METADATA MANAGEMENT FOR CLINICAL DATA INTEGRATION

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METADATA MANAGEMENT FOR CLINICAL DATA INTEGRATION

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Engineering at the University of Kentucky

By

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Clinical data have been continuously collected and growing with the wide adoption of electronic health records (EHR). Clinical data have provided the foundation to facilitate state-of-art researches such as artificial intelligence in medicine. At the same time, it has become a challenge to integrate, access, and explore study-level patient data from large volumes of data from heterogeneous databases. Effective, fine-grained, cross-cohort data exploration, and semantically enabled approaches and systems are needed. To build semantically enabled systems, we need to leverage existing terminology systems and ontologies. Numerous ontologies have been developed recently and they play an important role in semantically enabled applications. Because they contain valuable codified knowledge, the management of these ontologies, as metadata, also requires systematic approaches. Moreover, in most clinical settings, patient data are collected with the help of a data dictionary. Knowledge of the relationships between an ontology and a related data dictionary is important for semantic interoperability. Such relationships are represented and maintained by mappings. Mappings store how data source elements and domain ontology concepts are linked, as well as how domain ontology concepts are linked between different ontologies. While mappings are crucial to the maintenance of relationships between an ontology and a related data dictionary, they are commonly captured by CSV files with limits capabilities for sharing, tracking, and visualization. The management of mappings requires an innovative, interactive, and collaborative approach.

Metadata management servers to organize data that describes other data. In computer science and information science, ontology is the metadata consisting of the representation, naming, and definition of the hierarchies, properties, and relations between concepts. A structural, scalable, and computer understandable way for metadata management is critical to developing systems with the fine-grained data exploration capabilities.

This dissertation presents a systematic approach called MetaSphere using metadata and ontologies to support the management and integration of clinical research data through our ontology-based metadata management system for multiple domains. MetaSphere is a general framework that aims to manage specific domain metadata,
provide fine-grained data exploration interface, and store patient data in data warehouses. Moreover, MetaSphere provides a dedicated mapping interface called Interactive Mapping Interface (IMI) to map the data dictionary to well-recognized and standardized ontologies. MetaSphere has been applied to three domains successfully, sleep domain (X-search), pressure ulcer injuries and deep tissue pressure (SCIPUDSphere), and cancer. Specifically, MetaSphere stores domain ontology structurally in databases. Patient data in the corresponding domains are also stored in databases as data warehouses. MetaSphere provides a powerful query interface to enable interaction between human and actual patient data. Query interface is a mechanism allowing researchers to compose complex queries to pinpoint specific cohort over a large amount of patient data.

The MetaSphere framework has been instantiated into three domains successfully and the detailed results are as below. X-search is publicly available at https://www.x-search.net with nine sleep domain datasets consisting of over 26,000 unique subjects. The canonical data dictionary contains over 900 common data elements across the datasets. X-search has received over 1800 cross-cohort queries by users from 16 countries. SCIPUDSphere has integrated a total number of 268,562 records containing 282 ICD9 codes related to pressure ulcer injuries among 36,626 individuals with spinal cord injuries. IMI is publicly available at http://epi-tome.com/. Using IMI, we have successfully mapped the North American Association of Central Cancer Registries (NAACCR) data dictionary to the National Cancer Institute Thesaurus (NCIt) concepts.

KEYWORDS: Metadata, Fine-grained, Query Interface, Ontology, Data Dictionary, Mapping
METADATA MANAGEMENT FOR CLINICAL DATA INTEGRATION

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CHAPTER 1. Introduction

1.1 Motivation and Challenges in Metadata Management for Clinical Data Integration

Patient data are growing at an explosive rate in the medical field with the wide adoption of electronic health records (EHR) [1]. Patient data cover patient demographics, diagnosis, laboratory tests, medications, images, and genome sequences. With a large amount of clinical data integrated, efficient data retrieval and exploration have become a challenging issue. Specific challenges include:

- Barriers between data exploration and research hypotheses. In a traditional clinical research workflow, research hypotheses come before patient data acquisition. If the research hypotheses and acquired patient data do not support the hypotheses, then the study design needs to be adjusted. A new and efficient data exploration tool is needed to accelerate the process. With such a tool, researchers can explore the data to provide preliminary evidence to their research hypotheses before the start of a clinical trial.

- The lack of fine-grained, cross-cohort query, and exploration interfaces and systems. Although many data repositories allow users to browse their content, few of them support fine-grained, cross-cohort query, and exploration at the study-subject level. To understand the challenge, we provide a review of the key concepts.

  - Fine-grained. A fine-grained query is a highly-customizable query with low granularity and high details.

  - Cross-cohort. A cohort study is a particular form of a longitudinal study that samples a cohort through time. A cross-cohort query means to query and fetch data from multiple cohort studies at the same time.
– **Study-subject.** The United States Department of Health and Human Services (HHS) defines a human study subject as a living individual about whom a research investigator obtains data through 1) intervention or interaction with the individual, or 2) identifiable private information [2].

Exploration at the study-subject level is the result of a fine-grained query.

To find a male patient with asthma under 50 years old, a typical SQL statement is:

```
SELECT * FROM patients WHERE gender = 0 AND asthma = 0 AND age < 50
```

From the perspective of end-users, an interface with SQL-like query capability can help their data exploration capability.

- Tools for building mappings between data dictionaries and ontologies are missing. In some clinical settings, patient data are collected with the help of a data dictionary. To integrate these patient data and build ontology enabled data query interfaces, mappings between multiple data dictionaries and ontology are critical. Traditionally, these mappings are built and maintained using the CSV files. CSV file is the abbreviation of the comma-separated values (CSV) file. CSV file is a delimited text file that uses a comma to separate values. Each line of the file is a data record. Each record consists of one or more fields, separated by commas. The use of the comma as a field separator is the source of the name for this file format. A CSV file typically stores tabular data (numbers and text) in plain text. Management and maintenance of these mappings become cumbersome and time-consuming when the mapping size increases. More importantly, it cannot be reused by other researchers. Such mappings are usually built and maintained by a group of researchers and domain experts, therefore an efficient tool for collaboration and result visualization is required.

There are other challenges such as storage challenges which will not be addressed in this dissertation. In some research areas, collected data are stored or archived
locally or externally using hard drives. Such data would suffer from hardware failure, data corruption with limited data sharing capability, and scalability.

This dissertation focuses on addressing these challenges to help facilitate hypothesis generation, data exploration, and provide a tool to build a mapping between data dictionary and ontologies.

The approach proposed in the dissertation has been applied to three different domains 1) sleep domain; 2) spinal cord injury; 3) cancer. We highlight the specific challenges and requirements in these three domain specifically.

1.1.1 From Raw Data to Metadata

Essentially, data can be categorized into three types:

- **Structured data.** Data that is easy to search and well-organized as it is contained in a fixed dimension and its elements can be mapped into fixed pre-defined fields. Examples of structured data include transactions, tables, records, logs, etc.

- **Unstructured data.** A bigger percentage of all the data is unstructured data. Unstructured data is data without fixed dimension nor well-defined meaning. Photos, video, audio files are unstructured data.

- **Semi-Structured data.** Semi-structured data is a mix of structured data and unstructured data. Semi-structured data is data without a fixed dimension but with some organizational properties such as metadata. Email messages, web pages are semi-structured data.

Even with such classifications, it is still not enough to describe data from the perspective of knowledge presentation. We need metadata that can capture the characteristics of instance data from a data source [3] possibly including the format and structure of the populated instance data, its organization, and its underlying conceptual context. Metadata is used in locating information, interpreting information, and
integrating/transforming data. Metadata can be characterized as the abstraction of other data and the abstraction is multi-level. Figure 1.1 shows a pyramid of multi-level metadata abstraction in biomedical fields. There are five levels of abstraction. From raw data to knowledge, there are four levels of abstraction. Each level of data describes its next level data. The expressivity of knowledge decreases from top to bottom.

![Figure 1.1: The pyramid of multi-level metadata abstractions. (Diagram taken from GQ Zhang’s presentation at Rice University Fall 2019 Data Science Symposium)](image)

- **Raw data.** Raw data, also known as primary data, is data collected from a source.

- **Data dictionaries.** A data dictionary is an extract of structured data elements and their metadata, taken from a given data model or data architecture scope.

- **Common data elements.** Common data elements (CDE) is a combination of a precisely defined question (variable) paired with a specified set of responses to the question that is common to multiple datasets or used across different studies. It can be common across a multi-site study or scientific research area.
• *Controlled vocabularies.* The controlled vocabularies is an alphabetical list of terms in a particular domain of knowledge with the definitions for those terms.

• *Ontologies.* An ontology is a formal naming and definitions of the types, properties, and interrelationships of the entities that fundamentally exist for a particular domain of discourse. An ontology compartmentalizes the variables needed for some set of computations and establishes the relationships between them. An ontology represents a set of knowledge for a particular domain.

1.1.2 Fine-grained Data Exploration of Heterogeneous Datasets

In clinical research, investigators tend to work independently or in clusters of research teams. Raw data collected from experiments or clinical trials are usually stored electronically on a computer. However, to perform independent analysis or verify experimental results, sharing data between different researchers or teams is necessary. Furthermore, sharing and reuse of data is important for facilitating scientific discovery and enhancing research reproducibility [4–7]. Multiple data repositories have been built and are accessible to researchers, such as GDC - the National Cancer Institute’s Genomic Data Commons [8], BioPortal - a repository of biomedical ontologies [9], OpenfMRI - a repository for sharing task-based fMRI data [10], and NSRR - the National Sleep Research Resource [11, 12]. These data repositories allow an investigator to browse and download data under certain restrictions. However, not many of them can enable users to conduct fine-grained, cross-dataset query, and explore of the study-subject level before users decide which dataset to gain further access. Study-subject level exploration can help researchers to quickly assess the feasibility of studies or verify the research hypothesis without requesting further access and avoid unnecessary data analysis. Researchers will be able to have a sense of the dataset without downloading the whole dataset.
1.1.3 Ontology-focused Metadata Discovery

Ontologies describe domain knowledge to explicitly representing the semantics of the metadata. Fine-grained query interfaces rely heavily on these formal ontologies that structure underlying metadata enabling comprehensive and transportable machine understanding [13]. There are many ontologies have been widely used, such as SNOMED CT [14]. However, there are domains which do not have well-established ontologies such as Pressure Injuries (PrI) and Deep Tissue Pressure Injury (DTPrI). PrI/DTPrI are serious and costly complications for many people with limited mobility, such as those with spinal cord injury (SCI), who remain at high risk throughout their lifetimes. Clinical observations and research have demonstrated staggering costs and human suffering [15–17] for PrI/DTPrI.

It has been estimated that PrI/DTPrI prevention is approximately 2.5 times more economical than treatment [18]. Clinical practice guidelines (CPG) provide best recommendations for PrI/DTPrI prevention [19–21]. However, the multitudes of recommendations in CPG reflect the multivariate nature and complexity of PrI/DTPrI management. In order to successfully prevent and treat PrI/DTPrI in the SCI population, it is essential to consider multiple risk factors because they contribute to the formulation of treatment and rehabilitation strategies [22]. The integration of PrI/DTPrI risk data, ranging from the living environment and age to tissue blood flow, requires a robust and scalable informatics approach to cope with data integration and exploration challenges. A comprehensive data repository for PrI/DTPrI that can provide fine-grained data exploration will be able to facilitate the researches on analyzing risk factors related to PrI/DTPrI and provide personalized prevention for individual patients.
1.1.4 Mappings among Data Dictionaries and Ontologies

Biomedical ontologies have gained a certain degree of intention in the past few years. As more and more domains mature, ontologies have been developed for these domains but part of these ontologies contain overlapping information. Knowledge of the relationships between ontologies is important in terms of interoperability among these ontologies and to promote ontology usage. Interoperability can be described as the capability to communicate, transfer information among several various systems. Otherwise, newly or individually created ontologies are within limited usage. The situation is also true for data dictionaries. Data dictionaries are created by different research groups and institutes. These data dictionaries are used for data collections. For instance, the Kentucky Cancer Registry (KCR) receives data about new cancer cases from all healthcare facilities and physicians in Kentucky within 4 months of diagnosis. These patient data are collected under the guidance of the North American Association of Central Cancer Registries (NAACCR) [23] data dictionaries. NAACCR is a collaborative umbrella organization for cancer registries. The NAACCR data standards and data dictionary provide detailed specifications and codes for each data item in the NAACCR data. Such a data dictionary is not hierarchical or standardized.

To enable an ontology powered system, we need a mapping from a data dictionary to an ontology. The National Cancer Institute Thesaurus [24] is a public domain description logic-based terminology produced by the National Cancer Institute. It is hierarchical and complex compared to most broad clinical vocabularies, with rich semantic interrelationships between the nodes of its taxonomies. The mapping between the NAACCR data dictionaries to NCIIt is needed in such a case.
1.2 Contributions

To overcome these gaps and challenges, we propose a general framework called MetaSphere. MetaSphere provides three major functionalities in terms of metadata management for clinical data integration. The first functionality is the structural, scalable, and computer understandable way of metadata storage. MetaSphere stores the ontology and its associated concepts, variables, and domains in a scalable database. Additionally, utilizing the database’s associations between tables, MetaSphere can represent the relationships between concepts, the relationships between concepts and variables, the relationships between variables and domains properly.

The second functionality is the fine-grained, cross-cohort query interface. MetaSphere hierarchically organizes ontology and its concepts and reflects such hierarchies in the interface. With direct interaction, users will be able to browse the ontology’s structures easily. Utilizing the query interface, users can compose complex queries to query and explore data at the study-subject level.

Finally, MetaSphere provides an interactive, intuitive, and collaborative mapping interface for building mapping between data dictionary to ontology, so as to facilitate data analytics through interoperability and integration and provide semantic access across aggregated data used in knowledge-based applications and services.

Our contributions are:

- We created a general framework which can apply to different domains to facilitate the data exploration and remove the barriers standing between researches hypothesis and data access.

- We created an informatics platform, that enables data extraction, integration, storage, and analysis to provide clinical decision support and user interfaces direct access to well-annotated and deidentified wide range PrI risk factors of data.
• We created a dedicated Spinal Cord Injury Pressure Ulcer and Deep tissue injury ontology (SCIPUDO) as the knowledge resource for processing specialized terms related to spinal cord injury and pressure ulcer; 4) we created an interactive and collaborative mapping interface aiming at connecting data dictionaries to ontologies.

1.3 Organization of the Dissertation

This dissertation is organized as follows:

1. Chapter 2 reviews the background knowledge and information about this dissertation;

2. Chapter 3 focuses on the design, methodology, and implementation of MetaSphere;

3. In Chapter 4 we go over the usage of MetaSphere for sleep domain, which is the National Sleep Research Resource (NSRR) and discusses the limitation of the traditional relational database in a high dimensional dataset. Besides, we compare the query performance of traditional relational database and NoSQL database;

4. Chapter 5 we present a NoSQL based MetaSphere applying in pressure ulcer domain with detail statistical result of query result;

5. Chapter 6 discusses the feature-rich web-based interactive mapping interface and the detailed mapping pipeline for building mappings from a data dictionary to an ontology. Moreover, we will present an algorithm for constructing the hierarchical structure from the source ontology.

6. Chapter 7 we conclude the work of this dissertation and discuss the future work we can do to improve MetaSphere.
CHAPTER 2. Background

2.1 FAIR Data Principles

The FAIR Data Principles propose that making data Findable, Accessible, Interoperable, and Reusable [7] is a widely recognized set of guiding principles for biomedical data management. The FAIR principles are essential for researchers to find the data of interest, which may be further reused for generating or testing hypotheses. We follow the FAIR Data Principles as our management guidelines while building our data repositories and systems.

- Findable. Finding data is the first step to use data. Data and supplementary materials should be described with adequate metadata and making sure the metadata and data are easy to find both humans and computers through a unique and persistent identifier. It is a critical component of the FAIR verification process to have both human and machine-understandable metadata.

- Accessible. Accessing the data is the second step. Data should be deposited in a trusted, reliable, and stable repository, and metadata are retrieval by their identifier using a standardized communication protocol. Even when the data are no longer available, the metadata should be accessible.

- Interoperable. Usually, the data need to be integrated with other things, which can provide a complete understanding of data and help users to apply the data with products or systems. Additionally, the data need to interoperate with applications or workflows for storage, processing, and analysis. To be interoperable, both the data and metadata will need to use a standard language for knowledge representation, which includes formal, accessible, shared, and broadly applicable formats and vocabularies [25].
Reusable. The overall goal of FAIR is to enhance and optimize the reuse of data. Metadata and data can be replicated or combined in different settings, and reusable data should maintain its initial richness and provenance information on how the data was formed. Besides, reusable data and metadata should meet domain-relevant community standards to provide rich contextual information that will allow for reuse [26].

2.2 The Role of Metadata

Metadata is information that describes instance data from a data source. Whenever data is created, modified, acquired, and deleted, metadata is generated. For instance, when you created a text file in the computer, metadata including the size of the file, date of creation, the owner of the file are also generated. Metadata provides an overview of the actual data. The goal of metadata is to make locating a specific digital asset easier and quicker. Metadata is common in the usage of the biomedical field, referred to as ontology in many cases.

Metadata is stored and maintained in a repository. Such a repository is usually a structured storage and retrieval system and implemented on top of a database management system. For a specific domain, Metadata that needed to be stored consists of the metadata schema and the semantics of metadata. The typical requirements for metadata repositories are presented in Figure 4.1.

The main purpose of a metadata repository is to provide necessary information for users to achieve their goals. Therefore, a metadata repository should offer the functionalities for querying, navigating, filtering, and browsing the metadata. Besides the query of fixed attributes, filtering refers to the selection of related information when search criteria are not necessarily provided by the schema of the repository. To browse a metadata repository, a user-friendly graphical interface is required. Browsing the content of a metadata repository is more than the metadata itself. Metadata is
the abstraction of the underlying actual data and it is extremely useful to fetch desired data from a large amount of data.

2.3 A Review of Ontology Mapping

In this section, we provide a brief review of ontology mapping. Even though this dissertation focuses on mapping from a data dictionary to an ontology, it is still useful to review the ontology mapping tools evaluation and algorithms. ontology mapping is essential for providing access across data used in knowledge-based applications and products. Different ontologies are used to annotate the same or similar domains. For example, disease ontology (DO) is widely used by the research community, and SNOMED CT is commonly used in healthcare researchers and clinicians. In such cases, ontology mapping can find exact or similar matching in the hierarchy between these two ontologies.

2.3.1 Ontology mapping tool functional requirements

Some basic requirements can be used to compare the exiting ontology mapping tools [27]. These functional requirements consist of three aspects: 1) user inter-
face to visualize the source ontology and mapping alignment editor 2) framework to include mapping workflow and mapping algorithm 3) import ontologies and export mappings. These functional requirements can also be applied to a mapping between a data dictionary and an ontology.

