HBaaS: Heterogeneous-accelerated Bioinformatics-as-a-Service

Final Project Report

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Senior Design Group 3
Stevens Institute of Technology

By

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"We pledge our honor that we have abided by the Stevens Honor System."

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Executive Summary

Modern applications call for solutions that handle “big data,” datasets that span multiple machines and cannot fit in main memory, and “big compute,” computation patterns that tax even the most advanced processors. Bioinformatics is no exception.

We present HBaaS, Heterogeneous-accelerated Bioinformatics-as-a-Service. Our platform leverages heterogeneous computer architectures to provide sequence matching and motif finding as a web service for users of bioinformatics data. We tackle big data by means of the Accumulo distributed database, and big compute by means of GPUs. Their integration delivers top-tier performance for our chosen applications.

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Section – I: Project Definition and Plan

I.1 Mission Statement

We aim to create an online Bioinformatics-as-a-Service (BaaS) platform, a web service providing sequence and motif alignment and search for proteins, accelerated by GPUs and the Accumulo Database. Our platform will run on a cluster of machines equipped with GPUs. Each machine will host data as part of the Accumulo distributed database and leverage their attached GPUs to accelerate parallel computation and data retrieval.

I.2 Background

Bioinformatics-as-a-Service (BaaS)

Bioinformatics is the use of mathematics and computer science to organize, analyze, and store the data generated in life science research and by the health industry. Bioinformatics often involves the development of software tools to understand biological processes through applications such as data mining, sequence analysis, gene and protein expression, protein structure modeling, and network and systems biology. Examples of bioinformatics applications include RNA and DNA sequencing, genome alignments and assemblies, mutation identification, microarrays, and database creation and management.

The very large amount of data that is collected in biological studies such as genomics or protein analysis must be processed using computers. Computer scientists combine algorithms, statistics, and mathematics, and engineering in order to make sense of the information.

HMMER is used for searching sequence databases for homologs of protein sequences, and for making protein sequence alignments. It implements methods using probabilistic models called profile hidden Markov models (HMMs).

Compared to BLAST, FASTA, and other sequence alignment and database search tools based on older scoring methodology, HMMER aims to be significantly *more* accurate and *more* able to detect remote homologs because of the strength of its underlying mathematical models [4, 5]. In the past, this strength came at significant computational expense, but in the new HMMER3 project, HMMER is now essentially as fast as BLAST.

We call the HMMER algorithm on data queried from Accumulo [6] using local graphical processing units (GPUs).

GPU

A graphics processing unit (GPU) is designed to rapidly manipulate and alter memory to in order to accomplish a particular task. GPUs are commonly used in devices that require image processing such as computers, smartphones, and work stations. GPUs have a highly parallel structure which makes them very effective for processing data that can be done in parallel. Researchers such as Burrage et al sped up biological computation with GPUs [7].

We use GPUs for accelerated computation on data queried from Accumulo. They are ideal because the HMMER algorithm is SIMD-- single instruction multiple data-- meaning that the same instructions can execute in parallel across all the data on a GPU.

Apache Accumulo

The Apache Accumulo sorted, distributed key/value store is a robust, scalable, high performance data storage and retrieval system. Apache Accumulo is based on Google's BigTable design and is built on top of Apache Hadoop, Zookeeper, and Thrift. Apache Accumulo features a few novel improvements on the BigTable design in the form of cell-based access control and a server-side programming mechanism that can modify key/value pairs at various points in the data management process.

In short, Accumulo is our database, delivering fault tolerance, distribution and availability for huge amounts of protein sequence and model data. Cell-based security may gain relevance if we need to restrict access to certain gene data.

I.3 Stakeholder List

Our target users range among physicians working in personalized medicine, forensic scientists working in crime scene identification, epidemiologists working in disease identification, genealogy consultants working in kinship analysis, biologists working in research generally, and other groups who use protein model-to-sequence scoring in their daily work. These users need scoring information fast, so that they may prescribe correct medication and catch criminals early, provide expedited genealogy services and more rapidly discover scientific advances.

Additional stakeholders are other bioinformatics-as-a-service providers. Janelia, a research group at the Howard Hughes Medical Institute (http://www.hhmi.org/), is the closest provider, hosting the online framework http://hmmer.janelia.org/. The Janelia group would be interested in our project, particularly our design, if we achieve sufficiently greater performance. The NCBI would also be interested if our performance increase is much greater. The NCBI hosts a similar protein sequence tool called BLASTp (http://www.ncbi.nlm.nih.gov/blast/Blast.cgi?PAGE=Proteins&PROGRAM=blastp), which has the same function as HMMER but uses a different algorithm.

I.4 Project Scope and Resources

We will provide the end user with a website that can be used to help deal with protein sequences. We will update the website based on customers needs and add new features such as additional hmmer classes and hmm profile uploading. We will add more gpu nodes if it is necessary to expand.

We aim to provide two service classes: *hmmsearch* and *hmmbuild*.

- In *hmmsearch*, a user provides HMMs (Hidden Markov Models) representing protein sequence motifs, and requests the top-scoring sequences for each model from existing, curated databases of protein sequences stored on our Accumulo platform. Users may alternatively store motifs in a server-side database.

All our software resources are open source. In terms of hardware resources, we have three levels:

- A server located in Stevens Burchard room 412, equipped with three GPUs. This is known as *b412srv*.
- A research cluster of 8 machines, all equipped with GPUs, located in the Stevens library basement.
- Access to very large clusters at MIT CSAIL

I.4.1 Budget

We have no budget as we have no material expenses. Hardware is supplied by Stevens and MIT CSAIL and software is open source. We bought a projector screen to display our final website on Senior Design Expo. All our costs are in human development time.

I.5 Project Plan

Here is our plan, broken into major goals with subgoals:

1. Web server frontend
    a. Create a basic set of web pages with project information
    b. Create a test webpage for use in development. The test webpage will display the results of internal queries to make sure they work.
    c. Create a production-level query webpage containing a form to enter in sequences, motifs and target databases.
    d. Create a file upload mechanism as an alternative to entering text.
    e. Create javascript to validate entered information.

2. Web server backend
    a. Set up our backend on our compute server b412srv or open required ports on b412srv to access it remotely. Determine which is the better strategy.
    b. Test that the backend receives information correctly from the front end.
    c. Determine a way to return results to the frontend asynchronously, since some query jobs will take a long time (on the order of hours).
    d. Setup the server for multithreading, to handle multiple jobs concurrently.
    e. Write code to connect to Accumulo and scan the tables
    f. Integrate in the custom iterators described below.

3. Accumulo setup
    a. Do prerequisites; create user accounts, install Hadoop and Zookeeper
    b. Install Accumulo on our server b412srv on our 1TB networked filesystem.
    c. Design an Accumulo schema to store protein data.
    d. Create a client to parse raw sequence data and ingest the sequences into

Accumulo

   e. Create a client to parse taxonomy information and ingest the data into Accumulo

4. Accumulo Iterators
   a. Create test iterators to ensure everything is working
   b. Learn how to run the HMMER C code in development at Stevens
   c. Create an iterator that uses JNI to call the HMMER C code, single-core CPU version
   d. Create an iterator that uses JNI to call the HMMER C code, multi-core CPU version
   e. Create an iterator that uses JNI to call the HMMER C code, single GPU version
   f. Create an iterator that uses JNI to call the HMMER C code, multi GPU version

5. Integration
   a. Unit test each of the above components
   b. Complete the pipeline-- data flow from a request at the front end to the back end to Accumulo scanning to Accumulo iterators to the back end to the front end
   c. Benchmark everything. Compare to Janelia's HMMER service specifically: http://hmmer.janelia.org/
   d. Work on the slowest components from benchmarking. If performance is ok, add features and datasets.
   e. Write up results.

Section – II: Design, Evaluation & Optimization

II.1 Requirements

Stakeholders:

HBaaS is a web service to answer protein sequencing queries. For example, given a user-provided HMM motif, what are the top 10 protein sequences in the NCBI Genbank database [3] that match that motif? What are their alignments? What if we restrict the database to only proteins from the species homo sapiens?

- Easy to use query forms and clear site design
- results are returned very quickly and accurately
- web service has high availability.
- Easy to understand and process results
- HBaaS must be able to return results to the user asynchronously, since some queries can take several hours to complete.
- HBaaS must be able to accept new data (protein sequences or HMM motifs) to ingest into the web server's backend database.

Design:

- We will use the front end for users to fill out information and submit their query
- We will use Accumulo to handle queries and protein sequence retrieval
- Java will call Accumulo to get protein sequences and pass them to the algorithm
- The HMMER3 algorithm will run on a GPU cluster to increase speed
- The algorithm will return the protein sequences that passed the filter to the server

Technical:

- The web service will be able to handle multiple requests at a time
- The web service will not process more requests than we can handle with our cluster resources. We will know this constraint better once we start benchmarking.
- We will not store more data than we have hard disk space, about 1TB on Dr. Ganesan's server.
- We assume data and queries are in correct format. We don't want to error check every sequence, model and query as this costs development time and possibly performance.
- We assume the result size of a query is relatively small, on the order of a handful of sequences or motifs that are the best matches for a given query. We are not in the business of transferring entire databases over the Internet.

II.2 Constraints and Assumptions

Constraints:

- the server must be connected to the internet
- the service will be accessible on different browsers
- we will use a cluster that contains four GPUs
- we will initially only use protein sequences from GenBank
- our project must be finished before the Senior Design Expo

Assumptions:

- users input a valid search query
- users understand what the results mean
- the server is available to process requests
- the GPUs are ready to be used

II.3 Applicable Codes/Standards/Regulations

OpenCL (https://www.khronos.org/opencl/) is an API industry standard for GPU computation. CUDA is another API specific to NVIDIA. We aspire to conform to OpenCL to guard against vendor lock-in but will use CUDA at first since it has greater support (more libraries, more examples, more of our team has background knowledge in CUDA).

FASTA (http://www.ncbi.nlm.nih.gov/BLAST/blastcgihelp.shtml) is an industry standard file format used for protein sequences and HMM motifs. We should be capable of handling input data written in the FASTA file format.

II.4 Concept Development and Selection

Our original project idea was to create a distributed graph library, offering graph algorithms on the Accumulo database that leverage local GPUs. GPUs accelerate computation and Accumulo enables scalability to big datasets. After investigating the graph library idea, we decided that it was too abstract: the team had trouble connecting with the project idea and motivation.

This sparked our shift to specialize on an application in bioinformatics. Dr. Ganesan and other students had some experience with biological computation, and everyone found the application more inspiring. Our central concept remains the same--which we will use **GPUs to accelerate computation** and **Accumulo to store and operate on massive data sets.**

Dr. Ganesan and Hanyu, as part of the Heterogeneous Computing and Mathematical Modeling group, have been developing HMMER for some time. HMMER is a C program that solves hmmsearch by doing sequence match scoring computations. Their NVIDIA GPU version of HMMER succeeds on parallelizing the search using multiple GPUs. We chose our architecture such that we could build on the existing HMMER work and use it. No need to develop solutions to protein sequence-motif scoring from scratch.

We decided to use a database in our architecture because user needs call for selective queries. It is helpful to users to do scoring over only the proteins within a selected group. For example, a user may wish to find the best motif for all the plant protein sequences or all the homo sapiens protein sequences. Databases give the ability to scan over targeted parts of the data, as opposed to non-database solutions that generally map over an entire dataset (e.g. MapReduce). How we are able to select certain subsets of data in a dataset depends on the database table format we use for storing data. Our table format is detailed below.

