

# 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 1<sup>st</sup> 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



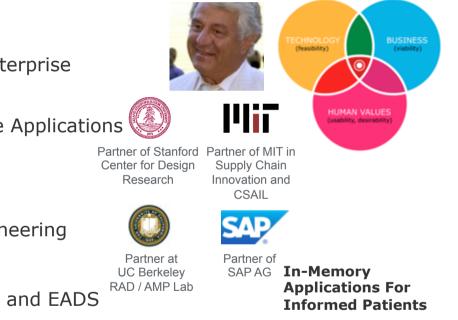
#### In-Memory Applications For Informed Patients

Dr. Schapranow, HPI, Aug 12, 2014 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
  - 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

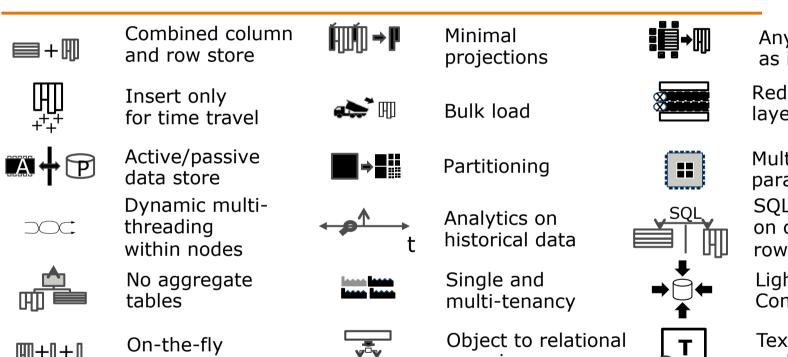
## Agenda



## **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





extensibility

Map reduce



Object to relational mapping

Group Key



Any attribute as index

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Reduction of layers

Multi-core/ parallelization SOL interface on columns & rows

Lightweight Compression

Text Retrieval and Extraction

No disk

#### 

- Row stores are designed for operative workload, e.g.
  - □ 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.
  - □ Evaluate the number of positive test results
  - Identification of correlations or test candidates
- In-Memory approach: Combination of both stores
  - □ Increased performance for analytical work

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□ 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.
  - Enable statistical observations





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





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

 $\rightarrow$ High data redundancy and maintenance efforts

IMDB computes aggregates from source data on the

Dramatical complexity decrease, easier maintenance
 10





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

#### Vertical Partitioning

- □ 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
  - □ 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
  - □ Consider each of the x\*y CPU core as individual workers
  - □ Each worker can perform one task at the same time in parallel

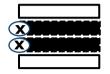
■ Full table scan of database table w/ 1M entries results in 1/x\*1/y search time when traversing in parallel

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

# Active and Passive Data Store

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





## Reduction of Application Layers

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





- Original use case in 2006: Enterprise software
  - Combining operational and analytical data into one database
  - □ 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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  - Pipeline Execution
  - IMDB Technology for Genome Data Analysis
  - IMDB Analysis Features for Applications

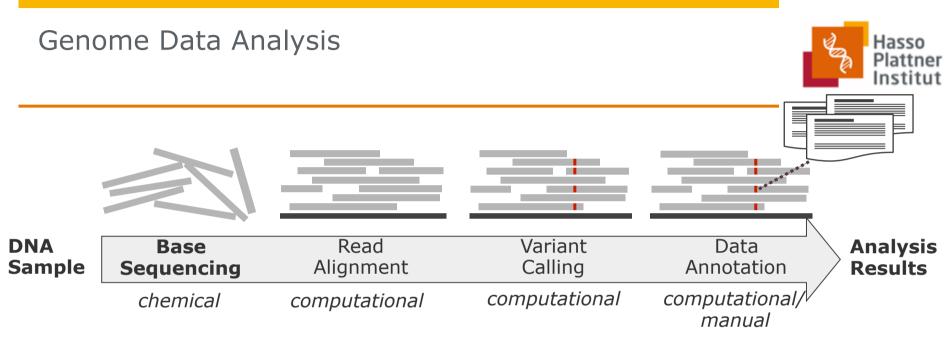




## "Personalized medicine aims at treating patients specifically based on their individual dispositions, e.g. genetic or environmental factors"