2.3.2 Ontology mapping algorithms

Ontology mapping algorithms are computational tools used to map between different ontologies. Ontology mapping algorithms are widely used beyond the healthcare domain [28]. It is useful to categorize the ontology mapping algorithms based on different features and techniques. These mapping algorithms can be borrowed to map from a data dictionary to an ontology. Figure 2.2 shows the detailed categorization.

**Figure 2.2:** Summary of ontology mapping algorithms. Extracted from the book "Ontology Matching" [28]

The categorization is not strictly enforced as some algorithms may implement several techniques at the same time.
• **String based**: these techniques are based on the similarity of string that represents the entities of ontologies such as names, descriptions (Cohen, Ravikumar, and Fienberg, 2003 [29]).

• **Language based**: these techniques based Natural Language Processing which considers names as words, not just simple string (He, Yang, and Huang, 2011 [30]).

• **Constraint based**: Consider the internal constraints applied to definitions of entities, such as the domain and range of the properties.

• **Informal resource based**: exploit external informal resources.

• **Formal resource based**: use a formal resource, such as upper ontologies, domain-specific ontology, and linked data.

• **Graph based**: these techniques consider source ontology as nodes on labeled graph (Joslyn, Paulson, and White, 2009 [31]).

• **Taxonomy based**: similar to graph-based techniques but only consider specialization relation (Warin and Volk, 2004 [32]).

• **Model based**: map source ontology based on semantic interpretation.

• **Instance based**: explore a set of instances of the class to check if they match (Loia, Fenza, De Maio, and Salerno, 2013 [33]).

All these aforementioned techniques could potentially be applied to building mapping from a data dictionary to an ontology.

### 2.4 National Sleep Resource Research (NSRR)

NSRR was funded by the National Heart, Lung, and Blood Institute and it was designed to share de-identified sleep data obtained from NIH-funded cohort studies.
and clinical trials from the sleep research community [11, 34]. NSRR provides a web-based data portal that aggregates and organizes signal and clinical data from over 26,000 patient subjects. NSRR has over 2,000 registered users since its launch in 2014. Up to date, over 80 terabytes of data have been downloaded by the sleep research community.

NSRR contains more than 14 sleep studies. These studies include Sleep Heart Health Stud (SHHS), Childhood Adenotonsillectomy Trial (Chat), Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT), Cleveland Family Study (CFS), Study of Osteoporotic Fractures (SOF), MrOS Sleep Study (MrOS), Cleveland Children’s Sleep and Health Study (CCSHS), Hispanic Community Health Study/Study of Latinos (HCHS/SOL), Honolulu-Asia Aging Study of Sleep Apnea (HAASSA), Multi-Ethnic Study of Atherosclerosis (MESA), Home Positive Airway Pressure (Home-PAP), Best Apnea Interventions for Research (BestAIR), and Apnea, Bariatric surgery and CPAP study (ABC).

2.5 VA Informatics and Computing Infrastructure (VINCI)

The Veterans Affairs (VA) provides care for a large number of individuals with spinal cord injuries. A large number of individuals combined with the extensive records for each patient provides us with an unprecedented opportunity to analyze the impacts of a wide range of PrI/DTPrI risk factors.

The VA has been developing electronic medical record systems since 1982 and its latest system, Vista, since 1996[35]. It provides a comprehensive record of all aspects of the VA healthcare system including each encounter a patient has with a provider. Data from the Vista system is extracted and loaded into the VINCI system daily, providing a rich pool of raw data for researchers.

The VA Informatics and Computing Infrastructure (VINCI) [36] is an initiative to improve researchers’ access to VA data and to facilitate the analysis of those data
while ensuring Veterans’ privacy and data security. VINCI welcomes all researchers in the VA community to explore the environment and tools available.

VINCI provides a rich data resource and a detailed personal characteristic database of tissue health. Some of the sample data set are:

- Corporate Data Warehouse (CDW) extractions from The Veterans Health Information Systems and Technology Architecture (VistA)
- MedSAS in SAS and SQL
- Decision Support System (DSS) in SAS and SQL
- Text Integration Utilities (TIU)
- Radiology notes

2.6 Cancer Registry

2.6.1 National Cancer Institute Thesaurus (NCIt)

Cancer is a genetic disease, in which a series of molecular events lead to the runaway reproduction of cancer cells. Over the past few years, the National Cancer Institute (NCI) has been putting efforts to integrate molecular and clinical cancer-related information within a unified biomedical informatics framework. NCI Thesaurus is designed to represent and integrate information from diverse areas, providing a structured and principled representation of key cancer-related concepts in areas such as cancers, findings, drugs, therapies, anatomy, genes, pathways, cellular and subcellular processes, proteins, and experimental organisms. NCIt [37] is the standard clinical and medical terminologies specifically for cancer. It can be accessed by the web.
2.6.2 North American Association of Central Cancer Registries

In the late 1980s, problems originated from insufficient data standardization had drawn attention from researchers. The lack of standardization had a substantial cost and limited the more widespread use of valuable data. It is more impactful on these three groups especially: state registries receiving data from hospital registries, the NAACCR Data Evaluation and Publication committee, and the Commission on Cancer’s (CoC) National Cancer Data Base (NCDB).

The lack of standardization occurred in many places. Data items that had the same name and were used to represent the same information varied in their definition and codes when used by different registries or software systems. Unknown data were annotated by blanks, dashes, and defined codes. Other substantial discrepancies were less easy to detect and correct. When hospitals and software providers were reporting to a central registry and maintaining database consistent with CoC standards, they faced conflicting standards and requirements.

The NAACCR’s (North American Association of Central Cancer Registries) was established in 1987. It is a collaborative umbrella organization for groups and organizations interested in enhancing the quality and use of cancer registry data such as cancer registries, governmental agencies, professional associations, and private groups in North America [23, 38–40]. Currently, there are five NAACCR standards volumes.

In order to facilitate compilation and comparison of information across different registries, one of the main goals for NAACCR was to standardize cancer registration among the many standard-setting organizations in the United States and Canada. Today, nearly all registries in North America have adopted the NAACCR consensus standards. NAACCR updates these standards annually to meet the changing needs of the registry community.
2.6.3 Kentucky Cancer Registry (KCR)

The Kentucky Cancer Registry (KCR) [41] is a central cancer registry that receives data about new cancer cases from all healthcare facilities and physicians in Kentucky within 4 months of diagnosis. KCR is part of the NCI’s Surveillance Epidemiology and End Results (SEER) program.
Agile methods of software development have been widely leveraged in recent years [42, 43]. Iterative and incremental development, evolving since the 1950s, has taken the place of the waterfall model as the main-stream style of software development [42]. In this chapter, we will discuss the detailed design and methodology for developing MetaSphere using agile development.

3.1 System Architecture

Figure shows the overall system architecture of MetaSphere. There are three major components: 1) Frontend query interface; 2) Backend application server; 3) Databases. These components are loosely decoupled but seamlessly combined as a functional application.

Figure 3.1: System Architecture Overview
### 3.2 Frontend Query Interface

#### 3.2.1 ReactJS - A JavaScript Library

ReactJS is a JavaScript library for building user interfaces [44]. It is created and maintained by Facebook. It is used as a base in developing high-performance single-page applications. ReactJS has become one of the widely used frameworks for building frontend interfaces. There are several features which make it extremely successful and these features perfectly match our development requirements.

- **Components based.** The design philosophy of ReactJS is to separate a web interface into different components. A root component is the entry point of the interface. Each component has its own children’s components. In such a way, an interface becomes a tree. Moreover, every component can be reusable since its a placeholder to render different data. A typical interface will have many repeated elements, such as many rows in one table. We then can make a row as an individual component and pass in different data. ReactJS enhances the reusability of codes even for frontend interface coding.

- **Virtual dom.** Another notable feature is the use of a virtual Document Object Model or virtual DOM. React creates an in-memory data structure cache, computes the resulting differences, and then updates the browser’s displayed DOM efficiently [45]. As shown in Figure 3.2, this allows the programmer to write code as if the entire page is rendered on each change, while the React libraries only render subcomponents that actually change. The virtual DOM feature makes ReactJS updates efficient.

- **Single direction data flow.** The data flows from the components itself to its children components. With such setting, developers will be able to catch unexpected bugs quickly and easily. Figure 3.3 demonstrate the data flow in ReactJS.
The aforementioned features make ReactJS a decent choice to build our MetaSphere frontend interface. Especially, we would like to represent the ontology hierarchical tree structure. In another way, we could view the component as a typical class in a programming language and we are turning the interface design into object-oriented programming. Figure 3.4 shows the detail of the core design. There are also other
components but the major components are QueryDashboard, ConceptList, Concept, ConceptWidget. Numerical and Categorical components are the two most common types for a ConceptWidget component.

- **QueryDashboard.** The QueryDashboard component is the root component for the query interface and its the entry point of our interface. Most of the uses would spend their visit in this component. When the user performs a query, QueryDashboard will gather all the QueryWidget information and send out a request to the backend server to perform a query.

- **ConceptList.** The ConceptList component is a functional component. It is the component that fetches data from the backend server and handles all the logic related to concept display.

- **Concept.** The Concept component is called a representational component or render component. The only responsibility for the Concept a component is to render actual concept data in the interface.

- **ConceptWidget.** The ConceptWidget component is a visual representation of a specific concept type. The ConceptWidget component will render different child components based on the passed in concept type.

- **Numerical.** The Numerical component is a QueryWidget. It is the corresponding component for a numerical concept. It contains a slider bar for users to perform a range-based query, which would produce a minimal and maximum value for the concept.

- **Categorical.** The Categorical component is also a QueryWidget and it is related to categorical concepts. It will render all the domains(options) for users to select. For instance, a gender concept will have options male and female.
3.2.2 From QueryWidget to Query Statement

From Figure 3.4, we notice that the Concept component has a function called **addQueryWidget**. When a user clicks on a Concept component, a QueryWidget will be added to the interface. Suppose the concept added by the user is a numerical concept. The Numerical component will be rendered. When the user specifies the minimal value and maximum value he/she would like to query, the function **addToStatement** is triggered. The **addToStatement** function will pass the concept identifier, minimal and maximum value to the QueryDashboard. Then the QueryDashboard will modify its attribute queryStatement. If a user clicks the close icon in the QueryWidget, function **removeQueryWidget** is triggered and the corresponding statement from queryStatement will be removed. For a categorical concept, a similar process but the
passed data is a little bit different. Instead of passing minimal and maximum values, a set of options selected by users will be passed into the QueryDashboard. Here, we demonstrate the process from QueryWidget to actual queryStatement. There are more types of concepts in actual usages. But, our design is scalable. A new type of concept can be added by adding a corresponding component without touching existing concept components. After constructing the query using our QueryDashboard, users submit the queryStatement and it is our backend server responsibilities to handle the incoming request.

3.3 Backend Application Server

In the previous section, we talked about the transformation from query widgets to actual query statements. In this section, we will describe how the backend server handles such requests.

The backend server is built using Ruby on Rails [46]. Ruby on Rails is a framework that makes it easier to develop, deploy, and maintain web applications.

3.3.1 Models, Views, and Controllers

Ruby on Rails follows the architecture known as MVC. Figure 3.5 shows MVC in abstract terms.

![Figure 3.5: The Model-View-Controller Architecture](image)

The *model* maintains the state of the application. The state of an application
could be temporary or permanent. Temporary state lasts a few interactions with the users, while the permanent state will be stored outside the application, typically a database. *model* is more than data. It enforces and handles rules applied to the data. *model* also represents the abstracted entities from the real world.

The *view* is responsible for generating a user interface, normally based view on data in the *model*. The aforementioned ReactJS falls in the *view* component. For example, a clinical discharge summary application will have a list of patients to be displayed on a dashboard screen. This list will be accessible via the *model*, but it will be a *view* that accesses the list from the *model* and formats it for the end-user. Although the view may present the user with various ways of inputting data, the view itself never handles incoming data. The *view*'s work is done once the data is displayed. There may well be many views that access the same model data, often for different purposes. In the clinical discharge summary application, there will be a view that displays patient information on a dashboard page and another set of views used by administrators to add and edit patient.

Controllers orchestrate the application. Controllers receive events from the Controllers outside world (normally user input), interact with the model, and display an appropriate view to the user.

There are three core data models in MetaSphere: 1) Concept; 2) Variable; 3) Domain as shown in Figure 3.6.

- **Concept.** The Concept model contains information about the ontology concept. Some common and required attributes are concept_name, concept_type, and description. Besides, ontology is with a hierarchical structure. To represent such a hierarchical structure, we have a special attribute called parent_id, which points to the parent concept of the current one. If a concept does not have a parent concept, it is a root concept.

- **Variable.** The Variable model represents the instance of a concept from a differ-
Figure 3.6: Core data model and their relationships in MetaSphere

tent data source. The variable is essential for a cross-cohort exploration interface. Imaging we have two data source and each of them contains information about patient gender. In data source one, gender is annotated as gender, but in data source two gender is annotated as sex. They denote the same concept, but with a different instance. To maintain the relationships between concepts and variables, we used dedicated mapping. A mapping will show the one-to-one relationship from a variable to a concept.

- **Domain.** The Domain model is critical for categorical concepts. The Domain model consists of possible options for a categorical concept. In reality, many options are commonly shared by multiple variables. Therefore, the domain model is a dedicated model to reduce the duplication of our data.

### 3.3.2 Query Translation and Query Execution

The frontend interface translates the QueryWidget into an actual query statement and sends these statements to our backend server. Once the backend server receives these statements, it will translate these statements into corresponding actual database query statements using predefined templates. The detail of these templates will be
discussed in the following chapters. Basically, we have two translations that occurred before acquiring the query results. Once all the translations are done, the backend server will be able to execute the query and return the result to the frontend interface.

3.4 Metadata storage and Data repository

There are two types of data we need to store in the database. One is the metadata, and the other one is the actual data. Metadata includes data aforementioned, like ontology concepts, data dictionaries from a different data source, and user-related data. The actual data is the data that users can query and explore. To store these data, we can use different types of databases. One option is the traditional relational database and the other one is the NoSQL databases. However, even for relational databases, there are databases like SQLite, MySQL, and PostgreSQL. We need to make MetaSphere scalable in terms of adding support for new databases. To achieve that, we utilized the abstract interface programming pattern.

![Figure 3.7: Abstract class for multiple databases](image)

As demonstrated in Figure 3.7, we have a abstract class (interface) called Database. The Database class specifies the URL and port for database connection and two im-
portant functions: connect and query. Once such interface is defined, then adding a new database will be implementing the interface for the corresponding database. In such a way, we leave the existing databases untouched and make adding new databases scalable.

In this chapter, we introduce a general framework called Metadata aiming to address the challenges mentioned in Chapter 2. In the next few chapters, we will talk about how we apply the framework to different domains.
CHAPTER 4. National Sleep Resource Research (NSRR)

In Chapter 3, we introduce a general framework called Metadata aiming to address the challenges mentioned in chapter two. In this chapter, we will talk about how we apply such a framework to sleep domains, specifically NSRR. Moreover, we will discuss the limitations of SQL-based MetaSphere and carry on a comparison study over SQL-based MetaSphere and NoSQL-based MetaSphere.

4.1 Motivation and Challenges

Sharing and reusing biomedical digital data have gained increasing attention to accelerate scientific discovery and enhance research reproducibility [4–7]. Various data repositories have been developed and made available for biomedical researchers, such as UniProt - a comprehensive resource for protein sequence and annotation data [47], GDC - the National Cancer Institute’s Genomic Data Commons [48], BioPortal - a repository of biomedical ontologies [9], OpenfMRI - a repository for sharing task-based fMRI data [10], and NSRR - the National Sleep Research Resource [11, 12, 34].

A widely endorsed set of guiding principles for biomedical data management in data repositories is FAIR: making data Findable, Accessible, Interoperable, and Reusable [7]. The FAIR principles are essential for researchers to find the data of interest, which may be further reused for generating or testing hypotheses. While most existing data repositories enable researchers to browse and download data - sometimes under data use or regulatory constraints, very few allow users to freely and openly perform fine-grained, cross-dataset query and exploration of the study-subject level before deciding which specific datasets to gain further access. Such fine-grained data exploration capabilities allow users to compose complex queries over a large number of cohorts, quickly assess the feasibility of research studies or generate/test potential hypotheses, and then make appropriate full data access requests.
4.2 Related work

To support the fast generation of hypotheses and assessment of the feasibility of research studies, various cohort discovery tools have been developed to facilitate the identification of potential research subjects satisfying certain characteristics.

Murphy et al. [49] had developed a cohort selection (or counting) system for the Informatics for Integrating Biology and the Bedside (i2b2) project, which has been widely adopted for querying the count of eligible patients in a single clinical data repository. To support patient cohort identification from multiple data sources, Weber et al. [50] have developed the Shared Health Research Information Network (SHRINE) based on i2b2. SHRINE requires the underlying data sources to have the same data structure based on i2b2. Distinct from SHRINE, our X-search was designed to query multiple data sources with heterogeneous data structures.

Zhang et al. [51] have designed and implemented a query interface VISAGE (VISual AGgregator and Explorer) for query patient cohorts. Our X-search shares a similar visual interface design with VISAGE (e.g., checkboxes for categorical variables, and slider bar for numerical variables), but differs from VISAGE in that it adopts a data warehouse approach to harmonize data sources before querying rather than a federated approach to directly query the data sources.

Bache et al. [52] defined and validated an adaptable architecture (we refer to it as Bache’s architecture) for identifying patient cohorts from multiple heterogeneous data sources. Bache’s architecture supports multiple data sources with heterogeneous data structures and handles the heterogeneity in the query translation step. Our X-search differs in that it handles the data heterogeneity in the data loading step, which saves users’ waiting time for query translation.

Another related work is the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [53] for representing healthcare data from diverse
sources in a standardized way, which is open-source and maintained by an international collaborative, Observational Health Data Sciences and Informatics (OHDSI) program [54]. OMOP CDM standardizes data structure and common vocabularies (e.g., SNOMED CT, ICD9CM, RxNorm) across disparate sources, such as electronic health records, administrative claims, and clinical data. A natural question would be whether the OMOP CDM could be directly used for modeling NSRR datasets. However, significant effort needs to be made to transform NSRR datasets into the utilization of standardized vocabularies, and there may not be direct transformation due to the fine-grained, sleep-related data elements. It would be interesting to explore the generalizability of OMOP CDM using the NSRR datasets.

There are existing tools on standardizing and harmonizing data elements for clinical research studies such as eleMAP [55] and D2Refine [56], which enable researchers to harmonize local data elements to existing metadata and terminology standards such as the caDSR (Cancer Data Standards Registry and Repository) [57] and NCI Thesaurus [58]. Such tools may be useful for us to map NSRR data elements to existing standards.