We chose Accumulo as our database because some team members had background knowledge of it and it offers iterators, a framework to to computation on data as it is scanned from a database. The beauty of iterators is that they execute in parallel across all tablet servers that retrieved data is stored at. We saw a natural opportunity to call HMMER code (which uses GPUs) from iterators.

With GPUs and Accumulo at the center of our design, the remaining component to link everything together is our web server.

II.4.1 Web Server Selection

Our web platform process starts with the web front-end, so it is necessary to have a good front-end design and development. For the front-end, we will first have three most important features which are Data Upload, Result Download, and Query Form. Data Upload function will be used by us, the designer; user would frequently use the result download and query form functions. Basically, users would input in the query form to start the process, and they will get the results through the web server technology, which is Java and Apache in our case. There are some candidates for the web server, which are Apache, IIS, C/C++, Ruby, Node.js, and Java.

Apache is at the core of the LAMP technology stack upon which a lot of server architecture is based: Linux, Apache, MySQL, and PHP/Python/Perl. It is a traditional web server that is very easy to configure but may require plug-ins or backend scripts, like ASP and PHP, when complex functions are needed.

On the list of IIS advantages, its Active Server Pages (ASP) percolates to the top. ASP enables developers to embed code into HTML pages. These ASP pages are parsed by the server before being supplied to the client as HTML. ASP enables developers to work in a number of different .NET languages, including C/C++, and C#. IIS is a good alternative for Apache but is far more expensive once we add in the cost of Microsoft Windows Server 2008 R2 and other back engine software.

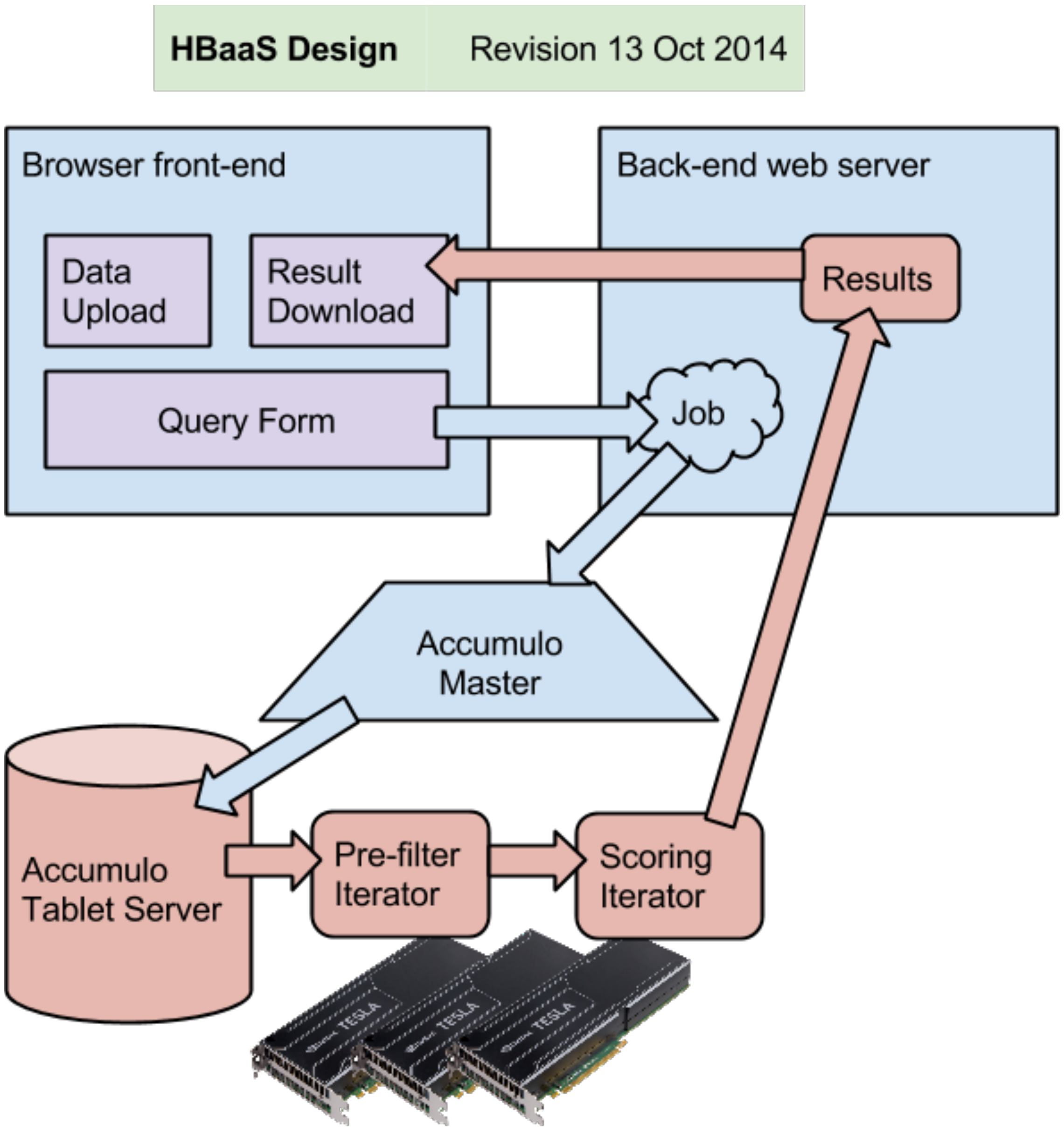
C/C++ is powerful but it is so underlying that requires a huge amount of details and specifications. C/C++ does not have existing libraries for constructing web server and offers manual memory management.

Ruby and Nodejs are both powerful software offering automatic memory management and a variety of libraries for constructing web server, which could save the group more time on functionalizing the web server.

Besides the advantages Ruby and node.js have, Java offers certain functions such as readymade API that make it convenient to exchange data with server backend, which is Accumulo Database and GPUs in our case. Also, even choosing web server language, it would eventually go through Java platform. Therefore, considering the time and money that Apache could save and convenient function that Java could provide, the group has been applying Apache and Java for web server construction by now.

II.5 Preliminary (Fall) and Detailed Design (Spring)

Design Overview



II.5.1 High-level HBaaS Pipeline

1. A user submits a query via our web interface.
2. Our web server backend creates a customized query-and-compute request for the Accumulo database and launches it.

3. In parallel, each machine on the Accumulo database searches through its locally stored protein sequences. The top scoring results are returned to the web server backend.
4. The web server backend forwards the results to display on the web interface.

II.5.2 Data Sources

Our initial protein database is NCBI's Genbank database, available for pubilc download at ftp://ftp.ncbi.nih.gov/ncbi-asn1/protein_fasta.

Proteins are most commonly identified by an accession number (also referred to as a seqID). Some organizations like the NCBI also have their own identifier for cases when an original sequence uploader re-uploads the same sequence due to an error. Additionally, organizations that aggregate proteins from multiple databases identify the original source database.

Originally we used the software BioJava3 (http://biojava.org/) to parse FASTA protein sequence files, as it saves us from writing our own parser [8]. Later on, we decided to switch parsers to an open source version created at the MIT Lincoln Laboratory because it formatted the taxonomic information in a cleaner fashion for database scanning. Specifically, the new parser created entire taxonomy strings in the form "taxonomy|kingdom_name; phylum_name; ...; species_name." The new parser is available here: https://github.com/doricke/BioTools/tree/master/GenBankParser. While using the GenBankParser, we discovered a bug in parsing the organism field of GenBank files, which we patched and submitted to the original author, documented here: https://github.com/doricke/BioTools/pull/1.

Sample Abridged Taxonomic Hierarchy
1 Eukayota
2 Metazoa
3 Chordata
4 Craniata
5 Verebrata
6 Mammalia
7 Primates
8 Haplorrhini
9 Hominidae
10 Homo
11 Sapiens

Taxonomic information about the protein sequences is also taken from NCBI at ftp://ftp.ncbi.nih.gov/pub/taxonomy/. This includes data linking sequences to the species identifier that that sequence is from, data on the standard biological hierarchy of identifiers from kingdom down to species and other related information. An example taxonomic lineage for humans is shown to the right.

II.5.3 Accumulo Table Design

The format we store protein sequence data in an Accumulo table determines how

easy it is to answer some queries over others. This is called table design for query planning. For example, if we knew that a very common query is “What are all the sequences associated with a certain family,” we could create an index structure to make the data access time for that query optimal. The tradeoff is either redundant data storage or slower access to other queries. Benchmarking will help indicate whether database access patterns are a performance bottleneck.
We chose our table design based on the following:

- There is far less data, in terms of bytes, in the sequence identifier and taxonomic information than the actual protein sequence. Therefore we should avoid repeating sequence data, whereas it is okay to repeat identifier and taxonomic data.
- We expect users to request alignment computations on all the sequences for a given taxonomic level. For example, what are the best scoring sequences within all Mammalia class sequences in the database? It should be relatively straightforward to answer this query.
- It should be easy to answer the reverse question: what is the taxonomic hierarchy for a given sequence? This is a common question after finding the best matching sequences, to discover what groups those sequences are from. Are they all viral sequences, for example?
- We should provide a way for users to search for a taxonomic ID by name, since we do not expect users to memorize that 9606 is the taxID for homo sapiens, for example.
- Accession number is the most common identifier for a protein sequence, though searching by genbank ID and by source database are good features to have.

To facilitate answers to the above expected questions, we base our schema on a design pattern called the D4M Schema [11]. Specifically, we use the pattern of storing a table alongside its transpose for the table containing sequence identifiers and taxonomic information. This double data storage, which is acceptable because the amount of data there is far smaller than the sequence data itself. In return, we gain full indexing across all rows and columns. We show how to answer the two questions below.

As alluded in the previous section, we changed our design at the same time as we changed our taxonomic information format. Below we present our original table design. Our final table design is shown in Appendix H.

Table Format Spec:

TableName	Col1	Col2	...
Row1	Val11	Val12	...
Row2	Val21	Val22	...
...	...	...	...

Ttax	species|1	species|2	species|3	genus|4	genus|5	name|a	name|b	name|c	name|d	name|e	name|f	BAC05839.1	AAB63305.1	AAB54048.1	AAB67604.1	AAB71326.1	AAB71327.1
species|1						1						1	1	1			
species|2							1								1		
species|3								1								1	1
genus|4	1	1							1								
genus|5			1							1							
family|6				1	1						1						

Tseq	gi|21928500	gi|1809231	gi|1809235	gi|1613900	gi|2341018	gi|2439516	db|gb|BAC05839.1	db|gb|AAB63305.1	db|dbj|AAB54048.1	db|gb|AAB67604.1	db|gb|AAB71326.1	db|gb|AAB71327.1
accid|BAC05839.1	1						1					
accid|AAB63305.1		1						1				
accid|AAB54048.1			1						1			
accid|AAB67604.1				1						1		
accid|AAB71326.1					1						1	
accid|AAB71327.1						1						1

TtaxT	species|1	species|2	species|3	genus|4	genus|5	family|6
species|1				1		
species|2				1		
species|3					1	
genus|4						1
genus|5						1
name|a	1					
name|b		1				
name|c			1			
name|d				1		
name|e					1	
name|f						1
BAC05839.1	1					
AAB63305.1	1					
AAB54048.1	1					
AAB67604.1		1				
AAB71326.1			1			
AAB71327.1			1			

TseqT	accid|BAC05839.1	accid|AAB63305.1	accid|AAB54048.1	accid|AAB67604.1	accid|AAB71326.1	accid|AAB71327.1
gi|21928500	1					
gi|1809231		1				
gi|1809235			1			
gi|1613900				1		
gi|2341018					1	
gi|2439516						1
db|gb|BAC05839.1	1					
db|gb|AAB63305.1		1				
db|dbj|AAB54048.1			1			
db|gb|AAB67604.1				1		
db|gb|AAB71326.1					1	
db|gb|AAB71327.1						1

TseqRaw	seq	desc
accid|BAC05839.1	MAAXA...	EGF rep...
accid|AAB63305.1	CLNNF...	coded f...
accid|AAB54048.1	CFRCG...	partial...
accid|AAB67604.1	TVKLLL...	seven t...
accid|AAB71326.1	LGAGES...	Rod tra...
accid|AAB71327.1	TIEEGT...	Sonic H...

