Graines et YASS

Quelques slides sur les graines espacées ...

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My Talk

in a few words ...

Motivation : pairwise sequence alignment.

Seeds : filtration to speed up the alignment.

Filtration :

- the *lossy* case
- the *lossless* case

Sequence Alignment

on a very small DNA example

```
TTTTGAACTGGGACGAAAGTGCATCAGTGCAAATGCGCAAGAAAAA
CGCCGAACGCTTCAGATCAGCGCAAATGCTCAAGAGGTCTCGTCGC
TGAGGCACTACGGCCAGCCGAGCCAGTCAT
```

Sequence Alignment

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TTTTGAACTGGGACGAAAGTGCATCAGTGCAAATGCGCAAGAAAAA
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ATCAGTGCAAATGCGCAAGA

ATCAGCGCAAATGCTCAAGA

Sequence Alignment

on a very small DNA example

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TTTTGAACTGGGACGAAAGTGCATCAGTGCAAATGCGCAAGAAAAA
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TGAGGCACTACGGCCAGCCGAGCCAGTCAT
```

```
ATCAGTGCAAATGCGCAAGA
|||||:|||||||||.|||||
ATCAGCGCAAATGCTCAAGA
```

Sequence Alignment

methods used to solve this problem ...

Algorithm: Smith-Waterman algorithm (in $\mathcal{O}(n^2)$).

Heuristic: Filtration principle

(1) some *clues* are detected using **seeds**.
(2) these clues are extended by local dynamic programming.

Contiguous Seeds

(*Fasta 85, Blast 91, Gapped-Blast 97, ...*)

Principle: A contiguous seed π detects one alignment motif of size k.

Notation: π is represented by a (fixed length) word over alphabet $\{\#\}$.
(# only accepts the | symbol from an alignment).

Example

seed pattern : $\pi =$ ######

```
ATCAGTGCAAATGCGCAAGA
|||||:|||||||||.|||||
ATCAGCGCAAATGCTCAAGA
```

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Spaced Seeds

(*PatternHunter 02, Burkhardt et al 01, BLASTz 03, YASS 04*)

Definition

A spaced seed π is defined as a binary word over the alphabet $\{\#, -\}$:

- `#` : accepts only match symbol | ,
- `-` : accepts all alignment symbols (*joker*) .

s : *span* (length), w : *weight* (number of `#`).

Example

seed pattern : $\pi =$ `###-#-##`

```
ATCAGTGCGAATGCGCAAGA
|||||:||:||||||.|||||
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|||||:||:||||||||||
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seed pattern : $\pi =$ `###-#-##`

```
###-#-##
ATCAGTGCGAATGCGCAAGA
|||||:||:||||||.|||||
ATCAGCGCAAATGCTCAAGA
```

Example

Example

$$\pi_c = \texttt{######}$$

$$\pi_s = \texttt{###--\#-\#\#}$$

Example

$$\pi_c = \texttt{######}$$

$$\pi_s = \texttt{###--#-##}$$

$$\alpha = \begin{array}{l} \texttt{ATCAGTGCAAATGCTCAAGA} \\ \texttt{||||||||||||||||||||} \\ \texttt{ATCAGTGCAAATGCTCAAGA} \end{array}$$

Example

$$\pi_c = \texttt{######}$$

$$\pi_s = \texttt{###--\#-\#\#}$$

$$\alpha = \begin{array}{l} \texttt{ATCAGTGCAAATGCTCAAGA} \\ \texttt{||||||||||||||||||||} \\ \texttt{ATCAGTGCAAATGCTCAAGA} \end{array}$$

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$$\alpha = \begin{array}{l} \texttt{ATCAGTGCAAATGCGCAAGA} \\ \texttt{|||||~|||||||~|||||} \\ \texttt{ATCAGCGCAAATGCTCAAGA} \end{array}$$

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$$\pi_c = \texttt{######}$$

$$\pi_s = \texttt{###--\#-\#\#}$$

$$\alpha = \begin{array}{l} \texttt{ATCAGTGCGAATGCGCAAGA} \\ \texttt{||||| || ||||| |||||} \\ \texttt{ATCAGCGCAAATGCTCAAGA} \end{array}$$

Example

Example

```
ATCAGTGCAAATGCTCAAGA
||||||||||||||||||||
ATCAGTGCAAATGCTCAAGA
```

```
ATCAGTGCAAATGCTCAAGA
||||||||||||||||||||
ATCAGTGCAAATGCTCAAGA
```

