Signal Processing on Databases

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Lecture 6: Bio Sequence Cross Correlation

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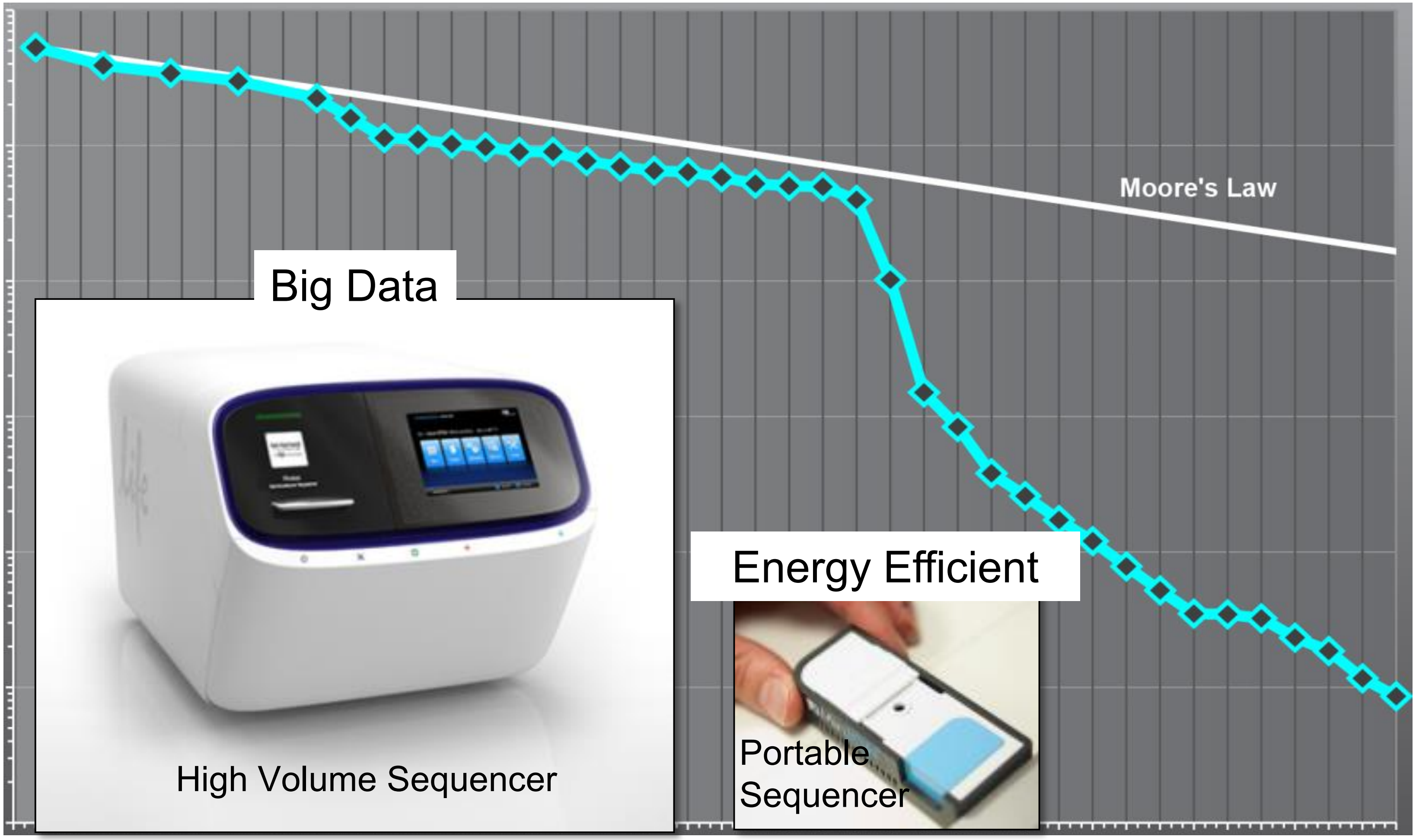
Outline

- Introduction
- Algorithm
- Implementation
- Results
- Summary

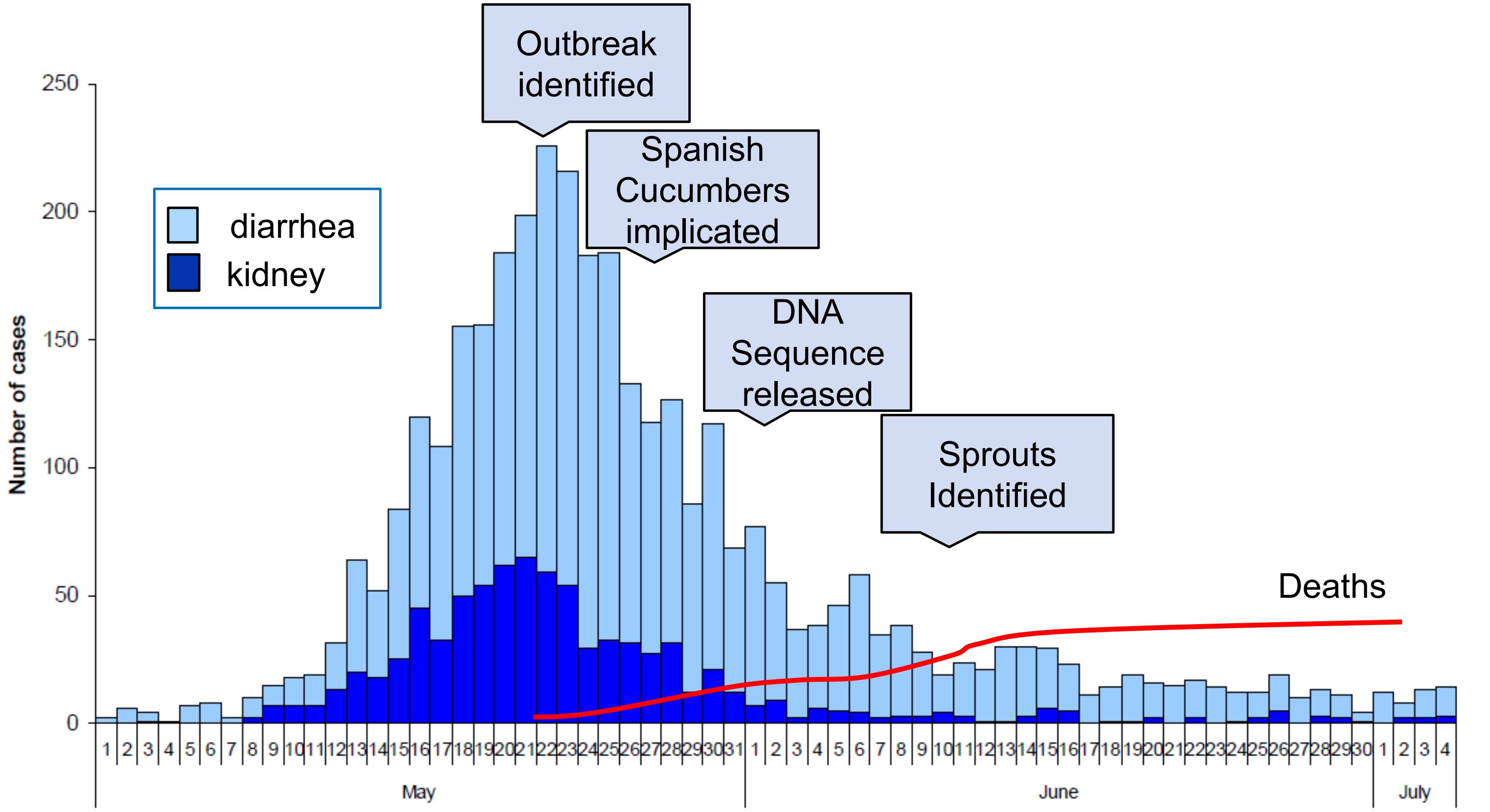
Relative Cost per DNA Sequence



Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program Available at: www.genome.gov/sequencingcosts. Accessed 03/08/2012

