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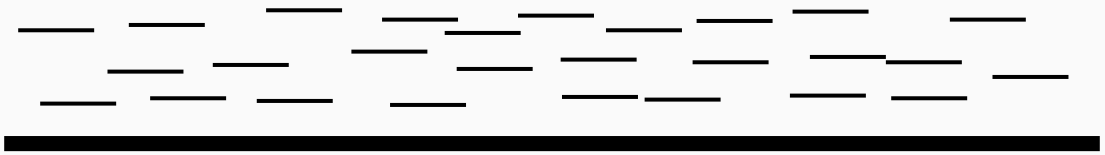
Generalization of the minimizers schemes

Guillaume Marçais, Dan DeBlasio, Carl Kingsford

Carnegie Mellon University

Computing read overlaps



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

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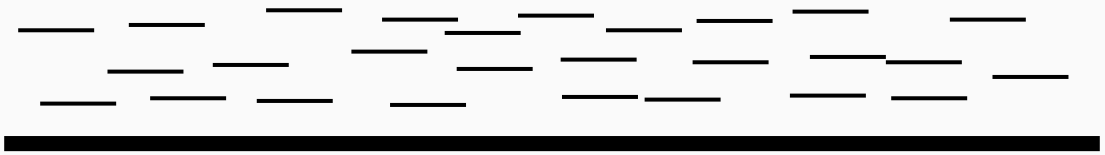

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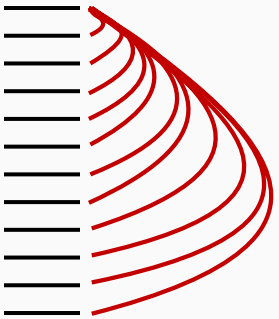

$O(n^2)$ alignments

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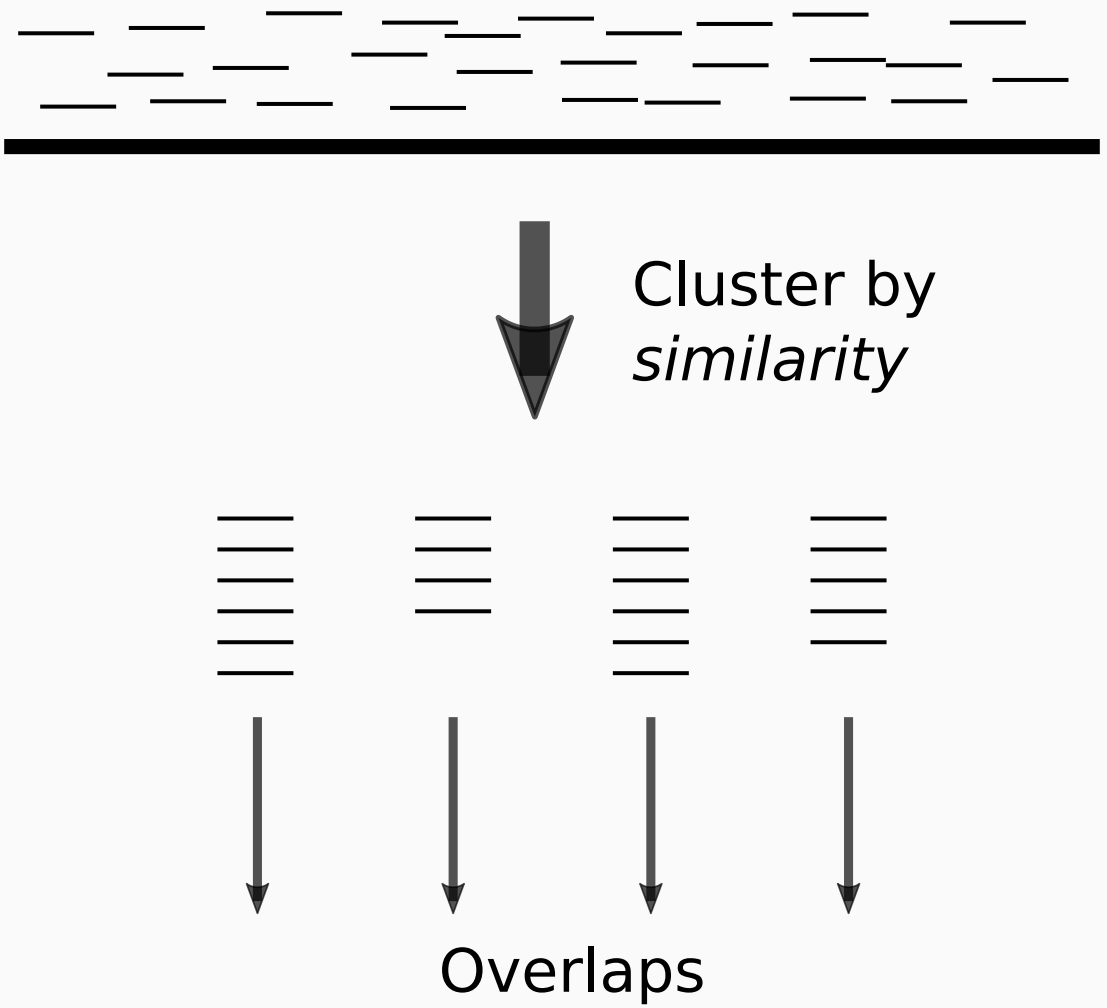
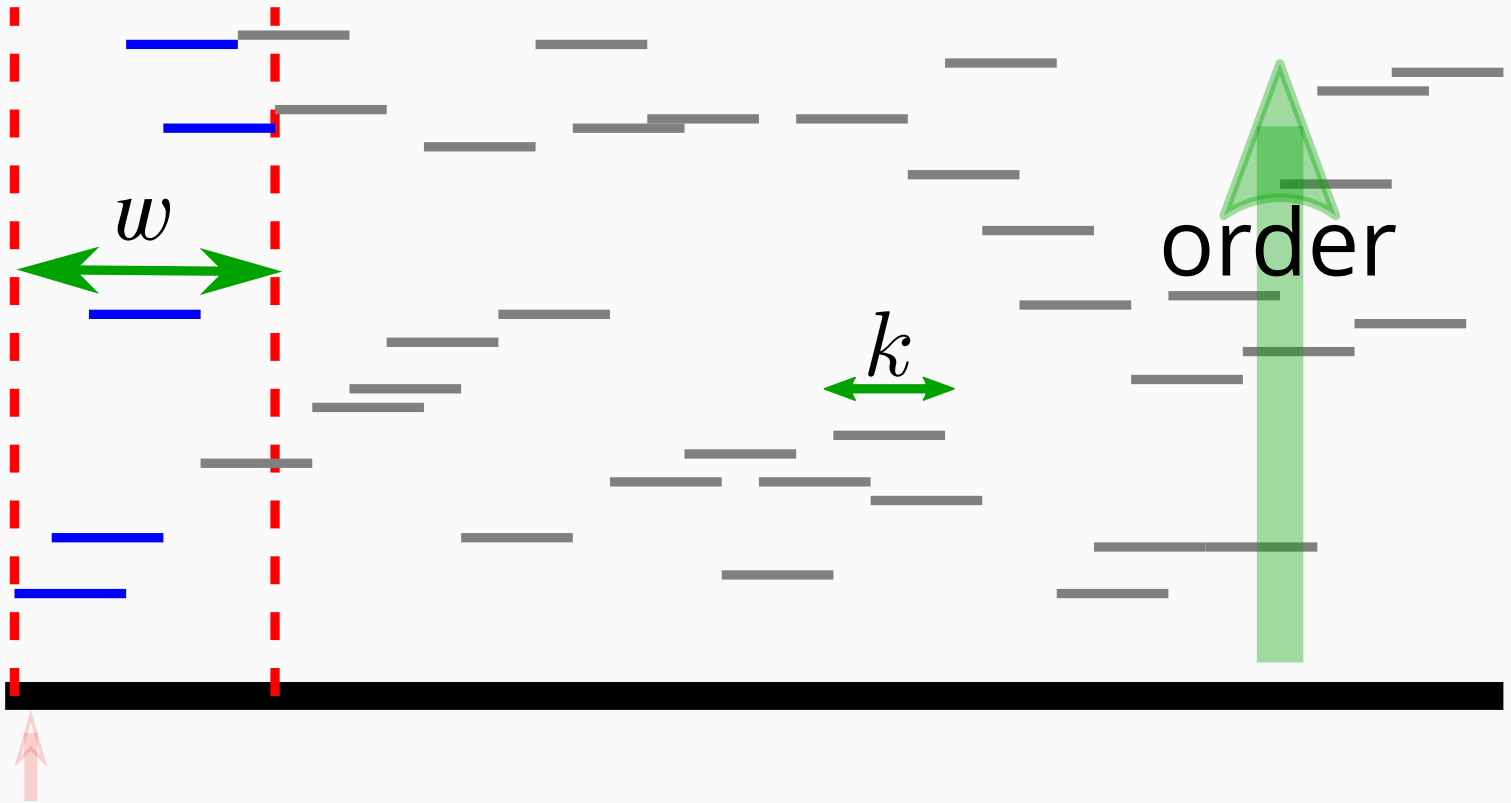


