V-Lab-Protein: Virtual Collaborative Lab for Protein Sequence Analysis

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Abstract

Recent development of genome and gene analysis technology enabled rapid accumulation of biological data. To utilize such huge data, a biologist needs to have resource-rich computing environment and user-friendly analysis tool invocation. To response such requirements, we designed and implemented a virtual lab, named Virtual Collaborative Lab (V-Lab-Protein), using an efficient and flexible computing resource management and workflow engine with a user-friendly graphical workflow composer. Utility of our system is demonstrated by analyzing sample protein sequence sets. This is the first system of its kind that combines flexible workflow systems and on-demand compute and data resources (Amazon EC2/S3 in this case). We believe that this system design principle will be a new and effective paradigm for small biology research labs to handle the ever-increasing biological data.

1. INTRODUCTION

Recent development of genome and gene analysis technology enables even a personal research laboratory to generate a large amount of raw sequence data, i.e., a whole bacteria genome sequence, using new high-throughput sequencing technologies such as Pyrosequencing [12]. However, most biologists do not have computational skill to handle such large amount of sequence data. In particular, there are two computational challenges.

The first challenge is to build a computing environment to handle a large amount of data. Although computing cost is getting cheaper, it is still expensive to purchase and maintain computing resources for biological data analysis. More importantly, setting up and managing the computing environment is typically beyond the ability of a small group of biologists. The second challenge is to combine bioinformatics tools and databases. Biologists use a Web-based system which is typically designed to serve a single computational tool or database. Thus combining multiple tools and databases in the Web environment is a very challenging task for biologists. To overcome these two problems, we designed and implemented a virtual computing lab where a scientist can assign a dedicated computing resource in an on-the-fly manner, use the instant resource to analyze the raw data, and save the results in persistent disk storage which can also be shared with collaborators.

In this paper, we present a virtual system for protein sequence analysis, called a virtual collaborative lab for protein sequence analysis, *V-Lab-Protein* in short. We address the following two challenges mentioned above:

1. To facilitate setting up and managing a high performance computing environment, we used Amazon's Elastic Computing Clouds, known as Amazon EC2, for virtual computing powers and Simple Storage Service, also known as Amazon S3, for persistent data storage.
2. To address the difficulty in combining multiple computational tools and databases, we used our in-house workflow management system: Generic Service Toolkit, known as Gfac [5], a wrapper which converts any command-line application into a Web application and XBaya [17], a user-friendly graphical workflow composer written in Java, which provides a workbench filled with Web applications converted by Gfac.

There are a number of systems for handling biological data and workflow (see Related Work section). However, this is the first system that combines flexible workflow management systems and on-demand compute and data resources (Amazon EC2/S3 in this case). We believe that this system design principle will be a new, effective paradigm for small biology research labs to handle the ever-increasing biological data.

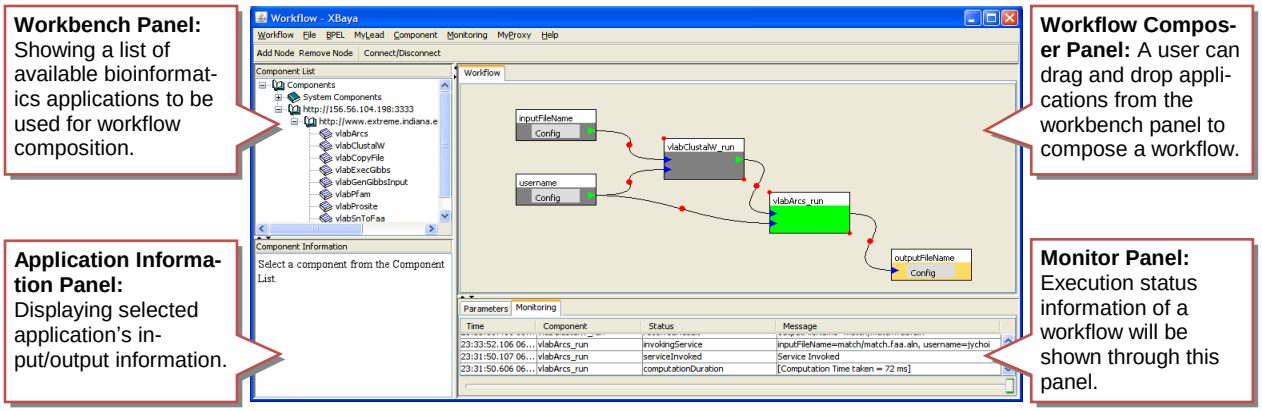


Figure 1. A screen shot of XBaya, a graphical Java GUI based workflow composer. XBaya consists of 4 main panels: a workbench panel, an application information panel, a workflow composer panel, and a monitor panel. The example shows a task of aligning biological sequences using ClustalW and computing conserved regions in the multiple sequence alignment using ARCS.

