Algorithms for Bioinformatics

Compressive Genomics

Ulf Leser

Hinweise

- Nächste Stunde (10.1.) entfällt
- Am 17.1.19 übernimmt Raik

Content of this Lecture

- Next Generation Sequencing
- Genome compression
- Approximate search in compressed genomes
- Using multiple references

- This lecture is not part of the examination

Large Scale Sequencing Projects

50.000 samples: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.

Genomics England … is creating a lasting legacy for patients, the NHS and the UK economy through the sequencing of 100,000 genomes: the 100,000 Genomes Project. [finished 5.12.2018]

The Veterans Affairs (VA) Office of Research and Development is launching the Million Veteran Program (MVP) …. The goal of MVP is to better understand how genes affect health and illness in order to improve health care.

Next Generation Sequencing

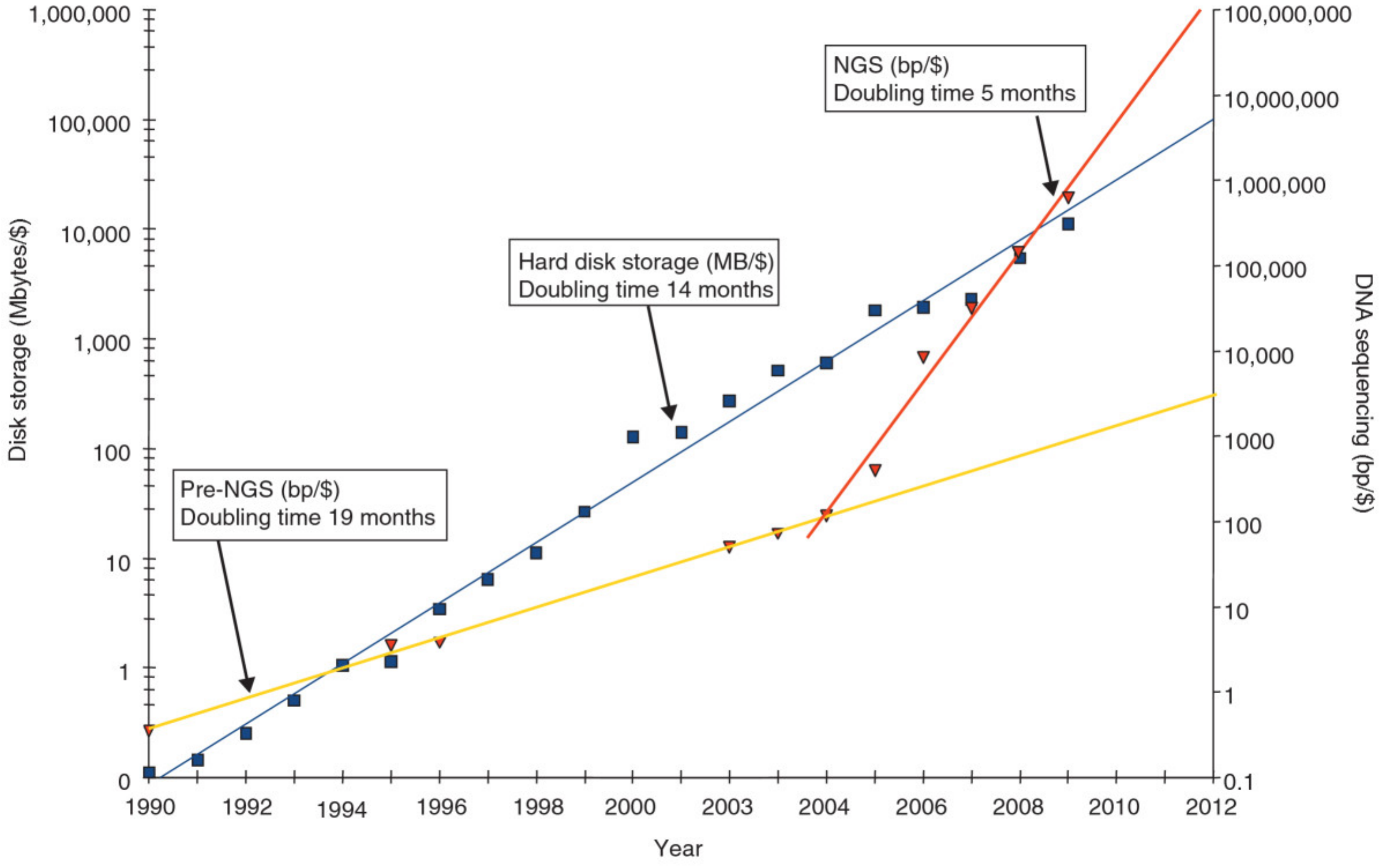
- New generation of sequencers since ~2005
  - Illumina, Solexa, 454, Solid, …
  - Massively parallel sequencing of short reads
- Much higher throughput
  - Terabytes of raw data per week
  - Cost for sequencing a genome down to ~1.000 USD
- 3rd generation sequencers
  - Single molecule sequencing
  - A (human) genome in a day
  - Sequence every human
  - Sequence different cells in every human

Illumina HiSeq 2000. DNAVision

2015: High-Seq

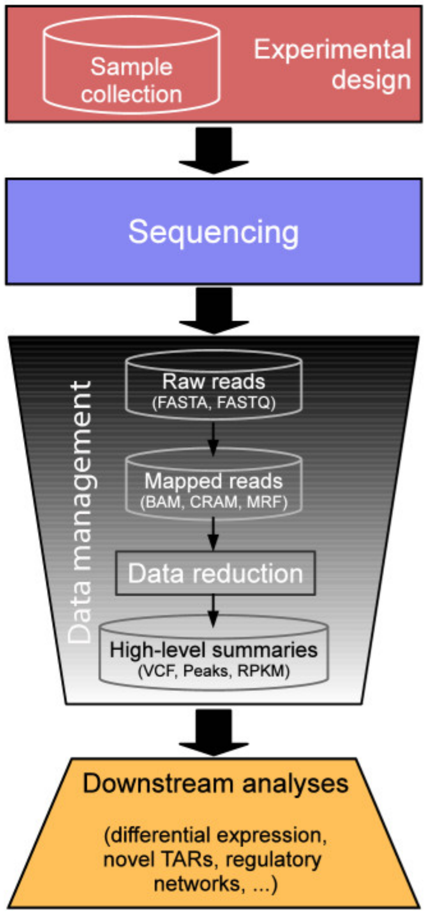
- 600GB / day, 18.000 genomes per year
- $1,000 genome at 30x coverage
  - Amortized over 18,000 genomes per year over four-year period

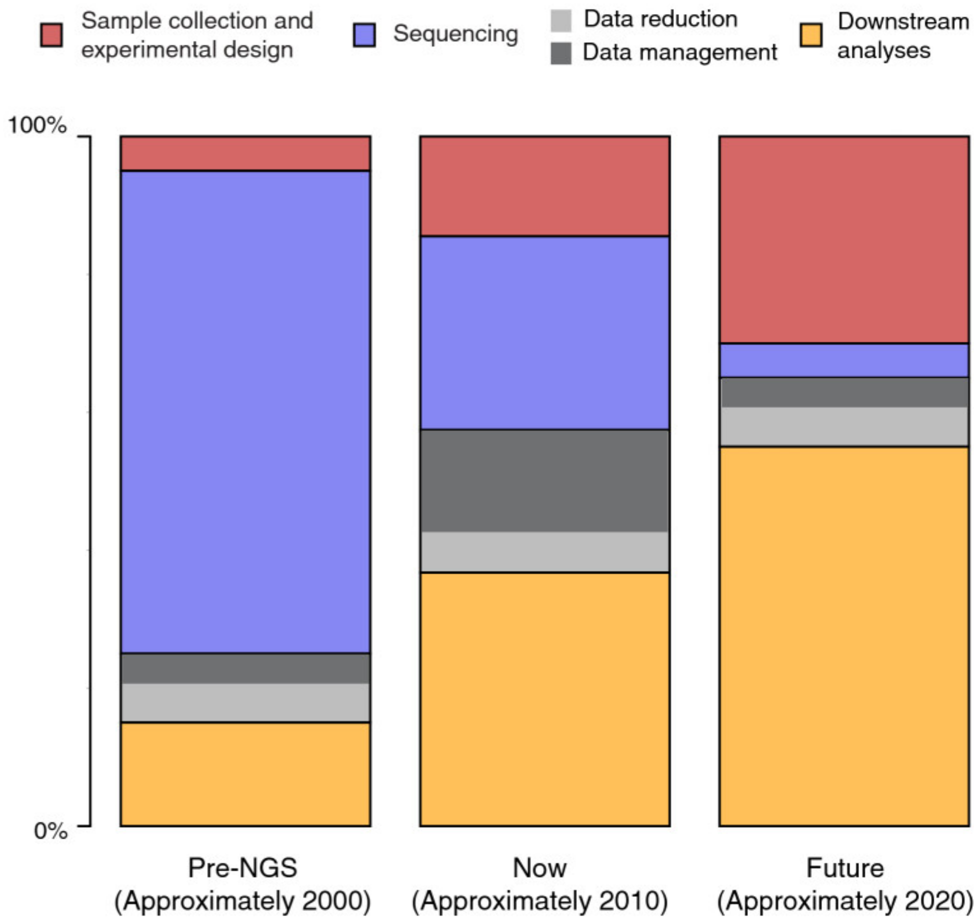
Data Tsunami



Stein, L. D. (2010). *Genome Biol*

The „real“ Cost of Genomic Sequencing





Sboner, A. (2011). The real cost of sequencing: higher than you think! Genome Biology 2011

New Problems

- Need to process huge amounts of data
  - Single genome at 30 fold coverage with read length 100bp: 900.000.000 reads
  - Single genome at 60 fold coverage with read length 100bp: 1.8E9 reads
  - 10.000 genomes per year ~ 30 genomes per day ~ processing of 60E9 reads per day
- Need to store huge amounts of sequence data
  - (Hundreds of) thousands of genomes

Content of this Lecture

- Next Generation Sequencing
- Genome compression
  - Referential compression
  - Four issues
- Approximate search in compressed genomes
- Using multiple references

Compressing Genomes

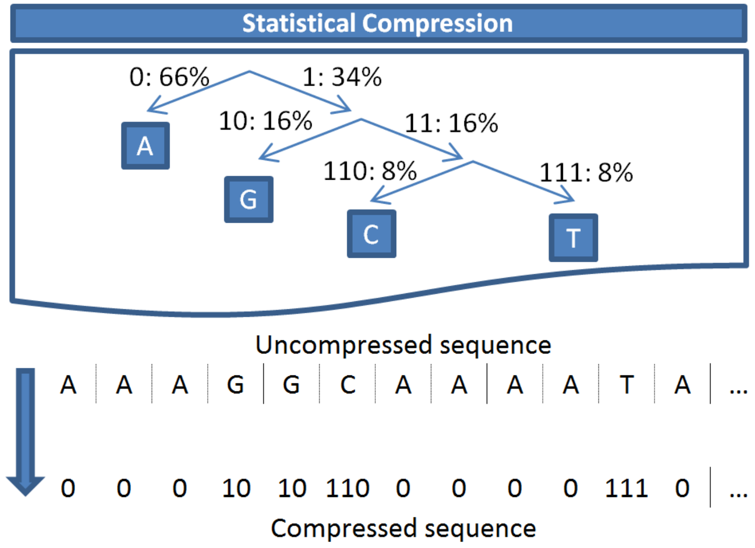
- Four basic techniques (lossless)
  - Bit packing
  - Statistical compression
  - Dictionary-based compression
  - Referential compression
- Criteria for compression methods
  - Compression ratio
  - Compression speed / decompression speed
  - Analyzing (searching) compressed data
- Compressing reads is another topic
  - Quality information, non-standard bases, short strings, …
- Another big topic: Lossy compression

1. Bit Packing

- A genome consists of 4 (5, 7, …) different bases
- Representing one bases thus requires 2 bits only
- One byte – four bases
- Compression ratio (compared to ASCII / FASTA): 1:4
- Advantages: Fast, universal, simple, all search operations can be easily adapated
- Disadvantage: Low compression ratio

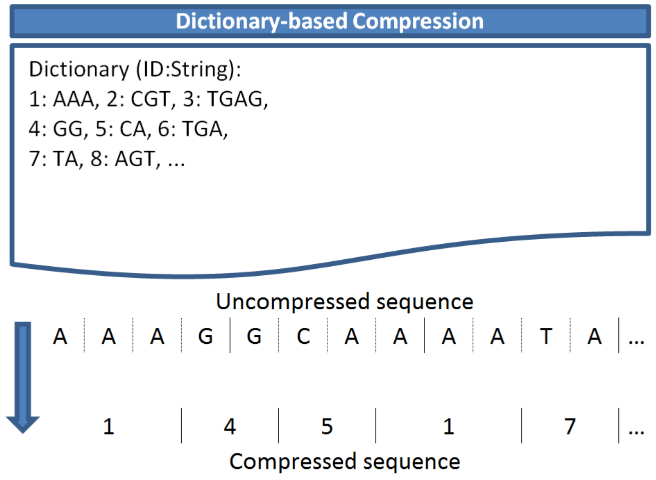
2. Statistical Compression

- Idea: Don't use the same number of bits for every char
- Frequent characters are represented with less bits
  - Example: Huffman coding, arithmetic coding
- Useful for larger alphabets with large differences in character frequencies
  - Can be applied to q-grams
- But: Even DNA q-gram are roughly equally frequent
- Disadvantage: Low compression ratio (~1:5)



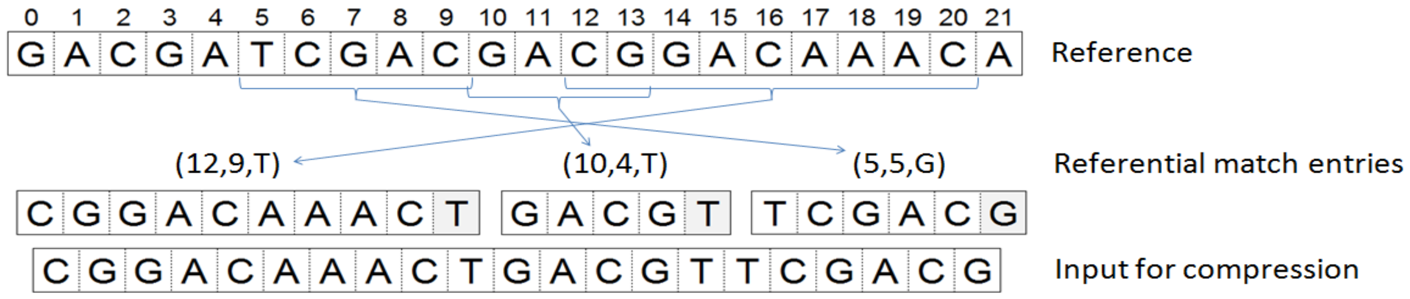
3. Dictionary-based Compression

- Idea: Represent frequent substrings with short codes
- Ziv-Lempel-Welch: Find most frequent substrings online
  - Stored in a dictionary
  - Index in dictionary is used as code
  - Trade-Off: Dictionary-size, compression speed, compression ratio
- Useful when large diffs in frequency of substrings exist
  - Recurring patterns: Images, language, tables, …
- Disadvantage: Low compression ratio (for DNA, ~1:4-6)