Example Disease Outbreak

May-July 2011 - Virulent *E. Coli* Outbreak Germany



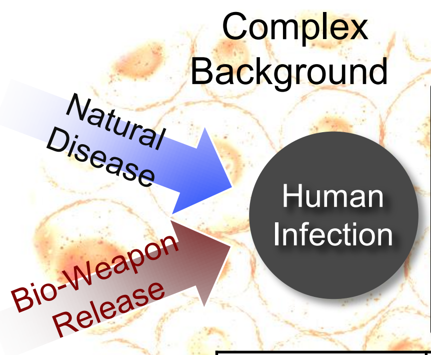
www.rki.de EHEC final report

Conclusions: Identification of E. Coli source too late to have substantial impact on illnesses
Publishing sequence data allowed for broad community to fully characterize pathogen

Courtesy of Robert Koch Institute. See Figure 2 in Report: Final presentation and evaluation of epidemiological findings in the EHEC O104:H4 outbreak, Germany 2011. Berlin 2011. Used with permission.

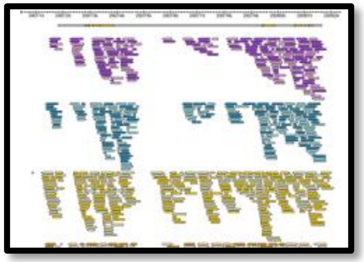
Sequencing and crowd source analysis showed promising potential -> Still too slow

Example Processing Timeline

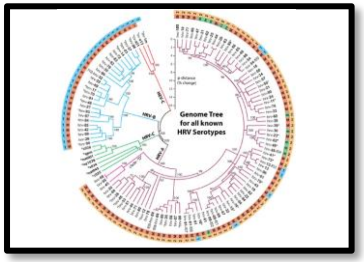


Collection & Shipment of Sample

Sample Preparation & Sequencing



Analysis of Samples



Time to Actionable Data

Current	2-30 days	1-3 days	7-14 days	10-45 days
Goal	on site	3 hours	<12 hours	**< 1 day**

- **Processing plays a key part in accelerating the overall time to solution**

Slide inspired by Nicole Rosenzweig, ECBC

DNA Sequence Matching

Goal

- Quickly compare two sets of DNA

Applications

- Identification
- Mixture Analysis
- Kinship Analysis
- Ancestry Analysis

Image courtesy of Wikimedia Commons and is in the public domain.

Uses: disease outbreaks, criminal investigations, personal medicine, …

- **Challenge: sequencing matching takes a long time, can we make it faster?**

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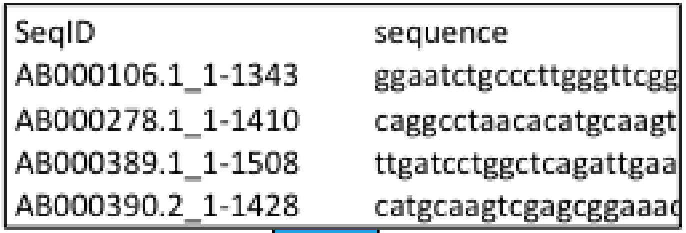
Sequence Matching ⇔ Sparse Matrix Multiply in D4M

RNA Reference Set

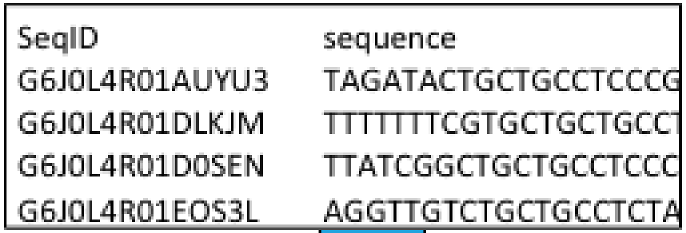
reference bacteria



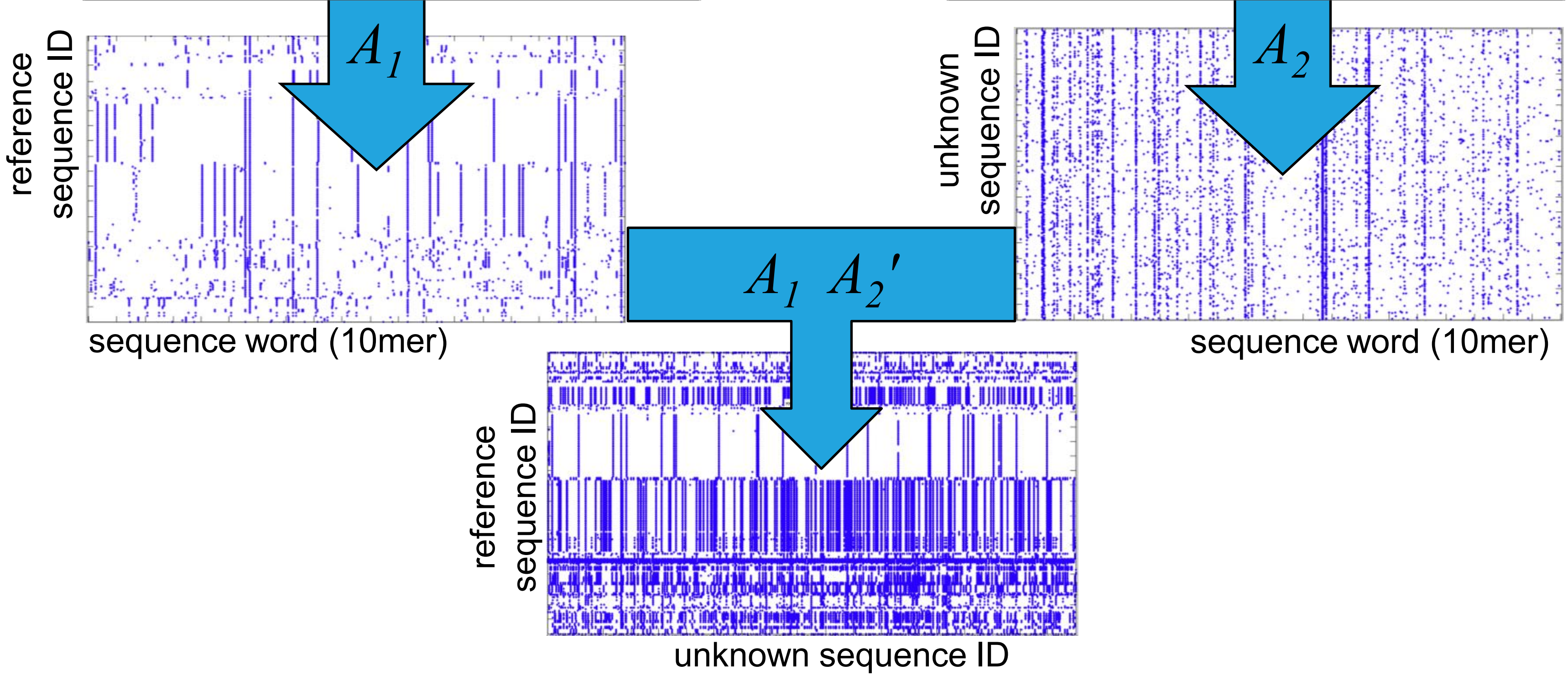
SeqID	sequence
AB000106.1_1-1343	ggaatctgcccttgggttcgg
AB000278.1_1-1410	caggcctaacacatgcaagt
AB000389.1_1-1508	ttgatcctggctcagattgaa
AB000390.2_1-1428	catgcaagtcgagcggaaac