### 4.3 Overview of NSRR

Funded by the National Heart, Lung, and Blood Institute, NSRR was designed to share de-identified sleep data obtained from NIH-funded cohort studies and clinical trials with the sleep research community [11]. NSRR provides a web-based data portal [34] that aggregates and organizes signal and clinical data from over 26,000 patient subjects. NSRR has over 2,000 registered users since its launch in 2014. Up to date, over 80 terabytes of data have been downloaded by the sleep research community.

Clinical data from eight datasets in NSRR [34] are used as data sources in this research, including *Sleep Heart Health Study (SHHS)* [59–61], *Childhood Adenotonsillecto-
tomy Trial (CHAT) [62–64], Cleveland Family Study (CFS) [65–67], Heart Biomarker Evaluation in Apnea Treatment (HEARTBEAT) [68], Study of Osteoporotic Fractures (SOF) [69], MrOS Sleep Study (MrOS) [70], Hispanic Community Health Study / Study of Latinos (HCHS) [71], and Multi-Ethnic Study of Atherosclerosis (MESA) [72].

In NSRR, clinical data are organized in comma-separated values (CSV) files by patient visits. Each patient visit has a CSV file with all the clinical data elements collected for this visit. Note that an NSRR dataset may involve one or multiple visits. For example, the SHHS dataset has two visits: shhs1 (1,266 data elements) and shhs2 (1,302 data elements); the CHAT dataset has two visits: baseline (2,897 data elements) and followup (2,897 data elements); and the CFS dataset has one visit: visit5 (2,871 data elements). Table 4.4 summarizes the detailed information for all eight datasets used in this work.

**Table 4.1:** Summary information for each of the eight datasets.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Visit(s)</th>
<th>Number of data elements</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHHS</td>
<td>shhs1</td>
<td>1,266</td>
<td>5,804</td>
</tr>
<tr>
<td></td>
<td>shhs2</td>
<td>1,302</td>
<td>4,080</td>
</tr>
<tr>
<td>CHAT</td>
<td>baseline</td>
<td>2,897</td>
<td>464</td>
</tr>
<tr>
<td></td>
<td>followup</td>
<td>2,897</td>
<td>453</td>
</tr>
<tr>
<td>CFS</td>
<td>visit5</td>
<td>2,871</td>
<td>735</td>
</tr>
<tr>
<td>HEARTBEAT</td>
<td>baseline</td>
<td>859</td>
<td>318</td>
</tr>
<tr>
<td></td>
<td>followup</td>
<td>731</td>
<td>301</td>
</tr>
<tr>
<td>SOF</td>
<td>visit8</td>
<td>1,114</td>
<td>461</td>
</tr>
<tr>
<td>MrOS</td>
<td>visit1</td>
<td>479</td>
<td>2,911</td>
</tr>
<tr>
<td></td>
<td>visit2</td>
<td>507</td>
<td>2,911</td>
</tr>
<tr>
<td>HCHS</td>
<td>sol</td>
<td>404</td>
<td>16,415</td>
</tr>
<tr>
<td></td>
<td>sueno</td>
<td>505</td>
<td>2,252</td>
</tr>
<tr>
<td>MESA</td>
<td>sleep</td>
<td>723</td>
<td>2,237</td>
</tr>
</tbody>
</table>
4.4 Method

Our overall objective is to create an open-access query interface that allows a user to perform an aggregated search on NSRR content before requesting full access to specific datasets. To do so, we designed the system architecture to be comprised of two major components: a semantically annotated data repository with heterogeneous datasets (Figure 4.1, left) and the cross-cohort exploration engine (Figure 4.1, right).

Figure 4.1: The architecture for query system. Left: Open data repository with heterogeneous data sources. Right: The cross-cohort exploration system.

We assume that the datasets (or data sources) are in the structured format which can be loaded to relational databases such as MySQL. Each data source has a dedicated data dictionary that originated from the source study and available for open access through NSRR. The data dictionary describes the data elements in the dataset, including names, definitions, data types, units, and value domains (or allowable values). The canonical data dictionary consists of core query terms (or common data elements) across different datasets. Here a common data element is a data element that is common to multiple NSRR data sets. Each mapping involves the data element mappings between the source data dictionary and the canonical data dictionary.
The cross-cohort exploration engine consists of five components: query builder, graphical exploration, case-control exploration, query translation, and query execution. The query builder, graphical exploration, and case-control exploration components involve visual interfaces and use the canonical data dictionary as the query and exploration terms. The query translation module translates a user query composed in the query builder to the actual query statement in SQL. The query execution module connects to each database (or data source) and executes the query statement.

4.4.1 Data repository

4.4.1.1 Data sources and data dictionaries

We used nine datasets in the NSRR data repository: Sleep Heart Health Study (SHHS), Childhood Adenotonsillectomy Trial (CHAT), Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT), Cleveland Family Study (CFS), Study of Osteoporotic Fractures (SOF), Osteoporotic Fractures in Men Study (MrOS), Cleveland Children’s Sleep and Health Study (CCSHS), Hispanic Community Health Study/Study of Latinos (HCHS/SOL), and Multi-Ethnic Study of Atherosclerosis (MESA). Each dataset may involve multiple patient visits, where the actual data records for each visit is stored in a comma-separated values (CSV) file.

Each data source has a data dictionary semantically defining the scope and characteristics of data elements (or variables) in the dataset, including the short name, display name, description, type, unit, domain, and synonyms. The short name of a variable is the actual column name used in the database storing the dataset and serves as the unique identifier for a variable (note that one dataset may have the same variable in different patient visits). The display name is the variable name shown to users in the visual interface, and it is more informative than the short name. The description provides more detailed information about the variable such as meta information. The type defines the data type of a variable, such as identifier, numeric,
and categorical. The unit is applicable to numeric variables describing a measurable quantity. The domain specifies the allowable values for a categorical variable. The label stores the synonyms or indexed terms that can be used to retrieve the variable. The data dictionary containing the above-mentioned information can be structurally specified in CSV files.

### 4.4.1.2 Canonical data dictionary and mappings

The canonical data dictionary specifies the common data elements across different data sources. These common data elements serve as the core query terms in the visual interface for users to browse or search. The core terms capture demographic information (e.g., age, gender, race), anthropometric parameters (e.g., body mass index, height, weight), physiological measurements (e.g., heart rate, diastolic blood pressure, systolic blood pressure), medical history (e.g., asthma, atrial fibrillation, insomnia, sleep apnea), medications (e.g., benzodiazepine, estrogen, progestin), sleep study data (e.g., sleep duration, quality of sleep, obstructive sleep apnea events, apnea hypopnea index, average oxygen saturation during sleep), and laboratory data (e.g., HDL cholesterol, creatinine). In addition, these data elements are mapped and linked to the NIH Common Data Element (CDE) repository [73] if applicable.

Since a data element in the canonical data dictionary may have different variable names in disparate data sources, there is a need for a mapping from each individual data source to the canonical data dictionary. Therefore, for each data source, a uniform mapping template is utilized to map the source data elements to the common data elements (m to 1 mapping). Take the common data element "body mass index" as an example, there are two data elements in the SHHS dataset mapping to it ("bmi_s1" in the baseline visit, and "bmi_s2" in the followup visit); and there are two data elements in the HeartBEAT dataset mapping to it ("bmi_scrn" and "calc_bmi" in the baseline visit).
4.4.1.3 Coding inconsistency harmonization

A unique challenge in exploring data in multiple heterogeneous data sources is to address the coding inconsistency issue, which involves the detection and harmonization of inconsistencies among the disparate value domains for the same data element. Such inconsistencies occur frequently for categorical variables. For instance, the "gender" variable has inconsistent codings across the nine datasets in NSRR (see Table 4.2), where 1 represents "Male" and 2 represents "Female" in SHHS, whereas 1 represents "Male" and 0 represents "Female" in HeartBEAT, and 1 represents "Female" and 2 represents "Male" in MrOS. Such heterogeneity must be harmonized to ensure that data exploration activities obtain accurate results. In order to achieve this, an automated program has been developed to detect the inconsistent codings among different datasets by leveraging the canonical data dictionary, each source data dictionary, and the mappings between source data dictionaries and the canonical data dictionary.

To harmonize the detected inconsistencies, a manual review has been involved to define the uniform codings and create appropriate mappings from heterogeneous codings to the uniform coding. Take the "gender" codings in Table 4.2 as an example, a uniform coding with 1 representing "Male" and 2 representing "Female" can be defined, and heterogeneous codings in the original data sources can be mapped to the uniform coding (each row is a mapping). This harmonization step is essential to ensure data interoperability across disparate data sources.

4.4.1.4 Data loading

To support the cross-cohort exploration activities, we need to import the actual data in each dataset, load common data elements in the canonical data dictionary and mappings, and harmonize coding inconsistencies. This process is described in the following three steps.
Table 4.2: Harmonizing coding inconsistencies among different datasets for the “gender” variable.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Code</th>
<th>Name</th>
<th>Harmonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHHS</td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td>CHAT</td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td>HeartBEAT</td>
<td>0</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td>CFS</td>
<td>0</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td>MrOS</td>
<td>1</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td>CCSHS</td>
<td>0</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td>HCHS</td>
<td>0</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
<tr>
<td>MESA</td>
<td>0</td>
<td>Female</td>
<td>2 - Female</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Male</td>
<td>1 - Male</td>
</tr>
</tbody>
</table>

In Step 1, for each dataset, we create a relational database in MySQL to store the actual data; and we leverage the data dictionary of the dataset to automatically create tables in the database and load actual data into tables. More specifically, the data type of a data element specified in the data dictionary (e.g., decimal) seamlessly determines the data type of a column in a MySQL table (e.g., DOUBLE), which enables the automated creation of MySQL statements to create tables and insert data records in CSV files to the tables.

In Step 2, we import common data elements in the canonical data dictionary to the backend database of the X-search web application, as well as the mappings between the data elements in each dataset and the common data elements. Such information will be leveraged to support the query translation of the web-based query widgets to the backend MySQL query statements.

In Step 3, we handle coding inconsistencies for heterogeneous data elements that
are mapped to the same common data element. There are two options: (1) harmonize
the actual data in each dataset according to the uniform codings, so that the query
translation step can directly use the uniform codings to create common SQL query
statements for disparate datasets; (2) keep the actual data in each dataset as is, and
rely on the query translation step to utilize the mappings to the uniform codings to
generate different SQL query statements for disparate datasets. Although the latter
option saves time and effort to update the loaded data, the former option saves the
query time due to less hassle on the query translation step. In this work, we have
adopted the first option to speed up the query translation process and reduce users’
waiting time when performing data exploration activities.

4.4.2 The X-search cross-cohort exploration engine

4.4.2.1 Query builder

A powerful and intuitive interface, called query builder, has been designed and
developed to enable researchers to quickly find the right common data elements and
perform an exploratory cross-cohort query. The query builder consists of the four
areas which are corresponding to four steps to perform cross-cohort queries as follows.
(1) Area to select datasets, where users can choose a collection of datasets to focus
on; (2) Area to add query terms, where users can look for query terms (or common
data elements) of interest; (3) Area to construct queries, where query criteria can
be specified for each query term; (4) Area for query results, where retrieved subject
counts satisfying query criteria are returned to users.

In the area to add query terms, there are two modes to look for common data
elements of interest: browsing and search. The browsing mode provides a hierarchical
view of query terms so that novice users can explore all the available common data
elements level by level. The search mode enables expert users to directly search for
query terms of interest. The query builder uses a dynamic mechanism to generate
visual query widgets corresponding to selected query terms. For instance, selecting a categorical term generates a widget with checkboxes for specifying possible values; and selecting a numerical term generates a widget with a slider bar for specifying a range of values.

The query builder interface is a general design such that each area serves as a placeholder where the content of each area can be filled automatically with research data in different domains. In this work, the area to select datasets is filled with the names of the nine datasets from NSRR, the area to add query terms consists of the canonical data dictionary terms, the area to construct queries contains dynamic query widgets corresponding to the selected query terms, and the area for query results is driven by the query criteria specified in the area to construct queries.

4.4.2.2 Graphical exploration

The graphical exploration interface has been designed to support the visual exploration of two common data elements (say x and y corresponding to x-axis and y-axis). The graphical views include bar plots and box plots. Bar plots are shown when the y-axis is a categorical common data element, and box plots are displayed when the y-axis is a numeric common data element. Such plots enable users to have a better understanding of the data distribution of y against x. Since there may be multiple variables in each individual dataset that are mapped to x or y, multiple plots are generated for each pair of variables.

4.4.2.3 Case-control exploration

The case-control exploration interface allows registered users to perform cross-cohort case-control analyses. It provides a general template for users to build a case-control exploration step by step. Step 1 is to set base query terms, where users can specify the criteria for the base population (e.g., age between 45 and 85 years, body mass index between 30 and 85 kilograms per square meter, and no history of
cardiovascular disease). Step 2 is to set the condition for cases (e.g., had diabetes). Step 3 is to set the condition for controls (e.g., no history of diabetes). Step 4 is to set the match terms (e.g., gender and ethnicity). Step 5 is to set outcome terms (e.g., obstructive sleep apnea). The result of the case-control exploration is displayed as a table with case and control counts for the match and outcome terms.

4.4.2.4 Query translation and execution

The query translation module automatically translates the user's specifications captured by the visual interface into actual MySQL statements to query backend databases. The translation relies on the query terms and values specified in the visual interface, as well as the mappings between each individual data dictionary and the canonical data dictionary. The query statements for multiple data sources are distinct since these data sources have different tables and column information mapping to a common data element.

For each type of common data elements, a general template is predefined and used for dynamically generating the actual MySQL statement for query translation. For example, the general template for querying a numeric common data element with a specified range (min, max) is predefined as:

```sql
SELECT COUNT (DISTINCT<mapping.table. identifier>)
FROM <mapping.table>
WHERE <mapping.column>
BETWEEN <min> AND <max>;
```

Here `mapping.table` and `mapping.column` represent the data source table and column to which the common data element is mapped to in a dataset. All the variables in the angle brackets can be replaced by real values to generate the actual MySQL statements for different datasets.
The translated MySQL statements are sent to the corresponding data sources to perform the query execution. For the query builder interface, the query execution returns numeric counts of potentially eligible subjects satisfying the query criteria. For the graphical exploration interface, the query execution returns the actual values of data elements for eligible subjects, which are further plotted visually. For the case-control interface, the query execution returns the actual values of data elements for both cases and controls, which are further processed to generate the table-format view with case- and control-counts displayed for the match and outcome terms.

4.5 Result

4.5.1 Data repository

We used MySQL databases to store the nine datasets. Table 4.3 lists the names of the datasets, the names of the visits, the numbers of data elements (or variables), the numbers of subjects, and the numbers of mapped variables to the canonical data dictionary. Note that the mapped variables in each visit of a dataset are a subset of all the variables in the visit. The canonical data dictionary contained a total of 919 common data elements (554 of them are specific to the sleep research domain and 365 of them are common across study domains). Among them, 42 were detected to have inconsistent codings across different datasets, including "gender," "race," "history of asthma," and "history of sleep apnea." A total of 830 mappings from heterogeneous codings to the uniform codings were created to harmonize the data with inconsistent codings. In addition, 57 elements in the canonical data dictionary were linked to the NIH Common Data Element (CDE).

4.5.2 Cross-cohort exploration engine

We implemented the X-search cross-cohort exploration engine using Ruby on Rails, an agile web development framework. It has been deployed at https://www.x-search.net/
Table 4.3: Summary information for each of the nine datasets.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Visit(s)</th>
<th>No. of variables</th>
<th>No. of subjects</th>
<th>No. of mapped variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHHS</td>
<td>shhs1</td>
<td>1266</td>
<td>5804</td>
<td>615</td>
</tr>
<tr>
<td></td>
<td>shhs2</td>
<td>1302</td>
<td>4080</td>
<td>592</td>
</tr>
<tr>
<td>CHAT</td>
<td>baseline</td>
<td>2897</td>
<td>464</td>
<td>826</td>
</tr>
<tr>
<td></td>
<td>followup</td>
<td>2897</td>
<td>453</td>
<td>823</td>
</tr>
<tr>
<td>HeartBEAT</td>
<td>baseline</td>
<td>859</td>
<td>318</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>followup</td>
<td>731</td>
<td>301</td>
<td>103</td>
</tr>
<tr>
<td>CFS</td>
<td>visit5</td>
<td>2871</td>
<td>735</td>
<td>1023</td>
</tr>
<tr>
<td>SOF</td>
<td>visit8</td>
<td>1114</td>
<td>461</td>
<td>350</td>
</tr>
<tr>
<td>MrOS</td>
<td>visit1</td>
<td>479</td>
<td>2911</td>
<td>261</td>
</tr>
<tr>
<td></td>
<td>visit2</td>
<td>507</td>
<td>2911</td>
<td>222</td>
</tr>
<tr>
<td>CCSHS</td>
<td>trec</td>
<td>143</td>
<td>517</td>
<td>94</td>
</tr>
<tr>
<td>HCHS</td>
<td>sol</td>
<td>404</td>
<td>16,415</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>sueno</td>
<td>505</td>
<td>2252</td>
<td>5</td>
</tr>
<tr>
<td>MESA</td>
<td>sleep</td>
<td>723</td>
<td>2237</td>
<td>512</td>
</tr>
</tbody>
</table>

and open to public access for free.

Figure 4.2 shows the query builder interface with the four areas annotated. In the area to select datasets, all the nine datasets are chosen - five of them can be directly seen, and the other four can be seen when scrolling down. The area to construct queries contains two query widgets for ”gender” (with checkboxes) and ”age” (with a slider bar), with specified query criteria: female, and age between 20 and 50. The area for query results shows the numbers of subject counts meeting the query criteria in each dataset, as well as the total number of subject counts.

Figure 4.3 gives an example of the graphical exploration interface, where the term for the y-axis is specified as ”body mass index” and the term for the x-axis is ”history of diabetes”. The box plot shown in the figure is generated based on two variables in the CFS dataset mapped to ”body mass index” and ”history of diabetes” respectively and indicates that the median body mass index of patients who had a history of diabetes is greater than that of patients who had no history of diabetes.

Figure 4.4 shows the case-control exploration interface illustrating the exemplar
Figure 4.2: Screenshot of the query builder interface. Four areas: (1) Select Datasets; (2) Add Query Terms; (3) Construct Query; (4) Query Results. This example queries the numbers of female patient subjects aged between 20 and 50.

steps mentioned in the Methods section. This example is to explore: In elderly (base query: age between 45 and 85 years), obese people (base query: body mass index between 30 and 85) without cardiovascular disease (base query: no history of cardiovascular disease), whether the presence of self-reported diabetes (case condition: had a history of diabetes, control condition: no history of diabetes) is related to sleep apnea (outcome term: obstructive sleep apneas/hours).

The cross-cohort exploration system supports additional functionalities, including the query manager, case-control manager, and International Classification of Sleep Disorders (ICSD) query builder. Query and case-control managers allow users to save queries and case-control explorations for reuse. ICSD query builder is a dedicated query builder for more complicated ICSD terms.
Figure 4.3: Screenshot of the graphical exploration interface. This example shows one of the box plots generated for body mass index (BMI) against diabetes.