The following notes aid interpreting the tables:

- The suffix 'T' in TseqT and TtaxT stands for *transpose*.
    - In 'species|1 ', 1 is a taxonomic ID at the species hierarchy level. Same pattern for genus, family and the rest of the hierarchy.
- In 'name|a', 'name' is a fixed constant and 'a' is the unique name given for the row's taxID.
- 'accid|BAC05839.1' is an accession number.

- ‘gi|21928500’ is an NCBI identifier.
- ‘gb’ refers to the NCBI Genbank database. ‘dbj’ refers to the DNA Data Bank of Japan (http://www.ddbj.nig.ac.jp/).
- A ‘1’ value indicates the presence of a column for a row. This is used when the column name contains the information traditionally stored in the value. Storing the data in the column instead of the value allows the database to index that value for significant search speedup.
- The column ‘seq’ contains raw sequence data, without any further processing.
- The column ‘desc’ contains the header description for a sequence. These headers are an ad hoc description of a sequence and do not have a standard format. Therefore, we do not index them for searching.

Example queries:

- Find all the sequences in the database under taxID genus|4.
    - First scan Ttax on the row ‘genus|4’ for columns starting with ‘species|’ and ‘gi|’. The result is ‘species|1’ and ‘species|2’.
    - Scan Ttax on the rows ‘species|1’ and ‘species|2’ for columns starting with ‘species|’ and ‘gi|’. The result is ‘accid|BAC05839.1’, ‘accid|AAB63305.1’, ‘accid|AAB54048.1’ and ‘accid|AAB67604.1’.
    - Scan Tseq on the rows ‘accid|BAC05839.1’, ‘accid|AAB63305.1’, ‘accid|AAB54048.1’ and ‘accid|AAB67604.1’ for column ‘seq’. The result are the sequences associated with ‘genus|4’.
- Build the taxonomic hierarchy of sequence ‘accid|AAB71326.1’.
    - First scan TtaxT on row ‘accid|AAB71326.1’ for all columns. The result is ‘species|3’.
    - Scan TtaxT on row ‘species|3’ for all columns. The result is ‘genus|5’.
    - Scan TtaxT on row ‘genus|5’ for all columns. The result is ‘family|6’.
    - The hierarchy is ‘accid|AAB71326.1’ < ‘species|3’ < ‘genus|5’ < ‘family|6’.
- Find the taxonomic IDs associated with names beginning with ‘homo’. (prefix search)
    - Scan TtaxT on rows beginning with ‘name|homo’. Result are the taxonomic IDs. We also have the full names from the row names.
- Find all sequences from the DNA Data Bank of Japan.
    - Scan TseqT on rows beginning with ‘dbj|’ for all columns. Result are the accession numbers for all relevant sequences.
    - Scan TseqRaw on the row accession numbers from (a) for column ‘seq’ to

obtain the actual sequences.

Possible points of expansion that we will consider if we have time and use case demand:

- We may add extra degree columns or degree tables to index the total count of sequences under a given taxonomic ID. Currently this is possible by scanning through the data and counting by recursive algorithm. For example, we would to count the number of sequences for a genus, we would find all species childs of that genus (table scan pass 1) and then count the child sequences of those species (table scan pass 2). Indexing the data reduces the access time to a constant.
- We may index the sequence header description by word, in order to find the sequences with a header that contains the words “helix receptor” for instance.
- Our design is flexible in that it allows the addition of properties associated with a taxID or a seqID, in case we find indexing such properties useful in the future. For example, we may store ‘sampleDate’ or ‘seqQuality’ as additional columns in Tseq.

II.5.4 Computing Alignments with HMMER

HMMER is a program written in C to compute sequence alignments and scores. In order to call HMMER from Java code, we use a technology called JNI, Java Native Interface. JNI allows a Java method to call a C method, passing parameters and return values in memory.

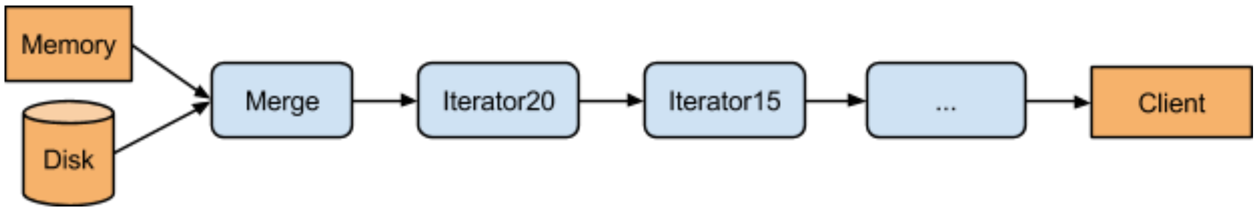
HMMER comes in several versions. The first original version runs in parallel on a CPU. We use the CPU version for our first prototype because it is the simplest. A version of HMMER in development at Stevens’ Heterogeneous Computing and Mathematical Modeling group runs on GPUs. This is our final target, to leverage GPUs for computational acceleration as part of an Accumulo platform that handles mass data.

II.5.5 Aligning and Scoring Scanned Sequences

While the Accumulo schema works well to select only sequences of interest, our goal is to compute sequence alignments, not to find sequences. Our use case is to find the best scoring sequence alignments for a given set of queried sequences.

One way to proceed is to gather all the queried sequences onto a single machine at the server and perform the computation on that machine. We will implement this approach for comparison purposes but it is not our final goal, because it ignores potential distributed computation of sequence alignments and unnecessarily transmits all the sequences over a local network. The only necessary transmissions ought to be the highest scoring sequences.

Our target design will compute sequence alignments locally, at the machine the data is stored at. We will do this by using Accumulo's iterator framework. Here is a diagram illustrating how scan-time iterators work in Accumulo:



The arrows here represent streams of data. The blue objects are in-memory processes and the orange objects are final data destinations.

Data originally resides in disk or in memory (if cached). All data matching the criteria of a scan is streamed and merged together in sorted order through an internal merging iterator. From there, data passes through a hierarchy of iterators, some system-defined and some user-defined. Iterator 20 is the typically a versioning iterator that filters away old data. We define a custom iterator after that at, say, priority 15 (higher priority iterators execute first).

Our custom iterator operates on data in three phases:

1. Prefiltering. A quick computation that filters out sequences with very low alignment scores.
2. Scoring. An intensive computation that returns a score (and an alignment) given a sequence.
3. Maxing. Only lets pass the top X scoring alignments, where X is query-defined (say 10).

For increased efficiency, we define our iterator to operate in batches. It will handle 100,000 scanned sequences at a time. This allows the HMMER platform to take advantage of parallelism by running on multiple sequences at once (SIMD style-- Single Instruction Multiple Data).

Keep in mind we have an outer level of parallelism since iterators simultaneously run on all tablet servers that store queries data. In order to maximize this parallelism, it is important that the protein sequence data is evenly distributed across all available tablet servers. We will gauge our performance by measuring load balance when we perform benchmarking. If necessary, we have three options to introduce load balance:

- Table splits. We designate places within the database to explicitly divide data onto different tablet servers. Accumulo usually does a good job determining tablet splits on its own (except during ingest phase), but we may manually set these if we identify a common query pattern does not load balance.
- Reversing sequence IDs. Because Accumulo stores rows in lexicographic order, reversing the sequence IDs will better shuffle rows around tablet servers. For example, the rows ‘abx’ and ‘acb’ are adjacent. When reversed, the rows ‘xba’ and ‘bca’ are on opposite ends of the alphabet and almost surely on different tablet servers.
- Using a hash function. If necessary, hashing seqIDs uniformly throughout the alphabet will guarantee load balancing, at the price of an additional computation.

II.5.6 Alternative Designs

One alternative to the Accumulo database is no database: just store our protein data inside a big data file system like Hadoop. We can then use a framework like MapReduce to run computations across all the data in Hadoop. MapReduce is a better design if our computations really do run on the entire database [10] . This is not our use case; we hope users will take advantage of selective access to data by taxonomic classification to only run computation on a subset of data. We may be able to offer the best of both worlds by running MapReduce jobs from Accumulo, for the cases where we need to score alignments on a whole database.

Another alternative is using a SQL database such as BioSQL [9]. SQL databases differ from NoSQL databases like Accumulo in that SQL databases provide more built-in services in exchange for lower performance. For example, the ability to JOIN tables of a database is built into SQL database engines whereas NoSQL database designers typically need to write routines to perform a JOIN by hand. Another way to think of the difference is that NoSQL databases provide finer control over storage format and access patterns yielding better performance, at the expense of additional development time. We choose a NoSQL database since performance is our primary concern.

We decided not to convert the C++ CUDA algorithm to Java's version of CUDA, JCUDA. This would have let us connect the HMMER3 algorithm to our backend much easier. However, a drawback to this would be that the existing C++ code would have to be rewritten. We determined it would be more time-effective to use JNI in order for the algorithm to communicate with our backend.

II.6 Design Evaluation Methods

Subsystem Tests:

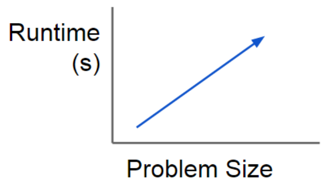
- We tested the front end and back end by entering string input and pressing radio buttons on the website. The server was able to echo back the results.
- The HMMER3 CUDA algorithm is compared against the results from http://hmmer.janelia.org/ and it is accurate.
- The JNI's job is to take in an array of strings from Java and pass them to the CUDA code. Afterwards, the CUDA code returns an array of booleans to the JNI and the JNI passes the array of booleans to Java. We did this with several sample sequences and were able to successfully pass data between Java, JNI, and CUDA.
- Because Accumulo is native to Java we are able to query the accumulo tables and easily get an array of raw protein sequences.
- Total pipeline - All components of the system appear to work together. Now, we need to verify our results with http://hmmer.janelia.org/ and benchmark our pipeline.

Performance Evaluation:

Benchmarking is the name of the game. Since our project is an online bioinformatics as a service platform, which works like a web search engine, runtime of the program is the most important criteria that can help us determine if our design is good or not. We will measure performance in terms of runtime and plot scalability of run times against query size, motif HMM size, and number of computing resources available.

- Runtime vs Query Size and Motif HMM Size by Weak Scaling

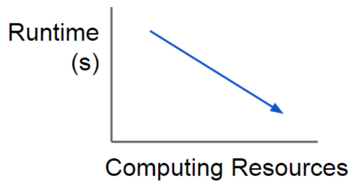
If users send a large number of protein sequences to our web server to make a request, the back end will spend a lot more time on computing. We therefore need to find out how runtime increases with the size of problem we process.



