Technologies for Genomic Medicine: MaPSeq, A Computational and Analytical Workflow Manager for Downstream Genomic Sequencing

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Lists of Technical Terms and Websites

Apache™ ActiveMQ, activemq.apache.org
Apache™ CXF RESTful (Representational State Transfer), www.ibm.com/developerworks/webservices/library/ws-restful
Apache™ CXF SOAP (Simple Object Access Protocol), axis.apache.org/axis2/java/core/docs/soapmonitor-module.html
Apache™ karaf software, karaf.apache.org
Apache™ OpenJPA (Java Persistence API), openjpa.apache.org
APIs (application programming interfaces), www.webopedia.com/TERM/A/API.html
CASAVA (Consensus Assessment of Sequence and Variation), www.illumina.com/software/genome_analyzer_software.ilmn
CPU (Central Processing Unit)
daemons, en.wikipedia.org/wiki/Daemon_computing
fastq files, www.broadinstitute.org/gatk/gatkdocs/org_broadinstitute_sting_gatk_walkers_qc_FlagStat.htm
FlagStat files, www.broadinstitute.org/gatk/gatkdocs/org_broadinstitute_sting_gatk_walkers_qc_FlagStat.html
Glidein, www.cl.cam.ac.uk/manuals/condor-V6_8_3-Manual/5_4Glidein.html
GlideinWMS, www.uscms.org/SoftwareComputing/Grid/WMS/glideinWMS/doc.prd/index.html
HTCondor™ , research.cs.wisc.edu/htcondor
JSON (JavaScript Object Notation), www.json.org
MaPSeq (Massively Parallel Sequencing system)
OSG (Open Science Grid), www.opensciencegrid.org
OSGi (Open Science Grid initiative). www.osgi.org/Main/HomePage

PostgreSQL (Structured Query Language) database, www.postgresql.org
SSH (Secure Shell) technology, www.webopedia.com/TERM/S/SSH.html
SOA (Service-Oriented Application), www.opengroup.org/soa/source-book/soa/soa.htm#soa_definition
TeraGrid™ Science Gateways Program, info.teragrid.org

Introduction

Genomic medicine is advancing at a remarkably fast past, with major technological achievements such as next-generation genomic sequencing producing large-scale genomic data sets within a reasonable timeframe and cost (Mardis, 2008; Horvitz and Mitchell, 2010; Koboldt et al., 2010; Kahn, 2011). Yet large-scale computation on the gigabyte- to petabyte-scale data sets that are generated from massively parallel genomic sequencing projects remains enormously challenging. Indeed, the National Consortium for Data Science (Ahalt et al., 2014), the Global Alliance to Enable Responsible Sharing of Genomic and Clinical Data (2013), and the BD2K Data and Informatics Working Group, National Institutes of Health BD2K Initiative (2012) have recognized computational and analytical challenges as significant barriers to the advancement of genomic medicine.

Herein, we describe the Massively Parallel Sequencing (MaPSeq) system—an open source, secure, centralized, grid-based SOA that facilitates, manages, and executes the complex, project-specific, computational and analytical downstream steps involved in high-throughput genomic sequencing.

MaPSeq

MaPSeq was developed by RENCI in collaboration with Information Technology Services (ITS) Research Computing at the University of North Carolina at Chapel Hill (UNC) to address a need for reliable and efficient high-throughput informatics processing of genomics data for both large and small research projects. The design of MaPSeq was informed by previous work with the OSG and TeraGrid™ Science Gateways Program. It includes a plugin architecture that provides researchers with a framework to facilitate the construction, deployment, and execution of sequence analysis workflows. MaPSeq is designed to make simultaneous, opportunistic use of multiple institution-wide and cloud-based computational resources from across administrative domains at UNC.