The rest of the paper is organized as follows: In Section 2, we introduce main features of our V-Lab-Protein system from a user's perspective. The architecture of V-Lab-Protein system is presented in Section 3 and related work is discussed in Section 4. Finally, in section 5, we briefly summarize our V-Lab-Protein system and discuss our future work.

2. Protein Sequence Analysis Using V-Lab-Protein

A typical procedure for analyzing and annotating protein sequences involves the use of multiple bioinformatics applications, such as Gibbs [19], ClustalW [8], and ARCS [2], and needs to run several queries against annotation databases such as Prosite [13] and Pfam [16].

For novice users, it is hard to learn how to correctly use such various applications and databases and execute them in the right order. Furthermore, many of the applications provide only a command-line interface running on the text-based terminal environment that biologists are not familiar with. To overcome such a problem and provide a user-friendly interface, a workflow concept with a graphical workflow composer can be used. By using a simple graphical workflow composer, a user can easily construct a complex workflow with several mouse movements. Once a composed workflow is activated with a list of applications and data input, a workflow engine automatically marshals the required compute and data resources needed to execute the pipeline. In our V-Lab-Protein system, we used the Generic Service Toolkit, known as Gfac [5], as a wrapper which converts any command-line application into a Web application and XBaya [17] (Figure 1) as a user-friendly graphical workflow composer written in Java. Note that XBaya can be executed virtually in any computing environment for the use of Java GUI. Details are discussed in the next subsection.

Another barrier to a novice user is the expensive cost for building computer infrastructure. Due to computation-rich characteristics of bioinformatics applications, the need for higher computing powers is increasing. For this reason, a super computer or a Grid system, which is a group of multitude computing units, is widely deployed and used among many bio research centers and institutes. However, the cost to build such powerful computing resources is still too expensive for a small group of researchers. On the other hand, cost of obtaining new biological data becomes cheaper and even a small lab can produce tons of protein sequences in an efficient way and thus the need for cheap and powerful computing resources is also increasing accordingly.

To respond this requirement, a virtual computing cloud service, which provides a collection of virtual computing instances in an on-demand manager, has been introduced by a few private sectors. The most prominent example is the Amazon Elastic Compute Cloud, which is a commercial pay-per-use service for anybody at surprising low cost. The model of dynamically loading a virtual machine onto a remote computing resource is also under evaluation by the NSF TeraGrid. By using a virtual computing cloud service, any computing resource can be dynamically assigned at any time. Instead of paying expensive cost for building or maintaining persistent computing resources, a user can pay only for the number of virtual computing instances he or she used in the cloud. In our V-Lab-Protein system, we use Amazon's Elastic Computing Cloud (EC2) service as a virtual computing cloud.

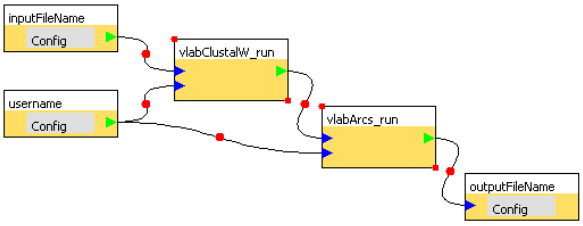


Figure 2. A simple workflow composed by XBaya. The given workflow will execute ClustalW and ARCS consecutively with an input name and a username as input parameters yields a file name as an output.

Our V-Lab-Protein system for protein sequence analysis is designed to provide the followings:

- A workflow engine with a user-friendly graphical workflow composer.
- Flexible computing infrastructure by using a virtual computing cloud.
- Simple Web interfaces.

In the following, we describe how to use our V-Lab-Protein system for protein analysis and annotation. We emphasize that ordinary users, biologists, do not have to know the details described in this section, which are described to explain how the system works.