Ideal:	Linear Growth
Actual:	*TBD*

Weak scaling is defined as how the run time varies with the number of processors for a fixed problem size *per processor*. We test weak scaling by holding problem size (query size and motif HMM size) assigned to each processing element (GPU on a database tablet server) constant and adding additional elements to solve a larger total problem. This type of measurement is a good indicator for performance because it tests how well we can meet additional demand by adding more hardware resources.

- Runtime vs Computing Resources by Strong Scaling



Ideal:	Linear Speedup
Actual:	*TBD*

We use parallel processing in our design. Parallel processing is the simultaneous use of more than one GPU core to execute a program, which splits up a programming task into sections. Ideally, parallel processing makes programs run faster because there are more GPUs running it, and thus runtime will decrease linearly as we add more nodes. However, in practice, it's often difficult to divide a program in such a way that separate GPUs can execute different portions without interfering with each other. As more processing nodes are added, each node will spend more time doing communication than useful processing. At some point, parallel slowdown occurs and adding more nodes will not help significantly. In other words, the improvement will no longer be linear.

In this benchmark we hold problem size (query size and motif HMM size) fixed and increase number of processing elements (GPUs and tablet servers). The goal is to find a "sweet spot" that allows the computation to complete in a reasonable amount of time, yet does not waste too many cycles due to parallel overhead. We aim to achieve as close to *strong scaling* as possible, when our performance (in terms of work units completed per unit time) scales linearly with number of resources used.

- Artificial and Real World Benchmarks

We will use artificial workloads to stress test and benchmark performance to see if the system meets our expectations. We will apply a standard benchmark currently applied by other Baas platforms, such as BioBench [14]. BioBench is a benchmark suite for a variety of bioinformatics applications, including BLASTn, BLASTp and most relevantly, HMMER. BioBench uses HMMER v2.3 to search the SwissPROT protein database against the consensus of a small selection of protein sequences. Because our platform is based on HMMER, we will use a similar set of tests to BioBench as a standard to benchmark our platform before use.

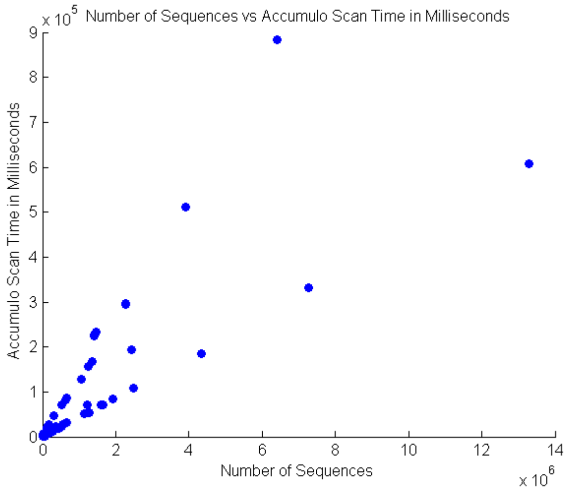
After successfully running results on BioBench, we will move to real world benchmarks. At this stage, we will open our web site and put our product into use. By inviting volunteers to use our service and monitoring performance of our program, we will locate bottlenecks and make targeted improvements.

II.7 Design Evaluation Report: Performance, Reducibility and Cost

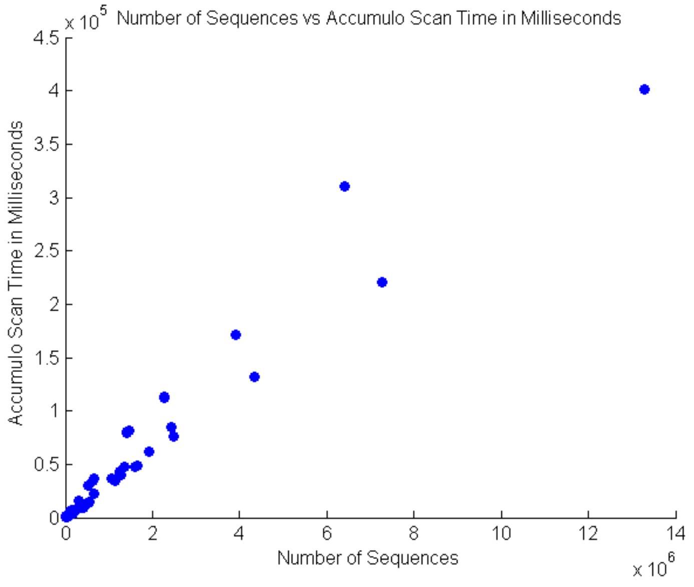
We will compare against HMMER's web service at <http://hmmer.janelia.org/search/hmmsearch> as a baseline. We expect performance improvements as a result of using Accumulo and GPUs. Now that we have a fully functioning pipeline we will be able to get more specific performance boosts.

Benchmarking Accumulo Scan Times

To generate graphs we queried Accumulo with a taxonomic identifies for example: *taxonomy*|*Bacteria; Cyanobacteria.* Accumulo will find all sequences that have the taxonomic identifier that begins with the string. We used many of these strings and recorded the time it took to retrieve and process the data. We scanned the database twice to retrieve accession IDs first and then get raw sequences.



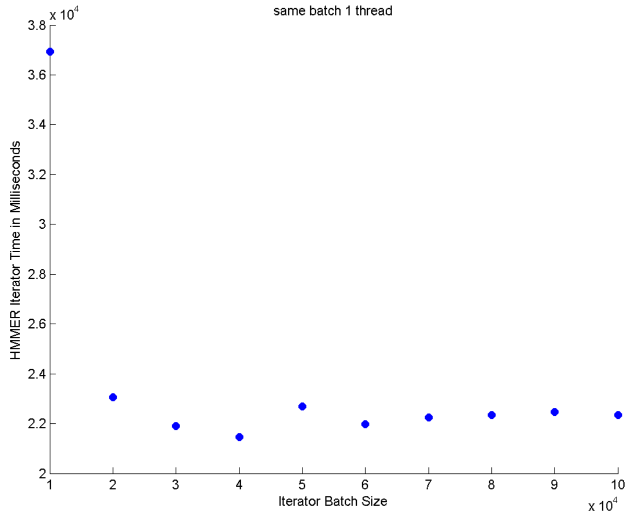
This graph shows us the number of sequences vs time it takes to scan. We can see two distinct lines which may be an artifact of how the data was ingested into accumulo. It takes roughly 10 minutes to scan 14 million sequences based on the line with a smaller slope. This is a very naive graph because we are using a small batch size of 10,000 and only have 1 thread. This is not using the full power of the GPUs. However, it shows that Accumulo is handling the data well because we are seeing data in a linear pattern instead of an exponential curve.



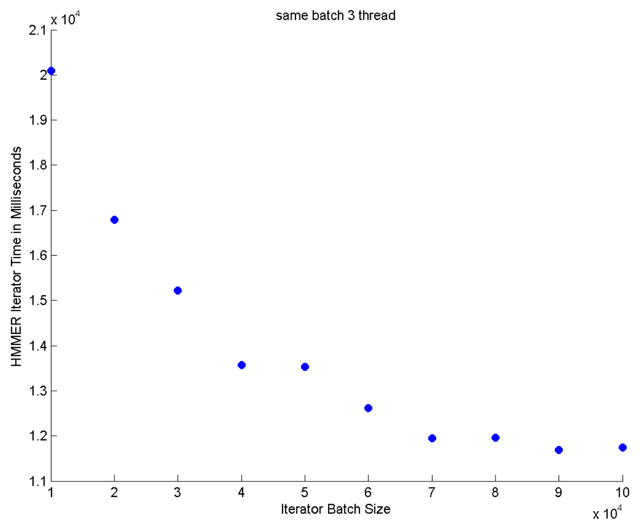
This graph shows the number of sequences vs time it takes to scan. We can see two distinct lines are converging. We used 4 threads with a batch size of 10,000 which resulted in a speedup of roughly two times to scan the database. We see that it only takes about 7.5 minutes to scan 14 million sequences. We plan on improving performance by installing Accumulo onto other nodes in order to further decrease scan times.

Benchmarking the HmmerIterator Scan Time

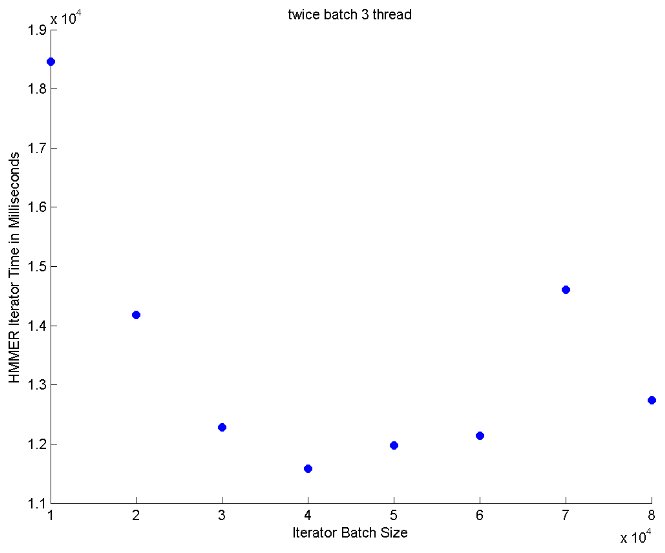
We were successfully able to create an advanced iterator that combines scanning of Accumulo to get raw sequences and the Hmmer code that calculates if each sequence passes the msv filter. For these graphs we wanted to test the best batchsize to feed into the iterator. We were restrained by 1GB of ram on the server. So if the batch sizes were too big, the program would crash or we would be slowed down. In addition, we used multiple threads to further parallelize our system. To generate these graphs we used a taxonomic string that gave us 250,000 sequences to feed into the iterator.



This is our worst performance graph. It uses only a single thread for the iterator. The time it takes for the iterator appears to be independent of the batchsize of a single thread.



This graph was the best performance graph because it took much less time to process the data. With a thread size of 3 and a batch size of 100,000, we were able to process the data in about 12 seconds. The graph shows an exponential decrease that levels off when we increase the batch size.



We also tried to prescan the tables to collect twice the amount of sequences that the batch iterator required. We reasoned this would speed the iterator time. However, we are memory restricted so holding more data will be a problem. We abandoned this approach because the speed up times are not much better.

We are creating a software service so there is no cost for materials. Therefore, we cannot do anything to reduce its physical size.

II.8 Design Revisions and Optimizations

The protein sequence alignment in the janelia website uses a typical database and regular CPUs. We recognized that HMMER3 algorithm can be designed to take advantage of both the parallel capabilities of Accumulo, the GPU architecture, and the GPU clusters.

Our initial Accumulo schema did not include nearly as much protein metadata. We had no taxonomic information or information on the source database of a sequence, for example. We added this additional information because (1) a database only adds value when used for indexing and (2) restricting queries to only sequences from a certain database or a certain taxonomic subgroup is useful to end users.

Our initial plan also included storing motifs in the Accumulo database. We decided to deprioritize motif storage and require the user to upload their own motifs (which are of far smaller size than sequences). We will revisit motif storage time permitting.

We create a platform to perform our plans and algorithm. There is already janelia website, so we do not want to build the same service. Instead, we would build something similar with higher performance which is on our HBaaS website. Considering the basic performance, we have sequence paste and file uploading function for user queries. In addition, we provide an Accession ID lookup feature for users to find information based on specific Accession ID. We expect these functionalities to have multiple inputs so that user can actually compare the results based on their inputs. Furthermore, we have a new feature which is for HMM profile only. Since HMM profile has a very unique format, we created a specific gateway for it to distinguish from normal input files. Also, users can input directly through the taxonomy restriction. All results under the taxonomy would be the output. Finally, in case of that users want to make the query in very detail, they can use all query features at the same time.