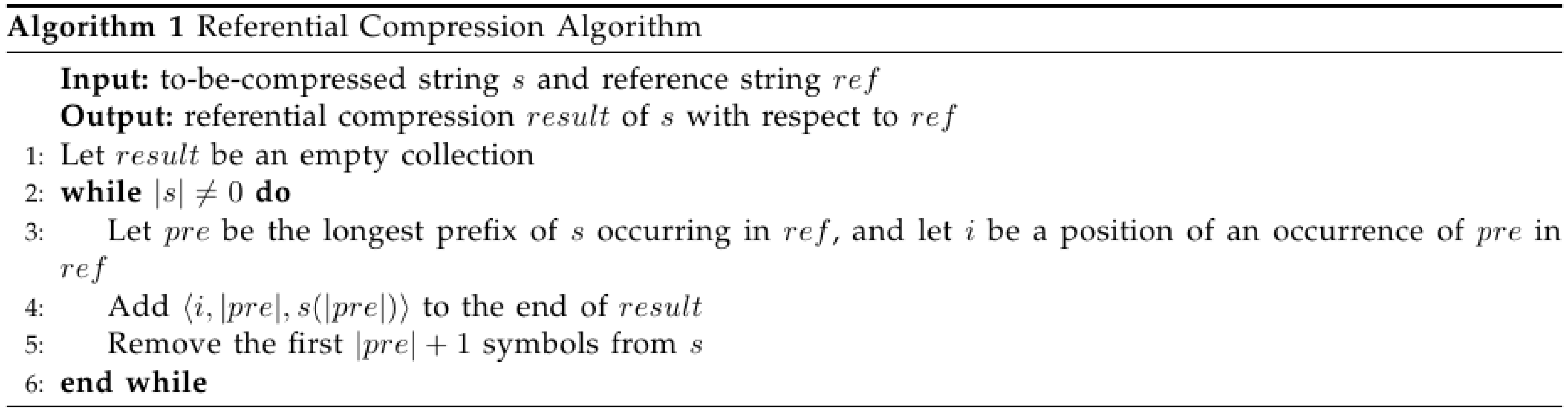


4. Referential Compression

- When sequencing humans, we know the reference genome
- Idea: Use reference as predefined "dictionary"
- Genomes are represented as lists of referential match entries (rme): (start, length, first mismatch)
- Issues
  - Find long matches fast
    - Trade-off: Long matches: ratio++; faster compression: ratio—
  - Efficient coding of RMEs



Greedy Algorithm



Algorithm 1 Referential Compression Algorithm

```
   Input: to-be-compressed string $s$ and reference string $ref$
   Output: referential compression $result$ of $s$ with respect to $ref$
1: Let $result$ be an empty collection
2: while $|s| \neq 0$ do
3:     Let $pre$ be the longest prefix of $s$ occurring in $ref$, and let $i$ be a position of an occurrence of $pre$ in $ref$
4:     Add $\langle i, |pre|, s(|pre|) \rangle$ to the end of $result$
5:     Remove the first $|pre| + 1$ symbols from $s$
6: end while
```

- Compression rate for human chromosomes: ~1:60
- Compression speed for human chromosomes : 80 MB/s
- Main memory usage during compression: ~4*|ref|+|s|
  - Using DNA-optimized compressed suffix trees

Content of this Lecture

- Next Generation Sequencing
- Genome compression
  - Referential compression
  - Four issues in referential compression
- Approximate search in compressed genomes
- Using multiple references

Issues

- Compact encoding of RMEs
- Main memory usage
- Faster compression / decompression
- Which reference?

- General: Balancing the trade-off between compression ratio and compression speed

1. Encoding RME’s

- Very frequent: Series of consecutive matches with short SNVs in between

Rare!

(1000,5,A), (1006,12,C), (1019,4,A), (1024,20,C), (1045,8,B), (9453,25,C), …

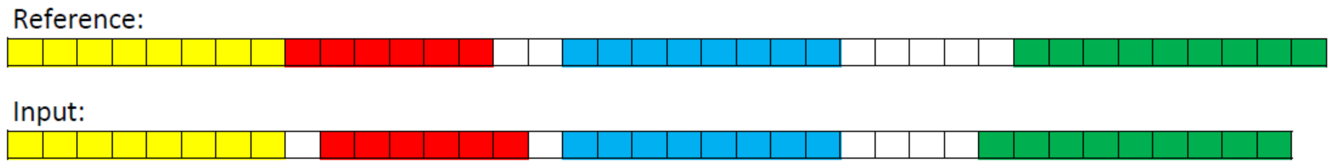
- Improvement: Delta encoding (with/out default stepsize)

(1000,5,A), (1006,12,C), (1019,4,A), (1024,20,C), (1045,8,B), (9453,25,C), …
(1000,5,A), (+6,12,C), (+13,4,A), (+5,20,C), (+21,8,B), (9453,25,C), …
(1000,5,A), (+0,12,C), (+0,4,A), (+0,20,C), (+0,8,B), (9453,25,C), …

- Large impact on compression ratio

2. Improving Main Memory Usage

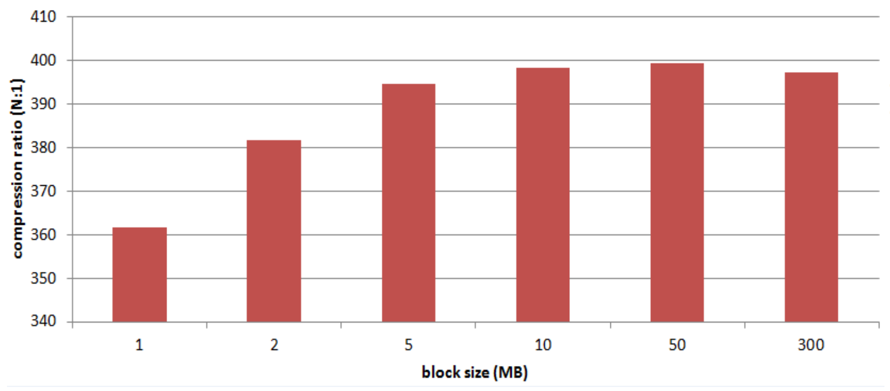
- Best (compressed) suffix tree libraries need ~4*|ref| space
- Observation: We often find consecutive matches in consecutive regions

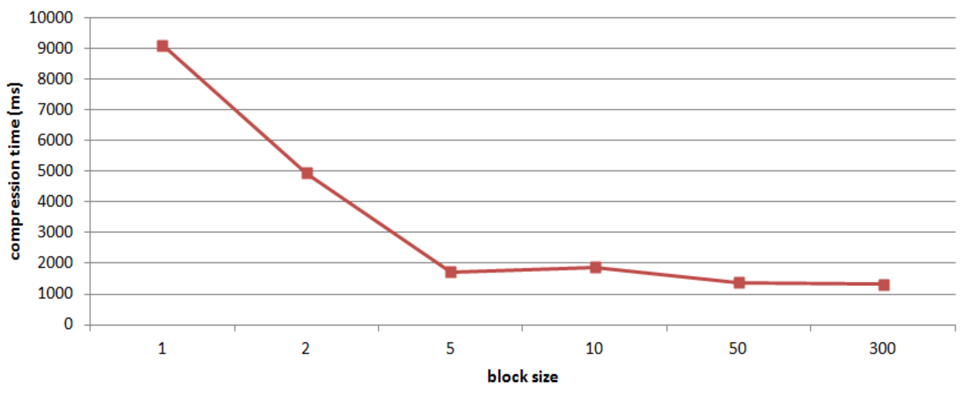


- Can be exploited to save main memory
  - Partition reference and input into blocks (e.g. 5MB)
  - Keep one (indexed) block at a time in main memory
  - Search other reference blocks only when no good match is found
- Switching blocks is costly: Avoid
  - Even if this means less optimal compression
  - Typical: Threshold on minimal length of RMEs; otherwise switch

Memory / compression speed / compression ratio

- Evaluation for human chromosome 1
  - Small blocks: Frequent block changes, bad ratio
  - Blocks larger than ~100MB: No further improvements of ratio
  - Compression/decompression requires only ~500MB for dictionary

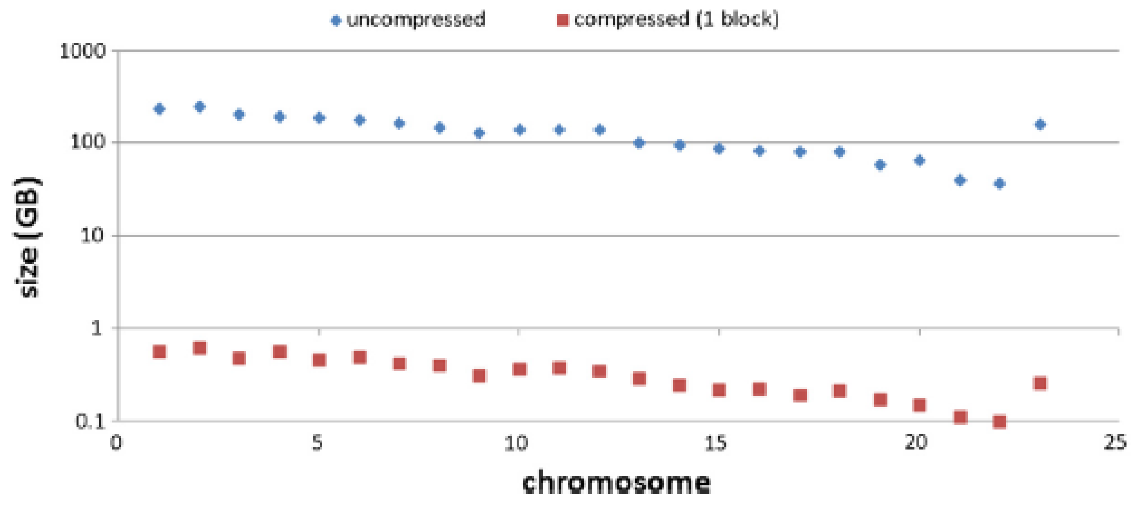




3. Improving compression speed

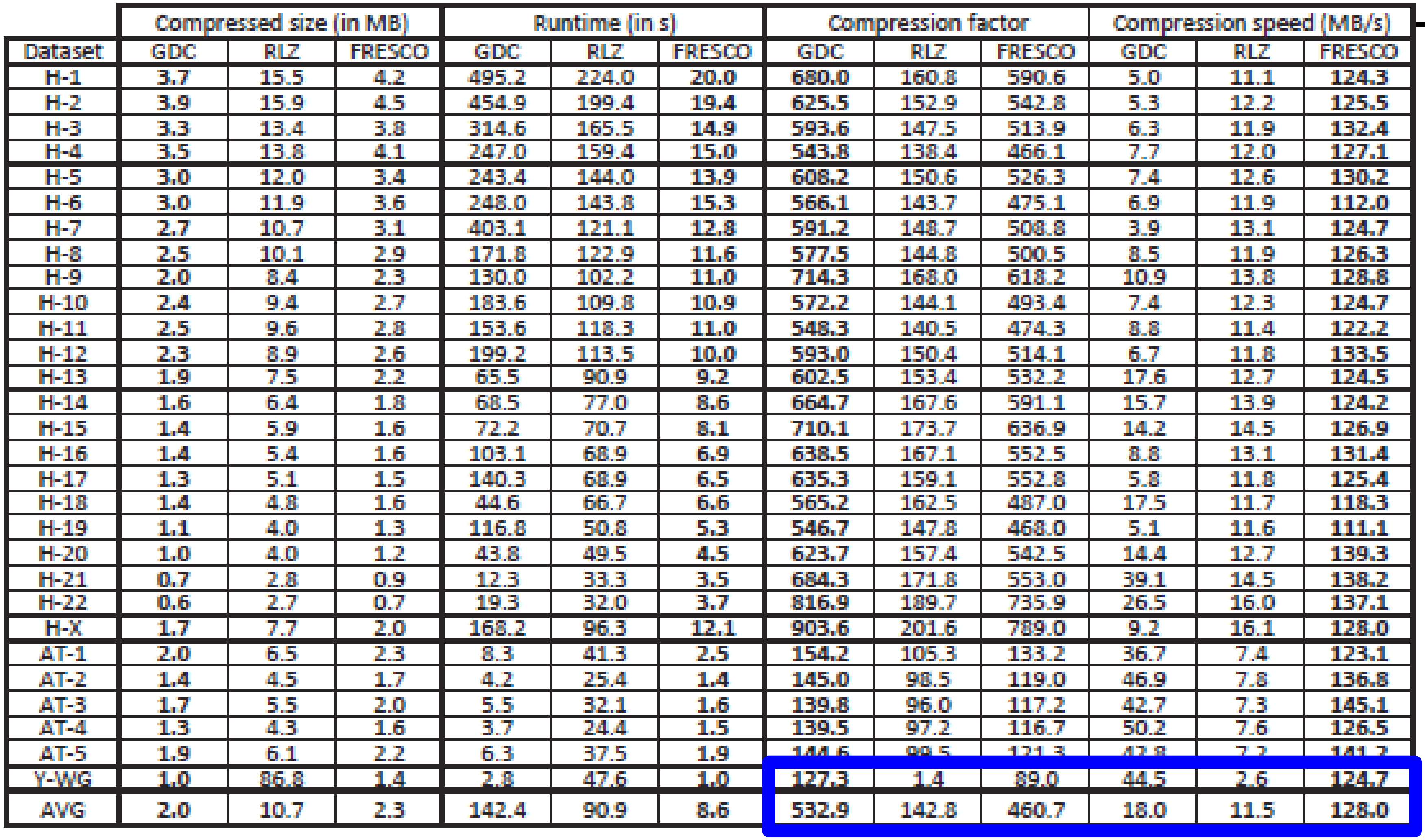
- Runtime dominated by looking up prefixes in the compressed suffix tree
  - Decoding the compressed suffix tree structure costs time
  - Maximal throughput: ~50.000 lookups / sec
- Improvement: Local matching
  - Search next RME near previous RME directly in the reference
    - Ignoring the index
  - Accept best next match iff RME sufficiently long
  - Speed-up by a factor of ~5-10
- Also improves compression ratio
  - Next matches close to previous ones – effective delta encoding
  - But may not find longest RME
  - Evaluation: Overall space reduction

