Asymptotically optimal minimizers schemes

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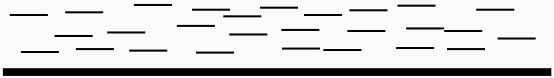
Computing read overlaps



Roberts, *et al.* (2004). Reducing storage requirements for biological sequence comparison.

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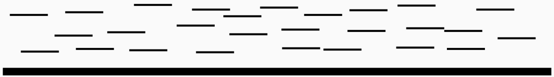

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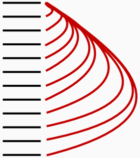

$O(n^2)$ alignments

Computing read overlaps

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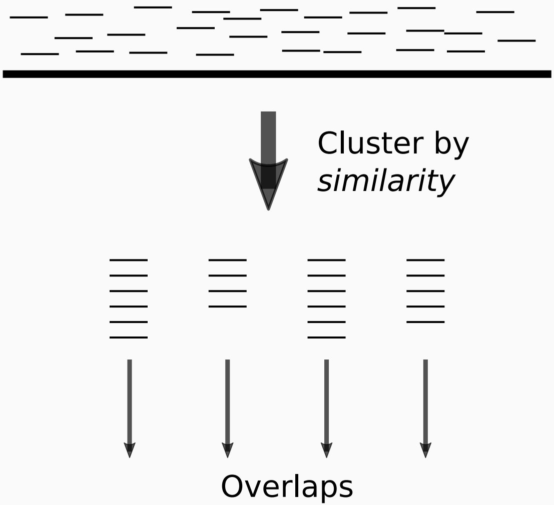

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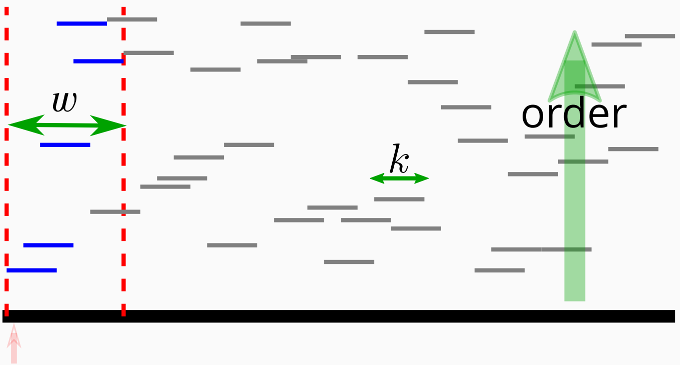

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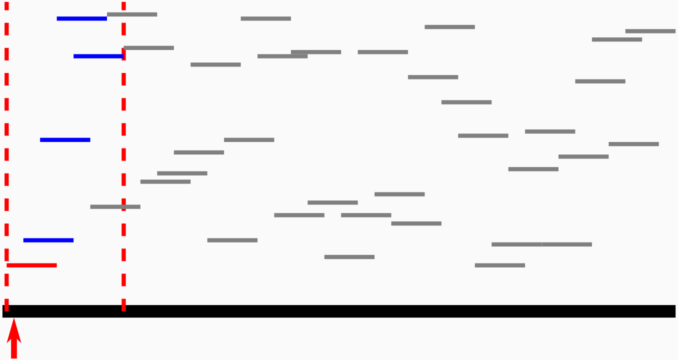

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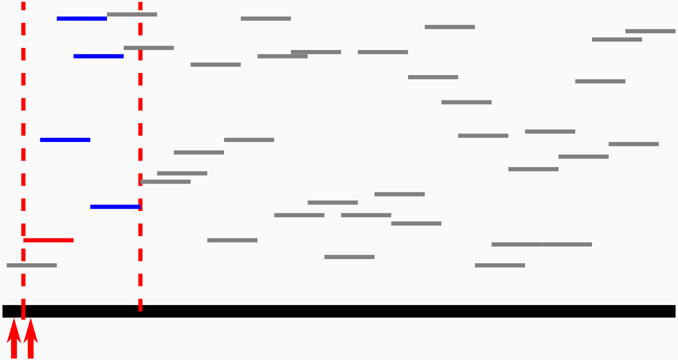

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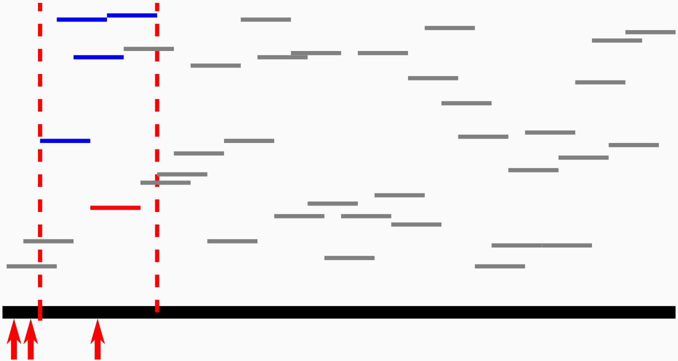