Figure 4.4: Screenshot of the case-control exploration interface. This example is to explore: In elderly, obese people without cardiovascular disease, whether the presence of self-reported diabetes is related to sleep apnea (apnea-hypopnea \( \geq 15 \) events/hour).

4.5.3 Usage

the cross-cohort exploration system has received 1,835 queries from users in a wide range of geographical regions (16 countries), including Australia, Canada, China,
France, India, South Africa, the United Kingdom, and the United States.

Figure 4.5 shows the number of times each of the nine datasets got queried (note that each user query may involve multiple datasets). And the top ten query terms are: "age," "obstructive sleep apneas/hour," "central sleep apneas/hour," "gender," "body mass index," "diabetes mellitus - history," "cardiovascular disease - history," "apnea hypopnea index greater than or equal to 15," "apnea hypopnea index," and "race."

![Number of times each dataset got queried](image)

**Figure 4.5:** Numbers of times each dataset got queried.

### 4.5.4 Limitations

X-search uses MySQL databases to load and store the actual datasets. However, a limitation of the MySQL database is the restriction on the maximum number of columns in a table. For clinical data with a large number of data elements (e.g., SHHS), split is needed to store all the data which may cause overhead on querying across multiple tables. It would be interesting to use NoSQL (Not Only SQL) databases to store and query NSRR datasets, and compare the performance of the NoSQL- and SQL-based approaches. In addition, we plan to explore how to expand our X-search cross-cohort exploration tool to support the OMOP Common Data Model.
4.6 Evaluation: A Comparison of Query Performance between SQL-based and NoSQL-based Query Interface

With the limitations introduced by the relational databases, we can explore other databases as alternative storage engines. In this section, we highlights the specific challenges and perform a comparative study of data modeling, data importing time, and query performance between the SQL-based and NoSQL-based query interface.

4.6.1 Specific Challenges for Identifying Patient Cohorts from Heterogeneous Sources

4.6.1.1 High-dimensional Data

Dealing with high-dimensional is one of the challenges for patient cohort identification using relational databases due to the limitation of the maximum number of columns in a table. For example, MySQL has a hard limit of 4,096 columns per table, but the actual maximum number for a given table may be even less considering the maximum row size and the storage requirements of the individual columns [74]. High-dimensional data (or column-intensive data), if exceeding a single table’s capacity, need to be split into multiple tables. For instance, in the CFS dataset, the “visit5” table needs to be split into 3 tables with the de-identified patient identifiers to connect the separated tables (see Figure. 4.6). The consequence of such splitting is that it would be more computationally expensive to query data elements located in different tables since it involves costly join operation of tables and matching of the unique identifiers. Therefore, the query performance may be significantly affected due to the split.

4.6.1.2 Heterogeneous Data

Querying heterogeneous data to find patient cohorts is also a challenging task, as disparate data sources may use different representations to express the same meaning.
An example of splitting a table with a large number of columns into multiple tables in MySQL due to the restriction on the table column count. For example, in NSRR, different codings for patient gender are used in disparate datasets: 1 means male, and 2 means female in the SHHS dataset, while 0 represents female, and 1 represents male in the CHAT dataset. Such coding inconsistencies happen frequently as the number of disparate datasets increases, thus need to be harmonized to guarantee accurate queries.

There are two ways to handle coding inconsistencies. One way is to harmonize the inconsistencies in the data loading step, where the source data of each dataset need to be updated to share uniform codings across all the datasets. The other way is to address the inconsistency issue in the data query step, where the mapping of the heterogeneous codings in each dataset to the uniform codings needs to be incorporated when the patient cohort identification system performs the query translation. In this work, we adapt the first way to perform harmonization in the data loading step so that we can evaluate both data harmonization and query performance of the SQL- and NoSQL-based systems.

### 4.6.2 NoSQL Databases

NoSQL [75] databases have been rapidly emerged, becoming a popular alternative to the existing relational databases that can better store, process, and analyze large-volume data. Without a fixed data schema, NoSQL databases are more flexible in

![Table Example](image)
dealing with various data sources and formats. NoSQL databases have shown the potential in managing big biomedical data [76–78]. For example, Tao et al. [78] had developed a prototype query engine for large clinical data repositories utilizing MongoDB as the backend database. There are two main components in MongoDB: 1) MongoDB Query Language; 2) MongoDB Data Model.

4.6.2.1 MongoDB Database System

MongoDB [79] is a free, open-source and cross-platform NoSQL database. It is a mature document-oriented NoSQL database with well-written documentation and large-scale commercial use. MongoDB also provides rich drivers for multiple programming languages.

- **MongoDB Query Language.** As a NoSQL database, MongoDB provides an expressive query language that is completely different from SQL. There are many ways to query documents: simple lookups, creating sophisticated processing pipelines for data analytics and transformation, or using faceted search, JOINs, and graph traversals.

- **MongoDB Data Model - Data As Document.** The major feature of MongoDB is that it stores data in a binary representation called BSON (Binary JSON). The encoding of BSON extends the widely used JSON (JavaScript Object Notation) representation to include additional types such as int, long, date, floating point, and decimal 128. BSON documents contain one or more fields, and each field contains a value of a specific data type, including arrays, binary data, and sub-documents. Documents that share a similar structure are organized as collections. One can think of collections as being analogous to tables in a relational database: documents are similar to rows, and fields are the equivalence of columns.
4.6.2.2 Cassandra Database System

Apache Cassandra [80] is another free and open-source distributed NoSQL database management system, which is designed to store large amounts of data from multiple servers. Cassandra can be considered as a hybrid of key-value- and column-based NoSQL database.

- **Cassandra Query Language (CQL).** CQL is a query language for Cassandra database. It enables users to query Cassandra using a language similar to SQL. Language drivers are available for Java (JDBC), Python (DBAPI2), Node.JS (Helenus), Go (gocql) and C++ [81].

- **Cassandra Data Model.** Cassandra consists of nodes, clusters, and data centers. A group of nodes or even a single node is a cluster and a group of clusters is a data center. It provides support for clusters across multiple data centers. Cassandra is a combination of key-value and column-oriented database management system. The main components of Cassandra data model are keyspace, tables, columns, and rows. A keyspace in Cassandra is a namespace that defines data replication on nodes. A cluster contains one keyspace per node. A table is a set of key-value pairs containing a column with its unique row keys. Rows are organized into tables. The first part of the primary key of a table is partition key, which clusters the rows by the remaining columns of the key.

4.6.3 Materials and Methods

Clinical data from eight datasets in NSRR [34] are used as data sources in this work, including Sleep Heart Health Study (SHHS) [59–61], Childhood Adenotonsillectomy Trial (CHAT) [62–64], Cleveland Family Study (CFS) [65–67], Heart Biomarker Evaluation in Apnea Treatment (HEARTBEAT) [68], Study of Osteoporotic Fractures (SOF) [69], MrOS Sleep Study (MrOS) [70], Hispanic Community Health Study /
Study of Latinos (HCHS) [71], and Multi-Ethnic Study of Atherosclerosis (MESA) [72]. Table 4.4 summarizes the eight datasets in terms of the patient visit, number of data elements, and number of patient subjects.

**Table 4.4:** Summary information for each of the eight datasets.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Visit(s)</th>
<th>Number of data elements</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHHS</td>
<td>shhs1</td>
<td>1,266</td>
<td>5,804</td>
</tr>
<tr>
<td></td>
<td>shhs2</td>
<td>1,302</td>
<td>4,080</td>
</tr>
<tr>
<td>CHAT</td>
<td>baseline</td>
<td>2,897</td>
<td>464</td>
</tr>
<tr>
<td></td>
<td>followup</td>
<td>2,897</td>
<td>453</td>
</tr>
<tr>
<td>CFS</td>
<td>visit5</td>
<td>2,871</td>
<td>735</td>
</tr>
<tr>
<td>HEARTBEAT</td>
<td>baseline</td>
<td>859</td>
<td>318</td>
</tr>
<tr>
<td></td>
<td>followup</td>
<td>731</td>
<td>301</td>
</tr>
<tr>
<td>SOF</td>
<td>visit8</td>
<td>1,114</td>
<td>461</td>
</tr>
<tr>
<td>MrOS</td>
<td>visit1</td>
<td>479</td>
<td>2,911</td>
</tr>
<tr>
<td></td>
<td>visit2</td>
<td>507</td>
<td>2,911</td>
</tr>
<tr>
<td>HCHS</td>
<td>sol</td>
<td>404</td>
<td>16,415</td>
</tr>
<tr>
<td></td>
<td>sueno</td>
<td>505</td>
<td>2,252</td>
</tr>
<tr>
<td>MESA</td>
<td>sleep</td>
<td>723</td>
<td>2,237</td>
</tr>
</tbody>
</table>

To evaluate SQL- and NoSQL-based approaches for patient cohort identification, we adapt the existing NSRR Cross Dataset Query Interface (CDQI) [82] based on MySQL, and develop two NoSQL-based query systems using MongoDB and Cassandra, respectively. Figure 4.7 shows the general system architecture of the three systems. It consists of four major components: (i) database management system; (ii) Ruby driver for the database management system; (iii) query translation; and (iv) web-based cross dataset query interface. The database component serves as the data warehouse to store the actual datasets. The web-based query interface receives queries composed by users, which are then translated into the statements in the corresponding query language. The Ruby driver then executes the translated query statements to retrieve data from the database. After receiving the query results, the interface
presents them to the end-users.

Figure 4.7: System Architecture.

4.6.3.1 Web-based Query Interface

We adapted the code base of the SQL-based NSRR CDQI in Ruby on Rails (RoR) to develop the two NoSQL-based query interface. RoR follows the model-view-controller architectural pattern, providing rich interaction with different types of databases and supporting HTML, CSS, and JavaScript for developing interactive user interfaces. The query translation, Ruby driver, and backend databases were newly implemented for MongoDB and Cassandra, respectively.

4.6.3.2 Query Translation - Dynamic Generation of Database Query Statement

Each time a user initiates a query through the web-based interface, the automated translation of this query (so-called query translation) into specified database query statement is needed. We illustrate the MongoDB-based query translation in the followings (MySQL- and Cassandra-based are similar). The dynamic query translation
relies on predefined general templates of MongoDB statement according to the types of queries. For example, the general template for querying a range of values for a numeric data element (or field) is predefined as:

```javascript
find("dataset" => <dataset.name>,
<field_1> => {'$gte' => <field_1_lower_value>,
'$lte' => <field_2_upper_value>}, ...
<field_n> => {'$gte' => <field_n_lower_value>,
'$lte' => <field_n_upper_value>});
```

where the variables `<dataset.name>` and `<field_n>` represent the specific dataset and the field that the user intend to query; and `<field_n_lower_value>`, `<field_n_upper_value>` represent the user-specified minimum value and maximum value of the field, respectively. All the variables in the angle brackets can be replaced by real values to generate the actual MongoDB statement. For instance, “finding patients in the SHHS dataset aged (field_1) from 20 to 80 with height in centimeters (field_2) between 145 and 188” will have the following values for the variables in the template:

```javascript
<dataset.name>: SHHS
<field_1>: age
<field_1_lower_value>: 20
<field_1_upper_value>: 80
<field_2>: height
<field_2_lower_value>: 145
<field_2_upper_value>: 188
```

Substituting the variables in the template with actual values obtains the following MongoDB statement:

```javascript
find("dataset" => "SHHS",
"age" => {'$gte' => 20, '$lte' => 80},
"height" => {'$gte' => 145, '$lte' => 188});
```
4.6.3.3 Ruby Driver for the Database Management System

As illustrated in Figure 4.7, we utilize certain types of databases (MySQL, MongoDB, Cassandra) as the data warehouse to store disparate datasets. All three database management systems used in this study support a Ruby driver, which can seamlessly work with RoR to interact with the database management systems. Take MongoDB as an example, we use MongoDB Ruby driver [83] (version 2.4.1), which enables the connection to the MongoDB data warehouse and executes query statements to retrieve patient cohorts satisfying the query criteria.

4.6.3.4 Data Modeling in NoSQL Databases

Utilizing NoSQL databases require different data model compared to SQL relational databases.

- **MongoDB.** The data schema for MongoDB in this study consists of one database, called *nsrr*, and one collection, called *nsrrdata*. All the eight datasets were integrated into the collection of *nsrrdata*. To differentiate records from different datasets, a key-value pair with a key as “source” was inserted into each record to indicate the source dataset of this record during the importing process. For those datasets which have more than one visit, another key-value pair with a key as “visitType” was inserted.

- **Cassandra.** The Cassandra database schema consists of a single cluster, called *nsrrcluster*, a single keyspace, called *nsrrdata*, and eight tables corresponding to the eight datasets. Similar to MongoDB, one extra column named “visitType” was added for those datasets with more than one visit. A keyspace in Cassandra is a namespace that defines data replication on nodes. The replication strategy for replicas and the replication factors are properties from the keyspace. By selecting the replication strategy for replicas, one can determine whether data is distributed through different networks. In this work, we chose the Simple
Strategy [84] since it was performed in a single cluster. Furthermore, the main purpose of this study is to compare performance rather than fault recovery, so we set the replication factor as one. Another reason we used a single cluster is that a larger number of replicas would also interfere with the data loading time.

4.6.4 Data Integration - Loading and Harmonization

The integration of disparate datasets into a data warehouse usually involves data loading and data harmonization.

4.6.4.1 Data Loading Procedure

In MySQL-based NSRR CDQI, to load the NSRR datasets into databases, we need to perform data preprocessing. A dedicated program is needed to split the data “horizontally” into separate data files and store them in different tables. The detailed procedures for a given dataset are as follows. First, the program reads the CSV file of a patient visit in the dataset, calculates the required number of tables, and splits the CSV file into multiple smaller CSV files. Then, the program reads the smaller files individually and imports them into corresponding tables. Apparently, the limitation of the maximum table column count in MySQL does increase the complexity from the data loading point of view. Even though each of the eight datasets contains thousands of data elements or columns, importing data into NoSQL databases is fairly straightforward, since (1) following the data model mentioned above, we can easily import all eight datasets into the NoSQL databases; and (2) no data split is needed.

4.6.4.2 Data Harmonization Procedure

We take three important steps to harmonize coding inconsistencies before the data can be used for query: (i) we run the inconsistency detection program to detect and extract all the inconsistent codings among different datasets; (ii) we manually har-
monize these inconsistency codings into uniform codings, and maintain the mappings between them in a CSV file; (iii) we run another program to update the harmonized codings in corresponding tables stored in different databases. All three query systems take similar steps to perform data harmonization.

4.6.5 Results

In this section, we first present the results for data loading and harmonization of the eight NSRR datasets, then we present the comparative evaluation of the three patient cohort query systems using MySQL, MongoDB, and Cassandra, respectively. All these evaluations were conducted on a computer with Intel Core i5/2.9 GHz processor and 8 GB RAM.

4.6.5.1 Data Loading and Harmonization

We integrated a total of 39,342 patient records from eight NSRR sleep datasets into MySQL, MongoDB, and Cassandra, respectively. Table 4.5 shows the numbers of tables needed for all three systems. MySQL required twenty tables due to the limitation on the table column count, while MongoDB only required one, and Cassandra required eight.

Table 4.5: Numbers of tables needed for each database system to load the eight datasets.

<table>
<thead>
<tr>
<th>Database System</th>
<th>Number of Tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>MySQL</td>
<td>20</td>
</tr>
<tr>
<td>MongoDB</td>
<td>1</td>
</tr>
<tr>
<td>Cassandra</td>
<td>8</td>
</tr>
</tbody>
</table>

We detected coding inconsistencies for 43 query concepts within eight datasets. These coding inconsistencies were harmonized into uniform codings. Take the heterogeneous codings for gender as an example, the harmonized coding is: 1 - male.
and 2 - *female*. For those datasets which are not consistent with this coding, the harmonization was performed to update the source data with the harmonized coding.

### 4.6.5.2 Comparison of Relational and NoSQL Databases

We performed a comparison between SQL and NoSQL databases in terms of the data loading, data harmonization, and query performance. For data loading, we compared the time spent on importing data into MySQL, MongoDB, and Cassandra, respectively. For data harmonization, we compared the detected number of concepts with coding inconsistency, detection time, and harmonization time. For query performance, we designed several sets of patient cohort queries that are composed of a single query concept or multiple query concepts to compare the query time. In the following, each reported time was obtained by performing the corresponding operation five times and taking the average time.

**Data Loading**

Table 4.6 shows the time taken for importing each dataset into the three database systems. It took MongoDB a total of 419.2 seconds, MySQL 337.0 seconds, and Cassandra 330.9 seconds, to load 39,342 records in the eight datasets. MongoDB took more time than MySQL and Cassandra for data loading.

Figure 4.8 visually demonstrates the loading time of eight datasets using MySQL, MongoDB, and Cassandra, respectively.

**Data Harmonization** Although utilizing different databases, the first two steps for data harmonization were identical in three systems. We were able to detect coding inconsistency for the same number (43) of concepts within eight datasets in five seconds. Table 4.7 shows the time taken to perform data harmonization in each system. It took all the three systems over 6 hours to complete the harmonization. The runtime complexities were similar since all these databases need to traverse all the records and update the corresponding column names, values (MySQL, Cassandra),
Table 4.6: Time to load eight datasets into MySQL, MongoDB, and Cassandra, respectively.

<table>
<thead>
<tr>
<th>Datasets</th>
<th>MySQL</th>
<th>MongoDB</th>
<th>Cassandra</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHHS</td>
<td>165.2s</td>
<td>207.7s</td>
<td>159.8s</td>
</tr>
<tr>
<td>CHAT</td>
<td>22.2s</td>
<td>29.3s</td>
<td>25.6s</td>
</tr>
<tr>
<td>CFS</td>
<td>22.2s</td>
<td>35.7s</td>
<td>29.8s</td>
</tr>
<tr>
<td>HEARTBEAT</td>
<td>1.9s</td>
<td>2.5s</td>
<td>2.2s</td>
</tr>
<tr>
<td>SOF</td>
<td>4.2s</td>
<td>4.5s</td>
<td>3.7s</td>
</tr>
<tr>
<td>MrOS</td>
<td>35.4s</td>
<td>39.1s</td>
<td>28.1s</td>
</tr>
<tr>
<td>HCHS</td>
<td>45.1s</td>
<td>56.9s</td>
<td>45.2s</td>
</tr>
<tr>
<td>MESA</td>
<td>40.8s</td>
<td>43.5s</td>
<td>36.5s</td>
</tr>
<tr>
<td>Total</td>
<td>337.0s</td>
<td>419.2s</td>
<td>330.9s</td>
</tr>
</tbody>
</table>

Figure 4.8: Data loading time comparison.

or key-values (MongoDB). Cassandra required the least time to harmonize the data as it provides the best performance on the write operation.

Table 4.7: Harmonization time for three systems.

