# Lecture 14: Mapping Reads to a Reference – Burrows Wheeler Transform and FM Index

Spring 2017
March 30, 2017

# Outline

- Problem Definition
- Different Solutions
- Burrows-Wheeler Transformation (BWT)
- Ferragina-Manzini (FM) Index
- Search Using FM Index
- Alignment Using FM Index

# Mapping Reads

*Problem:* We are given a read, *R,* and a reference sequence, *S*. Find the best or all occurrences of *R* in *S*.

Example:

R = AAACGAGTTA

S = TTAATGC*AAACGAGTTA*CCCAATATATAT*AAACCAGTTA*TT

Considering no error: one occurrence.

Considering up to 1 substitution error: two occurrences.

Considering up to 10 substitution errors: many meaningless occurrences!

# Mapping Reads (continued)

*Variations:*

- Sequencing error
  - No error: *R* is a perfect subsequence of *S.*
  - Only substitution error: *R* is a subsequence of *S* up to a few substitutions.
  - Indel and substitution error: *R* is a subsequence of *S* up to a few short indels and substitutions.
- Junctions (for instance in alternative splicing)
  - Fixed order/orientation

    $R = R_1R_2...R_n$ and $R_i$ map to different non-overlapping loci in *S*, but to the same strand and preserving the order.
  - Arbitrary order/orientation

    $R = R_1R_2...R_n$ and $R_i$ map to different non-overlapping loci in *S.*

# Different Solutions

- Alignment, such as Smith-Waterman algorithm:
  - Pro: adequate for all variations.
  - Con: computationally expensive, not suitable for next-generation sequencing.
- Seed-and-Extend
  - Pro: can handle errors and junctions more efficiently.
  - Con: slow when no (few) error(s).
- Ferragina Manzini (FM) Index Search
  - Pro: computationally efficient, when no error.
  - Con: exponential in the maximum number of errors.

# Burrows-Wheeler Transformation
## Example: mississippi

1. Append to the input string a special char, $, smaller than all alphabet.

mississippi$

# Burrows-Wheeler Transformation (cnt'd)

## Example: mississippi

2. Generate all rotations.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| m | i | s | s | i | s | s | i | p | p | i | $ |
| i | s | s | i | s | s | i | p | p | i | $ | m |
| s | s | i | s | s | i | p | p | i | $ | m | i |
| s | i | s | s | i | p | p | i | $ | m | i | s |
| i | s | s | i | p | p | i | $ | m | i | s | s |
| s | s | i | p | p | i | $ | m | i | s | s | i |
| s | i | p | p | i | $ | m | i | s | s | i | s |
| i | p | p | i | $ | m | i | s | s | i | s | s |
| p | p | i | $ | m | i | s | s | i | s | s | i |
| p | i | $ | m | i | s | s | i | s | s | i | p |
| i | $ | m | i | s | s | i | s | s | i | p | p |
| $ | m | i | s | s | i | s | s | i | p | p | i |

# Burrows-Wheeler Transformation (cnt'd)

## Example: mississippi

3. Sort rotations according to the alphabetica lorder.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $ | m | i | s | s | i | s | s | i | p | p | i |
| i | $ | m | i | s | s | i | s | s | i | p | p |
| i | p | p | i | $ | m | i | s | s | i | s | s |
| i | s | s | i | p | p | i | $ | m | i | s | s |
| i | s | s | i | s | s | i | p | p | i | $ | m |
| m | i | s | s | i | s | s | i | p | p | i | $ |
| p | i | $ | m | i | s | s | i | s | s | i | p |
| p | p | i | $ | m | i | s | s | i | s | s | i |
| s | i | p | p | i | $ | m | i | s | s | i | s |
| s | i | s | s | i | p | p | i | $ | m | i | s |
| s | s | i | p | p | i | $ | m | i | s | s | i |
| s | s | i | s | s | i | p | p | i | $ | m | i |

# Burrows-Wheeler Transformation (cnt'd)

## Example: mississippi

4. Output the last column.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $ | m | i | s | s | i | s | s | i | p | p | i |
| i | $ | m | i | s | s | i | s | s | i | p | p |
| i | p | p | i | $ | m | i | s | s | i | s | s |
| i | s | s | i | p | p | i | $ | m | i | s | s |
| i | s | s | i | s | s | i | p | p | i | $ | m |
| m | i | s | s | i | s | s | i | p | p | i | $ |
| p | i | $ | m | i | s | s | i | s | s | i | p |
| p | p | i | $ | m | i | s | s | i | s | s | i |
| s | i | p | p | i | $ | m | i | s | s | i | s |
| s | i | s | s | i | p | p | i | $ | m | i | s |
| s | s | i | p | p | i | $ | m | i | s | s | i |
| s | s | i | s | s | i | p | p | i | $ | m | i |