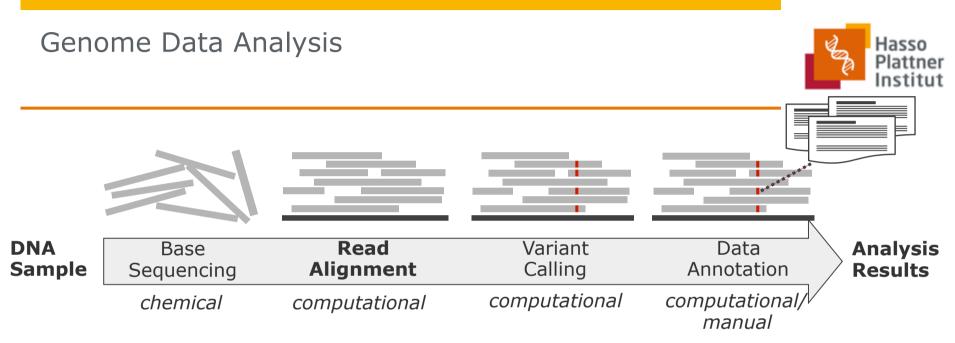
(K. Jain, Textbook of Personalized Medicine. Springer, 2009)

- Conventional cancer therapies often fail
  - One therapy does NOT fit all
  - 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)...



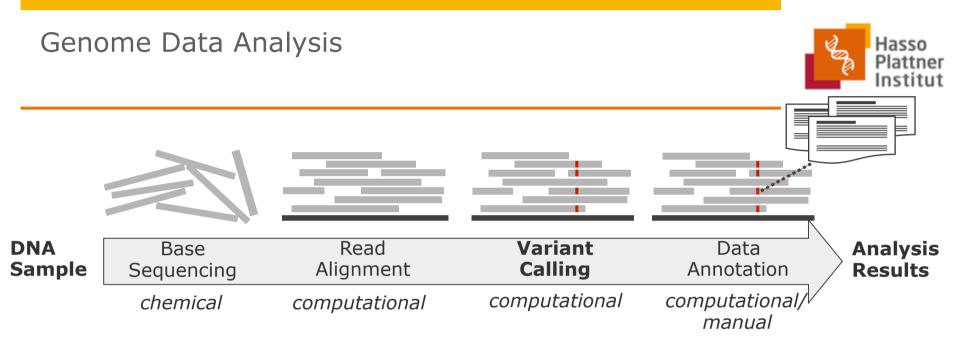
### **Base Sequencing**

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



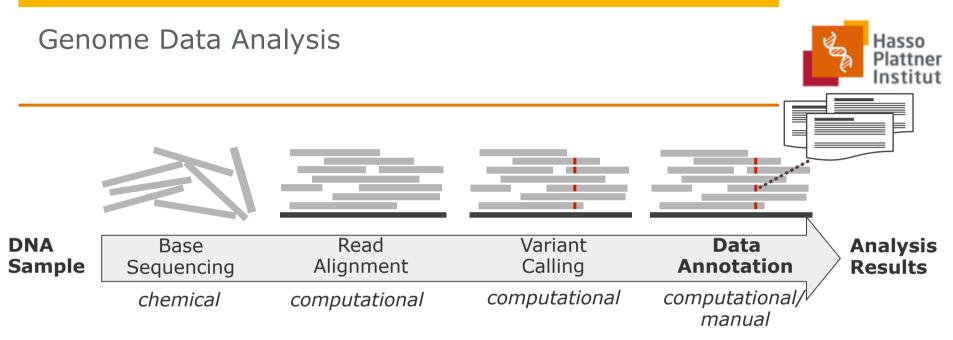
## Alignment

- 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

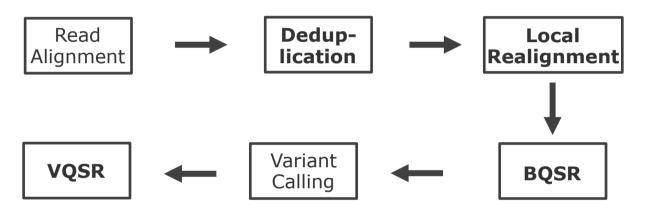


### **Data Annotation**

- 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)