Results: Ratio (Data: 1000 Genomes project)



Overall compression ratio: ~1:400

Results: Speed



	Compressed size (in MB)			Runtime (in s)			Compression factor			Compression speed (MB/s)		
Dataset	GDC	RLZ	FRESCO	GDC	RLZ	FRESCO	GDC	RLZ	FRESCO	GDC	RLZ	FRESCO
H-1	3.7	15.5	4.2	495.2	224.0	20.0	680.0	160.8	590.6	5.0	11.1	124.3
H-2	3.9	15.9	4.5	454.9	199.4	19.4	625.5	152.9	542.8	5.3	12.2	125.5
H-3	3.3	13.4	3.8	314.6	165.5	14.9	593.6	147.5	513.9	6.3	11.9	132.4
H-4	3.5	13.8	4.1	247.0	159.4	15.0	543.8	138.4	466.1	7.7	12.0	127.1
H-5	3.0	12.0	3.4	243.4	144.0	13.9	608.2	150.6	526.3	7.4	12.6	130.2
H-6	3.0	11.9	3.6	248.0	143.8	15.3	566.1	143.7	475.1	6.9	11.9	112.0
H-7	2.7	10.7	3.1	403.1	121.1	12.8	591.2	148.7	508.8	3.9	13.1	124.7
H-8	2.5	10.1	2.9	171.8	122.9	11.6	577.5	144.8	500.5	8.5	11.9	126.3
H-9	2.0	8.4	2.3	130.0	102.2	11.0	714.3	168.0	618.2	10.9	13.8	128.8
H-10	2.4	9.4	2.7	183.6	109.8	10.9	572.2	144.1	493.4	7.4	12.3	124.7
H-11	2.5	9.6	2.8	153.6	118.3	11.0	548.3	140.5	474.3	8.8	11.4	122.2
H-12	2.3	8.9	2.6	199.2	113.5	10.0	593.0	150.4	514.1	6.7	11.8	133.5
H-13	1.9	7.5	2.2	65.5	90.9	9.2	602.5	153.4	532.2	17.6	12.7	124.5
H-14	1.6	6.4	1.8	68.5	77.0	8.6	664.7	167.6	591.1	15.7	13.9	124.2
H-15	1.4	5.9	1.6	72.2	70.7	8.1	710.1	173.7	636.9	14.2	14.5	126.9
H-16	1.4	5.4	1.6	103.1	68.9	6.9	638.5	167.1	552.5	8.8	13.1	131.4
H-17	1.3	5.1	1.5	140.3	68.9	6.5	635.3	159.1	552.8	5.8	11.8	125.4
H-18	1.4	4.8	1.6	44.6	66.7	6.6	565.2	162.5	487.0	17.5	11.7	118.3
H-19	1.1	4.0	1.3	116.8	50.8	5.3	546.7	147.8	468.0	5.1	11.6	111.1
H-20	1.0	4.0	1.2	43.8	49.5	4.5	623.7	157.4	542.5	14.4	12.7	139.3
H-21	0.7	2.8	0.9	12.3	33.3	3.5	684.3	171.8	553.0	39.1	14.5	138.2
H-22	0.6	2.7	0.7	19.3	32.0	3.7	816.9	189.7	735.9	26.5	16.0	137.1
H-X	1.7	7.7	2.0	168.2	96.3	12.1	903.6	201.6	789.0	9.2	16.1	128.0
AT-1	2.0	6.5	2.3	8.3	41.3	2.5	154.2	105.3	133.2	36.7	7.4	123.1
AT-2	1.4	4.5	1.7	4.2	25.4	1.4	145.0	98.5	119.0	46.9	7.8	136.8
AT-3	1.7	5.5	2.0	5.5	32.1	1.6	139.8	96.0	117.2	42.7	7.3	145.1
AT-4	1.3	4.3	1.6	3.7	24.4	1.5	139.5	97.2	116.7	50.2	7.6	126.5
AT-5	1.9	6.1	2.2	6.3	37.5	1.9	144.6	99.5	121.3	42.8	7.2	141.2
Y-WG	1.0	86.8	1.4	2.8	47.6	1.0	127.3	1.4	89.0	44.5	2.6	124.7
AVG	2.0	10.7	2.3	142.4	90.9	8.6	532.9	142.8	460.7	18.0	11.5	128.0

Fig. 3: Compression statistics for 10 random sequences against a fixed reference (best values bold).

4. Which reference to use?

- Given a set of genomes: Which should be the reference?
- Similarity to reference is key to high compression rates
  - Compressing Human against Mouse: Disaster
  - Similarity in non-coding region is low
- Exhaustive reference selection is very time consuming (took 6 days for 1092 * 1091 H-22)

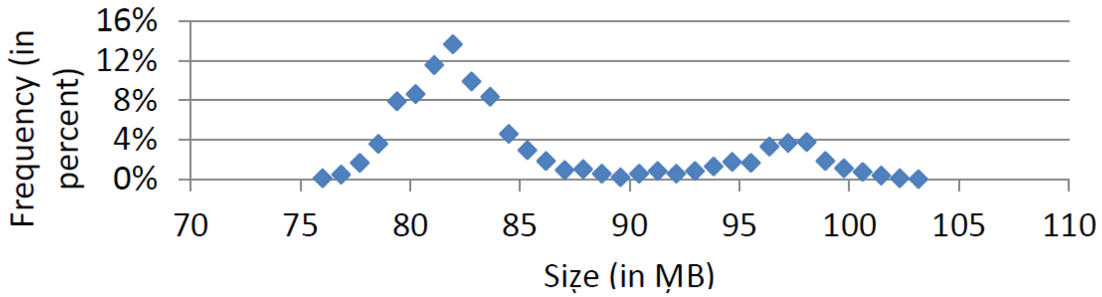
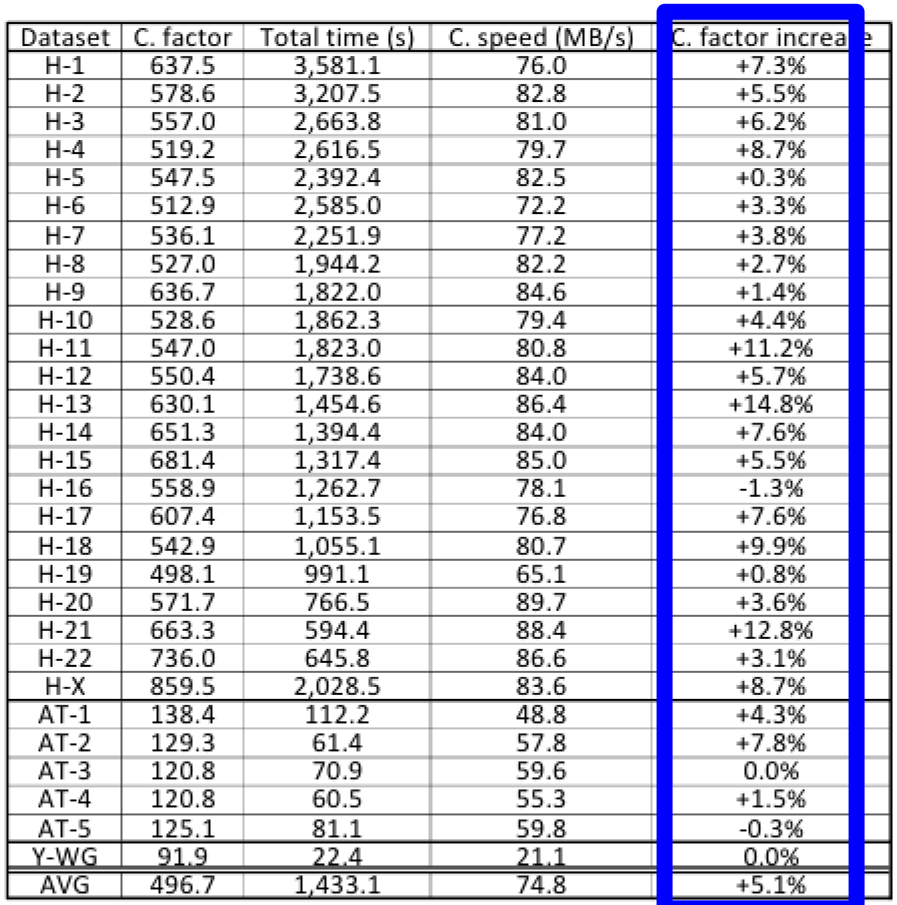


Fig.: Distribution of total storage requirements for all against all for H-22.

Two Alternatives

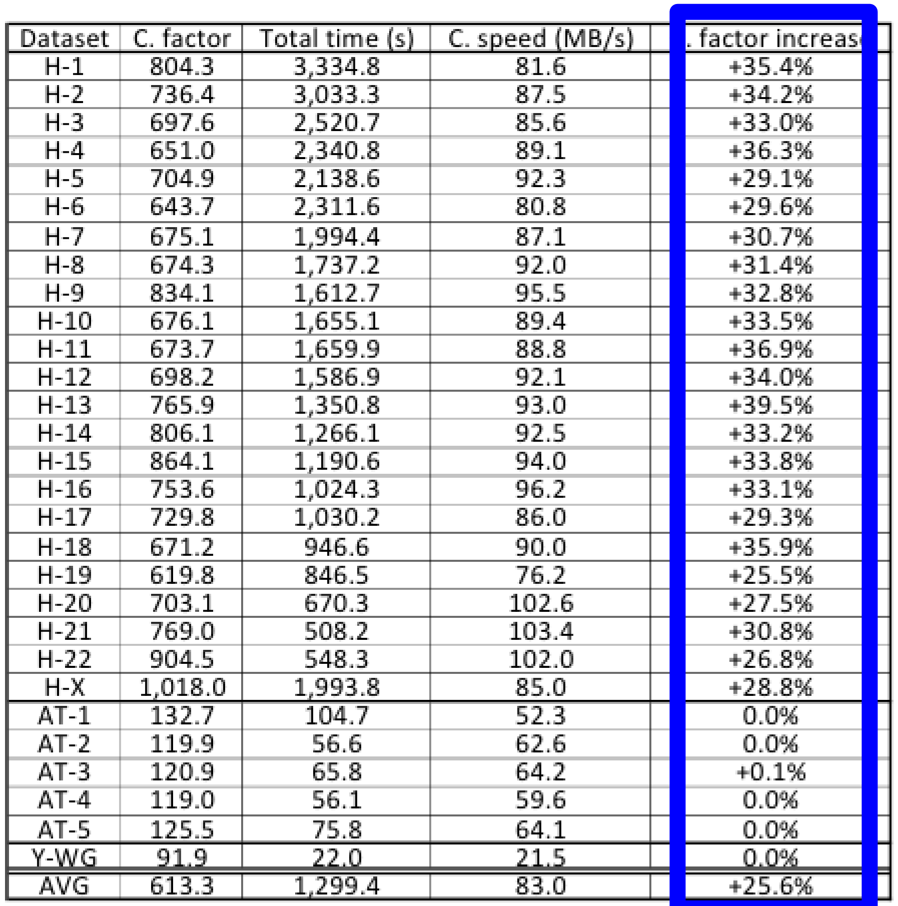
- Idea: Chose as reference the genome with highest average similarity to all other genomes
- Heuristic-based reference selection
  - Define a heuristic for the similarity of two sequences
    - For instance: Compute best reference based on small sample
    - Use any other fast similarity estimation method
  - Pick the sequence most similar to all other sequences according to this heuristic
- Better: Build your own reference
  - Reference rewriting
  - Given a reference, rewrite it in order to obtain higher compression ratios
    - Note: It doesn’t matter if the reference is a “real” genome

Selection versus Rewriting



Dataset	C. factor	Total time (s)	C. speed (MB/s)	C. factor increa e
H-1	637.5	3,581.1	76.0	+7.3%
H-2	578.6	3,207.5	82.8	+5.5%
H-3	557.0	2,663.8	81.0	+6.2%
H-4	519.2	2,616.5	79.7	+8.7%
H-5	547.5	2,392.4	82.5	+0.3%
H-6	512.9	2,585.0	72.2	+3.3%
H-7	536.1	2,251.9	77.2	+3.8%
H-8	527.0	1,944.2	82.2	+2.7%
H-9	636.7	1,822.0	84.6	+1.4%
H-10	528.6	1,862.3	79.4	+4.4%
H-11	547.0	1,823.0	80.8	+11.2%
H-12	550.4	1,738.6	84.0	+5.7%
H-13	630.1	1,454.6	86.4	+14.8%
H-14	651.3	1,394.4	84.0	+7.6%
H-15	681.4	1,317.4	85.0	+5.5%
H-16	558.9	1,262.7	78.1	-1.3%
H-17	607.4	1,153.5	76.8	+7.6%
H-18	542.9	1,055.1	80.7	+9.9%
H-19	498.1	991.1	65.1	+0.8%
H-20	571.7	766.5	89.7	+3.6%
H-21	663.3	594.4	88.4	+12.8%
H-22	736.0	645.8	86.6	+3.1%
H-X	859.5	2,028.5	83.6	+8.7%
AT-1	138.4	112.2	48.8	+4.3%
AT-2	129.3	61.4	57.8	+7.8%
AT-3	120.8	70.9	59.6	0.0%
AT-4	120.8	60.5	55.3	+1.5%
AT-5	125.1	81.1	59.8	-0.3%
Y-WG	91.9	22.4	21.1	0.0%
AVG	496.7	1,433.1	74.8	+5.1%

