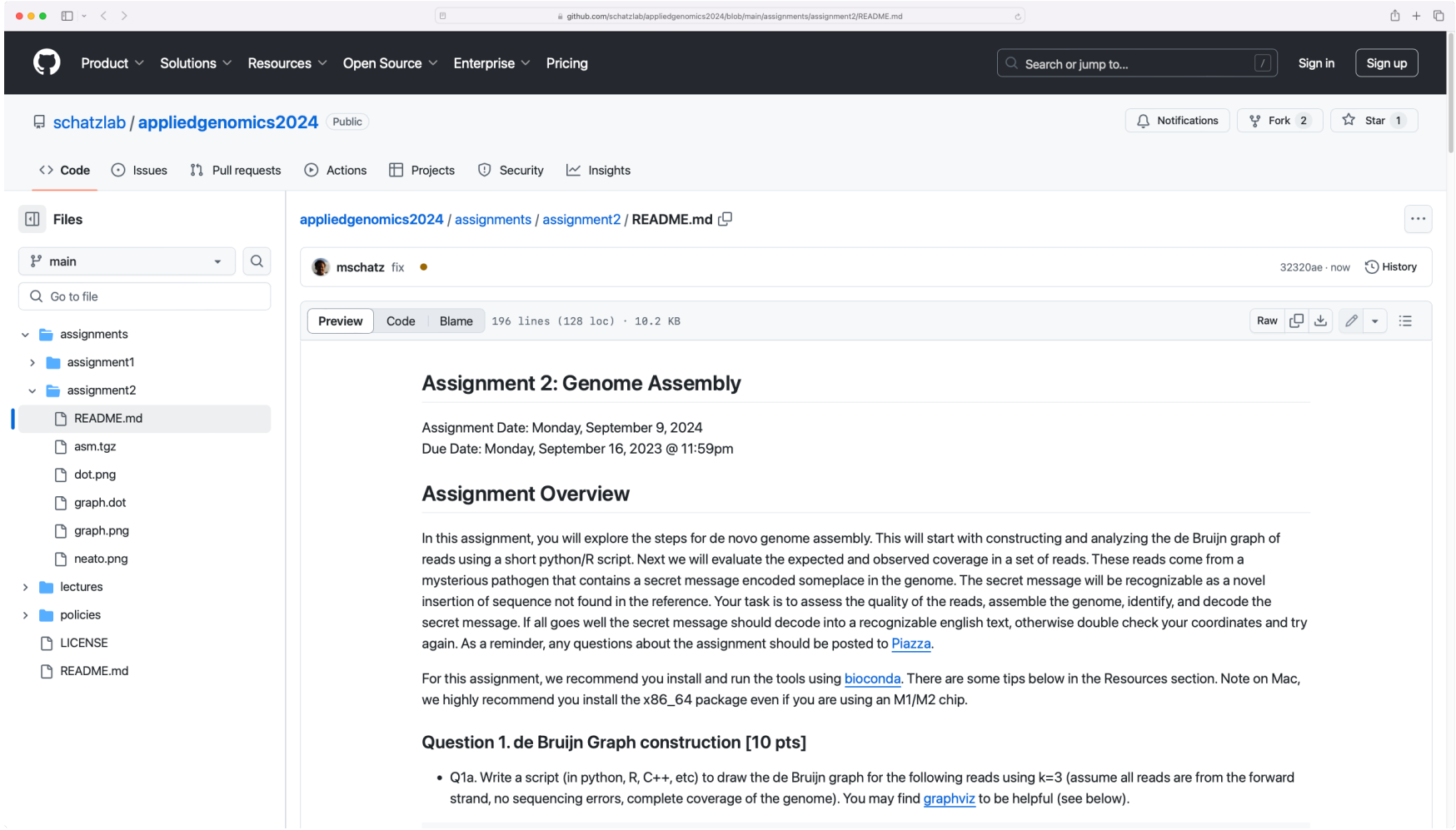
Dynamic Programming

Michael Schatz

Sept 18, 2024

Lecture 7: Applied Comparative Genomics

Assignment 2: Genome Assembly
Due Monday Sept 16 by 11:59pm



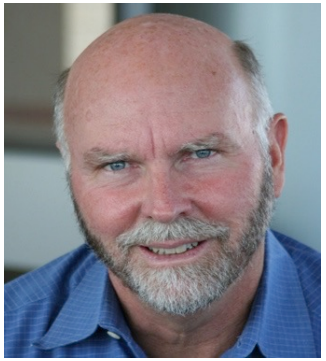
https://github.com/schatzlab/appliedgenomics2024/tree/main/assignments/assignment2

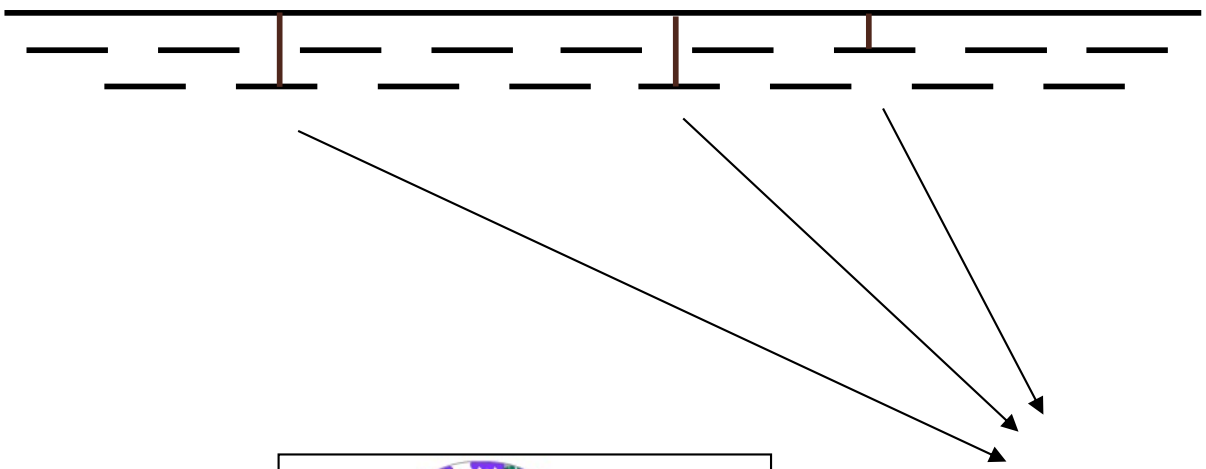
Check Piazza for questions!