We had several variables hard coded into the CUDA files that we needed to change. The HMM size was difficult to change because the size was used to statically allocated memory in a class file. At first we considered recompiling code each time there was a request. We found a simpler solution and implemented dynamic memory allocation based on input HMM size in order to allow for maximum parallelized processes to occur in each GPU node.

Because of the platform we chose for the backend is Spring, we build it in eclipse with Maven. To call any function in CUDA, we have to use JNI to communicate between Java and C++ since web server is build in Java and CUDA is build in C++. We had a big problem when we combine the Java server code and JNI code, because server part had a package but JNI does not. After we give JNI a package, it does not work any more, because of missing the function and files. To fix this, we modified the C++ code for JNI which added package name to function name such as Java_maven_wrap_seqpass. After changing the C++ code, we recompiled it to get updated native library file. Next step would be making a new head file by using Javah command or we could edit the head file manually to change the function name. And then, we can put all of those new files we made together with the server project, it works.

We created a custom iterator in accumulo in order to decrease the total time it takes to get results. Each thread can use the custom iterator to scan and uses the native library to get results. In other words, we are able to hide the compute time in the scan time. We determined that using three threads and batch sizes of 90,000 gives us optimal performance on a single node. We are unable to have greater threads or batch sizes because we are restricted by device memory.

Our future plans are to increase compute and scanning speed. We currently only have Accumulo running on a single tablet server. We plan to install Accumulo on four additional tablet servers. This way, we will be able to add another layer of parallelism and increase speeds even more. We would also like to convert the raw sequence data that is represented by characters to byte sequences. First, it will shrink the space allocated to each sequence and therefore will effectively increase the throughput of data from Accumulo to the native library. Second, because we are preprocessing the raw sequences, we will no longer need to process them on the GPU side. Lastly, we want to store and pass the data structure that represents our HMM file between Java and the Native Library. Currently, for each batch we are calculating the HMM file, but it is only necessary to do this once. Fixing this problem may result in a significant speed up to processing time.

II.9 Final Design Specification with BOM

Because this project is completely unphysical and the web server and GPU clusters have been provided by Dr. Ganesan, we do not have a bill of materials.

Section – III: Entrepreneurship & Business

III.1 Business Objectives and Risks

Business Objectives:

- Build the fastest bioinformatics-as-a-service platform
- Promote heterogeneous solutions for speeding up real world processes

Risks:

- Development time higher than expected
- Electricity bills for running servers too high
- We don't achieve the performance we expect. In this scenario, our contribution is a detailed analysis of why we don't achieve good performance. We have reduced our risk by researching database and GPU architectures. Our expectations have a solid theoretical basis.

III.2 Competitive Intelligence: Market Analysis

Other companies offering data analytics on Accumulo are Sqrrl and Argyle data [1, 2]. Their products are Sqrrl Enterprise and ArgyleDB, respectively. Companies like these two create general analytics platforms and offer some solutions to specific problems. Argyle's prime customers are financial companies in the context of fraud detection. Sqrrl's prime customers are in the healthcare industry, and other industries that need a strong privacy / access control layer on their data.

We target a very different customer base, providing a platform for specific problems in bioinformatics. We also distinguish ourselves from them by using GPUs, which few have used alongside databases. This is particularly relevant for problems with computational bottlenecks, not just data bottlenecks (big compute in addition to big data).

Two competing tools for protein sequence computations are HMMER and BLAST, affiliated with the Janelia group at the Howard Hughes Medical Institute and the NCBI, respectively. We aim to implement HMMER on GPUs within a database, so we expect our performance to scale higher than vanilla HMMER. We also expect our web server performance to improve over Janelia's compute farm by using the modern Accumulo database to index data. We're not sure where we will stand with respect to BLAST as their BLAST uses a different scoring algorithm.

III.3 Lean Canvas Business Model

Problem:

- Big data: the volume of protein sequence data is huge
- Big compute: computing alignments is computationally expensive
- Need fast and accurate protein sequence from searching

Solution:

- Leverage the Accumulo database to tackle big data
- Use GPUs to tackle big compute
- Visit our website to get a wonderful protein searching experience

Customer Segments:

- Biologists -- for research
- Forensic scientists -- crime scene identification -- catch criminals early
- Epidemiologists -- disease identification -- stop epidemics early
- Physicians -- prescribe correct, personalized medication
- Genealogy consultants -- expedited kinship analysts services
- Anyone using *protein model-to-sequence scoring* in their daily work

Unique Value Proposition:

We aim to create an online BaaS platform with improvement: a web service providing protein sequence-to-motif alignment, leveraging the *Accumulo database to tackle big data* and *GPUs to tackle big compute.*

Channels:

Our website and search engine, publish performance numbers in industry journals, directly market to companies, and use word of mouth in our specialized community.

Cost Structure:

Pay salaries and purchase hardware.

Revenue Streams:

Since we aim to open-source our program, primary revenue is by companies paying for a support agreement for us to help them setup, use, and maintain our program. Revenue also comes from advertisements we will have on our website.

Key metrics:

We will measure performance in terms of runtime and plot the scalability of run times against query size, motif HMM size, and number of computing resources available.

Unfair Advantage:

No one in the competition has combined the Accumulo database with GPUs as we will, and as such we expect unrivaled performance.

III.4 Financial Analysis

We have no budget; see project scope and resources in Section 1.

III.5 Intellectual Property

We do not intend to protect intellectual property. Everything we create is open source.

Instead, the project will derive profit by selling a service: a support / maintenance contract for a specified time period (say 1 year). This is the same business model that Red Hat (http://www.redhat.com/en) uses for selling support to Linux and that Hortonworks (http://hortonworks.com/) uses for Hadoop.

We hope many others “steal our idea” and build off it, deriving better products and citing our work, following academic and software development common courtesy.

Section – IV: Results

IV.1 Conclusions

This project was a success because we were able to complete our full pipeline. We benchmarked the pipeline and are fixing bottlenecks. We will be submitting a paper on May 15th to IEEE High Performance Extreme Computing. In the future, we plan to add more protein sequence databases to Accumulo and create advanced iterators. We also would like to use Lincoln Lab's GPU cluster to see how much it will speed up the process. Finally, we can add more features to the front end such as multiple hmms, more specifications and search options, and better data visualizations. Front end is highly based on the back end server, so more front end features require more powerful server function.

IV.2 Recommendations

We recommend any group actively working with Accumulo hire a full-time system administrator. Accumulo runs atop Hadoop and Zookeeper, all of which are nontrivial to set up. The workload compounds when one considers multiple systems networked together. On top of initial setup, the Accumulo stack has many configurable parameters, such as the compaction ratio that trades ingest for query performance. Tuning those is painstaking but necessary for top performance. A system administrator can also handle the mundane tasks of user management, especially if we need to enforce access control / user permissions. As implemented in the project, we configured Accumulo as open, hassle-free and unsecured as possible to speed development.

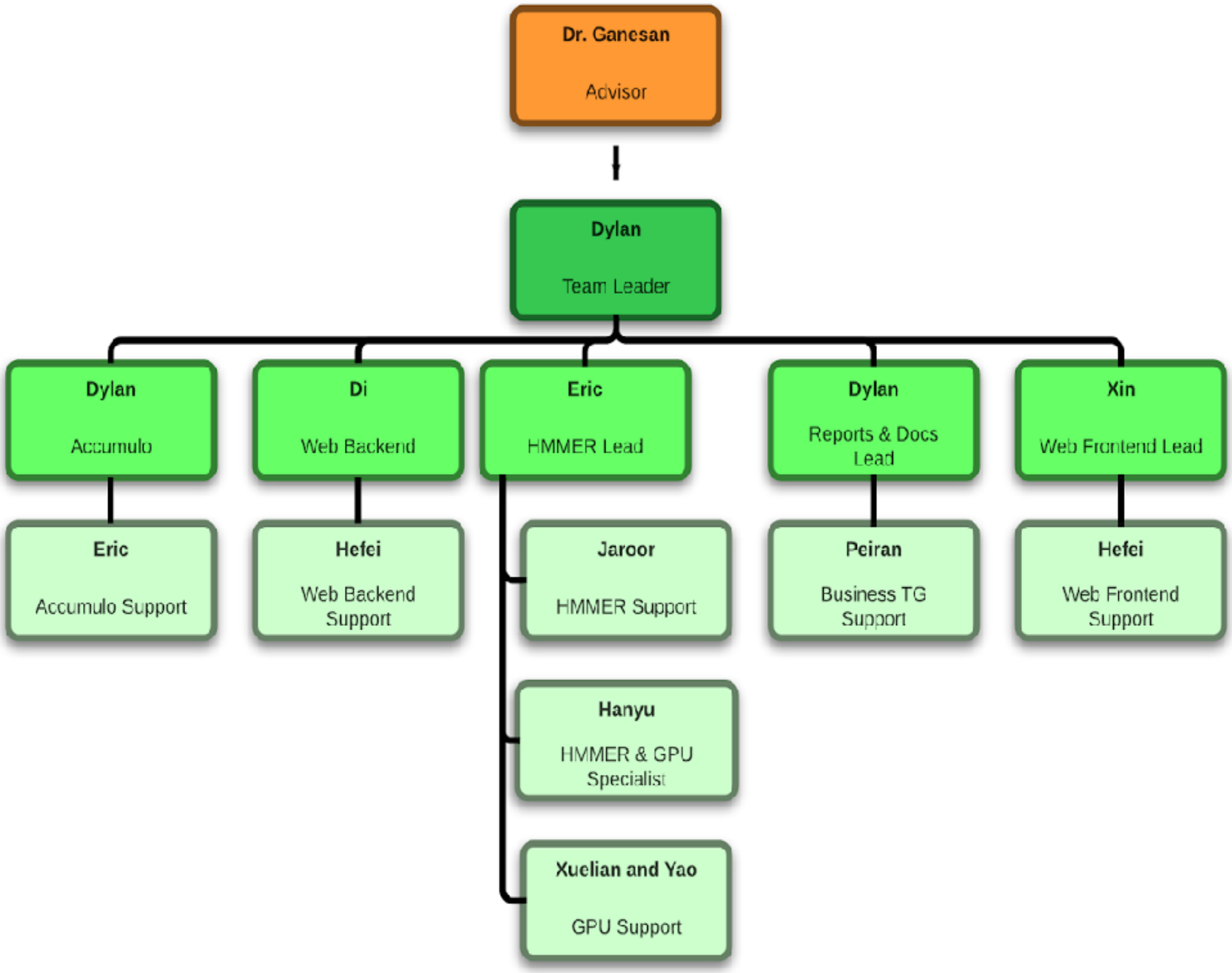
When dealing with JNI we recommend using C++. Although JNI supports both C and C++, C does not have as many features and libraries as C++. As always, choose the language that is most familiar and makes sense. In our application, we needed to pass an array of strings and return an array of boolean values. At first we used C and defined what a boolean using typedef and enumeration. However, the JNI did not either methods and we ended up with memory leaks. To solve this problem, we converted the JNI from C to C++ because C++ has booleans defined natively.

When there is necessary to perform the service on the website, we recommend the group to have one who can handle both front end and the web server, since these two parts connect to each other very closely. If they are taken care of by two, they have to work very hard to make sure there is no problem between the connection of each element, and it requires a huge amount of time.

