

STATISTICS 画 Applying In-Memory Technology to Genome Data Analysis Cindy Fähnrich Hasso Plattner Institute GLOBAL HEALTH '14 Tutorial

Hasso Plattner Institute Key Facts

- Founded as a public-private partnership in 1998 in Potsdam near Berlin, Germany
- Institute belongs to the University of Potsdam
- Ranked $1st$ in CHE since 2009
- 500 B.Sc. and M.Sc. students
- 10 professors, 150 PhD students
- Course of study: IT Systems Engineering

In-Memory Applications For Informed Patients

Dr. Schapranow, HPI, Aug 12, 2014

Hasso Plattner Institute Programs

- Full university curriculum
- Bachelor (6 semesters)
- Master (4 semesters)
- Orthogonal Activities:
	- □ E-Health Consortium
	- □ School of Design Thinking
	- □ Research School

Hasso Plattner Institute Enterprise Platform and Integration Concepts Group

Prof. Dr. h.c. Hasso Plattner

- Research focuses on the technical aspects of enterprise software and design of complex applications
	- □ In-Memory Data Management for Enterprise Applications
	- \Box Enterprise Application Programming Model
	- □ Scientific Data Management
	- □ Human-Centered Software Design and Engineering
- Industry cooperations, e.g. SAP, Siemens, Audi, and EADS
- Research cooperations, e.g. Stanford, MIT, and Berkeley

Dr. Schapranow, HPI, Aug 12, 2014

Agenda

1. Introduction to In-Memory Technology

- 2. Introduction to Genome Data Analysis
- 3. Combining In-Memory Technology with Genome Data Analysis
	- Pipeline Modeling
	- Pipeline Execution
	- IMDB Technology for Genome Data Analysis
	- IMDB Analysis Features for Applications

In-Memory Technology Building Blocks

Any attribute as index

Multi-core/ parallelization SQL interface on columns & rows

Lightweight Compression

T Text Retrieval and Extraction

\equiv + \parallel Combined Column and Row Store

- Row stores are designed for operative workload, e.g.
	- \Box Create and maintain meta data for tests
	- □ Access a complete record of a trial or test series
- Column stores are designed for analytical work, e.g.
	- \Box Evaluate the number of positive test results
	- \Box Identification of correlations or test candidates
- In-Memory approach: Combination of both stores
	- \Box Increased performance for analytical work
	- \Box Operative performance remains interactively

- Traditional databases allow four data operations: INSERT, SELECT, DELETE, UPDATE
- DELETE and UPDATE are destructive since original data is no longer available
- Insert-only requires only first two to store a complete history (bookkeeping systems)
- Insert-only enables time travelling, e.g. to
	- □ Trace changes and reconstruct decisions
	- □ Document complete history of changes, therapies, etc.
	- \neg Enable statistical observations

- Main memory access is the new bottleneck
- Lightweight compression can reduce this bottleneck, i.e.
	- \Box Improved usage of data bus capacity
	- □ Work directly on compressed data **recID fname** … … … … 39 John 40 Mary 41 Jane 42 John … … … … **Dictionary for "fname" valueID Value** … … … … 23 John 24 | Mary 25 Jane … … … … **positio n valueID** … … … … 39 23 40 24 41 25 42 23 … … … …

Attribute Vector for "fname"

- IMDB paradigm: data stored at highest possible level of granularity
- Contrast to current practice of business data centers
	- \Box Store on level of granularity required by application
	- \Box Multiple applications use same data but require different granularity

 \rightarrow High data redundancy and maintenance efforts

■ IMDB computes aggregates from source data on the

 \rightarrow Dramatical complexity decrease, easier maintenance **10**

- Horizontal Partitioning
	- □ Cut long tables into shorter segments
	- \Box E.g. to group samples with same relevance

■ Vertical Partitioning

- \Box Split off columns to individual resources
- □ E.g. to separate personalized data from experiment data
- Partitioning is the basis for
	- □ Parallel execution of database queries
	- \Box Implementation of data aging and data retention management

Multi-Core and Parallelization

- Modern server systems consist of x CPUs, e.g.
	- □ Each CPU consists of y CPU cores, e.g. 8
	- \Box Consider each of the x^{*}y CPU core as individual workers
	- \Box Each worker can perform one task at the same time in parallel

■ Full table scan of database table w/ 1M entries results in $1/x*1/y$ search time when traversing in parallel

- □ Reduced response time
- □ No need for pre-aggregated totals and redundant data
- \Box Improved usage of hardware
- \Box Instant analysis of data

A P Active and Passive Data Store

- Active data are accessed frequently & updates are expected, e.g.
	- \Box Most recent experiment results, e.g. last two weeks
	- \Box Samples that have not been processed yet
- Passive data are used for analytical & statistical purposes, e.g.
	- \square Samples that were processed 5 years ago
	- \Box Meta data about seeds that are not longer produced
- Moving passive data on slower storages
	- □ Reduces main memory demands
	- \Box Improves performance for active data