2.1. Application Services

To utilize the biological data for research projects, multiple tools should be combined. Thus, interoperability between tools is important. Unfortunately, however, most bioinformatics applications are not designed with such interoperability in mind. They are mostly standalone and platform-dependent. To overcome this problem, application services have been proposed. An application service is, as defined in [5], a Web service which can invoke a command line application.

To invoke a Web service, a user can simply use Simple Object Access Protocol (SOAP) messages or Representational State Transfer (REST) messages, which is a standard Web service protocol. Thus, once deployed as an application service, bioinformatics applications can be executed remotely through a unified way using SOAP or REST. Sometimes we call such a command-line application *a Web application* since the invocation is through the Web service.

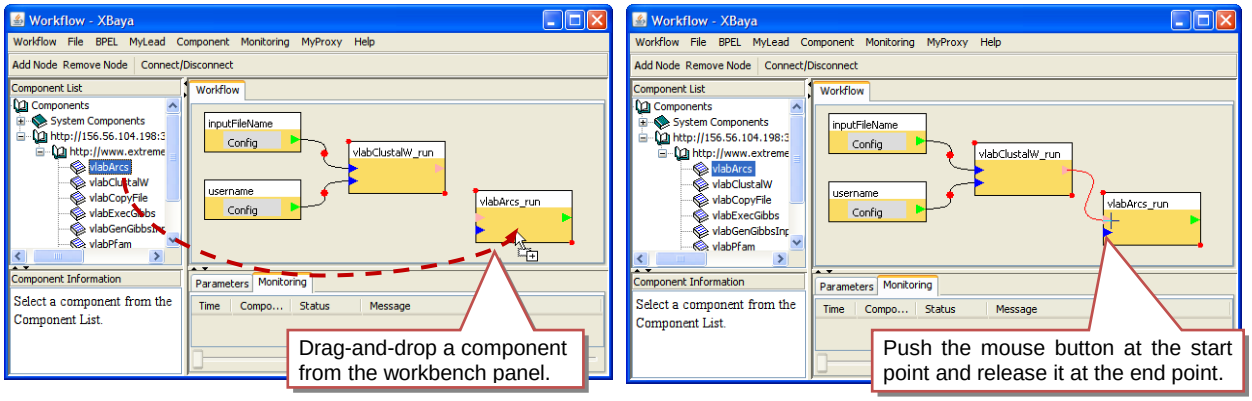
To convert a bioinformatics application into an application service, we use a tool, called Generic Service Toolkit (Gfac) [5]. Gfac provides two services, a factory service and a registry service. The Gfac's factory service allows users to *wrap* any command-line bioinformatics application to convert it into an application service and execute it by sending a Simple Object Access Protocol (SOAP) message.

To execute bioinformatics applications remotely through the Gfac's factory service, a user needs to know which applications are available to execute and what their specifications of input and output parameters are to build a SOAP message. For this purpose, Gfac provides a registry service with which a user can discover a list of available application services to execute and get information about input and output parameters. For example, by accessing Gfac's registry service, a graphical workflow composer, called XBaya [17], can provide the list of available applications in its workbench panel (Figure 1) and a user can use them to compose a workflow (More details are discussed in the next subsection).

In other words, to execute a command-line application through an application service, each command-line application needs to be registered with its input and output parameters' specification through a registration process. For this purpose, the Gfac provides a registration portlet which can be easily deployed in a Web portal. Registration is a one-time setup procedure which needs to be done by an administrator. Thus, normal users do not need to care about this procedure. For more detail information about registration process, we recommend readers refer to [5] and its user guide.

2.2. Workflow Composition

The workflow concept has been introduced in the scientific communities to execute a batch of multiple tasks by reducing a user's involvement and enables a user to repeat the same task with ease. A workflow is a directed acyclic graph where each inner node is an application to execute and an edge between two nodes represents a flow of data. A starting node and an end node in a workflow graph correspond to an input and an output data respectively. An example of a workflow is shown in Figure 2.



(a) Adding a node (b) Creating an edge between two nodes

Figure 3. Composing a workflow by using XBaya. A user can (a) add a node by doing drag-and-drop one of available applications from the workbench panel and (b) create an edge by pushing and releasing a mouse pointer between two nodes of a workflow.