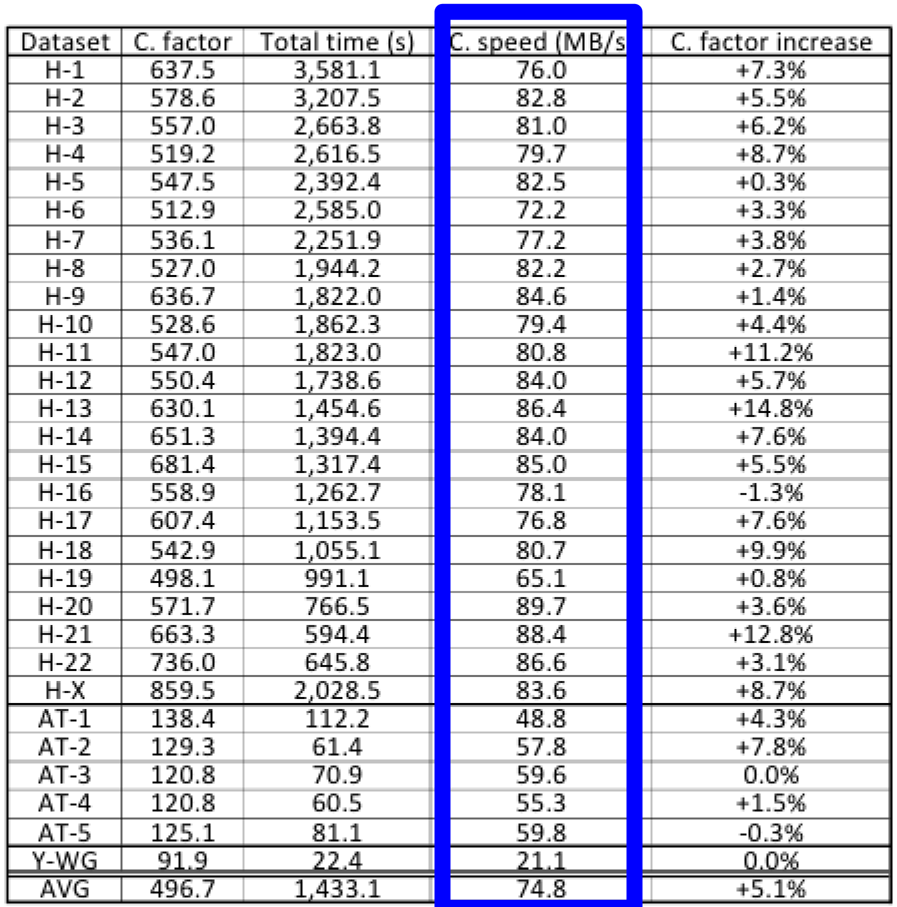
Fig. : Compression statistics for selecting references



Dataset	C. factor	Total time (s)	C. speed (MB/s)	. factor increas
H-1	804.3	3,334.8	81.6	+35.4%
H-2	736.4	3,033.3	87.5	+34.2%
H-3	697.6	2,520.7	85.6	+33.0%
H-4	651.0	2,340.8	89.1	+36.3%
H-5	704.9	2,138.6	92.3	+29.1%
H-6	643.7	2,311.6	80.8	+29.6%
H-7	675.1	1,994.4	87.1	+30.7%
H-8	674.3	1,737.2	92.0	+31.4%
H-9	834.1	1,612.7	95.5	+32.8%
H-10	676.1	1,655.1	89.4	+33.5%
H-11	673.7	1,659.9	88.8	+36.9%
H-12	698.2	1,586.9	92.1	+34.0%
H-13	765.9	1,350.8	93.0	+39.5%
H-14	806.1	1,266.1	92.5	+33.2%
H-15	864.1	1,190.6	94.0	+33.8%
H-16	753.6	1,024.3	96.2	+33.1%
H-17	729.8	1,030.2	86.0	+29.3%
H-18	671.2	946.6	90.0	+35.9%
H-19	619.8	846.5	76.2	+25.5%
H-20	703.1	670.3	102.6	+27.5%
H-21	769.0	508.2	103.4	+30.8%
H-22	904.5	548.3	102.0	+26.8%
H-X	1,018.0	1,993.8	85.0	+28.8%
AT-1	132.7	104.7	52.3	0.0%
AT-2	119.9	56.6	62.6	0.0%
AT-3	120.9	65.8	64.2	+0.1%
AT-4	119.0	56.1	59.6	0.0%
AT-5	125.5	75.8	64.1	0.0%
Y-WG	91.9	22.0	21.5	0.0%
AVG	613.3	1,299.4	83.0	+25.6%

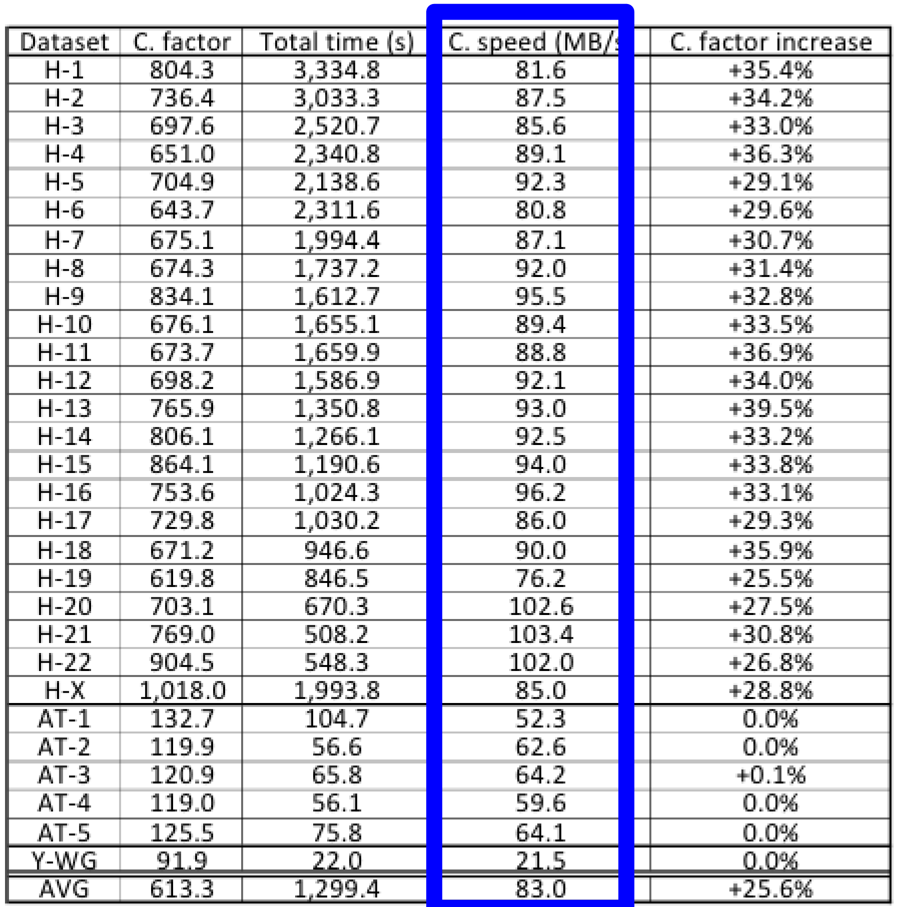
Fig. : Compression statistics for rewriting references

Selection versus Rewriting



Dataset	C. factor	Total time (s)	C. speed (MB/s	C. factor increase
H-1	637.5	3,581.1	76.0	+7.3%
H-2	578.6	3,207.5	82.8	+5.5%
H-3	557.0	2,663.8	81.0	+6.2%
H-4	519.2	2,616.5	79.7	+8.7%
H-5	547.5	2,392.4	82.5	+0.3%
H-6	512.9	2,585.0	72.2	+3.3%
H-7	536.1	2,251.9	77.2	+3.8%
H-8	527.0	1,944.2	82.2	+2.7%
H-9	636.7	1,822.0	84.6	+1.4%
H-10	528.6	1,862.3	79.4	+4.4%
H-11	547.0	1,823.0	80.8	+11.2%
H-12	550.4	1,738.6	84.0	+5.7%
H-13	630.1	1,454.6	86.4	+14.8%
H-14	651.3	1,394.4	84.0	+7.6%
H-15	681.4	1,317.4	85.0	+5.5%
H-16	558.9	1,262.7	78.1	-1.3%
H-17	607.4	1,153.5	76.8	+7.6%
H-18	542.9	1,055.1	80.7	+9.9%
H-19	498.1	991.1	65.1	+0.8%
H-20	571.7	766.5	89.7	+3.6%
H-21	663.3	594.4	88.4	+12.8%
H-22	736.0	645.8	86.6	+3.1%
H-X	859.5	2,028.5	83.6	+8.7%
AT-1	138.4	112.2	48.8	+4.3%
AT-2	129.3	61.4	57.8	+7.8%
AT-3	120.8	70.9	59.6	0.0%
AT-4	120.8	60.5	55.3	+1.5%
AT-5	125.1	81.1	59.8	-0.3%
Y-WG	91.9	22.4	21.1	0.0%
AVG	496.7	1,433.1	74.8	+5.1%

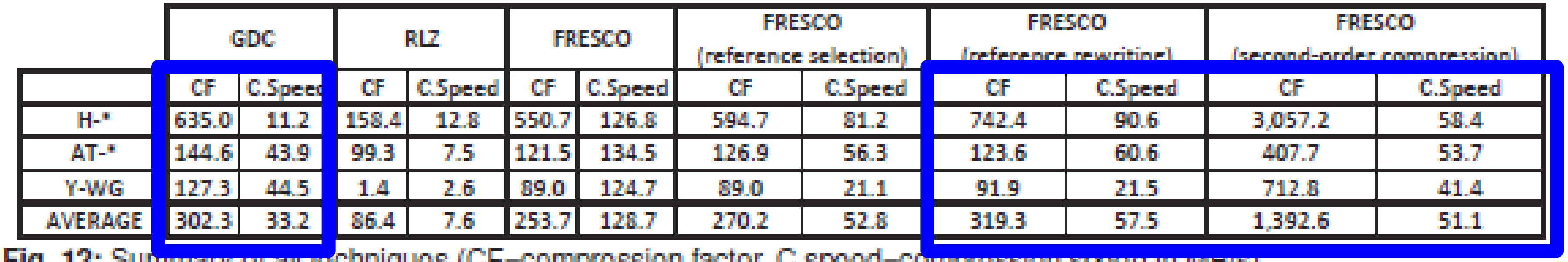
Fig. : Compression statistics for selecting references



Dataset	C. factor	Total time (s)	C. speed (MB/	C. factor increase
H-1	804.3	3,334.8	81.6	+35.4%
H-2	736.4	3,033.3	87.5	+34.2%
H-3	697.6	2,520.7	85.6	+33.0%
H-4	651.0	2,340.8	89.1	+36.3%
H-5	704.9	2,138.6	92.3	+29.1%
H-6	643.7	2,311.6	80.8	+29.6%
H-7	675.1	1,994.4	87.1	+30.7%
H-8	674.3	1,737.2	92.0	+31.4%
H-9	834.1	1,612.7	95.5	+32.8%
H-10	676.1	1,655.1	89.4	+33.5%
H-11	673.7	1,659.9	88.8	+36.9%
H-12	698.2	1,586.9	92.1	+34.0%
H-13	765.9	1,350.8	93.0	+39.5%
H-14	806.1	1,266.1	92.5	+33.2%
H-15	864.1	1,190.6	94.0	+33.8%
H-16	753.6	1,024.3	96.2	+33.1%
H-17	729.8	1,030.2	86.0	+29.3%
H-18	671.2	946.6	90.0	+35.9%
H-19	619.8	846.5	76.2	+25.5%
H-20	703.1	670.3	102.6	+27.5%
H-21	769.0	508.2	103.4	+30.8%
H-22	904.5	548.3	102.0	+26.8%
H-X	1,018.0	1,993.8	85.0	+28.8%
AT-1	132.7	104.7	52.3	0.0%
AT-2	119.9	56.6	62.6	0.0%
AT-3	120.9	65.8	64.2	+0.1%
AT-4	119.0	56.1	59.6	0.0%
AT-5	125.5	75.8	64.1	0.0%
Y-WG	91.9	22.0	21.5	0.0%
AVG	613.3	1,299.4	83.0	+25.6%

Fig. : Compression statistics for rewriting references

Fresco: Comparative Evaluation



	GDC		RLZ		FRESCO		FRESCO (reference selection)		FRESCO (reference rewriting)		FRESCO (second-order compression)	
	CF	C.Speed	CF	C.Speed	CF	C.Speed	CF	C.Speed	CF	C.Speed	CF	C.Speed
H-*	635.0	11.2	158.4	12.8	550.7	126.8	594.7	81.2	742.4	90.6	3,057.2	58.4
AT-*	144.6	43.9	99.3	7.5	121.5	134.5	126.9	56.3	123.6	60.6	407.7	53.7
Y-WG	127.3	44.5	1.4	2.6	89.0	124.7	89.0	21.1	91.9	21.5	712.8	41.4
AVERAGE	302.3	33.2	86.4	7.6	253.7	128.7	270.2	52.8	319.3	57.5	1,392.6	51.1

Fig. 12: Summary of all techniques (CF=compression factor, C.speed=compression speed in MB/s)

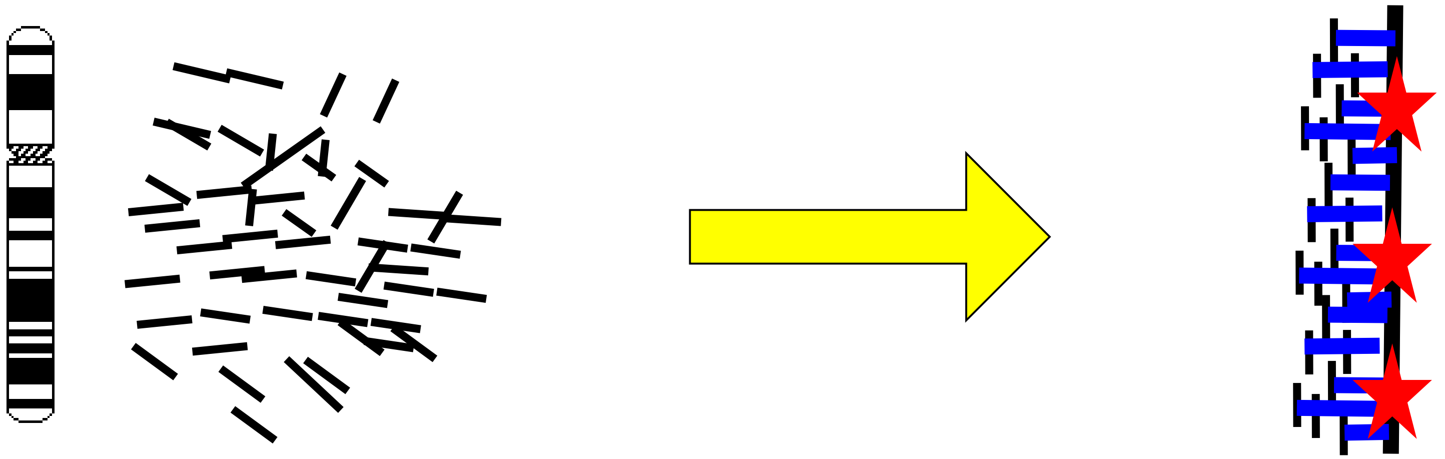
- Second Order Compression: Compress RME sets
  - All sequences are similar to each other
  - Thus, different sequences produce very similar RME lists
  - Idea: Compress (using “meta” referential compression)
- Best algorithms as of 2015 [Deorowisc 2015, GDC-2]
  - Compression ratio 1:9500
  - 7TB FASTA compressed to 700MB
  - Speed: 200MB/sec (beware: measured on different hardware)