# Burrows-Wheeler Transformation (cnt'd)

## Example: mississippi

ipssm$pissii

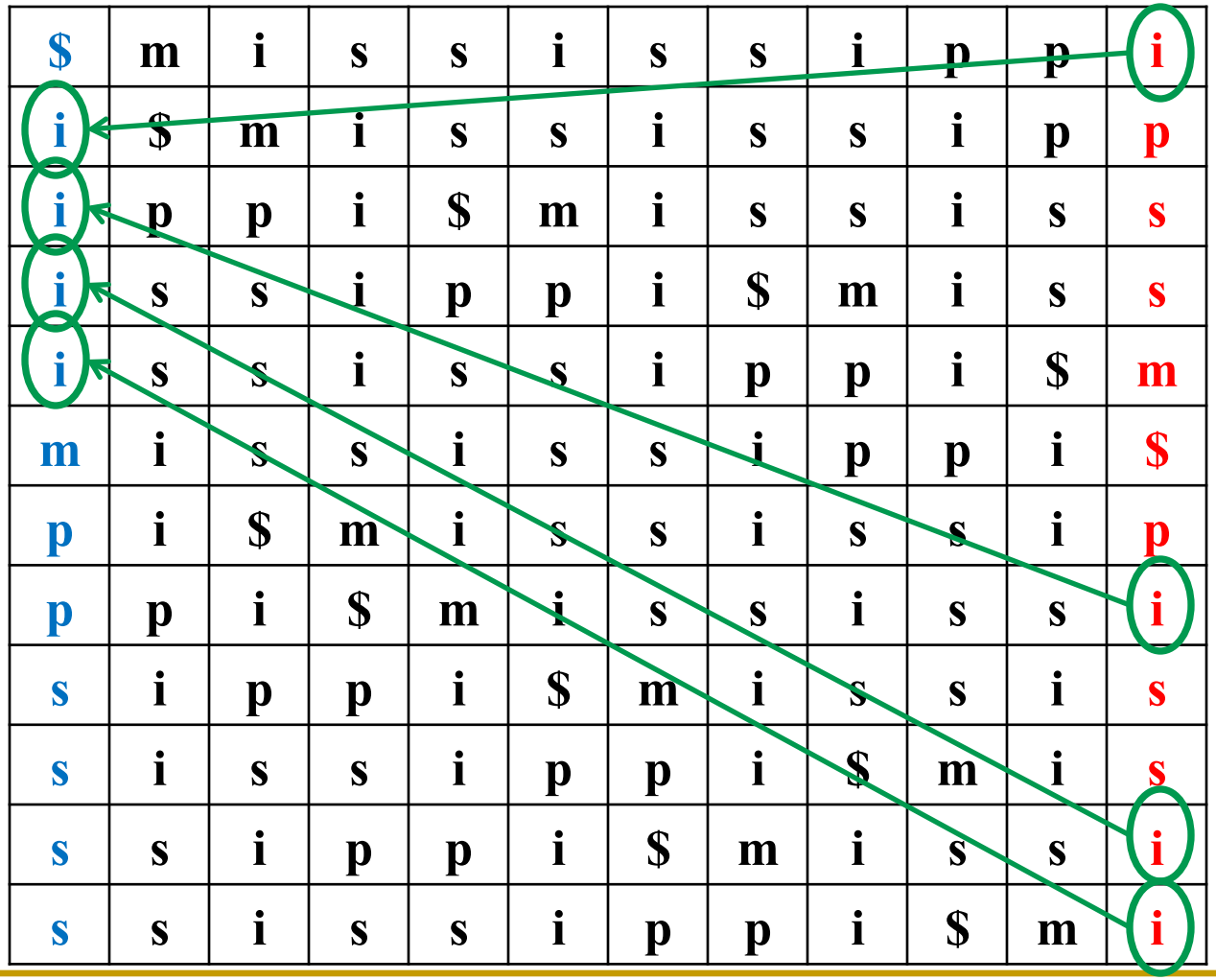
# Ferragina-Manzini Index
# Example: mississippi

First column: F

Last column: L

Let's make an L to F map.

Observation: The $n^{th}$ i in L is the $n^{th}$ i in F.



