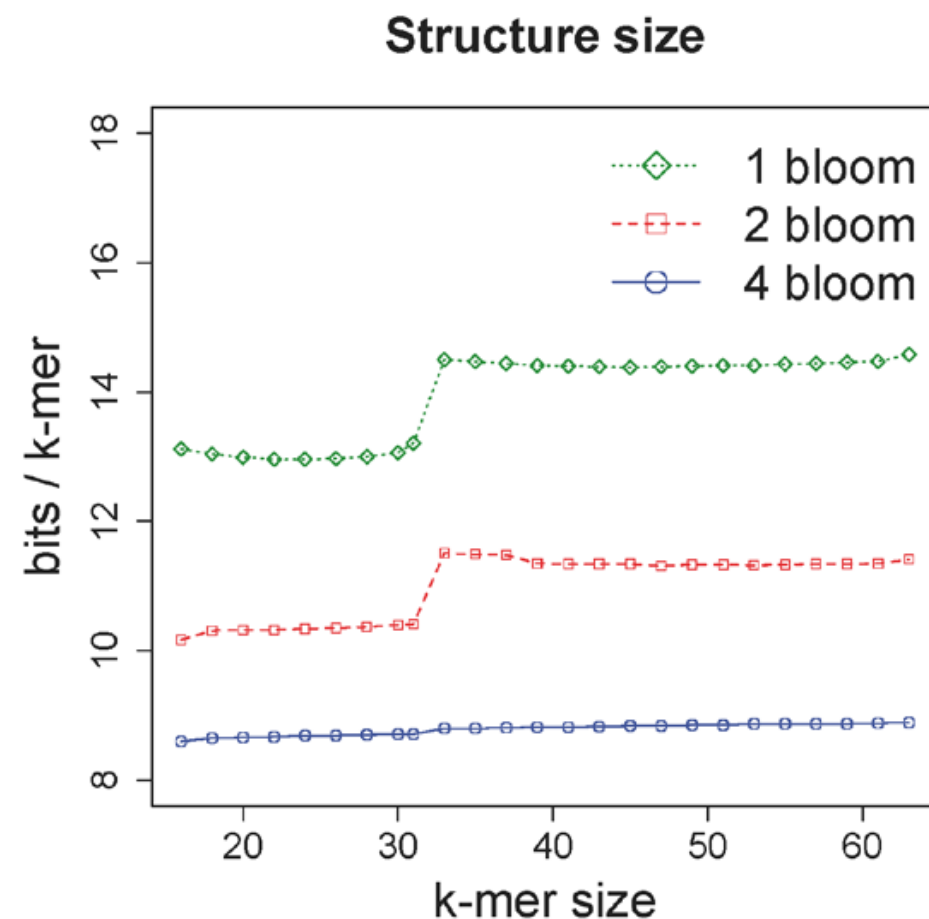
We can cut down a bit more ...

- Rather than using the same r for all filters B_1, B_2, \dots , we can use different properly chosen coefficients r_1, r_2, \dots
- This allows saving another 0.2 – 0.4 bits/k-mer



Experiments I: E.Coli, varying k

- 10M E.Coli reads of 100bp
- 3 versions compared: 1 Bloom (=Chikhi&Rizk), 2 Bloom ($t=2$) and 4 Bloom ($t=4$)

