Generalization of the minimizers schemes

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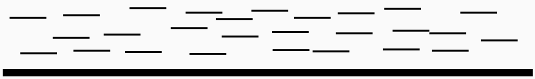
Computing read overlaps



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

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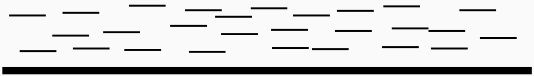

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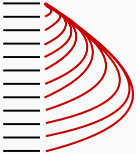

$O(n^2)$ alignments

Computing read overlaps

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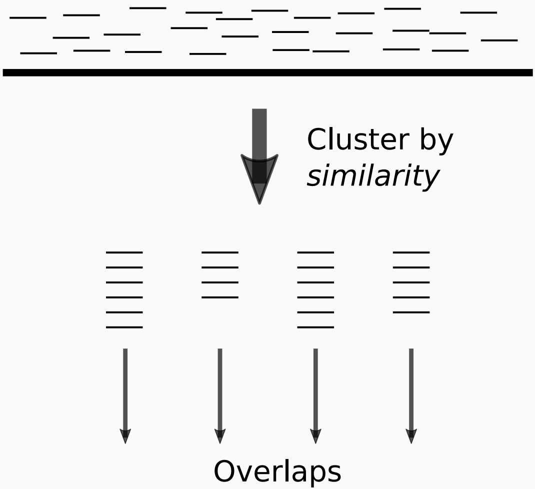

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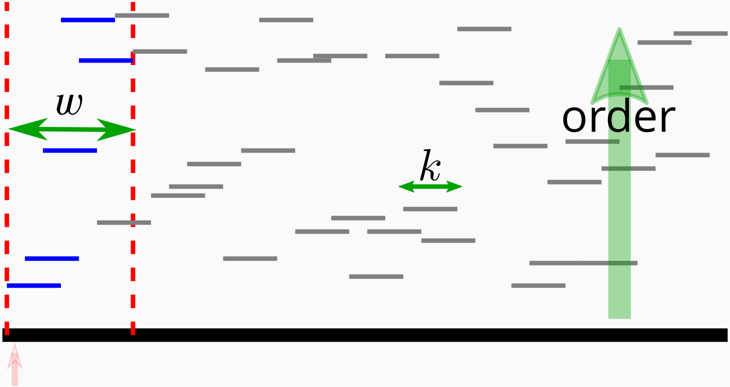

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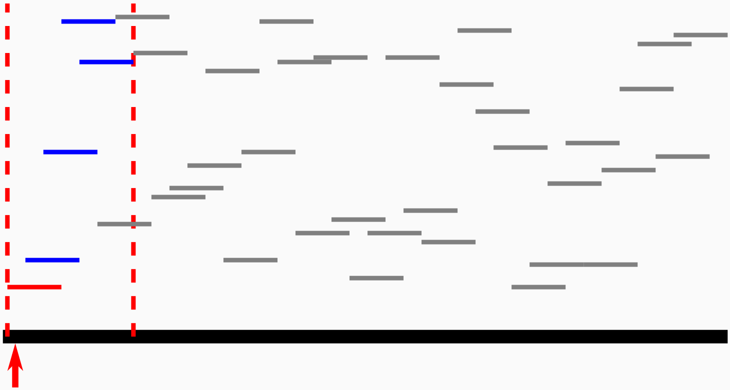

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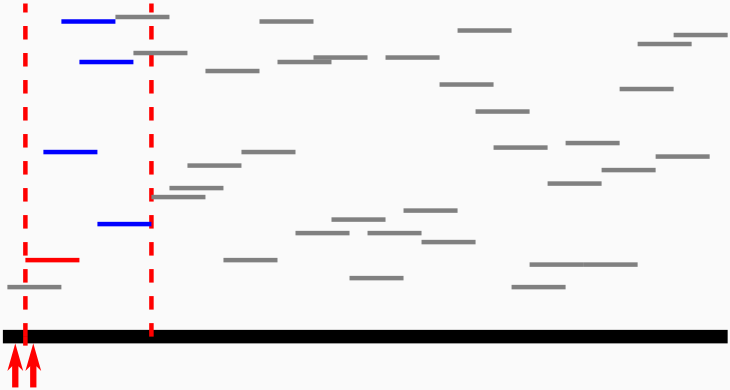