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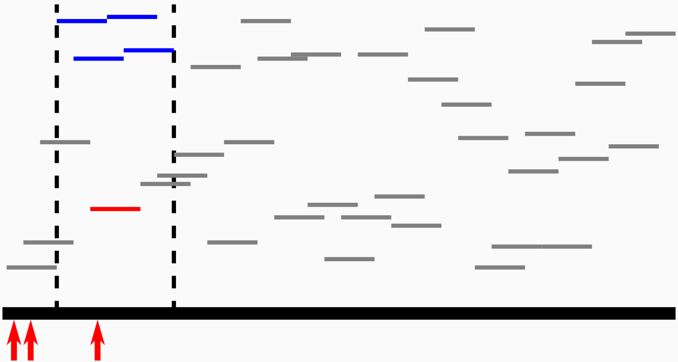

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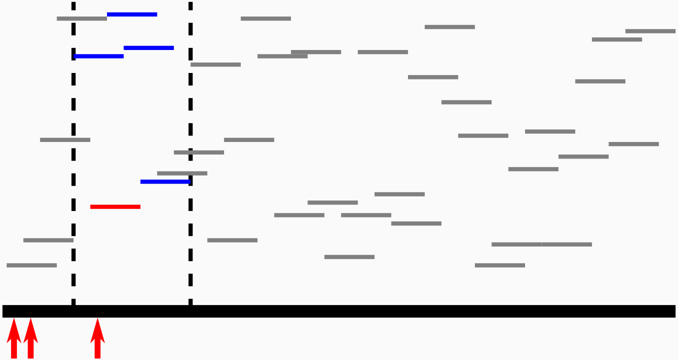

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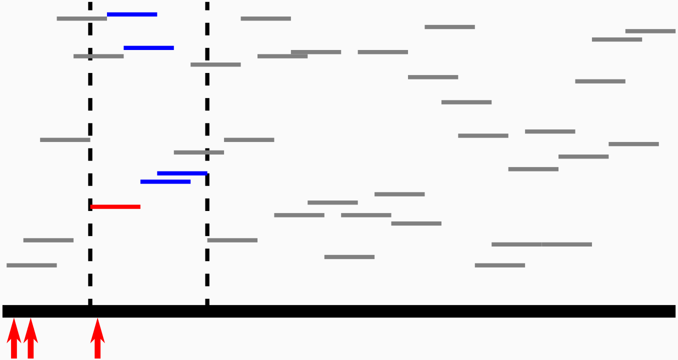

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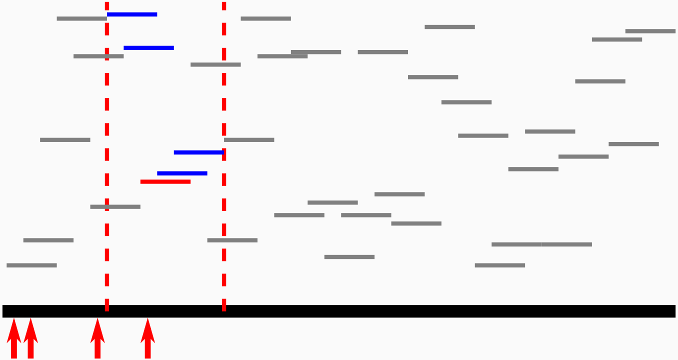

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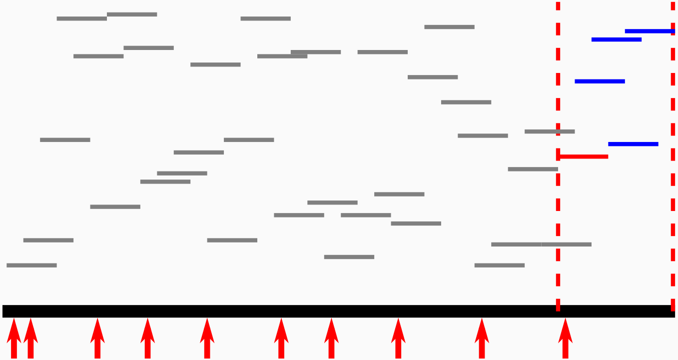


