Final Year Project Report

Full Unit - Final Report

Structural Bioinformatics Framework using a MapReduce formalism

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MSc in Computer Science

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Abstract

Need a abstract

1 Rationale: 10 marks

1.1 Aims

Aim provided in the Project Description

"The aim of this project is to be provide a framework where large numbers of protein structures can be analysed using a user-provided executable in the MapReduce formalism."

Aim

Analysing protein structures can provide insights into their properties and interactions with other molecules. However, analysing large numbers of protein structures can be computationally intensive, requiring significant computational resources and time. Thus, the aim is to provide a framework that allows for the analysis of large numbers of protein structures using a MapReduce formalism.

MapReduce: is a programming model for processing and generating large data sets. Allowing for parallel processing of data across multiple nodes in a cluster, making it well-suited for analysing large datasets.

More specifically the aim is to develop a framework that can take a user-provided executable and apply it to a large number of protein structures in a parallel, distributed manner using MapReduce. This will enable researchers to perform complex analyses on large datasets of protein structures more efficiently, saving time and computational resources. Essentially enabling researchers to analyse large numbers of protein structures more quickly and effectively than before.

1.2 Objectives

To achieve the aim of the project, the following objectives have been formulated:

- Develop a software framework that suppots the Mapreduce formalism and can process large numbers of protein structures.
- Implement a distributed computing system using MapReduce to parallelize protein structure analysis across multiple computing nodes.
- Optimize the software framework to reduce the processing time required for protein structure analysis.
- Validate the software framework by testing it with a variety of protein structure analysis tools and evaluating its performance in comparison to other available tools.

The software must provide the ability to perform quicker and efficiently by allowing executables to be perfomred on multple files in a parallel compared to current solutions.

- Design an interface that allows users to manipulate the pdbs that are being passed into the executable for protein structure analysis.

The software revolves around using and manipulatting PDB files so the framework should give the user a method/function which is able to search and input pdb files automatically

- Ensure the software framework is scalable and can handle increasingly large datasets.
- Ensure the software framework can be eaisly updated to keep pace with advancements in protein structure analysis techniques and computing technology.

The pdb database is changing frequently with more protein structres being added exponetialy. The software should be able to cope with changes and by working with the fundamental set out standerds set out for uploaded protien structures.

- Provide documentation and user support to enable researchers to use the software framework effectively.

The framework should contain multiple functions that the user can use in order to perform executables on a set number of pdb files and query the pdb database in order to set up the files required by the user.

Software Framework and MapReduce

The software framework must support a Mapreduce formalism that can process large numbers of protein structures. Where the MapReduce formalism consists of two main functions: Map and Reduce. The Map function takes a set of data and transforms it into another set of data, where individual elements are broken down into key-value pairs. The Reduce function then takes the output of the Map function and combines all the values associated with a given key, producing a final output for each key. More specifically each map and reduce step can be conducted through multiple nodes.

The objective of the software framework is to

Interface and Documentation

Further Objectives

1.3 Introduction

Structural bioinformatics plays a critical role in the development of new drugs and therapies, as well as in understanding the molecular basis of biological processes. It involves the analysis and interpretation of large amounts of complex data, including the three-dimensional structures of proteins, DNA, and other macromolecules. As the size and complexity of these data sets continue to increase, the need for efficient and scalable computational tools for their analysis and processing becomes ever more pressing.

One promising approach to addressing this challenge is the use of MapReduce, a programming model for large-scale data processing in distributed computing environments. MapReduce enables the parallel processing of large data sets across multiple nodes in a cluster, which can significantly improve the speed and efficiency of data analysis tasks.

In this report, we present a structural bioinformatics framework that utilizes a MapReduce formalism for the efficient analysis of large-scale structural data. Our framework is based on a distributed computing architecture that allows for the parallel processing of structural data, including protein structures, protein-protein interactions, and other molecular structures. We describe the key components of our framework, including the data preprocessing, map, and reduce phases, as well as the parallel algorithms and data structures used to implement these phases.

We demonstrate the effectiveness of our framework through a series of experiments on real-world structural data sets, showing that our approach can significantly reduce the time and resources required for complex bioinformatics tasks. Our results highlight the potential of MapReduce-based approaches for accelerating the analysis of large-scale structural data in the field of bioinformatics.

NOTE: Need to read and re write

2 Literature Review and Background Reading: 15 marks

2.1 Protein Structures

Introduction

Amino acids are molecules that when combined forms proteins. All of the 20 amino acids, see table 1 have in common a central carbon atom which is attached to a hydrogen atom, an amino group, and a carboxyl group [BT98].

Proteins are responsible for catalysing most of the chemical reactions in cells. They can function as enzymes catalysing a wide variety of reactions important for life and thus also important for the structure of living systems such as proteins involved in the cytoskeleton. The size of protein can vary [Zve08].

Definition 2.1 (Catalysing) *Catalysing is to make a chemical reaction happen or happen more quickly by acting as a catalyst.*

Definition 2.2 (Cytoskeleton) *A dynamic network of interlinking protein filaments present in the cytoplasm of all cells [Zve08].*

Primary, Secondary, Tertiary and Quaternary Structure

Please refer to 1 for a visual representation.

The **primary structure** of a peptide or protein is the linear sequence of its amino acids. It is read and written from the amino-terminal to the carboxyl-terminal end. [SFB04].

The **secondary structure** refers to the local arrangement of a peptide chain. Where several common secondary structures have been identified in proteins [SFB04].

Tertiary structure is a three-dimensional structure of a protein the formation is built up of bonds and interactions that serve to change the shape of the overall protein [God22].

The **quaternary structure** of a protein is built-up of several protein chains/subunits. Each of the subunits has its primary, secondary, and tertiary structure [OR15].

Considering Protein structure on several different levels

The fold of the protein plays part in determining the way the protein will function, and also whether it will function correctly. As there are Protein structures on different levels we need to consider the analysis of protein structure by experimental techniques such as X-ray crystallography, nuclear magnetic resonance, and RNAseq which show that proteins adopt distinct structural elements [Zve08].

Amino Acids

Sequence of amino acids 1 will build up the linear protein chain [Zve08]. Amino acids are different from each other due to their side chains and due to this the functional properties of

Amino acid	Three-letter code	One-letter code
Glycine	Gly	G
Alanine	Ala	A
Valine	Val	V
Leucine	Leu	L
Isoleucine	Ile	I
Proline	Pro	P
Phenylalanine	Phe	F
Methionine	Met	M
Tryptophan	Trp	W
Cysteine	Cys	C
Asparagine	Asn	N
Glutamine	Gln	Q
Serine	Ser	S
Threonine	Thr	T
Tyrosine	Tyr	Y
Aspartic acid	Asp	D
Glutamic acid	Glu	E
Histidine	His	H
Lysine	Lys	K
Arginine	Arg	R

Table 1: The 20 amino acids. The amino acid name, the three-letter code, and the one-letter code are given. The Amino acids are split up into Nonpolar, Polar, Acidic and Basic respectfully

various different proteins are different [Zve08]. You can see the amino acids grouped here 1.