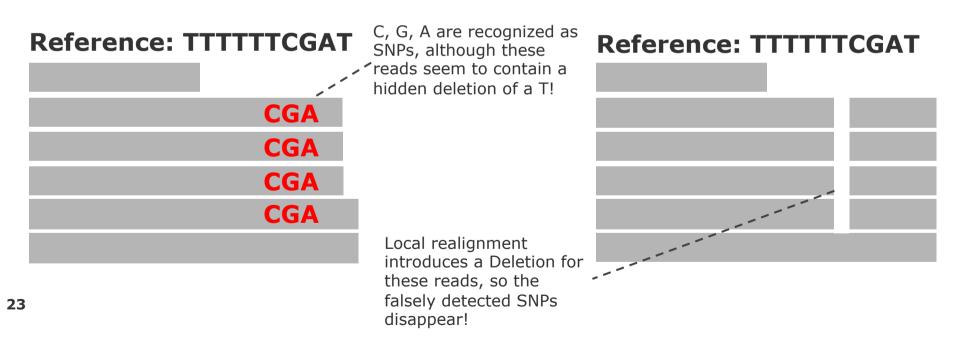




- Process requires intermediate steps to improve data quality
- Deduplication: Exclude duplicate reads from analysis
- Local Realignment: Reduce false posivites caused by Indels
- Base Quality Score Recalibration (BQSR): Adjust error probabilities of bases
- Variant Quality Score Recalibration (VQSR):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

Additional Info: Local Realignment around InDels

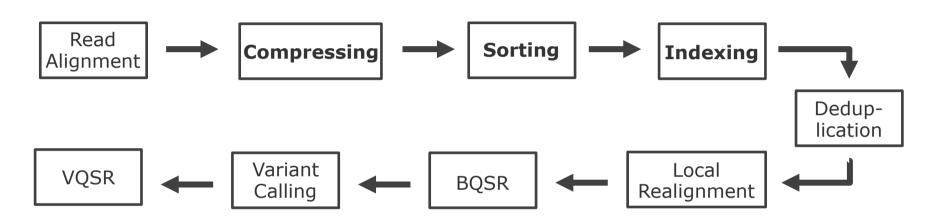
 Insertions or Deletions (InDels) in reads can "trick" alignment algorithms into misaligning reads and introducing false positive Single Nucleotide Polimorphisms (SNPs)





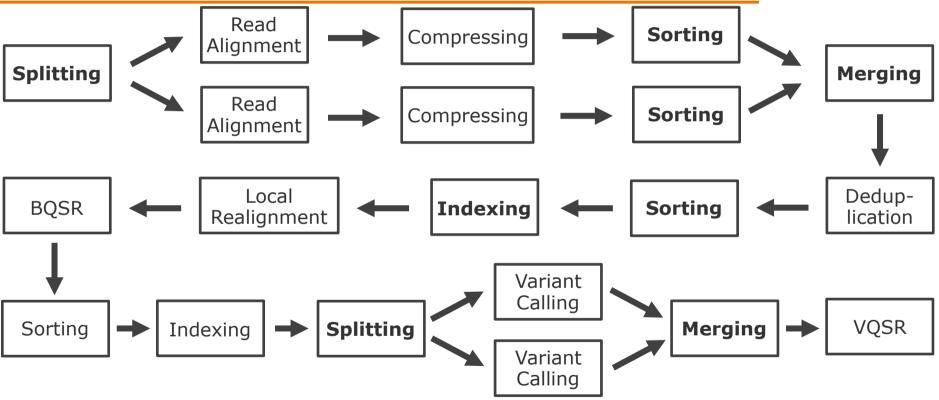
Genome Data Analysis – Alignment and Variant Calling Refined (2/3)





- 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)



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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 ...
  - $\hfill\square$  ... a graphical representation that is ...
  - $\hfill\square$  ... easy to understand and adapt
- Prerequisite: Graphical notation with standardized, machine readable representation