Computing minimizers



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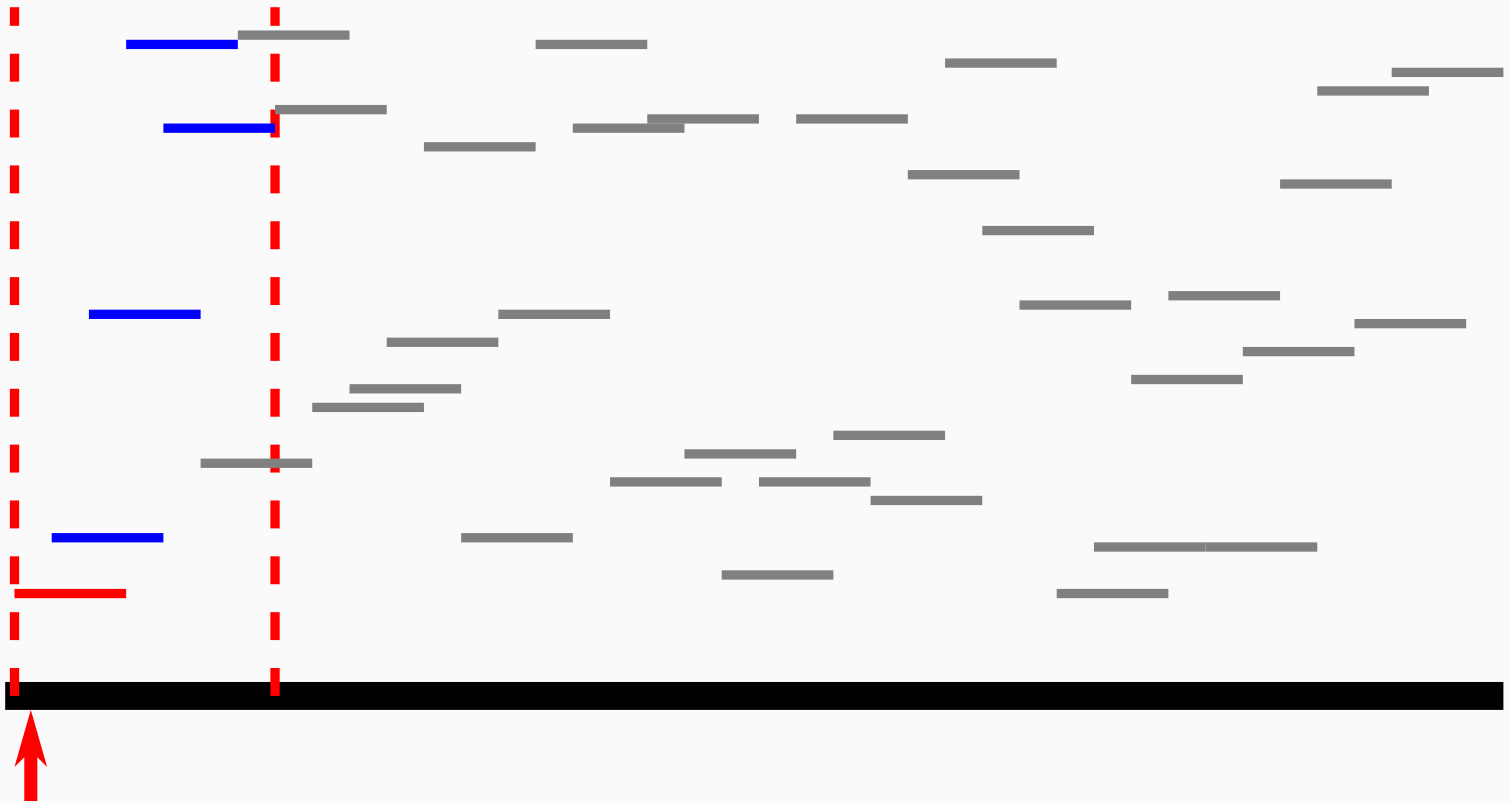

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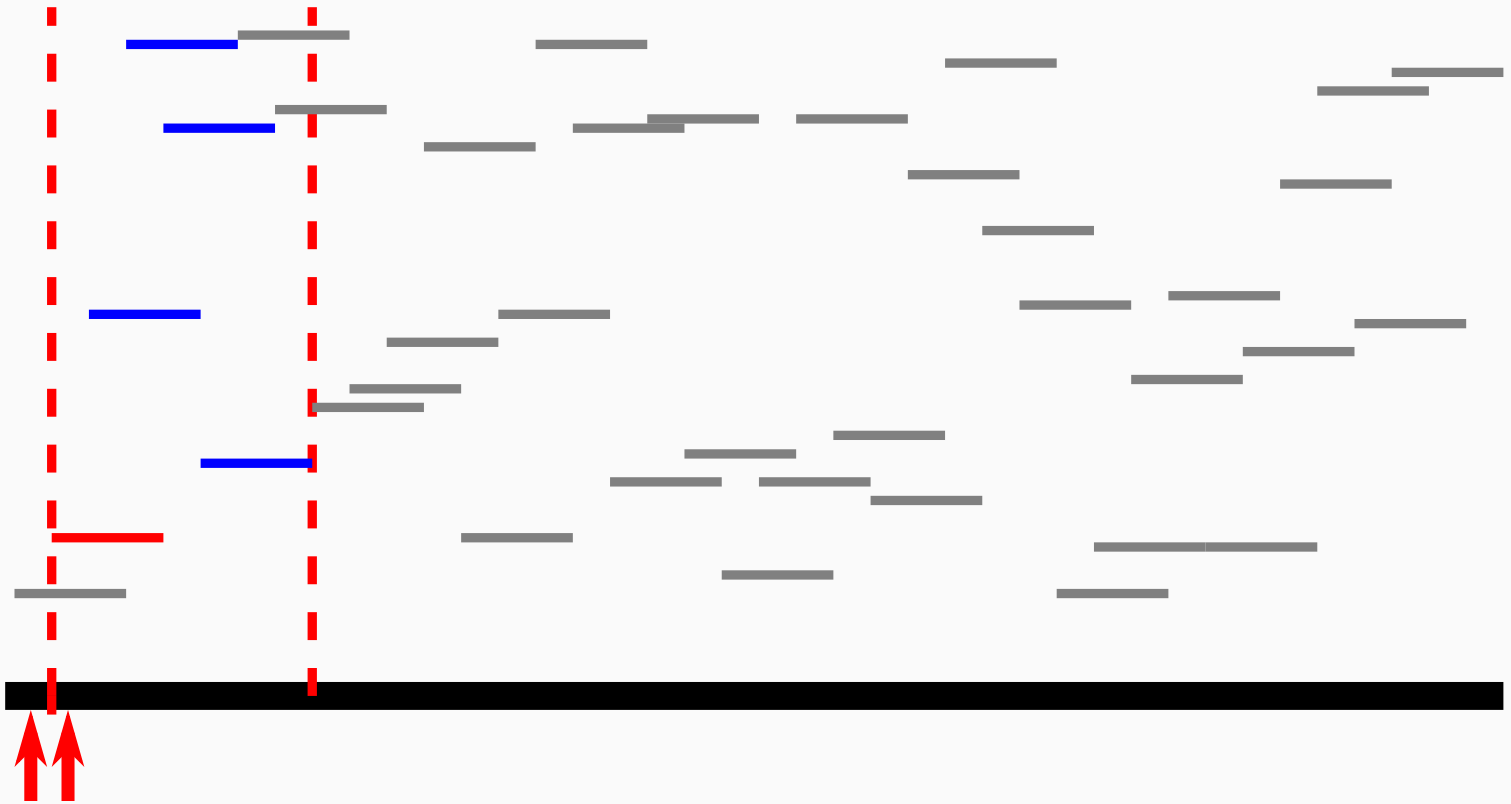