Content of this Lecture

- Next Generation Sequencing
- Sequence compression
  - Referential compression
  - Four issues
- Approximate search in compressed genomes
- Using multiple references

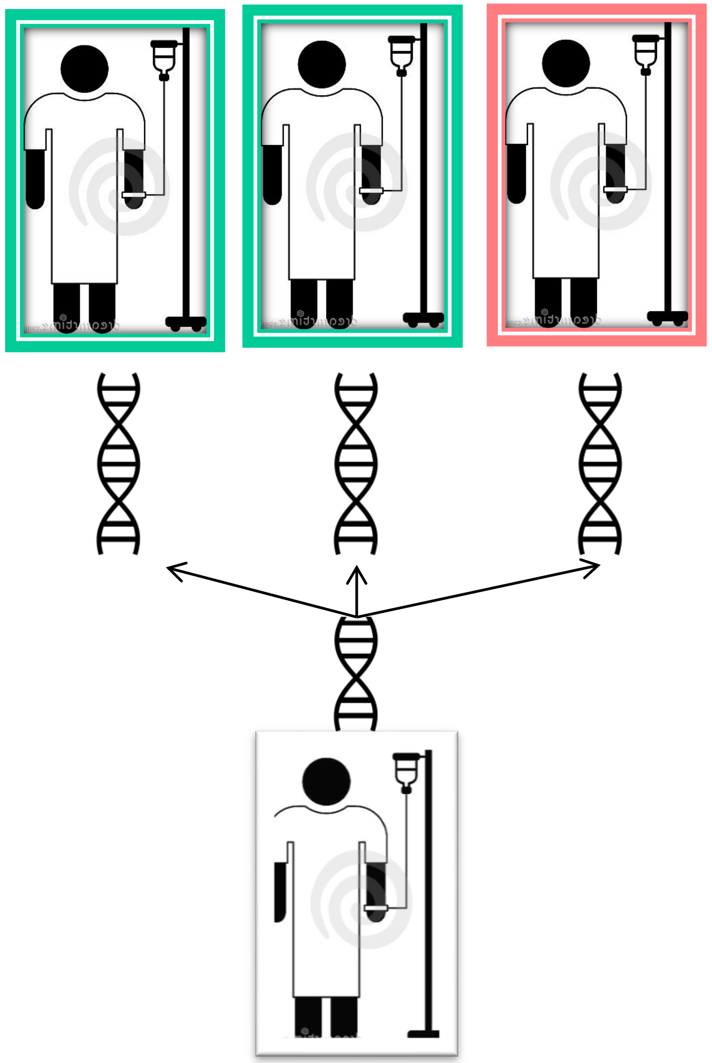
K-Approximate Matching (k-difference Mathcing)

- Given a collection of referentially compressed genomes S, find all k-approximate matches of a query q

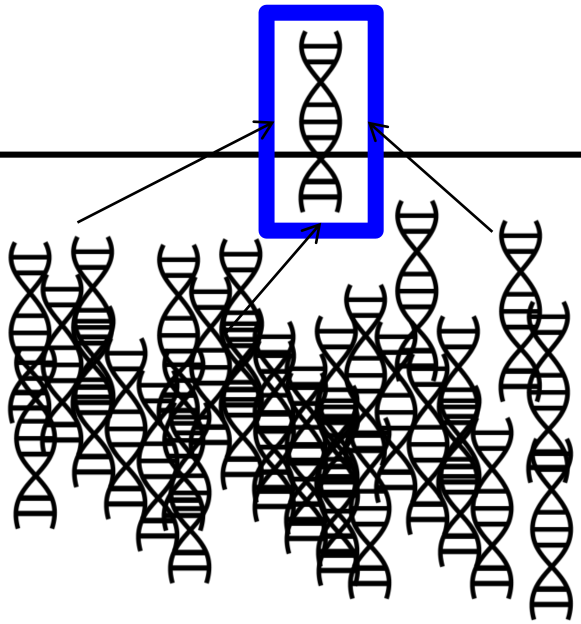


Example Application: Personalized Medicine

- Modern cancer drugs depend on genotype of patients
- Genotype: Mutations in certain cancer genes
- Clinics sequence thousands of human genomes
- Given a set of patient genomes S with known outcome and the sequence of a cancer gene g in a new patient q – what is the most similar occurrence of g in S?



Storing Similar Strings



- Referential Compression
  - Choose a reference string p from S
  - When adding a new string s, only store differences between s and p

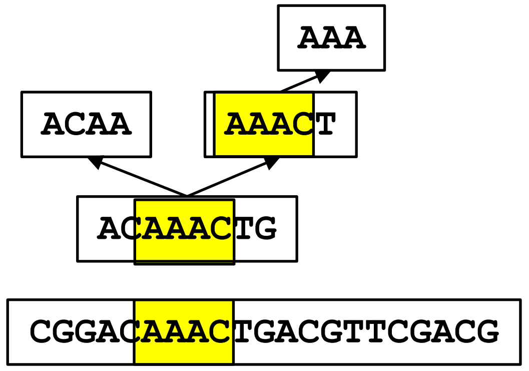
```
        012345678901234567 8
p:      Kohala Coast-Hawaii
s2:     Kohala Cost
s3:     Koala Coast/Hawaii
```

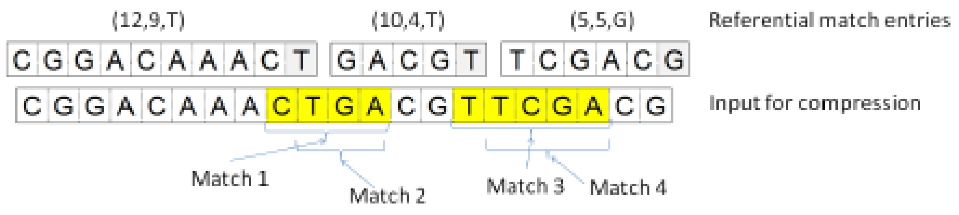
```
s2: (p,0,9,s),(p,11,1,_)
s3: (p,0,2,a),(p,4,8,/),(p,13,6,_)
```

RME: Referential Match Entries

RCSI: Referentially Compressed Search Index

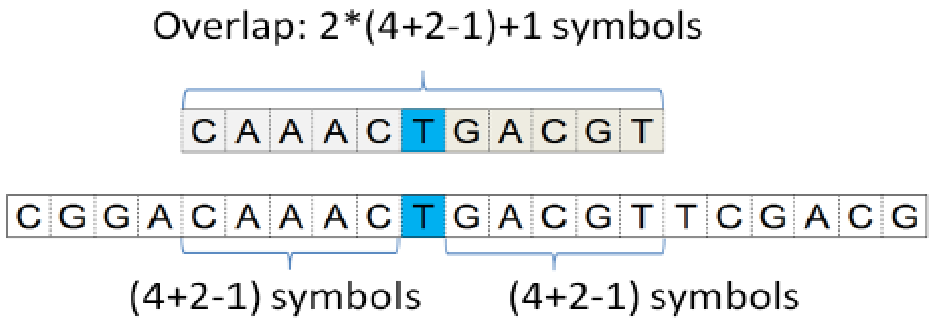
- Key idea: Find matches in all compressed sequences simultaneously by searching the reference
  - Store reference as suffix tree
  - Search using standard BYP-algorithm
  - For every match, find all RME completely containing that match
    - Build an interval tree over all RMEs
    - If RME X contains match, only children of X may contain other matches
- Problem: Matches not contained in the reference





RCSI Approach

- Fix maximal query length q_{max} and maximal k_{max}
- Compute overlap sequences
  - One for every mismatch leading to two consecutive RMEs
- How long must these overlaps be?
  - Answer: $2*|q_{max} + k_{max}|$
  - Very conservative estimation, guaranteed to not loose any match
- Index set of overlap sequences
- This index can be searched using BYP
  - Additional to searching the reference


Overlap: 2*(4+2-1)+1 symbols
C A A A C T G A C G T
C G G A C A A A C T G A C G T T C G A C G
(4+2-1) symbols
(4+2-1) symbols

RCSI: Architecture

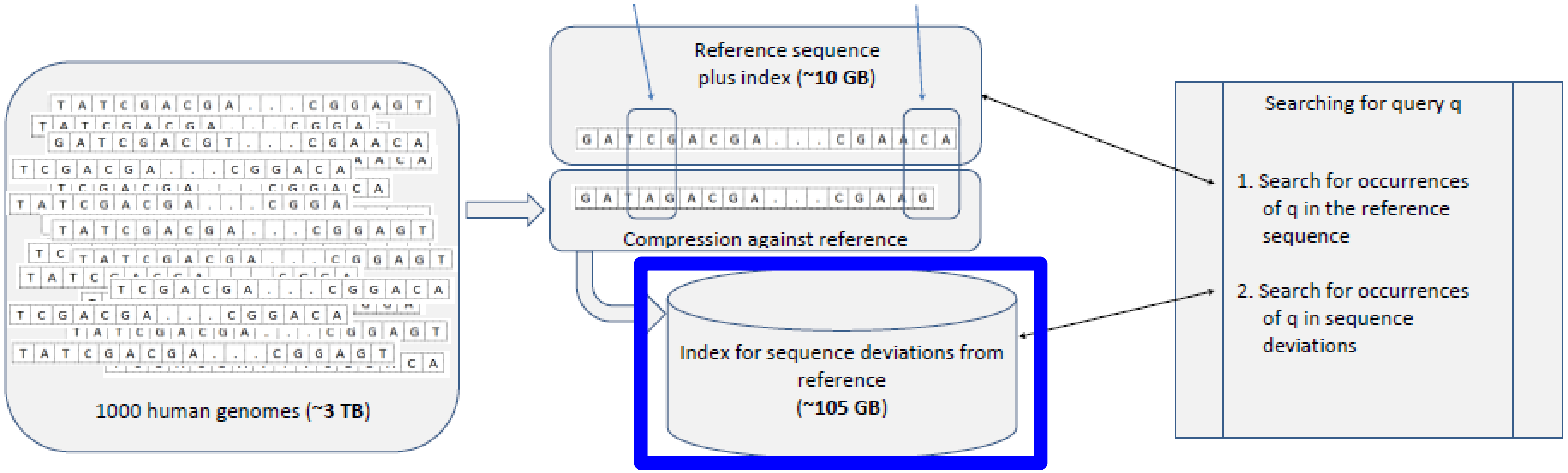

Reference sequence plus index (~10 GB)
Compression against reference
1000 human genomes (~3 TB)
Index for sequence deviations from reference (~105 GB)
Searching for query q
1. Search for occurrences of q in the reference sequence
2. Search for occurrences of q in sequence deviations

Figure 1: Overview of our Referentially Compressed Search Index.

Evaluation: Indexing time

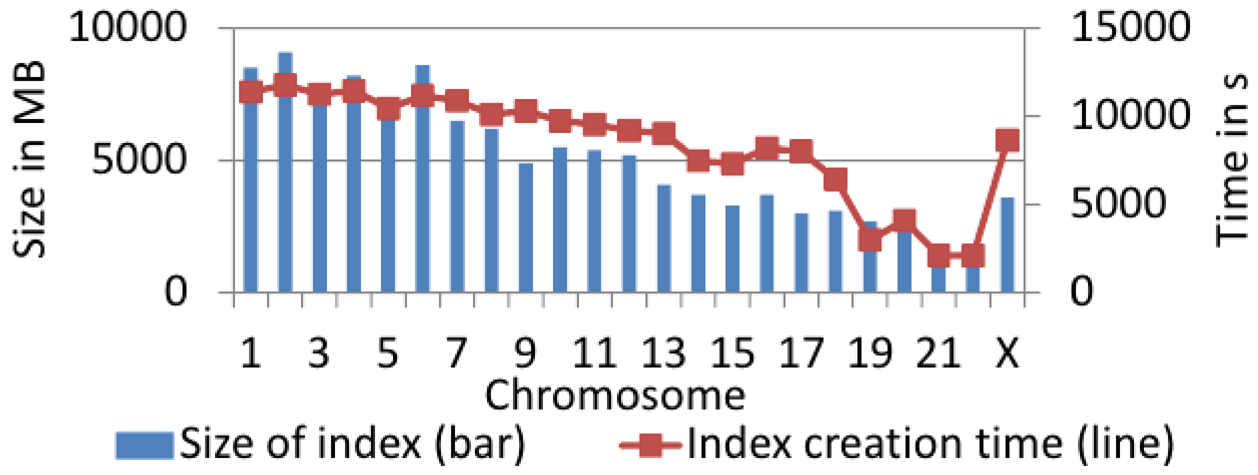
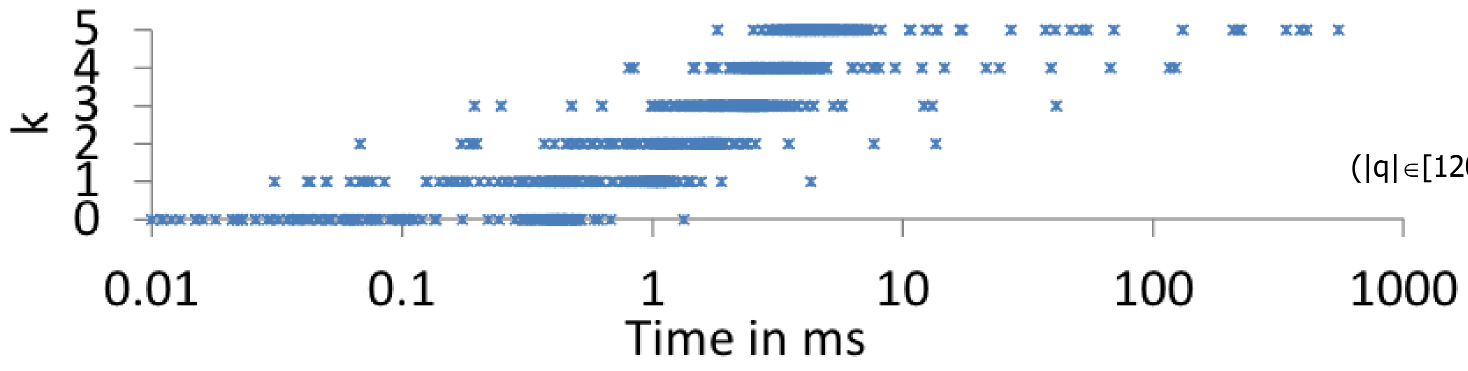


Figure: Size and creation time of RCSI per chromosome.