Collected Sample

unknown bacteria

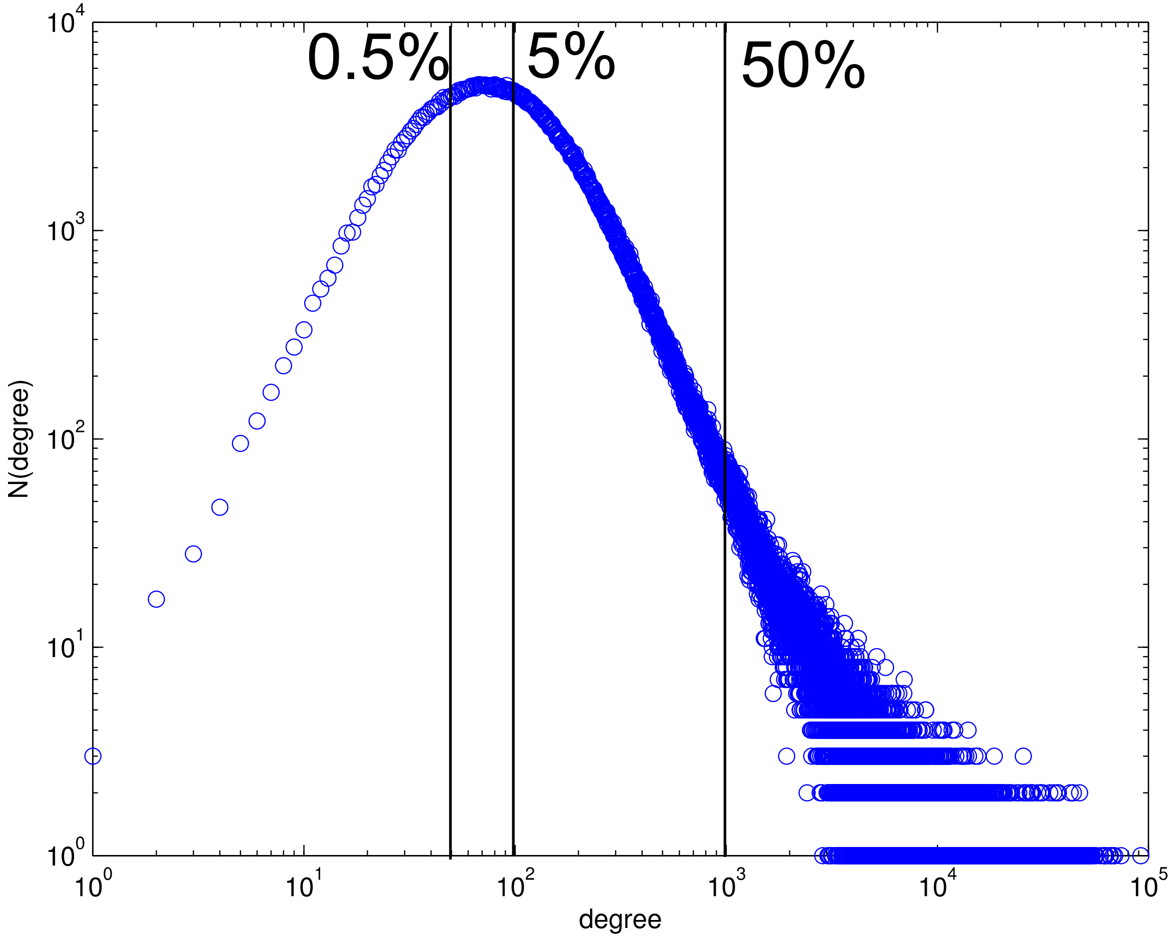


SeqID	sequence
G6J0L4R01AUYU3	TAGATACTGCTGCCTCCCG
G6J0L4R01DLKJM	TTTTTTTCGTGCTGCTGCCT
G6J0L4R01D0SEN	TTATCGGCTGCTGCCTCCC
G6J0L4R01EOS3L	AGGTTGTCTGCTGCCTCTA



- **Associative arrays provide a natural framework for sequence matching**

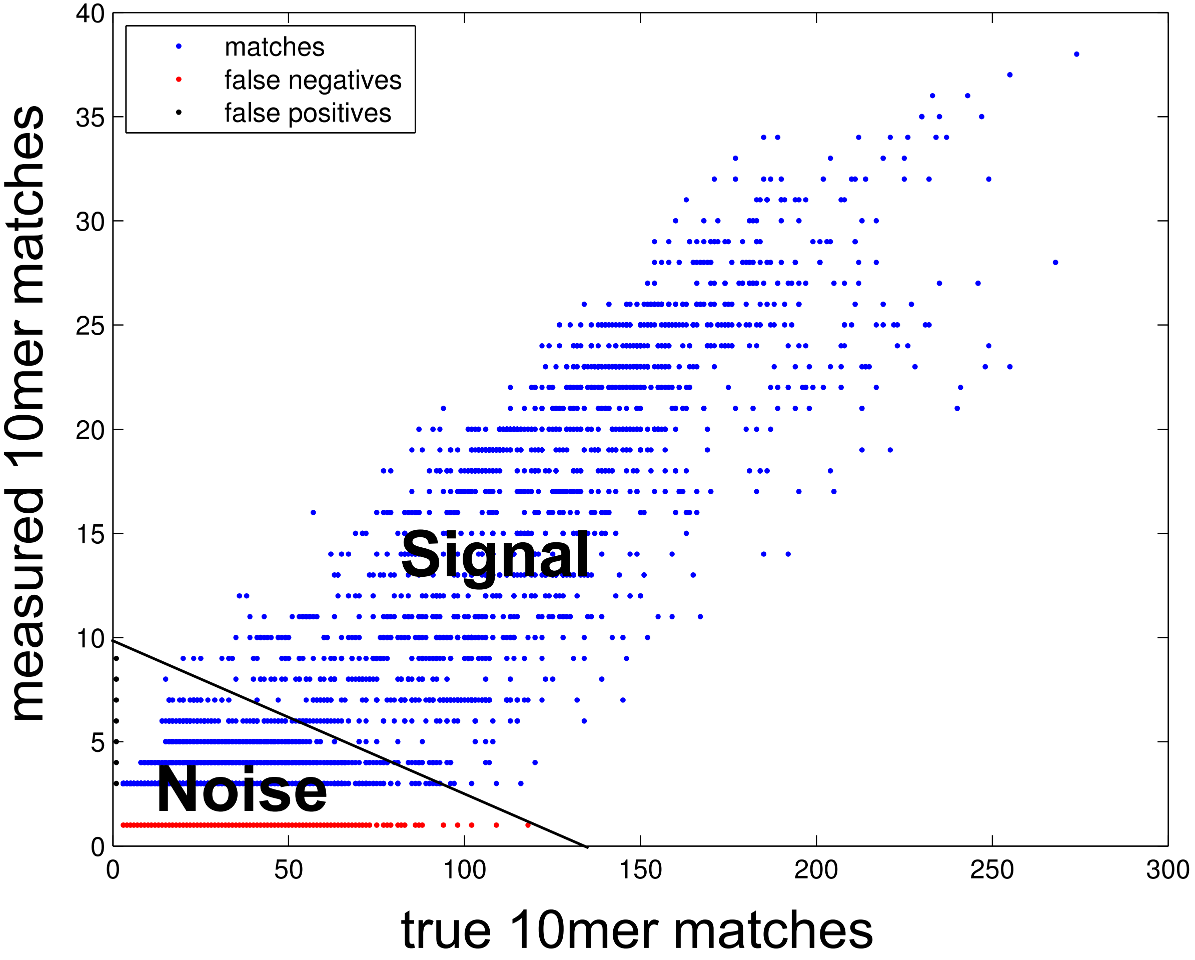
Database Automatically Computes Reference 10mer Distribution