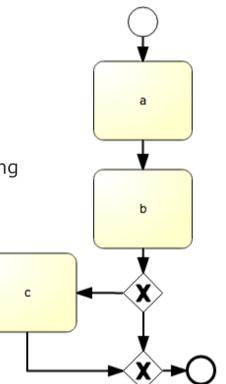


Pipeline Modeling – BPMN 2.0

- 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

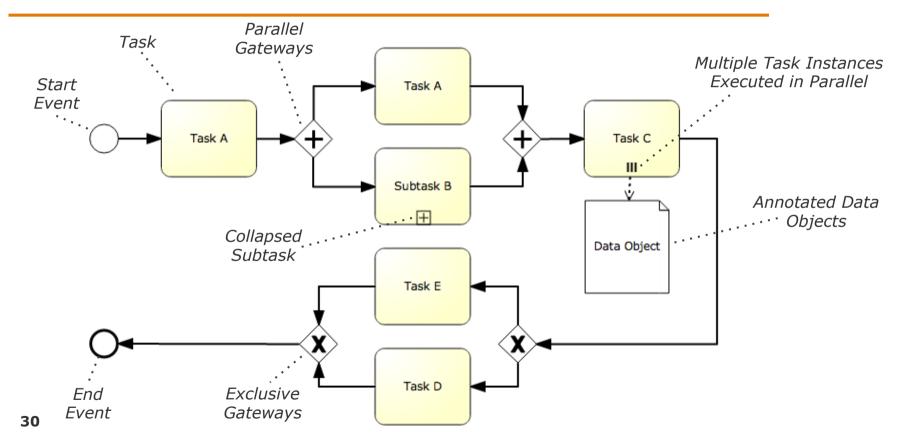






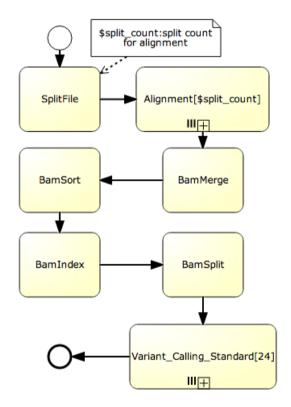






Pipeline Modeling with BPMN

- Model and adapt your models in your tool of choice
- Only using a subset of BPMN, adapted with own constructs:
  - Modular structure
  - Degree of parallelization
  - Parameters
  - Variables

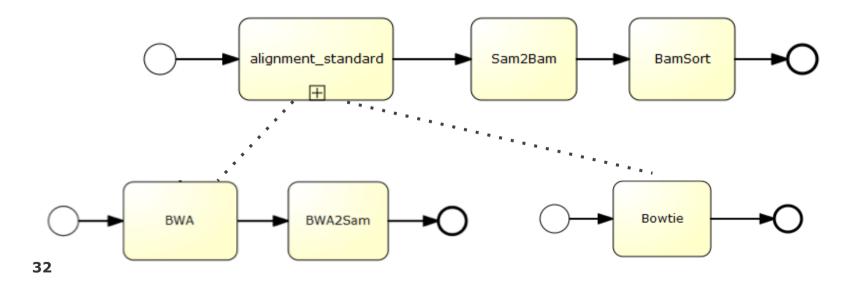




Pipeline Modeling – Modular Structure



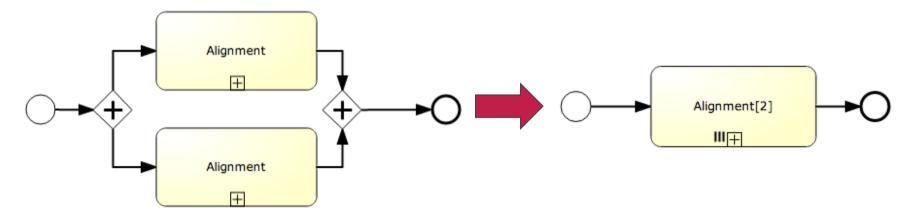
- Pipeline models can be nested hierarchically
- Reuse existing pipeline components, e.g. for alignment
- Make pipeline flexible regarding the tools used



Pipeline Modeling – Degree of Parallelization

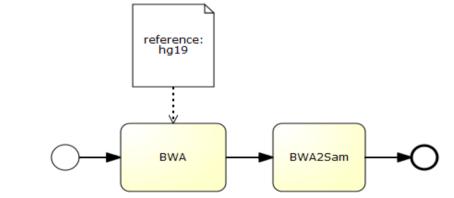


- Execute parts of the pipeline in parallel
- Configure the explicit amount of parallel instances



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

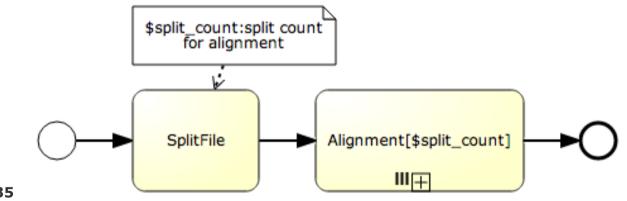




Pipeline Modeling -Variables



- 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
  - $\hfill\square$  List of subprocess IDs
  - □ List of parameters and variables