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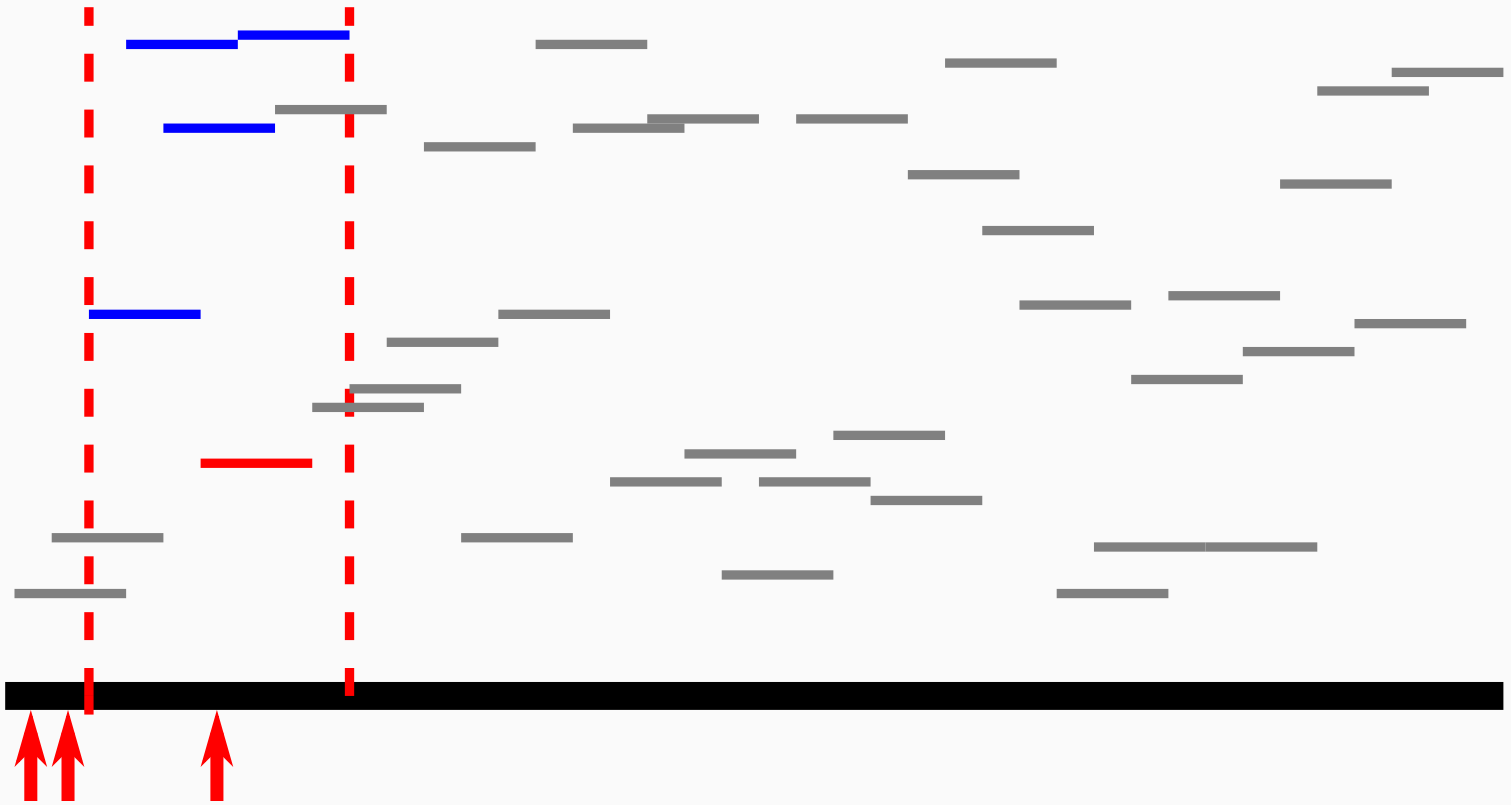

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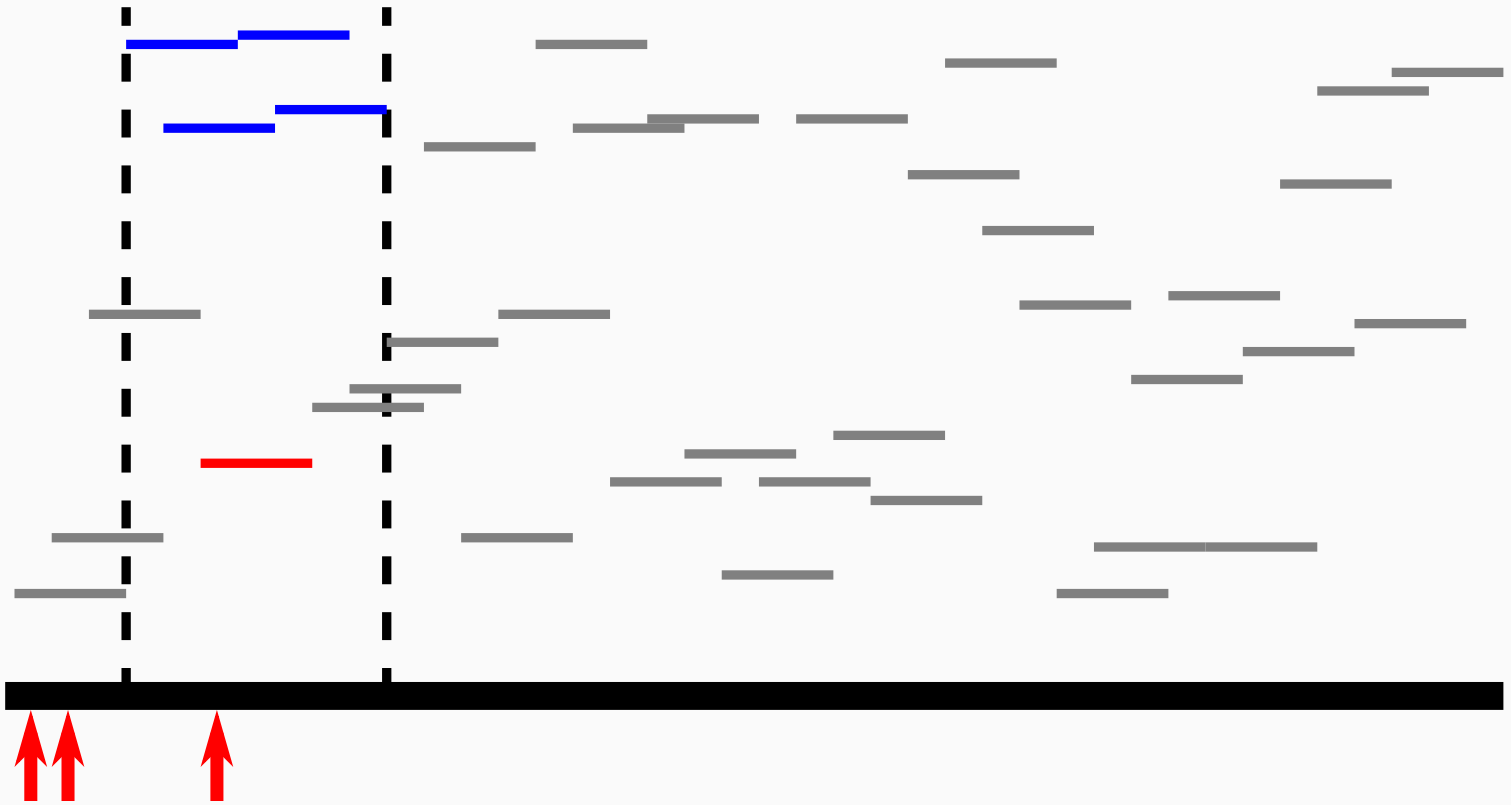