- Indexing one genome: ~30 sec
- Indexing 1000 genomes: ~8 hours

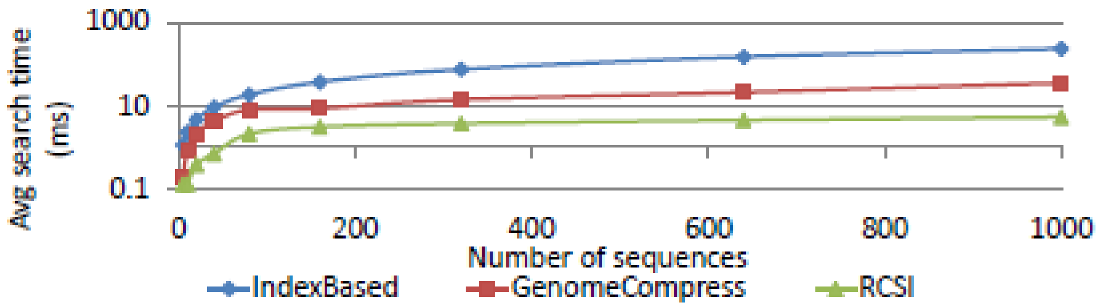
Evaluation: Approx. search in 1000 genomes



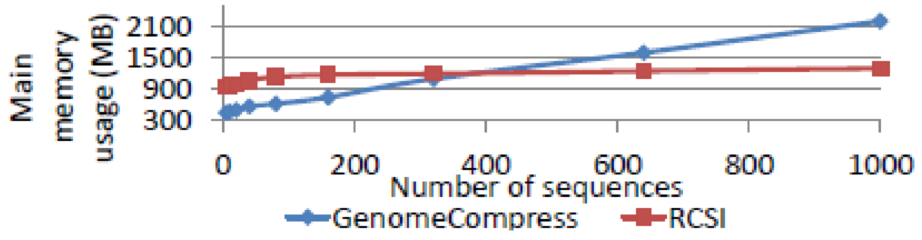
(|q|∈[120,170])

- Until k=5, almost all queries finish in <10ms
- For k=1, almost all queries finish in <1ms
- Outliers: Queries matching repetitive regions

Competitors



(b) 3-approximate search.



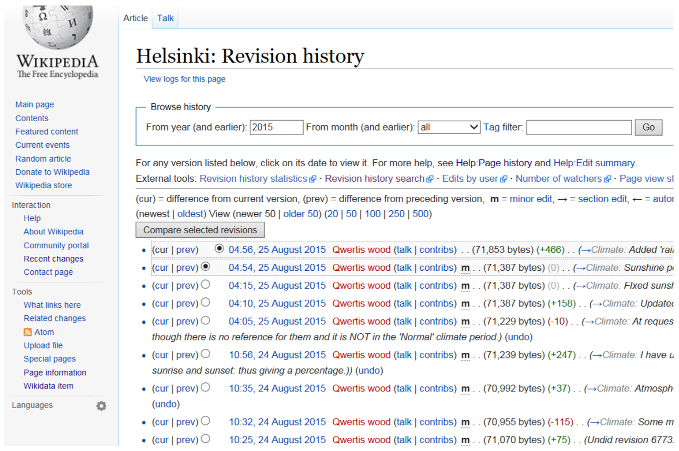
- GC open source code lacks important preprocessing step
  - We could only compare using the data from GC paper
- RCSI between 10 and 100 times faster
  - And computes all results

Content of this Lecture

- Next Generation Sequencing
- Sequence compression
  - Referential compression
  - Four issues
- Approximate search in compressed genomes
- Using multiple references

Collections of Similar Strings

- Often (not always): Strings are similar to each other
  - All human genomes are 99% identical
  - All mammal genomes are >90% identical
  - All elements of a Wikipedia revision histories are highly similar
  - Elements of version histories are very similar (SVN, subversion, …)
  - …



Article Talk

Helsinki: Revision history

View logs for this page

Browse history

From year (and earlier): 2015 From month (and earlier): all Tag filter: Go

For any version listed below, click on its date to view it. For more help, see Help:Page history and Help:Edit summary.

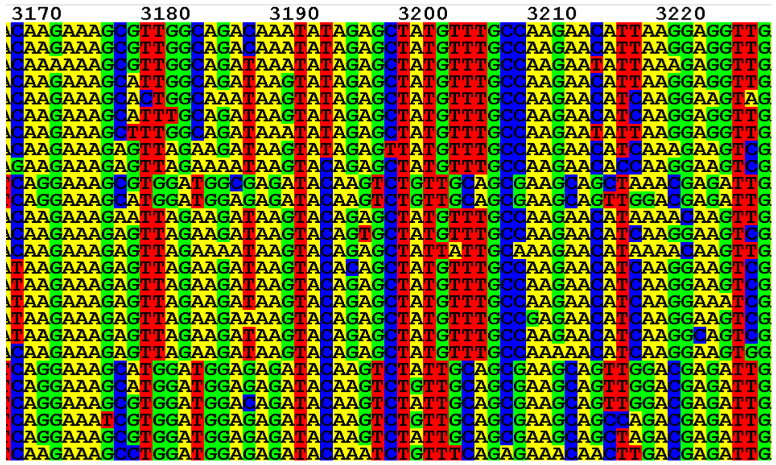
External tools: Revision history statistics · Revision history search · Edits by user · Number of watchers · Page view st

(cur) = difference from current version, (prev) = difference from preceding version, **m** = minor edit, → = section edit, ← = autor

(newest | oldest) View (newer 50 | older 50) (20 | 50 | 100 | 250 | 500)

Compare selected revisions

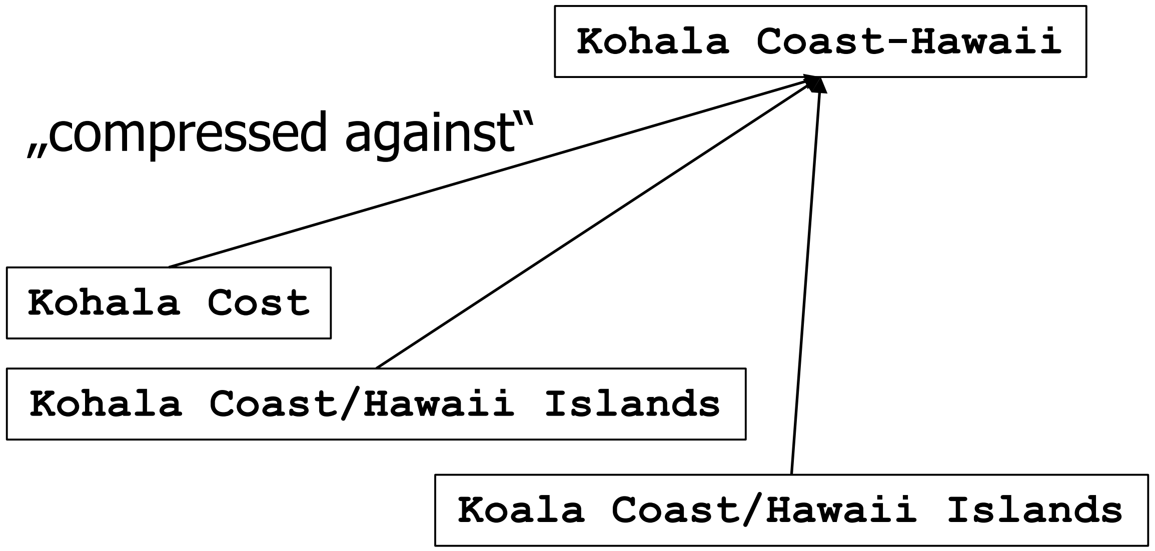
- (cur | prev) ● 04:56, 25 August 2015 Qwertis wood (talk | contribs) . . (71,853 bytes) (+466) . . (→*Climate: Added 'rai*
- (cur | prev) ● 04:54, 25 August 2015 Qwertis wood (talk | contribs) **m** . . (71,387 bytes) (0) . . (→*Climate: Sunshine pe*
- (cur | prev) ○ 04:15, 25 August 2015 Qwertis wood (talk | contribs) **m** . . (71,387 bytes) (0) . . (→*Climate: FIxed sunsh*
- (cur | prev) ○ 04:10, 25 August 2015 Qwertis wood (talk | contribs) **m** . . (71,387 bytes) (+158) . . (→*Climate: Updatec*
- (cur | prev) ○ 04:05, 25 August 2015 Qwertis wood (talk | contribs) **m** . . (71,229 bytes) (-10) . . (→*Climate: At reques* *though there is no reference for them and it is NOT in the 'Normal' climate period.)* (undo)
- (cur | prev) ○ 10:56, 24 August 2015 Qwertis wood (talk | contribs) **m** . . (71,239 bytes) (+247) . . (→*Climate: I have u* *sunrise and sunset: thus giving a percentage.))* (undo)
- (cur | prev) ○ 10:35, 24 August 2015 Qwertis wood (talk | contribs) **m** . . (70,992 bytes) (+37) . . (→*Climate: Atmosph* (undo)
- (cur | prev) ○ 10:32, 24 August 2015 Qwertis wood (talk | contribs) **m** . . (70,955 bytes) (-115) . . (→*Climate: Some m*
- (cur | prev) ○ 10:25, 24 August 2015 Qwertis wood (talk | contribs) **m** . . (71,070 bytes) (+75) . . (*Undid revision 6773.*



```
 3170          3180          3190          3200          3210          3220
ACAAGAAAGCGTTGGCAGACAAATATAGAGCTATGTTTGCCAAGAACATTAAGGAGGTTG
ACAAGAAAGCGTTGGCAGACAAATATAGAGCTATGTTTGCCAAGAACATTAAGGAGGTTG
ACAAAAAAGCGTTGGCAGATAAATATAGAGCTATGTTTGCCAAGAATATTAAAGAGGTTG
ACAAGAAAGCATTGGCAGATAAGTATAGAGCTATGTTTGCCAAGAACATTAAGGAGGTTG
ACAAGAAAGCACTGGCAAATAAGTATAGAGCTATGTTTGCCAAGAACATCAAGGAAGTAG
ACAAGAAAGCATTTGCAGATAAGTATAGAGCTATGTTTGCCAAGAACATCAAGGAGGTTG
ACAAGAAAGCTTTGGCAGATAAATATAGAGCTATGTTTGCCAAGAATATTAAGGAGGTTG
ACAAGAAAGAGTTAGAAGATAAGTATAGAGTTATGTTTGCCAAGAACATCAAAGAAGTCG
AGAAGAAAGAGTTAGAAAATAAGTACAGAGCTATGTTTGCCAAGAACACCAAGGAAGTCG
TCAGGAAAGCGTGGATGGCGAGATACAAGTCTGTTGCAGCGAAGCAGCTAAACGAGATTG
TCAGGAAAGCATGGATGGAGAGATACAAGTCTGTTGCAGCGAAGCAGTTGGACGAGATTG
ACAAGAAAGAATTAGAAGATAAGTACAGAGCTATGTTTGCCAAGAACATAAAACAAGTTG
ACAAGAAAGAGTTAGAAGATAAGTACAGTGCTATGTTTGCCAAGAACATCAAGGAAGTCG
ACAAGAAAGAGTTAGAAAATAAGTACAGAGCTATTATTGCAAAGAACATAAAACAAGTTG
ATAAGAAAGAGTTAGAAGATAAGTACACAGCTATGTTTGCCAAGAACATCAAGGAAGTCG
ATAAGAAAGAGTTAGAAGATAAGTACAGAGCTATGTTTGCCAAGAACATCAAGGAAGTCG
ATAAGAAAGAGTTAGAAGATAAGTACAGAGCTATGTTTGCCAAGAACATCAAGGAAATCG
ATAAGAAAGAGTTAGAAGAAAAGTACAGAGCTATGTTTGCCGAGAACATCAAGGAAGTCG
ATAAGAAAGAGTTAGAAGATAAGTACAGAGCTATGTTTGCCAAGAACATCAAGGCAGTCG
ACAAGAAAGAGTTAGAAGATAAGTACAGAGCTATGTTTGCCAAAAACATCAAGGAAGTGG
TCAGGAAAGCATGGATGGAGAGATACAAGTCTATTGCAGCGAAGCAGTTGGACGAGATTG
TCAGGAAAGCATGGATGGAGAGATACAAGTCTGTTGCAGCGAAGCAGTTGGACGAGATTG
TCAGGAAAGCGTGGATGGACAGATACAAGTCTATTGCAGCGAAGCAGTTGGACGAGATTG
TCAGGAAATCGTGGATGGAGAGATACAAGTCTGTTGCAGCGAAGCAGCCAGACGAGATTG
TCAGGAAAGCGTGGATGGAGAGATACAAGTCTATTGCAGCGAAGCAGCTAGACGAGATTG
TCAAGAAAGCCTGGATGGAGAGATACAAATCTGTTTCAGAGAAACAACTTGACGAGATTG
```

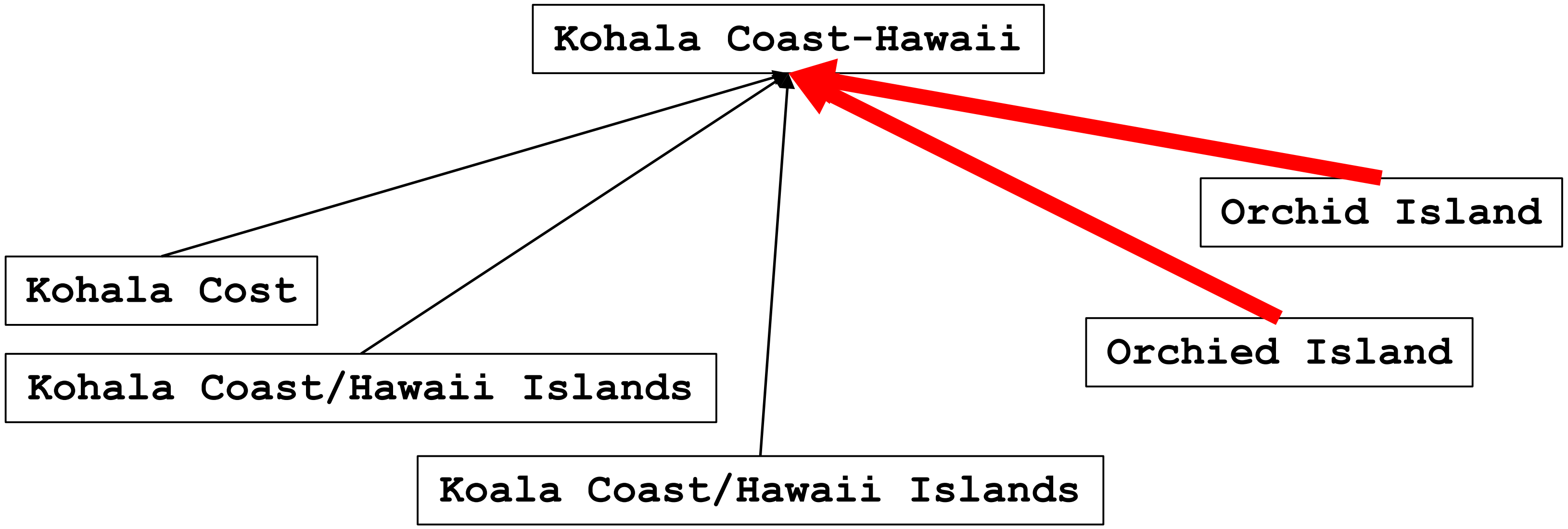
Heterogeneous String Collections

p:	Kohala Coast-Hawaii
s_2:	Kohala Cost
s_3:	Koala Coast/Hawaii Islands
s_4:	Kohala Coast-Hawaii Islands
s_5:	Orchid Island
s_6:	Orchied Island