Example

```
ATCAGTGCAAATGCTCAAGA
||||||||||||||||||||
ATCAGTGCAAATGCTCAAGA
######
 ######
  ######
   ######
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          ######
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            ######
             ######
              ######
               ######
```

```
ATCAGTGCAAATGCTCAAGA
||||||||||||||||||||
ATCAGTGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
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        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
             ###--#-##
```

Example

```
ATCAGTGCAAATGCTCAAGA
|||||||||||||||||||
ATCAGTGCAAATGCTCAAGA
######
 ######
  ######
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          ######
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            ######
             ######
              ######
               ######
```

```
ATCAGTGCAAATGCTCAAGA
|||||||||||||||||||
ATCAGTGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
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        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
             ###--#-##
```

Example

```
ATCAGTGCAAATGCTCAAGA
||||| ||||||||||||||
ATCAGCGCAAATGCTCAAGA
######
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   ######
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            ######
             ######
              ######
               ######
```

```
ATCAGTGCAAATGCTCAAGA
||||| ||||||||||||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
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        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
             ###--#-##
```

Example

```
ATCAGTGCAAATGCTCAAGA
||||| ||||||||||||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
   ######
    ######
     ######
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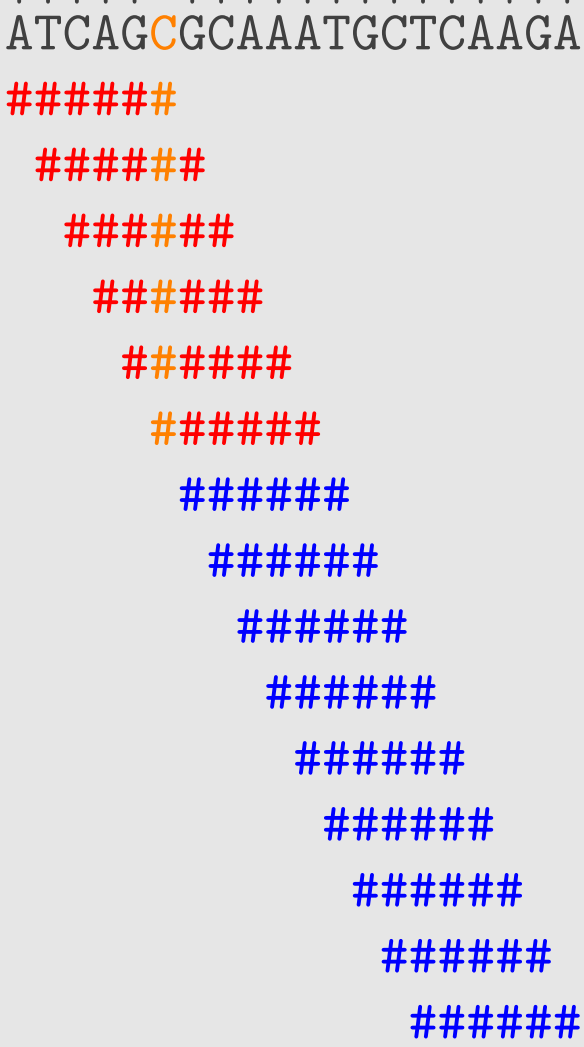
       ######
        ######
         ######
          ######
           ######
            ######
             ######
              ######
```

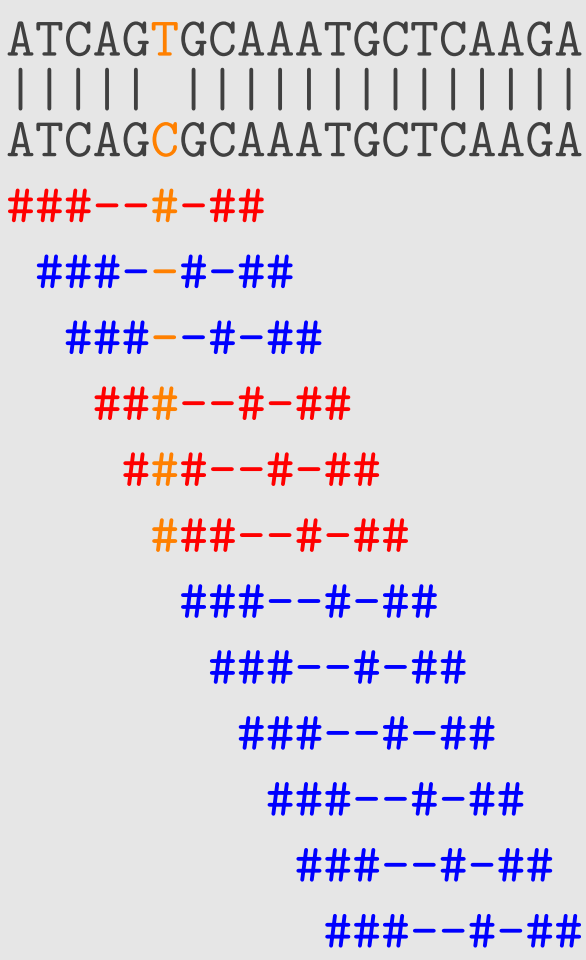
```
ATCAGTGCAAATGCTCAAGA
||||| ||||||||||||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
       ###--#-##
        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
```