MaPSeq evolved from a Science Portal that RENCI had created to assist researchers with large-scale, high-throughput, computational science problems (McGee, 2010). The Science Portal served as a computational science platform, and it had several desirable features: (1) it was user-friendly and accessible via a web browser and a variety of APIs application programming interfaces; and (2) it provided high throughput, in that it triaged job requests to multiple, high-capacity, computational clusters (namely, OSG, TeraGrid™, and clusters available at RENCI and UNC's Department of Computer Science). At the core of the Science Portal was HTCondor™, which is a high-throughput computing platform used extensively in academic research. HTCondor™ also is at the core of the OSG and services hundreds of millions of compute jobs, data transfers, and CPU (Central Processing Unit) hours per year (display.grid.iu.edu).

MaPSeq was developed using a strategy and structure similar to the Science Portal, as a plugin-based, centralized, SOA environment comprised of a database-backend, user-friendly web services, multiple programmatic interfaces, server-side applications, and persistence (Figure 1). As with the Science Portal, HTCondor™ provides the underlying high-throughput computing capabilities. MaPSeq utilizes SSH technology for authentication and data management and transfer.

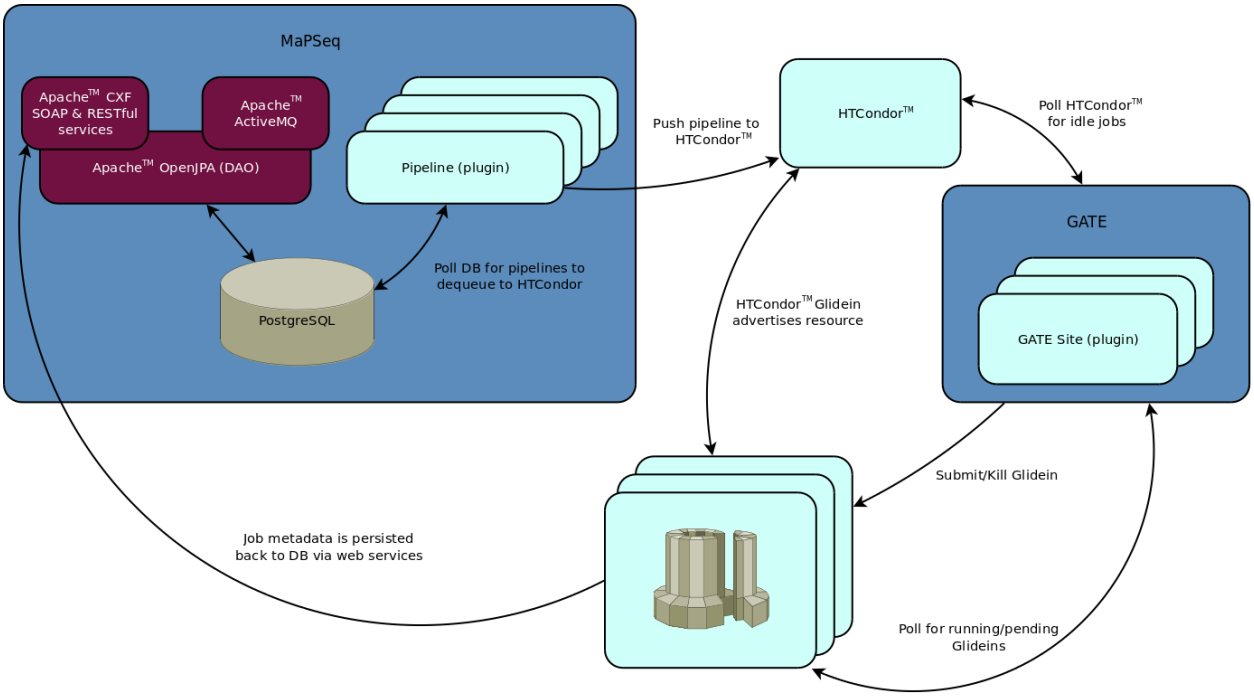

Figure 1. A schematic showing the architecture of MaPSeq, with arrows depicting the flow of information. DB = database; GATE = Gate Access Triage Engine; RESTful = Representational State Transfer; SOAP = Simple Object Access Protocol.