Heterogeneous String Collections

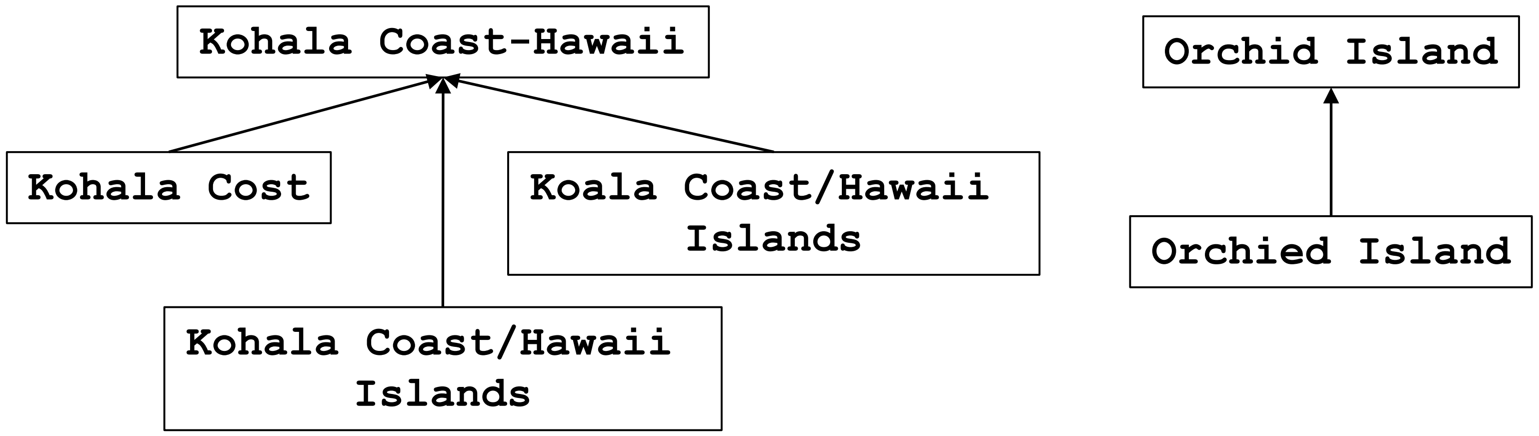
p:	Kohala Coast-Hawaii
s_2:	Kohala Cost
s_3:	Koala Coast/Hawaii Islands
s_4:	Kohala Coast-Hawaii Islands
s_5:	Orchid Island
s_6:	Orchied Island



Novel Idea: Use Multiple References

Strings are compressed against different references

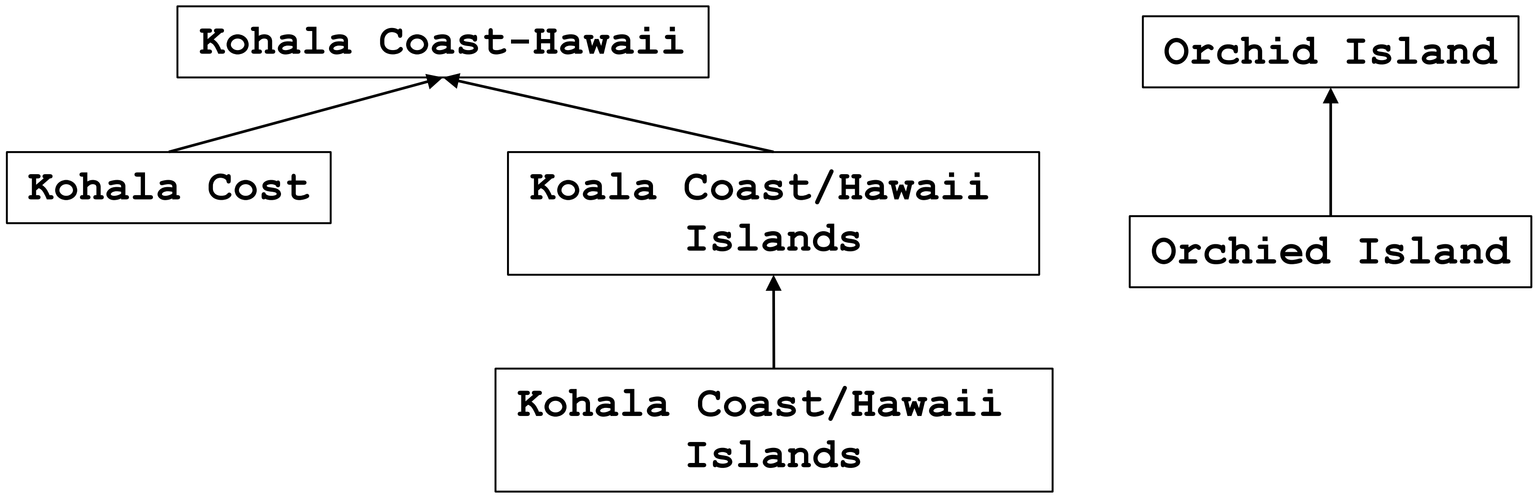
Challenge: Which are the best references?



Novel Idea: Allow Hierarchical Compressions

Compression dependencies can form hierarchies

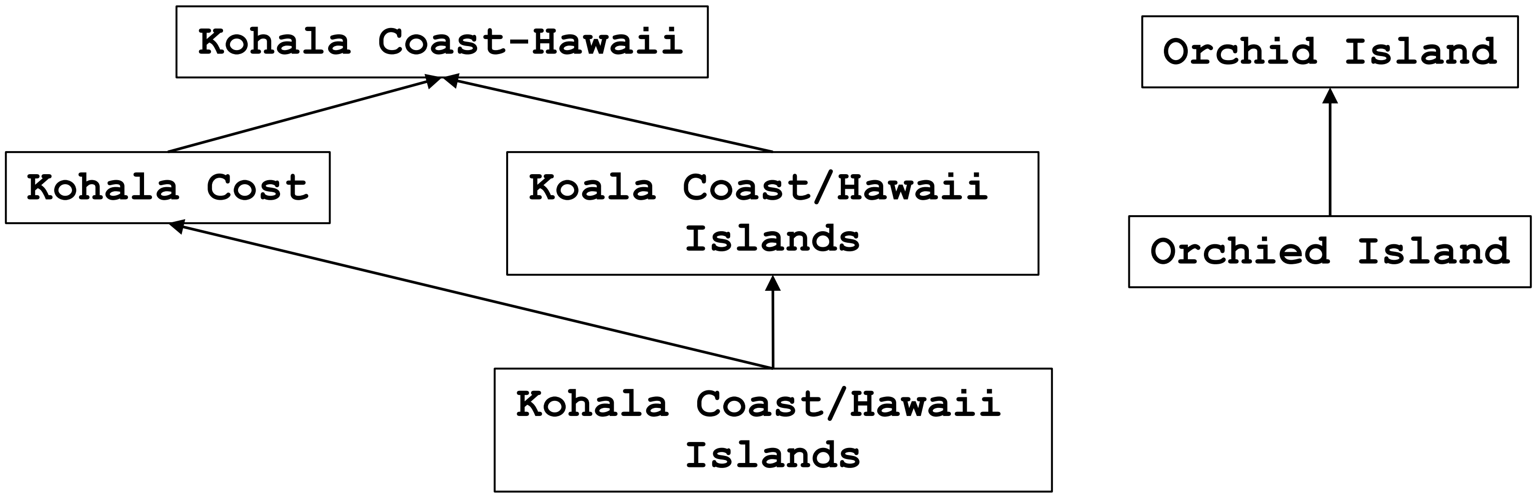
Challenge: Which is the best parent?



Novel Idea: Compress against Multiple References

Strings are compressed against multiple other strings

Challenge: Which is the best set of parents?

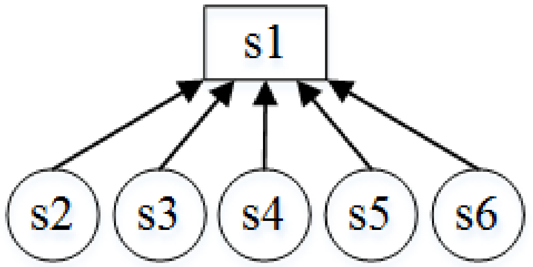


MRSCI: Multiple Reference Compression

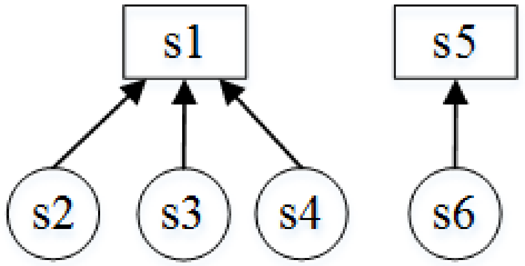
- Challenges during compression
  - Which strings should be references – and how many?
  - How can we efficiently find good parents?
  - What is the optimal compression hierarchy?
- How to perform k-approximate search in a multi-reference compression hierarchy?
- Findings
  - Proof that finding an optimal compression hierarchy is NP-hard
  - Three heuristics to build increasingly complex CHs
    - Increasingly better compression rates
    - Moderate increase in indexing time, roughly same search speed

Overview

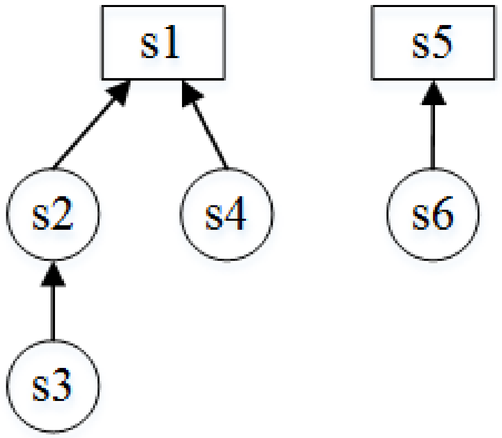
RCSI: VLDB 2014



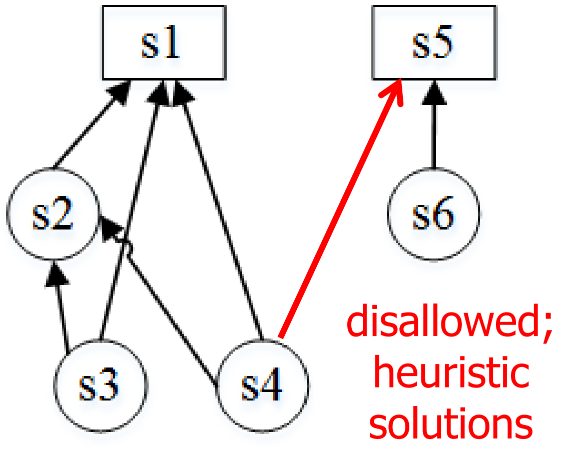
CPart



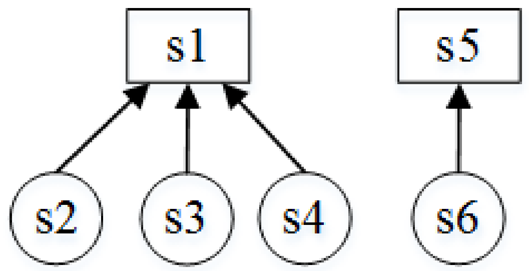
CForest



CDAG



CPart: Using Multiple References



- Iteratively and greedily compress strings from S
  - Choose first string as first reference p, set P={p}
  - Compress all other strings s one-by-one
    - Find reference p' from P "most similar" to s
    - If p' and s are sufficiently similar – compress s against p'
    - If not, add s to P (new reference, new root)
- Needs fast method for assessing string similarity
- Essentially performs a greedy clustering of C

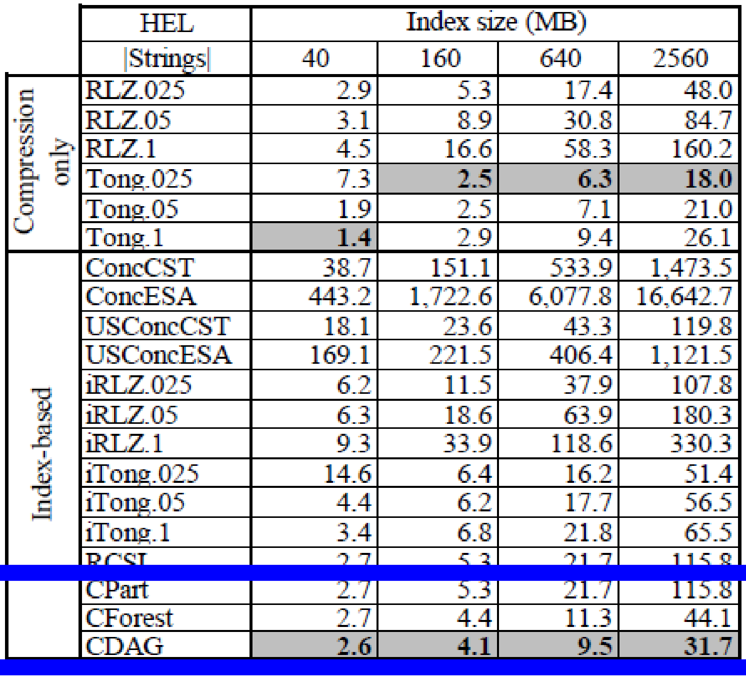
Competitors

- Sweet spot: Strong and fast compression, fast search
- Two classes of competitors
  - Pure indexer: ESA, CST: Large memory footprint, fast search
  - Pure compressors: Strong compression, slow search
  - Variations we built: Compressors with additional search indexes
    - RLZ / Tong after modification: iRLZ, iTong