Example

```
ATCAGTGCAAATGCTCAAGA
||||| ||||||||||||||
ATCAGCGCAAATGCTCAAGA
```



```
ATCAGTGCAAATGCTCAAGA
||||| ||||||||||||||
ATCAGCGCAAATGCTCAAGA
```



Example

```
ATCAGTGCAAATGCTCAAGA
|||||  |||||||||||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
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    ######
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        ######
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            ######
             ######
              ######
```

```
ATCAGTGCAAATGCTCAAGA
|||||  |||||||||||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
       ###--#-##
        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
```

Example

```
ATCAGTGCAAATGCGCAAGA
||||| |||||||| |||||
ATCAGCGCAAATGCTCAAGA
######
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            ######
             ######
              ######
```

```
ATCAGTGCAAATGCGCAAGA
||||| |||||||| |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###-#-##
  ###-#-##
   ###-#-##
    ###-#-##
     ###-#-##
      ###-#-##
       ###-#-##
        ###-#-##
         ###-#-##
          ###-#-##
           ###-#-##
            ###-#-##
```

Example

```
ATCAGTGCAAATGCGCAAGA
|||||  ||||||||  |||||
ATCAGCGCAAATGCTCAAGA
######
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  ######
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          #####
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            ######
             ######
              ######
               ######
```

```
ATCAGTGCAAATGCGCAAGA
|||||  ||||||||  |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###-#-##
  ###-#-##
   ##--#-##
    ##--#-##
     ##--#-##
      ##--#-##
       ##--#-##
        ##--#-##
         ##--#-##
          ##-#-##
           ##--#-##
            ##-#-##
             ##--#-##
```

Example

```
ATCAGTGCAAATGCGCAAGA
||||| |||||||| |||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
   ######
    ######
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        ######
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            ######
             ######
              ######
               ######
```

```
ATCAGTGCAAATGCGCAAGA
||||| |||||||| |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###-#-##
  ###-#-##
   ###--#-##
    ###--#-##
     ##--#-##
      ###--#-##
       ###--#-##
        ###--#-##
         ###--#-##
          ###-#-##
           ###-#-##
```

Example

```
ATCAGTGCAAATGCGCAAGA
|||||  |||||||  |||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
   ######
    ######
     ######
      ######
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        ######
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          ######
           ######
            ######
             ######
              ######
               ######
```

```
ATCAGTGCAAATGCGCAAGA
|||||  |||||||  |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###-#-##
  ###-#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
       ###--#-##
        ###--#-##
         ###--#-##
          ###-#-##
           ###-#-##
```

Example

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
   ######
    ######
     ######
      ######
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         ######
          ######
           ######
            ######
             ######
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               ######
```

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###-#-##
  ###-#-##
   ###--#-##
    ##--#-##
     #--#-##
      --#-##
       #-##
        -##
         ##
          #
           -
            #
             -
              #
               -
```

Example

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
   ######
    ######
     ######
      ##### #
       #####
        #####
         #####
          #####
           #####
            #####
             #####
              #####
               #####
                #####
                 #####
```

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
       ###--#-##
        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
             ###--#-##
              ###--#-##
               ###--#-##
                ###--#-##
```

Example

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
######
 ######
  ######
   ######
    ######
     ######
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        ######
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          ######
           ######
            ######
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              ######
               ######
```

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
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         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
             ###--#-##
              ###--#-##
               ###--#-##
```

Example

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
######
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  ######
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             ######
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```

```
ATCAGTGCGAATGCGCAAGA
||||| || ||||| |||||
ATCAGCGCAAATGCTCAAGA
###--#-##
 ###--#-##
  ###--#-##
   ###--#-##
    ###--#-##
     ###--#-##
      ###--#-##
       ###--#-##
        ###--#-##
         ###--#-##
          ###--#-##
           ###--#-##
            ###--#-##
             ###--#-##
              ###--#-##
               ###--#-##
```