2.2 Large Scale Experssion

Gene expression begins when genes are transcribed into messenger RNAs, which are then translated to produce proteins.

Total gene expression in cultured cells or a tissue sample can be detected in three main ways:

1. DNA microarray technology.
2. Two-dimensional Gel electrophoresis or Chromatography.
3. RNAseq

Both DNA microarray technology and Two-dimensional Gel electrophoresis, produce enormous amounts of raw data [Zve08] due to this, many proteins currently evade high-resolution structure determination.

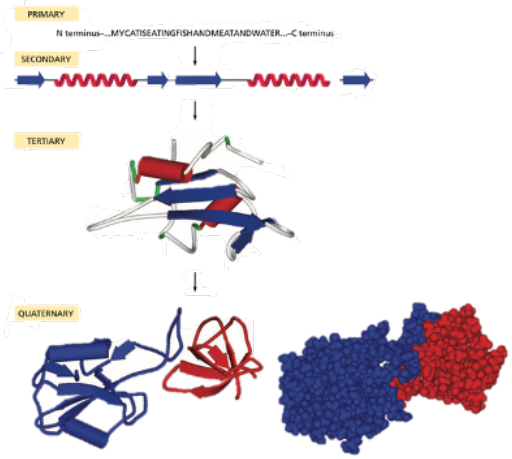


Figure 1: From the sequence alone, the primary structure to secondary structure, to tertiary structure(3D), to finally quaternary structure found when several tertiary structures form a multisubunit complex [Zve08].

Structural mass spectrometry

Structural mass spectrometry is a powerful approach used to determine the 3D structure of biological protiens it has nearly an unlimited size constraint and speed. Although the data provided by mass spectrometry is vague for full high-resolution structure elucidation, structural mass spectrometry can be used to examine the size, solvent accessibility, and topography of proteins [LLV18] [LZG20].

We can have computational methods that aid experimental technique intending to elucidate protein structures [SL20] [LWL$^+$20]. Software packages can be used to combine data with advanced structure sampling and scoring techniques. Computational tools for protein structure modeling, include the Rosetta software suite [LWL$^+$20] [ALFJ$^+$17], I-TASSER [YYR$^+$15], Phyre2 [KMY$^+$15], Integrative Modeling Platform [RLW$^+$12], HADDOCK [DBB03], and MODELLER [EWMR$^+$06] [BL22].

Large Scale Gene Expression

Genome DNA microarray experiments produce large amount of data can be computationaly heavy on where methods can yield alternative conclusions from inceasing the computational effort.

The goal of these experiments is to determine biological or functional meaning from the lists of genes, either by:

1. Identify critical genes that are responsible for a biological effect.
2. Find patterns within the genes that point to an underlying biological process.

[Zve08]

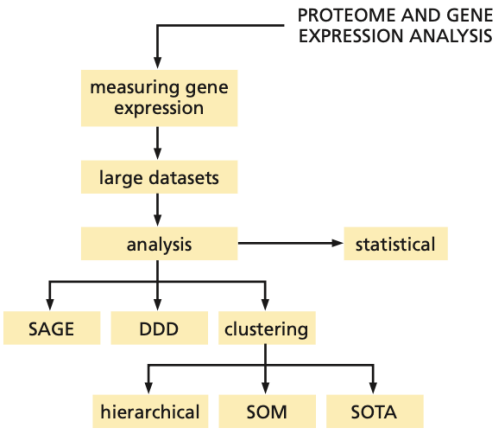
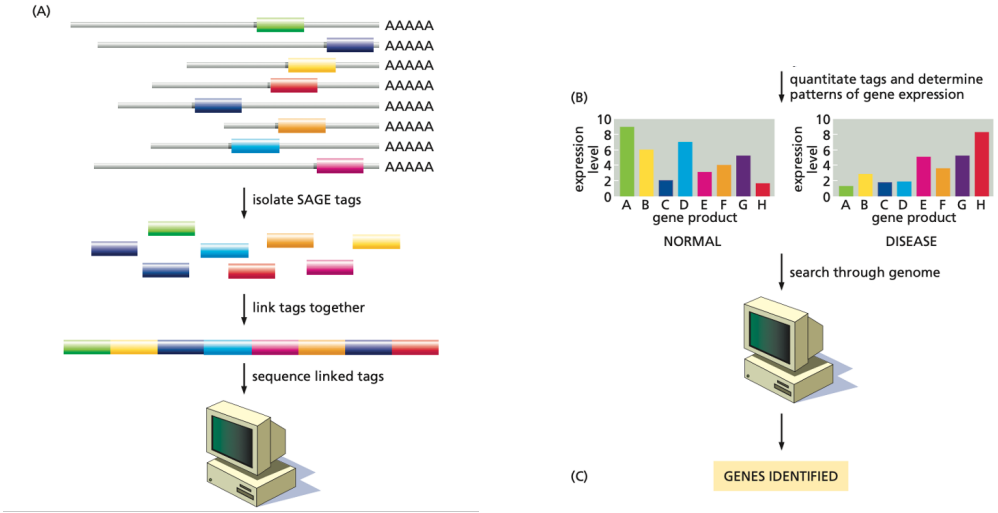


Figure 2: Describing Common experimental aspects of gene expression and of the analysis of the resulting data [Zve08].

Serial analysis of gene expression

Serial analysis of gene expression is the alternative compared to microarrays when trying to investigate patterns of gene expression.



(a) (b)

Figure 3: *An outline of the SAGE method for comparing levels of gene expression. (A) Short sequence tags. The sequence tags are isolated and are linked together to produce long DNA molecules that can be cloned and sequenced. (B) Once sequenced, each tag can be calculated, resulting in a value that gives the expression level of the corresponding transcript [Zve08].*

A short sequence contains enough information to uniquely identify a gene. The sequence tags from the total cellular RNA can be linked together to form long DNA molecules. The total number of times a particular tag is observed the concatemers approximates the expression level of the corresponding gene. The data produced by SAGE include a list of the tags with their corresponding counts, providing a digital output of cellular gene expression. Which allows the user to specify which organ is to be investigated. Libraries consisting of gene lists organized by the various types of tissues or cell lines are provided for further choice. The output from SAGE provides the SAGE tag, the UniGene ID, the gene description, and color and letter-coded differences in expression levels [Zve08].

Clustered gene expression data

Clustered pattern data obtained from gene expression microarrays/genome bioinformatics can be used as a tool to identify new transcription factors or other cell-regulatory proteins.

The clustered genes/proteins can be analyzed. Leading to a vast collection of data from many gene/protein expression experiments being available on the Web [Zve08].