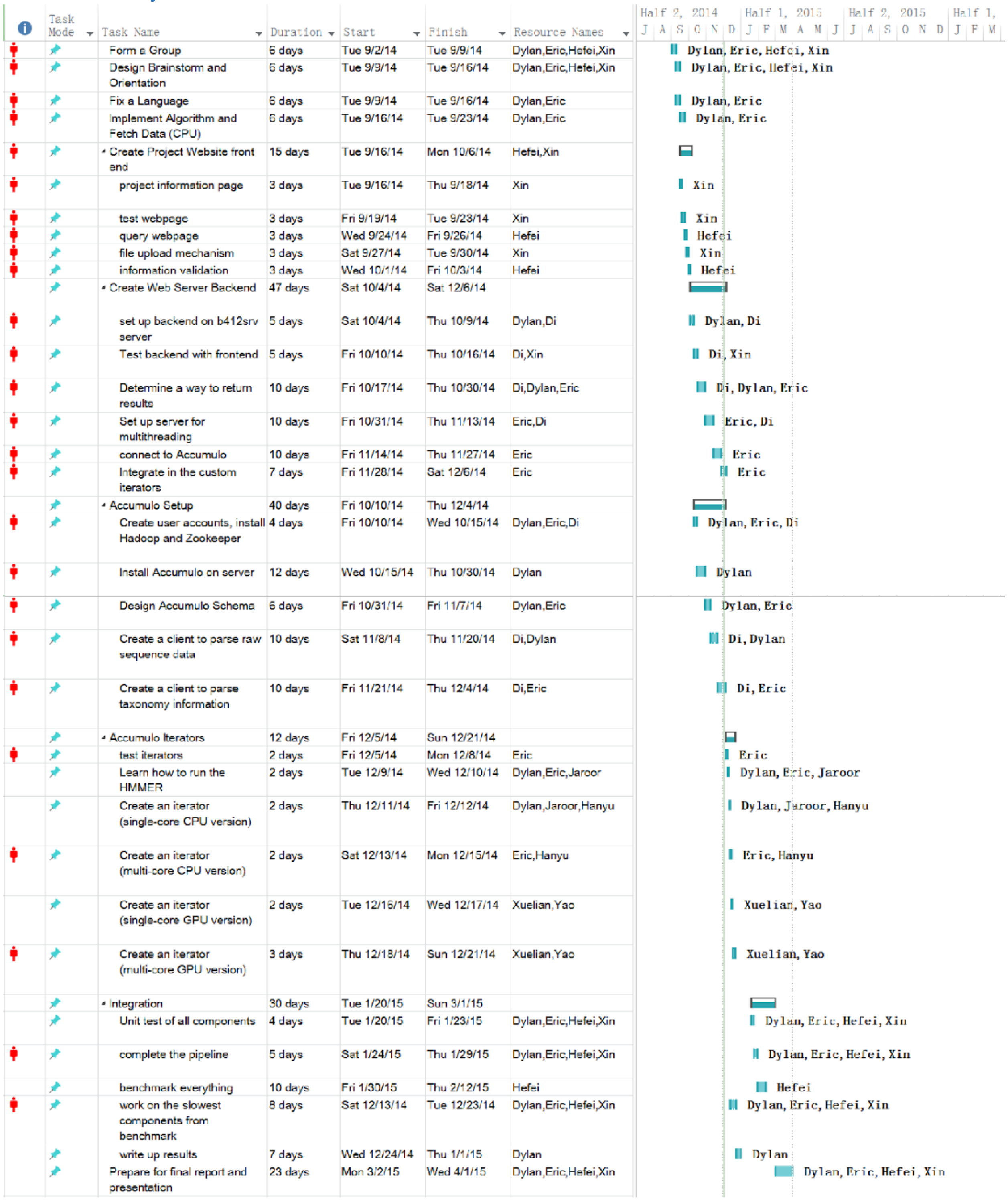
When benchmarking it is a good idea to try to automate as many variables as possible. The overall process should be run code that prints an output to a file. Then use a graphing program such as Matlab to parse and graph the results. Benchmarking should push the limits of the available specifications that you have such as memory and processing power. Once you get results, you should look for the largest bottleneck and then proceed to fix it.

Appendices

A. Team Organization Chart



B. Project Gantt Chart



Task Mode	Task Name	Duration	Start	Finish	Resource Names
📌	Form a Group	6 days	Tue 9/2/14	Tue 9/9/14	Dylan,Eric,Hefei,Xin
📌	Design Brainstorm and Orientation	6 days	Tue 9/9/14	Tue 9/16/14	Dylan,Eric,Hefei,Xin
📌	Fix a Language	6 days	Tue 9/9/14	Tue 9/16/14	Dylan,Eric
📌	Implement Algorithm and Fetch Data (CPU)	6 days	Tue 9/16/14	Tue 9/23/14	Dylan,Eric
📌	◂ Create Project Website front end	15 days	Tue 9/16/14	Mon 10/6/14	Hefei,Xin
📌	project information page	3 days	Tue 9/16/14	Thu 9/18/14	Xin
📌	test webpage	3 days	Fri 9/19/14	Tue 9/23/14	Xin
📌	query webpage	3 days	Wed 9/24/14	Fri 9/26/14	Hefei
📌	file upload mechanism	3 days	Sat 9/27/14	Tue 9/30/14	Xin
📌	information validation	3 days	Wed 10/1/14	Fri 10/3/14	Hefei
📌	◂ Create Web Server Backend	47 days	Sat 10/4/14	Sat 12/6/14	
📌	set up backend on b412srv server	5 days	Sat 10/4/14	Thu 10/9/14	Dylan,Di
📌	Test backend with frontend	5 days	Fri 10/10/14	Thu 10/16/14	Di,Xin
📌	Determine a way to return results	10 days	Fri 10/17/14	Thu 10/30/14	Di,Dylan,Eric
📌	Set up server for multithreading	10 days	Fri 10/31/14	Thu 11/13/14	Eric,Di
📌	connect to Accumulo	10 days	Fri 11/14/14	Thu 11/27/14	Eric
📌	Integrate in the custom iterators	7 days	Fri 11/28/14	Sat 12/6/14	Eric
📌	◂ Accumulo Setup	40 days	Fri 10/10/14	Thu 12/4/14	
📌	Create user accounts, install Hadoop and Zookeeper	4 days	Fri 10/10/14	Wed 10/15/14	Dylan,Eric,Di
📌	Install Accumulo on server	12 days	Wed 10/15/14	Thu 10/30/14	Dylan
📌	Design Accumulo Schema	6 days	Fri 10/31/14	Fri 11/7/14	Dylan,Eric
📌	Create a client to parse raw sequence data	10 days	Sat 11/8/14	Thu 11/20/14	Di,Dylan
📌	Create a client to parse taxonomy information	10 days	Fri 11/21/14	Thu 12/4/14	Di,Eric
📌	◂ Accumulo Iterators	12 days	Fri 12/5/14	Sun 12/21/14	
📌	test iterators	2 days	Fri 12/5/14	Mon 12/8/14	Eric
📌	Learn how to run the HMMER	2 days	Tue 12/9/14	Wed 12/10/14	Dylan,Eric,Jaroor
📌	Create an iterator (single-core CPU version)	2 days	Thu 12/11/14	Fri 12/12/14	Dylan,Jaroor,Hanyu
📌	Create an iterator (multi-core CPU version)	2 days	Sat 12/13/14	Mon 12/15/14	Eric,Hanyu
📌	Create an iterator (single-core GPU version)	2 days	Tue 12/16/14	Wed 12/17/14	Xuelian,Yao
📌	Create an iterator (multi-core GPU version)	3 days	Thu 12/18/14	Sun 12/21/14	Xuelian,Yao
📌	◂ Integration	30 days	Tue 1/20/15	Sun 3/1/15	
📌	Unit test of all components	4 days	Tue 1/20/15	Fri 1/23/15	Dylan,Eric,Hefei,Xin
📌	complete the pipeline	5 days	Sat 1/24/15	Thu 1/29/15	Dylan,Eric,Hefei,Xin
📌	benchmark everything	10 days	Fri 1/30/15	Thu 2/12/15	Hefei
📌	work on the slowest components from benchmark	8 days	Sat 12/13/14	Tue 12/23/14	Dylan,Eric,Hefei,Xin
📌	write up results	7 days	Wed 12/24/14	Thu 1/1/15	Dylan
📌	Prepare for final report and presentation	23 days	Mon 3/2/15	Wed 4/1/15	Dylan,Eric,Hefei,Xin

C. Design Documents: Drawings, Layouts, Analysis reports

Our code is online here: https://github.com/Stevens-GraphGroup/

We invite interested readers to view our code on GIthub rather than kill 50 trees to view it here.

D. Team Logistics Systems

We use several services to communicate and store information:

- Github - repository to share code and the website
- Todoist - online task manager for productivity
- Google Drive - file storage and synchronization, collaborative editing
- PuTTy and WinSCP - SSH and SFTP (communicating with remote servers)
- Intellij IDEA - IDE with great Java support
- Git - version control system to track, branch and merge changes
- Todoist and FollowUpThen - task managements and reminder systems
- LucidChart - charting tool used to create the Team Organization Chart

E. References List

1 "Sqrrl Enterprise - Linked Data Analysis for Hadoop." *Sqrrl*. N.p., n.d. Web. 30 Nov. 2014. <http://sqrrl.com/product/sqrrl-enterprise/>.

- A general data analytics platform, powered by Apache Accumulo. Genetic sequence alignment is possible with Sqrrl Enterprise. HBaaS offers a specialized solution for bioinformatics problems instead. Sqrrl's main customer base uses its cell-level securty emphasis for Accumulo.

2 "ArgyleDB Simplifies Real-time Fraud and Security Analytics." *Argyle Data Realtime Analytics for Big Data*. N.p., n.d. Web. 30 Nov. 2014. <http://www.argyledata.com/product/>.

- Similar to Sqrrl Enterprise, ArgyleDB is a general data analytics platform, with an emphasis on fraud data.

3 Bilofsky, Howard S, and Burks Christian. "The GenBank® genetic sequence data

bank." *Nucleic acids research* 16.5 (1988): 1861-1863.

- Genbank is our primary data source of protein sequence data. We will expand to other sources as time permits.

4 "Basic Local Alignment Search Tool." *BLAST:*. N.p., n.d. Web. 30 Nov. 2014. <http://blast.st-va.ncbi.nlm.nih.gov/Blast.cgi>.

- A website that gives researchers the ability to compare amino acid sequences to ones stored in the database.

5 Finn, Robert D, Jody Clements, and Sean R Eddy. "HMMER web server: interactive sequence similarity searching." *Nucleic acids research* (2011): gkr367.

- Introduces the web server delivering HMMER as a service. Uses hidden markov models to align protein sequences. It aims to be more accurate than older scoring methods such as BLAST. We base a great deal of our design on HMMER and use it for performance comparison.

6 "Apache Accumulo." *Apache Accumulo*. N.p., n.d. Web. 30 Nov. 2014. <https://accumulo.apache.org/>.

- A high performance database at the center of our design.

7 Bustamam, A.; Burrage, Kevin; Hamilton, N.A., "Fast Parallel Markov Clustering in Bioinformatics Using Massively Parallel Graphics Processing Unit Computing," *Parallel and Distributed Methods in Verification, 2010 Ninth International Workshop on, and High Performance Computational Systems Biology, Second International Workshop on* , vol., no., pp.116,125, Sept. 30 2010-Oct. 1

- As Burrage et al sped up biological computation with GPUs, we aim to do the same on protein sequence computations.

8 Prlić, Andreas et al. "BioJava: an open-source framework for bioinformatics in 2012." *Bioinformatics* 28.20 (2012): 2693-2695.