Reduction of Application Layers

- Layers are introduced to abstract from complexity
- Each layer offers complete functionality, e.g. meta data of samples
- Less layer result in
	- \Box Less code to maintain
	- □ More specific code
	- □ Reduced resource demands
	- \Box Improves performance of applications due to eliminating obsolete processing steps

- Original use case in 2006: Enterprise software
	- \Box Combining operational and analytical data into one database
	- \Box Enable real-time analysis on latest data
- Big data context: Business and accounting data, customer records, sales orders, invoices, …
- Started 2009 to use in-memory technology in the context of life sciences
- Big data context: Genomic/biological data, prescriptions, patient and cancer records, clinical information systems, medical publications, …

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"Personalized medicine aims at treating patients specifically based on their individual dispositions, e.g. genetic or environmental factors"

(K. Jain, Textbook of Personalized Medicine. Springer, 2009)

- Conventional cancer therapies often fail
	- □ One therapy does NOT fit all
	- \Box Relation between genetic mutations and disease not considered/understood
	- \rightarrow Analyze genetic profile of a patient to define customized therapies
- Challenge: Complex and time-consuming data processing tasks (analysis of one patient takes up to weeks)…

Base Sequencing

- Deriving DNA in digital format from sample via imaging procedures
- Output are unordered DNA snippets (=reads)
- High error rate \rightarrow Sequencing at multiple coverage

Alignment

- Reconstruct genome by reassembling all reads
- Pattern-matching vs. similarity search
- Matching strictness vs. runtime performance

Variant Calling

- Detecting genetic variants in the sample genome
- Comparison to a reference
- Incorporating error probability of data

Data Annotation

- Find out impact of detected genetic variants on organism
- Connect known information, e.g. from studies/research papers, to genetic variants
- Gain new research insights, e.g. relations between genes and diseases,
- **21** for personalized medicine

Genome Data Analysis – Alignment and Variant Calling Refined (1/3)

- Process requires intermediate steps to improve data quality
- Deduplication: Exclude duplicate reads from analysis
- Local Realignment: Reduce false posivites caused by Indels
- Base Quality Score Recalibration (BQSR): Adjust error probabilities of bases
- Variant Quality Score Recalibration (VQSR): Adjust variant probabilities **22**

Additional Info: Local Realignment around InDels

■ Insertions or Deletions (InDels) in reads can "trick" alignment algorithms into misaligning reads and introducing false positive Single Nucleotide Polimorphisms (SNPs)

Genome Data Analysis – Alignment and Variant Calling Refined (2/3)

- Process requires intermediate steps to prepare data for faster processing
- More complicated when splitting up Alignment and Variant Calling ...

Genome Data Analysis – Alignment and Variant Calling Refined (3/3)

Genome Data Analysis – How it is done today

Alignment and Variant Calling

■ Single tasks are triggered manually or in scripts invoking tools via command line:

bwa aln ref.fa sample.fastq| bwa samse ref.fa – sample.fastq | samtools view -Su - | samtools sort …

- Effective parallelization?
- Error handling?
- Distribution to a cluster?

Data Annotation

- Mostly manual analysis, e.g. via keyword search in portals on the web
- Efficient analysis of data from a patient/cohort?

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Pipeline Modeling – How to Set Up a Pipeline

- Analysis pipeline is constructed from combining tools for the different analysis steps
	- □ Currently manual work via command line piping/scripts
	- □ Hard to understand/document/maintain
- Objective: Model the analysis pipeline with ...
	- □ … a graphical representation that is …
	- □ … easy to understand and adapt
- Prerequisite: Graphical notation with standardized, machine readable representation

Pipeline Modeling – BPMN 2.0

- Business Process Model and Notation (BPMN) 2.0
- Functional modeling of business processes and workflows
- **Intended for both business and technical users** \rightarrow **intuitive modeling**
- XPDL available as XML standard for representing BPMN

Pipeline Modeling with BPMN

- Only using a subset of BPMN, adapted with own constructs:
	- □ Modular structure
	- □ Degree of parallelization
	- □ Parameters
	- □ Variables

Pipeline Modeling – Modular Structure

- Reuse existing pipeline components, e.g. for alignment
- Make pipeline flexible regarding the tools used

Pipeline Modeling – Degree of Parallelization

- Execute parts of the pipeline in parallel
- Configure the explicit amount of parallel instances

Pipeline Modeling – Parameter

- Some tasks require parameters to be executed
	- □ Reference genome
	- □ Thread size
	- □ Number of parallel instances
- Annotation of tasks with explicit parameters via data objects

Pipeline Modeling – Variables

- □ Number of parallel instances
- □ Reference genome
- Annotate tasks with variables that are set at runtime

Pipeline Modeling – Creating the Final Analysis Pipeline

- Specify all subprocess models, parameters, variables
- Import all models in XPDL format into database
- Database entry of a pipeline model consists of
	- □ Name
	- □ Model ID
	- □ List of subprocess IDs
	- \Box List of parameters and variables

