FM Index

Michael Schatz

Feb 18, 2013

Lecture 7: Applied Comparative Genomics

Assignment 3: Due Monday Feb 25

Assignment 3: Coverage, Genome Assembly, and the BWT

Assignment Date: Monday, Feb. 18, 2019
Due Date: Monday, Feb. 25, 2019 @ 11:59pm

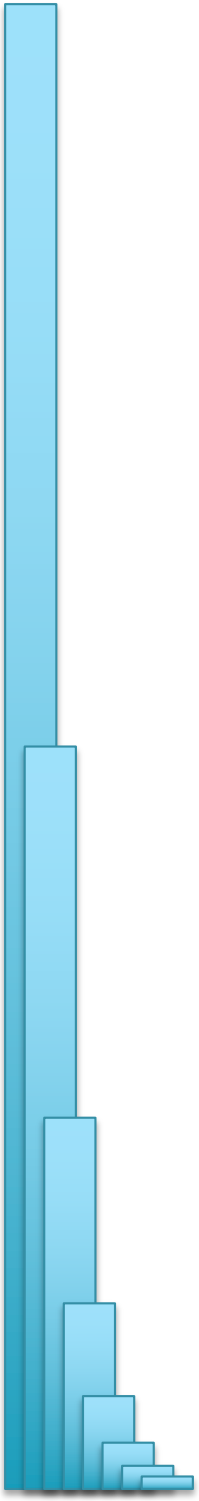
Question 1. Coverage simulator [10 pts]

- Q1a. How many 100bp reads are needed to sequence a 1Mbp genome to 5x coverage?
- Q1b. In the language of your choice, simulate sequencing 5x coverage of a 1Mbp genome and plot the histogram of coverage. Note you do not need to actually output the sequences of the reads, you can just randomly sample positions in the genome and record the coverage. You do not need to consider the strand of each read. The start position of each read should have a uniform random probabilty at each possible starting position (1 through 999,900). You can record the coverage in an array of 1M positions. Overlay the histogram with a Poisson distribution with lambda=5
- Q1c. Using the histogram from 1b, how much of the genome has not been sequenced (has 0x coverage). How well does this match Poisson expectations?
- Q1d. Now repeat the analysis with 15x coverage: 1. simulate the appropriate number of reads, 2. make a histogram, 3. overlay a Poisson distribution with lambda=15, 4. compute the number of bases with 0x coverage, and 5. evaluated how well it matches the Poisson expectation.

Question 2. de Bruijn Graph construction [10 pts]

- Q1a. Draw (by hand or by code) the de Bruijn graph for the following reads using k=3 (assume all reads are from the forward strand, no sequencing errors, complete coverage of the genome)

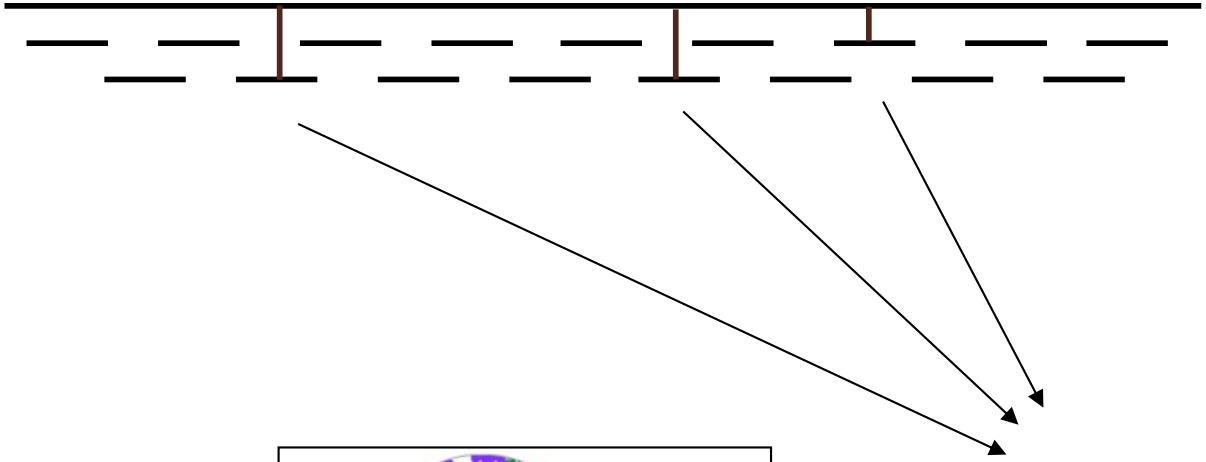
```
ATTC
ATTG
CATT
CTTA
GATT
TATT
TCAT
TCTT
```

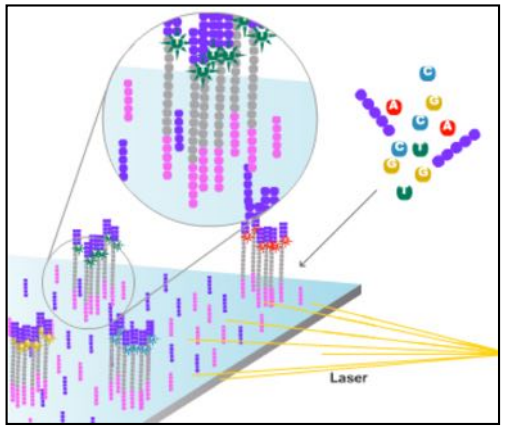


Part 1: Suffix Arrays

Personal Genomics

How does your genome compare to the reference?





Heart Disease

Cancer

Presidential smile

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?]

Brute Force Reflections

Why check every position?