MaPSeq Operations Overview

To provide an overview of MaPSeq operations, suppose a client wishes to process the output from a sequencing run. The client will use a web service to send the job request via a JSON-formatted message to Apache™ ActiveMQ. The message specifies the data (format, size) and the workflow pipeline needed to process the data. ActiveMQ evokes SSH technology to determine if the object layer (i.e., the input raw sequencing data) in the message is legitimate (e.g., Does the file contain sequencing metadata?) for subsequent pipeline workflow parsing. If so, then MaPSeq uses CASAVA software to transform the raw sequencing data (typically ~500 gigabytes/project) into compressed fastq files. In a single-end run, one compressed fastq file is produced per sample. In a paired-end run, two compressed fastq files are produced per sample. The two fastq files share the same base name and thus can be matched against each other. The metadata for the fastq files are stored in a PostgreSQL database. MaPSeq then activates the workflow run attempts, which persist in a queue in the PostgreSQL database via Apache™ OpenJPA. Note that the pipeline workflows are comprised of the detailed, often complex,

computational steps required for tailored downstream analysis of sequencing data (e.g., sequence alignment, variant calling).

The pipeline workflows themselves continuously check the PostgreSQL database for pipeline run attempts. When pipeline run attempts are identified by the workflow pipelines, the pipeline is dequeued and sent to the HTCondor™ meta-scheduler. HTCondor™ sequentially reads each task in the dequeued pipeline, with a specific task being read only after the previous one has been read. HTCondor™ reads both the job attributes (e.g., CPU and memory needs, transfer file needs, etc.) and the machine/cluster needs (e.g., availability, computing power, etc.) and matches the two using OSG assumptions/premises. HTCondor™ can opportunistically take advantage of multiple clusters. Of note, HTCondor™ does not execute jobs; rather, it catalogs job tasks and machine/cluster needs, matches the results, and then sits idle.

To promote software reusability, the pipeline workflows are typically broken into smaller computational sub-pipelines, with each sub-pipeline modified and/or reused as needed. Pipeline workflow tasks are dictated by the needs of a given project and defined by the researcher; thus, pipeline workflows can be tailored, revised, and reused.

[Call Out Box: Software sustainability promoted through workflow sub-pipelines

- **Example: Hello World**
  - **Echo1 "Hello" → file1 (3rd party library)**
  - **Echo2 "World" → file2**
  - **Cat file1 file2**
    → Hello World
- **Example: Genomic Research Project**
  - **Echo1 "Alignment sub-pipeline" → file1**
  - **Echo2 "Variant calling sub-pipeline" → file2**
  - **Cat file1 file2**
    →Alignment + Variant calling]

GATE (Grid Access Triage Engine)

GATE serves as a sister technology for MaPSeq. It is also plugin-based and provides a dynamically expanding and contracting set of compute resources available to service MaPSeq computational work across a distributed set of computational clusters. GATE is conceptually modeled after GlideinWMS, which provides critical resource elasticity services for the OSGi and manages the vast majority of OSG job submissions.

GATE runs in the background to determine if a Glidein, or temporary addition of one or more grid resources, is needed for a given pipeline workflow. GATE continuously monitors HTCondor™ for idle jobs. If there are any idle jobs, then GATE profiles clusters for availability and, after identifying available clusters, submits an HTCondor™ instance on a compute node to a remote batch scheduler, which then registers back to the initial instance of HTCondor™. The local instance of HTCondor™ then executes the catalogued match-making and activates the pipeline jobs on the remote compute node. In this manner, GATE enables opportunistic use of all available clusters to ensure computational efficiency.

Of importance, metadata about a given job's progress persists from the compute node to the PostgreSQL database. This allows the client to send a message to the web-based Apache™ CXF SOAP and RESTful (Rodriguez, 2008) services, with a request to retrieve information regarding the status of a job; the web services can then pull that information from the database and send it back to the client. In addition, the pipelines house their own web services via MaPSeq's web services (i.e., Apache™ CXF SOAP Monitor and RESTful). For example, FlagStat files collect metadata on a pipeline's analytical results, including simple statistics, such as the % complete reads, % missing data, and number of duplicate reads; this information persists back to the database, which allows the client to send a request to MaPSeq's web services to access the information.