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Pipeline Execution – Bringing the Model to Life

- Parser converts XML into executable, directed graph of task objects
- Execution environment is cluster of worker machines coordinated by scheduler
- Each task object has a corresponding implementation, e.g. tool invocation

Pipeline Execution – Worker Framework

Pipeline Execution – Worker Framework

- Task implementation imported as modules to worker at runtime
- One super class for administrative things, all tasks implement particular method

Pipeline Execution – **Scheduler**

- Scheduler is responsible for holding the structure of task objects
- Starts task when all predecessors are finished
- High availability of scheduler by storing global pipeline status in IMDB
- \rightarrow In case of scheduler crash another worker can take scheduler role without any delay
- Scheduler uses workload information and execution statistics based on logs in IMDB

Insert Only For Time Travel

 $+\frac{1}{2}$

Pipeline Execution – Scheduling Policies

- Different scheduling algorithms
	- □ First-come first-served
	- □ Lottery
	- □ Shortest task first
	- □ Priority-based assignment
	- □ User-based assignment
- Prioritize tasks to maximize utilization of workers

Pipelines – Traditional vs. IMDB-supported Approach

■ (Intermediate) results are imported into database

Pipelines – Traditional vs. IMDB-supported Approach

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IMDB Technology for Genome Data Analysis – Alignment

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Alignment – Performance

Variant Calling – Motivation

- Common variant calling tools all process files residing on disk space
	- □ Slow storage media
	- \Box Large data files, e.g. >100GB per individual
- Idea: Access data from main memory and profit from built-in database features
	- □ Partitioning
	- □ Multi-core and parallelization
	- □ Lightweight compression

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Chart **49**

- Reference genome: Base sequence for comparison
- Read alignments: Reads from reconstructed sample genome
- All data is imported into database beforehand, with implicit
	- □ Data indexing
	- □ Lightweight compression
- Variant calling results conform to standard format and can easily be exported from database or used for further analyses

Chart **50**

Variant Calling – Extending the Database Core

- Implementation as Application Function Library (AFL)
- Variant calling per chromosome
- Parallelization with MapReduce-like approach
- Invocation via stored procedure call

```
CALL " SYS AFL". "VARCALL AREA CALL SNP VARIANTS PROC"(
SAMIMPORT.NA19240, GENES.HG19CHR22,
'chr22', 20,
20, 30,
40, VARIANTS.OUTPUTTAB) WITH OVERVIEW;
```
Variant Calling – Performance

- Built-in database functionalities simplify and speed up data preprocessing
- Average time saving of factor 22 compared to standard tools at equal accuracy
- SNP calling of high-coverage (64x) whole genome on cluster
	- □ 873M read alignments
	- $\Box \sim 18$ min

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IMDB Analysis Features for Applications – Textual Analysis of Medical Documents

- IMDB provides text analysis features, e.g.
	- □ Fulltext indexing
	- □ Entity Recognition
	- $\n **Tokenization**\n$
	- □ Fuzzy search
- Mechanisms can be made domain-specific by specifying
	- □ Dictionaries
	- \Box CGUL rules containing regular expressions with linguistic attributes

Multi-Core and Parallelization

Text Retrieval and Extraction

IMDB Analysis Features for Applications – Textual Analysis of Medical Documents

1. Specify dictionary in XML and/or CGUL rules:

2. Compile XML dictionary for database and reference them in config file

IMDB Analysis Features for Applications – Textual Analysis of Medical Documents

3. Create fulltext index:

CREATE FULLTEXT INDEX "EXAMPLE"."EXAMPLE_INDEX" ON EXAMPLE"."EXAMPLE_DATA" ("TEXT") CONFIGURATION 'PROJECT::MED_TERMS' ASYNC **LANGUAGE DETECTION ('EN')** FUZZY SEARCH INDEX ON TEXT ANALYSIS ON TOKEN SEPARATORS '\/;,.:-_()[]<>!?*@+{}="&'

IMDB Analysis Features for Applications – Statistical Analyses Functions

- IMDB provides specific **analysis functions** tightly integrated within the database, e.g. k-means or hierarchical clustering
- Highly parallelized and efficient using database framework
- Invoked as stored procedures via SQL statement:

CALL _SYS_AFL.PAL_HC(DATA_TAB, PARAM_TAB, COMBINEPROCESS_TAB, RESULT_TAB);

Analyze Genomes – An In-Memory Computing Platform

Keep in contact with us.

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Chart **60**

Medical Knowledge Cockpit for Clinicians Pathway Topology Analysis

Unified access to multiple formerly disjoint data sources \blacksquare

Pathway analysis of genetic variants with graph engine

- Search in pathways is limited to "is a certain element contained" today
- Integrated $>1,5k$ pathways from international sources, e.g. KEGG, HumanCyc, and WikiPathways, into HANA
- Implemented graph-based topology exploration and ranking based on patient specifics
- Enables interactive identification of possible dysfunctions affecting the course of a therapy before its start

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