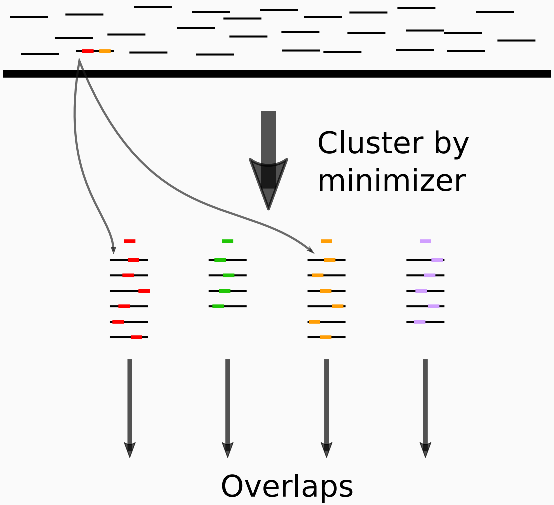
Minimizers definition and properties

Minimizers (k, w, o)
In each window of w consecutive k-mers, select the smallest k-mer according to order o.

1. **No large gap**: distance between selected k-mers is $\leq w$
2. **Deterministic**: two strings matching on w consecutive k-mers select the same minimizer

Computing read overlaps

1. **No large gap**: no sequence ignored
2. **Deterministic**: reads with overlap in same bin

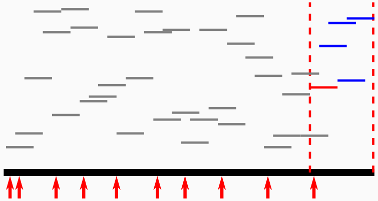


Many applications of minimizers

- **UMDOverlapper (Roberts, 2004)**: bin sequencing reads by shared minimizers to compute overlaps
- **MSPKmerCounter (Li, 2015), KMC2 (Deorowicz, 2015), Gerbil (Erber, 2017)**: bin input sequences based on minimizer to count *k*-mers in parallel
- **SparseAssembler (Ye, 2012), MSP (Li, 2013), DBGFM (Chikhi, 2014)**: reduce memory footprint of de Bruijn assembly graph with minimizers
- **SamSAMi (Grabowski, 2015)**: sparse suffix array with minimizers
- **MiniMap (Li, 2016), MashMap (Jain, 2017)**: sparse data structure for sequence alignment
- **Kraken (Wood, 2014)**: taxonomic sequence classifier

- **Schleimer *et al.* (2003)**: winnowing

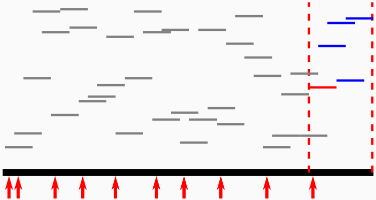
Improving minimizers by lowering density

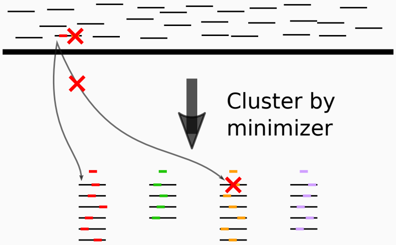


Density
Density of a scheme is the expected proportion of selected k-mer in a random sequence:

$$d = \frac{\#\text{ of selected } k\text{-mers}}{\text{length of sequence}}$$

Improving minimizers by lowering density





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Lower density
$\Longrightarrow$ smaller bins
$\Longrightarrow$ less computation

Minimizers density minimizing problem

For fixed k and w:

- Properties “No large gap” & “Deterministic” unaffected by order
- Density changes with ordering o
- Lower density $\implies$ sparser data structures and/or less computation
- Benefit existing and new applications

Density minimization problem
For fixed w, k, find k-mer **order** o giving the lowest expected density

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Density and density factor trivial bounds

$$\underbrace{\frac{1}{w}}_{\text{Pick every other } w \text{ } k\text{-mer}} \leq d \leq \overbrace{1}^{\text{Pick every } k\text{-mer}}$$

Random order *usual* expected density $d = \frac{2}{w+1}$

$$1 + \frac{1}{w} \leq \text{df} = (w+1) \cdot d \leq w+1$$

Random order usual expected *density factor* $\text{df} = 2$

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$$d \geq \frac{1.5 + \frac{1}{2w}}{w + 1} \qquad \text{(Schleimer \textit{et al.})}$$

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$$d \geq \frac{1.5 + \frac{1}{2w} + \max\left(0, \lfloor \frac{k-w}{w} \rfloor\right)}{w+k}$$

Valid for **any** k, w and **any** order

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Applies only if $w \gg k$, or for *random* orders

$$d \geq \frac{1.5 + \frac{1}{2w} + \max\left(0, \lfloor\frac{k-w}{w}\rfloor\right)}{w+k} \qquad \left(\xrightarrow[k\to\infty]{} \frac{1}{w}\right)$$