– GATTACA can't possibly start at position 15 [WHY?]

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	…
T	G	A	T	T	A	C	A	G	A	T	T	A	C	C	…
								G	A	T	T	A	C	A	

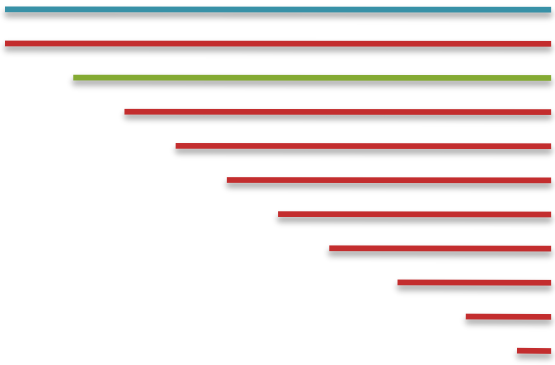
– Improve runtime to O(n + m) [3B + 7]
  - If we double both, it just takes twice as long
  - Knuth-Morris-Pratt, 1977
  - Boyer-Moyer, 1977, 1991

– For one-off scans, this is the best we can do (optimal performance)
  - We have to read every character of the genome, and every character of the query
  - For short queries, runtime is dominated by the length of the genome

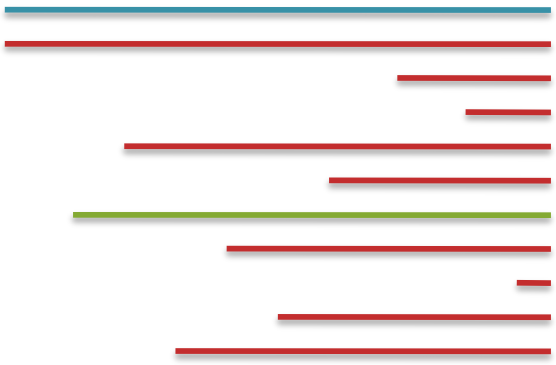
Suffix Arrays: Searching the Phone Book

- What if we need to check many queries?
  - We don't need to check every page of the phone book to find 'Schatz'
  - Sorting alphabetically lets us immediately skip 96% (25/26) of the book *without any loss in accuracy*

- Sorting the genome: Suffix Array (Manber & Myers, 1991)
  - Sort every suffix of the genome



Split into n suffixes



Sort suffixes alphabetically

[Challenge Question: How else could we split the genome?]

Searching the Index

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

- Searching for GATTACA
  - Lo = 1; Hi = 15;

Lo →

#	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
9	GATTACAGATTACC…	2
10	GATTACC…	9
11	TACAGATTACC…	5
12	TACC…	12
13	TGATTACAGATTACC…	1
14	TTACAGATTACC…	4
15	TTACC…	11

Hi →

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

Lo →

#	Sequence	Pos
1	ACAGATTACC…	6
2	ACC…	13
3	AGATTACC…	8
4	ATTACAGATTACC…	3
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  - Middle = Suffix[8] = CC
    => Higher: Lo = Mid + 1

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  - Lo = 1; Hi = 15; Mid = (1+15)/2 = 8
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    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15;

#	Sequence	Pos
1	ACAGATTACC…	6
2	ACC…	13
3	AGATTACC…	8
4	ATTACAGATTACC…	3
5	ATTACC…	10
6	C…	15
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Lo →

Hi →

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- 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

#	Sequence	Pos
1	ACAGATTACC…	6
2	ACC…	13
3	AGATTACC…	8
4	ATTACAGATTACC…	3
5	ATTACC…	10
6	C…	15
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Lo →

Hi →

Searching the Index

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- 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;

Lo →

Hi →

#	Sequence	Pos
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  - 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

Lo →

Hi →

#	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
9	GATTACAGATTACC…	2
10	GATTACC…	9
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12	TACC…	12
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    => 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;

Lo →
Hi →

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2	ACC…	13
3	AGATTACC…	8
4	ATTACAGATTACC…	3
5	ATTACC…	10
6	C…	15
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8	CC…	14
9	GATTACAGATTACC…	2
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  - 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
9	GATTACAGATTACC…	2
10	GATTACC…	9
11	TACAGATTACC…	5
12	TACC…	12
13	TGATTACAGATTACC…	1
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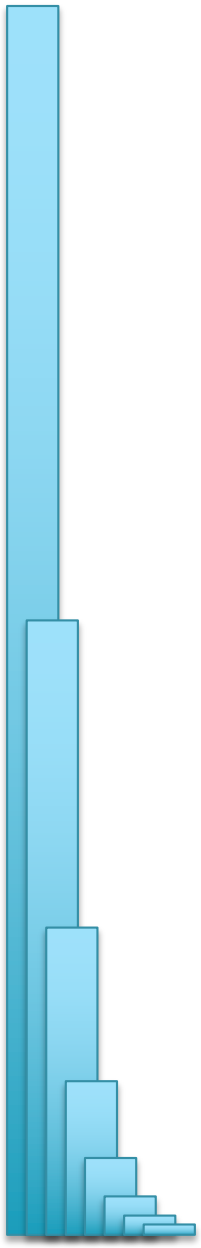
Binary Search Analysis



- 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

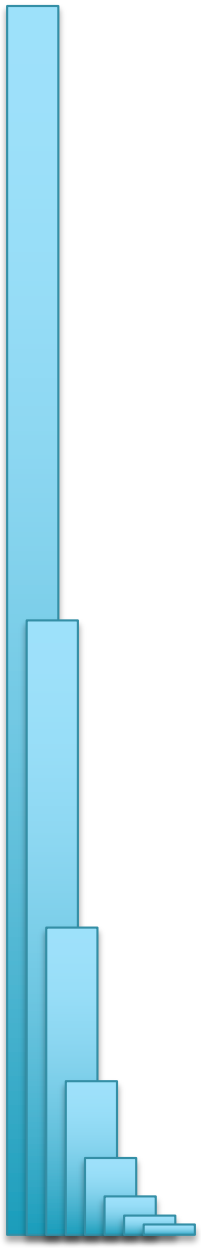
  Repeat until done or empty range [WHEN?]