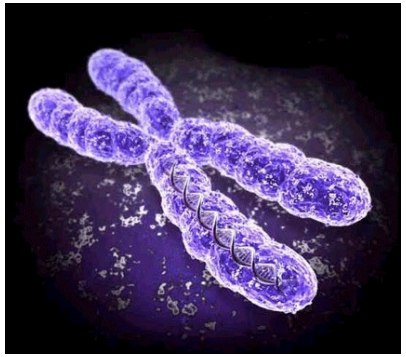
Read Mapping

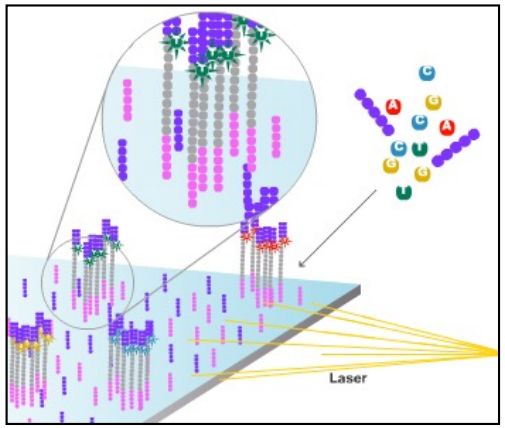
Personal Genomics

How does your genome compare to the reference?









Heart Disease

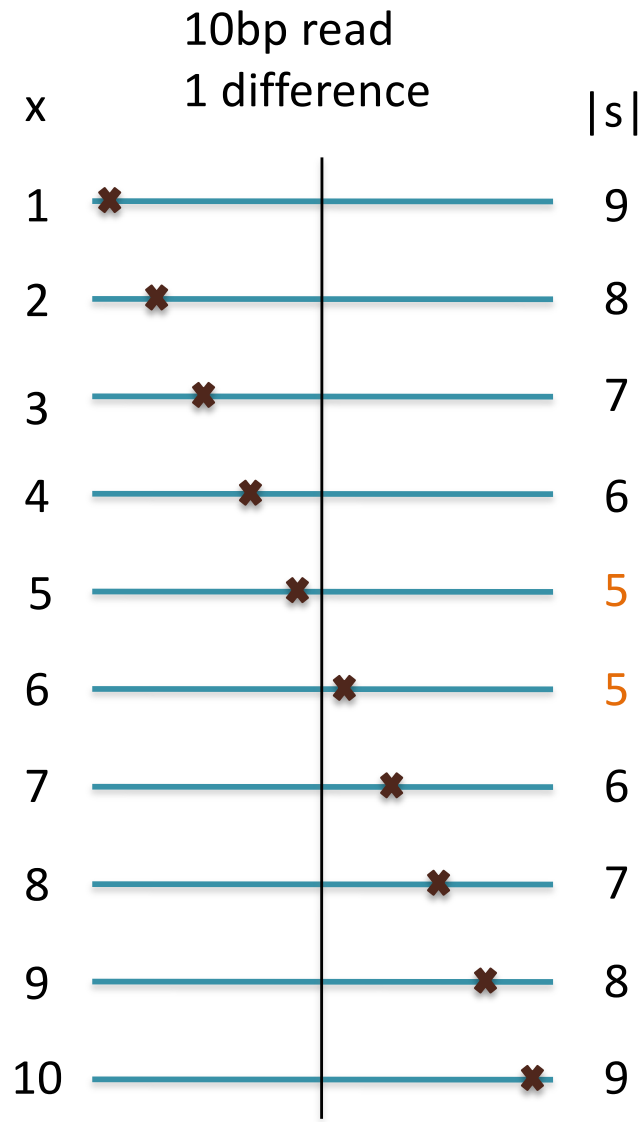
Cancer

Presidential smile

Seed-and-Extend Alignment

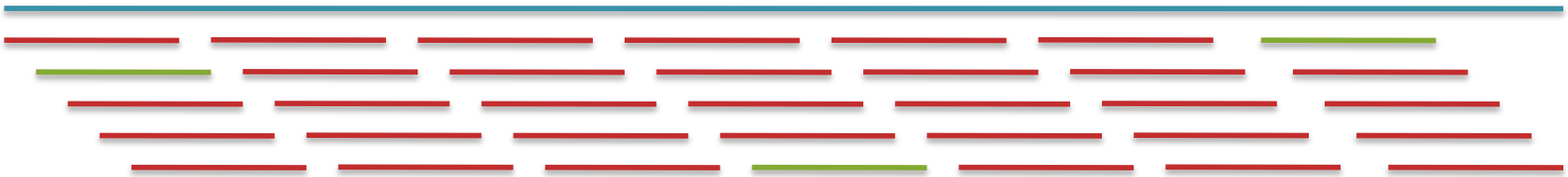
Theorem: An alignment of a sequence of length *m* with at most *k* differences ***must*** contain an exact match at least $s=m/(k+1)$ bp long

(*Baeza-Yates* and Perleberg, 1996)



- Proof: Pigeonhole principle
  - 1 pigeon can't fill 2 holes
- Seed-and-extend search
  - Use an index to rapidly find short exact alignments to seed longer in-exact alignments
    - BLAST, MUMmer, Bowtie, BWA, SOAP, …
  - Specificity of the depends on seed length
    - Guaranteed sensitivity for k differences
    - Also finds some (but not all) lower quality alignments <- heuristic

Brute Force Analysis



- Brute Force:
  - At every possible offset in the genome:
    - Do all of the characters of the query match?

- Analysis
  - Simple, easy to understand
  - Genome length = n [3B]
  - Query length = m [7]
  - Comparisons: (n-m+1) * m [21B]

- Overall runtime: O(nm)

[How long would it take if we double the genome size, read length?]

[How long would it take if we double both?]

Searching the Index

- Strategy 2: Binary search
  - Compare to the middle, refine as higher or lower

- Searching for GATTACA
  - Lo = 1; Hi = 15; Mid = (1+15)/2 = 8
  - Middle = Suffix[8] = CC
    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15; Mid = (9+15)/2 = 12
  - Middle = Suffix[12] = TACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 11; Mid = (9+11)/2 = 10
  - Middle = Suffix[10] = GATTACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 9; Mid = (9+9)/2 = 9
  - Middle = Suffix[9] = GATTACA…
    => Match at position 2!

	#	Sequence	Pos
	1	ACAGATTACC…	6
	2	ACC…	13
	3	AGATTACC…	8
	4	ATTACAGATTACC…	3
	5	ATTACC…	10
	6	C…	15
	7	CAGATTACC…	7
	8	CC…	14
Lo → Hi →	9	GATTACAGATTACC…	2
	10	GATTACC…	9
	11	TACAGATTACC…	5
	12	TACC…	12
	13	TGATTACAGATTACC…	1
	14	TTACAGATTACC…	4
	15	TTACC…	11

Binary Search Analysis

- Binary Search

  Initialize search range to entire list

  mid = (hi+lo)/2; middle = suffix[mid]

  if query matches middle: done

  else if query < middle: pick low range

  else if query > middle: pick hi range

  Repeat until done or empty range [WHEN?]