To build a workflow and execute it, our V-Lab-Protein system uses a graphical workflow composer, called XBaya [17]. In addition to the easy-to-use interface, the XBaya is coupled with Gfac to fetch the list of available Web applications or send a request to execute an application through a Web service standard protocol using SOAP messages. (Workflow execution is discussed in the next subsection.)

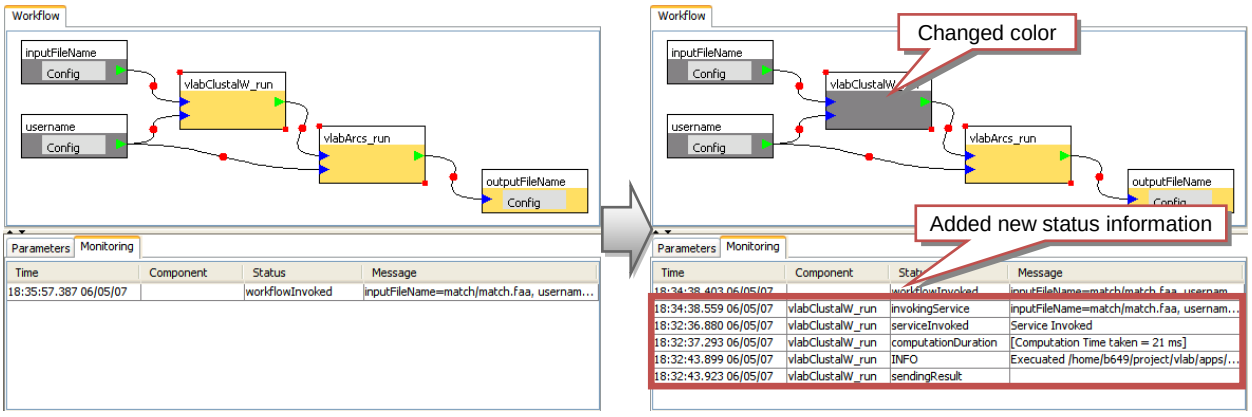
A list of available Web applications to execute in the XBaya is shown in the workbench panel (Figure 1). To build a workflow, a user can simply do drag-and-drop one of the available applications from the workbench panel as shown in Figure 3 (a). In the same way, input and output parameters can be added from the same panel. To create an edge between nodes, a user can simply push and release a mouse pointer over them (Figure 3 (b)). For more information about using XBaya, we recommend readers refer to [17].

2.3. Workflow Execution and Monitoring

Once a workflow is ready, a user can execute the workflow by using the XBaya. XBaya will follow a workflow sequences on the behalf of a user by sending an execution request to the Gfac's factory service as discussed in 2.1.

When starting a workflow, the XBaya will prompt a dialog to a user to get necessary input data. After then, the XBaya will start to execute a workflow. For each execution in the workflow, it sends SOAP messages to the Gfac's factory service which in turn invokes corresponding Web applications.

After starting execution, XBaya can also monitor



(a) Before execution (b) After execution

Figure 4. Monitoring execution status in XBaya. Status messages will be automatically added in the monitor panel. Pictures are example screenshots for (a) before-execution and (b) after-execution of ClustalW.

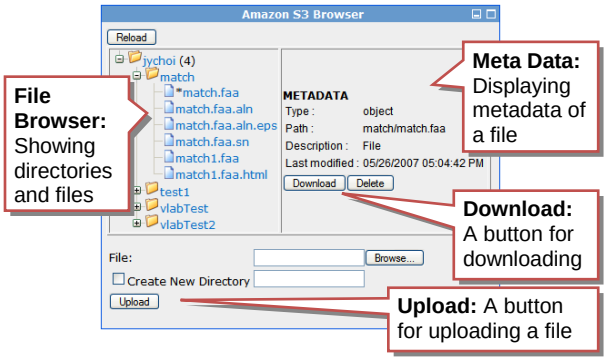


Figure 5. A Web interface for browsing Amazon S3 files. A user can simply use a Web browser to explore files stored in S3.

the status of a workflow execution by using a standard publish-subscription (pub/sub) notification system as follows: (i) The XBaya subscribes to the pub/sub system to get the execution status information. (ii) For each invocation of an application service, the Gfac's factory service will publish information about execution status, such as time stamps, exceptions, parameters, elapsed times, to the pub/sub system which logs them and notify to subscribers like XBaya. (iii) Status messages delivered by the pub/sub system are displayed in the monitor panel as shown in Figure 4 so that a user can check whether the execution goes well without any error.