<table>
<thead>
<tr>
<th>System</th>
<th>Harmonization Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>MySQL-based</td>
<td>6h 53m 53s</td>
</tr>
<tr>
<td>MongoDB-based</td>
<td>7h 9m 47s</td>
</tr>
<tr>
<td>Cassandra-based</td>
<td>6h 25m 15s</td>
</tr>
</tbody>
</table>
Query Performance To evaluate the query performance of the SQL- and NoSQL-based systems, we conducted experiments on performing patient cohort queries across the eight datasets. Each cohort query consists of one or more query concepts. Three sets of cohort queries were used. The first set of queries involved only one concept, while the second set and the third set involved two and four concepts, respectively.

Note that due to the limit of the table column count in MySQL, data elements exceeding the limit need to be split into multiple tables. In addition, there might be multiple data elements corresponding to the same query concept. For instance, in the SHHS dataset, there are three data elements mapped to the query concept Hypertension as follows.

- \( htn\text{erv}_s1 \): Hypertension Status based on 2nd and 3rd blood pressure readings or being treated with HTN meds;
- \( sr\text{hype} \): Self-Reported Hypertension; and
- \( htn\text{erv}_s2 \): Derived Hypertension classification (based on blood pressure measurements, history of HTN dx, and medication use).

Such related data elements may be stored within the same table or across multiple tables. Therefore, a query concept may involve data elements within the same table or across multiple tables in the MySQL-based query system. We refer to query concepts involving data elements across multiple tables as cross-table query concepts.

Table 4.8 presents the time taken for each query using MySQL-based system. The highlighted time indicates that the corresponding query involves cross-table query concepts in the corresponding dataset. For example, in the SHHS dataset, Age, Asthma, Hypertension, and Time Awake after Sleep Onset are the cross-table query concepts.

As can be seen from Table 4.8, when querying Age in the CFS dataset, the query time was relatively short, since Age was a within-table query concept. Even when
**Table 4.8**: Cohort query time for the MySQL-based system.

<table>
<thead>
<tr>
<th>Query Concept</th>
<th>SHHS</th>
<th>CHAT</th>
<th>CFS</th>
<th>HEARTBEAT</th>
<th>SOF</th>
<th>MoOS</th>
<th>HCHS</th>
<th>MESA</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.10s</td>
<td>1.53s</td>
<td>0.039s</td>
<td>0.56s</td>
<td>NA</td>
<td>NA</td>
<td>0.04s</td>
<td>NA</td>
<td>1.04s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.05s</td>
<td>0.00s</td>
<td>0.006s</td>
<td>0.06s</td>
<td>0.10s</td>
<td>0.24s</td>
<td>0.04s</td>
<td>5.21s</td>
<td>0.38s</td>
</tr>
<tr>
<td>Asthma</td>
<td>3.63s</td>
<td>0.00s</td>
<td>0.01s</td>
<td>0.04s</td>
<td>0.006s</td>
<td>NA</td>
<td>0.03s</td>
<td>NA</td>
<td>0.83s</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.33s</td>
<td>0.04s</td>
<td>0.01s</td>
<td>0.008s</td>
<td>0.004s</td>
<td>NA</td>
<td>1.64s</td>
<td>0.01s</td>
<td>NA</td>
</tr>
<tr>
<td>Time Awake after Sleep Onset</td>
<td>3.55s</td>
<td>0.13s</td>
<td>0.12s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.06s</td>
<td>NA</td>
<td>0.97s</td>
</tr>
<tr>
<td>Weight</td>
<td>0.10s</td>
<td>0.05s</td>
<td>0.009s</td>
<td>0.02s</td>
<td>NA</td>
<td>1.14s</td>
<td>NA</td>
<td>NA</td>
<td>0.21s</td>
</tr>
<tr>
<td>Gender &amp; Weight</td>
<td>0.05s</td>
<td>0.00s</td>
<td>0.007s</td>
<td>0.02s</td>
<td>0.04s</td>
<td>0.21s</td>
<td>0.07s</td>
<td>NA</td>
<td>0.28s</td>
</tr>
<tr>
<td>Asthma &amp; Gender</td>
<td>0.51s</td>
<td>0.05s</td>
<td>0.014s</td>
<td>0.013s</td>
<td>NA</td>
<td>1.41s</td>
<td>0.26s</td>
<td>NA</td>
<td>2.21s</td>
</tr>
<tr>
<td>Atrial &amp; Hypertension</td>
<td>0.18s</td>
<td>0.12s</td>
<td>0.028s</td>
<td>0.006s</td>
<td>NA</td>
<td>2.71s</td>
<td>0.05s</td>
<td>NA</td>
<td>1.43s</td>
</tr>
<tr>
<td>Hypertension &amp; Time Awake after Sleep Onset</td>
<td>5.27s</td>
<td>0.12s</td>
<td>0.072s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.81s</td>
</tr>
<tr>
<td>Asthma &amp; Gender &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>12.90s</td>
<td>0.31s</td>
<td>0.034s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.42s</td>
</tr>
<tr>
<td>Asthma &amp; Weight &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>10.21s</td>
<td>0.31s</td>
<td>0.029s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.48s</td>
</tr>
</tbody>
</table>

NA means unavailable information & Bold numbers indicate that corresponding query concept(s) involve data elements from multiple tables.

**Table 4.9**: Cohort query time for the MongoDB-based system.

<table>
<thead>
<tr>
<th>Query Concept</th>
<th>SHHS</th>
<th>CHAT</th>
<th>CFS</th>
<th>HEARTBEAT</th>
<th>SOF</th>
<th>MoOS</th>
<th>HCHS</th>
<th>MESA</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.15s</td>
<td>0.06s</td>
<td>0.05s</td>
<td>0.05s</td>
<td>NA</td>
<td>NA</td>
<td>0.15s</td>
<td>NA</td>
<td>0.092s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.06s</td>
<td>0.06s</td>
<td>0.05s</td>
<td>0.05s</td>
<td>0.04s</td>
<td>0.06s</td>
<td>0.11s</td>
<td>0.05s</td>
<td>0.06s</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.45s</td>
<td>0.05s</td>
<td>0.06s</td>
<td>0.06s</td>
<td>NA</td>
<td>0.08s</td>
<td>0.14s</td>
<td>NA</td>
<td>0.14s</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.31s</td>
<td>0.05s</td>
<td>0.05s</td>
<td>0.04s</td>
<td>NA</td>
<td>0.08s</td>
<td>0.14s</td>
<td>NA</td>
<td>0.12s</td>
</tr>
<tr>
<td>Time Awake after Sleep Onset</td>
<td>0.36s</td>
<td>0.11s</td>
<td>0.13s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.12s</td>
<td>NA</td>
<td>0.18s</td>
</tr>
<tr>
<td>Weight</td>
<td>0.10s</td>
<td>0.13s</td>
<td>0.04s</td>
<td>0.05s</td>
<td>NA</td>
<td>0.05s</td>
<td>0.10s</td>
<td>NA</td>
<td>0.074s</td>
</tr>
<tr>
<td>Gender &amp; Weight</td>
<td>0.15s</td>
<td>0.04s</td>
<td>0.06s</td>
<td>0.05s</td>
<td>NA</td>
<td>0.06s</td>
<td>NA</td>
<td>NA</td>
<td>0.07s</td>
</tr>
<tr>
<td>Asthma &amp; Gender</td>
<td>0.56s</td>
<td>0.05s</td>
<td>0.08s</td>
<td>0.07s</td>
<td>NA</td>
<td>0.08s</td>
<td>0.14s</td>
<td>NA</td>
<td>0.138s</td>
</tr>
<tr>
<td>Atrial &amp; Hypertension</td>
<td>0.60s</td>
<td>0.60s</td>
<td>0.14s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.44s</td>
</tr>
<tr>
<td>Hypertension &amp; Time Awake after Sleep Onset</td>
<td>0.61s</td>
<td>0.68s</td>
<td>0.12s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.47s</td>
</tr>
<tr>
<td>Asthma &amp; Weight &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>0.51s</td>
<td>0.63s</td>
<td>0.11s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.42s</td>
</tr>
</tbody>
</table>

NA means unavailable information.

**Table 4.10**: Cohort query time for the Cassandra-based system.

<table>
<thead>
<tr>
<th>Query Concept</th>
<th>SHHS</th>
<th>CHAT</th>
<th>CFS</th>
<th>HEARTBEAT</th>
<th>SOF</th>
<th>MoOS</th>
<th>HCHS</th>
<th>MESA</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.92s</td>
<td>0.11s</td>
<td>0.05s</td>
<td>0.11s</td>
<td>NA</td>
<td>NA</td>
<td>0.52s</td>
<td>NA</td>
<td>0.492s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.19s</td>
<td>0.06s</td>
<td>0.04s</td>
<td>0.10s</td>
<td>0.06s</td>
<td>0.11s</td>
<td>0.12s</td>
<td>NA</td>
<td>0.15s</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.95s</td>
<td>0.07s</td>
<td>0.08s</td>
<td>0.11s</td>
<td>NA</td>
<td>0.07s</td>
<td>0.59s</td>
<td>NA</td>
<td>0.36s</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.82s</td>
<td>0.16s</td>
<td>0.09s</td>
<td>0.15s</td>
<td>NA</td>
<td>0.07s</td>
<td>0.31s</td>
<td>NA</td>
<td>0.355s</td>
</tr>
<tr>
<td>Time Awake after Sleep Onset</td>
<td>0.89s</td>
<td>0.22s</td>
<td>0.07s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.28s</td>
<td>NA</td>
<td>0.36s</td>
</tr>
<tr>
<td>Weight</td>
<td>0.39s</td>
<td>0.19s</td>
<td>0.09s</td>
<td>0.11s</td>
<td>NA</td>
<td>0.11s</td>
<td>NA</td>
<td>NA</td>
<td>0.18s</td>
</tr>
<tr>
<td>Gender &amp; Weight</td>
<td>0.55s</td>
<td>0.10s</td>
<td>0.13s</td>
<td>0.09s</td>
<td>NA</td>
<td>0.13s</td>
<td>1.14s</td>
<td>NA</td>
<td>0.35s</td>
</tr>
<tr>
<td>Asthma &amp; Gender</td>
<td>0.83s</td>
<td>0.13s</td>
<td>0.14s</td>
<td>0.12s</td>
<td>NA</td>
<td>0.13s</td>
<td>1.21s</td>
<td>NA</td>
<td>0.43s</td>
</tr>
<tr>
<td>Asthma &amp; Hypertension</td>
<td>1.01s</td>
<td>0.12s</td>
<td>0.13s</td>
<td>0.16s</td>
<td>NA</td>
<td>0.11s</td>
<td>0.12s</td>
<td>NA</td>
<td>0.275s</td>
</tr>
<tr>
<td>Hypertension &amp; Time Awake after Sleep Onset</td>
<td>1.38s</td>
<td>0.14s</td>
<td>0.13s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.16s</td>
</tr>
<tr>
<td>Asthma &amp; Gender &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>1.29s</td>
<td>1.14s</td>
<td>0.22s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.85s</td>
</tr>
<tr>
<td>Asthma &amp; Weight &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>1.04s</td>
<td>1.21s</td>
<td>0.25s</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.83s</td>
</tr>
</tbody>
</table>

NA means unavailable information.

querying two or more concepts at the same time, as long as they were from the same table, the query times were almost less than 0.1 seconds.

For the SHHS dataset, querying within-table concept Gender only took 0.03 seconds. However, when executing “AND” logic queries that contain two concepts involving different tables in MySQL, the query took more than 3 seconds. The situation could get even worse if the query consisted of multiple cross-table concepts. For in-
Figure 4.9: Average query time for each query using MySQL, MongoDB, and Cassandra.

stance, four query concepts *Asthma, Gender, Hypertension*, and *Time Awake after Sleep Onset* took about 12 seconds to complete. These illustrate that the MySQL-based system encountered a dramatic query time increase when querying cross-table concepts. The major reason for such increment is that when performing such queries, the traditional relational database needs to perform costly JOIN operations.

Tables 4.9 and 4.10 show the query time taken for the MongoDB-based and Cassandra-based systems, respectively. There is no highlighted time in these two tables since no data split operations were needed for these two NoSQL databases. For the *SHHS* dataset, both MongoDB and Cassandra achieved better performance when querying MySQL cross-table concepts (see the highlighted times in Table 4.8); however, for single-table concepts, the performance varied. For the *CHAT* dataset, all the queries were the cross-table concepts in MySQL, the performance of MongoDB and Cassandra were sometimes better than that of MySQL, while sometimes worse. This may be because the *CHAT* dataset contains a small number of patient records (917, see Table 4.4), in which case MySQL was efficient in performing the JOIN operation on data across tables.
Figure 4.9 shows the average time taken for each query using three different database systems. We can see that both MongoDB and Cassandra achieved consistently faster query performance compared to MySQL. MongoDB demonstrated the best query performance. MySQL performance was highly dependent on the query concepts.

### 4.6.5.3 Statistical Evaluation of Average Query Time

To evaluate the statistical significance of the differences in the average query times, we conducted t-test using two independent means with 0.05 significance level and two-tailed hypothesis. If the p-value is less than 0.05, then query performances are considered significantly different. As shown in Table 4.11, we can see the p-values are less than 0.05 for MySQL vs. MongoDB and MySQL vs. Cassandra. This indicates that the two NoSQL-based systems achieved a significantly better query performance than the MySQL-based system did.

**Table 4.11:** T-test result for two independent means using average query time.

<table>
<thead>
<tr>
<th>Comparative Pair</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MySQL &amp; MongoDB</td>
<td>3.5785</td>
<td>0.001676</td>
</tr>
<tr>
<td>MySQL &amp; Cassandra</td>
<td>2.93414</td>
<td>0.007678</td>
</tr>
</tbody>
</table>

### 4.6.5.4 Scalability

To evaluate the scalability of the SQL and NoSQL-based system, we conducted experiments on performing patient cohort queries across SHHS datasets with different scales. The rationale to use the SHHS dataset for scalability evaluation were in two folds: (i) it contained the largest number of data records among these eight datasets; (ii) it contained data elements mapping to both within-table and cross-table query concepts.
We scaled up the SHHS dataset by duplicating the original data records by three, five, and ten times, which are denoted as SHHSx3, SHHSx5, and SHHSx10 respectively. Note that these duplicated data also had unique identifiers starting from the last identifier of the original data record. The cohort queries were identical to those that were previously used for evaluating the query performance.

Table 4.12 shows the time taken for each query in different scales using the MySQL-based system. Each highlighted time indicates that the corresponding query involved cross-table query concepts.

<table>
<thead>
<tr>
<th>Query Concept</th>
<th>MySQL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHHS</td>
</tr>
<tr>
<td>Age</td>
<td>3.10s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.03s</td>
</tr>
<tr>
<td>Asthma</td>
<td>3.63s</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.33s</td>
</tr>
<tr>
<td>Time Awake after Sleep Onset</td>
<td>3.59s</td>
</tr>
<tr>
<td>Weight</td>
<td>0.10s</td>
</tr>
<tr>
<td>Gender &amp; Weight</td>
<td>0.05s</td>
</tr>
<tr>
<td>Asthma &amp; Gender</td>
<td>6.51s</td>
</tr>
<tr>
<td>Asthma &amp; Hypertension</td>
<td>6.18s</td>
</tr>
<tr>
<td>Hypertension &amp; Time Awake after Sleep Onset</td>
<td>5.27s</td>
</tr>
<tr>
<td>Asthma &amp; Gender &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>12.90s</td>
</tr>
<tr>
<td>Asthma &amp; Weight &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>10.21s</td>
</tr>
</tbody>
</table>

As we can see from Table 4.12, when querying Gender for these scaled datasets, the query times were short, since Gender was a within-table query concept. Even for a query with two or more concepts, the query time remained short if these concepts were within-table (e.g., concepts Gender and Weight). However, when performing cross-table queries, the query times increased dramatically along with the scales. For instance, when querying Age, the query times were 3.10s, 31.76s, 87.1s, and 318.56s for SHHS, SHHSx3, SHHSx5, and SHHSx10, respectively. The query time for concept Age was over 5 minutes when the number of data records was ten times larger. The situation could get even worse for queries consisting of multiple cross-table concepts. For instance, it would take 917 seconds to query four concepts Asthma, Gender,
Hypertension, and Time Awake after Sleep Onset. These illustrate that the MySQL-based system did not provide decent scalability for high-dimensional data in our case.

Tables 4.13 and 4.14 present the query times taken for the MongoDB-based and Cassandra-based systems. For these NoSQL-based systems, there was no need to split tables for a single dataset. We can see from the tables, both MongoDB-based and Cassandra-based system achieved tremendously better performance when querying MySQL cross-table concepts.

To better demonstrate the scalability of these three systems, Figure. 4.10, 4.11, and 4.12 show the query times of different scaled SHHS datasets for each query. In these figures, Q1 to Q12 are corresponding to the queries in Table 4.12 from top to bottom. We can see that the increment of query time along with the size of datasets for both MongoDB-based and Cassandra-based system was small. These NoSQL-based systems demonstrated better scalability in terms of query performance compared to the MySQL-based system.

Table 4.13: Cohort query time for the MongoDB-based system.

<table>
<thead>
<tr>
<th>Query Concept</th>
<th>SHHS</th>
<th>SHHSx3</th>
<th>SHHSx5</th>
<th>SHHSx10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.15s</td>
<td>0.12s</td>
<td>0.15s</td>
<td>0.25s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.06s</td>
<td>0.06s</td>
<td>0.08s</td>
<td>0.10s</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.45s</td>
<td>0.45s</td>
<td>0.56s</td>
<td>0.66s</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.31s</td>
<td>0.35s</td>
<td>0.47s</td>
<td>0.67s</td>
</tr>
<tr>
<td>Time Awake after Sleep Onset</td>
<td>0.36s</td>
<td>0.29s</td>
<td>0.46s</td>
<td>0.56s</td>
</tr>
<tr>
<td>Weight</td>
<td>0.10s</td>
<td>0.13s</td>
<td>0.14s</td>
<td>0.21s</td>
</tr>
<tr>
<td>Gender &amp; Weight</td>
<td>0.15s</td>
<td>0.14s</td>
<td>0.16s</td>
<td>0.25s</td>
</tr>
<tr>
<td>Asthma &amp; Gender</td>
<td>0.31s</td>
<td>0.38s</td>
<td>0.47s</td>
<td>0.65s</td>
</tr>
<tr>
<td>Asthma &amp; Hypertension</td>
<td>0.50s</td>
<td>0.55s</td>
<td>0.56s</td>
<td>0.67s</td>
</tr>
<tr>
<td>Hypertension &amp; Time Awake after Sleep Onset</td>
<td>0.60s</td>
<td>0.62s</td>
<td>0.66s</td>
<td>0.77s</td>
</tr>
<tr>
<td>Asthma &amp; Gender &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>0.61s</td>
<td>0.68s</td>
<td>0.76s</td>
<td>0.86s</td>
</tr>
<tr>
<td>Asthma &amp; Weight &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>0.51s</td>
<td>0.63s</td>
<td>0.65s</td>
<td>0.91s</td>
</tr>
</tbody>
</table>

4.6.5.5 Distinction with Related Work

Weber et al. [50] have developed a prototype Shared Health Research Information Network (SHRINE) based on i2b2 for the federated query of clinical data repositories.
Table 4.14: Cohort query time for the Cassandra-based system.