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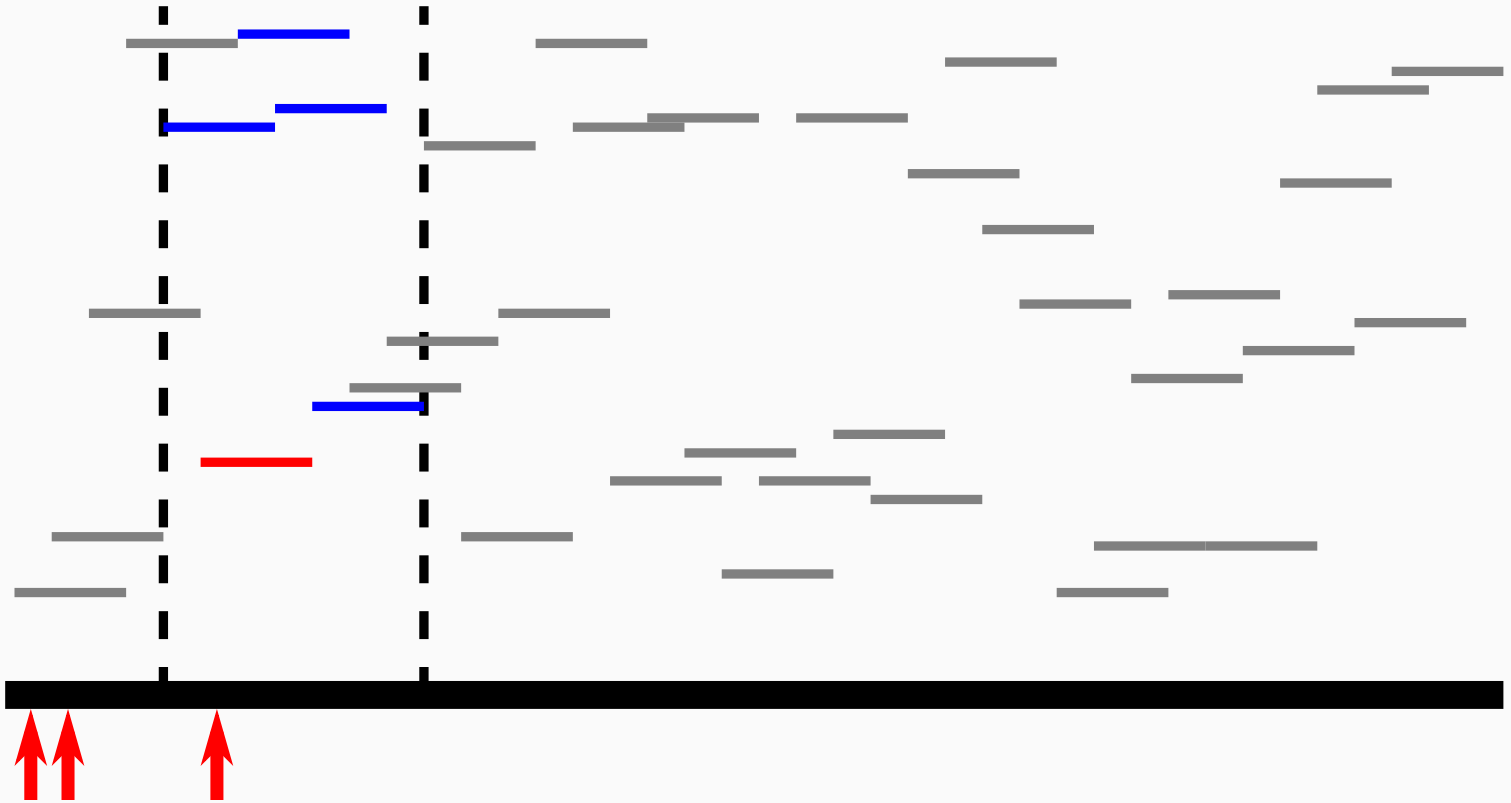

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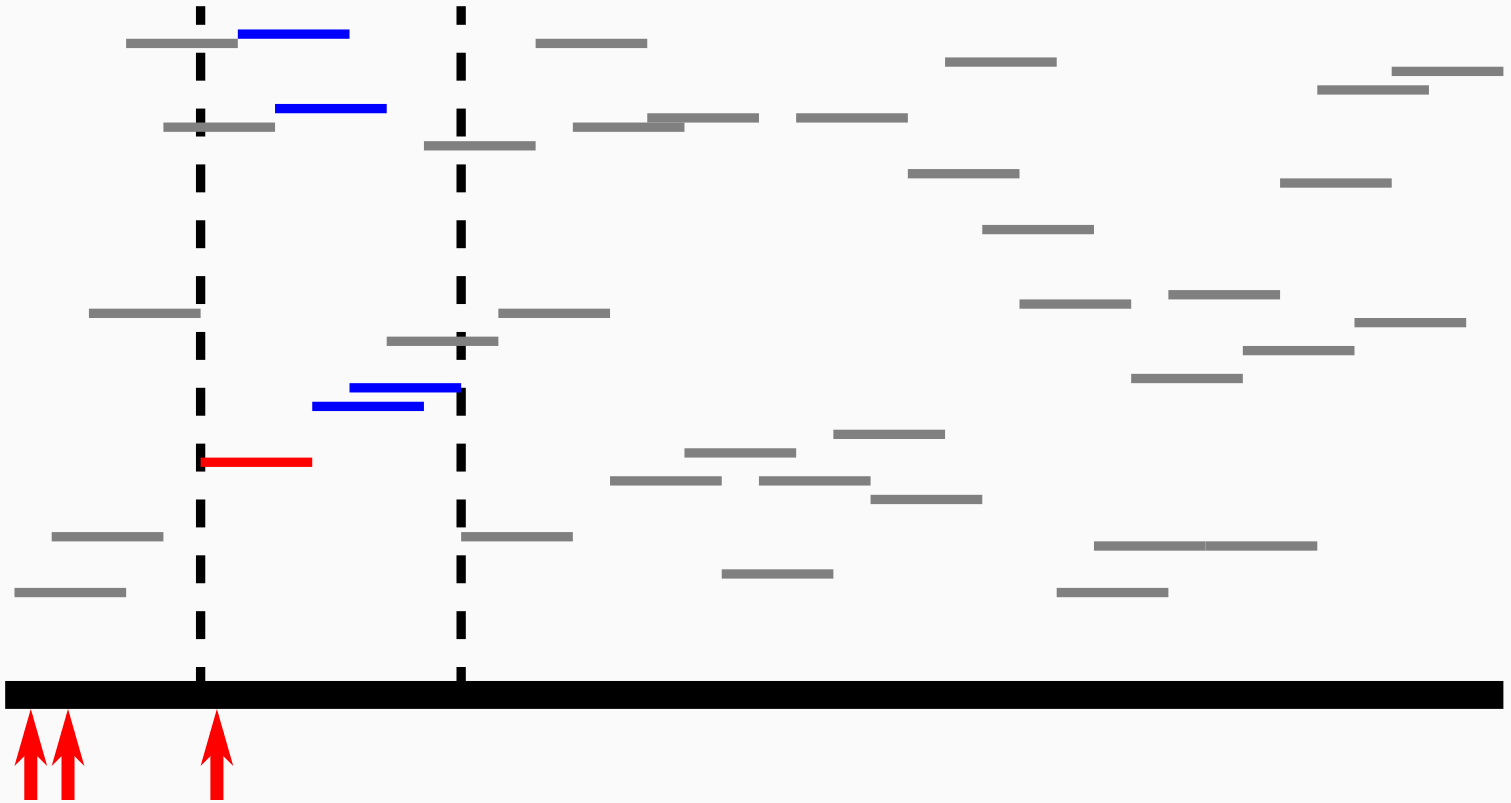