- We use BioJava for FASTA file parsing. BioJava has components for computing sequence alignments, 3D models and much more that we do not use.

9 BioSQL. http://www.biosql.org/

- BioSQL is a SQL-based database for storing sequences, features, annotations, etc. We use Accumulo instead.

10 Hung, Che-Lun, and Yaw-Ling Lin. "Implementation of a parallel protein structure alignment service on cloud." *International journal of genomics* 2013 (2013).

- A web service that provides sequence alignments on demand using Hadoop MapReduce in the back end. We expect MapReduce is a better solution for the use case of running alignments against an entire database, as opposed to a selected subset of a database.

11 Kepner, Jeremy et al. "D4M 2.0 schema: A general purpose high performance schema for the Accumulo database." *High Performance Extreme Computing Conference (HPEC), 2013 IEEE* 10 Sep. 2013: 1-6.

- The D4M Schema inspired our database table schema. It is a generic schema template that allows for high flexibility while maintaining decent performance.

12 Michelle Magrane and UniProt Consortium "UniProt Knowledgebase: a hub of integrated protein data" *Oxford Journals*. N.p., n.d. Web. 24 Nov. 2010. <http://database.oxfordjournals.org/content/2011/bar009.full.pdf+html>.

- Discusses prowess of UniProt KB as a powerful protein Markov Model database. Also reveals how UniProt KB allows for taxonomic restriction of search and how data is added to the database. UniProt KB is the database we will examine after Genbank.

13 Pruitt, Kim D., Tatiana Tatusova, and Donna R. Maglott. "NCBI Reference Sequences (RefSeq): A Curated Non-redundant Sequence Database of Genomes, Transcripts and Proteins." National Center for Biotechnology Information. U.S. National Library of Medicine, 27 Nov. 2006. Web. 02 Dec. 2014. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1716718/>

- The NCBI RefSeq database is a non-redundant database that we can use as a possible road for future expansion.

14 "BioBench: A benchmark suite of bioinformatics applications." K. Albayraktaroglu, A. Jaleel, X. Wu, M. Franklin, B. Jacob, C.-W. Tseng, and D. Yeung. Proc. 2005 IEEE International Symposium on Performance Analysis of Systems and Software (ISPASS 2005), pp. 2-9. Austin TX, March 2005

- We intend to use similar benchmarking tests as BioBench.

Conference and Journals of Interest for publishing results

- IEEE Transactions on Parallel and Distributed Systems (TPDS). http://www.computer.org/portal/web/tpds
- IEEE High Performance and Extreme Computing (HPEC) Conference. http://www.ieee-hpec.org/
- Supercomputing Conference (SC). http://www.supercomp.org/

F. Example Data

gbpri1.fsa_aa -- FASTA file from NCBI GENBANK containing protein sequences

```
>gi|1809232|gb|AAB46355.1| coded for by human cDNA N49626 (NID:g1190792) [Homo sapiens]
MFSSSFLDKKLYVSRGSASTSLPNETLSELETPGKYSLTPPNHWGHPHRYLQHL
>gi|2078460|gb|AAB54048.1| Rod transducin (alpha-1 subunit) [Homo sapiens]
MGAGASAEEKHSRELEKKLKEDAEKDARTVKLLLLGAGESGKSTIVKQMKIIHQDGYSLEECLEFIAIIY
GNTLQSILAIVRAMTTLNIQYGDSARQDDARKLMHMADTIEEGTMPKEMSDIIQRLWKDSGIQACFERAS
EYQLNDSAGYYLSDLERLVTPGYVPTEQDVLRSRVKTTGIIETQFSFKDLNFRMFDVGGQRSERKKWIHC
FEGVTCIIFIAALSAYDMVLVEDDEVNRMHESLHLFNSICNHRYFATTSIVLFLNKKDVFFEKIKKAHLS
ICFPDYDGPNTYEDAGNYIKVQFLELNMRRDVKEIYSHMTCATDTQNVKFVFDAVTDIIIKENLKDCGLF
>gi|561733|gb|AAB63305.1| MHC class II DRA [Macaca mulatta]
MAESGVPVLGFFIIAVLMSAQESWAIKEEHVIIQAEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRL
EEFGRFASFEAQGALANIAVDKANLEIMTKRSNNTPITNVPPEVTVLTNSPVELGEPNVLICFIDKFSPP
VVKVTWLKNGKPVTTGVSETVFLPREDHLFRKFHYLPFLPSTEDIYDCKVEHWCLDAPLLKHWEFDAPSP
LPETTENVVCALGLIVGLVGIIVGTVFIIKGVRKSNAAERRGPL
```

globins4.hmm -- example motif Hidden Markov Model file

```
HMMER3/b [3.0 | March 2010]
NAME  globins4
LENG  149
ALPH  amino
RF    no
CS    no
MAP   yes
DATE  Sun Mar 28 09:50:46 2010
NSEQ  4
EFFN  0.964844
CKSUM 2027839109
STATS LOCAL MSV       -9.9014  0.70957
STATS LOCAL VITERBI  -10.7224  0.70957
STATS LOCAL FORWARD   -4.1637  0.70957
HMM          A        C        D        E        F        G        H        I        K        L        M        N        P        Q        R        S        T        V        W        Y
            m->m     m->i     m->d     i->m     i->i     d->m     d->d
  COMPO   2.36553  4.52577  2.96709  2.70473  3.20818  3.02239  3.41069  2.90041  2.55332  2.35210  3.67329  3.19812  3.45595  3.16091  3.07934  2.66722  2.85475
2.56965  4.55393  3.62921
          2.68640  4.42247  2.77497  2.73145  3.46376  2.40504  3.72516  3.29302  2.67763  2.69377  4.24712  2.90369  2.73719  3.18168  2.89823  2.37879  2.77497  2.98431
4.58499  3.61525
          0.57544  1.78073  1.31293  1.75577  0.18968  0.00000        *
      1   1.70038  4.17733  3.76164  3.36686  3.72281  3.29583  4.27570  2.40482  3.29230  2.54324  3.63799  3.55099  3.93183  3.61602  3.56580  2.71897  2.84104  1.67328
5.32720  4.10031      9 - -
          2.68618  4.42225  2.77519  2.73123  3.46354  2.40513  3.72494  3.29354  2.67741  2.69355  4.24690  2.90347  2.73739  3.18146  2.89801  2.37887  2.77519  2.98518
4.58477  3.61503
          0.03156  3.86736  4.58970  0.61958  0.77255  0.34406  1.23405
      2   2.62748  4.47174  3.31917  2.82619  3.63815  3.49607  2.75382  3.03401  2.75280  2.74783  3.65114  3.24714  2.62341  3.12082  3.11124  2.79244  2.89355  1.88003
5.06315  3.77128     10 - -
          2.68618  4.42225  2.77519  2.73123  3.46354  2.40513  3.72494  3.29354  2.67741  2.69355  4.24690  2.90347  2.73739  3.18146  2.89801  2.37887  2.77519  2.98518
4.58477  3.61503
          0.02321  4.17053  4.89288  0.61958  0.77255  0.48576  0.95510
```

globins4.out -- Example scores for sequences against a motif HMM, followed by alignments

```
Scores for complete sequences (score includes all domains):
   --- full sequence ---   --- best 1 domain ---    -#dom-
    E-value  score  bias    E-value  score  bias    exp  N  Sequence             Description
    ------- ------ -----    ------- ------ -----   ---- --  --------             -----------
      6e-65  222.7   3.2    6.7e-65  222.6   2.2    1.0  1  sp|P02185|MYG_PHYCA  Myoglobin OS=Physeter catodon GN=MB PE
    3.1e-63  217.2   0.1    3.4e-63  217.0   0.0    1.0  1  sp|P02024|HBB_GORGO  Hemoglobin subunit beta OS=Gorilla gor
    4.5e-63  216.6   0.0      5e-63  216.5   0.0    1.0  1  sp|P68871|HBB_HUMAN  Hemoglobin subunit beta OS=Homo sapien
```

```
…
Domain annotation for each sequence (and alignments):
>> sp|P02185|MYG_PHYCA  Myoglobin OS=Physeter catodon GN=MB PE=1 SV=2
   #    score  bias  c-Evalue  i-Evalue hmmfrom  hmm to    alifrom  ali to    envfrom  env to     acc
 ---   ------ ----- --------- --------- ------- -------    ------- -------    ------- -------    ----
   1 !  222.6   2.2   1.4e-67   6.7e-65       2     149 .]       2     148 ..       1     148 [. 0.99


  Alignments for each domain:
  == domain 1    score: 222.6 bits;  conditional E-value: 1.4e-67
           globins4   2 vLseaektkvkavWakveadveesGadiLvrlfkstPatqefFekFkdLstedelkksadvkkHgkkvldAlsdalakldekleaklkdL 91
                        vLse+e++ v++vWakveadv+++G+diL+rlfks+P+t+e+F++Fk+L+te+e+k+s+d+kkHg++vl+Al+++l+k ++++ea+lk+L
  sp|P02185|MYG_PHYCA   2 VLSEGEWQLVLHVWAKVEADVAGHGQDILIRLFKSHPETLEKFDRFKHLKTEAEMKASEDLKKHGVTVLTALGAILKK-
KGHHEAELKPL 90
                        8****************************************************************************.99********* PP


           globins4  92 selHakklkvdpkyfkllsevlvdvlaarlpkeftadvqaaleKllalvakllaskYk 149
                        +++Ha+k+k+++ky++++se++++vl++r+p++f+ad+q+a++K+l+l++k++a+kYk
  sp|P02185|MYG_PHYCA  91 AQSHATKHKIPIKYLEFISEAIIHVLHSRHPGDFGADAQGAMNKALELFRKDIAAKYK 148
                        *********************************************************7 PP


>> sp|P02024|HBB_GORGO  Hemoglobin subunit beta OS=Gorilla gorilla gorilla GN=HBB PE=1 SV=2
   #    score  bias  c-Evalue  i-Evalue hmmfrom  hmm to    alifrom  ali to    envfrom  env to     acc
 ---   ------ ----- --------- --------- ------- -------    ------- -------    ------- -------    ----
   1 !  217.0   0.0   7.4e-66   3.4e-63       1     149 []       2     147 .]       2     147 .] 0.99


  Alignments for each domain:
  == domain 1    score: 217.0 bits;  conditional E-value: 7.4e-66
           globins4   1 vvLseaektkvkavWakveadveesGadiLvrlfkstPatqefFekFkdLstedelkksadvkkHgkkvldAlsdalakldekleaklkd 90
                        v+L+++ek++v+a+W+kv  +v+e+G+++L rl++++P+tq+fFe+F+dLst+d+++++++vk+Hgkkvl+A+sd+la+ld +l++++++
  sp|P02024|HBB_GORGO   2 VHLTPEEKSAVTALWGKV--
NVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLD-NLKGTFAT 88
                        69***************..*************************************************************.******** PP


           globins4  91 LselHakklkvdpkyfkllsevlvdvlaarlpkeftadvqaaleKllalvakllaskYk 149
                        LselH++kl+vdp++fkll++vlv+vla++++keft++vqaa++K++a va++la+kY+
  sp|P02024|HBB_GORGO  89 LSELHCDKLHVDPENFKLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH 147
                        **********************************************************7 PP
```

G. Accumulo Database Table Formats

The following snippets from our Accumulo database illustrate our database schema. A solid schema is essential in order to answer queries at the front end flexibly and efficiently.