Large Scale Protein Expression

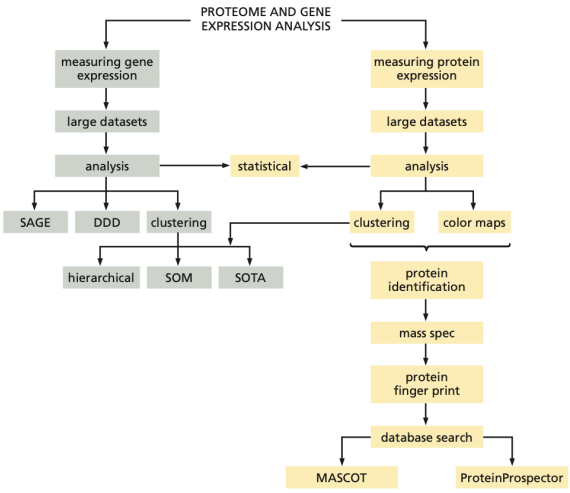


Figure 4: Describing some experimental aspects of protein expression and of the analysis of the resulting data. [Zve08].

For functional protein, mRNAs need to be translated, whilst the protein products can change which influence their function. For this reason we can measure and anlayse different proteins.

There is more proteins than there are genes in a genome. Transcripts can be spliced in various ways to give different mRNAs, providing different protein products, from the same gene. However, proteins that can be modified after translation giving more different protien products.

Protien expressions can vary in a organism depending on the origin and it will also differ between the separate stages of an organism's life cycle and under different environmental conditions [Zve08].

Definition 2.3 (proteome) *The proteome refers to all the proteins that make up an organism at a specific point in time and under specific conditions.*

RNAseq

The transcriptome is important for revealing the molecular constituents of cells and tissues, interpreting the functional aspects of the genome, also for understanding development and disease [WGS09].

Many methods deduce and quantify the transcriptome, including hybridization or sequence-based approaches. For example, hybridization-based approaches involve incubating fluores-

cently labeled cDNA with microarrays or commercial high-density oligo microarrays [WGS09].

However, these methods have several limitations, such as:

- Dreliance upon existing knowledge about genome sequence.
- Limited dynamic range of detection owing to both background.
- High background levels owing to cross-hybridization [OM06] [RRG07].
- saturation of signals.

Definition 2.4 (transcriptome) *The transcriptome is the complete set of transcripts in a cell, and their quantity, for a specific developmental stage or physiological condition.*

Sequence-based approaches directly determine the cDNA sequence such as Tag-based methods which include SAGE, CAGE [KKN+06], MPSS [RBL+02].

Each approach is high throughput and can provide precise, gene expression levels. However, a significant portion of the short tags can not be uniquely mapped to the reference genome [WGS09].

RNA-Seq RNA sequencing has clear advantages over existing approaches it uses deep sequencing technologies where a population of RNA is converted to a library of cDNA fragments with adaptors attached to one or both ends. Each molecule is then sequenced in a high-throughput manner to obtain short sequences from one or both ends [WGS09].

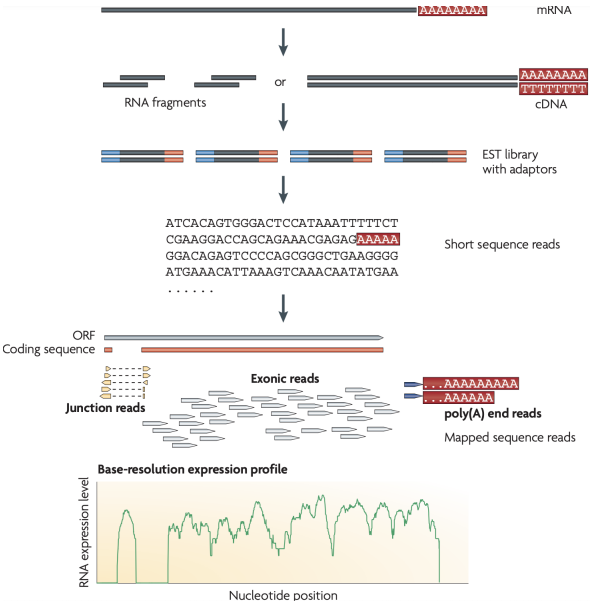


Figure 5: A typical RnA-seq experiment. RNAs are first converted into a library of cDNA fragments through either RNA fragmentation or DNA fragmentation. Sequencing adaptors are subsequently added to each cDNA fragment and a short sequence is obtained from each cDNA using high-throughput sequencing technology. The resulting sequence reads are aligned with the reference genome or transcriptome.

Bioinformatic Difficulties with Predictions on Proteins

It is difficult to define the precise ends of the helices(The secondary structure of proteins is made up of a-helices and b-strands) for structures found in globular proteins that are

not perfectly regular. Making it one step more difficult when trying to predict these structures [Zve08].

To Note:

- Several different types of b-sheet are found in protein structures.
- Turns, hairpins, and loops connect helices and strands.
- Any chain between two regular structures is referred to as a loop.
- Mostly a loop will contain a turn (or even several).

In antibody recognition, immunoglobulins employ loops at the edge of a b-sheet. All immunoglobulin structures with the same overall chain fold, but it is the difference at these loops that results in different results. Loops take up one of a limited number of structures called canonical forms. This type of classification is another reason why trying to predict both the structure and function of the protein is difficult [Zve08].

Definition 2.5 (Immunoglobulin) *Immunoglobulins are heterodimeric proteins composed of two heavy and two light chains. Types of white blood cells that helps the body fight infection [SC10].*

NOTE: Need to read and re write and move to before we talk about alphafold

Alpha Fold

AlphaFolds' goal is to predict the 3D coordinates of all heavy atoms for a given protein using the primary amino acid sequence and aligned sequences of homologues as inputs [JEP+21].

Mutations in proteins can lead to misfolding which is often associated with disease states, for example, Alzheimer's and Parkinson's which is one of the challenges for alphaFold [Fel].

The output is a file containing the 3D coordinates for every non-hydrogen atom in the protein. whilst showing the confidence levels for every amino acid residue, providing the reliability of the predicted structure [Fel].

Bioinformatics with Alpha Fold

In July 2021, AlphaFold was developed by DeepMind and was made available to the public [TAW+21].

Where it tries to solve the issue of invariant protein structures that are under translations and rotations [BP03].

AlphaFold is trained on protein chains from the PDB using the input sequence to query databases of protein sequences to generate a multiple sequence alignment [JEP+21]. Although we still do not exactly know how a protein sequence folds and alpha fold do not help in figuring this out its impact will likely be in accelerating and improving the production of new medications [NZLJ22].

AlphaFold 2

The CASP14 was recently held which is a blind trial that critically assesses techniques for protein structure prediction [DITS22], AlphaFold2 was entered and out-performed all competitors.