Valid for **any** k, w and **any** order

Asymptotic behavior in k and w

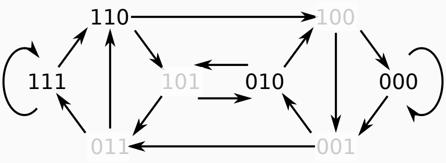
What is the best ordering possible when:

- w is fixed and $k \to \infty$
- k is fixed and $w \to \infty$

A universal set defines an ordering

Universal set
A set M of k-mers that intersects every path of w nodes in the de Bruijn graph of order k.

- $w = 2 \implies M$ is a vertex cover
- From M, get order with density $d \leq \frac{|M|}{\sigma^k}$



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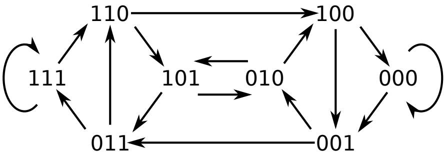
Universal set of size $\frac{\sigma^k}{w}$

$$\Downarrow$$

Order with density $\frac{1}{w}$

Creating a universal set, $k = 3, w = 3$, algorithm overview

Start with a de Bruijn graph



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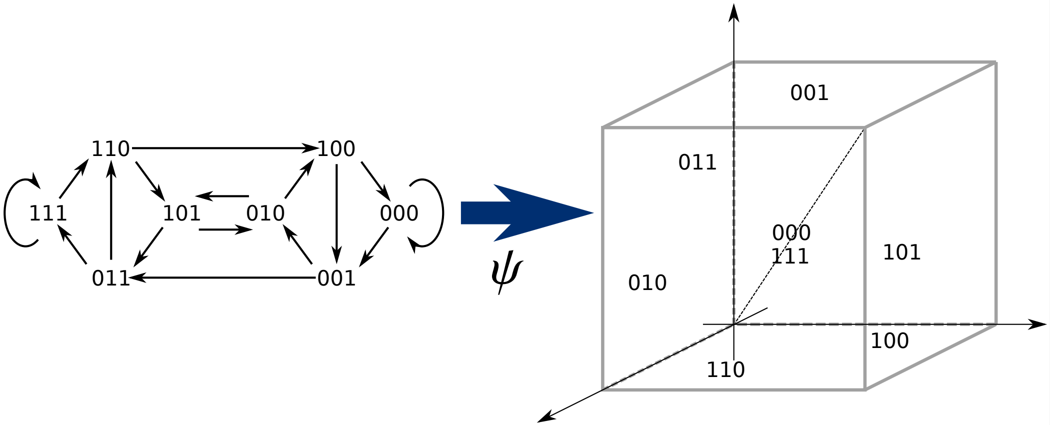
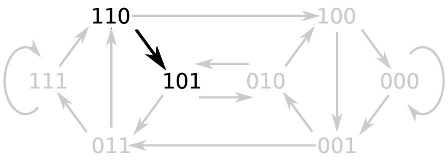
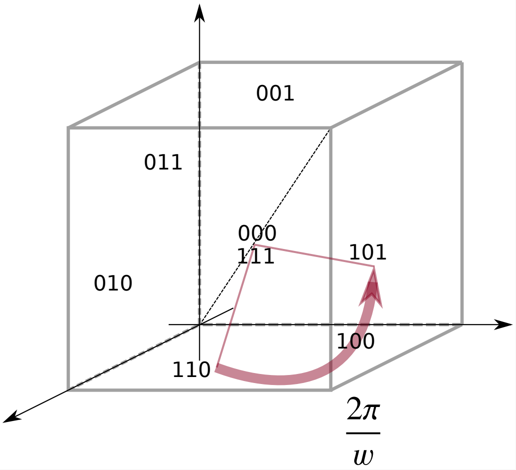
Embed into a w dimensional space using ψ