## Agenda

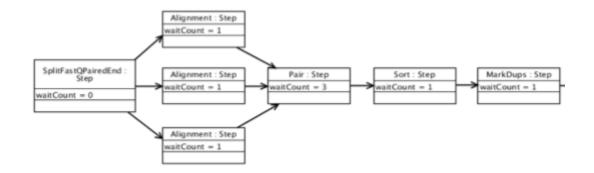


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Pipeline Execution – Bringing the Model to Life

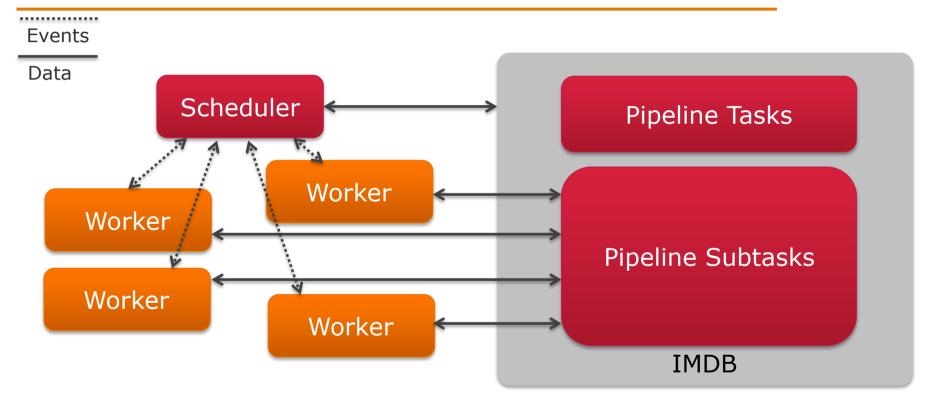


- Parser converts XML into executable, directed graph of task objects
- Execution environment is cluster of worker machines coordinated by scheduler
- Each task object has a corresponding implementation, e.g. tool invocation