Recently, RoseTTAFold was developed, trying to implement similar principles. Since then, other end-to-end structure predictors have emerged using different principles such as fast multiple sequence alignment processing in DMPFold218 and language model representations.[BPE22].

We use the root mean square deviation, to calculate the similarity between the two structures, AlphaFold models had an accuracy of 0.96 compared to 2.80 which was the second-best score. AlphaFold models also had a high level of accuracy in predicting the position of residue side chains when the protein backbone prediction was accurate [DITS22] [JEP$^+$21].

2.3 The Protein Data Bank and the File Formats

Protein Data Bank

The Protein Data Bank was established at Brookhaven National Laboratories [BKW$^+$77] in 1971 as an archive for biological macromolecular crystal structures [BWF$^+$00].

Definition 2.6 (Macromolecular) *Macromolecular is any very large molecule, usually with a diameter ranging from about 100 to 10,000 angstroms*

It is an information source for data retrieved from atomic structures, crystallography, and three-dimensional structures of biomolecules, including nucleic acids and proteins [BG21].

At the time this was the first open-access digital data resource in biology which started with just seven protein structures [BBB$^+$22b].

Various groups such as the Protein Data Bank in Europe, Protein Data Bank Japan help manage the Protein Data Bank archive. Current wwPDB members also include the ElectronMicroscopy Data Bank and the Biological Magnetic Resonance Bank [BBB$^+$22b].

Protein Data Bank China has recently joined the wwPDB as an Associate Member with its role as wwPDBdesignated PDB Archive Keeper. Where they are responsible for weekly updates of the archive and safeguarding both digital information and a physical archive of correspondence [BBB$^+$22a].

The management of PDB must comply with FAIR (the acronym depicts: Findable, Accessible, Interoperable, Reusable) and FACT [vdABH17] guiding principles for scientific data [WDA$^+$16] [WSHB20].

Aims and Objectives of PDB

Enzymology, electron microscopy, computational chemistry small molecule crystallography, biochemistry, biophysics, macromolecular crystallography and nuclear magnetic resonance spectrometry all help the aims and goals of the PDB archive [BG21].

The FAIR Guiding Principles	
To be Findable:	F1. (meta)data are assigned a globally unique and persistent identifier F2. data are described with rich metadata (defined by R1 below) F3. metadata clearly and explicitly include the identifier of the data it describes F4. (meta)data are registered or indexed in a searchable resource
To be Accessible:	A1. (meta)data are retrievable by their identifier using a standardized communications protoco A1.1 the protocol is open, free, and universally implementable A1.2 the protocol allows for an authentication and authorization procedure, where necessary A2. metadata are accessible, even when the data are no longer available
To be Interoperable:	I1. (meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation. I2. (meta)data use vocabularies that follow FAIR principles I3. (meta)data include qualified references to other (meta)data
To be Reusable:	R1. meta(data) are richly described with a plurality of accurate and relevant attributes R1.1. (meta)data are released with a clear and accessible data usage license R1.2. (meta)data are associated with detailed provenance R1.3. (meta)data meet domain-relevant community standards

Table 2: The guidlines to what builds up the FAIR principles [WDA+16]

Definition 2.7 (Enzymology) *Enzymology is the branch of biochemistry aiming to understand how enzymes work*

Definition 2.8 (Electron Microscopy) *Electron microscopy is a technique for obtaining high resolution images of biological and non-biological specimens.*

PDBs provide open access to nearly 200 000 archived, validated, and biocurated experimentally determined three-dimensional structures of biological macromolecules.3D structures archived in the PDB have enabled important scientific breakthroughs by basic and applied researchers [Bur21]. Open access to PDB data without restrictions on usage has also aided structural bioinformatics in areas such as computational biology.

Recent Project

A project was undertaken to change the information management services for RCSB.org. The idea was to have developed a primary place for studying 3D biostructures by extending RCSB.org web portal functionality to support parallel delivery of more than one million CSMs publicly available from AlphaFold DB and ModelArchive together [BBB+22a].

Covid

During the COVID-19 pandemic, more than 2000 structures associated with the agent of the coronavirus disease were released and have become accessible to global users for free. The properties of these structures give us this opportunity to find out the ligand binding sites, the spatial conformation of ligands, protein-to-protein interactions, and amino acid substitutions regarding different viral proteins. Moreover, chemical, functional and energetic characteristics can also be gained to describe the potential capabilities of each molecule. These properties might aid us to determine the potential drug targets for drug design and vaccine preparation [LZD+20].

PDB Currently

As of 2022, the PDB has a vast number of 3D biostructures, eukaryotic protein structures exceeded 105 000. Bacterial protein structures were also numerous, totaling nearly 66 000. Archaeal protein structures were the least numerous totaling 5500. However the PDB coverage is decidedly limited, with mouse protein structures being most numerous at 8000 structures [BB21].

We have powerful tools developed by RCSB PDB for searching and analysis which include structure, sequence, sequence motif, structure motif, and visualization [BBB+22a].

Upon reaching the RCSB.org home page, users can query, organize, visualize, analyse, compare, and explore PDB structures and CSMs side-by-side. Searching 3D structure information can encompass PDB structures and CSMs or be limited to PDB structures only. Either PDB structures or CSMs can be excluded from the search results. The two types of structure information accessible via RCSB.org are clearly distinguished from each other. Top bar searching and data delivery for PDB structures and CSMs [BBB+22a].

Figure 6: Search options at RCSB.org include Top Bar or Basic Search; Advanced Search; and Browse Annotations [BBB+22a].

Figure 7: *Top Bar or Basic Search options available from every RCSB.org web page. Examples of searching for 3D structures using (A) simple text string insulin receptor; (B) drop down autosuggestions based on the text string insulin receptor; (C) Boolean operators to combine insulin + receptor (+ = AND); or (D) an amino acid sequence. (E) Searching RCSB.org documentation using a text string biological assembly [BBB+22a]*

Recent RCSB PDB data architecture improvements

In 2020, RCSB PDB had an upgrade of its delivery architecture [RDL+21]at RCSB.org [BBB+21].

The legacy monolithic data delivery application was changed into a distributed deployment of individual microservices, each with a single responsibility.

Data access services provide both Representational State Transfer and GraphQL API access to a data warehouse hosted in a MongoDB documentoriented database. Originally, advanced Search QueryBuilder functionality encompassed text, PDB data attributes, 3D structure, sequence, biopolymer sequence motif, and chemical similarity. Every search function is implemented as an independent service.

A separate search service is responsible for launching each search function, combining and delivering their integrated results to public programmatic search APIs. When each service has a single responsibility, we have greater flexibility in scaling the deployment of services in response to changes in user load and significant reductions in the time required to develop, test, and deploy new features. The Sequence Motif search function has been extended with a new 3D Structure Motifsearch capability [BBR20].