- Analysis
  - More complicated method
  - How many times do we repeat?
    - How many times can it cut the range in half?
    - Find smallest x such that: $n/(2^x) \leq 1$; $x = \lg_2(n)$ [32]

- Total Runtime: O(m lg n)
  - More complicated, but much faster!
  - Looking up a query loops 32 times instead of 3B

[How long does it take to search 6B or 24B nucleotides?]

Algorithmic challenge

How can we combine the speed of a suffix array O(m + lg(n)) (or even O(m)) with the size of a brute force analysis (n bytes)?

What would such an index look like?

Bowtie: Ultrafast and memory efficient alignment of short DNA sequences to the human genome

Slides Courtesy of Ben Langmead

Algorithm Overview

1. Split read into segments

Read

CCAGTAGCTCTCAGCCTTATTTTACCCAGGCCTGTA

Read (reverse complement)

TACAGGCCTGGGTAAAATAAGGCTGAGAGCTACTGG

Policy: extract 16 nt seed every 10 nt

Seeds

+, 0: CCAGTAGCTCTCAGCC
+, 10: TCAGCCTTATTTTACC
+, 20: TTTACCCAGGCCTGTA

-, 0: TACAGGCCTGGGTAAA
-, 10: GGTAAAATAAGGCTGA
-, 20: GGCTGAGAGCTACTGG

2. Lookup each segment and prioritize

Seeds

+, 0: CCAGTAGCTCTCAGCC
+, 10: TCAGCCTTATTTTACC
+, 20: TTTACCCAGGCCTGTA
-, 0: TACAGGCCTGGGTAAA
-, 10: GGTAAAATAAGGCTGA
-, 20: GGCTGAGAGCTACTGG

→ Ungapped alignment with FM Index

→ Seed alignments (as B ranges)

{ [211, 212], [212, 214] }
{ [653, 654], [651, 653] }
{ [684, 685] }
{ }
{ }
{ [624, 625] }

3. Evaluate end-to-end match

Extension candidates

SA:684, chr12:1955
SA:624, chr2:462
SA:211: chr4:762
SA:213: chr12:1935
SA:652: chr12:1945

→ SIMD dynamic programming aligner

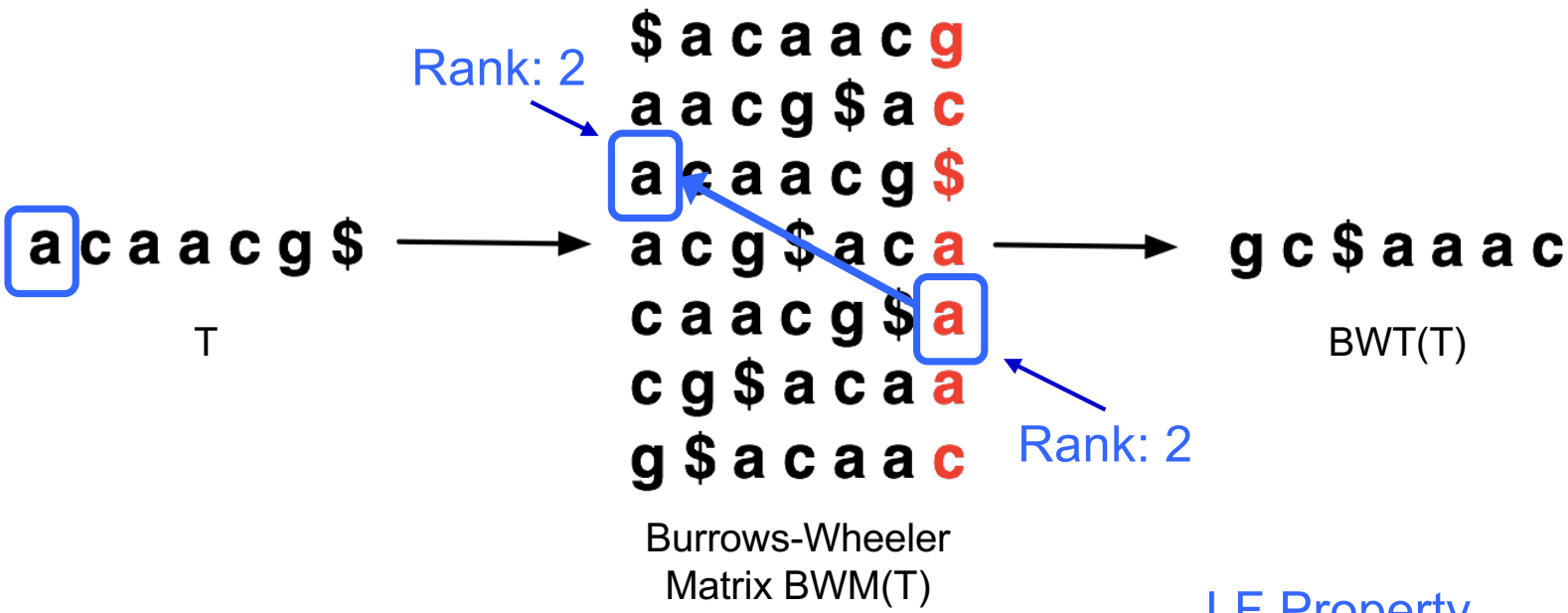
→ SAM alignments

```
r1   0    chr12    1936     0
     36M  *    0    0
     CCAGTAGCTCTCAGCCTTATTTTACCCAGGCCTGTA
     IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
     AS:i:0    XS:i:-2   XN:i:0
     XM:i:0    XO:i:0    XG:i:0
     NM:i:0    MD:Z:36   YT:Z:UU
     YM:i:0
...
```

(Langmead & Salzberg, 2012)

Burrows-Wheeler Transform

- Reversible permutation of the characters in a text



LF Property
implicitly encodes
Suffix Array

- BWT(T) is the index for T

A block sorting lossless data compression algorithm.
Burrows M, Wheeler DJ (1994) *Digital Equipment Corporation.* Technical Report 124