Finally, MaPSeq was designed such that clients can create, modify, and deploy their own pipeline workflows without MaPSeq administrator involvement. In particular, MaPSeq and GATE use an instance of Apache™ karaf software to run lightweight plugin tools using the OSGi framework. SSH, running with daemons, can be used to access the karaf container for MaPSeq and GATE and deploy a new or modified pipeline for any particular project. Thus, the researcher or developer of a pipeline workflow can directly control the pipeline itself.

Conclusion

MaPSeq is an open source, secure, centralized, grid-based, SOA that facilitates, manages, and executes the complex, project-specific, downstream analytical steps involved in high-throughput genomic sequencing.

Key Features:

- Architecture is open source
- System requires minimal user intervention after system configuration
- Multiple, remote computational clusters are accessed opportunistically
- Software reusability is promoted through sub-pipelines
- Pipeline workflows can be tailored, modified, and updated as needed
- Pipeline workflows can house web services
- Pipeline workflows can be revised and deployed by clients, thus minimizing administrator burden

Underlying Software and Technologies:

- **MaPSeq/GATE:**
  - Apache™ ActiveMQ
  - Apache™ CXF SOAP
  - Apache™ CXF RESTful
  - Apache™ karaf
  - Apache™ OpenJPA
  - CASAVA
  - HTCondor™
  - PostgreSQL
  - Secure Shell Technology

- **Local Computational Clusters Currently Accessed by MaPSeq/GATE:**
  - KillDevil (ITS Research Computing)
    - Dell blade-based Linux Cluster
    - 604 Compute Nodes: 48GB RAM
    - 68 Compute Nodes: 96GB RAM
    - 2 Compute Nodes: 1TB RAM
    - 32 GPU compute nodes with 64 Nvidia Tesla GPU cards
  - Kure (ITS Research Computing)
    - 2.2 PB Isilon system (ITS Research Computing)
    - HP blade-based Linux Cluster
    - 136 Compute Nodes: 48GB RAM
    - 80 Compute Nodes: 72GB RAM
    - 2 Compute Nodes: 96GB RAM
    - 3 Compute Nodes: 192GB RAM
    - Infiniband 4x QDR
  - BlueRidge (RENCI)
    - Dell blade-based Linux Cluster
    - 128 Dell PowerEdge m610 blades (1024 cores total)
    - 32 Dell PowerEdge m610 blades (384 cores total)
    - 2 NVidia Teslas s1070-500
    - 2 Dell PowerEdge R910 4 x 2.00Ghz Intel Nehalum-EX, 8 core, 1 TB 1066Mhz memory

Impact:

- Three installations of MaPSeq have been deployed at UNC, with ~30 active pipelines, ~21,000 samples processed in 2013 alone, and 250–300 TB of data in MaPSeq's PostgreSQL database.
- Currently supports numerous research programs, including: (1) National Institute on Drug Abuse–funded NIDASeq, "Deep Sequencing Studies for Cannabis and Stimulant Dependence" (Dr. Kirk Wilhelmsen, PI), which is conducting whole genome sequencing of ~5,500 patient samples; (2) National Human Genome Resource Institute–funded NCGENES, "North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing" (Dr. James Evans, PI), which is conducting whole exome sequencing of >2,000 patient samples drawn from multiple disease categories; (3) National Institute of Child Health and Development–funded NC Nexus, "North Carolina Newborn Exome Sequencing and Newborn Screening Disorders" (Dr. Cynthia Powell, PI), which aims to conduct whole exome sequencing on 400 patient samples; and (4) Cancer and Leukemia Group B (CALGB) (Dr. Charles Perou, PI), which comprises >900 samples.

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