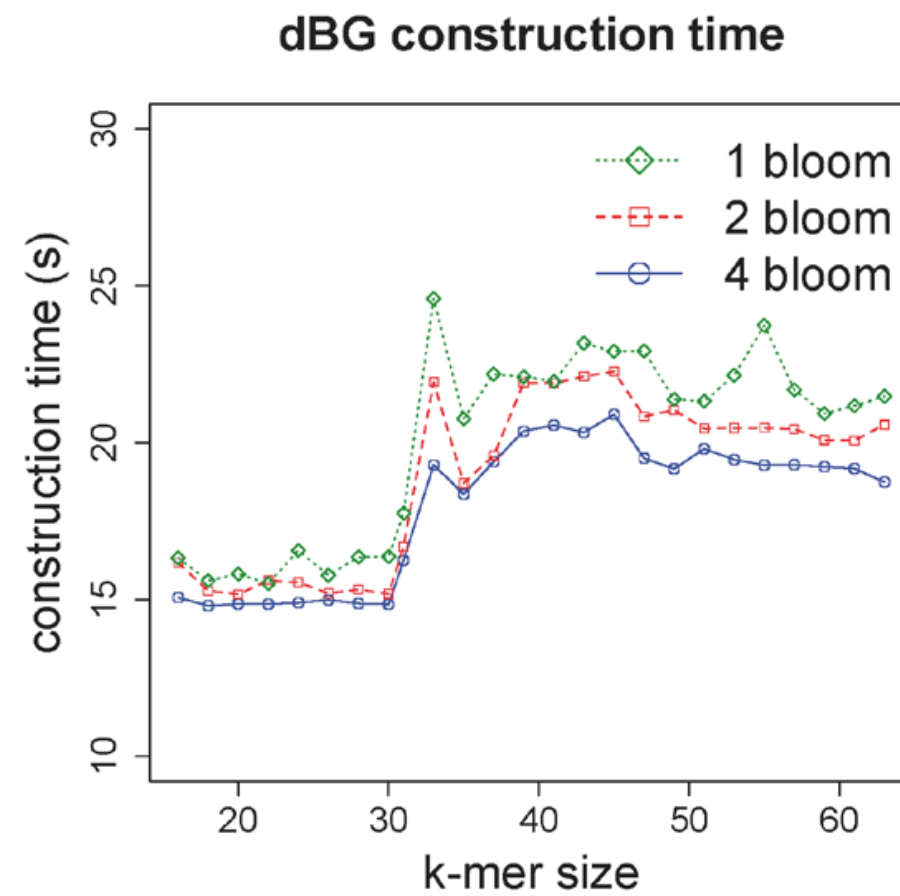
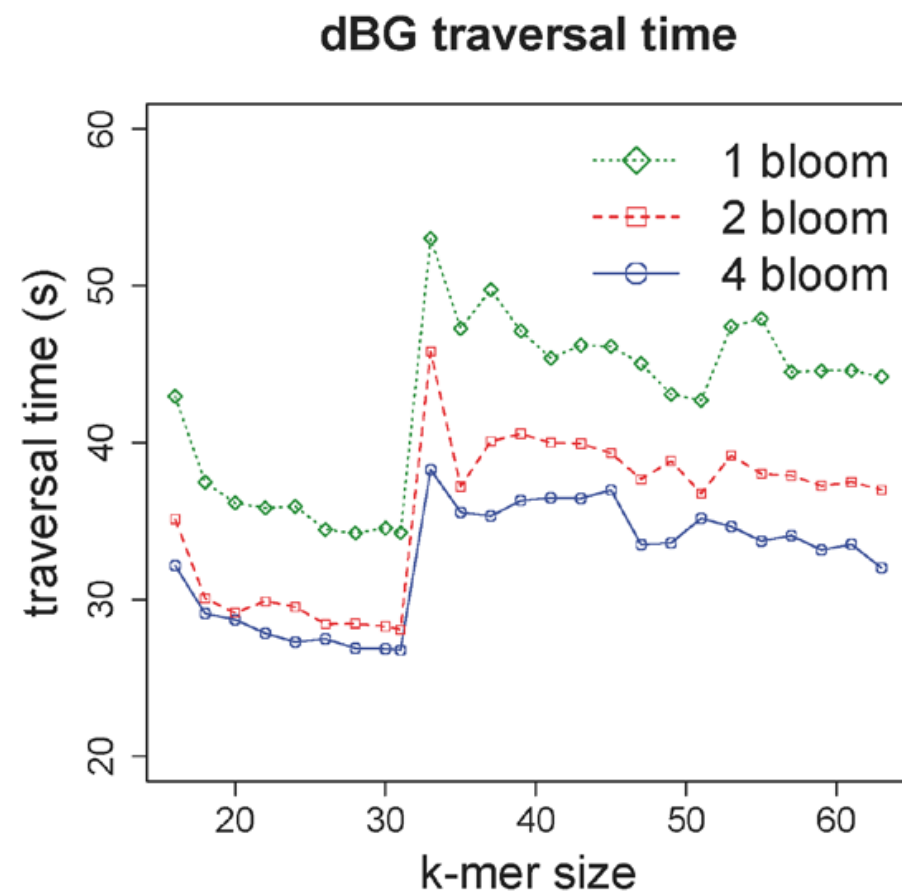


Experiments II: Human dataset

- 564M Human reads of 100bp (~17X coverage)

| Method | 1 Bloom | 2 Bloom | 4 Bloom |
|--------------------------------|-----------------|-----------------------------------|---|
| Construction time (s) | 40160.7 | 43362.8 | 44300.7 |
| Traversal time (s) | 46596.5 | 35909.3 | 34177.2 |
| r (bits) | 11.10 | 8.10 | 6.56 |
| Bloom filters size (MB) | $B_1 = 3250.95$ | $B_1 = 2372.51$ $B_2 = 292.65$ | $B_1 = 1921.20$ $B_2 = 496.92$ $B_3 = 83.39$ $B_4 = 21.57$ |
| False positive table size (MB) | $T_1 = 545.94$ | $T_2 = 370.96$ | $T_4 = 24.07$ |
| Total size (MB) | 3796.89 | 2524.12 | 2547.15 |
| Size (bits/ k -mer) | 12.96 | 10.37 | 8.70 |

Experiments I (cont)



Efficiently enumerating cFP

Algorithm 1 Constant-memory enumeration of critical false positives

- 1: **Input:** The set \mathcal{S} of all nodes in the graph, the Bloom filter constructed from \mathcal{S} , the maximum number M of elements in each partition (determines memory usage)
 - 2: **Output:** The set cFP
 - 3: Store on disk the set \mathcal{P} of extensions of \mathcal{S} for which the Bloom filter answers *yes*
 - 4: Free the Bloom filter from memory
 - 5: $D_0 \leftarrow \mathcal{P}$
 - 6: $i \leftarrow 0$
 - 7: **while** end of \mathcal{S} is not reached **do**
 - 8: $P_i \leftarrow \emptyset$
 - 9: **while** $|P_i| < M$ **do**
 - 10: $P_i \leftarrow P_i \cup \{\text{next } k\text{-mer in } \mathcal{S}\}$
 - 11: **for each** k -mer m in D_i **do**
 - 12: **if** $m \notin P_i$ **then**
 - 13: $D_{i+1} \leftarrow D_{i+1} \cup \{m\}$
 - 14: Delete D_i, P_i
 - 15: $i \leftarrow i + 1$
 - 16: cFP $\leftarrow D_i$
-

Bloom filters & De Bruijn Graphs

So, we can make very small representation of the dBG.
But it's navigational! We can also make them:

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Original Paper



Sequence analysis

Practical dynamic de Bruijn graphs

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Dynamic &
membership



and even
weighted



deBGR: an efficient and near-exact representation of the weighted de Bruijn graph

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