- 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?]

Binary Search Analysis



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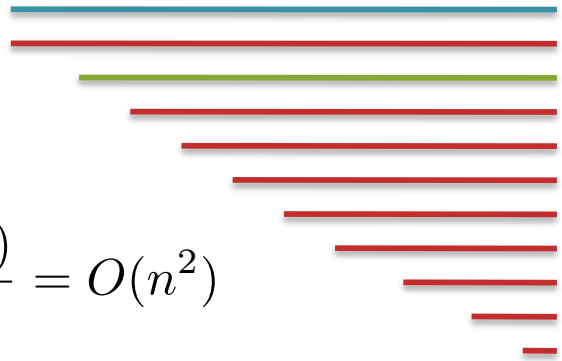
- Total Runtime: O(m lg n)
  - More complicated, but much faster!
  - Looking up a query loops 32 times instead of 3B

Can be reduced to O(m + lg n)
using an auxiliary data structure called the LCP array

Suffix Array Construction

- How can we store the suffix array?

  [How many characters are in all suffixes combined?]



$$S = 1 + 2 + 3 + \cdots + n = \sum_{i=1}^{n} i = \frac{n(n+1)}{2} = O(n^2)$$

  - Hopeless to explicitly store 4.5 billion billion characters
  - Instead use implicit representation
    - Keep 1 copy of the genome, and a list of sorted offsets
    - Storing 3 billion offsets fits on a server (12GB)

- Searching the array is very fast, but it takes time to construct
  - This time will be amortized over many, many searches
  - Run it once "overnight" and save it away for all future queries

Pos
6
13
8
3
10
15
7
14
2
9
5
12
1
4
11

TGATTACAGATTACC

Exact Matching Review & Overview

Where is GATTACA in the human genome?

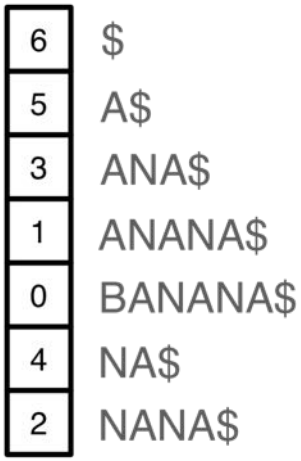
Brute Force (3 GB)

```
BANANA
BAN
  ANA
    NAN
      ANA
```

O(m * n)

Slow & Easy

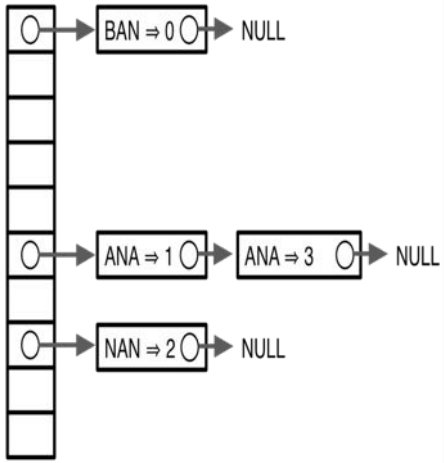
Suffix Array (>15 GB)



O(m + lg n)

Full-text index

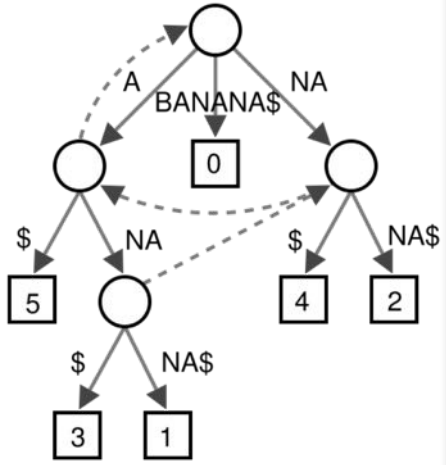
Hash Table (>15 GB)



O(1)

Fixed-length lookup

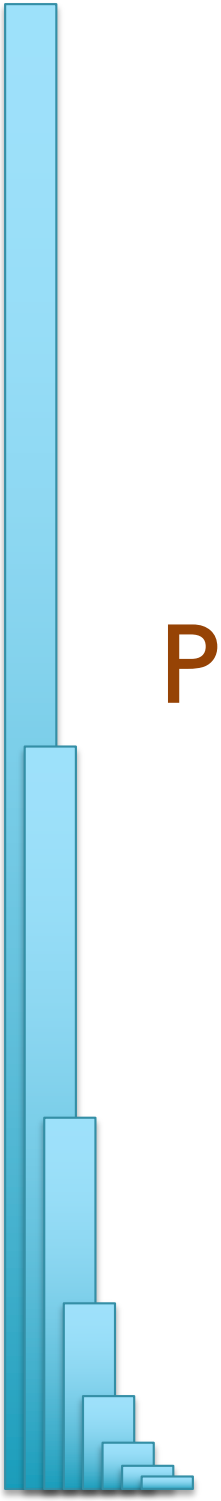
Suffix Tree (>51 GB)



O(m)

Full-text, but bulky

*** These are general techniques applicable to any text search problem ***

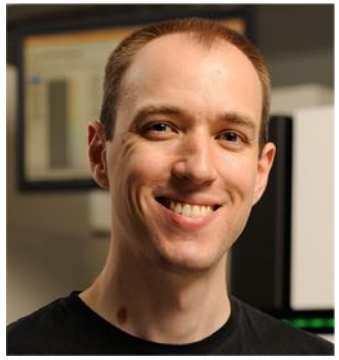


Part 2: Burrows Wheeler Transform

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?