06.BWTNotes.pdf
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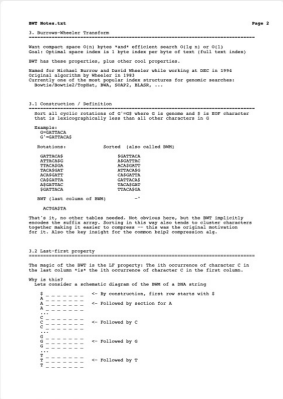
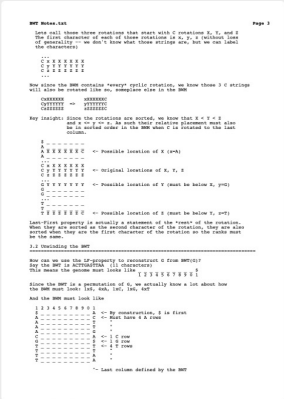
06.BWTNotes.pdf

1



2



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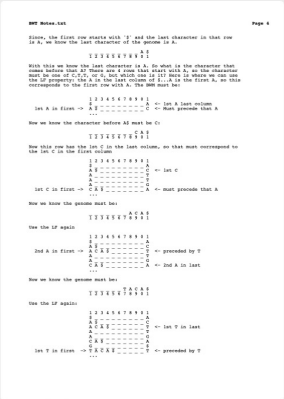

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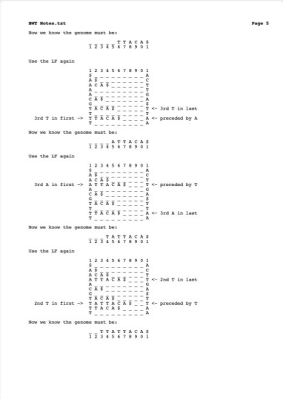

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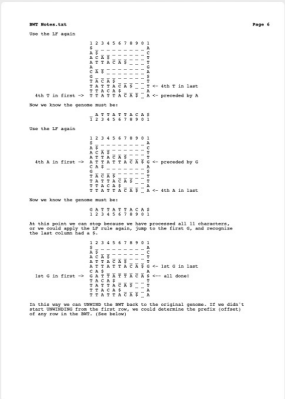
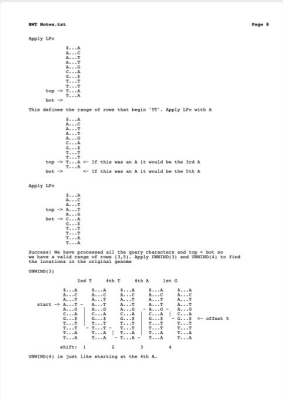


6

7



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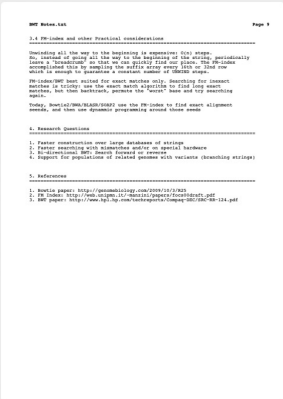


9

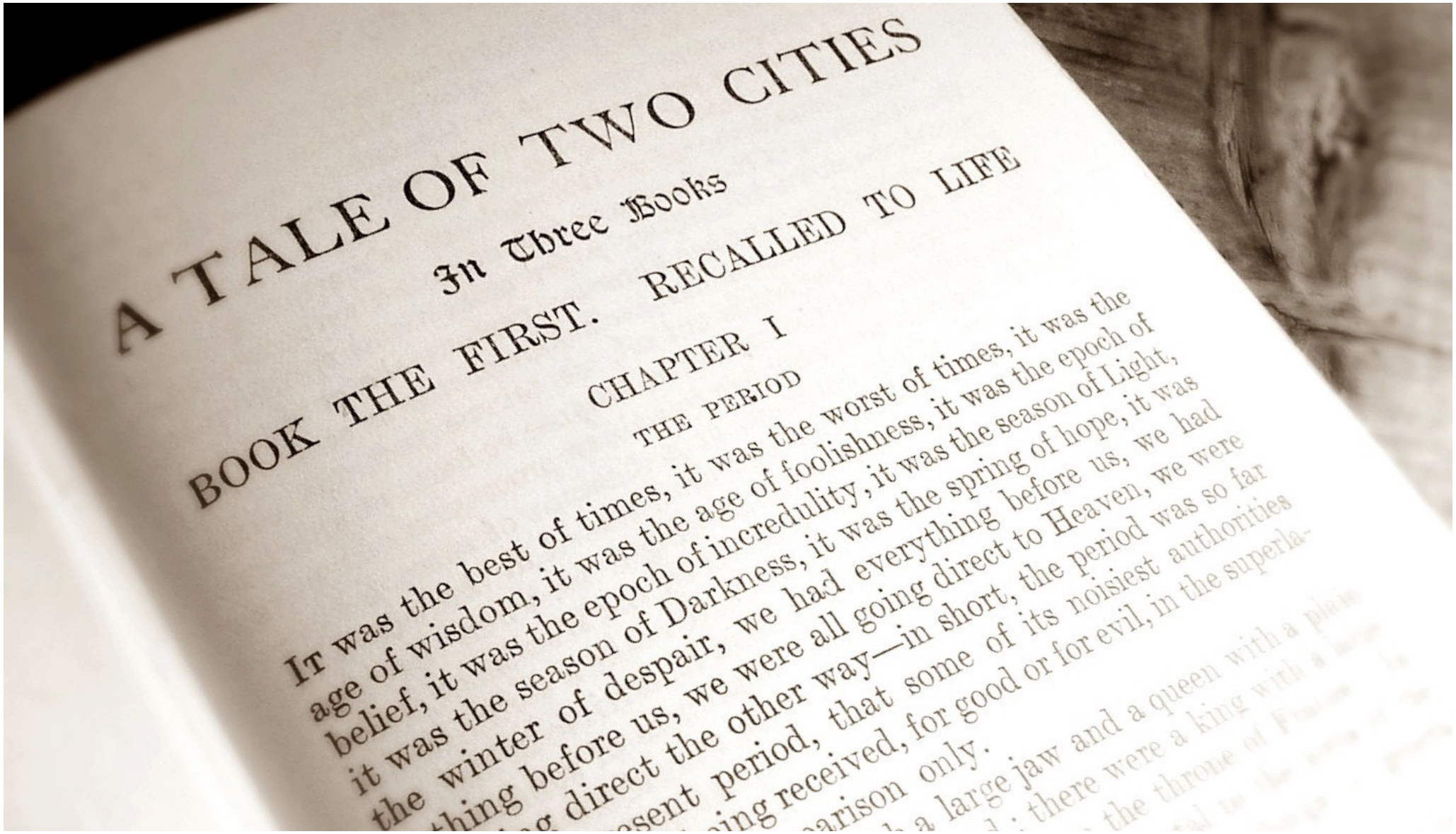
Recompute the original text when the BWT is ACTTGA$TTAA