Recent advances in RCSB PDB data integration

RCSB PDB integrates the content of each expertly biocurated Entry with information from more than 50 external data resources.

Integrated external data needs to follow a data schema that defines the organization of the RCSB PDB data warehouse. Finally, it is available to RCSB PDB front-end services, public data access APIs, and our text search indexing service [BBB+22b].

Recent PDBx/mmCIF data standard improvements

The PDBx/mmCIF data standard is maintained by the wwPDB organization in collaboration with wwPDBPDBx/mmCIF Working Group domain experts recruited from the scientific community. The PDBx/mmCIF web resource supports browse and search access to standard terminology. The Working Group includes developers for many of the widely used structure determination software systems, who ensure that data produced by these programs comply with the PDBx/mmCIF data standard, generating complete and correct data files for PDB deposition. The wwPDB and the Working Group collaborate on developing terminologies for new and rapidly evolving methodologies such as Free Electron Laser, 3DEM, Serial Crystallography, and X-ray, whilst improving representations for existing data content. Most recently, the Working Group has focused on modernizing content descriptions for processed X-ray diffraction data, including extensions describing anisotropic diffraction limits, unmerged reflection data, and new quality metrics of anomalous diffraction data. Deposition and delivery improve our ability to assess experimental data quality, and every PDB data consumer's ability to Find and Reuse relevant PDB Entries [BBB+22b].

External Resources	
AlphaFold DB	Computed Structure Models by AlphaFold2
ATC	Anatomical Therapeutic Chemical (ATC) Classification System from World Health Organization
Binding MOAD	Binding affinities
Binding DB	Binding affinities
BMRB	BMRB-to-PDB mappings
Cambridge structural Database	Crystallographic small molecule data from the Cambridge Crystallographic Data Centre
CATH	Protein structure classification- Class, Architecture, Topology/fold, and Homologous superfamily
ChEMBL	Manually curated database of bioactive molecules with drug-like properties
CSD	Cambridge Structural Database: Validated and curated small-molecule organic and metal-organic crystal structures from the Cambridge Crystallographic Data Centre
DrugBank	Drug and drug target data
ECOD	Evolutionary Classification of Protein Domains
EMDB	3DEM density maps and associated metadata
ExplorEnz	IUBMB Enzyme nomenclature and classification
Gencode	Human and Mouse Gene annotations

Table 3: Some of the External Resources Integrated Into RCSB PDB

Future and struggles of PDB

Future

As the PDB archive has started its 52nd year, it gives open access to analyses of structures and much more to: basic and applied researchers, educators, and students spanning fundamental biology, biomedicine, bioenergy, bioengineering, and biotechnology, with key points that help many communities that use this facility. Firstly It delivers Data In and Data Out services efficiently to a user base that is now numbering many millions worldwide. Secondly, it has wwPDB partners that process, validate, and biocurate the growing number of increasingly complex PDB depositions received. Manages and safeguards the growing PDB archive in its role as wwPDB designated Archive Keeper. Thirdly it enables searching, visualization, exploration, and analysis of experimentally-determined PDB structures integrated with more

than one million CSMs through its web portal. [BBB+22a].

Struggles

Even after all the advancments PDB has gone through there are still additional challenges lying ahead which include:

- Rapid growth in public-domain CSMs of individual polypeptide chains, already numbering ¿200 million at the time of writing.
- Anticipated advances in AI/ML-based prediction of structures of multi-protein complexes.
- Continued development of biomolecular structure determination methods using X-ray Free Electron Lasers, revealing the microscopic details of chemical reactions in real time.
- Growth in the number and complexity of atomic-level cryoelectrontomography structures of macromolecular machines.
- Integration of PDB structures and CSMs with complementary information coming from correlative light microscopy and related imaging methods across length scales ranging from atoms to small molecules to individual biomolecules to macromolecular assemblies to organelles to cells and ultimately tissues
- Merging of the PDB-Dev prototype archiving system for integrative methods structures with the PDB archive
- Federating other biodata resources, such as the SmallAngle Scattering Database and the Proteomics Identification Database, with the PDB, EMDB and BMRB core archives jointly managed by the wwPDB partnership

[BBB+22a].

File Formats

The PDB archive holds a few different types of file types that hold data such as atomic coordinates and other information describing proteins and other biological macromolecules. Depending on what the data is created from it can fall into a different category.

PDB Data

The main information in the PDB archive is coordinate files for biological molecules. These files list the atoms in each protein and their 3D coordinates.

These files are available in several formats:

- PDB
- mmCIF

- XML

The header section of the text summarizes the protein, citation information, and the details of the structure solution, which is then followed by the sequence and a long list of the atoms and their coordinates. It also contains the experimental observations used to determine atomic coordinates [Goo].

.pdb Files

The PB format consists of a collection of records that describe the atomic coordinates, chemical and biochemical features, and experimental details of the structure determination [WF03].

Each item of data in the PDB format is assigned to a one of PDB record types (HEADER. SOURCE. REMARK, etc.). The ATOM records the atomic coordinate data [WF03].

PDB format has been extended with new REMARK records. For example, REMARK 3 that encodes refinement information has been modified and extended for each new refinement program and program version [WF03].

The PB format uses fixed-width fields to represent data, so we have limits on the size of certain items of data. For example, we cant have more then 99,999 atoms and polymer chain can be only one character. This means some structures are devided into multiple files [WF03].

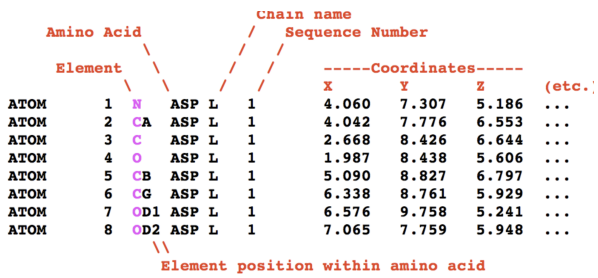


Figure 8: Showing contents of a PDB file for the Atom values [AAB+19].

.mmCIF Files

Mmcif is a dictionary-based approach to data extracted from crystallographic experiments [WF03].

It includes all the data we can find in a pdb file. Also, we have sufficient data names so that the experimental section of a structure paper can be written automatically and to facilitate the development of tools i.e. computer programs could easily access and validate mmCIF data files [WF03].

.xml

XML builds from a PDB Exchange dictionary. Although presented in very different syntaxes, the PDB Exchange and XML representations use the same logical data organization. [WIN+05].

The dictionary data block is mapped to the standard top-level XML schema element, and the data file data block is mapped to a datablock element. Category or table definitions in the Exchange dictionary are described as XML complex types. The category definition. [WIN+05].