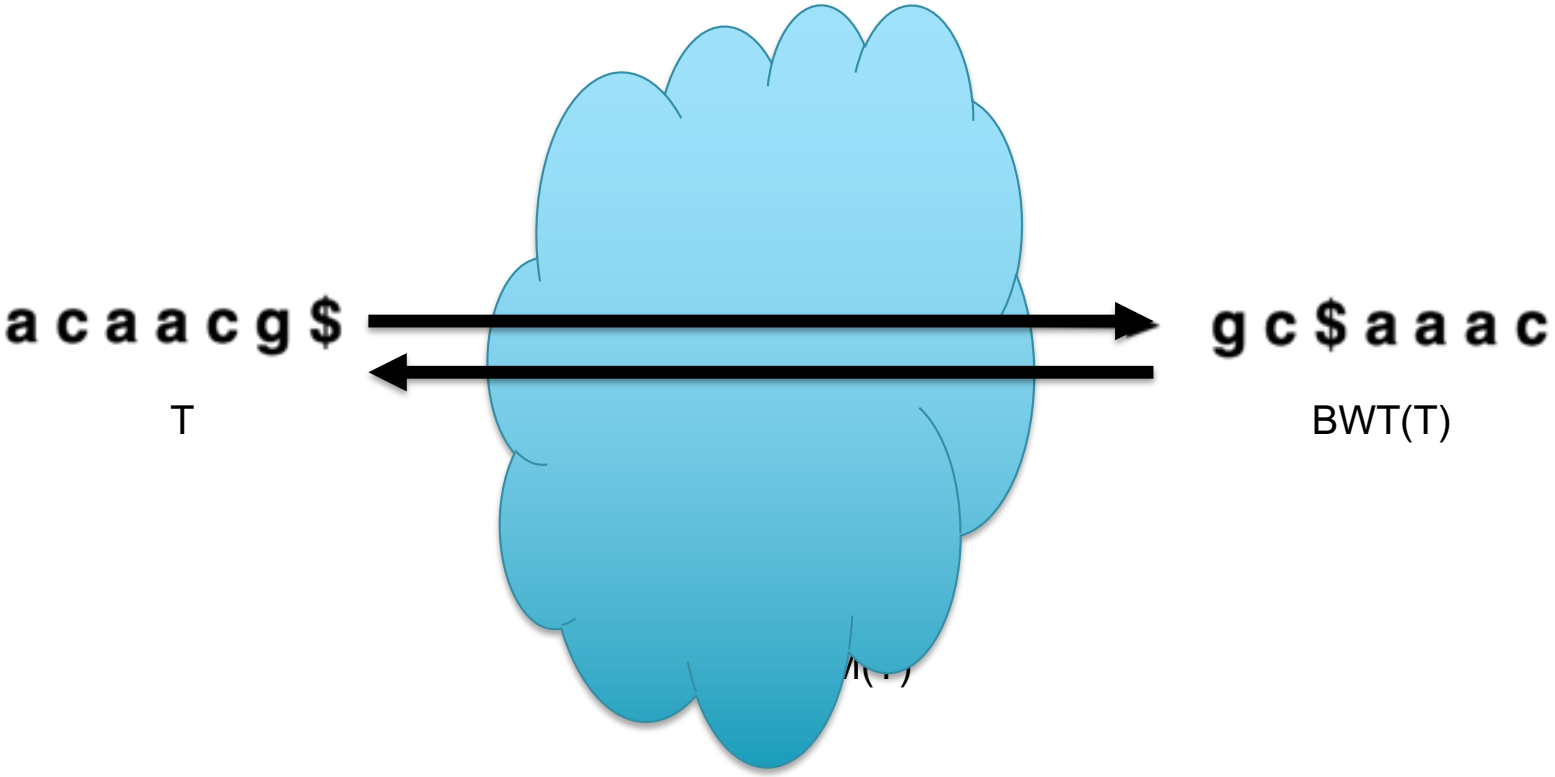


Bowtie: Ultrafast and memory efficient alignment of short DNA sequences to the human genome