Burrows-Wheeler Transform

- Recreating T from BWT(T)
  - Start in the first row and apply **LF** repeatedly, accumulating predecessors along the way

[Decode this BWT string: ACTGA$TTA]

Run Length Encoding



Run Length Encoding

ref[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_foolishness,_it_was_the_epoch_of_belief
,_it_was_the_epoch_of_incredulity,_it_was_the_season_of_Light,_it_wa
s_the_season_of_Darkness,_it_was_the_spring_of_hope,_it_was_the_wint
er_of_despair,_we_had_everything_before_us,_we_had_nothing_before_us
,_we_were_all_going_direct_to_Heaven,_we_were_all_going_direct_the_o
ther_way_-_in_short,_the_period_was_so_far_like_the_present_period,_
that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_good_or_for_evil,_in_the_superlative_degree_of_comparison_only.$
```

Run Length Encoding:

- Replace a "run" of a character X with a single X followed by the length of the run
- GAAAAAAAATTACA => GA8T2ACA (reverse is also easy to implement)
- If your text contains numbers, then you will need to use a (slightly) more sophisticated encoding

Run Length Encoding

ref[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_foolishness,_it_was_the_epoch_of_belief
,_it_was_the_epoch_of_incredulity,_it_was_the_season_of_Light,_it_wa
s_the_season_of_Darkness,_it_was_the_spring_of_hope,_it_was_the_wint
er_of_despair,_we_had_everything_before_us,_we_had_nothing_before_us
,_we_were_all_going_direct_to_Heaven,_we_were_all_going_direct_the_o
ther_way_-_in_short,_the_period_was_so_far_like_the_present_period,_
that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_good_or_for_evil,_in_the_superlative_degree_of_comparison_only.$
```

rle(ref)[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_fo2lishnes2,_it_was_the_epoch_of_belief
,_it_was_the_epoch_of_incredulity,_it_was_the_season_of_Light,_it_wa
s_the_season_of_Darknes2,_it_was_the_spring_of_hope,_it_was_the_wint
er_of_despair,_we_had_everything_before_us,_we_had_nothing_before_us
,_we_were_al2_going_direct_to_Heaven,_we_were_al2_going_direct_the_o
ther_way_-_in_short,_the_period_was_so_far_like_the_present_period,_
that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_go2d_or_for_evil,_in_the_superlative_degre2_of_comparison_only.$
```

Run Length Encoding

ref[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_foolishness,_it_was_the_epoch_of_belief
,_it_was_the_epoch_of_incredulity,_it_was_the_season_of_Light,_it_wa
s_the_season_of_Darkness,_it_was_the_spring_of_hope,_it_was_the_wint
er_of_despair,_we_had_everything_before_us,_we_had_nothing_before_us
,_we_were_all_going_direct_to_Heaven,_we_were_all_going_direct_the_o
ther_way_-_in_short,_the_period_was_so_far_like_the_present_period,_
that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_good_or_for_evil,_in_the_superlative_degree_of_comparison_only.$
```

bwt[614]:

```
.dlmssftysesdtrsns_y__$_yfofeeeetggsfefefggeedrofr,llreef-,fs,,,,,,,
,,nfrsdnnhereghettedndeteegeenstee,ssssst,esssnssffteedtttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eoooooo
oooooo____eennnnnnaai___ecc__tttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooooiiihkiiiiiio__iei
tsppioi___________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiisn_______________oyoui__a_iiids__aiiaee_____________________tlar
```

Run Length Encoding

ref[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_foolishness,_it_was_the_epoch_of_belief
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,_we_were_all_going_direct_to_Heaven,_we_were_all_going_direct_the_o
ther_way_-_in_short,_the_period_was_so_far_like_the_present_period,_
that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_good_or_for_evil,_in_the_superlative_degree_of_comparison_only.$
```

bwt[614]:

```
.dlmssftysesdtrsns_y__$_yfofeeeetggsfefefggeedrofr,llreef-,fs,,,,,,,
,,nfrsdnnhereghettedndeteegeenstee,ssssst,esssnssffteedtttttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eoooooo
oooooo____eennnnnnaai___ecc__tttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooooiiihkiiiiiio__iei
tsppioi____________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiisn_____________________________________________________tlar
```

Why does the BWT tend to make runs in english text?

Run Length Encoding

bwt[614]:

```
.dlmssftysesdtrsns_y__$_yfofeeeetggsfefefggeedrofr,llreef-,fs,,,,,,,
,,nfrsdnnhereghettedndeteegeenstee,ssssst,esssnssffteedtttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eoooooo
oooooo____eennnnnnaai___ecc__tttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooiiihkiiiiiio__iei
tsppioi____________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiisn_______________oyoui__a_iiids__aiiaee_____________________tlar
```

rle(bwt)[464]:

```
.dlms2ftysesdtrsns_y_2$_yfofe4tg2sfefefg2e2drofr,l2re2f-,fs,9nfrsdn2
hereghet2edndete2ge2nste2,s5t,es3ns2f2te2dt10r,4e3feh2_2p_2fpDw11e2h
l_ew_5eo2_ne3oa2eo2_4seph2r2hvh2w2egmgh7kr2w2h2s2Hr3vtr2ib2dbcbvs_2t
hw2p3vm2irdn2ib_2eo12_4e2n6a2i_3ec2_2t18s_tsgltsLlvt2_3h2o2re_wr2ad2
wlors_9r_2lteiril2re_oua2no2i2oeo4i3hki6o_2ieitsp2ioi_12g2nodsc_s3_g
fhf_f3hwh_nsmo_2ue2_sio3ae4o2_i2cgp2e2aoaeo2e2s2eu2teta11i_2ei_in_2a
2ie_e3rei_hrs3nac2i2Ii7sn_15oyoui_2a_i3ds_2ai2ae2_21tlar
```

Run Length Encoding

bwt[614]:

```
.dlmssftysesdtrsns_y__$_yfofeeeetggsfefefggeedrofr,llreef-,fs,,,,,,,
,,nfrsdnnhereghettedndeteegeenstee,ssssst,esssnssffteedtttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eoooooo
oooooo____eennnnnnaai___ecc__tttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooiiihkiiiiiio__iei
tsppioi____________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiisn_________________oyoui__a_iiids__aiiaee_____________________tlar
```

rle(bwt)[464]:

```
.dlms2ftysesdtrsns_y_2$_yfofe4tg2sfefefg2e2drofr,l2re2f-,fs,9nfrsdn2
hereghet2edndete2ge2nste2,s5t,es3ns2f2te2dt10r,4e3feh2_2p_2fpDw11e2h
l_ew_5eo2_ne3oa2eo2_4seph2r2hvh2w2egmgh7kr2w2h2s2Hr3vtr2ib2dbcbvs_2t
hw2p3vm2irdn2ib_2eo12_4e2n6a2i_3ec2_2t18s_tsgltsLlvt2_3h2o2re_wr2ad2
wlors_9r_2lteiril2re_oua2no2i2oeo4i3hki6o_2ieitsp2ioi_12g2nodsc_s3_g
fhf_f3hwh_nsmo_2ue2_sio3ae4o2_i2cgp2e2aoaeo2e2s2eu2teta11i_2ei_in_2a
2ie_e3rei_hrs3nac2i2Ii7sn_15oyoui_2a_i3ds_2ai2ae2_21tlar
```

Run Length Encoding

ref[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_foolishness,_it_was_the_epoch_of_belief
,_it_was_the_epoch_of_incredulity,_it_was_the_season_of_Light,_it_wa
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,_we_were_all_going_direct_to_Heaven,_we_were_all_going_direct_the_o
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that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_good_or_for_evil,_in_the_superlative_degree_of_comparison_only.$
```

rle(bwt)[464]:

```
.dlms2ftysesdtrsns_y_2$_yfofe4tg2sfefefg2e2drofr,l2re2f-,fs,9nfrsdn2
hereghet2edndete2ge2nste2,s5t,es3ns2f2te2dt10r,4e3feh2_2p_2fpDw11e2h
l_ew_5eo2_ne3oa2eo2_4seph2r2hvh2w2egmgh7kr2w2h2s2Hr3vtr2ib2dbcbvs_2t
hw2p3vm2irdn2ib_2eo12_4e2n6a2i_3ec2_2t18s_tsgltsLlvt2_3h2o2re_wr2ad2
wlors_9r_2lteiril2re_oua2no2i2oeo4i3hki6o_2ieitsp2ioi_12g2nodsc_s3_g
fhf_f3hwh_nsmo_2ue2_sio3ae4o2_i2cgp2e2aoaeo2e2s2eu2teta11i_2ei_in_2a
2ie_e3rei_hrs3nac2i2Ii7sn_15oyoui_2a_i3ds_2ai2ae2_21tlar
```

Run Length Encoding

ref[614]:

```
It_was_the_best_of_times,_it_was_the_worst_of_times,_it_was_the_age_
of_wisdom,_it_was_the_age_of_foolishness,_it_was_the_epoch_of_belief
,_it_was_the_epoch_of_incredulity,_it_was_the_season_of_Light,_it_wa
s_the_season_of_Darkness,_it_was_the_spring_of_hope,_it_was_the_wint
er_of_despair,_we_had_everything_before_us,_we_had_nothing_before_us
,_we_were_all_going_direct_to_Heaven,_we_were_all_going_direct_the_o
ther_way_-_in_short,_the_period_was_so_far_like_the_present_period,_
that_some_of_its_noisiest_authorities_insisted_on_its_being_received
,_for_good_or_for_evil,_in_the_superlative_degree_of_comparison_only.$
```

rle(bwt)[464]:

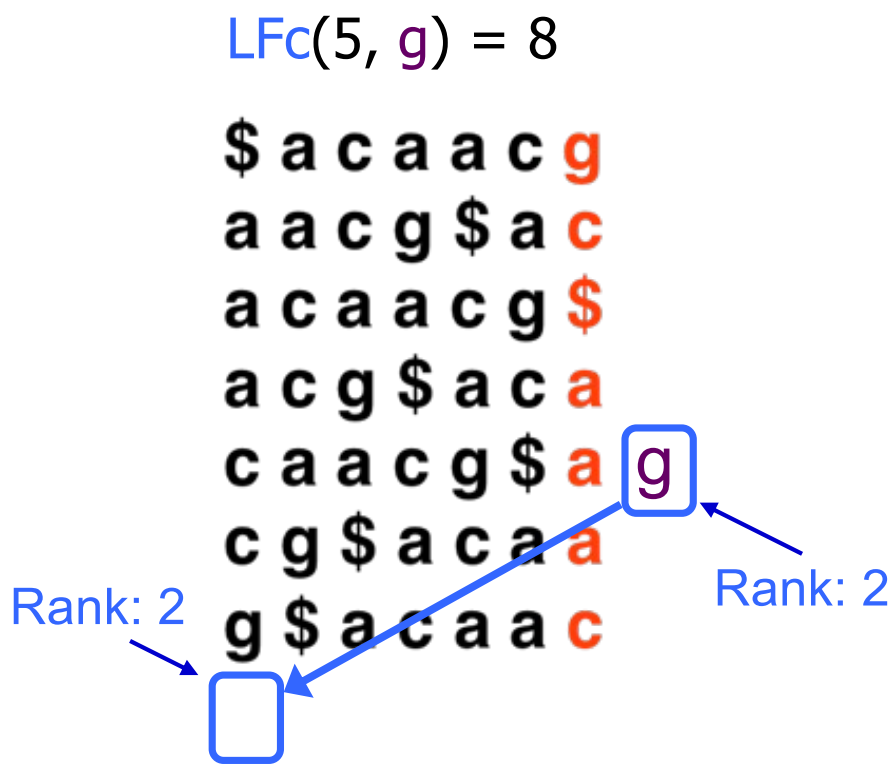
```
.dlms2ftysesdtrsns_y_2$_yfofe4tg2sfefefg2e2drofr,l2re2f-,fs,9nfrsdn2
hereghet2edndete2ge2nste2,s5t,es3ns2f2te2dt10r,4e3feh2_2p_2fpDw11e2h
l_ew_5eo2_ne3oa2eo2_4seph2r2hvh2w2egmgh7kr2w2h2s2Hr3vtr2ib2dbcbvs_2t
hw2p3vm2irdn2ib_2eo12_4e2n6a2i_3ec2_2t18s_tsgltsLlvt2_3h2o2re_wr2ad2
wlors_9r_2lteiril2re_oua2no2i2oeo4i3hki6o_2ieitsp2ioi_12g2nodsc_s3_g
fhf_f3hwh_nsmo_2ue2_sio3ae4o2_i2cgp2e2aoaeo2e2s2eu2teta11i_2ei_in_2a
2ie_e3rei
```

Saved 614-464 = 150 bytes (24%) with zero loss of information!