PDB Exchange data dictionary attributes	XML schema mapping
Data block	Root level *schema element*
Category groups	
Categories	*complexTypes*
Definition	*annotation* and *documentation* elements
Examples	*annotation* and *documentation* elements
Primary keys	*attributes* of the data category
Items	*elements* of the data category
Definition	*annotation* and *documentation* elements
Examples	annotation and documentation elements
Data types	*simpleTypes*
Range restrictions and allowed values	*restrictions* within *simpleTypes* or *unions* of *simpleTypes*
Mandatory data code	Element attributes *minOccurs* and *nillable*
Parent-child relationships	*key/keyref* elements
Interdependency/exclusivity	
Units of measurement	Additional *fixed attributes*
Subcategory membership	

Figure 9: Summary of the correspondences between PDB Exchange data dictionary and XML schema metadata [WIN+05].

Visualizing Structures

PDB files can be viewed from text editors but we can also use a browsing or visualization program. RCSB PDB allows you to search and explore the information, including information on experimental methods and the chemistry and biology of the protein. Visualization programs allow to read of the PDB file and, display the protein structure generating custom pictures of it. These programs can contain analysis tools that allow you to measure distances and bond angles, and identify interesting structural features [Goo].

Reading Coordinate Files

Before exploring structures in the PDB archive we need some prior understanding of the coordinate files. For example, we can find a diverse mixture of biological molecules, small molecules, ions, and water which can get confusing we can use the names and chain IDs to help sort these out. In structures determined from crystallography, atoms are annotated with temperature factors that describe their vibration and occupancies that show if they are seen in several conformations. NMR structures often include several different models of the molecule [Goo].

Potential Challanges

There are some things to note as you could fall into some challenges when browsing through the PDB archive. Many structures, particularly those determined by crystallography, only include information about part of the functional biological assembly. One thing to note is that the PDB can aid with this. Another note is many PDB entries are missing portions of the molecule that were not observed in the experiment. These include structures that include only alpha carbon positions, structures with missing loops, structures of individual domains, or subunits from a larger molecule. In addition, most of the crystallographic structure entries do not have information on hydrogen atoms [Goo].

2.4 Hadoop spark and pyspark

What is Hadoop

Hadoop is an open-source framework for writing and running distributed applications that process large amounts of data. Key aspects making it valuable such 1. Accessible 2.Robust 3. Scalable 4.simple [Lam10].

HDFS is used in haddop which is a filessystem and a MapReduce engine. With one master node and many worker nodes. The master node provides instructions to the worker nodes and computations are performed on the worker nodes. [HRJ17].

Mapper

Input key/value pairs are mapped to a set of key/value pairs. The mapper then sorts the key-value pairs by the keys. Partitioners are mainly responsible for providing intermediate key/values to the reducers [PBN12] [HRJ17].

Reducer

Firstly, the reducer combines data having the same key from different map functions. The values having the same key are reduced to a smaller set of values and output is produced [HRJ17].

What is Spark

Apache Spark is a popular open-source platform for large-scale data processing used for iterative machine learning tasks [MBY+16].

Spark is a cluster computing system providing APIs in Java, Scala, Python (pySpark), and R, along with an optimized engine that supports general execution graphs. Moreover, Spark is efficient at iterative computations so it is suited for the development of large-scale machine learning applications [MBY+16].

Spark is a quick and general engine used for analysing large-scale data stored across a cluster of computers. Spark uses in-memory cluster computing which is its most important feature for increasing the processing speed of an application. It combines SQL streaming and complex analytics [HRJ17].

Spark Architecture

There are five core components that make Spark so powerful and easy to use. The core architecture of Spark consists of the following layers:

- Storage
- Resource management
- Engine

- Ecosystem
- APIs

[Sin22].

Storage

Before using Spark, data must be made available in order to process it. This data can reside in any kind of database. Spark offers multiple options to use different categories of data sources, to be able to process it on a large scale. Spark allows you to use traditional relational databases as well as NoSQL, such as Cassandra and MongoDB [Sin22].

Resource Management

The next layer consists of a resource manager. As Spark works on a set of machines (it also can work on a single machine with multiple cores), it is known as a Spark cluster. Typically, there is a resource manager in any cluster that efficiently handles the workload between these resources. The two most widely used resource managers are YARN and Mesos. The resource manager has two main components internally [Sin22]:

- Cluster manager
- Worker

It's kind of like master-slave architecture, in which the cluster manager acts as a master node, and the worker acts as a slave node in the cluster. The cluster manager keeps track of all information pertaining to the worker nodes and their current status. Cluster managers always maintain the following information [Sin22]:

- Status of worker node (busy/available)
- Location of worker node
- Memory of worker node
- Total CPU cores of worker node

The main role of the cluster manager is to manage the worker nodes and assign them tasks, based on the availability and capacity of the worker node. On the other hand, a worker node is only responsible for executing the task it's given by the cluster manager [Sin22].

The tasks that are given to the worker nodes are generally the individual pieces of the overall Spark application. The Spark application contains two parts [Sin22]:

- Task
- Spark driver

The task is the data processing logic that has been written in either PySpark or Spark R code. It can be as simple as taking a total frequency count of words to a very complex set of instructions on an unstructured dataset. The second component is Spark driver, the main controller of a Spark application, which consistently interacts with a cluster manager to find out which worker nodes can be used to execute the request. The role of the Spark driver is to request the cluster manager to initiate the Spark executor for every worker node [Sin22].

Engine and Ecosystem

The base of the Spark architecture is its core, which is built on top of RDDs (Resilient Distributed Datasets) and offers multiple APIs for building other libraries and ecosystems by Spark contributors. It contains two parts: the distributed computing infrastructure and the RDD programming abstraction. The default libraries in the Spark toolkit come as four different offerings [Sin22].

Spark SQL

SQL being used by most of the ETL operators across the globe makes it a logical choice to be part of Spark offerings. It allows Spark users to perform structured data processing by running SQL queries. In actuality, Spark SQL leverages the catalyst optimizer to perform the optimizations during the execution of SQL queries. Another advantage of using Spark SQL is that it can easily deal with multiple database files and storage systems such as SQL, NoSQL, Parquet, etc [Sin22].

MLlib

Training machine learning models on big datasets was starting to become a huge challenge, until Spark's MLlib (Machine Learning library) came into existence. MLlib gives you the ability to train machine learning models on huge datasets, using Spark clusters. It allows you to build in supervised, unsupervised, and recommender systems; NLP-based models; and deep learning, as well as within the Spark ML library [Sin22].

Structured Streaming

The Spark Streaming library provides the functionality to read and process real-time streaming data. The incoming data can be batch data or near real-time data from different sources. Structured Streaming is capable of ingesting real-time data from such sources as Flume, Kafka, Twitter, etc [Sin22].

Graph X

This is a library that sits on top of the Spark core and allows users to process specific types of data (graph dataframes), which consists of nodes and edges. A typical graph is used to model the relationship between the different objects involved. The nodes represent the object, and the edge between the nodes represents the relationship between them. Graph dataframes are mainly used in network analysis, and Graph X makes it possible to have distributed processing of such graph dataframes [Sin22].