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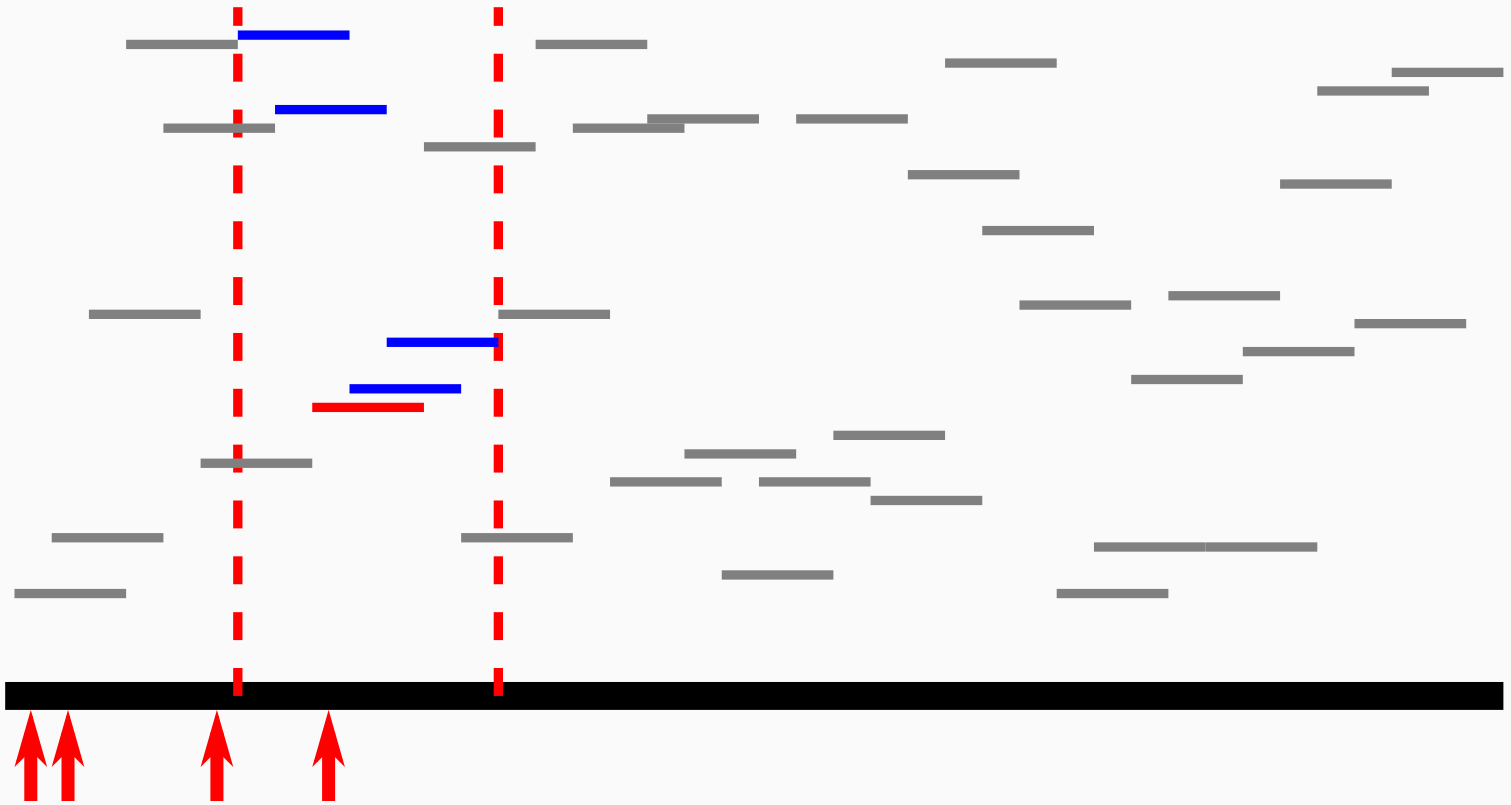

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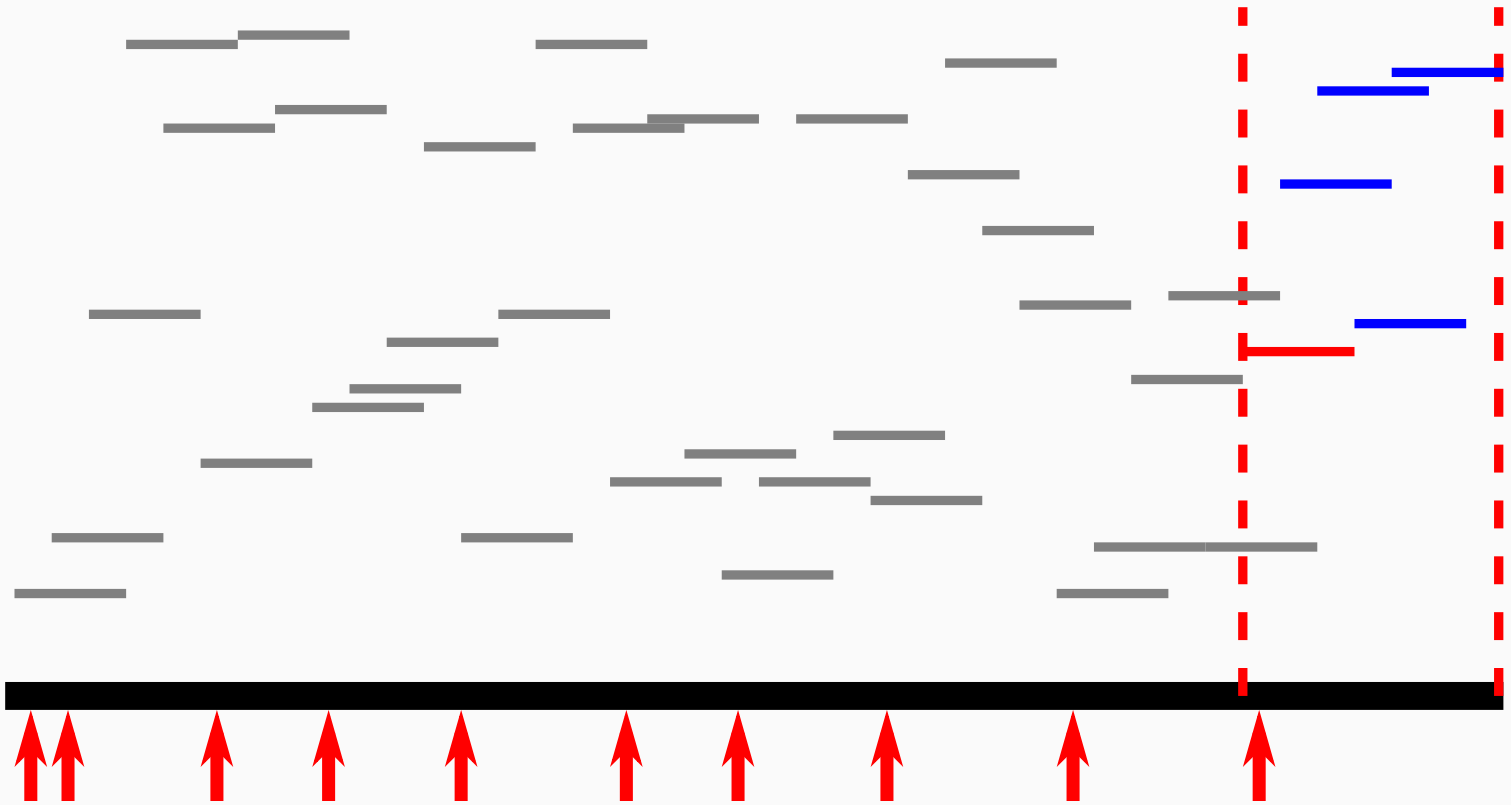