Common to save 50% to 90% on real world files with bzip2

BWT Exact Matching

- **LFc**(r, c) does the same thing as **LF**(r) but it ignores r's actual final character and "pretends" it's c:

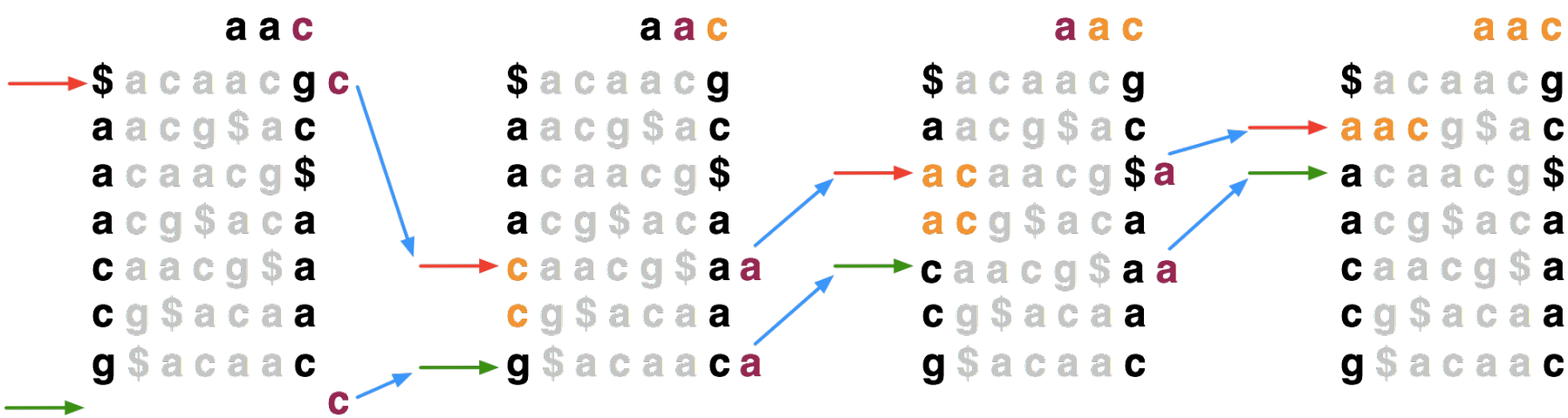


BWT Exact Matching

- Start with a range, (**top**, **bot**) encompassing all rows and repeatedly apply **LFc**:

  top = **LFc**(**top**, **qc**); **bot** = **LFc**(**bot**, **qc**)

  qc = the next character to the left in the query



Ferragina P, Manzini G: Opportunistic data structures with applications. *FOCS. IEEE Computer Society; 2000.*

[Search for TTA this BWT string: ACTGA$TTA]

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BWT construction and search at the terabase scale

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Abstract

Motivation: Burrows-Wheeler Transform (BWT) is a common component in full-text indices. Initially developed for data compression, it is particularly powerful for encoding redundant sequences such as pangenome data. However, BWT construction is resource intensive and hard to be parallelized, and many methods for querying large full-text indices only report exact matches or their simple extensions. These limitations have hampered the biological applications of full-text indices.

Results: We developed ropebwt3 for efficient BWT construction and query. Ropebwt3 could index 100 assembled human genomes in 21 hours and index 7.3 terabases of commonly studied bacterial assemblies in 26 days. This was achieved using 82 gigabytes of memory at the peak without working disk space. Ropebwt3 can find maximal exact matches and inexact alignments under affine-gap penalties, and can retrieve all distinct local haplotypes matching a query sequence. It demonstrates the feasibility of full-text indexing at the terabase scale.

Availability and implementation: `https://github.com/lh3/ropebwt3`

Algorithm Overview

1. Split read into segments

Read

CCAGTAGCTCTCAGCCTTATTTTACCCAGGCCTGTA

Read (reverse complement)

TACAGGCCTGGGTAAAATAAGGCTGAGAGCTACTGG

Policy: extract 16 nt seed every 10 nt

Seeds

+, 0: CCAGTAGCTCTCAGCC
+, 10: TCAGCCTTATTTTACC
+, 20: TTTACCCAGGCCTGTA

-, 0: TACAGGCCTGGGTAAA
-, 10: GGTAAAATAAGGCTGA
-, 20: GGCTGAGAGCTACTGG

2. Lookup each segment and prioritize

Seeds

+, 0: CCAGTAGCTCTCAGCC
+, 10: TCAGCCTTATTTTACC
+, 20: TTTACCCAGGCCTGTA
-, 0: TACAGGCCTGGGTAAA
-, 10: GGTAAAATAAGGCTGA
-, 20: GGCTGAGAGCTACTGG

→ Ungapped alignment with FM Index

→ Seed alignments (as B ranges)

{ [211, 212], [212, 214] }
{ [653, 654], [651, 653] }
{ [684, 685] }
{ }
{ }
{ [624, 625] }

3. Evaluate end-to-end match

Extension candidates

SA:684, chr12:1955
SA:624, chr2:462
SA:211: chr4:762
SA:213: chr12:1935
SA:652: chr12:1945

→ SIMD dynamic programming aligner

→ SAM alignments

```
r1   0    chr12    1936     0
     36M  *    0    0
     CCAGTAGCTCTCAGCCTTATTTTACCCAGGCCTGTA
     IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
     AS:i:0    XS:i:-2   XN:i:0
     XM:i:0    XO:i:0    XG:i:0
     NM:i:0    MD:Z:36   YT:Z:UU
     YM:i:0
...
```

(Langmead & Salzberg, 2012)

Similarity metrics

- Hamming distance
  - Count the number of substitutions to transform one string into another

```
MIKESCHATZ
||X||XXXX|
MICESHATZZ
     5
```

- Edit distance
  - The minimum number of substitutions, insertions, or deletions to transform one string into another

```
MIKESCHAT-Z
||X||X|||X|
MICES-HATZZ
     3
```

Edit Distance Example

AGCACACA → ACACACTA in 4 steps

AGCACACA → (1. change G to C)
ACCACACA → (2. delete C)
ACACACA → (3. change A to T)
ACACACT → (4. insert A after T)
ACACACTA → done

[Is this the best we can do?]

Edit Distance Example

AGCACACA → ACACACTA in 3 steps

AGCACACA → (1. change G to C)
ACCACACA → (2. delete C)
ACACACA → (3. insert T after 3rd C)
ACACACTA → done

[Is this the best we can do?]