Slides Courtesy of Ben Langmead

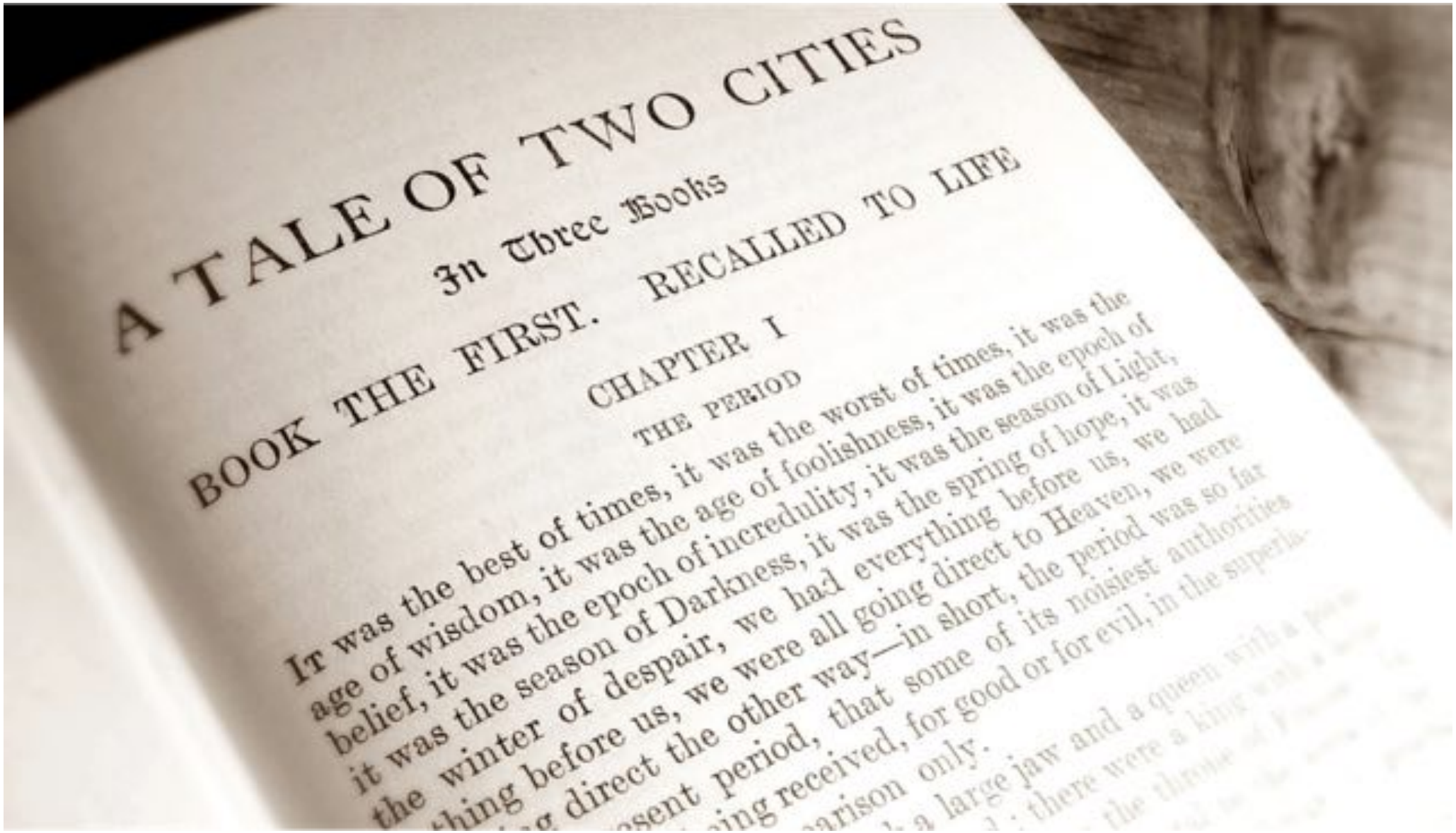
Burrows-Wheeler Transform

- Reversible permutation of the characters in a text



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

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,_
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```

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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.$
```

bwt[614]:

```
.dlmssftysesdtrsns_y__$_yfofeeeetggsfefefggeedrofr,llreef-,fs,,,,,,,
,,nfrsdnnhereghettedndeteegeenstee,ssssst,esssnssffteedtttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eooooo
oooooo____eennnnnnaai___ecc__ttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooooiiihkiiiiiio__iei
tsppioi_____________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiiisn_____________oyoui__a_iiids__aiiaee_____________________tlar
```

Run Length Encoding

bwt[614]:

```
.dlmssftysesdtrsns_y__$_yfofeeeetggsfefefggeedrofr,llreef-,fs,,,,,,,
,,nfrsdnnhereghettedndeteegeenstee,ssssst,esssnssffteedtttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eooooooo
oooooo____eennnnnnaai___ecc__ttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooooiiihkiiiiiio__iei
tsppioi___________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiiisn_____________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,esssnssffteedtttttttttttr,,
,,eeefehh__p__fpDwwwwwwwwwwweehl_ew_____eoo_neeeoaaeoo____sephhrrhvh
hwwegmghhhhhhhkrrwwhhssHrrrvtrribbdbcbvs__thwwpppvmmirdnnib__eooooooo
oooooo____eennnnnnaai___ecc__ttttttttttttttttttts_tsgltsLlvtt___hhoor
e_wrraddwlors_________r__lteirillre_ouaanooiioeoooooiiihkiiiiiio__iei
tsppioi____________ggnodsc_sss_gfhf_fffhwh_nsmo__uee_siooooaeeeeoo_ii
cgppeeaoaeooeesseuutetaaaaaaaaaaaai__ei_in__aaie_eeerei_hrsssnacciiIi
iiiiiiisn_________________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
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_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]:

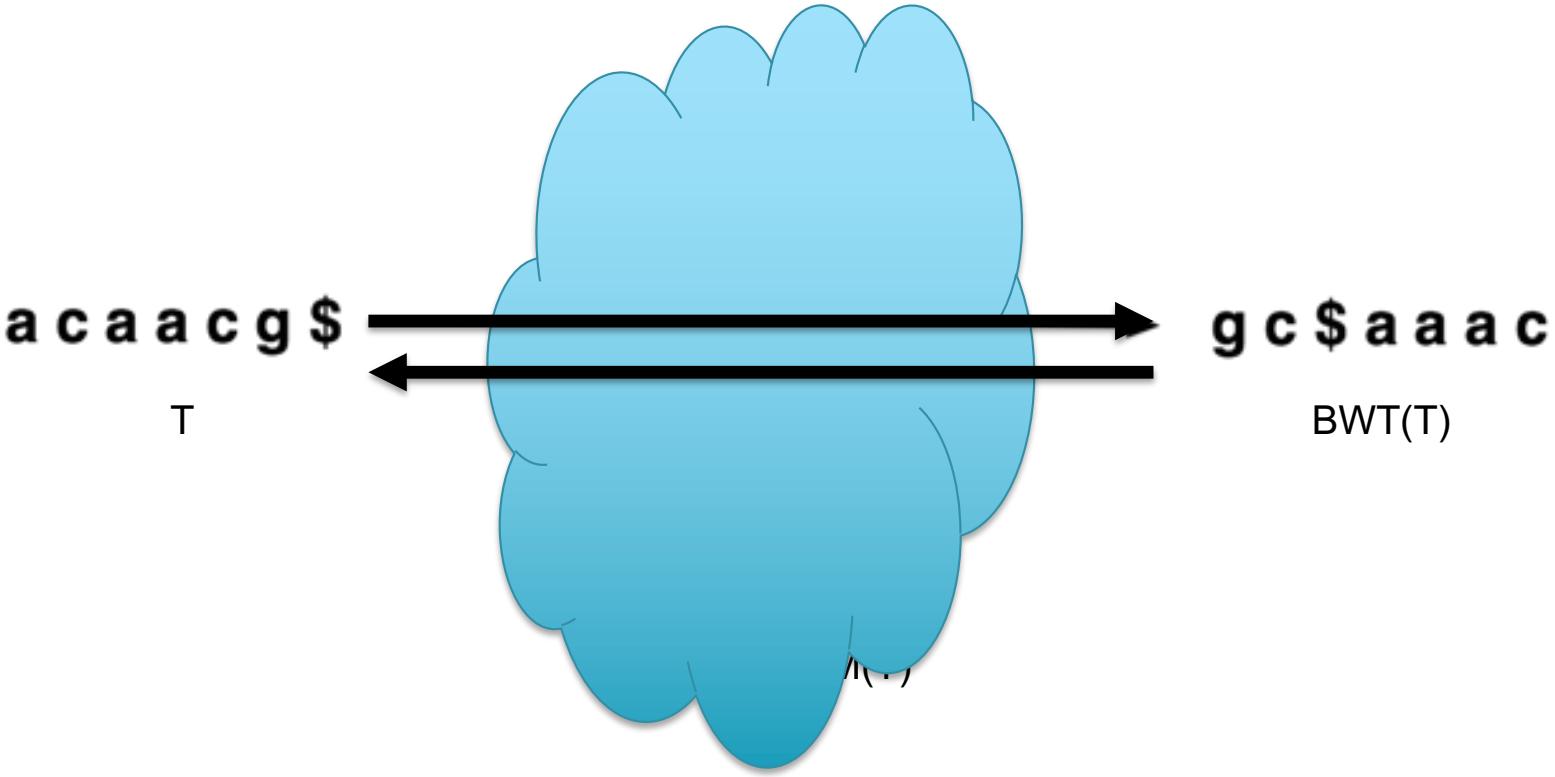
```
.dlms2ftysesdtrsns_y_2$_yfofe4tg2sfefefg2e2drofr,l2re2f-,fs,9nfrsdn2
hereghet2edndete2ge2nste2,s5t,es3ns2f2te2dt10r,4e3feh2_2p_2fpDw11e2h
l_ew_5eo2_ne3oa2eo2_4seph2r2hvh2w2egmgh7kr2w2h2s2Hr3vtr2ib2dbcbvs_2t
hw2p3vm2irdn2ib_2eo12_4e2n6a2i_3ec2_2t18s_tsgltsLlvt2_3h2o2re_wr2ad2
wlors_9r_2lteiril2re_oua2no2i2oeo4i3hki6o_2ieitsp2ioi_12g2nodsc_s3_g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

Burrows-Wheeler Transform

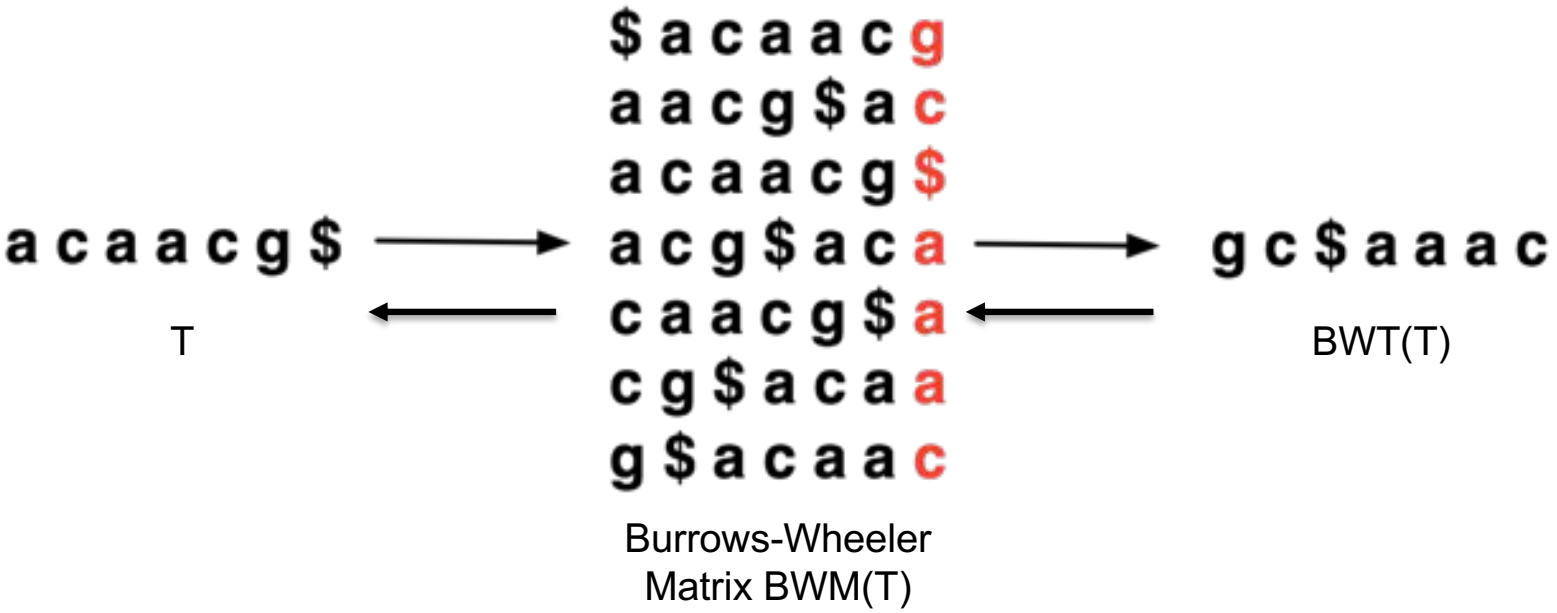