Example

`######` `###--#-##`

Example

```
######
 ###### (5)
```

```
###--#-##
 ###--#-## (3)
```

Example

```
######
   ###### (5,4)
```

```
###--#-##
   ###--#-## (3,2)
```

Example

```
######
    ###### (5,4,3)
```

```
###--#-##
    ###--#-## (3,2,2)
```

Example

######

(5,4,3,2)

###--#-##

###--#-## (3,2,2,1)

Example

```
######
```

```
###--#-##
```

```
######  (5,4,3,2,1)
```

```
###--#-##  (3,2,2,1,2)
```

Example

(5,4,3,2,1)

###--#-## ###--#-## (3,2,2,1,2,2)

Example

######
(5,4,3,2,1)

###--#-##
###--#-## (3,2,2,1,2,2,2)

Example

(5,4,3,2,1)

###--#-## ###--#-## (3,2,2,1,2,2,2,1)

Example

######	###--#-##
(5,4,3,2,1)	(3,2,2,1,2,2,2,1)

Spaced Seeds

Research threads

- Burkhardt, Karkkainen, CPM 2001: *spaced seeds for (lossless) approximate pattern matching*
- Ma, Tromp, Li 2002 (*PatternHunter*): *spaced seeds for (lossy) similarity search*
- Califano, Rigoutsos 1993 (*FLASH*), Buhler 2001 (*LSH*)

Spaced Seeds

Research threads (cont.)

- **Estimating the sensitivity of a seed:** Keich et al 2002, Buhler et al 2003, Brejova et al 2003, Choi et al 2004, Kucherov et al 2004, Mak&Benson 2007
- **Extended seed models:** BLASTZ 2003, Brejova et al 2003, Chen&Sung 2003, Noe&Kucherov 2004, Sun&Buhler 2006, Mak et al 2006, Zhou&Florea 2007
- **Statistical foundations:** Choi&Zhang 2004, Zhang 2005, Kong 2007, Ma&Yao 2008
- **Efficient implementation of spaced seeds:** Csuros 2004, Csuros&Ma 2004
- **Multiple spaced seeds:** Li et al 2004 (PatternHunter II), Sun&Buhler 2004, Kong 2007
- **Designing (multiple) seeds:** Xu et al 2004, Brown 2004, Ilie&Ilie 2007
- **Lossless (multiple) seeds:** Burkhardt&Karkkainen 2001, Kucherov et al 2004, Farach et al 2004, Fontaine et al 2004, Nicolas&Rivals 2005
- **Surveys:** Brown&Li&Ma 2005, Brown 2008

Spaced Seeds

How to choose the best one

The main question in (most of) these papers: how to choose the best *seed* ...

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Sensitivity : defined as the *probability* to have at least one *hit* (seed occurrence) inside an alignment.

Spaced Seeds

How to choose the best one

The main question in (most of) these papers: how to choose the best *seed* ...

Sensitivity : defined as the *probability* to have at least one *hit* (seed occurrence) inside an alignment.

Best Seed : defined as the one that maximize the sensitivity (among the seeds of a given class).

Mutations on DNA

Transitions and Transversions ...

Two kinds of mismatches : *transitions* and *transversions*

Definition

Transistions are substitutions between **purins** ($A \leftrightarrow G$) or between **pyrimidins** ($T \leftrightarrow C$). Transitions are usually overrepresented mutations ...

Example

```
ATCAGTGCGAATGCGCAAGA
|||||:||:||||||.|||||
ATCAGCGCAAATGCTCAAGA
```

- : is a transition symbol.
- . is a transversion symbol.

Transition Constrained Seeds

(*YASS 04, Zhou&Florea 07*)

Definition

A transition constrained seed π is defined as a ternary word over the alphabet $\{\texttt{\#}, \texttt{@}, \texttt{-}\}$ with :

- `#` : accepts only match symbol `|`,
- `-` : accepts all alignment symbols (*joker*),
- `@` : accepts match symbol `|` or transition mismatch symbol `:`,

Example

seed pattern : $\pi =$ `##@#-@##`

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```

Seed examples

- *spaced* and *transition constrained* seeds.
- *multiple* seeds.

Example

parameters :

Alignment length : *64*

Alignment model : *Bernoulli (match:0.7,transition:0.15,transversion:0.15)*

results :

- `##########` 0.412080
- `##-##---##-#-###` 0.595740
- `#@#-##--##-@-@#@#` 0.603236
- `####---#--#---#--###,##-#-##--#-#-###` 0.748452
- `#@##@----@-@#-@@#-##,##@-#@#-#--####` 0.756022

Problem :

seed sensitivity IS difficult, seed design MUST BE difficult

- *Computing sensitivity is NP-Hard* (Li&Ma 04, Nicolas&Rivals 05).
- *Golomb ruler* and *seeds* (Nicolas&Rivals 05, Ma&Yao 08).