Reverse Engineering Edit Distance

```
D(AGCACACA, ACACACTA) = ?
```

Imagine we already have the optimal alignment of the strings, the last column can only be 1 of 3 options:

```
...M      ...I      ...D
...A      ...-      ...A
...A      ...A      ...-
```

The optimal alignment of last two columns is then 1 of 9 possibilities

```
...MM  ...IM  ...DM      ...MI  ...II  ...DI      ...MD  ...ID  ...DD
...CA  ...-A  ...CA      ...A-  ...--  ...A-      ...CA  ...-A  ...CA
...TA  ...TA  ...-A      ...TA  ...TA  ...-A      ...A-  ...A-  ...--
```

The optimal alignment of the last three columns is then 1 of 27 possibilities…

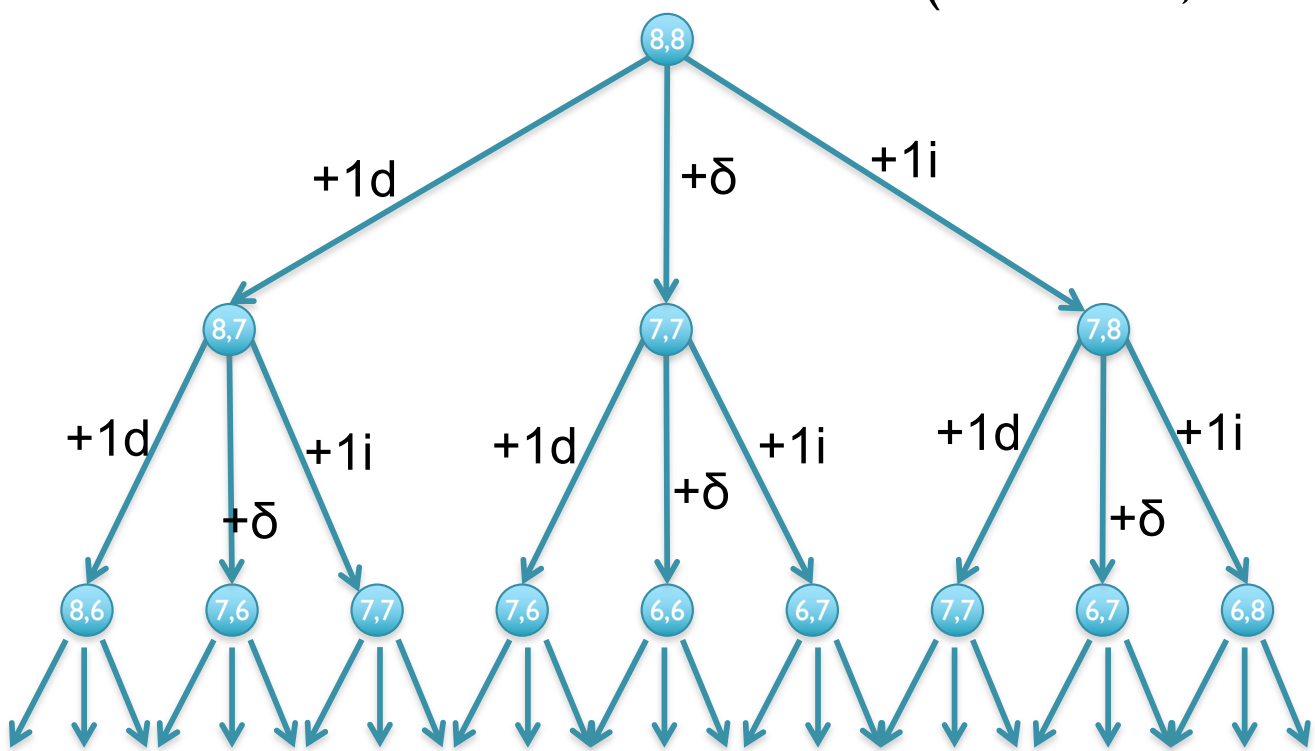
```
...M...      ...I...      ...D...
...X...      ...-...      ...X...
...Y...      ...Y...      ...-...
```

Eventually spell out every possible sequence of {I,M,D}

Recursive solution

- Computation of D is a recursive process.
  - At each step, we only allow matches, substitutions, and indels
  - D(i,j) in terms of D(i’,j’) for i’ ≤ i and j’ ≤ j.

D(AGCACACA, ACACACTA) = min{D(AGCACACA, ACACACT) + I,
D(AGCACAC, ACACACTA) + I,
D(AGCACAC, ACACACT) +δ(A, A)}



[What is the running time?]

Dynamic Programming

- We could code this as a recursive function call...

  ...with an exponential number of function evaluations

- There are only (n+1) x (m+1) pairs i and j
  - We are evaluating D(i,j) multiple times

- Compute D(i,j) bottom up.
  - Start with smallest (i,j) = (1,1).
  - Store the intermediate results in a table.
    - Compute D(i,j) *after* D(i-1,j), D(i,j-1), and D(i-1,j-1)

Recurrence Relation for D

Find the edit distance (minimum number of operations to convert one string into another) in O(mn) time

- Base conditions:
  - $D(i,0) = i$, for all $i = 0,\ldots,n$
  - $D(0,j) = j$, for all $j = 0,\ldots,m$

- For $i > 0$, $j > 0$:

$$
\begin{aligned}
D(i,j) = \min \{ & \\
& D(i-1,j) + 1, && \text{// align 0 chars from S, 1 from T} \\
& D(i,j-1) + 1, && \text{// align 1 chars from S, 0 from T} \\
& D(i-1,j-1) + \delta(S(i),T(j)) && \text{// align 1+1 chars} \\
\} &
\end{aligned}
$$

[Why do we want the min?]

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1								
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

[What does the initialization mean?]

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0							
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

$$D[A,A] = \min\{D[A,]+1,\ D[,A]+1,\ D[,]+\delta(A,A)\}$$

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1						
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

$$D[A,AC] = \min\{D[A,A]+1,\ D[,AC]+1,\ D[,A]+\delta(A,C)\}$$

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2					
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

D[A,ACA] = min{D[A,AC]+1, D[,ACA]+1, D[,AC]+δ(A,A)}

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2								
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

D[A,ACACACTA] = 7

```
-------A
*******|
ACACACTA
```

[What about the other A?]

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2	1	1	2	3	4	5	6	7
C	3								
A	4								
C	5								
A	6								
C	7								
A	8								

D[AG,ACACACTA] = 7

```
----AG--
****|***
ACACACTA
```

Dynamic Programming Matrix

		A	C	A	C	A	C	T	A
	0	1	2	3	4	5	6	7	8
A	1	0	1	2	3	4	5	6	7
G	2	1	1	2	3	4	5	6	7
C	3	2	1	2	2	3	4	5	6
A	4	3	2	1	2	2	3	4	5
C	5	4	3	2	1	2	2	3	4
A	6	5	4	3	2	1	2	3	3
C	7	6	5	4	3	2	1	2	3
A	8	7	6	5	4	3	2	2	2

D[AGCACACA,ACACACTA] = 2

```
AGCACAC-A
|*|||||*|
A-CACACTA
```

[Can we do it any better?]