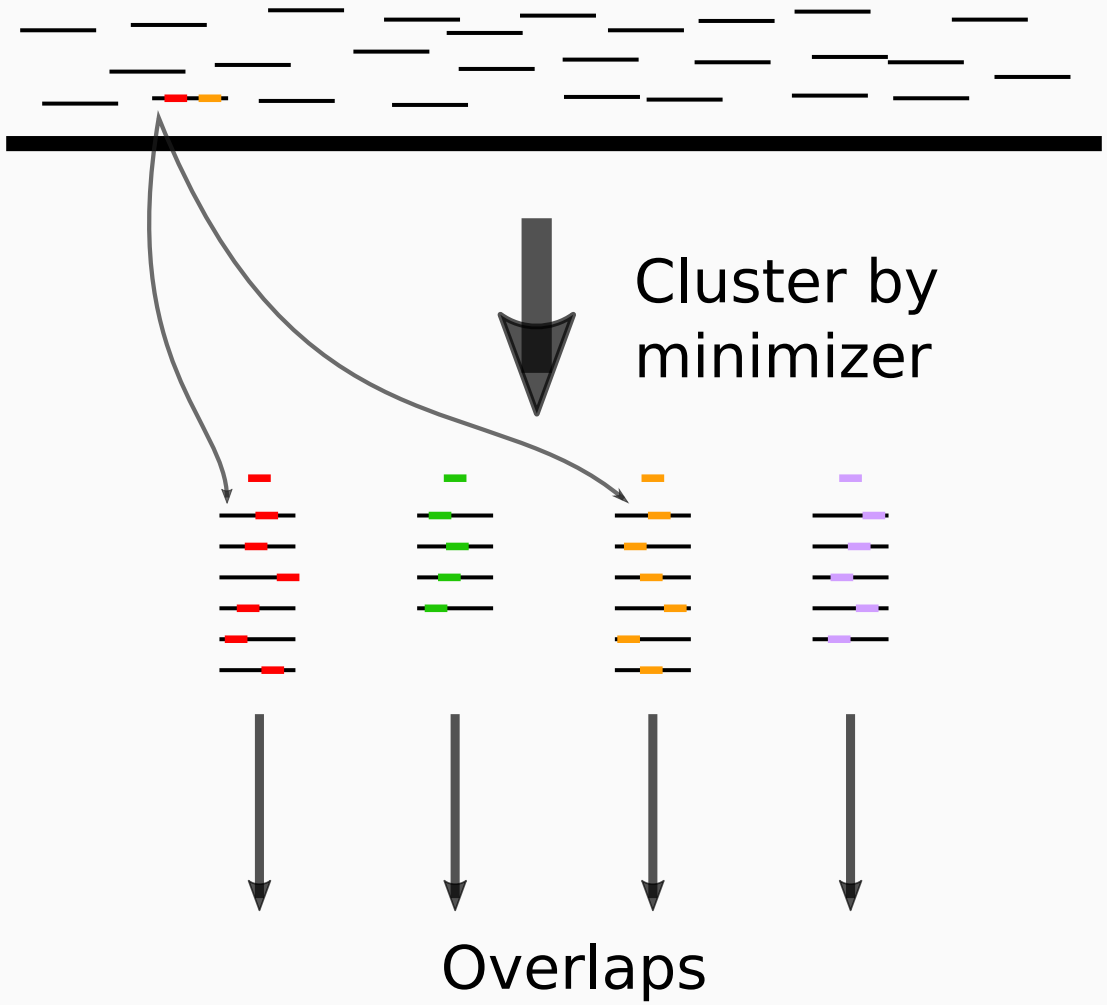
Minimizers definition and properties

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

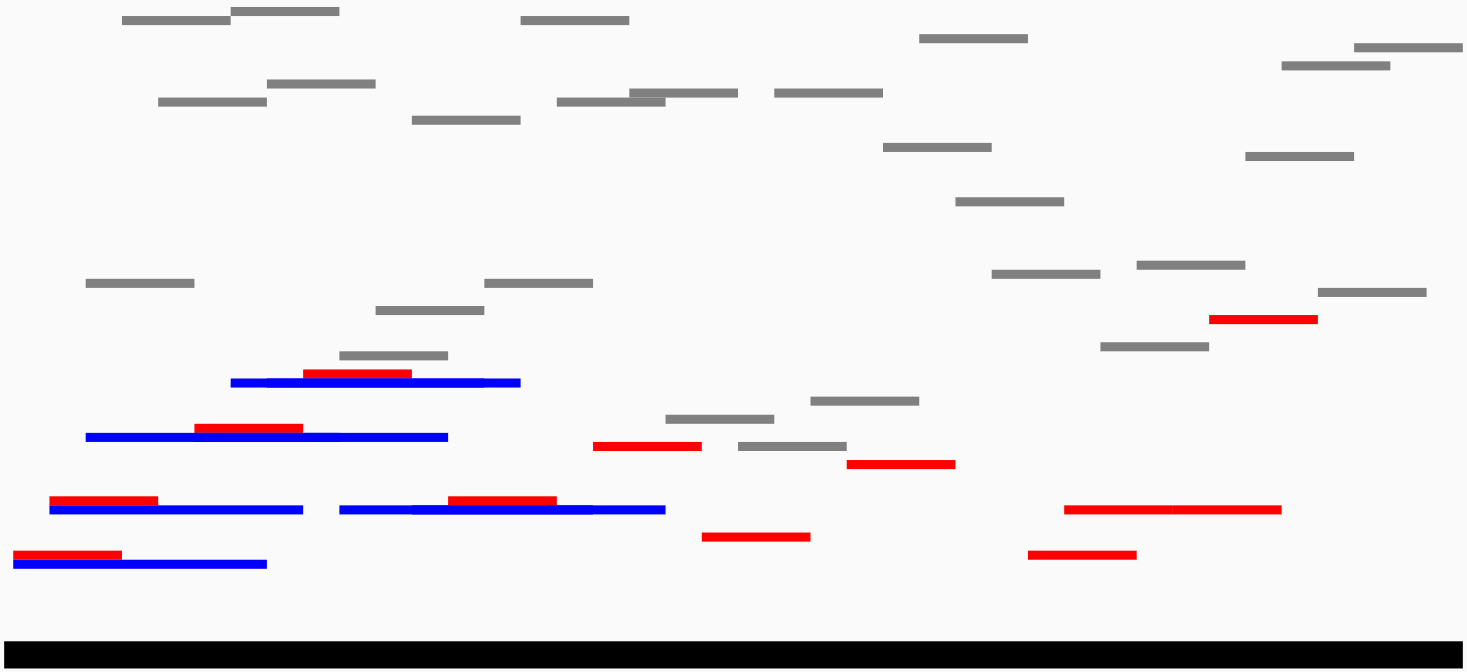
Computing read overlaps

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



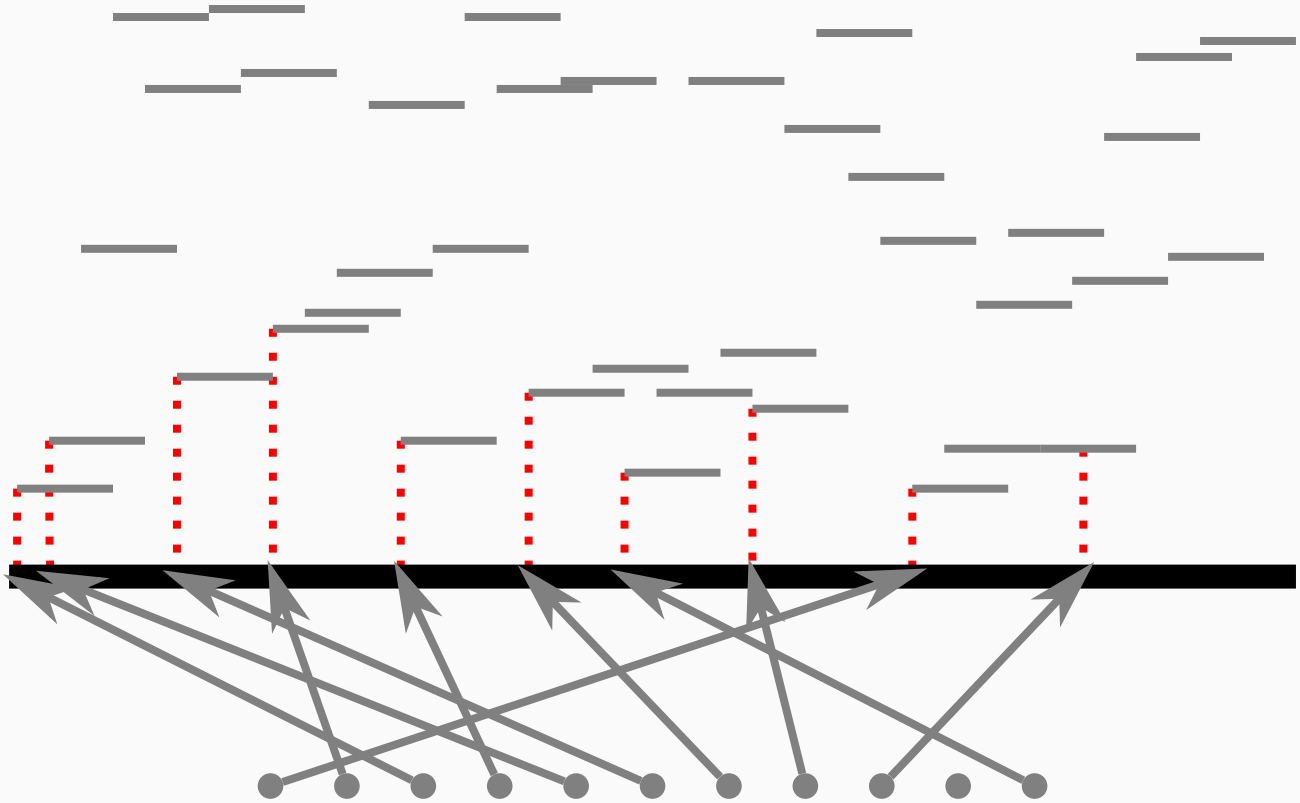
Counting k-mers: super-windows

- Minimizers: m-mer ($m = 7$)
- k-mers: window with $k = w + m - 1$



Count k-mers in parallel in buckets of blue super-windows

Sparse suffix-array

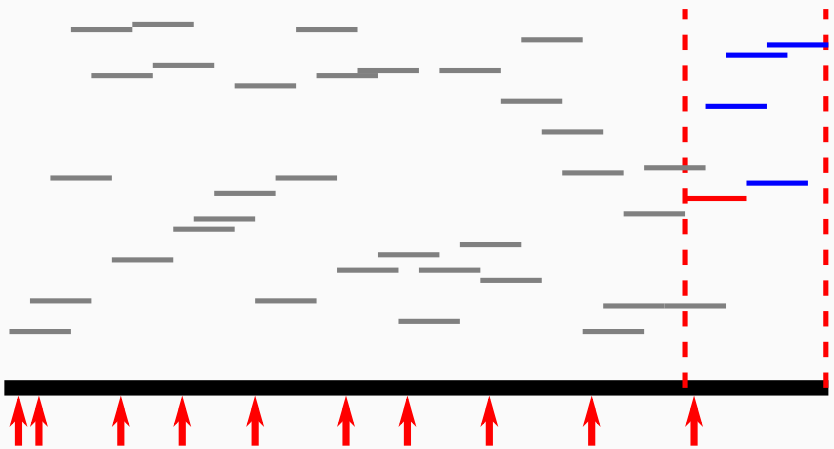


Check only for minimizers in query sequence in SA

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, text fingerprinting

Improving minimizers by lowering density

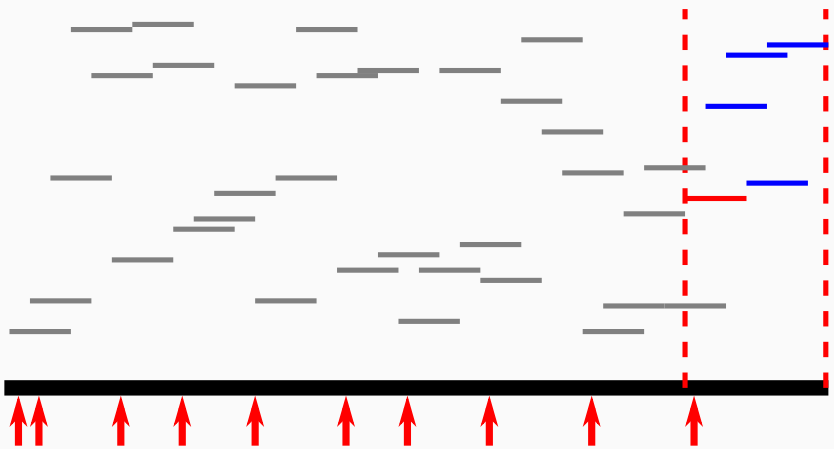


Density