### Pipeline Execution – Worker Framework





# Pipeline Execution – Worker Framework

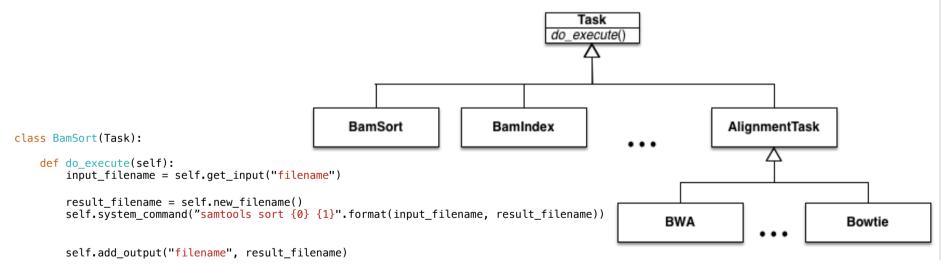


ID	STATUS PI	PELINE_ID PARAMETERS C	CREATED_AT	USER
1.655	3	69 {"filename":"SRR389458.filt.fastq2263","typ":"file","read_count":2263,"priority":0} 0	07.08.2014 15:42:01.021	74
1.640	2	22 {"filename":"400.fastq2263","typ":"file","read_count":2263,"priority":0} 0	05.08.2014 13:47:31.818	3
1.639	2	22 {"filename":"BC_1.fastq3228864","typ":"file","read_count":3228864,"priority":0} 2	21.07.2014 13:01:06.877	75
1.638	2	73 {"filename":"s_G1_L001_I1_001.fastq.1250000","typ":"file","read_count":250000,"priority":0} 2	21.07.2014 10:28:32.352	68
1.637	2	70 {"filename":"HN-10960_S9_L001_R1_001.fastq794380","typ":"file","read_count":794380,"priority":0} 1	18.07.2014 00:17:32.737	3
1.636	2	22 {"filename":"L2I500000_2.fastq","typ":"file","read_count":5000002,"priority":0} 2	20.06.2014 11:46:39.73	59
1.634	2	22 {"filename":"BC_1.fastq3228864","typ":"file","read_count":3228864,"priority":0} 1	12.06.2014 13:10:08.204	3
1.633	2	22 {"filename":"HN-10960_S9_L001_R1_001.fastq794380","typ":"file","read_count":794380,"priority":0} 1	12.06.2014 13:09:25.584	3
1.632	2	22 {"filename":"HN-10960_S9_L001_R1_001.fastq794380","typ":"file","read_count":794380,"priority":0} 1	12.06.2014 13:09:19.777	3
1.631	2	22 {"filename":"HN-10960_S9_L001_R1_001.fastq794380","typ":"file","read_count":794380,"priority":0} 1	12.06.2014 13:09:06.365	3
1.630	2	73 {"filename":"SRR389458.filt.fastq2263","typ":"file","read_count":2263,"priority":0} 1	10.06.2014 17:03:57.696	68
SUBTAS	K TASK	STATUS JOB PARAMETER	WORKER UPDATED_AT	
82.33	4 1.639	0 BamSort {"number_of_instances": 1, "filename": "0kr6909vy0m0jvnr.bam"}	1 21.07.2014 13:03	3:42.865
82.33	4 1.639	1 BamSort {"number_of_instances": 1, "filename": "0kr6909vy0m0jvnr.bam"}	1.000 21.07.2014 13:03	3:43.427
82.334	4 1.639	2 BamSort {"filename": "cbts8ltwevluy5es.bam"}	1.000 21.07.2014 13:04	1:15.317
82.33	5 1.639	0 BamIndex {"number_of_instances": 1, "filename": "cbts8ltwevluy5es.bam"}	1 21.07.2014 13:04	1:15.333
82.33		1 BamIndex {"number_of_instances": 1, "filename": "cbts8ltwevluy5es.bam"}	1.000 21.07.2014 13:04	1:15.636
82.33		2 Bamindex {"filename": "cbts8ltwevluy5es.bam"}	1.000 21.07.2014 13:04	
82.33		0 Indel_Calling {"index": 0, "number_of_instances": 1, "filename": "cbts8ltwevluy5es.bam"}	1 21.07.2014 13:04	
82.33		1 Indel_Calling {"index": 0, "number_of_instances": 1, "filename": "cbts8ltwevluy5es.bam"}	1.000 21.07.2014 13:04	
82.33		2 Indel_Calling {"filename": "hmgrk3w4bxchxrsc.indels.vcf"}	1.000 21.07.2014 13:32	
82.33		0 SNP_Calling {"index": 0, "number_of_instances": 1, "filename": "cbts8ltwevluy5es.bam"}	1 21.07.2014 13:32	
82.33		1 SNP_Calling {"index": 0, "number_of_instances": 1, "filename": "cbts8ltwevluy5es.bam"}	1.000 21.07.2014 13:32	
82.33	7 1.639	2 SNP_Calling {"filename": "o6skoc0fsu4w7j90.snps.vcf"}	1.000 21.07.2014 15:01	1:20.045

Pipeline Execution – Task Implementation



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

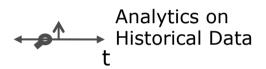


Pipeline Execution – Scheduler

- 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
- → 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



Pipeline Execution – Scheduling Policies

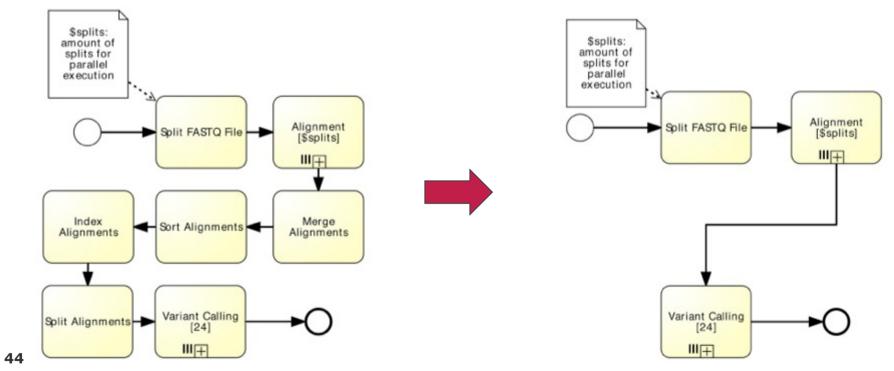


- □ First-come first-served
- Lottery
- Shortest task first
- Priority-based assignment
- User-based assignment
- Prioritize tasks to maximize utilization of workers



