**SEQMapPDB**: A Standalone Pipeline to Identify Representative Structures of Protein Sequences and Mapping Residue Indices in Real-Time at Proteome Scale

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**Abstract**

**Motivation**: 3D structures of proteins provide rich information for understanding their biochemical roles. Identifying the representative protein structures for protein sequences is essential for analysis of proteins at proteome scale. However, there are technical difficulties in identifying the representative structure of a given protein sequence and providing accurate mapping of residue indices. Existing databases of mapping be-
tween structures and sequences are usually static that are not suitable for studying proteomes with frequent gene model revisions. They often do not provide reliable and consistent representative structures that maximizes sequence coverage. Furthermore, proteins isomers are usually not properly resolved.

**Results:** To overcome these difficulties, we have developed a computational pipeline called SeqMapPDB to provide high-quality representative PDB structures of given sequences. It provides mapping to structures that fully cover the sequences when available, or to the set of partial non-overlapping structural domains that maximally cover the query sequence. The residue indices are accurate mapped and isomeric proteins are resolved. SeqMapPDB is efficient and can rapidly carry out proteome-wide mapping to the selected version of reference genomes in real-time. Furthermore, SeqMapPDB provides the flexibility of a stand-alone pipeline for large scale mapping of in-house sequence and structure data.

**Availability:** Our method is available at [https://bitbucket.org/lianglabuic/seqmappdb](https://bitbucket.org/lianglabuic/seqmappdb) with GNU GPL license.

## 1 Introduction

The proteomes of over 1,600 species in Eukarya and over 8,400 species in Prokarya and Archaea have been deposited in the UniProt database [1]. Analysis of these proteomes can identify relevant protein domains and sequence motifs to gain knowledge of the biochemical roles of the proteins [2, 3]. In addition, a large number of proteins have their 3D structures resolved. The Protein Data Bank (PDB) currently contains the atomic coordinates of over 167,000 proteins, with thousands more added every year [4]. As protein 3D structures can provide detailed information on catalytic residues, binding pockets, and potential allostery sites
important for biochemical functions [5, 6, 7, 8], incorporating structural information in analysis can reveal new insight into the biochemical roles of the proteins.

To incorporate protein structural information, an important task is to connect protein sequences in the proteomes to protein structures in the PDB database in an accurate and robust fashion. Although databases such as UniProt [1] and SIFTS [9] do provide mappings between structures in the PDB database and sequences, there are a number of difficulties in identifying representative PDB structures and in providing accurate mapping of residue indice that these databases currently do not resolve.

First, mapping to a fixed sequence databases is problematic. As protein sequences are inferred from gene models, they are often updated once a refined gene model is validated [10, 11]. Furthermore, proteins may have several isoforms due to alternative splicing [12]. A static mapping is inadequate in these cases. These problems are further compounded by the occasional irregular index assignment some protein chains have (e.g. chain A of 6EC3 starts at index -13) [13], which requires correction to indice of the query sequences.

Second, many proteins have structures resolved only for domains that do not cover the full-length sequences, likely due to experimental difficulties in resolving the structures of certain protein regions [14]. A single protein sequence is often mapped to several non-overlapping structural domains and these need to be reconciled.

Third, there are proteins whose structures have been resolved in multiple experimental studies, leading to redundant entries in the PDB database. It is desirable to identify the representative structures with maximum coverage.

Fourth, not all structures in the PDB are of equally high quality. PDB structures may often have several undetermined residues, which
would cause mismatch to the query sequences. In addition, there are cases where only the coordinates of $C_{\alpha}$ exist, with information of all other atoms missing (e.g., PDB JW2S). These PDB entries with large proportion of missing atoms should be avoided.

We have developed a pipeline that can retrieve non-overlapping and high-quality PDB structures for any given sequence. This pipeline works in a stand-alone fashion and can be used to provide mapping to the most current version of protein sequences and structures. It is efficient and can be employed at proteome-wide scale.