# Ferragina-Manzini Index (cnt'd)

## L to F map

Store/compute a two dimensional Occ(*j*,'c') table of the number of occurrences of char 'c' up to position *j* (inclusive).

and a one dimensional Cnt('c') table.

| | $ | i | m | p | s |
|---|---|---|---|---|---|
| i | 0 | 1 | 0 | 0 | 0 |
| p | 0 | 1 | 0 | 1 | 0 |
| s | 0 | 1 | 0 | 1 | 1 |
| s | 0 | 1 | 0 | 1 | 2 |
| m | 0 | 1 | 1 | 1 | 2 |
| $ | 1 | 1 | 1 | 1 | 2 |
| p | 1 | 1 | 1 | 2 | 2 |
| i | 1 | 2 | 1 | 2 | 2 |
| s | 1 | 2 | 1 | 2 | 3 |
| s | 1 | 2 | 1 | 2 | 4 |
| i | 1 | 3 | 1 | 2 | 4 |
| i | 1 | 4 | 1 | 2 | 4 |

Occ(*j*,'c')

Cnt('c')

| $ | i | m | p | s |
|---|---|---|---|---|
| 1 | 4 | 1 | 2 | 4 |

# Ferragina-Manzini Index
# L to F map

[Cnt('$') +

Cnt('i') +

Cnt('m') +

Cnt('p') = 8]

+

[Occ(9, 's')= 3]