The format of the schema is:

row_id :column_qualifier [] value

Most entries have value "1," as an indicator that a relationship exists between the row and column. We use an empty column family. The "[]" indicates empty column visibility, as we do not worry about security authorizations in our current work. See here for a description of the Accumulo data format: https://accumulo.apache.org/1.6/accumulo_user_manual.html#_data_model

- Table **Tseq**

Tseq allows a user to lookup all the properties of a sequence by accession ID. The properties are stored in the columns of an accession ID's row.

```
BAA22448.1 :Exons|89-406 []    1
BAA22448.1 :codon_start|1 []    1
BAA22448.1 :date|2006-12-02 []    1
BAA22448.1 :db_xref|GI:2446889 []    1
BAA22448.1 :def|Synechococcus elongatus PCC 6301 genes for ribosomal proteins, complete cds. []    1
BAA22448.1 :molecule|DNA []    1
BAA22448.1 :note|unnamed protein product []    1
BAA22448.1 :organism|Synechococcus elongatus PCC 6301 []    1
BAA22448.1 :strain|PCC 6301 []    1
BAA22448.1 :taxon_id|269084 []    1
BAA22448.1 :taxonomy|Bacteria; Cyanobacteria; Oscillatoriophycideae; Chroococcales; Synechococcus. []
1
```

- Table **TseqT**

TseqT allows lookup of sequence accession IDs by property. The properties are the row identifiers and the accession IDs are columns. This is the "transpose" of table TseqT.

One common operation is to find all the accession IDs that have a certain property, e.g., all the accession IDs that have the property organism|Synechococcus elongatus. Lookup by "start" of a property is also possible, as by finding all accession IDs of sequences that have a property that starts with taxonomy|Bacteria; Cyanobacteria.

```
Exons|89-406 :BAA22448.1 []    1
codon_start|1 :BAA22448.1 []    1
date|2006-12-02 :BAA22448.1 []    1
db_xref|GI:2446889 :BAA22448.1 []    1
def|Synechococcus elongatus PCC 6301 genes for ribosomal proteins, complete cds. :BAA22448.1 []    1
molecule|DNA :BAA22448.1 []    1
note|unnamed protein product :BAA22448.1 []    1
organism|Synechococcus elongatus PCC 6301 :BAA22448.1 []    1
strain|PCC 6301 :BAA22448.1 []    1
taxon_id|269084 :BAA22448.1 []    1
taxonomy|Bacteria; Cyanobacteria; Oscillatoriophycideae; Chroococcales; Synechococcus. :BAA22448.1
[]    1
```

- Table **TseqDegT**

This table lists the number of sequences that have a property. We store the number as the value of the Accumulo entry. The table snippet below was constructed from a small test dataset and so shows all 1s, but in our full database there are many more entries. For example, the number of sequences from a DNA molecule is

```
molecule|DNA :deg []    20251058
```

We use degree tables to gauge how much computation and data traffic a query requires.

```
Exons|89-406 :deg []    1
codon_start|1 :deg []    1
date|2006-12-02 :deg []    1
db_xref|GI:2446889 :deg []    1
def|Synechococcus elongatus PCC 6301 genes for ribosomal proteins, complete cds. :deg []    1
molecule|DNA :deg []    1
note|unnamed protein product :deg []    1
organism|Synechococcus elongatus PCC 6301 :deg []    1
strain|PCC 6301 :deg []    1
taxon_id|269084 :deg []    1
taxonomy|Bacteria; Cyanobacteria; Oscillatoriophycideae; Chroococcales; Synechococcus. :deg []    1
```

- Table **TseqFieldT**

TseqFileldT is similar to TseqDegT, except that it counts all the sequences that have some property of a given type. Again, the snippet below is from example data. Here is a listing from our live database

```
molecule :deg []    22851661
Exons :deg [] 5
codon_start :deg []    5
date :deg []    5
db_xref :deg []    5
def :deg []    5
ec_number :deg []    1
gene :deg []    3
molecule :deg []    5
note :deg []    2
organism :deg []    5
product :deg []    3
strain :deg []    5
```

```
taxon_id :deg []    5
taxonomy :deg []    5
```

- Table **TseqRaw**

    TseqRaw stores the actual sequence data for each accession ID in our system.

```
BAA22448.1 :seq []
MLARISELTKIGTTIFIVAIDQVAEPNSWGSSQLVLLAKIAGALKAIPPNPVCTSRHRQAASVSPFRSAIVGTLLQ
LEAIKNLLTVSVDTIQQNGVLFIFVALLR
```

- Table **TseqRawNumBases**

TseqRawNumBases counts the number of bases (each letter is a base) in a particular sequence, organized by accession ID. This is another way to estimate the amount of computation a query requires.

```
BAA22448.1 :num []    105
```

- Table **TseqInfo**

TseqInfo stores metadata on how many sequences we ingested into our database from each database file, how long it took to process that file, how many property entries we ingested among all the sequences in that file, and the total number of bases for that file.

```
gbbct1._aas :statNumBasePut []    1.53868e+07
gbbct1._aas :statNumMetaPut []    663812
gbbct1._aas :statNumSeqPut []    53229
gbbct1._aas :statTimePut []    655.389
```

- Table **Ttax**

Ttax allows a user to lookup all the properties of a taxonomic identifier. The properties are stored in the columns of an accession ID's row. Note that these identifiers (stored in the row) correspond to the taxon_id property of a sequence, listed above in Tseq, TseqT and other tables.

```
1 :division|Unassigned [] 1421654426882 false 1
1 :rank|no rank [] 1421654426882 false 1
1 :scientific name|root [] 1421654426995 false 1
1 :synonym|all [] 1421654426995 false 1
```

```
10 :division|Bacteria [] 1421654426882 false 1
10 :parent|135621 [] 1421654426882 false 1
10 :rank|genus [] 1421654426882 false 1
10 :scientific name|Cellvibrio [] 1421654426995 false 1
10 :synonym|"Cellvibrio" Winogradsky 1929 [] 1421654426995 false 1
10 :synonym|Cellvibrio (ex Winogradsky 1929) Blackall et al. 1986 em... TRUNCATED [] 1421654426995
false 1
11 :authority|"Cellvibrio gilvus" Hulcher and King 1958 [] 1421654426995 false 1
11 :division|Bacteria [] 1421654426882 false 1
11 :equivalent name|Cellvibrio gilvus [] 1421654426995 false 1
11 :parent|1707 [] 1421654426882 false 1
11 :rank|species [] 1421654426882 false 1
11 :scientific name|[Cellvibrio] gilvus [] 1421654426995 false 1
```

- Table **TtaxT**

TtaxT performs a similar function to TseqT, allowing efficient lookup of the taxonomic IDs that have a certain property. The taxonomic ID is the column qualifier.

This table will enable "search" capabilities over species. For example, we may find all the taxonomic identifiers that contain the name "bacteria" in either the genbank common name, the equivalent name, a misspelling, or the scientific name. We may also traverse the taxonomic hierarchy through the "parent" property. Part of the hierarchy is also indexed in table Tseq(T).

```
authority|"Angiococcus disciformis" (Thaxter 1904) Jahn 1924 :38 [] 1421654426996 false 1
authority|"Angiococcus" Jahn 1924 :42 [] 1421654426996 false 1
authority|"Cellvibrio gilvus" Hulcher and King 1958 :11 [] 1421654426996 false 1
...
blast name|bacteria :2 [] 1421654426996 false 1
division|Bacteria :10 [] 1421654426883 false 1
division|Bacteria :11 [] 1421654426883 false 1
division|Bacteria :13 [] 1421654426883 false 1
...
equivalent name|Methyliphilus methylitrophus :17 [] 1421654426996 false 1
equivalent name|Methyliphilus methylotrophus :17 [] 1421654426996 false 1
equivalent name|Methylophilus methylitrophus :17 [] 1421654426996 false 1
genbank common name|eubacteria :2 [] 1421654426996 false 1
genbank common name|fruiting gliding bacteria :29 [] 1421654426996 false 1
...
misspelling|Shewanella putrifaciens :24 [] 1421654426996 false 1
parent|13 :14 [] 1421654426883 false 1
```

```
parent|131567 :2 [] 1421654426883 false 1
parent|135621 :10 [] 1421654426883 false 1
parent|16 :17 [] 1421654426883 false 1
...
rank|family :39 [] 1421654426883 false 1
rank|family :49 [] 1421654426883 false 1
rank|genus :10 [] 1421654426883 false 1
rank|genus :13 [] 1421654426883 false 1
...
rank|no rank :1 [] 1421654426883 false 1
rank|order :29 [] 1421654426883 false 1
rank|species :11 [] 1421654426883 false 1
rank|species :14 [] 1421654426883 false 1
...
rank|superkingdom :2 [] 1421654426883 false 1
scientific name|Angiococcus disciformis :38 [] 1421654426996 false 1
scientific name|Archangium :47 [] 1421654426996 false 1
scientific name|Archangium gephyra :48 [] 1421654426996 false 1
scientific name|Azorhizobium :6 [] 1421654426996 false 1
```

- Table **TtaxDeg**

This stores the number of properties of each taxonomic ID.

```
1 :deg [] 1421654426987 false 4
10 :deg [] 1421654426987 false 6
11 :deg [] 1421654426987 false 6
13 :deg [] 1421654426987 false 5
14 :deg [] 1421654426987 false 8
16 :deg [] 1421654426987 false 7
```

- Table **TtaxDegT**

This stores the number of taxonomic IDs that have a property. The most useful portion is the “parent” property, as this effectively stores the number of children in the taxonomic hierarchy of a given taxonomic ID.

To give perspective on the scope of our database, the following is from our live database and shows how many taxonomic identifiers at the species level are stored:

```
          rank|species :deg []    944894

authority|"Angiococcus disciformis" (Thaxter 1904) Jahn 1924 :deg [] 1421654426994 false 1
authority|"Angiococcus" Jahn 1924 :deg [] 1421654426994 false 1
authority|"Cellvibrio gilvus" Hulcher and King 1958 :deg [] 1421654426994 false 1
...
parent|32199 :deg [] 1421654426882 false 1
parent|335928 :deg [] 1421654426882 false 1
parent|39 :deg [] 1421654426882 false 4
parent|39643 :deg [] 1421654426882 false 1
parent|40 :deg [] 1421654426882 false 1
parent|42 :deg [] 1421654426882 false 2
parent|83461 :deg [] 1421654426882 false 1
rank|family :deg [] 1421654426882 false 3
rank|genus :deg [] 1421654426882 false 18
rank|no rank :deg [] 1421654426882 false 1
rank|order :deg [] 1421654426882 false 1
rank|species :deg [] 1421654426882 false 31
rank|superkingdom :deg [] 1421654426882 false 1
scientific name|Angiococcus disciformis :deg [] 1421654426994 false 1
scientific name|Archangium :deg [] 1421654426994 false 1
```

- Table **TtaxFieldT**

  Similar to the use of TseqFieldT.

```
authority :deg [] 1421654426988 false 66
blast name :deg [] 1421654426988 false 1
division :deg [] 1421654426868 false 55
equivalent name :deg [] 1421654426988 false 7
genbank common name :deg [] 1421654426988 false 2
genbank synonym :deg [] 1421654426988 false 1
in-part :deg [] 1421654426988 false 6
includes :deg [] 1421654426988 false 7
misspelling :deg [] 1421654426988 false 6
parent :deg [] 1421654426868 false 54
rank :deg [] 1421654426868 false 55
scientific name :deg [] 1421654426988 false 55
synonym :deg [] 1421654426988 false 59
type material :deg [] 1421654426988 false 101
```