2.4. Computing Cloud

Running a bioinformatics application often requires that a user should use several computers, running in parallel, to save the computation time. To build such computing resources and manage them is very expensive, especially, to a small group of researchers. Moreover, those computing environments are often persistent rather than flexible in that it is hard to change their capacities or configurations. To overcome this problem, we used virtual computing instances provided by a virtual computing cloud service, instead of using persistent and fixed computing resources.

In a virtual computing cloud, a user can have any number of computing units at any time and release them whenever a job is finished. The cost for a user is mainly depends on the number of computing resources he or she used and the duration of the service time. In this way, a user can achieve flexibility in using computing resources and efficiency in the computing costs.

The V-Lab-Protein system uses Amazon's Elastic Computing Cloud (EC2) and Simple Storage Service (S3) as a computing cloud and a persistent storage respectively. EC2 provides a computing cloud service where a user can have virtually any number of virtual computing instances at any time and S3 is a data storage service inside the computing cloud, EC2. In EC2, data storage is volatile since the storage will be destroyed together as a virtual computing instance is terminated. However, storage in S3 is persistent and reliable as data saved in S3 can be accessible at any time regardless of EC2.

To access files saved in S3, we provides a Web interface, as shown in Figure 5, with which a user can upload input files to S3 or download outputs simply by using a Web browser.

Another important use of S3 is for the storage of an Amazon Machine Image (AMI) which contains all necessary application files and data to be used by a virtual computing instance in EC2. Each virtual computing unit will be instantiated based on this image file. For our V-Lab-Protein system, we created a customized AMI which contains Fedora Linux operating system plus all bioinformatics applications we used in this paper (see section 3.2).

In the V-Lab-Protein system, each bioinformatics application is to be executed in one of virtual computing instances inside a computing cloud, EC2, and all input and output data are saved in a persistent storage, S3. More precisely, when the Gfac's factory service is called to execute a command-line application, it creates an instance of a virtual computing unit in the EC2 cloud and remotely executes the application in that instance. In our V-Lab-Protein system, we simply use a Secure Shell (SSH) client to perform the remote execution. Any general remote execution application, such as rsh, Globus' GRAM [9], and Condor-G [7], can be used as well.

When using an external and commercial computing cloud service, like Amazon EC and S3, a user should pay for what he or she consumes. Thus, it is also important for a small group of users to efficiently manage the number of virtual computing instances in order to save the cost to pay. For this purpose, the V-Lab-Protein system has a broker component, called an "instance manager", between the Gfac and the EC2 cloud. The instance manager will regularly check available resource status of running instances in EC2 and help Gfac to reuse one of instances which are idle or not heavily loaded to run another job. By using the instance manager, a user does not need to create an instance per every execution.

In our implementation, the instance manager simply counts the number of processes for running bioinformatics applications per each virtual instance in the EC2 cloud. If there is any instance whose process counter is lower than a user-defined threshold number, Gfac will reuse that instance to execute an application. Otherwise,

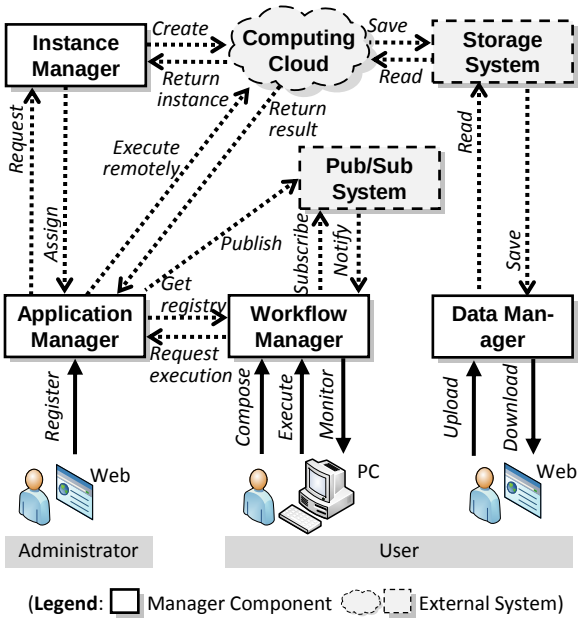


Figure 6. V-Lab-Protein system components.

the instance manager will create a new instance in an on-the-fly manner and Gfac will use the new one for execution of bioinformatics application.