Programming Language APIs

Spark is available in four languages. Because Spark is built using Scala, that becomes the native language. Apart from Scala, we can also use Python, Java, and R [Sin22].

Spark Execution

Any Spark application spins off a single driver process (that can contain multiple jobs) on the master node that then directs executor processes (that contain multiple tasks) distributed to a number of worker nodes shown 10.

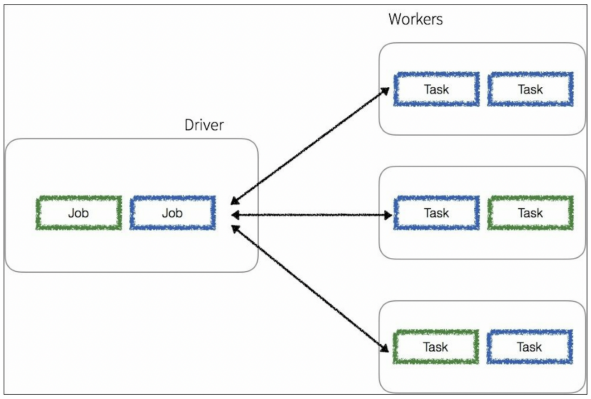


Figure 10: Think of somthing to say [DL17].

The driver process determines the number and the composition of the task processes directed to the executor nodes based on the graph generated for the given job. Note, that any worker node can execute tasks from a number of different jobs [DL17].

Spark vs Hadoop

Summarising the results shows Spark to be quicker in both experiments. Spark also provides an API for python which will be very helpful in this project seeing its easy nature to be able to read files and work with text-based files. Therefore I have decided to work with Pyspark for this project.

Software Architectural Bottlenecks

HDFS has scheduling delays in the architecture which results in cluster nodes waiting for new tasks as the access pattern is periodic.HDFS client code, serializes computation and I/O instead of decoupling and pipelining those operations. [SRC10].

Definition 2.9 (HDFS) *The Hadoop Distributed File System (HDFS) is a distributed file system designed to run on commodity hardware*

Portability Limitations

Some performance-enhancing features in the filesystem are not available such as bypassing the filesystem page cache and transferring data directly from the disk into user buffers.

Hadoop Map Reduce	Spark
For Applications that repeatedly reuse the same set of data, map reduce is very inefficient.	Spark uses in-memory processing, reusing it for faster computation.
MapReduce is quite faster in batch processing.	As memory size is limited, it would be quite slower in batch processing of huge data set.
Data is stored in disk for processing.	Data is stored in main memory. As it is an inmemory computation engine entire data is copied.
Difficulty in processing and modifying data in real time due to its high latency.	Used to process and modify data in real time due to its low latency.
Predominantly used to process from bygone datasets.	Predominantly used for streaming, batch processing and machine learning
For fault tolerance, MapReduce uses replication.	For fault tolerance, Spark uses RDDs.
It merges and partitions shuffle files.	It does not merges and partition shuffle files.
Primarily disk based computation.	Primarily RAM based computation.

Table 4: Showing the differences between haddop and spark [HRJ17].

Number of words	Hadoop (Sec)	Spark(Sec)
100	79	28.841
1000	91	31.185
10000	96	35.181
100000	103	36.969
1000000	116	39.569

Table 5: Comparision of Execution time for wordcount program [HRJ17].

Thus, HDFS implementation runs less efficiently and has higher processor usage than would otherwise be necessary [SRC10].

2.5 Analysis of existing systems that solve similar tasks

There are a few systems that solve similar tasts these include:

Number of words	Hadoop (Sec)	Spark(Sec)
5	2.541	0.9030
10	3.370	1.459
50	6.420	2.840
100	9.383	3.452
200	10.100	5.749

Table 6: Comparison of Execution time for logistic regression program [HRJ17].

- SparkMD: This is a Spark-based framework for molecular dynamics simulations. It uses a distributed version of the GROMACS simulation engine to enable large-scale simulations of protein systems.
- BioSpark: This is a Spark-based framework for processing and analyzing large-scale genomics and proteomics datasets. It provides a set of APIs for analyzing DNA sequences, protein structures, and other biological data.
- Pysparkling: This is a Python-based library for parallelizing computations using Spark. It can be used for a range of bioinformatics analyses, including sequence alignment, protein structure prediction, and gene expression analysis.
- SparkProt: This is a Spark-based framework for protein structure prediction. It uses a combination of machine learning algorithms and structural bioinformatics tools to predict the 3D structure of proteins from their amino acid sequences.
- DeepChem: This is a deep learning-based framework for drug discovery and development. It uses Spark to parallelize computations and can be used for a range of tasks, including protein-ligand docking, virtual screening, and compound synthesis planning.

3 Contents and Knowledge: 20 marks

3.1 Description of relevant theory

Structural Bioinformatics is a field of study that involves the development and application of computational methods to study the structure and function of biological macromolecules such as proteins, DNA, and RNA. The field relies on several theories and approaches, including mathematical, algorithmic, hardware, and software-oriented theories. In this context, your dissertation on a Structural Bioinformatics Framework using a MapReduce formalism should include a detailed description of relevant theories that underpin the computational methods and techniques used in your research.

Mathematical Theory

Mathematical theory plays a crucial role in Structural Bioinformatics by providing a solid foundation for the development of algorithms and models. The mathematical theory falls into three sections which are used to develop algorithms that analyze and interpret the structural and functional properties of biological macromolecules.

- Graph Theory
- Probability theory
- Linear algebra

Graph Theory

Graph theory is used to represent the three-dimensional structure of a protein as a network of nodes and edges,

Probability theory

Probability theory is used to predict the likelihood of a given amino acid sequence folding into a particular protein structure.

Linear algebra

Linear algebra provides powerful tools for analyzing these sets of points, such as calculating distances between atoms, determining the orientation and alignment of protein structures, and identifying similarities and differences between different protein structures.

One example of how linear algebra is used in structural bioinformatics is in the calculation of principal component analysis (PCA) of protein structures. PCA is a method of reducing the complexity of a protein structure by identifying the most significant features that contribute to its overall shape and structure. This involves computing the eigenvectors and eigenvalues of a matrix that represents the distribution of atoms in the protein structure, which can be done using linear algebra.

Another example is in the field of molecular dynamics simulations, where linear algebra is used to solve the differential equations that describe the motion of atoms in a protein structure over time. This allows researchers to simulate the behavior of proteins under different conditions and to predict how they will interact with other molecules.

Algorithmic Theory

Algorithmic theory is another important aspect of Structural Bioinformatics, which focuses on developing efficient algorithms for analyzing and interpreting large-scale biological data. The development of algorithms is critical to the success of Structural Bioinformatics since the analysis of large datasets is computationally intensive and requires specialized tools and techniques. For example, algorithms based on dynamic programming are used to compare protein sequences and identify conserved regions, while clustering algorithms are used to group similar protein structures.