Pipelines – Traditional vs. IMDB-supported Approach

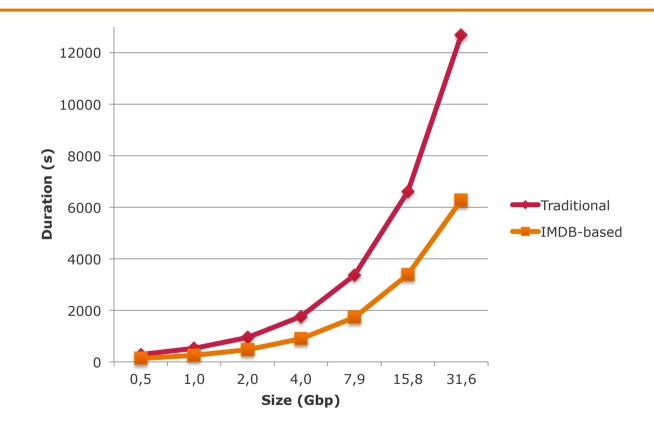
• (Intermediate) results are imported into database





# Pipelines – Traditional vs. IMDB-supported Approach



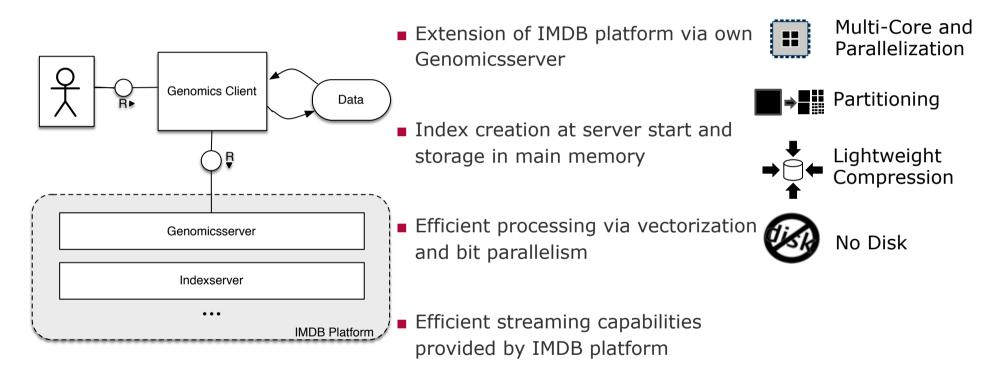


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IMDB Technology for Genome Data Analysis – Alignment

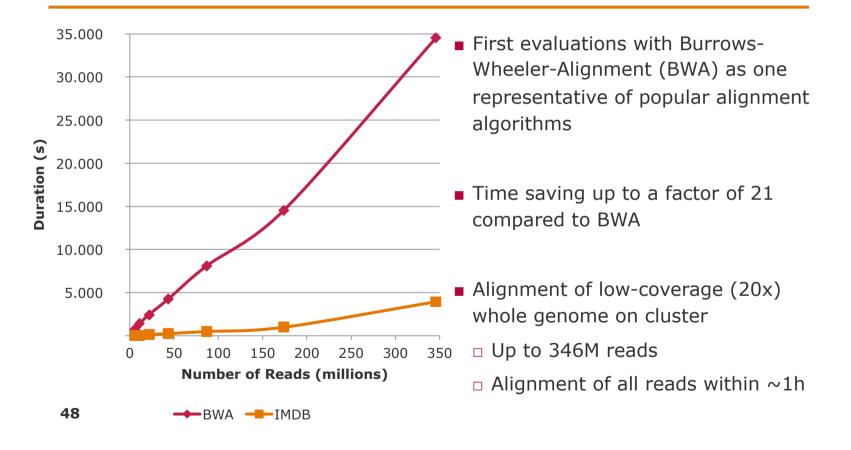


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### Alignment – Performance





Variant Calling – Motivation

- Common variant calling tools all process files residing on disk space
  - Slow storage media
  - □ 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

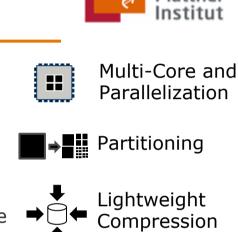




Chart 49

Variant Calling – Data

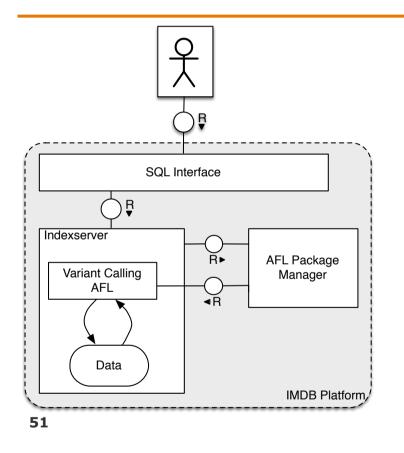


- Reference genome: Base sequence for comparison
- Read alignments: Reads from reconstructed sample genome
- All data is imported into database beforehand, with implicit
  - Data indexing
  - Lightweight compression
- Variant calling results conform to standard format and can easily be exported from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