From the user's perspective, however, execution of an application is transparent in the V-Lab-Protein system in that creation of virtual computing instances and remote execution will be done behind the scenes.

3. V-LAB-PROTEIN SYSTEM ARCHITECTURE

In this section, we describe the details of our V-Lab-Protein system.

3.1. System Architecture Overview

As shown in Figure 6, V-Lab-Protein system consists of 4 manager components: an application manager, a workflow manager, a data manager, and an instance manager. In addition, 3 external systems are used: a computing cloud system, a storage system, and a publish/subscription (pub/sub) system. External systems are replaceable in that we can use any other similar system to provide the same functionalities.

Most of V-Lab-Protein's components and systems are implemented in the form of Web services and service-oriented architectures, which allows our system to interoperate with other systems with easy. Thus, SOAP, REST or HTTP is the basis for our communication protocol. We use only Secure Shell (SSH) protocol for remote execution between the application manager and a virtual machine instance in the computing cloud. However, we can easily replace SSH with other Web service-based protocols such as WS-GRAM in the Globus Toolkit [9].

In the next, we describe each component of our V-Lab-Protein system.

A. Application manager

The application manager provides two main services: a registry service, which is to maintain the information of bioinformatics applications to serve, and a factory service which is to execute an application in a remote virtual machine instance in the computing cloud upon receiving a request from the workflow manager.

Before executing an application remotely, the application manager can contact the instance manager to fetch the list of available instances that have extra power to run the job. If there is no such an instance, the instance manager will create a new one. In this way, we can efficiently control the number of virtual computing instances in the computing cloud to cut the costs. After execution, the application manager will publish execution status to the pub/sub system in order for a user to be able to monitor execution status.

We use Gfac [5] for our application manager. Gfac also kindly provides a registry portlet, with which an administrator can manage registry information through any Web browser.

B. Workflow manager

The workflow manager enables a user to compose a workflow through a graphical user interface, execute a workflow on the behalf of the user, and monitor the status of execution.

When composing a workflow, a user needs to know the list of available bioinformatics applications to execute. This information is available through the application manager's registry service. Before starting to execute a workflow, the workflow manager subscribes the execution status information to the pub/sub system where the application manager will publish such information. After completing subscription, the workflow manager begins to orchestrate the execution of a workflow. To execute an application, the application manager's factory service is used. Due to the subscription, the workflow manager will either be notified the information about the execution status or can poll the information from the pub/sub system.

As our workflow manager, we use XBaya [17], which can be run virtually every platform since it is written in Java programming language.

C. Data manager

In our system, a user can upload and download inputs and outputs of bioinformatics applications through the data manager, which is designed to provide a con-

Table 1. The list of main bioinformatics applications installed in the V-Lab-Protein system.

Name	Purpose
Gibbs Motif Sampler[18]	To identify motifs or conserved regions within the given DNA or protein sequences as an input.
Prosite [12]	To find a conserved pattern from a newly sequenced protein by assigning a protein family or domain to distinguish it from all other unrelated proteins.
WebLogo [4]	Known as "Sequence Logo". To get a graphical representation of an amino acid or nucleic acid multiple sequence alignment.
ARCS [2]	To highlight the conserved regions among aligned biological sequences.
Pfam [15]	A database of hidden Markov models from multiple alignments of protein domains or conserved protein regions.

venient interface for users to access data stored in the storage service. We developed a Web interface so that a user can upload and download files simply by using a Web browser (Figure 5).

D. Instance manager

It is designed to manage the number of instances in a computing cloud service for saving the cost using a cloud service. Instead of creating a new instance for each request from the application manager, the instance manager tries to reuse available instances in the computing clouds in a way a user can save the cost for creating a new one. For this purpose, it monitors the instances in the computing cloud and their available resources.

E. Computing cloud service

We use Amazon's Elastic Compute Cloud (EC2) as a computing cloud service. Amazon EC2 service provides a resizable virtual computing cloud in which a user can request any number of virtual computing units at any time. Each instance predictably provides the equivalent of a system with a 1.7Ghz x86 CPU, 1.75GB of RAM, 160GB of local disk, and 250Mb/s of network bandwidth. Creating virtual computing instances in EC2 is very flexible and cheap. A user can create any number of units in minutes with less than 10 cents per instance-hour consumed.