<table>
<thead>
<tr>
<th>Query Concept</th>
<th>Cassandra</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHHS</td>
</tr>
<tr>
<td>Age</td>
<td>0.92s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.16s</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.95s</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.82s</td>
</tr>
<tr>
<td>Time Awake after Sleep Onset</td>
<td>0.89s</td>
</tr>
<tr>
<td>Weight</td>
<td>0.39s</td>
</tr>
<tr>
<td>Gender &amp; Weight</td>
<td>0.55s</td>
</tr>
<tr>
<td>Asthma &amp; Gender</td>
<td>0.83s</td>
</tr>
<tr>
<td>Asthma &amp; Hypertension</td>
<td>1.01s</td>
</tr>
<tr>
<td>Hypertension &amp; Time Awake after Sleep Onset</td>
<td>1.32s</td>
</tr>
<tr>
<td>Asthma &amp; Gender &amp; Hypertension</td>
<td>1.22s</td>
</tr>
<tr>
<td>Asthma &amp; Weight &amp; Hypertension &amp; Time Awake after Sleep Onset</td>
<td>1.04s</td>
</tr>
</tbody>
</table>

Figure 4.10: Query time of MySQL for SHHS Dataset with Different Scales.

Figure 4.11: Query time of MongoDB for SHHS Dataset with Different Scales.

Figure 4.12: Query time of Cassandra for SHHS Dataset with Different Scales.
However, the i2b2/SHRINE system deals with uniform data across different i2b2 instances, where these instances share the same data structure. In this work, we mainly focused on the heterogeneous and high-dimensional data across disparate datasets, where these datasets have different data structures.

Another related work is the MongoDB-based cohort query tool for clinical repositories [78], where the tool can be used to query a single data source. In this work, we deal with multiple data sources and explored another NoSQL-based approach.

4.6.5.6 Limitations

A limitation of this work is that the sizes of the NSRR datasets are limited in the number of patient records (39,342 records). Although it was shown that the NoSQL-based systems outperformed the SQL-based system on the NSRR datasets, it would be interesting to see how they perform when the number of patient records gets extremely large and to compare the actual storage required by different databases. Another limitation is that we only explored two NoSQL database systems to facilitate the patient cohort queries across disparate sources. Compared with these two, how other NoSQL databases perform still needs further investigation.

We developed two NoSQL-based patient cohort identification systems, in comparison to a SQL-based system, to evaluate their performance on supporting high-dimensional and heterogeneous data sources in NSRR. Utilizing NoSQL databases, we overcame the limitation of maximum table column count in traditional relational databases. We successfully integrated eight NSRR cross-cohort datasets into NoSQL databases, which largely enhanced the query performance compared to the MySQL-based system, while maintained similar performance for data loading and harmonization. This study indicates that NoSQL-based systems offer a promising approach for developing patient cohort query systems across heterogeneous data sources.
4.7 Conclusion

In this chapter, we presented X-search, NSRR’s cross-cohort exploration system to query patient cohort counts across heterogeneous datasets in the National Sleep Research Resource. X-search follows the FAIR principles and enforces the findable, accessible principles. X-search allows users to query and explore datasets in the NSRR data repository, making the data from NSRR findable. After finding the data, users can use the identifiers acquired from the x-search and request data access from NSRR.

X-search has received queries from 16 countries and enabled researchers to perform cross-cohort queries and exploration to evaluate the feasibility of potential research studies using shared data in the NSRR repository. Additionally, we compare the performance between SQL-based and NoSQL-bases backend storage engines. From the comparison, the NoSQL-based query engine works better in our case. Therefore, in the next chapter, we will present a NoSQL-based query interface.
CHAPTER 5. An Integrative Data Repository for Studying Risk Factors Associated with Pressure Injuries Resulting from Spinal Cord Injury

In the previous chapter, we compared the performance between SQL-based and NoSQL bases MetaSphere and found out that the NoSQL-based MetaSphere performed better. In this chapter, we will discuss the application of NoSQL-based MetaSphere to spinal cord injuries domain.

5.1 Motivation and Challenges

Pressure Injuries (PrI) and Deep Tissue Injury (DTI) are serious conditions among those individuals with spinal cord injury (SCI), resulting in tremendous personal and societal costs. Primary PU/DTI prevention plays a critical role in the first line of defense, while it is also challenging as there are many risk factors to consider ranging from the individual’s environment to local tissue health. The integration of PU/DTI risk data, ranging from the living environment and age to tissue blood flow, requires a robust and scalable informatics approach to cope with big-data challenges in volume and complexity. This chapter presents SCIPUDSphere - a data repository, that extracts, integrates, stores a wide range of PU/DTI risk factors of data and provides a user query interface for identifying subgroups hypothesis generation. We extracted a total of 268,562 records containing 282 ICD9 codes related to SCI among 105,599 individuals from the Veterans Administration’s VA Informatics and Computing Infrastructure (VINCI) electronic health records. These records consist of demographics, comorbidities, medications, and patient SCI diagnosis, and they are integrated into SCIPUDSphere. SCIPUDSphere is being utilized as the data source to develop a model aiming to identify major risk factors based on individual cases.
5.2 Pressure Injuries (PrI) and Deep Tissue Pressure Injury (DTPrI)

Pressure Ulcer (PU) and Deep Tissue Injury (DTI) are serious and costly complications for some populations, such as those with spinal cord injury (SCI), who remain at high risk throughout their lifetimes. Clinical observations and research have demonstrated staggering costs and human suffering [15–17] for PU/DTI. In addition to the psychological distress and detrimental effects on quality of life (QoL) for the individual, chronic wounds place a significant burden on health care systems. US costs estimated to be up to $15 billion per year, with an individual PU costing as much as $37,800 - $70,000 to treat [85–87]. It has been estimated that PU prevention is approximately 2.5 times more economical than treatment [18]. Clinical practice guidelines (CPG) provide best practice recommendations for PU/DTI prevention [19–21], however, the many recommendations in a CPG reflect the multivariate nature of PU/DTI management. In order to successfully prevent and treat PU/DTI in the SCI population, it is essential to consider multiple risk factors because they contribute to the formulation of treatment and rehabilitation strategies [22]. These factors involve multiple domains, from the environmental factors related to the location of the patient (inpatient/nursing home/community dwelling) to the individual’s tissue health profile. These domains can interact, working in opposition, or in concert. This complexity highlights the challenge of PU/DTI prevention and is indicative of the need for a holistic and systematic approach. However, the integration of PU/DTI risk data, ranging from the living environment and age to tissue blood flow, requires a robust and scalable informatics approach to cope with big-data challenges in volume and complexity. PU/DTI risk data is collected using systems with a variety of different sampling rates and resolutions, with non-standard (often proprietary) data formats. For example, the clinical and demographic data of interest in PU/DTI is collected in the electronic medical record (EMR) at annual evaluations or when the
Veteran attends the outpatient clinic for wound care with clinical information coded and in free form clinical text notes. Conversely, tissue oxygenation data is collected during tissue health assessments at a rate of 5Hz in a standardized format. Thus data extraction, data integration, and data sharing are complex and challenging problems in PU/DTI risk data. To overcome these challenges, we developed an integrating repository called SCIPUDSphere following the FAIR [7] principles. SCIPUDSphere is a web-based system provides researchers with access to a large, curated dataset of de-identified patients with SCI and the tools to explore those data. It uses a novel Spinal Cord Injury Pressure Ulcer and Deep tissue injury ontology (SCIPUDO) as the knowledge resource for processing specialized terms related to SCI, PU, and DTI. Its data originates from SCI patients who are provided care by the Veterans Administration (VA) medical system through its VA Informatics and Computing Infrastructure (VINCI).

5.3 VA Informatics and Computing Infrastructure (VINCI)

The VA provides care for a large number of individuals with spinal cord injuries. The large number of individuals combined with the extensive records for each patient provides us with an unprecedented opportunity to integrate and analyze the impacts of a wide range of PU/DTI risk factors of data, we need a rich data resource which can be provided by the VA Informatics and Computing Infrastructure (VINCI).

The VA has been developing electronic medical record systems since 1982 and its latest system, Vista, since 1996. It provides a comprehensive record of all aspects of the VA healthcare system including each encounter a patient has with a provider. Data from the Vista system is extracted and loaded into the VINCI system on a daily basis, providing a rich pool of raw data for researchers.

VINCI is an initiative to improve researchers’ access to VA data and to facilitate the analysis of those data while ensuring Veterans’ privacy and data security. VINCI
hosts many datasets and provides many types of analytical applications. Researchers can access the VA data and tools for reporting and analysis in a secure Workspace called VINCI Workspace.

5.4 Related work

Zhang et al. developed the National Sleep Research Resource (NSRR) [11], a data-sharing system for integrating clinical data and physiological signals from NIH-funded epidemiological cohort studies in sleep research. NSRR fully supports the FAIR principles. We adapted some of the methodologies from NSRR for building the SCIPUDSphere system and followed FAIR [7] principles. X-search [82] is a tool developed by the NSRR team. It is an open-access interface for cross-cohort exploration of the National Sleep Research Resource, provides a flexible framework featuring an ontology-driven query module. In the front-end, X-search provides query widgets that allow users to build queries for cohort searching and exploring. The X-search query interface consists of two major components. In the left part of the interface, there is a list of concepts along with concept construction widget and query results on the right side. Our SCIPUDSphere shares a similar interface layout with X-search but supported by our new SCIPUDO ontology.

5.5 Method

The design of SCIPUDSphere involves three seamlessly integrated modules: 1): Ontology Support, 2): environmental, social, and clinical domain database and 3): SCIPUDSphere User Interface. Agile development and agile project management methodologies were used to achieve a flexible, modern, and user-friendly web-based data management tool using the Ruby on Rails framework [46]. Figure 5.1 illustrates the architecture of SCIPUDSphere system.

As shown in Figure 5.1, risk data is first extracted from the VINCI system. After
data processing, these risk data are transformed into mapped risk data which is then be imported into the domain database using MongoDB. MongoDB is a document-based NoSQL database that does not require a data schema and provides fast query performance. Finally, Researchers and clinicians are able to query the risk data using our query interface enhanced through our SCIPUDO by helping users formulate their queries via graphical construction of their queries in a step by step fashion. The query results are rendered immediately after the query executions are done. The results consist of a unique patient identifier and patient data related to queried concepts. Unique patient identifiers are extremely useful for complete patient data retrieval if more information is needed for these patients. Researchers and clinicians are able to download the results to facilitate their researches.

We followed the agile development process where developers work closely with the end-users to identify desired changes to the application. As users make use of the application, the provide suggestions for desired functionalities and describe problems with the current system. Developers implement desired functionality changes and resolve issues with each update cycle. This process allowed us to implement the most valuable features as quickly as possible. This development process provided many small changes applied to the servers rather than a few large updates.

![Figure 5.1: SCIPUDSphere System Architecture.](image-url)
5.5.1 Ontology Support

The dedicated domain ontology Spinal Cord Injury Pressure Ulcer and Deep tissue injury ontology was created by reusing terminology from existing systems ranging from anatomy (SNOMED CT), disease classification (ICD-9 and 10), medication (RxNorm), and National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements. The SCIPUDO consists of a set of concepts (terms) in the PrI/DTPrI domain and the relationships between the concepts. Table 5.1 shows the main ontological dimensions of SCIPUDO. By employing the SCIPUDO, a standard set of terminologies can be employed by the application while allowing individual data contributors to maintain data according to their desired schema. SCIPUDO was then plugged into our MEDCIS system to power the operation of SCIPUDSphere User Interface.

Table 5.1: SCIPUDO Ontological Main Dimensions.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal</td>
<td>Demographics, Smoking, BMI, Nutritional status</td>
</tr>
<tr>
<td>Environmental</td>
<td>Access to specialized care, Access to transportation, Rural or urban location, Air quality</td>
</tr>
<tr>
<td>Clinical</td>
<td>AIS level, Duration of injury, Comorbidities, Medications</td>
</tr>
<tr>
<td>Social</td>
<td>Equipment use, Domestic living status</td>
</tr>
<tr>
<td>Tissue health</td>
<td>Tissue oxygenation under load, Skin and muscle blood flow under load, Muscle composition</td>
</tr>
</tbody>
</table>

5.5.2 SCIPUDSphere Environmental, Social and Clinical Domain Database

5.5.2.1 Data Extraction

The development of the enhanced Spinal Cord Injury Pressure Ulcer and Deep tissue injury (SCIPUD) Resource was created at the Louis Stokes Cleveland VA Medical Center (LSCDVAMC) by a multidisciplinary team led by biomedical engineer and a physician and included, staff nurses, physical and occupational therapists, a dietician, biostatisticians and a public health specialist. Multiple factors known to be associated
with PrI development were assessed at the admission timepoint. An initial study was carried out to investigate the significance of risk factors for rehospitalization (RHA) for severe (Stage III or IV) PrI. Using SCIPUD, researchers found that factors previously found to be predictive of initial PrI development may not be predictive of RHA. Specifically, demographic factors showed no significant association with RHA, while clinical factors such as duration of injury and sub-optimally managed spasticity (SMS) were significantly associated with higher RHA. These preliminary findings provide indications of the ongoing need to develop and review adaptive PrI prevention care plans.

The development of SCIPUD provided us with a foundation and direction for extracting risk factors data from VINCI. We leverage the rich data resource provided by the VINCI, which provides access to the world’s largest EMR data source and the many veterans with SCI served by the VHA. The VA has built a Corporate Data Warehouse (CDW) within VINCI to support this and other efforts to improve veteran care. The CDW contains detailed data about each patient and each encounter of these patients has a VA medical service. We extracted, de-identified, and exported patient data from the CDW to use for our system. Hosting SCIPUDSphere in VINCI’s secure infrastructure would allow us to use identified data and provide quick updates to its data. However, it would restrict access to the application and its data due to the strict security measures imposed by the VA for access to VINCI. We also expected to encounter challenges with implementing and maintaining the application within the security disciplines imposed by the VINCI environment. We observed that our study data were restricted to a five-year time span before the VA transitioned to ICD10, thus we expected few, if any, updates needed once we developed and completed our data extraction process. We also had no requirements for the identified data. Thus we could de-identified records and export them. We decided to host our application external to VINCI based on these considerations and make our system available to a
wider range of researchers.

5.5.2.2 Data Processing

Once we extract and de-identify data, we convert the data to the CSV format for export. Prior to importing data into the SCIPUDSphere database, we need to process the data in order to identify the comprehensive and hierarchical concept structures of the risk factors and handle the potential missing values. Therefore, we extracted the hierarchical concept structures of the risk factors from the extracted data by a Ruby program. After acquiring the hierarchical concept structures of the risk factors, we mapped the data into corresponding concepts value and saved these data into new CSV files. Finally, we imported the mapped data into the SCIPUDSphere database.

Prior to importing data into SCIPUDSphere, we need to associate each datum with a concept in the SCIPUDO (described in subsection 5.5.1). Each concept in SCIPUDO has an associated domain consisting of the values that it may have and we analyzed the data from our cohort to derive acceptable values for each domain. Once completed, we load the data into the SCIPUDSphere database.

5.5.3 SCIPUDSphere Query Interface

Validated extracted data were collected using our established standard data collection forms and imported to the PrI risk assessment SCIPUDSphere platform. The adapted X-search engine provides extensible, scalable, and high-performance data management for storing and rapidly accessing large volumes of data. A visual query interface was also adapted from X-search to allow researchers and clinicians to directly query the PrI risk data via a set of easily usable visual widgets. These are directly populated with the SCIPUDO concepts to allow clinicians to flexibly construct queries, specific to the patient. The Query Builder provides the user interface to formulate the patterns necessary to construct a logical query. The logical query
is translated dynamically into a local database query based on the mapping between the ontology model and the database-specific data model.

5.5.3.1 MongoDB as Data Warehouse

While developing SCIPUDSphere, we decide to use MongoDB [79] as our backend database. MongoDB is a free, open-source and cross-platform NoSQL database. It is a mature document-oriented NoSQL database with large-scale commercial usage. The reasons we use MongoDB are as follow:

- MongoDB provides a comprehensive API for Ruby on Rails developer. There is a mature Object-Relational Mapping (ORM) that lets our query and manipulate data from a database using an object-oriented paradigm.

- From chapter 4, we find out that MongoDB performs better than traditional relational databases e.g. MySQL in terms of querying high dimensional patient data. Traditional relational databases have restrictions on the number of columns in one single table. Therefore, high dimensional patient data will need to be split into multiple tables, which will affect queries performance if such queries require costly join operations. The situation for MongoDB is different. As MongoDB is a document-based NoSQL, there will be no columns restrictions for one single collection (analog to a table in MySQL). Therefore, MongoDB can guarantee fast query performance.

- MongoDB supports flexible and dynamic schema design. No predefined data schema is required compared to MySQL.

5.5.3.2 Dynamic Database Query Statement Generation

Queries are constructed using our SCIPUDSphere query interface. Once a user clicks the query button, the backend database query statements are generated automatically. Here we utilize similar techniques in our previous work [82] where we de-
veloped a dynamic query translation engine for query interface with multiple datasets as data sources. The query statement generation for SCIPUDSphere is a simplified version since we only have one dataset to query. We illustrate the statement generation processing as follows. The dynamic query statement generation is based on predefined statement templates according to specific concept types. For instances, the general query template for querying a range of value for a numerical data element is defined as:

```javascript
db.getCollection("scipud").find(
    <field_1> => {'$gte' => <field_1_lower_value>,
    '$lte' => <field_2_upper_value>},
    ...
    <field_n> => {'$gte' => <field_n_lower_value>,
    '$lte' => <field_n_upper_value>});
```

where the variables `<field_n>` represent the field that the user intend to query; and `<field_n_lower_value>`, `<field_n_upper_value>` represent the user-specified minimum value and maximum value of the field, respectively. All the variables in the angle brackets can be replaced by real values to generate the actual MongoDB statement.

The general template for query options for categorical data elements is defined as:

```javascript
db.getCollection("scipud").find(
    <field_1> => {'$in' => [<value1>, <value2>, ...<valueN>]},
    ...
    <field_n> => {'$in' => [<value1>, <value2>, ...<valueN>]});
```

where the variables `<field_n>` represent the field that the users intend to query, and `<value1>`, ..., `<valueN>` represent the queried options of the field, respectively. All the variables in the angle brackets can be replaced by real values to generate the actual MongoDB statement.