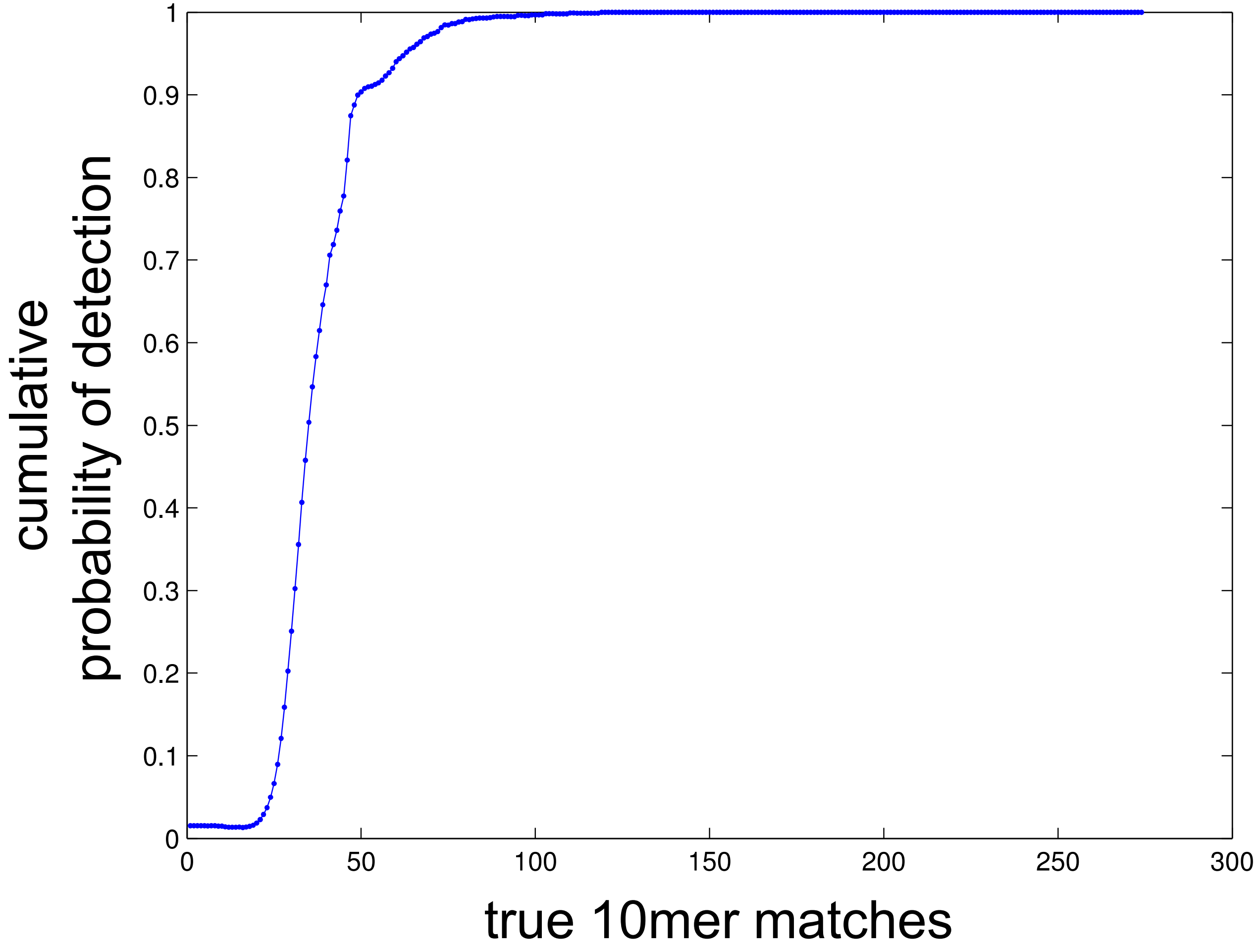
- **Using 10mer distribution can quickly select reference 10mers that maximally differentiate sample sequences and eliminate most 10mers**

0.5% Selection Results

- **Sample (20MB):**
  - **NGS from Roche 454**
- **Reference (500MB):**
  - **Virus DNA from GenBank**
- **All strong matches detected using 0.5% of data**