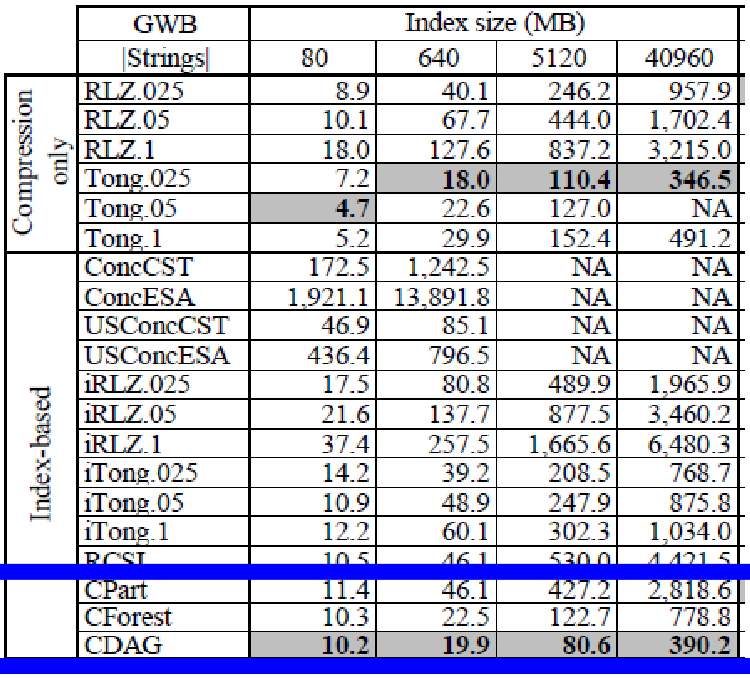
Evaluation: Indexing WikiPedia Revisions

Wikipedia Helsinki, ~3K versions
577 MB

Wikipedia GW Bush, ~45K versions
1400 MB



	HEL	Index size (MB)			
	|Strings|	40	160	640	2560
Compression only	RLZ.025	2.9	5.3	17.4	48.0
	RLZ.05	3.1	8.9	30.8	84.7
	RLZ.1	4.5	16.6	58.3	160.2
	Tong.025	7.3	**2.5**	**6.3**	**18.0**
	Tong.05	1.9	2.5	7.1	21.0
	Tong.1	**1.4**	2.9	9.4	26.1
Index-based	ConcCST	38.7	151.1	533.9	1,473.5
	ConcESA	443.2	1,722.6	6,077.8	16,642.7
	USConcCST	18.1	23.6	43.3	119.8
	USConcESA	169.1	221.5	406.4	1,121.5
	iRLZ.025	6.2	11.5	37.9	107.8
	iRLZ.05	6.3	18.6	63.9	180.3
	iRLZ.1	9.3	33.9	118.6	330.3
	iTong.025	14.6	6.4	16.2	51.4
	iTong.05	4.4	6.2	17.7	56.5
	iTong.1	3.4	6.8	21.8	65.5
	RCSI	2.7	5.3	21.7	115.8
	CPart	2.7	5.3	21.7	115.8
	CForest	2.7	4.4	11.3	44.1
	CDAG	**2.6**	**4.1**	**9.5**	**31.7**

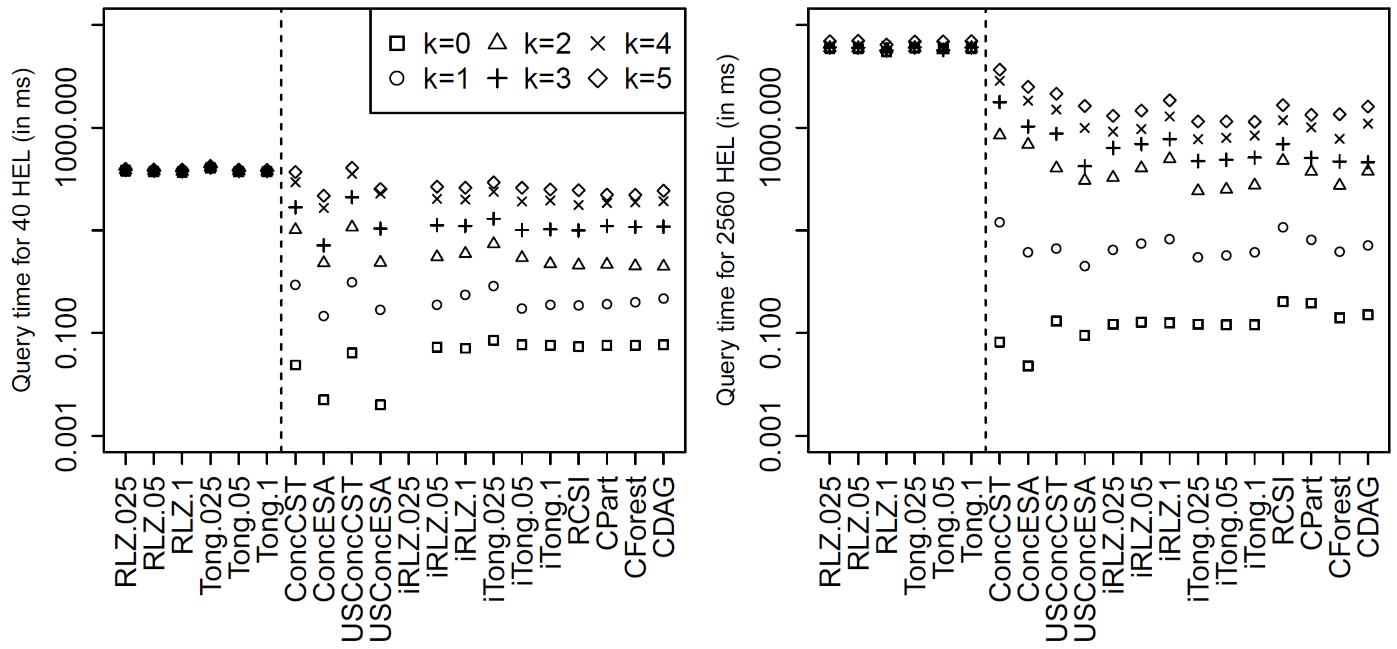


	GWB	Index size (MB)			
	|Strings|	80	640	5120	40960
Compression only	RLZ.025	8.9	40.1	246.2	957.9
	RLZ.05	10.1	67.7	444.0	1,702.4
	RLZ.1	18.0	127.6	837.2	3,215.0
	Tong.025	7.2	**18.0**	**110.4**	**346.5**
	Tong.05	**4.7**	22.6	127.0	NA
	Tong.1	5.2	29.9	152.4	491.2
Index-based	ConcCST	172.5	1,242.5	NA	NA
	ConcESA	1,921.1	13,891.8	NA	NA
	USConcCST	46.9	85.1	NA	NA
	USConcESA	436.4	796.5	NA	NA
	iRLZ.025	17.5	80.8	489.9	1,965.9
	iRLZ.05	21.6	137.7	877.5	3,460.2
	iRLZ.1	37.4	257.5	1,665.6	6,480.3
	iTong.025	14.2	39.2	208.5	768.7
	iTong.05	10.9	48.9	247.9	875.8
	iTong.1	12.2	60.1	302.3	1,034.0
	RCSI	10.5	46.1	530.0	4,421.5
	CPart	11.4	46.1	427.2	2,818.6
	CForest	10.3	22.5	122.7	778.8
	CDAG	**10.2**	**19.9**	**80.6**	**390.2**

- CDAG strongest of index-based, almost as small as best
- CDAG (or CPart) are fastest (2-4 times faster than iTong)

Evaluation: Searching (HEL)

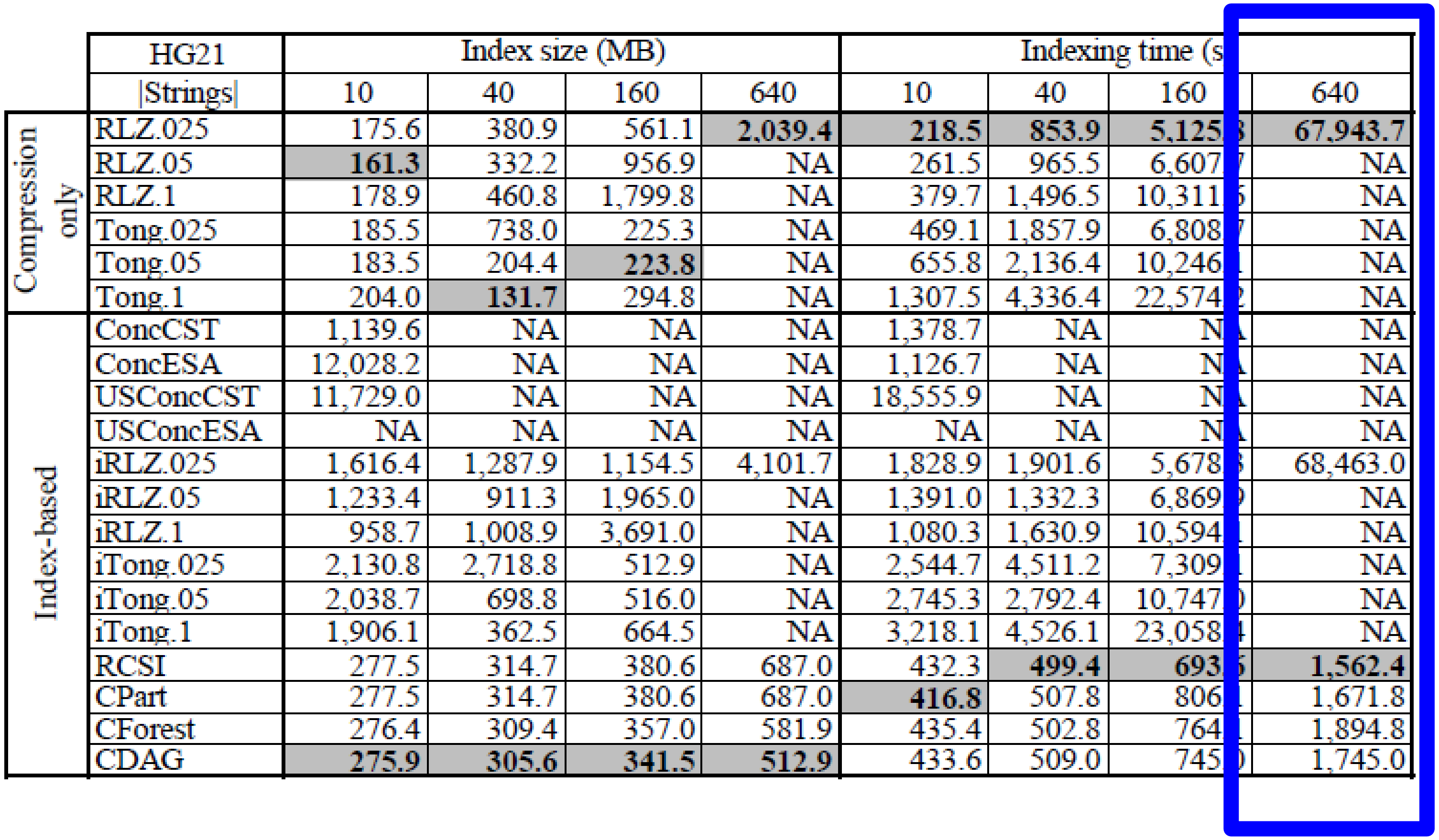
5000 random queries, length 12-18 char



- ESA fastest in search
- All compressing methods perform roughly the same

Evaluation: Large Datasets

Human chromosome 21, up to 640 versions, up to 51GB



	HG21	Index size (MB)				Indexing time (s			
	|Strings|	10	40	160	640	10	40	160	640
Compression only	RLZ.025	175.6	380.9	561.1	**2,039.4**	**218.5**	**853.9**	**5,125.8**	**67,943.7**
	RLZ.05	**161.3**	332.2	956.9	NA	261.5	965.5	6,607.7	NA
	RLZ.1	178.9	460.8	1,799.8	NA	379.7	1,496.5	10,311.6	NA
	Tong.025	185.5	738.0	225.3	NA	469.1	1,857.9	6,808.7	NA
	Tong.05	183.5	204.4	**223.8**	NA	655.8	2,136.4	10,246.1	NA
	Tong.1	204.0	**131.7**	294.8	NA	1,307.5	4,336.4	22,574.2	NA
Index-based	ConcCST	1,139.6	NA	NA	NA	1,378.7	NA	NA	NA
	ConcESA	12,028.2	NA	NA	NA	1,126.7	NA	NA	NA
	USConcCST	11,729.0	NA	NA	NA	18,555.9	NA	NA	NA
	USConcESA	NA	NA	NA	NA	NA	NA	NA	NA
	iRLZ.025	1,616.4	1,287.9	1,154.5	4,101.7	1,828.9	1,901.6	5,678.8	68,463.0
	iRLZ.05	1,233.4	911.3	1,965.0	NA	1,391.0	1,332.3	6,869.9	NA
	iRLZ.1	958.7	1,008.9	3,691.0	NA	1,080.3	1,630.9	10,594.1	NA
	iTong.025	2,130.8	2,718.8	512.9	NA	2,544.7	4,511.2	7,309.1	NA
	iTong.05	2,038.7	698.8	516.0	NA	2,745.3	2,792.4	10,747.0	NA
	iTong.1	1,906.1	362.5	664.5	NA	3,218.1	4,526.1	23,058.4	NA
	RCSI	277.5	314.7	380.6	687.0	432.3	**499.4**	**693.6**	**1,562.4**
	CPart	277.5	314.7	380.6	687.0	**416.8**	507.8	806.1	1,671.8
	CForest	276.4	309.4	357.0	581.9	435.4	502.8	764.1	1,894.8
	CDAG	**275.9**	**305.6**	**341.5**	**512.9**	433.6	509.0	745.0	1,745.0

Conclusions

- Referential compression beats standard compression tools by orders of magnitude for highly-similar sequences (w.r.t. storage and speed)
- Inherent trade-off between compression ratio and de-/compression speed
- Given a referential index, some (many?) string matching problems can be solved much more efficiently – ample room for further research
  - "Compressive genomics"

References

- Deorowicz, Sebastian, Agnieszka Danek, and Marcin Niemiec. "GDC 2: Compression of large collections of genomes." arXiv preprint arXiv:1503.01624 (2015).
- Wandelt, S. and U. Leser (2014). “MRCSI: Compressing and Searching String Collections with Multiple References”. PVLDB. Kona, Hawaii.
- Wandelt, S. and U. Leser (2013). "FRESCO: Referential Compression of Highly-Similar sequences." Transactions on Computational Biology and Bioinformatics 10(5): 1275-1288.
- Wandelt, S. and U. Leser (2012). "Adaptive efficient compression of genomes." Algorithms for Molecular Biology 7(30).
- Wandelt, S., J. Starlinger, M. Bux and U. Leser (2013). “RCSI: Scalable similarity search in thousand(s) of genome”s. PVLDB, Hangzhou, China.
- Wandelt, S., Rheinländer, A., Bux, M., Thalheim, L., Haldemann, B. and Leser, U. (2012). "Data Management Challenges in Next Generation Sequencing." Datenbank Spektrum