Based on these two templates, composite queries can be constructed this way:
A concrete example is "finding male patients aged from 20 to 80". After substituting the variables, the corresponding query statement becomes:

db.getCollection("scipud").find(
  'age' => {'$gte' => 20, '$lte' => 80}, ..., 
  <field_n> => {'$in' => [male]});

5.6 Result

In this section, we first present the results for data extraction, integration in our domain database, then show the query interface. We utilize MongoDB as our SCIPUD-Sphere domain database and input data for the database are provided by synthesizing available EMR clinical data from VINCI, using a protocol based on our preliminary work.

5.6.1 Creation of the SCIPUDSphere environmental, social and clinical domain database

5.6.1.1 Data Extraction

VINCI provided a cohort of 36,628 VA patients having ICD9 codes associated with SCI. Our study is limited to interactions with patients over a five year time period prior to the VA conversion to using ICD10 coding. We extracted data from twelve tables containing identified patient data and resulted in 18,808,408 records containing ICD9 codes for 36,581 individuals. We filtered this data to produce a table with 76,553 de-identified records containing 66 ICD9 codes related to SCI for 36,580 individuals and another de-identified table containing 153,930 records of 32,396 individuals with a total of 216 ICD9 codes for comorbidities included in our study.
We de-identified the data to comply with HIPAA and VA requirements by substituting a unique, randomized identifier for each patient and using only years to denote dates for patients 89 years old and younger and a single value for patients 90 years of age and older. We computed the number of times a particular ICD9 code was associated with a given patient. The unique, randomized identifier allows us to associate data from multiple sources with a given patient without compromising their privacy.

We also extracted demographic data for the patients in our cohort. This data contains the age, sex, and marital status of each patient. The age is computed at the time of the patient’s first encounter within the study period of this project and recorded as years. All ages 90 and over are assigned a single value to comply with the HIPAA safe harbor standard.

We found 283 individuals age 90 and above in our data. The resulting table contains 38,068 records with the extra records compared to the number of patients resulting from multiple values being recorded for the race or marital status. We investigated the discrepancy between the number of patients contained in the original cohort provided by VINCI and the number of patients for which we have data. We discovered 3 test patients in the original cohort, that is, ”patients” who have records in the system that do not exist but provide data quality checks. We have removed these from our data. That leaves 43 patients in the original cohort for whom we do not have data. We are investigating whether we should include additional CDW tables in our search or if their dates of encounters fall outside of the dates of our study or some other reason. Table 5.2 shows the detailed number of data records and the number of patients of the extracted data.

5.6.2 SCIPUDSphere User Interface

SCIPUDSphere system provides an integrated environment for investigators to identify risk factors for PrI/DTPrI and its user interface helps guide researchers in this
Table 5.2: Summary of Extracted Risk Data from VINCI.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Number of Data Records</th>
<th>Number of Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>38,068</td>
<td>36,623</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>153,930</td>
<td>32,396</td>
</tr>
<tr>
<td>Medications</td>
<td>368,997</td>
<td>36,610</td>
</tr>
<tr>
<td>Patient SCI Diagnosis</td>
<td>76,553</td>
<td>36,580</td>
</tr>
</tbody>
</table>

5.6.2.1 Query Builder

Figure 5.2 shows the query builder interface which consists of a set of drop-down menus populated with SCIPUDO classes. The menus guide users to construct their queries. The Query Manager saves queries for future reuse, which can be searched by keywords in title, description, or the query itself. We omit to describe the Query Manager since its functionality is similar to that of an email management application.

- SCIPUDO is displayed in the form of a set of drop-down menus. Users can construct queries in two ways. The browse mode lets users expand drop-down menus and select desired risk factors. Users can also search for specific risk factors by typing their names in a search box.

- Query Widgets provide the mechanism for users to express their criteria which will be dynamically translated into the server database query language and executed on the server. Users can interactively select concepts they are interested in and specify numeric ranges by selecting the minimum and maximum values for the range. For example, the query in Figure 5.2 will be translated into selecting male or female patients with PrI history.

- Query Result will show the distinct number of patients who satisfy the criteria built in the query widget. In Figure 5.2 2, the query returns the result of 8,774.
5.6.2.2 Query Results Statistical Visualization and Downloading

Figure 5.3: Query Results Statistical Visualization.

In addition to query cohort counts, SCIPUDSphere can provide statistical visualization based on each query as shown in Figure 5.3. For those categorical concepts
such as gender, SCIPUDSphere will draw a distribution graph. For continuous concepts, the interface will display a box plot. And for comorbidities, which will have a corresponding code, SCIPUDSphere will show the detailed counts for each code as shown in Figure 5.3.

Researchers can use the download link shown in Figure 5.2 to download the query results. These query results consist of de-identified data and researches can use the data in their studies. Before downloading data, researchers must complete our Data Access and Use Agreement online and get approved. SCIPUDSphere provide query access to a large, well-document cohort of spinal cord patients, both with and without pressure ulcer and deep tissue injuries coupled with a modern web-based user interface making it easy for researchers find data of interest to their studies or medical providers to find patients with conditions similar to theirs. We have a process for users to gain access to actual data through a Data Access and Use Agreement.

5.7 Evaluation

5.7.1 Usability

The evaluation is to assess SCIPUDSphere’s usability. To perform the evaluation, we chose some queries. These queries consist of a single concept and multiple concepts. The usability measurement was the time cost to compose queries. We invited four non-technical users to complete the query building task and counted the time cost. Table 5.3 shows the average time cost in seconds to build the 9 selected queries using browse mode and search mode. We can see from the result. For a user, it could take about 40 seconds to build a query using browse mode while using search mode will be a little bit faster.
Table 5.3: Statistics for query building in usability evaluation.

<table>
<thead>
<tr>
<th>Query concept</th>
<th>Browse</th>
<th>Search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40s</td>
<td>30s</td>
</tr>
<tr>
<td>Gender</td>
<td>32s</td>
<td>26s</td>
</tr>
<tr>
<td>Race</td>
<td>43s</td>
<td>25s</td>
</tr>
<tr>
<td>MaritalStatus</td>
<td>45s</td>
<td>30s</td>
</tr>
<tr>
<td>Smoking</td>
<td>30s</td>
<td>32s</td>
</tr>
<tr>
<td>PUHistory</td>
<td>42s</td>
<td>33s</td>
</tr>
<tr>
<td>Neurogenic Bowel</td>
<td>35s</td>
<td>30s</td>
</tr>
<tr>
<td>Age, Neurogenic Bowel</td>
<td>62s</td>
<td>50s</td>
</tr>
<tr>
<td>PU History, Neurogenic Bowel</td>
<td>65s</td>
<td>55s</td>
</tr>
<tr>
<td>Average</td>
<td>43s</td>
<td>34s</td>
</tr>
</tbody>
</table>

5.7.2 Query Performance

To illustrate the query performance of SCIPUDSphere, we conduct experiments on performing patient cohort queries. Each cohort query consists of one or more query concepts. For each query, we perform 10 times and calculated their average values. All these experiments are conducted on a computer with Intel Core i5/2.9 GHz processor and 8 GB RAM.

Table 5.4: Cohort Query Time for SCIPUDSphere.

<table>
<thead>
<tr>
<th>Query concept</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
<th>No. 5</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.15s</td>
<td>0.12s</td>
<td>0.15s</td>
<td>0.25s</td>
<td>0.2s</td>
<td>0.17s</td>
</tr>
<tr>
<td>Gender</td>
<td>0.14s</td>
<td>0.13s</td>
<td>0.17s</td>
<td>0.12s</td>
<td>0.15s</td>
<td>0.14s</td>
</tr>
<tr>
<td>Race</td>
<td>0.13s</td>
<td>0.11s</td>
<td>0.12s</td>
<td>0.15s</td>
<td>0.14s</td>
<td>0.13s</td>
</tr>
<tr>
<td>MaritalStatus</td>
<td>0.14s</td>
<td>0.13s</td>
<td>0.14s</td>
<td>0.11s</td>
<td>0.15s</td>
<td>0.13s</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.11s</td>
<td>0.12s</td>
<td>0.12s</td>
<td>0.13s</td>
<td>0.12s</td>
<td>0.12s</td>
</tr>
<tr>
<td>PUHistory</td>
<td>0.14s</td>
<td>0.14s</td>
<td>0.13s</td>
<td>0.15s</td>
<td>0.12s</td>
<td>0.14s</td>
</tr>
<tr>
<td>Neurogenic Bowel</td>
<td>0.12s</td>
<td>0.11s</td>
<td>0.15s</td>
<td>0.14s</td>
<td>0.15s</td>
<td>0.13s</td>
</tr>
<tr>
<td>Age, Neurogenic Bowel</td>
<td>0.22s</td>
<td>0.19s</td>
<td>0.15s</td>
<td>0.2s</td>
<td>0.21s</td>
<td>0.19s</td>
</tr>
<tr>
<td>PU History, Neurogenic Bowel</td>
<td>0.21s</td>
<td>0.17s</td>
<td>0.16s</td>
<td>0.19s</td>
<td>0.2s</td>
<td>0.18s</td>
</tr>
</tbody>
</table>

Age is a numerical concept and other concepts are categorical concepts. From Table 5.4, we can see that the query times for all these queries are around 200ms
without indexes. SCIPUDSphere query performance is consistent and fast for both single concept query and combined concepts query.

5.7.3 Evidence of Usage

Evidence of SCIPUDSphere usage for scientific and clinical research includes research proposals submitted and publications. One recent publication characterizing individualized clinical practice guidelines for pressure injury management. In this publication, the authors aim to develop the Spinal Cord Injury Pressure Ulcer and Deep Tissue Injury Resource to support personalized care planning for primary and secondary PU/DTI prevention by utilizing our SCIPUDSphere as a single point of web-based access to well-annotated and de-identified data generated from multiple domains.

5.8 Discussion

5.8.1 Features

SCIPUDSphere is a web-based system provides researchers with access to a comprehensive, curated dataset of de-identified patients with SCI and the tool to explore those data.

- Guide a user to find data of interest to them.
- Support dedicated domain ontology, in this case about pressure ulcers and their treatment.
- Extract and integrate large-scale PrI risk data for a large cohort of patients.
- Provides a single point of web-based access to de-identified and analysis-ready PrI risk data.

SCIPUDSphere is serving as a data source for researches aiming to build a model that can identify major risk factors for individual patients. The facts that SCIPUD-
Sphere supports dedicated domain ontology and provides web-based access to de-identified risk data was acknowledged by the researchers. However, they also pointed out that the query statistical results visualization is superficial and provides limited insights into the data. Building a more sophisticated data visualization widget is challenging and requires more inputs from a larger group of researchers.

5.8.2 Limitations

Extracting all the designed PrI risk data is in progress. We have currently extracted four main categories data, specifically demographics, comorbidities, medications, and patient SCI diagnosis data respectively. The second limitation is that our system is under inner testing and usage without conducting any scalability evaluations in terms of large-scale user usage. Our ultimate goal is to extract all PrI risk data from VINCI and import those data into our SCIPUDSphere system. At that time, SCIPUDSphere will enable researchers to query patients cohort counts and explore these risk data to use in their research studies.

SCIPUDSphere has been used by individuals for testing and usage. We have not conducted any scalability evaluations in terms of large-scale user usage. Once SCIPUDSphere is fully populated, we can perform more comprehensive and systematic evaluations, including usability and scalability evaluations.

5.8.3 Conclusions

In this chapter, we introduce SCIPUDSphere, an informatics platform followed our MetaSphere diagram, that enables data extraction, integration, storage, and analysis to provide clinical decision support and user interfaces direct access to well-annotated and de-identified wide range PrI risk factors of data. We created a dedicated Spinal Cord Injury Pressure Ulcer and Deep tissue injury ontology (SCIPUDO) as the knowledge resource for processing specialized terms related to SCI, PrI, and DTPrI. We
extracted the demographics, comorbidities, medications, and patient SCI diagnosis data from VINCI. By adapting existing tools: NSRR and MEDCIS, we successfully implemented a powerful and intuitive user interface that empowers researchers to quickly pinpoint possible risk factors and perform exploratory queries. We believe that SCIPUDSphere can help researchers to find a comprehensive range of PrI risk factor data and promotes clinical researches for preventing PrI and DTPrI.

SCIPUDSphere follows the FAIR principles and enforces the findable, accessible, and reusable principles. Similar to X-search, SCIPUDSphere allows users to query and explore PrI/DTPrI related risk factor data, making the extracted risk data findable and accessible. The risk factor data are persisted in our data repository and can be reused by researchers.
CHAPTER 6. Interactive and Collaborative Mapping Interface from Data Dictionaries to Ontologies

In Chapter 2, we introduced the challenges a cross-cohort query interface which use CSV files to manage mappings between different data source to a domain ontology. In this chapter, we will discuss an innovative, interactive, and collaborative mapping management system for managing and building mappings from a data dictionary to an ontology.

6.1 Motivation and Challenges

Ontologies are critical in semantically enabled applications, such as MEDCIS [88], X-search [89], and DataSphere [78]. In recent years, ontologies have been widely used in biomedicine. Knowledge captured through mappings allows the integration, search, and analysis of data in a clinical setting where different data sources in the same domain have been annotated with different but similar ontologies. The misalignment has become a major issue and a large number of researches have been conducted on ontology mapping in order to find mappings between concepts and relations in different ontologies [28]. Abundant ontology mapping systems and tools have been built [90–94] and overviews can be found at the matching web site [95]. The majority of these studies mainly focus on the mapping algorithm between ontologies. In most cases, patient data are collected with the help of the data dictionary. Therefore, mappings between unified metadata and data dictionaries are critical in such cases, especially when data are from different sources. For example X-search, a dedicated sleep ontology is used to power up the interface for querying and exploring heterogeneous datasets in the NSRR (National Sleep Research Resource) [11, 12, 34] data repository. To facilitate the dynamic query translation, a set of mappings between the canonical data dictionary and different datasets are built and maintained by a
group of domain experts using CSV files. The file-based approach is straightforward but with limitations in terms of cooperativeness and traceability. Besides, it is label-intensive and error-prone to integrate and synchronize contents from different sources. Management and maintenance of these mappings become cumbersome and time-consuming when the mapping size increases. More importantly, it cannot be reused by other researchers. An interactive, collaborative, and web-based mapping system would be beneficial to utilize the power of crowdsourcing.

The Kentucky Cancer Registry was founded at the University of Kentucky (UK) Markey Cancer Center (MCC) in 1991. KCR is a central cancer registry that receives data about new cancer cases from all healthcare facilities and physicians in Kentucky within 4 months of diagnosis. In 2000, KCR became a part of the NCI’s Surveillance Epidemiology and End Results (SEER) program. The North American Association of Central Cancer Registries (NAACCR) was established in 1987 to meet the needs of central cancer registries. NAACCR provides a standardized data dictionary which is utilized by KCR when it is collecting patient data.

To reduce the data access barriers and facilitate query and exploration tools for accessing data resources, we need to transform and implement terminology systems such as National Cancer Institute Thesaurus (NCIt) into a faceted system [96]. A mapping between the KCR data dictionary and NCIt is needed.

In this chapter, we introduce a deployed, web-based mapping interface, called IMI, enabling researchers to carry an interactive and collaborative mapping process and crowdsourcing. IMI was successfully used to construct a mapping between KCR data dictionary and NCIt. At the current stage, IMI supports two ontologies as an ontology library with over 150,000 concepts and the ontology library can be expanded easily when more ontologies are required. Moreover, IMI has a decoupled recommendation system that is open to researchers so that they can override the current default recommendation algorithm to perform and test their mapping algorithms.
IMI has been designed as a general framework with three decoupled components: 1) ontology library; 2) mapping interface; 3) recommendation system. The ontology library provides a list of ontologies as a target ontology for constructing mappings. The mapping interface consists of six modules: project management system, interactive mapping interface, access control, logs and comments, ontology hierarchy visualization, and mapping exportation. The recommendation system serves as primitive auto mapping and provides a list of potential matching concepts from target ontology.

IMI is publicly accessible at http://epi-tome.com with two supported ontologies over 150,000 concepts. IMI has been applied to KCR successfully and 47 out of 301 frequently used concepts have been mapped to NCI Thesaurus (NCIt), where the rest do not have matching concepts from NCIt.

6.2 Method

The goal is to create an interactive, collaborative, and web-based mapping interface which leverages the power of crowdsourcing. To achieve this objective, the system architecture of IMI consists of three major components: ontology library, mapping interface, and recommendation system. Figure 6.1 shows the overall architecture of our system.

![Figure 6.1: Functional Architecture of IMI.](image)

As illustrated in Figure 6.1, there are three functional components, which are Data Import, IMI application, and Result Export. The Data Import component
is for importing data dictionaries. IMI application component provides a mapping interface for building mappings. Then all the mappings can be exported using the Result Export component.

The mapping interface consists of six modules: project manage system, interactive mapping interface, access control, logs and comments, mapping exportation, and ontology hierarchy visualization. The source ontology uploader is used to upload source ontology by users. The mapping interface provides an interactive and highly configurable interface to perform mapping. The access control module is implemented to grant or remove access from particular users. Logs and comments can keep track of mapping activities and enable information sharing during the mapping process. The logs and comments module is critical for crowdsourcing. Mapping can be exported using the mapping exportation module. The ontology hierarchy visualization module visualizes the mapped ontology hierarchy based on the target ontology hierarchy.

### 6.2.1 Ontology Library

Ontology library serves as the foundation of mapping. It is managed and maintained by the system admin. We assume the ontologies are in a structured format that can be populated into NoSQL database like MongoDB [79]. A rich source of well-structured ontologies can be found via bioportal [9]. The reason we choose MongoDB as our backend storage engine is that for clinical data with a large number of data elements, split is needed to store all the data which may cause overhead on querying across multiple tables [97]. The ontology library can be expanded easily as IMI provides a dedicated management interface. All the importing is done via the interface and import fields are configurable by simple clicks on the interface. A well-structured and widely recognized ontology may contain a large amount of information, some of this information is not needed and it is not feasible to import all the fields into our database. Therefore, making import fields configurable can be beneficial to reduce
the storage requirement and make our ontology library more compact.

6.2.2 Interactive Mapping Interface

The mapping pipeline of IMI is demonstrated by Figure 6.2. There are five main steps showed in the figure, which are project creation, source ontology upload, mapping, visualization, and exportation.

![Mapping pipeline](image)

Figure 6.2: Mapping pipeline.

6.2.2.1 Project Management Module

To start the mapping process, a user starts from creating a project. There are several non-trivial things to specify when creating a new project. First of all, the project owner needs to specify the target ontology from the ontology library. Secondly, the project owner needs to decide whether the project will be public or not. If the project is public, then it can be accessed by all users in IMI. Otherwise, the project can only be accessible by users with permission granted by the project owner. Users assigned to a project can access the project from their own project management system. Several display fields of the target ontology will be picked by the project owner since it could be overwhelming if all fields in the ontology are displayed in the interface. After the creation of the project, users would proceed to the mapping interface to perform the actual mapping.