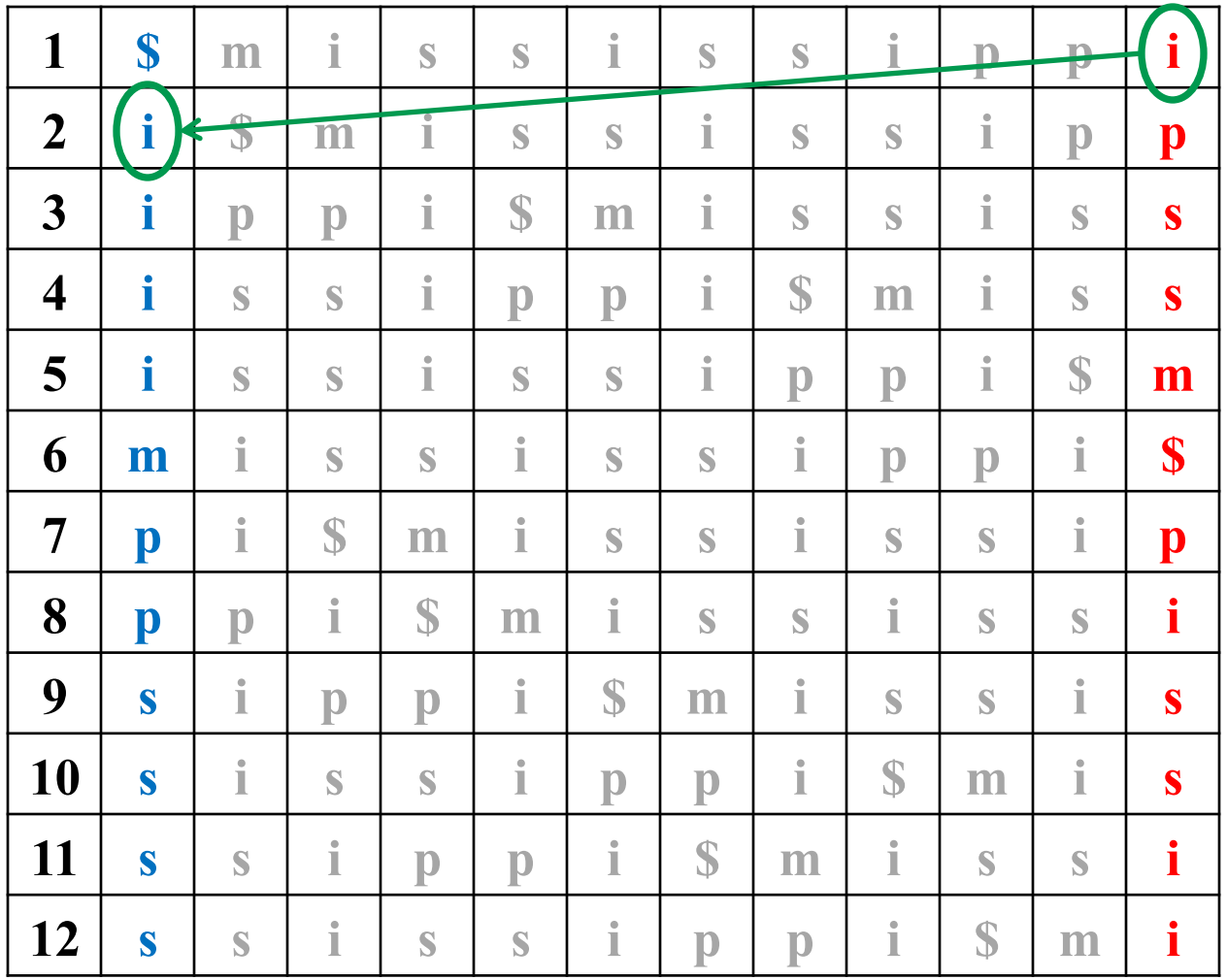
= 11 before 's' →

's' section

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $ | m | i | s | s | i | s | s | i | p | p | i |
| 2 | i | $ | m | i | s | s | i | s | s | i | p | p |
| 3 | i | p | p | i | $ | m | i | s | s | i | s | s |
| 4 | i | s | s | i | p | p | i | $ | m | i | s | s |
| 5 | i | s | s | i | s | s | i | p | p | i | $ | m |
| 6 | m | i | s | s | i | s | s | i | p | p | i | $ |
| 7 | p | i | $ | m | i | s | s | i | s | s | i | p |
| 8 | p | p | i | $ | m | i | s | s | i | s | s | i |
| 9 | s | i | p | p | i | $ | m | i | s | s | i | s |
| 10 | s | i | s | s | i | p | p | i | $ | m | i | s |
| 11 | s | s | i | p | p | i | $ | m | i | s | s | i |
| 12 | s | s | i | s | s | i | p | p | i | $ | m | i |

# Ferragina-Manzini Index
## Reverse traversal

(1) i
(2) p
(7) p
(8) i
(3) s
(9) s
(11) i
(4) s
(10) s
(12) i
(5) m
(6) $



| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $ | m | i | s | s | i | s | s | i | p | p | i |
| 2 | i | $ | m | i | s | s | i | s | s | i | p | p |
| 3 | i | p | p | i | $ | m | i | s | s | i | s | s |
| 4 | i | s | s | i | p | p | i | $ | m | i | s | s |
| 5 | i | s | s | i | s | s | i | p | p | i | $ | m |
| 6 | m | i | s | s | i | s | s | i | p | p | i | $ |
| 7 | p | i | $ | m | i | s | s | i | s | s | i | p |
| 8 | p | p | i | $ | m | i | s | s | i | s | s | i |
| 9 | s | i | p | p | i | $ | m | i | s | s | i | s |
| 10 | s | i | s | s | i | p | p | i | $ | m | i | s |
| 11 | s | s | i | p | p | i | $ | m | i | s | s | i |
| 12 | s | s | i | s | s | i | p | p | i | $ | m | i |

# Ferragina-Manzini Index

## Search *issi*

(1)-(12)

i (2)-(5)

si (9)-(10)

ssi (11)-(12)

issi (4)-(5)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **$** | m | i | s | s | i | s | s | i | p | p | **i** |
| **2** | **i** | $ | m | i | s | s | i | s | s | i | p | **p** |
| **3** | **i** | p | p | i | $ | m | i | s | s | i | s | **s** |
| **4** | **i** | s | s | i | p | p | i | $ | m | i | s | **s** |
| **5** | **i** | s | s | i | s | s | i | p | p | i | $ | **m** |
| **6** | **m** | i | s | s | i | s | s | i | p | p | i | **$** |
| **7** | **p** | i | $ | m | i | s | s | i | s | s | i | **p** |
| **8** | **p** | p | i | $ | m | i | s | s | i | s | s | **i** |
| **9** | **s** | i | p | p | i | $ | m | i | s | s | i | **s** |
| **10** | **s** | i | s | s | i | p | p | i | $ | m | i | **s** |
| **11** | **s** | s | i | p | p | i | $ | m | i | s | s | **i** |
| **12** | **s** | s | i | s | s | i | p | p | i | $ | m | **i** |

# Ferragina-Manzini Index

## Search *pi*

(1)-(12)

i

pi

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **$** | m | i | s | s | i | s | s | i | p | p | **i** |
| **2** | **i** | $ | m | i | s | s | i | s | s | i | p | **p** |
| **3** | **i** | p | p | i | $ | m | i | s | s | i | s | **s** |
| **4** | **i** | s | s | i | p | p | i | $ | m | i | s | **s** |
| **5** | **i** | s | s | i | s | s | i | p | p | i | $ | **m** |
| **6** | **m** | i | s | s | i | s | s | i | p | p | i | **$** |
| **7** | **p** | i | $ | m | i | s | s | i | s | s | i | **p** |
| **8** | **p** | p | i | $ | m | i | s | s | i | s | s | **i** |
| **9** | **s** | i | p | p | i | $ | m | i | s | s | i | **s** |
| **10** | **s** | i | s | s | i | p | p | i | $ | m | i | **s** |
| **11** | **s** | s | i | p | p | i | $ | m | i | s | s | **i** |
| **12** | **s** | s | i | s | s | i | p | p | i | $ | m | **i** |