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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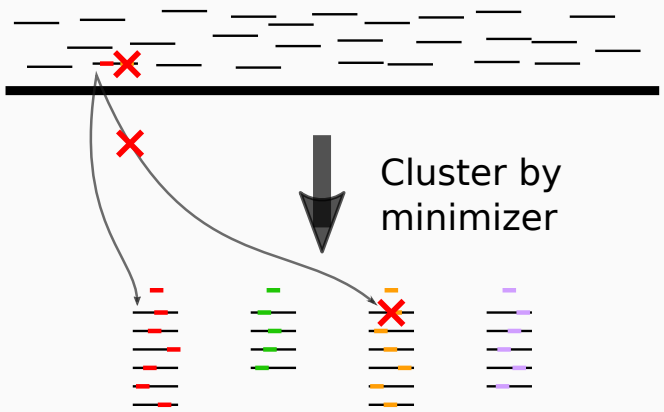

Lower density

$\Longrightarrow$ smaller bins

$\Longrightarrow$ less computation

Minimizers density minimizing problem

For fixed k and w:

- Properties “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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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:

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

Requires ≥ 1.5 minimizers per window

Schleimer 2003, Roberts 2004

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Not valid for $w \gg k$

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Valid only for $w \gg k$

Schleimer 2003, Roberts 2004

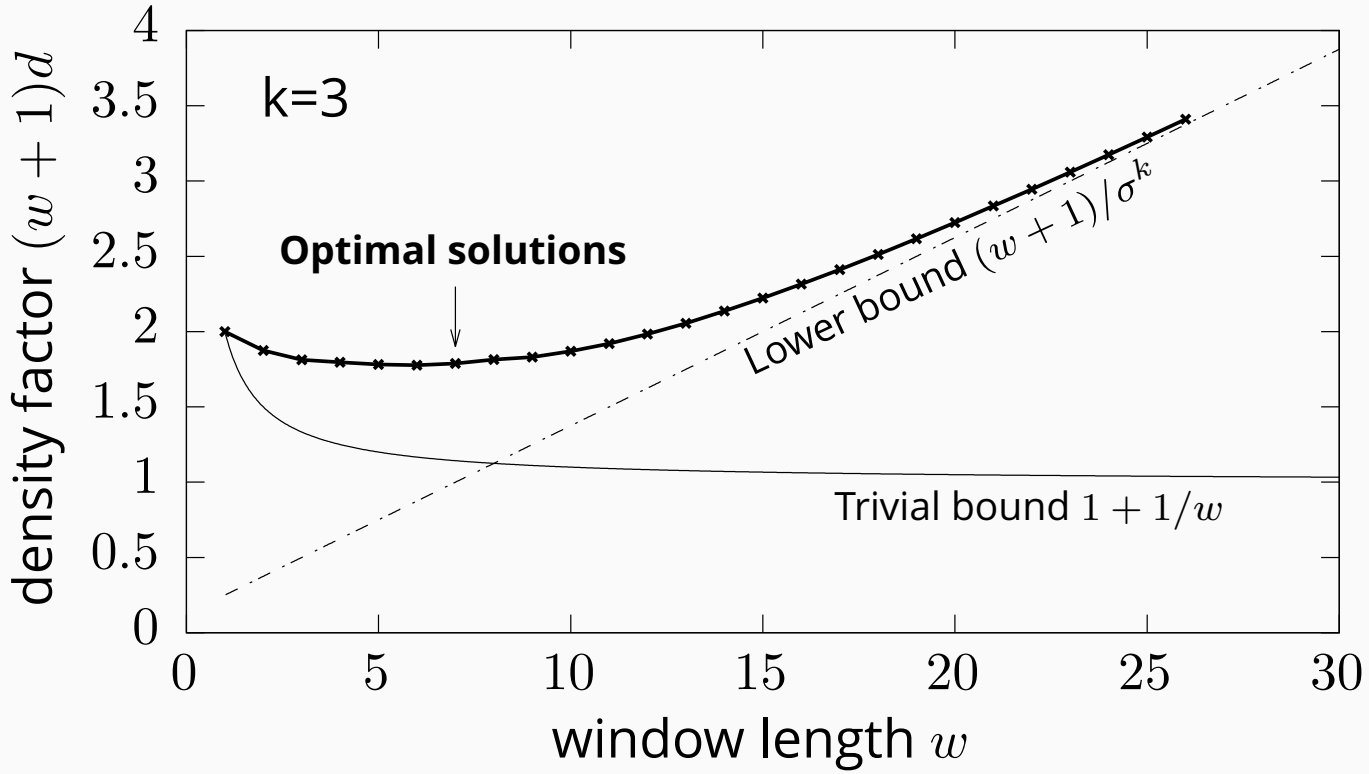
Asymptotic behavior in k and w

What is the best ordering possible when:

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

Marçais *et al.*, ISMB 2018

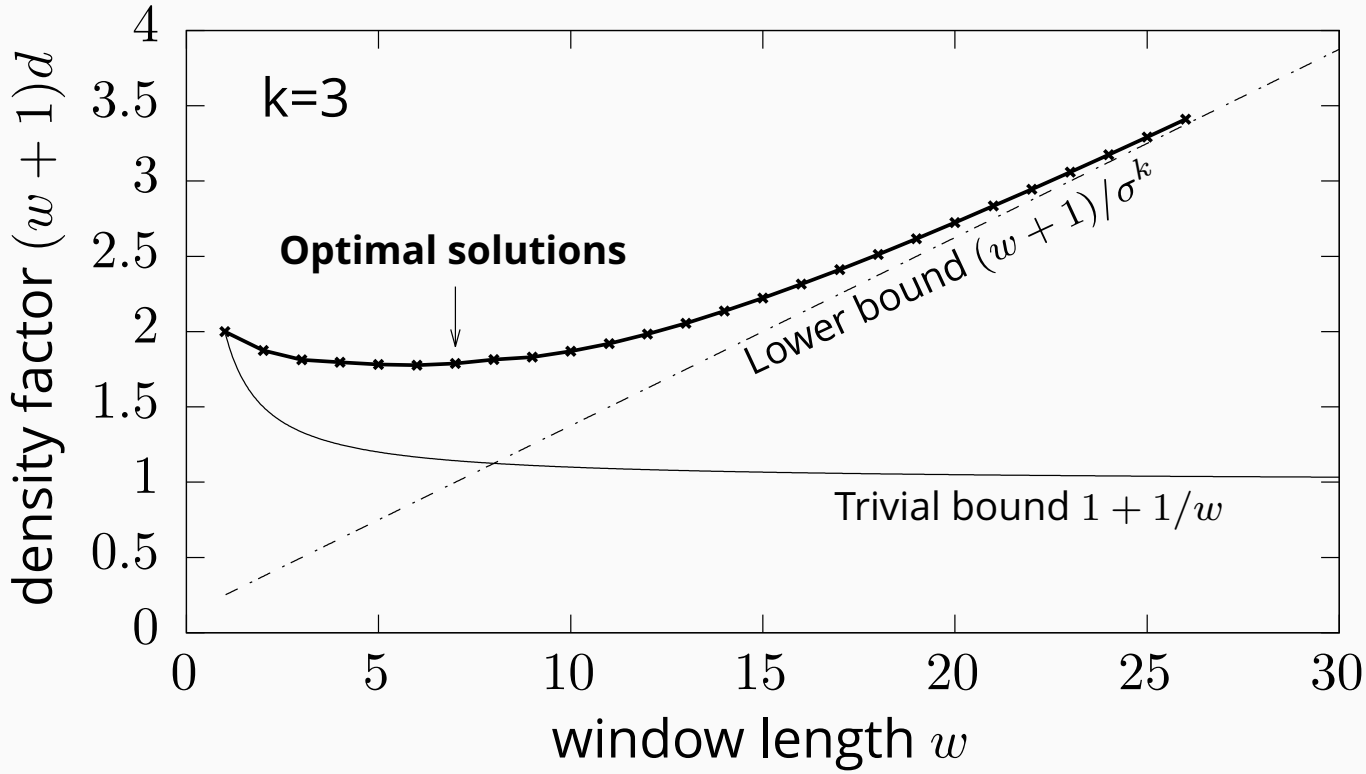
Asymptotic behavior in w



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

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

Asymptotic behavior in w



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Asymptotic behavior in k

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

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

Asymptotic behavior in k

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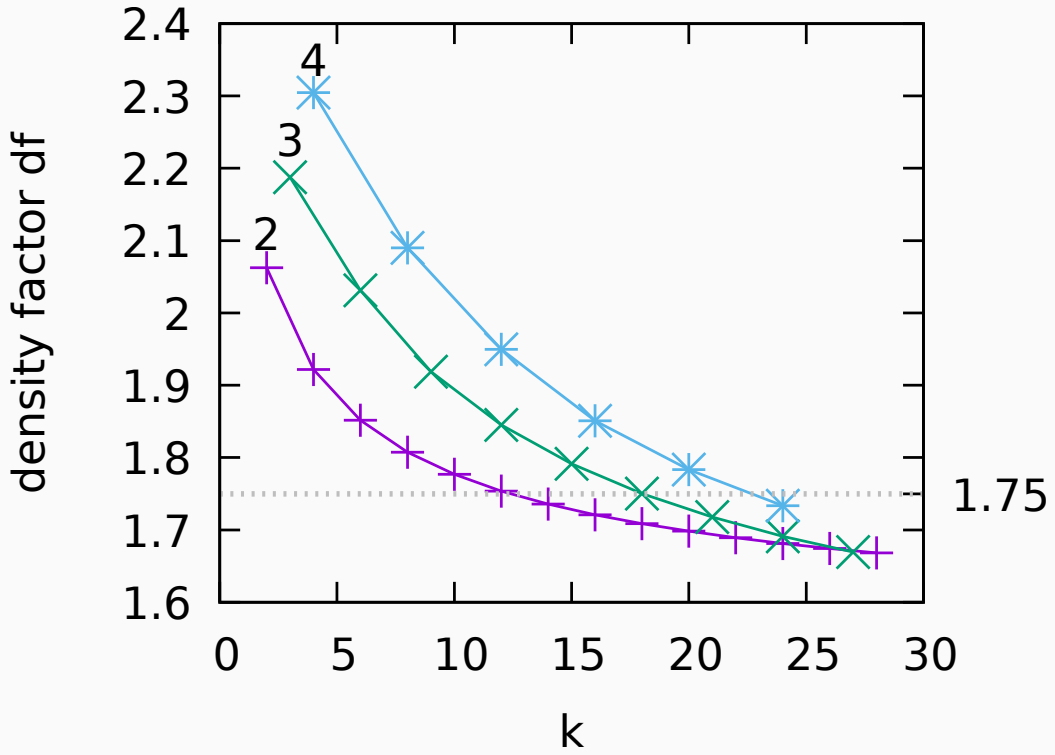

Density factor of minimizers

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 practical than large w
- 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 $f(\omega)$.

Generalizing minimizers: local and forward schemes

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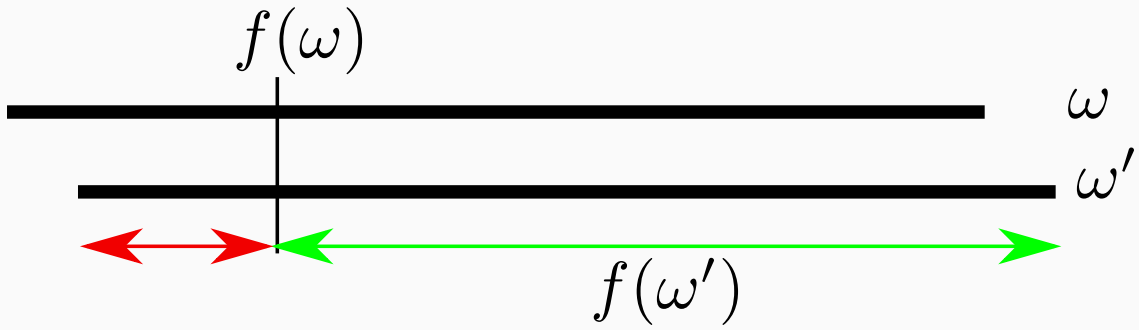
Forward scheme
Local scheme such that $f(\omega') \geq f(\omega) - 1$ if suffix of ω' equals prefix of ω



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

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Forward			
Local			

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Local	$1 + \frac{1}{w}$	$O(\sqrt{w})$	$1 + \frac{1}{w}$

Conclusion: the quest for optimal constant density factor

- Minimizers schemes:
  - **can't** achieve **constant** density factor
  - **can't** be optimal for large *w*
- Forward schemes
  - **may** achieve **constant** density factor
  - **can't** be optimal for large *w*
- Local schemes
  - **may** achieve **constant** density factor
  - **may** be optimal for large *w*

- Design of **optimal** orders or functions f still open

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