- Reversible permutation of the characters in a text



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

Burrows-Wheeler Transform

- Reversible permutation of the characters in a text

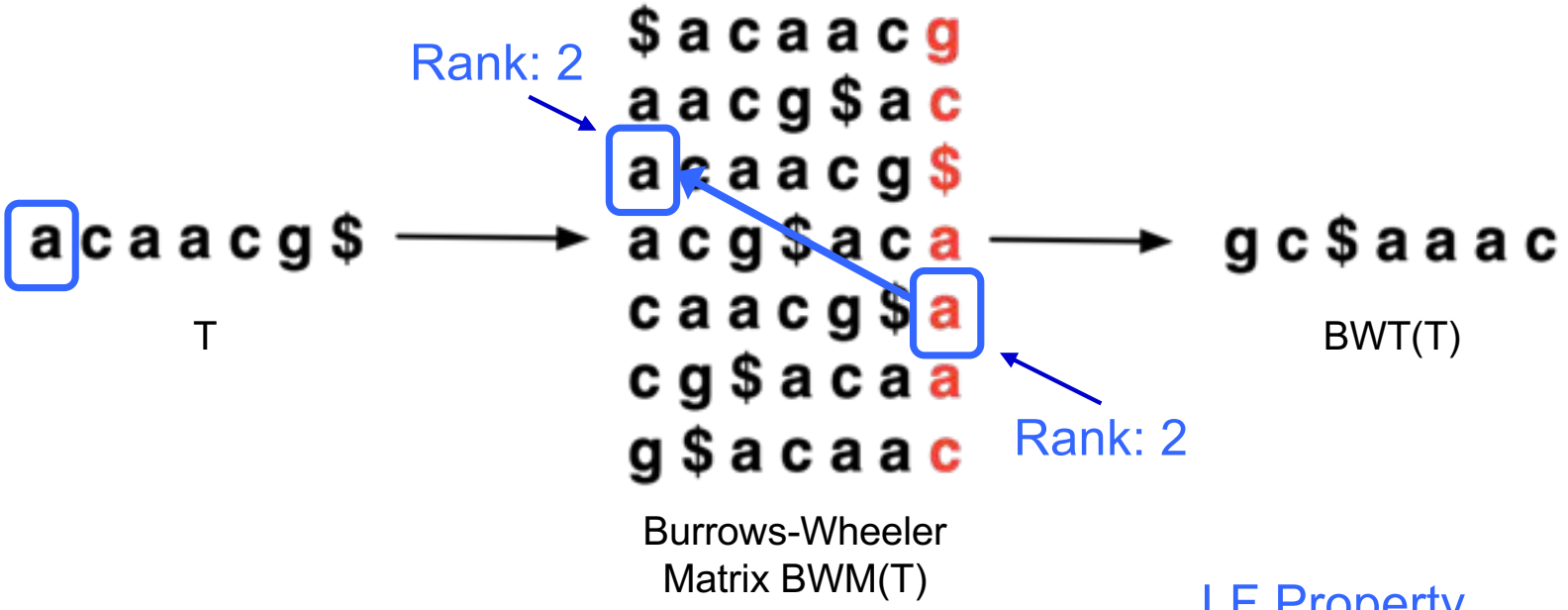


- BWT(T) is the index for T

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

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

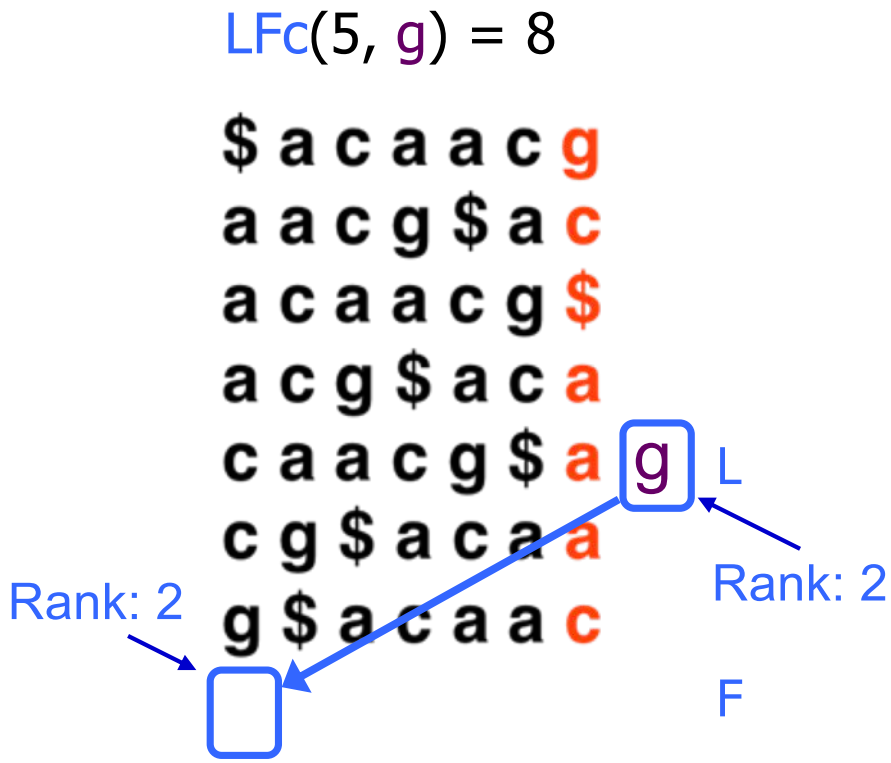
Burrows-Wheeler Transform

- 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]