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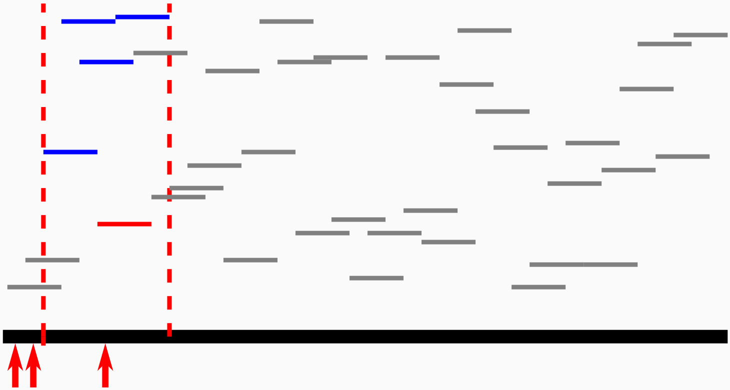

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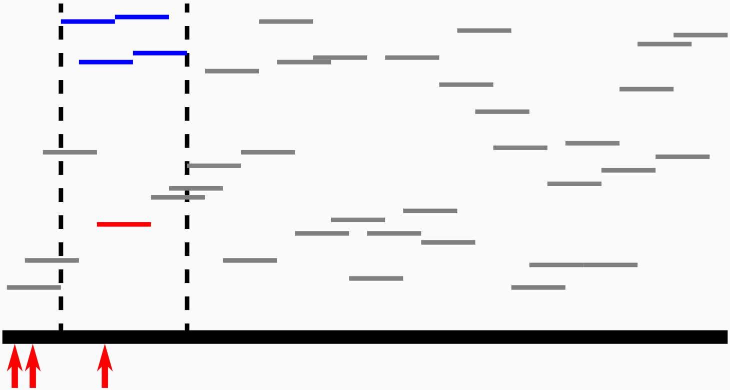

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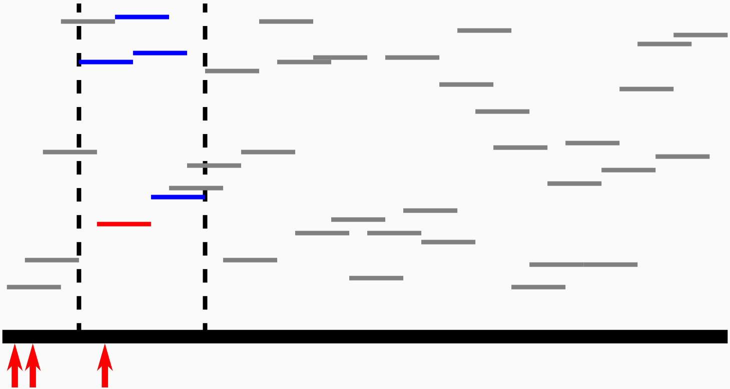

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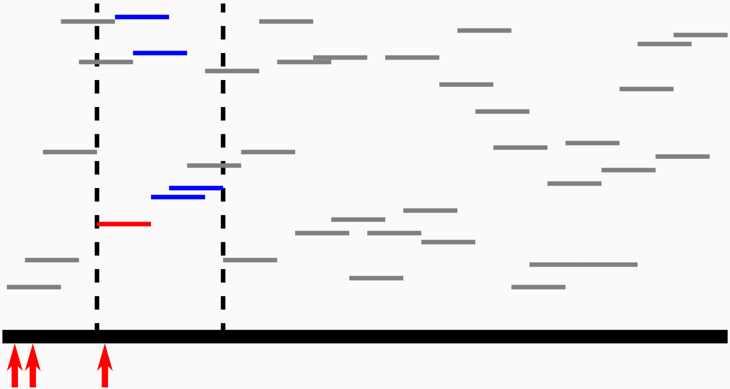

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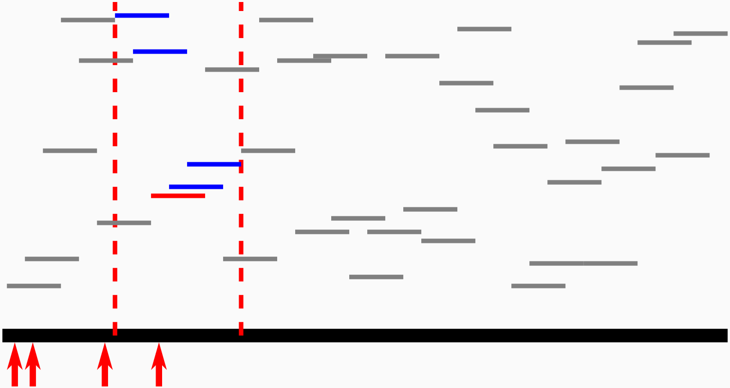