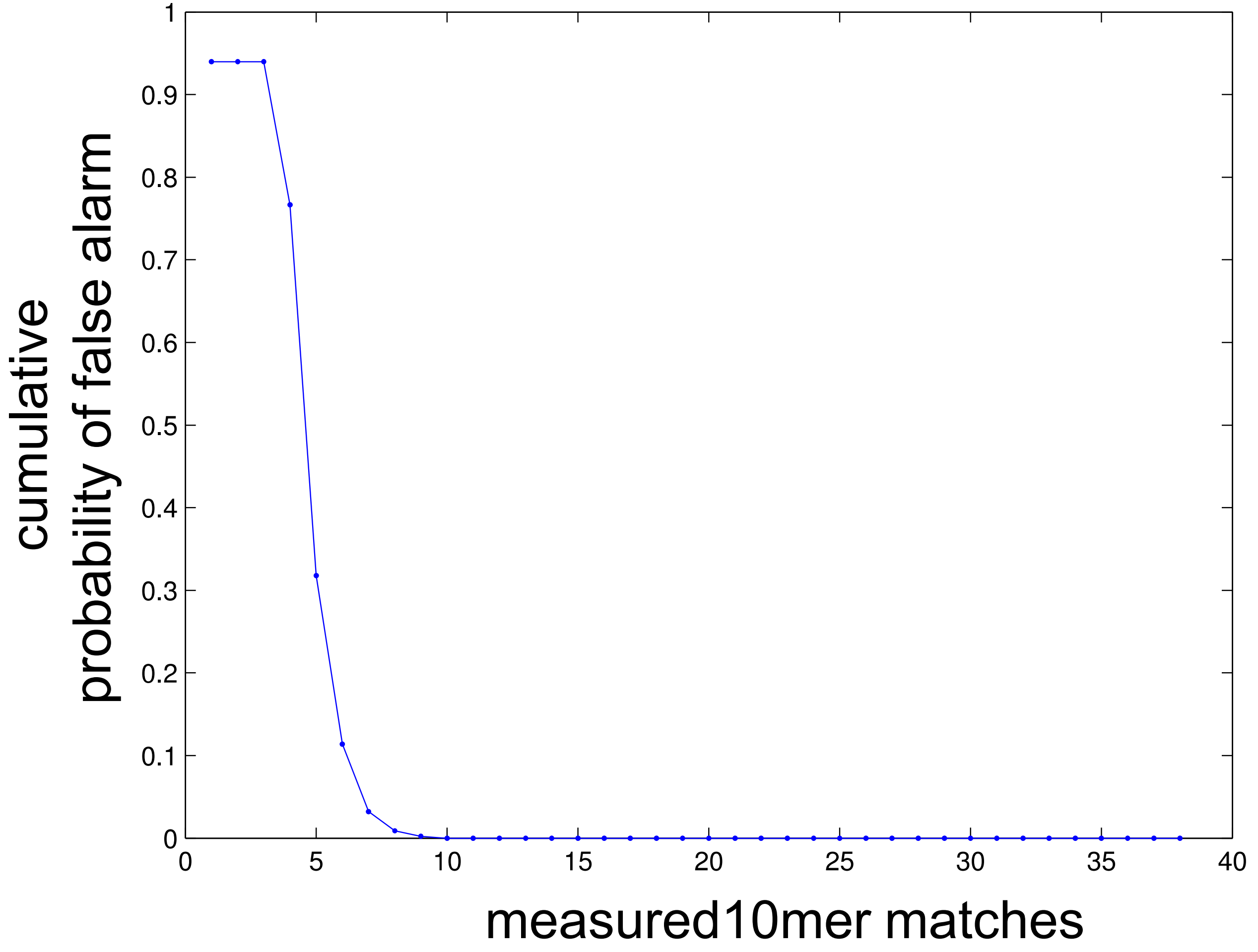


Cumulative Probability of Detection



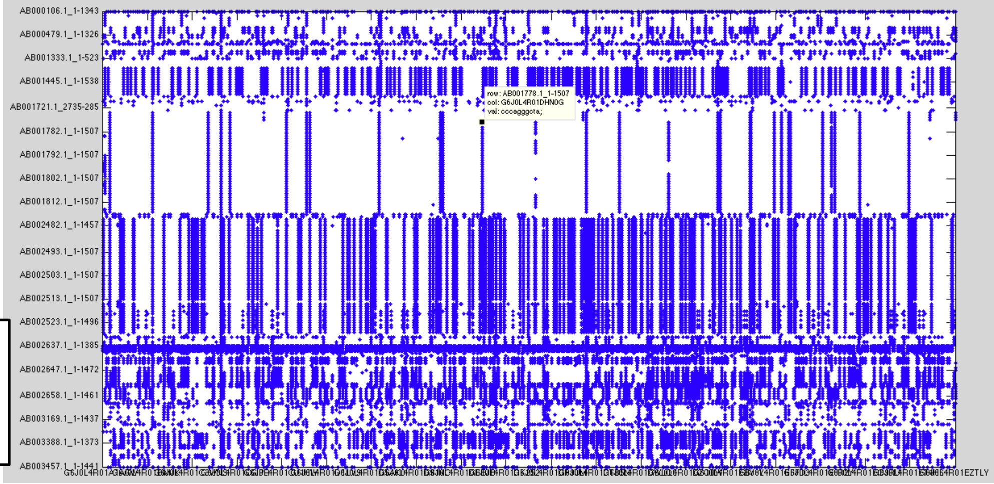
- **100% detection of all true matches > 100**

Cumulative Probability of False Alarm



- **Measured matches > 10 are always matches**

Finding Matches



A = A1 * A2'

Ak = CatKeyMul(A1,A2')

- **Find sequences with >6 word matches**

Am = Ak(Row(A > 6),Col(A > 6))

(AB001520.1_1-1428,G6J0L4R01B4UPM)
aaatctttaa;aatctttaaa;ctttaaataa;ggggaccagc;taaatcttta;ttaaataaaa;tttaaataaa;,

(AB002634.1_1-1419,G6J0L4R01EDJVA)
aaatgtcgtt;aatgtcgttt;atgtcgtttc;gtcgtttccc;gtctcagttc;tcgtttccct;tgtcgtttcc;,

- **Associative array cat multiply preserves pedigree of matches**

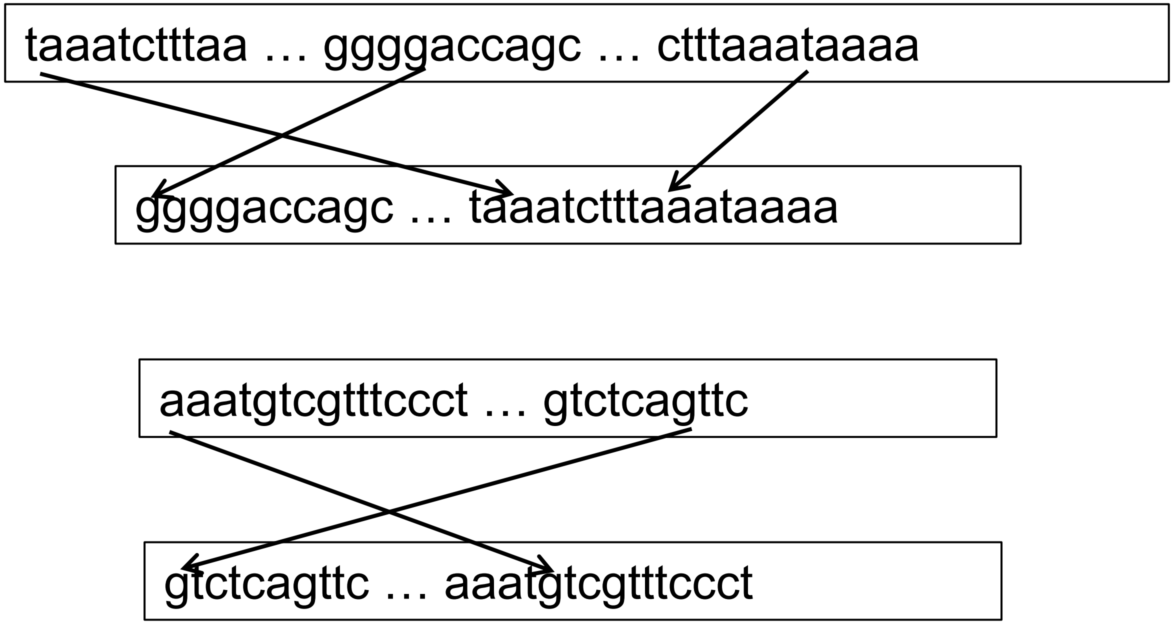
Sequence Alignment

- **Show relative alignments of sequences**

A1(Row(Am),Val(Am)) + A2(Row(Am),Val(Am))