Chart **50** 

Variant Calling – Extending the Database Core



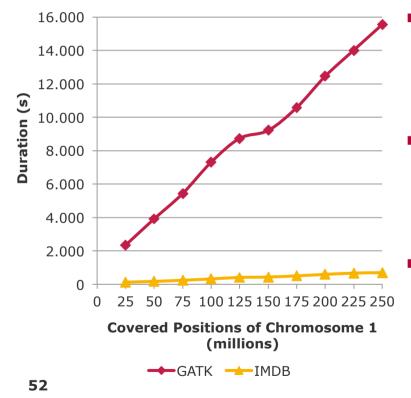


- Implementation as Application Function Library (AFL)
- Variant calling per chromosome
- Parallelization with MapReduce-like approach
- Invocation via stored procedure call

```
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
  - □ ~18min

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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
  - Tokenization
  - Fuzzy search
- Mechanisms can be made domain-specific by specifying
  - Dictionaries
  - 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 '\/;,.:-\_()[] <> !?\*@+{}="&'

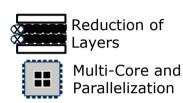
4. Get results in database table and use for further analyses:

TA_RULE	TA_TOKEN	TA_LANGUAGE	TA_NORMALIZED	TA_PARAGRAPH	TA_SENTENCE	TA_CREATED_AT	TA_OFFSET
Entity Extraction	woman	en	patient	3	3	11.06.2014 16:38:28.779	473
Entity Extraction	man	en	patient	3	3	11.06.2014 16:38:28.827	437
Entity Extraction	Inpatient	en	patient	1	3	11.06.2014 16:38:28.827	211
Entity Extraction	woman	en	patient	3	3	11.06.2014 16:38:28.827	460
Entity Extraction	Inpatient	en	patient	2	3	11.06.2014 16:38:28.827	223
Entity Extraction	Inpatient	en	patient	1	1	11.06.2014 16:38:28.827	227
Entity Extraction	Patient	en	patient	4	4	11.06.2014 16:38:28.865	273

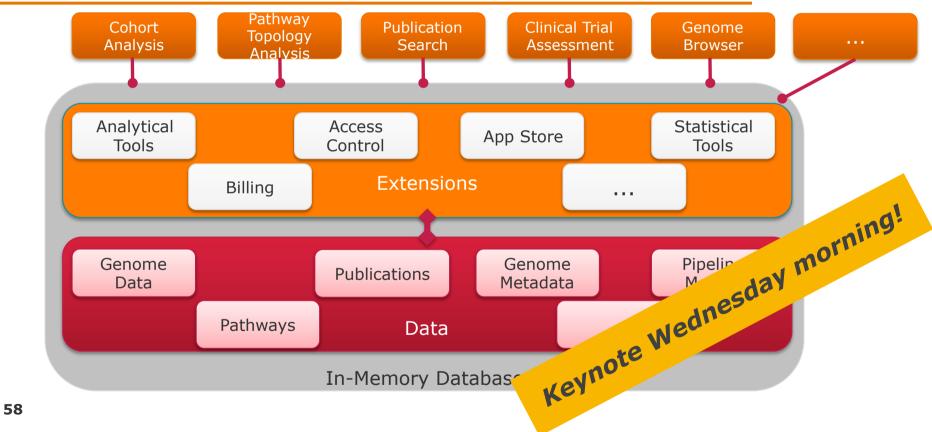
IMDB Analysis Features for Applications – Statistical Analyses Functions

- 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



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Keep in contact with us.



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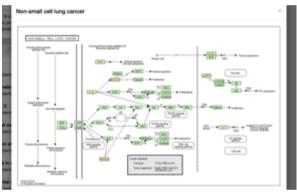
Hasso Plattner Institute Enterprise Platform & Integration Concepts August-Bebel-Str. 88 14482 Potsdam, Germany Backup/Further Questions



Chart **60** 

# Medical Knowledge Cockpit for Clinicians Pathway Topology Analysis







Unified access to multiple formerly disjoint data sources



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
- In-Memory Applications For Informed Patients

Dr. Schapranow, HPI, Aug 12, 2014