Creating a universal set, $k = 3, w = 3$, algorithm overview

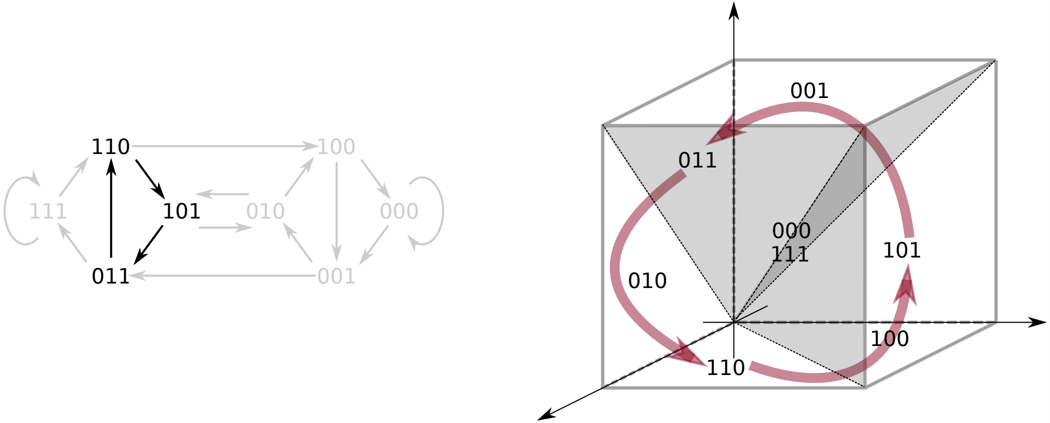
An edge correspond (almost) to a rotation by $2\pi/w$





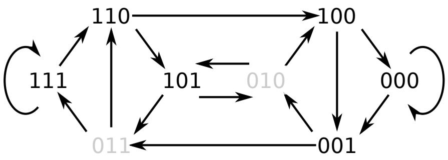
Creating a universal set, $k = 3, w = 3$, algorithm overview

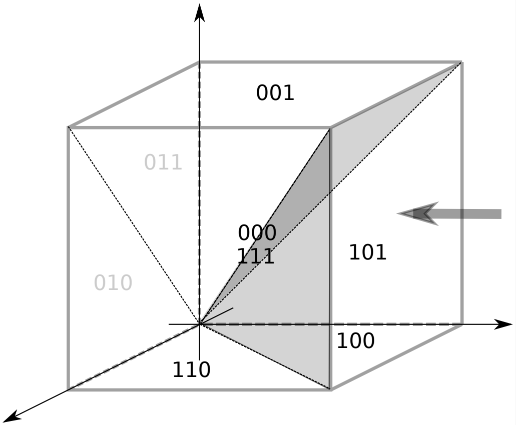
After w edges return to same sub-volume



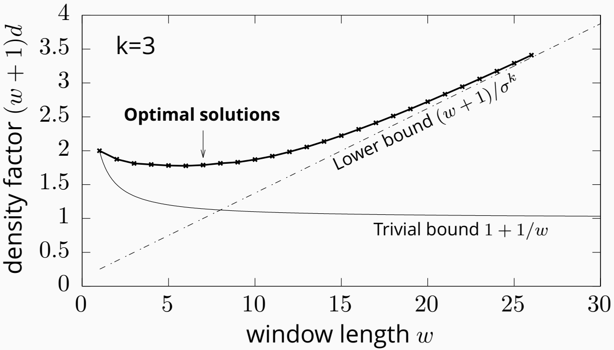
Creating a universal set, $k = 3, w = 3$, algorithm overview

Pick *k*-mers in the highlighted "wedge"





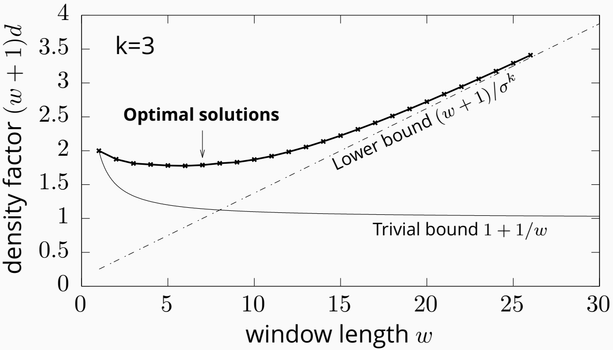
Asymptotic behavior in w



$$d \geq \frac{1}{\sigma^k}, \quad \mathrm{df} \geq \frac{w+1}{\sigma^k}$$

Density factor is $\theta(w)$, not constant

Asymptotic behavior in w



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Summary

Asymptotic behavior of minimizers is fully characterized:

- Minimizers scheme is optimal for large k: $d \xrightarrow[k\to\infty]{} \frac{1}{w}$
- Minimizers scheme is not optimal for large w: $\mathrm{df} = \theta(w)$
- Tighter lower bound

$$d \geq \frac{1.5 + \frac{1}{2w} + \max\left(0, \lfloor\frac{k-w}{w}\rfloor\right)}{w+k}$$

- Comparison between k-mers take $O(k)$

Future work

- Local scheme: $f : \Sigma^{w+k-1} \to [1, w]$
- Local schemes *might* be optimal for large w

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