<u>reference</u>   <u>sample</u>

	AB001520.1_1-1428	G6J0L4R01B4UPM
aaatctttaa	564	155
aatctttaaa	1227	156
ctttaaataa	1376	159
ggggaccagc	877	58
taaatcttta	563	154
ttaaataaaa	1378	161
tttaaataaa	1377	160
	AB002634.1_1-1419	G6J0L4R01EDJVA
aaatgtcgtt	933	300
aatgtcgttt	934	301
atgtcgtttc	935	302
gtcgtttccc	937	304
gtctcagttc	1211	37
tcgtttccct	938	305
tgtcgtttcc	936	303



taaatctttaa … ggggaccagc … ctttaaataaaa

ggggaccagc … taaatctttaaataaaa

aaatgtcgtttccct … gtctcagttc

gtctcagttc … aaatgtcgtttccct

- **Sequence alignment found by indexing into associative array**

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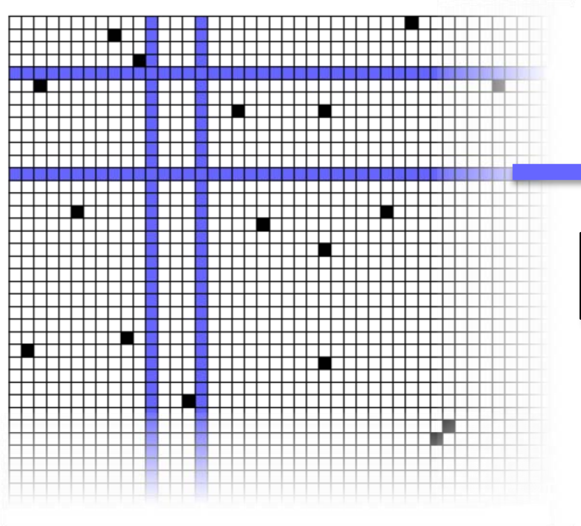
D4M Stores Giant Sparse Matrices in Accumulo Triple Store Database

Triple Store

Distributed Database



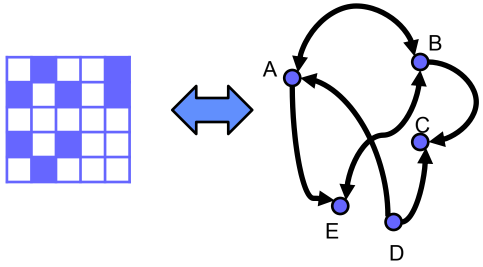
D4M

Dynamic
Distributed
Dimensional
Data
Model

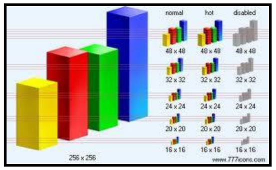
Query:
T(:,ggaatctgcc)

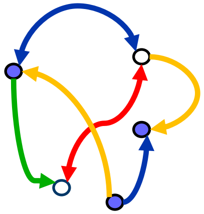
Associative Arrays

Numerical Computing Environment



A D4M query returns a sparse matrix or graph from a triple store…

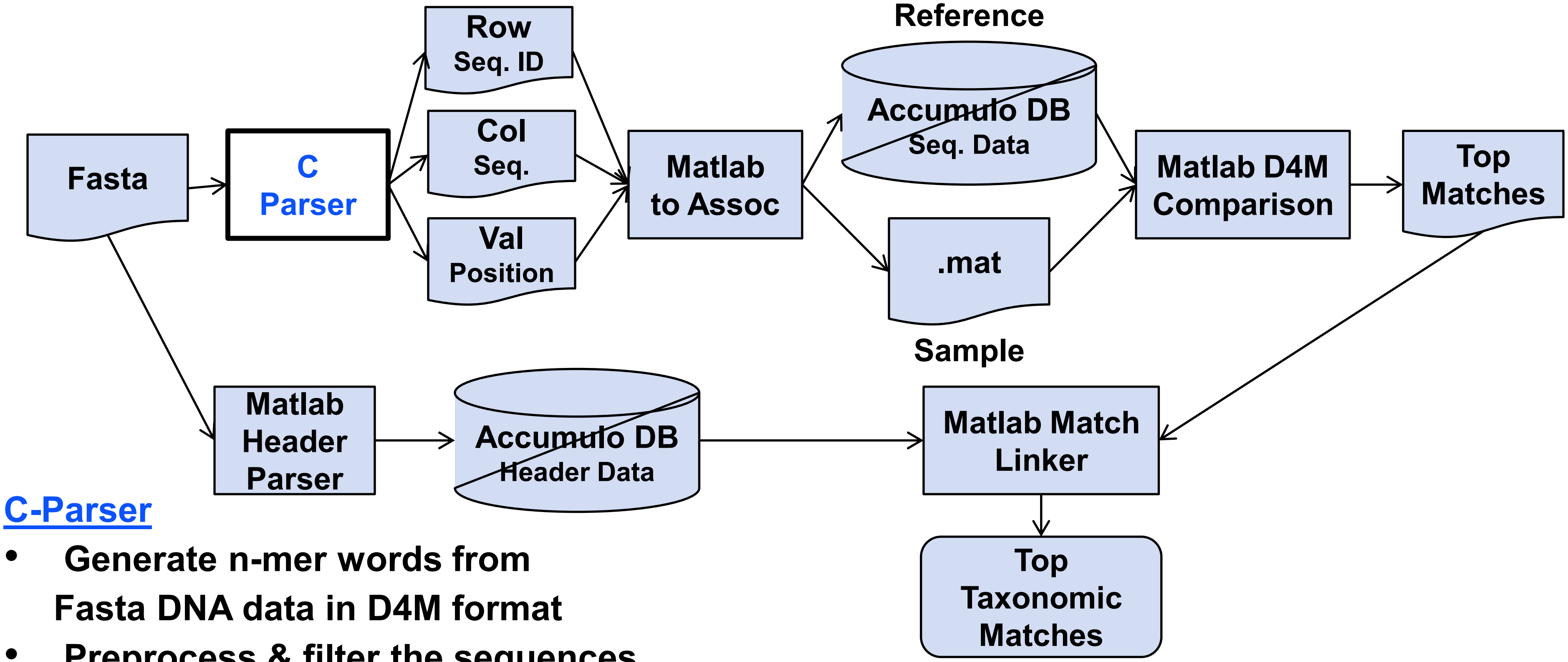




…for statistical signal processing or graph analysis in Matlab

Triple store are high performance distributed databases for heterogeneous data

Sequence Processing Pipeline



C-Parser

- Generate n-mer words from Fasta DNA data in D4M format
- Preprocess & filter the sequences
  - Ignore bad, common sequences
  - Break output files into manageable chunks, say 5MB
  - Generate reverse sequences
  - Break up big sequences into subsequences to preserve locality

Database Table Splits

- Initial inserts bottleneck on one tablet server until it fills up and splits
- Performance booster: pre-split table among several tablet servers for instant parallel insertion
  - Use advanced knowledge of row data patterns to choose splits
- Created functions to set and query table splits