2 Methods

2.1 Structural Mapping of Human Proteome

We apply the SeqMapPDB pipeline to the canonical forms of sequences from the human reference proteome (June 2021 release by UniProt). Among the 20,610 proteins, 5,885 can be mapped to PDB structures, 2,617 of which have full-coverage structures, and 3,268 have partially-covered structures. 763 of the partial covered proteins have structures for at least two non-overlapping partial domains. The full task of mapping takes about 2.2 hours on a machine equipped with an Intel i9-10850K CPU, 64Gb RAM and 1Tb solid state drive.

2.2 Mapping to Non-Overlapping Partial Structural Domains

There are 763 proteins whose reference sequences are mapped to multiple non-overlapping partial domain structures. We use the protein prosaposin (UniProt: P07602) encoded by gene PSAP as an example. Prosaposin consists of 524 amino acids, but there are no structures that cover its full sequence. Its sequence can be mapped to four individual non-overlapping
structural domains. SeqMapPDB maps prosaposin to the structures of 2DOB chain A (covering the segment of residues 60–140), 4V20 chain C (residues 184–272), 1W12 chain A (residues 311–403), and 3BQQ chain A (residues 405–484). Overall, 64.7% of residues in prosaposin can be mapped to structures.

Mapping provided by SeqMapPDB produces a non-redundant set of structures to the sequence of prosaposin. In contrast, the database SIFTS returns 33 PDB chains for prosaposin, with many entries mapped redundantly to the same segment. For example, SIFTS produces 13 candidate PDB structures for the segment of residues 405–484, 7 of which are not 100% identical to the segment of the query sequence. In contrast, SeqMapPDB maps this segment to chain A of 3BQQ, which is 100% identical in sequence.

Overall, SeqMapPDB provides mapping to non-overlapping partial structural domains of 763 proteins in the human proteome, where the aggregates of mapped domains cover from 0.7% for long proteins (e.g. 5JDE chain A for protein titin with 34,350 residues) to 69.9% (e.g. HLA-DRA) of the full protein sequences, with the median coverage of 20.6% per structural domain.

2.3 Retrieving Paired Structures for Protein Isoforms

A gene can encode multiple protein isoforms due to the events of alternative splicing [12]. These isoforms may fold into significantly different structures [15]. SeqMapPDB can be used to identify paired structure of different isoforms. As an illustration, the gene CRK encodes adapter molecule crk (UniProt: P46108), and has two isoforms deposited in UniProt. Isoform 1 has 304 residues, which is mapped by SeqMapPDB to the PDB structure of 2EYZ (chain A), covering the full length except
one unmatched residue. Isoform 2 has 204 residues, which is mapped to 2EYY (chain:A) that covers its full length except 2 unmatched residues. Overall, SeqMapPDB can obtain accurate structural mappings of 52 isoforms of 26 human proteins with each pair of isoforms differs at least by 30 residues.

3 Conclusion

We have developed a standalone pipeline SeqMapPDB that can accurately map protein sequences to high-quality protein structures in the PDB database. It can be used to select representative structures for batch processing a large number of query sequences, including isoforms. For protein sequences whose full structures are not available, SeqMapPDB can provide non-overlapping partial protein structural domains that collectively covers a significant portion of the query sequence. Furthermore, as protein sequences are often revised when reference genomes are updated, SeqMapPDB can be employed in a stand-alone fashion to obtain accurate and up-to-date residue index mapping. Our pipeline is efficient, the short mapping time of the whole human proteome demonstrates that SeqMapPDB can be efficiently deployed for large scale mapping of databases. Furthermore, SeqMapPDB provides the flexibility enabling users to obtain mapping between in-house databases of sequences and structures.

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Figure 1: Overview of SeqMapPDB Pipeline. SeqMapPDB generates a sequence database of the protein structures in the PDB using coordinate records. A query sequence is then searched against this database using BLASTP, and a set of candidate structures is then identified. SeqMapPDB then calculates the two-way identities and coverage based on ClustalW2 alignment between the query sequence and each candidate sequence. SeqMapPDB then either identify the full-length structure, or a set of non-overlapping partial structural domains with maximal coverage, with indices mapped.