Hardware theory

Hardware theory is also relevant in Structural Bioinformatics since the analysis of large biological datasets requires specialized hardware resources such as high-performance computing clusters and graphics processing units (GPUs). The use of specialized hardware resources allows for the efficient processing of large datasets, which is essential for the analysis of complex biological systems. For example, GPUs are used to accelerate molecular dynamics simulations, while high-performance computing clusters are used to analyze large-scale genomic and proteomic datasets.

Software Theory

Software theory is another critical aspect of Structural Bioinformatics, which focuses on the development of specialized software tools and frameworks for the analysis and interpretation of biological data. The use of specialized software tools and frameworks is essential to the success of Structural Bioinformatics since the analysis of large datasets requires sophisticated data processing and visualization tools. For example, software tools such as PyMOL and Chimera are used to visualize protein structures, while frameworks such as Hadoop and Spark are used to process large-scale genomic and proteomic datasets using a MapReduce formalism.

Note: In summary, your dissertation on a Structural Bioinformatics Framework using a MapReduce formalism should include a detailed description of the relevant theories that underpin the computational methods and techniques used in your research. Theories such as mathematical theory, algorithmic theory, hardware theory, and software theory are all critical to the success of Structural Bioinformatics and should be described in detail in your dissertation.

3.2 Development and Software Engineering

Adequate development and software engineering are critical components of any software project, and they are particularly important in the context of developing a structural bioinformatics framework using a MapReduce formalism. In this response, we will discuss the

key concepts of adequate development and software engineering and their relevance to this specific project.

Adequate development refers to the process of developing software in a way that meets the needs of its users and stakeholders. This includes developing software that is reliable, efficient, and maintainable, and that meets the requirements of its users. Adequate development also involves ensuring that the software is tested thoroughly and that it is secure.

Software engineering, on the other hand, refers to the systematic approach to developing software. This involves using engineering principles and best practices to design, develop, and maintain software. Software engineering encompasses a range of activities, including requirements analysis, design, coding, testing, and maintenance.

In the context of developing a structural bioinformatics framework using a MapReduce formalism, adequate development and software engineering are particularly important. This is because the development of such a framework involves complex algorithms and data structures, as well as large amounts of data. As a result, it is essential to ensure that the software is developed using best practices and that it is designed in a way that is scalable and efficient.

The following topics cover the adequate development and software engineering for my project:

- Requirements analysis
- Design
- Coding
- Testing
- Maintenance

Requirements analysis

It is essential to understand the requirements of the framework's users and stakeholders, including their needs for data processing, visualization, and analysis.

Design

The framework should be designed in a modular and scalable way, to allow for easy integration of new features and functionalities. The use of established design patterns and principles can help to ensure that the framework is maintainable and extensible.

Coding

The code should be written using best practices, such as using descriptive variable names, following a consistent coding style, and ensuring that the code is well-documented. Testing should be an integral part of the coding process, with both unit tests and integration tests used to ensure that the code works as intended.

Testing

The framework should be thoroughly tested, using both automated and manual testing methods. This can help to identify bugs and issues early in the development process, and ensure that the software is reliable and secure.

Maintenance

The software should be designed and developed with maintainability in mind, to ensure that it can be easily updated and improved over time.

In summary, adequate development and software engineering are critical components of developing a structural bioinformatics framework using a MapReduce formalism. By following best practices and using established engineering principles, developers can ensure that the software is reliable, efficient, and maintainable, and that it meets the needs of its users and stakeholders.

4 Technical decision making: 10 marks

4.1 Are important (technical) decisions well made and argued?

When it comes to technical decisions, it is crucial that they are well made and argued. This is especially true in the field of structural bioinformatics, where the accuracy and reliability of results are critical.

One of the key reasons why technical decisions need to be well made and argued is that they can have a significant impact on the outcome of a project. For example, if a decision is made to use a particular algorithm or method for analyzing data, this could affect the accuracy and speed of the results. If the decision is not based on solid reasoning and evidence, it could lead to incorrect conclusions and wasted time and resources.

Another reason why technical decisions need to be well made and argued is that they can have long-term implications. In the field of structural bioinformatics, for instance, decisions made about the design of a framework or software architecture can impact the development and use of the system for years to come. Therefore, it is essential that technical decisions are based on a thorough understanding of the problem, the available solutions, and the potential consequences of each decision.

In addition, well-made technical decisions can lead to greater collaboration and more effective communication among team members. When decisions are based on clear reasoning and evidence, team members can more easily understand and agree with the choices that are made. This can lead to greater trust and cooperation, which are essential for successful collaboration in any technical project.

Finally, well-made technical decisions can also lead to greater innovation and progress. When decisions are based on solid reasoning and evidence, they can open up new possibilities and solutions that were not previously considered. This can lead to breakthroughs and advancements in the field of structural bioinformatics and other technical fields.

In conclusion, technical decisions are crucial in the field of structural bioinformatics and other technical fields. It is essential that they are well made and argued, based on a thorough understanding of the problem, the available solutions, and the potential consequences of each decision. This can lead to greater accuracy, reliability, collaboration, innovation, and progress.

4.2 good design decisions, choice or development of algorithms

5 Critical analysis and discussion: 10 marks

5.1 A discussion of actual project achievements

A list of all the things achived in my project:

- PySpark
- Cluster Setup
- Key Value Pair
- TMalign
- API Post
- API Get
- Benchmarking

5.2 how successful the project was

The project was quite successful with me completing most to all project set objectives. Being able to search and download pdb files from the framework. The user is also able to call out two user executables on the pdbs they require. At the end of this project we have a software framework that suppots the Mapreduce formalism and can process large numbers of protein structures. Whilst being able to do so by parallelize protein structure analysis across multiple computing nodes. The framework is optimized to reduce the processing time required for protein structure analysis.

The framework has a interface that allows users to manipulate the pdbs that are being passed into the executable for protein structure analysis.

Finally the software framework is scalable and can handle increasingly large datasets and can be eaisly updated to keep pace with advancements in protein structure analysis techniques and computing technology.

5.3 Reflection on the project process

The project went according to plan by completing most to all the set out objectives however seting up the clusetr with correct rdd and key value pairs took much more time then expected. For this reason i didnt have enough time to create a good interface keeping at a bash level of interaction for the user. A readme has been created which helps the user understand the functions within the framework however a more user frienly user interface would be benifitial for eaxmple when running the functions that implement the api to search or download pdbs a better user interafce can be created that would be easier to use to be able to set up the pdb files the user would like to run the executables on to.

5.4 its difficulties, successes and future enhancements

5.5 conclusions or results analysed or discussed

6 Professional Issues: 10 marks

6.1 Should be a topic relevant to the project undertaken.

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