No Splitting

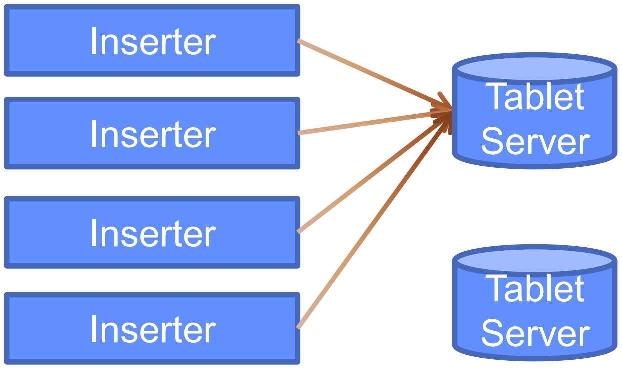
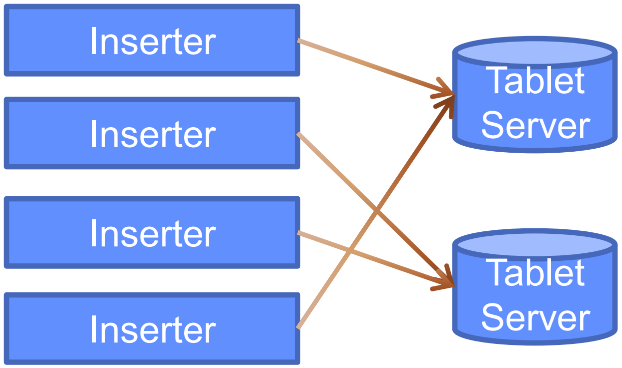
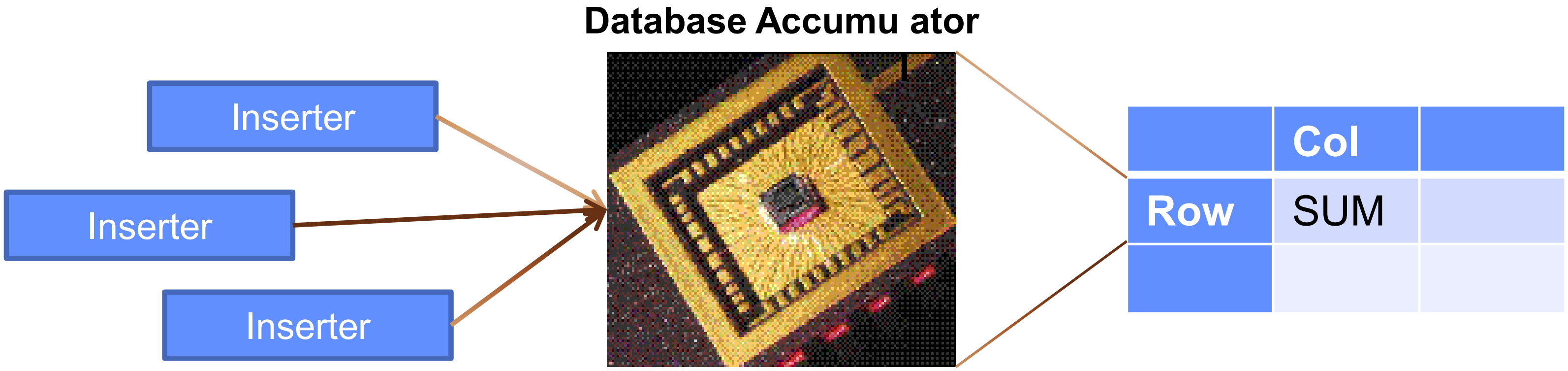


Table Splits



Accumulator Columns

- Accumulator columns allow counting to be done on insert
  - Example: sequence counting
    - Row ID = 10 mer
    - Column = Count
    - Value = Count
  - Insert (aaatctttaa,Count,2) → DB has (Doc1, ‘bird’, 2)
  - Insert (aaatctttaa,Count,3) → DB has (aaatctttaa,Count,5)
- Works with any commutative operation
  - Addition, maximum, minimum, etc.



	Col	
Row	SUM	

Courtesy of Jan Van der Spiegel.
Used with permission.

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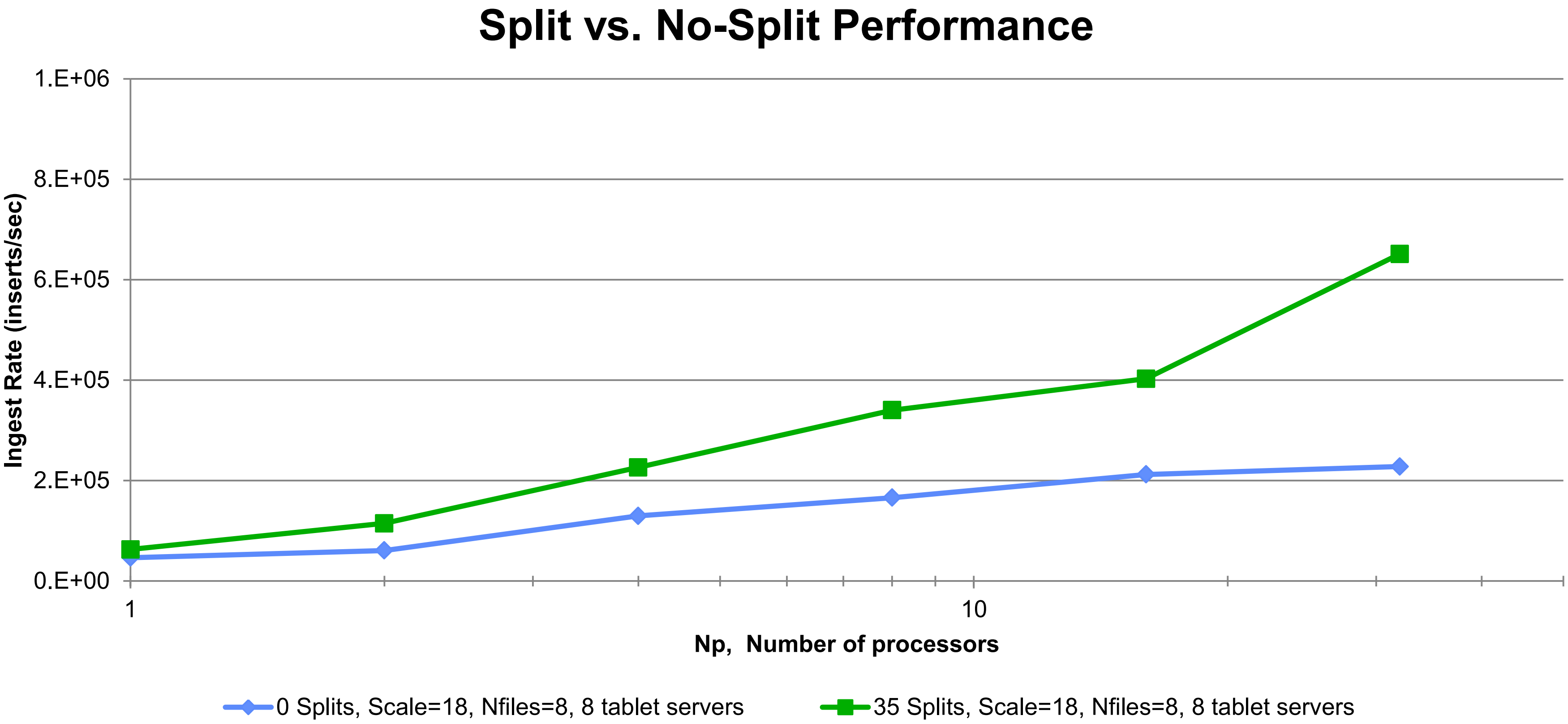
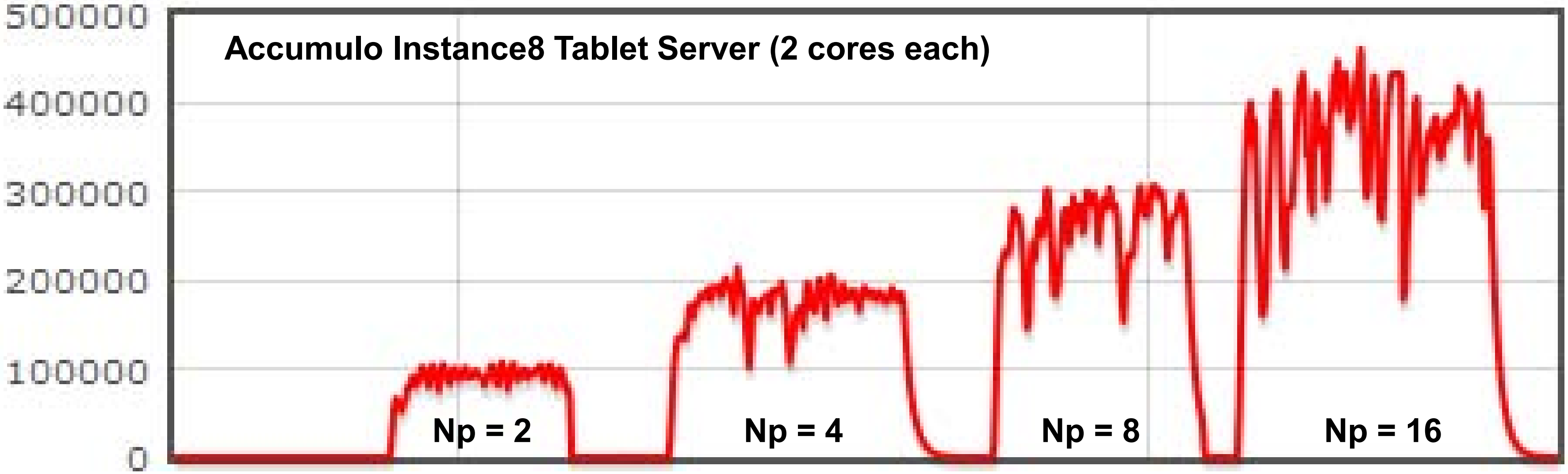
Table Split Performance