(m, k)-similarities

Definition

Given two integers m, k, find **all** the similarities of length $\geq m$ with $\leq k$ mismatches.

Example

if $m = 18, k = 3$, then

```
1110111101111101111
```

and

```
1111101011110111111
```

are similarities that must be detected by the filter.

(m, k)-similarities and lossless seeds

(*Burkhardt&Karkkainen 01*)

one can use

- a contiguous seed filter $\pi =$ ####,
- a spaced seed filter $\pi =$ ##-###.

Example

1111101011110111111

(m, k)-similarities and lossless seeds

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    ####
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Example

```
          ##-###
1111101011110111111
            ##-###
```

(m, k)-similarities and lossless multiple seeds

(*Kucherov et al 04, Farach et al 04*)

using more than one *single* seed improves the filter ...

Example

$$\pi \quad = \quad \{ \quad \texttt{\#\#-\#\#\#}$$

(m, k)-similarities and lossless multiple seeds

(*Kucherov et al 04, Farach et al 04*)

using more than one *single* seed improves the filter ...

Example

$$\pi = \{ \texttt{\#\#-\#\#\#} \}$$

$$\pi_2 = \left\{ \begin{array}{l} \texttt{\#\#-\#-\#\#\#\#} \\ \texttt{\#\#\#---\#--\#\#-\#} \end{array} \right.$$

(m, k)-similarities and lossless multiple seeds

(*Kucherov et al 04, Farach et al 04*)

using more than one *single* seed improves the filter ...

Example

$$\pi = \{ \texttt{\#\#-\#\#\#} \}$$

$$\pi_2 = \left\{ \begin{array}{l} \texttt{\#\#-\#-\#\#\#\#} \\ \texttt{\#\#\#---\#--\#\#-\#} \end{array} \right.$$

$$\pi_6 = \left\{ \begin{array}{l} \texttt{\#\#-\#\#-\#\#\#\#\#}, \\ \texttt{\#\#\#-\#\#\#\#--\#\#}, \\ \texttt{\#\#\#-\#\#---\#-\#\#\#}, \\ \texttt{\#\#----\#\#\#\#-\#\#\#}, \\ \texttt{\#\#\#---\#-\#-\#\#-\#\#}, \\ \texttt{\#\#\#-\#-\#-\#-----\#\#\#} \end{array} \right.$$

(m, k)-similarities and lossless multiple seeds

Example

1111111011101110 11

(m, k)-similarities and lossless multiple seeds

Example

1111111011101110 11

$$\pi_2 = \begin{cases} \texttt{\#\#-\#-\#\#\#\#} \\ \texttt{\#\#\#---\#--\#\#-\#} \end{cases}$$

(m, k)-similarities and lossless multiple seeds

Example

```
1111111011101110 11
###---#--##-#
     ###---#--##-#
```

$$\pi_2 = \left\{ \begin{array}{l} \texttt{\#\#-\#-\#\#\#\#} \\ \texttt{\#\#\#---\#--\#\#-\#} \end{array} \right.$$

(m, k)-similarities and lossless multiple seeds

Example

1111111011101110 11

$$\pi_6 = \begin{cases} \texttt{\#\#-\#\#-\#\#\#\#\#}, \\ \texttt{\#\#\#-\#\#\#\#--\#\#}, \\ \texttt{\#\#\#-\#\#---\#-\#\#\#}, \\ \texttt{\#\#----\#\#\#\#-\#\#\#}, \\ \texttt{\#\#\#---\#-\#-\#\#-\#\#}, \\ \texttt{\#\#\#-\#-\#-\#-----\#\#\#} \end{cases}$$

(m, k)-similarities and lossless multiple seeds

Example

```
1111111011101110 11
 ###-##---#-###
```

$$\pi_6 = \begin{cases} \texttt{\#\#-\#\#-\#\#\#\#\#}, \\ \texttt{\#\#\#-\#\#\#\#--\#\#}, \\ \texttt{\#\#\#-\#\#---\#-\#\#\#}, \\ \texttt{\#\#----\#\#\#\#-\#\#\#}, \\ \texttt{\#\#\#---\#-\#-\#\#-\#\#}, \\ \texttt{\#\#\#-\#-\#-\#-----\#\#\#} \end{cases}$$

Potential applications

- *oligonucleotide* selection
- *loop* detection ?
- ...