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)

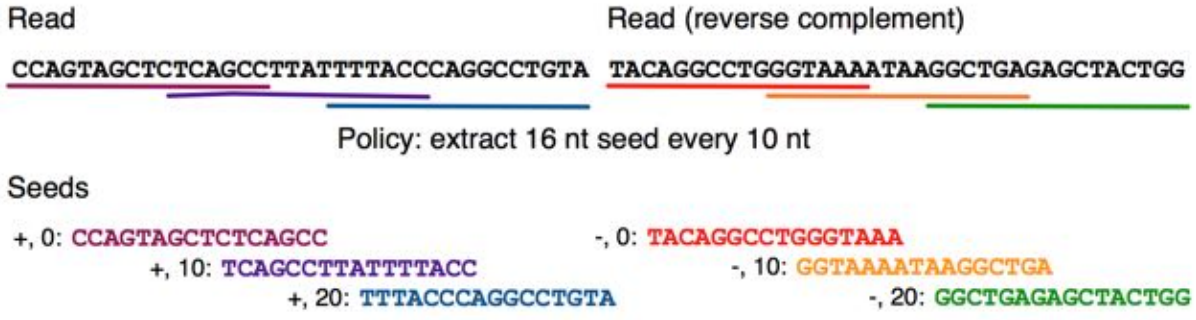
  qc = the next character to the left in the query

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

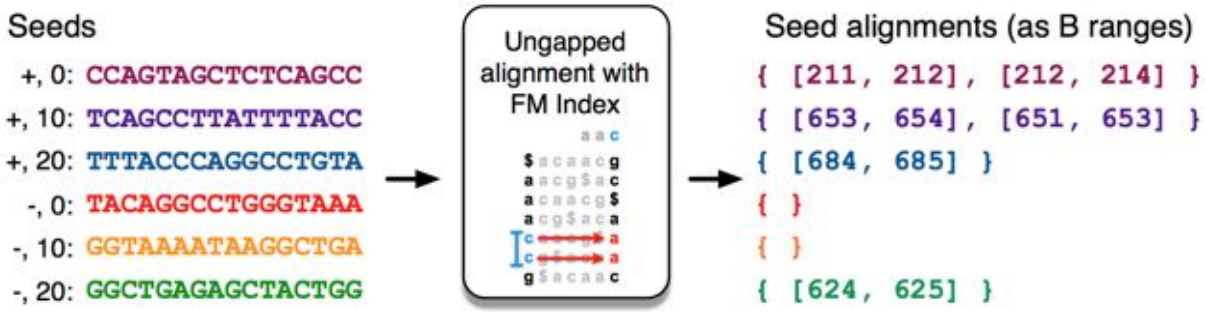
[Search for TTA this BWT string: ACTGA$TTA]

Algorithm Overview

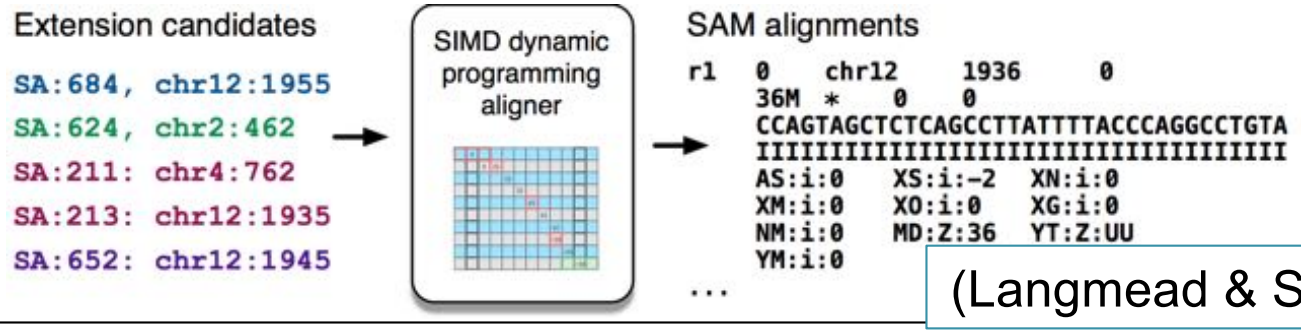
1. Split read into segments



2. Lookup each segment and prioritize



3. Evaluate end-to-end match



(Langmead & Salzberg, 2012)