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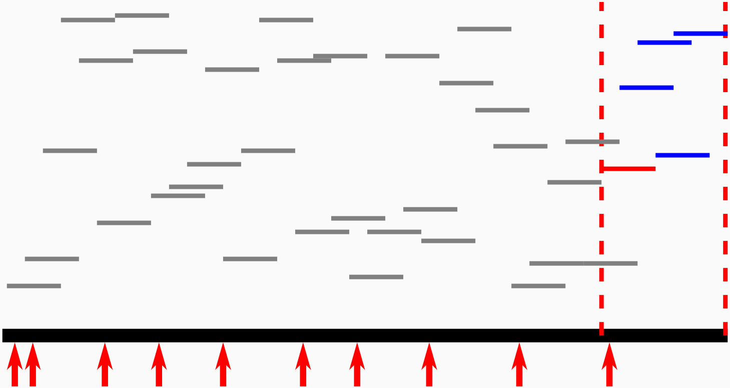


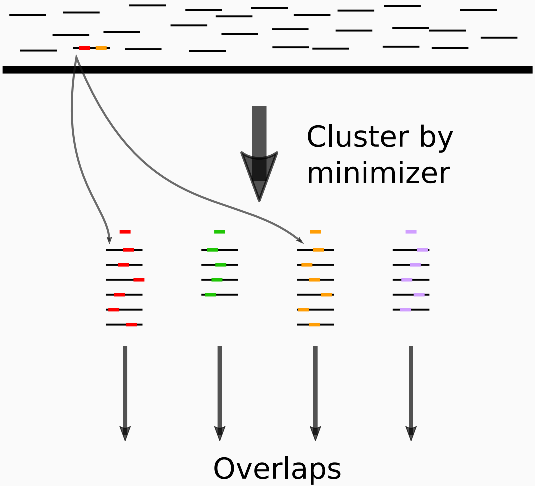
Minimizers definition and properties

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

1. **Uniform**: 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

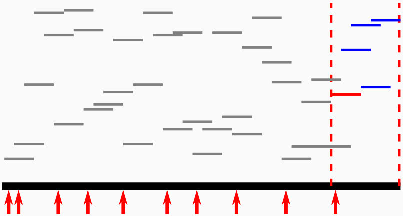
1. **Uniform**: no sequence ignored
2. **Deterministic**: reads with overlap in same bin



Many applications of minimizers

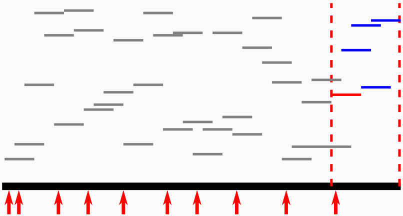
- **UMDOverlapper (Roberts, 2004)**: bin sequencing reads by shared minimizers to compute overlaps
- **MSPKmerCounter (Li, 2015), KMC2 (Deorowicz, 2015), Gerbil (Erber, 2017)**: bin input sequences based on minimizer to count *k*-mers in parallel
- **SparseAssembler (Ye, 2012), MSP (Li, 2013), DBGFM (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

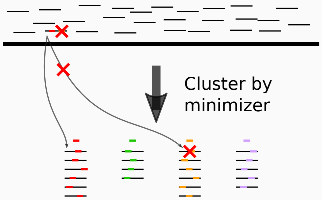
Improving minimizers by lowering density



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

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





Density

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

Lower density

$\implies$ smaller bins

$\implies$ less computation

Minimizers density minimizing problem

For fixed k and w:

- Properties “Uniform” & “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

Density

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

$d =$ # of minimizers per base

Density and density factor trivial bounds

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Density factor

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

$df \approx$ # of minimizers per window

Expected and bound on density

For an *idealized random* order o:

$$d = \frac{2}{w+1} \qquad df = 2$$

Expect ≈ 2 minimizers per window

For any order o:

$$d \geq \frac{1.5 + \frac{1}{2w}}{w+1} \quad df \geq 1.5 + \frac{1}{2w}$$

Requires ≥ 1.5 minimizers per window

Schleimer 2003, Roberts 2004

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Valid only for $w \gg k$

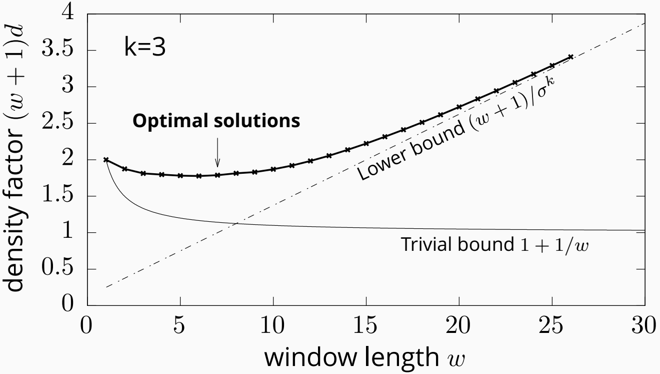
Schleimer 2003, Roberts 2004

Asymptotic behavior in k and w

What is the best ordering possible when:

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

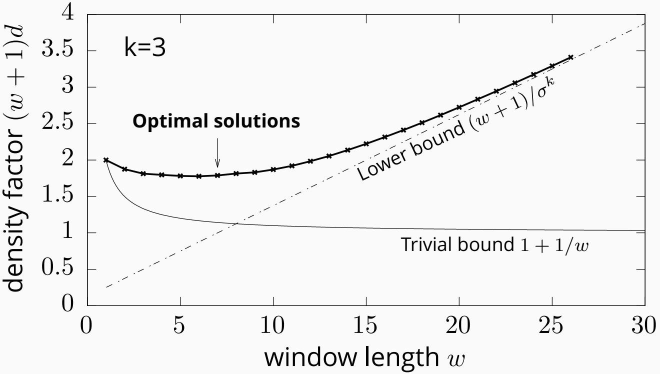
Asymptotic behavior in *w*



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

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

Asymptotic behavior in w



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

Asymptotic behavior in k

Asymptotically optimal minimizers schemes
There exists a sequence of orders $(o_k)_{k \in \mathbb{N}}$ which are asymptotically optimal:

$$d_{o_k} \xrightarrow[k \to \infty]{} \frac{1}{w} \qquad df_{o_k} \xrightarrow[k \to \infty]{} 1 + \frac{1}{w}$$

Optimal vertex cover of the de Bruijn graph (Lichiardopol 2006)
There exists a sequence of vertex cover V_k of DB_k which is asymptotically optimal in size:

$$|V_k| \xrightarrow[k\to\infty]{} \frac{\sigma^k}{2}$$

Optimal depathing of the de Bruijn graph
For a fixed w, there exists a sequence $(U_k)_{k\in\mathbb{N}}$ of sets of k-mers that covers every path of length w in DB_k such that

$$|U_k| \xrightarrow[k\to\infty]{} \frac{\sigma^k}{w}$$

Bound on density

For **all** k, w and order o:

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

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

$$df \geq 1 + \frac{1}{w} \qquad \text{for large } k$$

$$df \geq 1.5 + \frac{1}{2w} \qquad \text{for large } w$$

Density factor of minimizers

Asymptotic behavior of minimizers is fully characterized:

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

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Good:

- First example of optimal minimizers scheme
- Constructive proof

Not good:

- Large k less interesting in practice
- Minimizers **don't** have **constant** density factor

Generalizing minimizers: local and forward schemes

Local scheme
Given $f : \Sigma^{w+k-1} \to [0, w-1]$, for each window ω, select k-mer at position $f(\omega)$.

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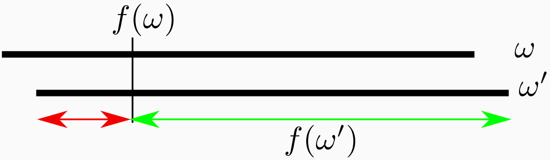
Forward scheme
Local scheme such that $f(\omega') \geq f(\omega) - 1$ if suffix of ω' equals prefix of ω



Local & forward as better minimizers schemes

$$\text{Minimizers} \subsetneq \text{Forward} \subsetneq \text{Local}$$

- Properties “Uniform” & “Deterministic” also satisfied
- Drop-in replacement for minimizers
- Potential for lower density

Density factor overview

Density factor df			
	$k \to \infty$	$w \to \infty$	
Scheme		Best	Bound
Minimizers			
Forward			
Local			

Density factor overview

Density factor *df*

Scheme	$k \to \infty$	$w \to \infty$ Best	$w \to \infty$ Bound
Minimizers	$1 + \frac{1}{w}$	$O(w)$	$\Omega(w)$
Forward			
Local			

Density factor overview

Density factor *df*			
	$k \to \infty$	$w \to \infty$	
Scheme		Best	Bound
Minimizers	$1 + \frac{1}{w}$	$O(w)$	$\Omega(w)$
Forward	$1 + \frac{1}{w}$	$O(\sqrt{w})$	$\sim 1.5 + \frac{1}{2w}$
Local			

Density factor overview

Density factor *df*			
	$k \to \infty$	$w \to \infty$	
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Minimizers	$1 + \frac{1}{w}$	$O(w)$	$\Omega(w)$
Forward	$1 + \frac{1}{w}$	$O(\sqrt{w})$	$\sim 1.5 + \frac{1}{2w}$
Local	$1 + \frac{1}{w}$	$O(\sqrt{w})$	$1 + \frac{1}{w}$

Conclusion: the quest for constant density factor

- Minimizers schemes **can't** achieve **constant** density factor
- Local and forward schemes **may** achieve **constant** density factor

- Design of optimal orders or functions f still open

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