F. Storage service

We use Amazon Simple Storage Service (S3) as a storage service. Amazon S3 is a persistent storage which is scalable, reliable, and inexpensive. A disk image for an instance of EC2, called Amazon Machine Image (AMI), and input and output files of bioinformatics applications are the main objects stored in S3. Costs are about $0.15 per GB-Month of storage plus $0.20 per GB of data transfer.

G. Publish/subscription (Pub/sub) system

A pub/sub system is used to deliver messages in a loosely coupled fashion. We use the pub/sub system to route execution status messages from the application manager to the workflow manager in a way the application manager publishes execution status messages and the workflow manager subscribes them.

3.2. Sequence analysis resources

The purpose of V-Lab-Protein is to provide common tools and database applications to help gene analysis process. For this purpose, we chose the most well-known and frequently used bioinformatics applications as shown in Table 1 and enabled a user to execute them in a virtual computing instance. The list is not final. An administrator can add, remove, and update any relevant application.

4. RELATED WORK

In recent years, a number of research projects on building a workflow system in the field of biology and bioinformatics have been conducted in order to provide biologists with an integrated workspace for using various bioinformatics applications. Those efforts to build such systems can be categorized under two main directions: one is to develop efficient and user-friendly workflow composers and execution engines and the other is to use distributed and multiple computing resources, such as a Grid system, combined with a workflow system to enhance computing capability.

Researches on bioinformatics workflows and workflow engines can be found in SIBIOS [11], BioWBI [14], and KDE Bioscience [15]. SIBIOS (Systems for the Integration of Bioinformatics Services) [11] has been developed in the focus of dynamic workflow execution and interoperability between distributed and heterogeneous bioinformatics services. BioWBI (Bioinformatics Workflow Builder Interface) [14] is a Web tool to provide researchers with a virtual workspace for sharing data with collaborators and a graphical workflow composer. In addition to the graphical workflow composer, it also has a workflow execution engine, called WEE, which is based on Web-service technology. KDE Bioscience (Knowledge Discovery Environment of Bioscience) [15] is a Java-based platform which integrates more than 60 bioinformatics tools and provides a Java GUI-based workflow composer and its execution engine.

The other research direction to build a workflow system is to use a group of distributed and multiple computing resources, called Grid system, as a back-end computing resource. Among many efforts, Taverna [18], Triana [6], Kepler [1], GNARE [3], and RENCI-Bioportal [10] are worth mentioning. Taverna [18] has been developed as a part of the myGrid project and it is a workflow system running bioinformatics Web services and existing bioinformatics applications over distributed resources. Triana [6] is designed to offer more a general approach to integrate with other Grid based systems, such as Globus and GridLab, or service oriented system like Web services. Kepler [1] is a scientific workflow system based on a dataflow-oriented model, so called an actor-oriented model. To make the use of Grid systems, Kepler provides various ready-to-use proxies, call Grid actors. A user can easily combine these actors together to design a workflow. GNARE [18] is a bioinformatics server equipped with automated workflows and a Grid-based computational backend to perform high throughput analysis of genomes with an aid of the workflow engine, GADU, which has access to thousands of CUPs from various large-scale Grid resources such as Open Science Grid (OSG) and TeraGrid.

Our V-Lab-Protein system shares similarity with the workflow systems such as Taverna [18], Triana [6], Kepler [1], and GNARE [3], for example, which are using a Grid system as a main computing resource. However, our V-Lab-Protein system is different from those systems in that we enable a user to use on-demand computing powers supplied from a virtual computing cloud service. Using virtual instances, instead of persistent resources, is more flexible and cost-efficient way for a small group of users to have such computing infrastructure for running computation-intensive bioinformatics applications.

5. CONCLUSION

We designed and implemented a virtual lab, named a virtual collaborative lab for protein sequence analysis (V-Lab-Protein), using an efficient and flexible computing resources management and workflow engine with a user-friendly graphical workflow composer. This is the first system of its kind that combines flexible workflow management systems and on-demand compute and data resources (Amazon EC2/S3 in this case).

Utilizing the ever-increasing biological data is a huge challenge for small research labs and we believe that this system design principle will be a new and effective paradigm for biology research that requires computational analysis of genome data. The prototype system presented in this paper is being extended significantly in collaboration with biologists at Indiana.

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