6.2.2.2 Interactive Mapping Interface

Recalling when we are creating a mapping project, we only specify the target ontology. We also need a source data dictionary in order to perform the mapping. IMI makes the data dictionary uploading process easy by providing an upload interface
with a similar configurable function enabled. Users can specify fields to import, default field to display in the mapping interface, and fields to show when a concept is selected.

The mapping interface consists of three major areas:

- Area to list all the upload concepts of source ontology.
- Area to show detailed content of the display fields specified in the above steps of the source ontology.
- Area to show the top 5 recommended concepts and detailed content of the display fields from target ontology.

There are two modes to look up concepts from the source ontology: browsing and search. The browsing mode provides a list of all concepts from source ontology so that users can explore all concepts one by one. The search mode enables expert users to directly search for concepts of interest. Along with the concept default display field, a small rectangle box with a number will indicate the mapping status of the concept and the comments for the concept. Green color with a character ”M” represents that the concept is mapped while red color with a character ”U” means the concept is not mapped. The number inside the rectangle box simply shows the number of comments for the current concept.

When a concept from area one is selected, area two will show the content of specified fields from a data dictionary. The message icon on the top right in area two is used to open the logs and comments module where users can view the mapping activities and comments for the current concept. In the meanwhile, if the current concept is not mapped, a list of recommended concepts from target ontology will be fetched and showed in area three. Below the recommendation list, there is a search widget that can be used by users to search concepts from target ontology. Once users find a matching concept, they can click the match button to make a match. If the
concept is mapped, the list of recommendations will not show but the detailed content of the mapped concept from target ontology will show instead. In such a case, users will be able to remove the match for the current pair of concepts.

Algorithm 1 describes the steps involved in using depth first search to trace back from the leaf node to the root node. Then finally, mapping can be exported using the exportation module.

**Algorithm 1:** Depth first search from leaf node to root node

**Data:** $DFS(\text{current\_node}, \text{all\_nodes}, \text{roots})$

```
if \text{current\_node} is root node then
    add \text{current\_node} into \text{roots} list;
else
    \text{parent\_node} ← \text{current\_node}.parent;
    if \text{parent\_node} not in \text{all\_nodes} then
        create new node as \text{parent\_node};
    end
    add \text{parent\_node} to \text{current\_node}.parent
    add \text{current\_node} to \text{parent\_node}.children
    \text{current\_node} ← \text{parent\_node};
    DFS(\text{current\_node}, \text{all\_nodes}, \text{roots})
end
```

6.2.3 Recommendation System

IMI comes with a built-in recommendation system. As mentioned above, when an unmapped concept is selected from the source concept list, a list of recommendation concepts from target ontology is fetched. They are generated by the IMI default recommendation system. By default, the IMI implemented fuzzy matching algorithm [98]. The fuzzy matching algorithm can calculate the similarity between two sequences and return a score to represent the similarity. We use a priority queue to keep track
of the top five concepts from target ontology with the highest scores. The list of recommended concepts can be generated on-the-fly but the time is highly dependent on the size of the target ontology.

6.3 Result

In this section, we demonstrate the result by making a mapping between KCR data dictionary and NCIt using our IMI. Here, we extracted 301 used KCR terms from the actual data and verified with domain experts. 47 out of 301 are mapped, leaving the rest unmapped. Five branches of the hierarchical tree are constructed from the target ontology.

6.3.1 Ontology Library

Figure 6.3 presents the ontology library system of IMI. We can see that all uploaded ontologies are listed in a table. Currently, we have two ontologies. To add a new ontology, the admin user can simply click the ”Add a New Ontology” button and use the interface shown at the right of Figure 6.3.

When an ontology file is selected from the local disk, IMI will scan through and retrieve the header of the CSV file. Here, we assume that the uploaded ontology file format is CSV file which can found on the web like bioportal. Shown in Figure 6.4 The admin user will be able to select fields to import into the database. Currently, IMI has uploaded two ontologies with over 150,000 concepts. More ontologies can be incorporated into the ontology library when these ontologies are requested by users.

6.3.2 Interactive Mapping Interface

We implemented the IMI using Ruby on Rails, an agile web development framework. IMI has been deployed and is publicly available at http://epi-tome.com for free.
6.3.2.1 Project Management Module

The mapping pipeline is initiated by creating a project using our project management module. The project management is a standard CRUD (create, read, update, delete) interface where users can specify the project name, project description, and more importantly select the target ontology and one default search field. The default search field for the target ontology will become the default search field when users
try to search matching concepts from target ontology. Besides, users can determine if the project is public. All users from IMI will be able to contribute to the mapping for public projects. Once a project is created, the pipeline proceeds to the data dictionary uploading. The uploading is done using the data dictionary upload interface. IMI reuse a similar mechanism from the ontology library uploader but apply that in the data dictionary.

6.3.2.2 Mapping Dashboard

The mapping dashboard is the core module for the IMI system. From the mapping dashboard, users can navigate to other modules:

- access control
- logs and comments
- visualization
- mapping result review and exportation

![Mapping dashboard](image)

**Figure 6.5:** Mapping dashboard.

Figure 6.5 shows the mapping dashboard consists of two major columns. The left column lists all the uploaded data dictionary. The default mode is browsing mode and
users can switch to search mode using the switch widget. Those mapped concepts are denoted by a green box with "M" while unmapped concepts are denoted by a red box with "U". The right column shows the selected variable from the data dictionary. The display fields are set when users uploading the data dictionary. Below the selected variable is the target ontology area. If the concept is mapped, the mapped concept from the target ontology will be shown in this area. Moreover, users can delete the existing match and utilize the search widget down below to search other candidates and redo the matching again. In this example, we can see "Race 1" from KCR data dictionary is mapped to concept the "Race" in NCIt. If the concept is unmapped, a list of recommendations will show up the ranking by their scores.

![Share OncoSphere](image)

**Figure 6.6:** Access control.

Figure 6.6 demonstrates the access control module and the logs and comments module. If the current project is not public, the project owner can use the access control module to grant privilege to certain users. The access control module provides two privileges: 1) Can edit; 2) Can map. The first privilege is the admin level privilege and the second one will only allow users to perform mapping. The logs and comments module keeps track of each map and remove mapping activities as logs. Besides, users can leave comments about current mapping.
6.3.2.3 Interactive Tool for Ontology Hierarchy Curation and Rectification

We identified five branches from the NCIt for our extracted KCR terms. Figure 6.9 shows all these branches. The green nodes in the figure denote concepts that are mapped from KCR data dictionary. Red nodes represent intermediate nodes from target ontology. The edge between two nodes represents the hierarchical relations. The upper node is the parent node of the lower node. Table 6.1 summarize the root concept, number of nodes, and maximum levels for these five branches. In IMI, we have two modes for visualization. The first one is a typical tree-based visualization. The second one is the interactive mode powered by D3 library force layout. In the second mode, the root concepts are positioned in the center of the graph, and users
can drag nodes in the graph to interact with the graph.

**Table 6.1:** Summary of five branches.

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>B5</th>
</tr>
</thead>
<tbody>
<tr>
<td>root</td>
<td>Conceptual Entity</td>
<td>Property or Attribute</td>
<td>Disease, Disorder or Finding</td>
<td>Diagnostic or Prognostic Factor</td>
<td>Activity</td>
</tr>
<tr>
<td>No. of nodes</td>
<td>60</td>
<td>27</td>
<td>4</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>maximum levels</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

![Hierarchy tree of the first branch.](image1)

**Figure 6.9:** Hierarchy tree of the first branch.

![Hierarchy tree of the second branch.](image2)

**Figure 6.10:** Hierarchy tree of the second branch.
Figure 6.11: Hierarchy tree of the third branch.

Figure 6.12: Hierarchy tree of the fourth branch.

The mapping result view and exportation module summarize the number of mapped and unmapped concepts. To export the mapping file, users simply click the "Export To CSV File" button, and a one to one mapping file will be downloaded automatically.
6.4 Evaluation

The evaluation was designed to assess IMI’s performance and usability by comparing it with the CSV based mapping.

6.4.1 Usability

To perform usability evaluation, we choose ten most commonly used data dictionaries from NAACCR and map them to NCIt using two approaches. The first approach is to use our mapping interface IMI, the second approach is to use the CSV file. We choose to compare with the CSV file based method as it is the most common and popular approach when researchers are doing small scale mapping. Ten data dictionary elements are selected out of 301 data dictionary elements, shown in Table 6.2. The approach we do mapping in IMI is to select the data element one by one and search on our built-in searching function shown in the figure. CSV file does not provide searchable ontology. But the NCIt official website provides a similar search function. Therefore, we utilize the search function on the NCIt website. All the mapping will
be conducted 3 times and we calculated the average time for each mapping pair.

**Table 6.2:** Average mapping time for ten selected data dictionary elements.

<table>
<thead>
<tr>
<th>Data dictionary element</th>
<th>IMI</th>
<th>CSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>12.3s</td>
<td>30.6s</td>
</tr>
<tr>
<td>Race Coding Sys–Current</td>
<td>30.1s</td>
<td>55.3s</td>
</tr>
<tr>
<td>Race Coding Sys–Original</td>
<td>33.2s</td>
<td>64.1s</td>
</tr>
<tr>
<td>Spanish/Hispanic</td>
<td>15.4s</td>
<td>37.5s</td>
</tr>
<tr>
<td>Computed Ethnicity</td>
<td>17.1s</td>
<td>29.7s</td>
</tr>
<tr>
<td>Computed Ethnicity Source</td>
<td>18.1s</td>
<td>40.3s</td>
</tr>
<tr>
<td>Sex</td>
<td>15.1s</td>
<td>36.2s</td>
</tr>
<tr>
<td>Date of Birth</td>
<td>17.6s</td>
<td>28.1s</td>
</tr>
<tr>
<td>Nhia Derived Hisp Origin</td>
<td>32.5s</td>
<td>55.1s</td>
</tr>
<tr>
<td>Birthplace–State</td>
<td>20.6s</td>
<td>43.2s</td>
</tr>
</tbody>
</table>

### 6.4.2 The Evaluation of the Recommendation System

The 47 mapped concepts are mapped by the domain experts, which can be viewed as ground truth. If we treated the first concept from the recommendations as to the matched concept and calculated our recommendation system accuracy. 25 of these recommended concepts are correct. So the accuracy is 53%. For some terms, many of the recommended concepts are actually with same scores. If one from the five recommended concepts is correct, we consider that mapping is correct. For such a case, the accuracy would increase to 66%.

### 6.5 Discussion

#### 6.5.1 Usability

For the efficiency or mapping time of IMI, we observed improvements compared to the CSV-based approach. Since NCIt also provides a nice searching function on its official website, time for searching matching concepts did not make a huge difference. The difference is mainly from building mapping contents. The CSV-based approach requires additional time to copy contents from the NCIt website and paste them
back to the CSV file while IMI requires a single click. Besides, some concepts are more time consuming as these concepts do not have the corresponding mapping from the NCIt, building mapping for such concepts required additional validations. For ontologies without similar searching functions like NCIt, we can assure IMI would perform better. What’s more, IMI can provide richer features than the CSV-based method.

6.5.2 Generalization

Although our IMI was developed for the KCR, its framework has been designed and implemented to be generally applicable to other data dictionary for building mapping other ontologies.

6.5.3 Limitation and future work

Currently, IMI only supports two ontologies as target ontology. More widely used ontologies should be incorporated. In the meanwhile, with more ontologies uploaded, the performance for searching concepts among millions of concepts should be evaluated. Besides, only the data dictionary and ontologies in CSV format are supported in the current stage. If the ontology file is in OWL format, it will need to be converted to CSV format. In addition, our recommendation system is native. More sophisticated mapping algorithms are needed. Last but not least, we plan to enable add, edit and remove node operations for the visualization graph.

6.6 Concluding remarks

In this work, we presented IMI. IMI provides an interactive, intuitive, and collaborative mapping interface for building mapping between data dictionary to ontology, so as to facilitate data analytics through interoperability and integration and provide semantic access across aggregated data used in knowledge-based applications and ser-
vices. IMI enforces the accessible and reusable principle from the FAIR principles, as IMI acts as a central mapping hub making mappings available to the public and therefore existing mappings can be reused by other researchers.
CHAPTER 7. Conclusion

In this dissertation, we develop a FAIR principles guided general framework for building the fine-grained, cross-cohort query, and exploration systems and propose an interactive, collaborative mapping for building mapping from a data dictionary to an ontology. To address the common challenges existing in various biomedical research regarding data access and heterogeneous data integration such as:

- Barriers between data exploration and research hypothesis. In a traditional workflow, the research hypothesis comes before patient data exploration. A new and efficient data exploration tool is needed to accelerate such a process.

- The lack of fine-grained, cross-cohort query and exploration interfaces, and systems. Although many data repositories allow users to browse their content, few of them support fine-grained, cross-cohort query, and exploration at the study-subject level.

- Tools for building mappings between data dictionary and ontologies are missing. In some researches, patient data are collected with the help of a data dictionary. To integrate these patient data and build ontology enabled data query interfaces, a mapping between multiple data dictionaries and ontology are critical. Such mappings usually are built by a group of researchers and domain experts, an efficient tool for collaboration and result visualization is required.

First of all, to break the traditional data access barriers between data exploration and research Hypotheses. We proposed a general framework that can apply to different domains.

We firstly applied MetaSphere on National Sleep Research Resource (NSRR) [11] and developed X-search [89]. X-search has been designed as a general framework with
two loosely-coupled components: semantically annotated data repository and cross-cohort exploration engine. The semantically annotated data repository is comprised of a canonical data dictionary, data sources with a data dictionary, and mappings between each individual data dictionary and the canonical data dictionary. The cross-cohort exploration engine consists of five modules: query builder, graphical exploration, case-control exploration, query translation, and query execution. The canonical data dictionary serves as the unified metadata to drive the visual exploration interfaces and facilitate query translation through the mappings.

While developing X-search, we found out that some query performance issues are introduced by the traditional relational databases. Such query performance issues can be improved but not solved completely. To address that, we tried out the NoSQL databases and conduct a comparison experiment. We developed two NoSQL-based patient cohort identification systems, in comparison to a SQL-based system, to evaluate their performance on supporting high-dimensional and heterogeneous data sources in NSRR. Utilizing NoSQL databases, we overcame the limitation of maximum table column count in traditional relational databases. We successfully integrated eight NSRR cross-cohort datasets into NoSQL databases, which largely enhanced the query performance compared to the MySQL-based system, while maintained similar performance for data loading and harmonization. This study indicates that NoSQL-based systems offer a promising approach for developing patient cohort query systems across heterogeneous data sources in our case.

From the NoSQL-based MetaSphere, we introduce SCIPUDSphere in Chapter 5, an informatics platform, that enables data extraction, integration, storage, and analysis to provide clinical decision support and user interfaces direct access to well-annotated and deidentified wide range PrI risk factors of data. We created a dedicated Spinal Cord Injury Pressure Ulcer and Deep tissue injury ontology (SCIPUDO) as the knowledge resource for processing specialized terms related to SCI, PrI, and DTPrI.
We extracted the demographics, comorbidities, medications, and patient SCI diagnosis data from VINCI [36]. By adapting existing tools: NSRR and MEDCIS [88], we successfully implemented a powerful and intuitive user interface that empowers researchers to quickly pinpoint possible risk factors and perform exploratory queries. We believe that SCIPUDSphere can help researchers to find a comprehensive range of PrI risk factor data and promotes clinical researches for preventing PrI and DTPrI.

While we are trying to introduce MetaSphere to a domain like cancer, we encounter a similar problem when we are working on NSRR. Mapping from data dictionaries to ontology are needed. However, the building of such mappings is mostly done using the excel program which is not easy to share and work collaboratively. Besides, there is no way to visualize the hierarchical structure from the mapping. To address that, we presented the Interactive Mapping Interface (IMI). IMI has been designed as a general framework with three decoupled components: 1) ontology library; 2) mapping interface; 3) recommendation system. The ontology library provides a list of ontologies as the target ontology for constructing mappings. The mapping interface consists of six modules: project management system, interactive mapping interface, access control, logs and comments, ontology hierarchy visualization, and mapping exportation. The recommendation system serves as primitive auto mapping and provides a list of potential matching concepts from target ontology. IMI is publicly accessible at http://epi-tome.com with two supported ontologies over 150,000 concepts. IMI has been applied to KCR successfully and 47 out of 301 frequently used concepts have been mapped to NCI Thesaurus (NCIt), where the rest do not have matching concepts from NCIt. IMI provides an interactive, intuitive, and collaborative mapping interface for building mapping between data dictionary and ontologies, so as to facilitate data analytics through interoperability and integration and provide semantic access across aggregated data used in knowledge-based applications and services.
7.1 Contributions

We propose a general framework called MetaSphere. MetaSphere provides three major functionalities in terms of metadata management for clinical data integration. The first functionality is the structural, scalable, and computer understandable way of metadata storage. MetaSphere stores the ontology and its associated concepts, variables, and domains in a scalable database. Additionally, utilizing the database’s associations between tables, MetaSphere can represent the relationships between concepts, the relationships between concepts and variables, the relationships between variables and domains properly.

The second functionality is the fine-grained, cross-cohort query interface. MetaSphere hierarchically organizes an ontology’s concepts and reflects such hierarchies in the interface. With direct interaction, users will be able to browse the ontology’s structures easily. Utilizing the query interface, users can compose complex queries to query and explore data at the study-subject level.

Finally, MetaSphere provides an interactive, intuitive, and collaborative mapping interface for building mapping between data dictionary to ontology, so as to facilitate data analytics through interoperability and integration and provide semantic access across aggregated data used in knowledge-based applications and services.

Our contributions are:

- We created a general framework which can apply to different domains to facilitate the data exploration and remove the barriers standing between researches hypothesis and data access.

- We created an informatics platform, that enables data extraction, integration, storage, and analysis to provide clinical decision support and user interfaces direct access to well-annotated and deidentified wide range PrI risk factors of data.
• We created a dedicated Spinal Cord Injury Pressure Ulcer and Deep tissue injury ontology (SCIPUDO) as the knowledge resource for processing specialized terms related to spinal cord injury and pressure ulcer; 4) we created an interactive and collaborative mapping interface aiming at connecting data dictionaries to ontologies.

7.2 Future Work

There are several aspects to the work of MetaSphere that can be improved. We will focus on the following aspects in the future.

For X-search, we have built a pipeline for integrating new datasets. Currently, the pipeline is in a raw form. The pipeline involves many trivial procedures and many manual works are necessary for checking the correctness. One important future work is to build an online task tracking and live feedback monitoring system. Basically, we would like to make the pipeline semi-auto and reduce unnecessary manual workload.

For IMI, we provide two ways to visualize the hierarchical structure for the mapped data dictionary. Currently, the generated graph cannot be edited. One interesting future work would be providing an editable visualization interface. Users can edit on the system generated graphs and save even share their work with other users.
REFERENCES


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