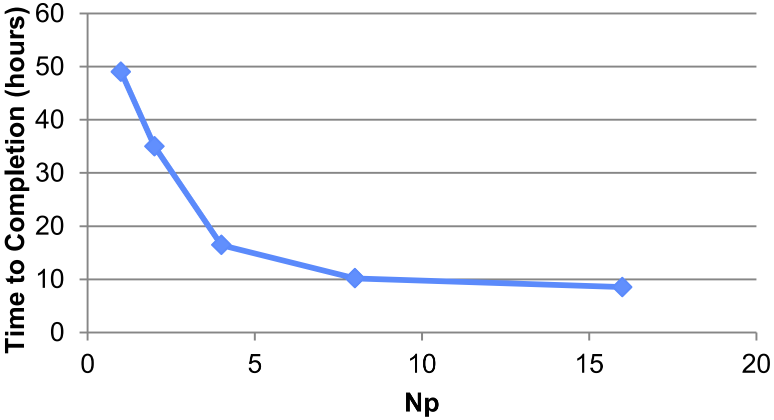


- **Pre-Splitting tables appropriately can double ingest rates at higher Np in multinode database environments**

Human DNA DB Ingest Performance

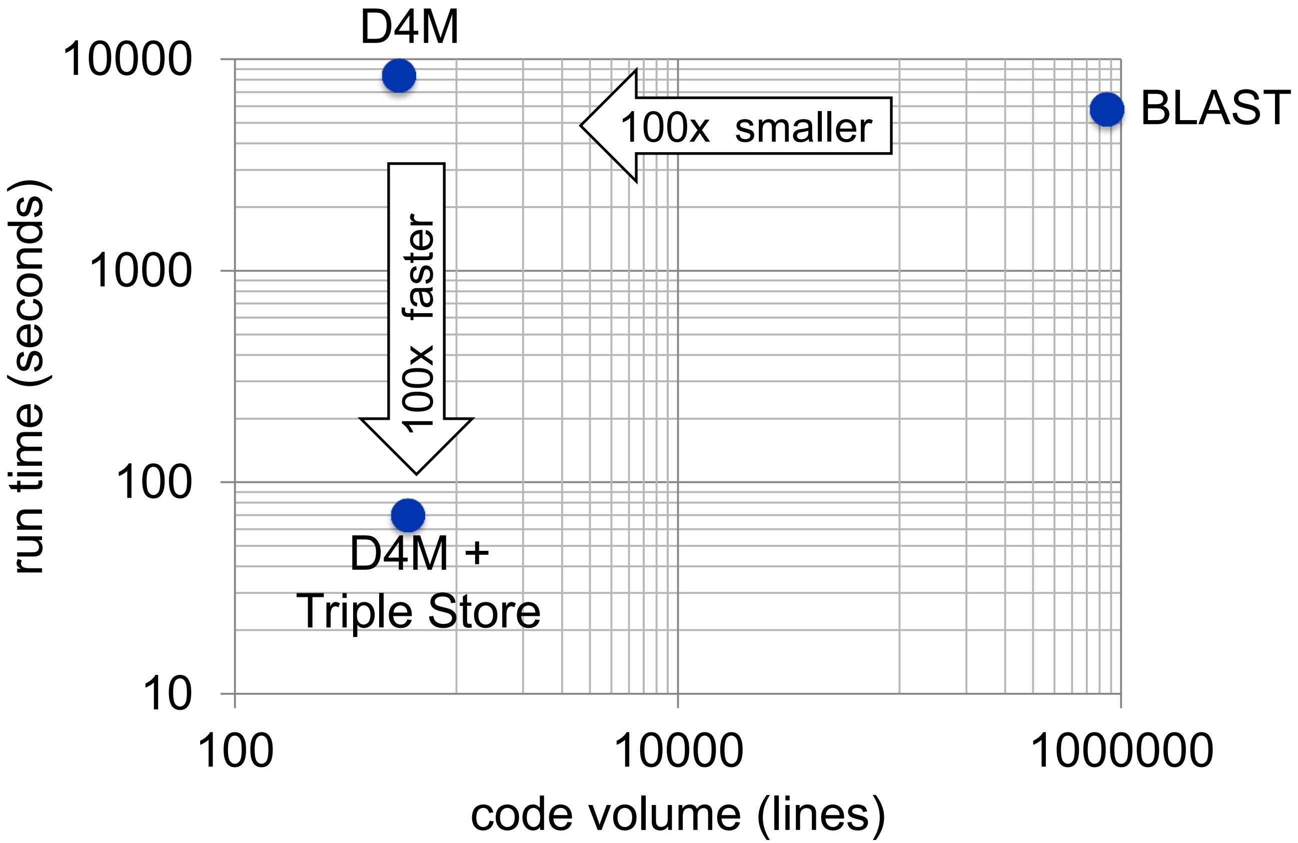


Extrapolated Run Times



- 4.5 GB human Fasta file
- C Parser took 25 minutes
- 101 GB of row, col files
- Database ingest time ~10 hours

Leveraging "Big Data" Technologies for High Speed Sequence Matching



- High performance triple store database trades computations for lookups
- Used Apache Accumulo database to accelerate comparison by 100x
- Used Lincoln D4M software to reduce code size by 100x

Summary

- Big data is found across a wide range of areas
  - Document analysis
  - Computer network analysis
  - DNA Sequencing

- Currently there is a gap in big data analysis tools for algorithm developers

- D4M fills this gap by providing algorithm developers composable associative arrays that admit linear algebraic manipulation

Example Code & Assignment

- **Example Code**
  - d4m_api/examples/2Apps/4BioBlast
- **Assignment**
  - None