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## Using Content-Based Filtering to Infer Direct Associations between the CATH, Pfam, and SCOP Domain Databases

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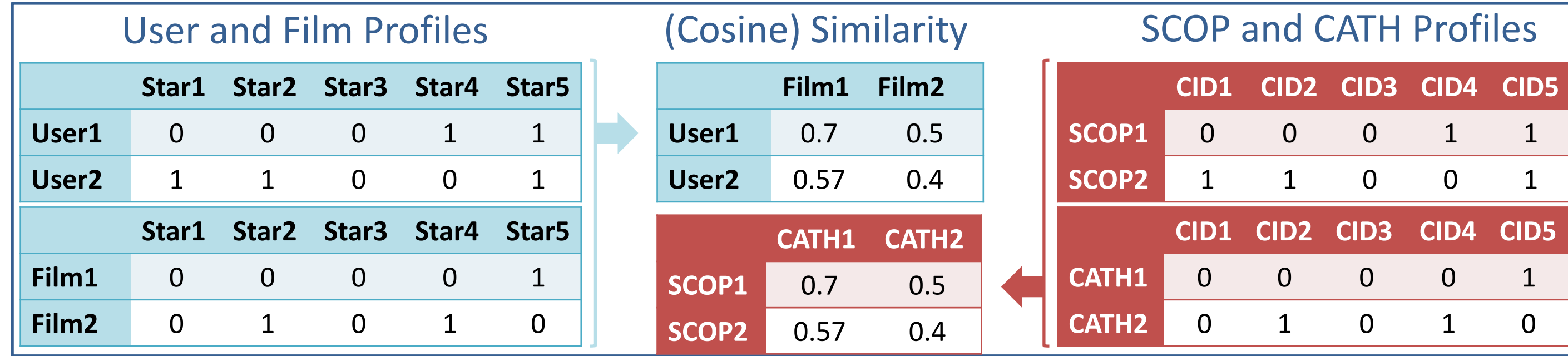
## INTRODUCTION

Protein domain structure classification systems such as CATH and SCOP provide a useful way to describe evolutionary structure-function relationships. Similarly, the Pfam sequence-based classification identifies sequence-function relationships. Nonetheless, there is no complete direct mapping from one classification to another. This means that functional annotations that have been assigned to one classification cannot always be assigned to another. Here, we

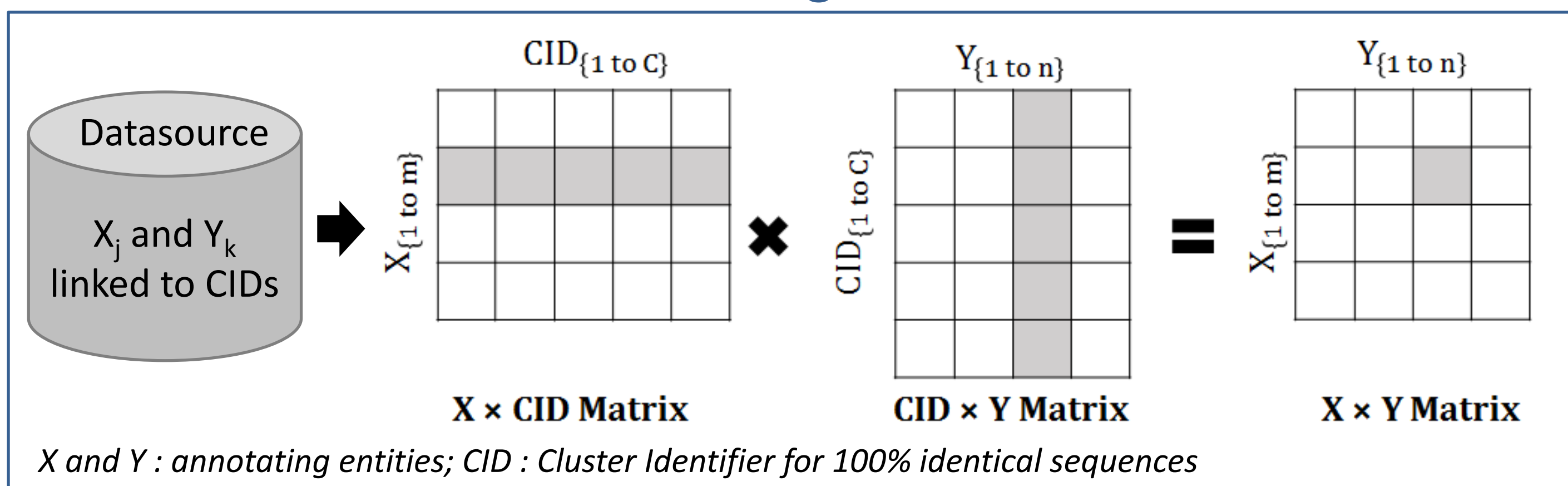
present a novel content-based filtering approach called **CAPS (Computing direct Associations between annotations of Protein Sequences and Structures)** to systematically analyze multiple protein-domain relationships in the SIFTS and UniProt databases in order to infer direct mappings between CATH superfamilies, Pfam clans or families, and SCOP superfamilies. We then compare the result with existing mappings in Pfam, InterPro, and Genome3D.

## MATERIALS & METHODOLOGY

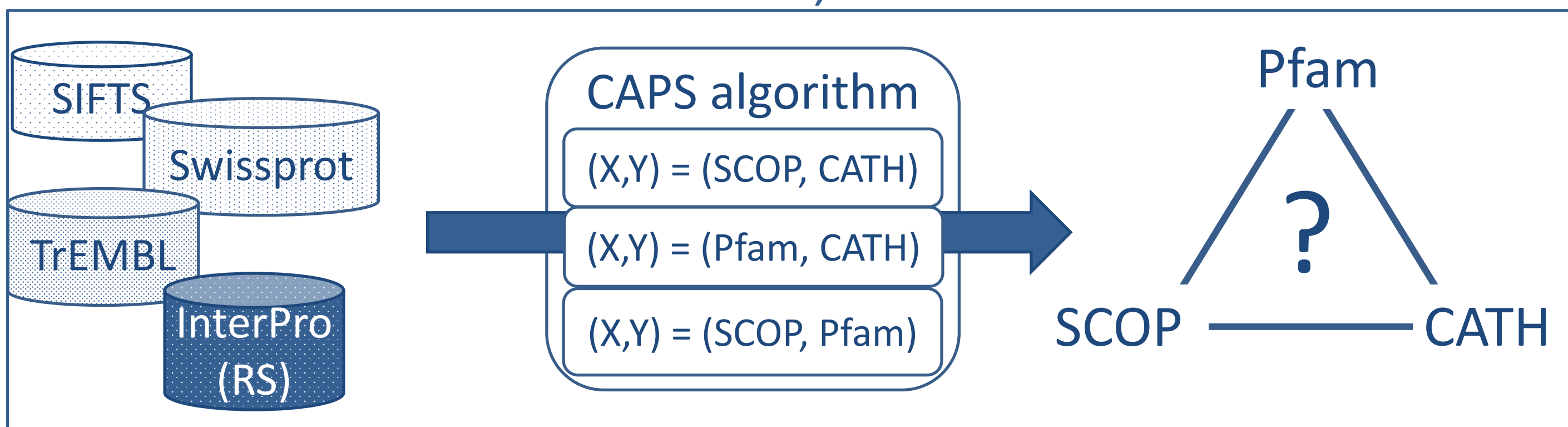
### Content-Based Filtering Intuition



### Generalization: Scoring Matrix Calculation



### Instantiation: CATH, Pfam and SCOP



### The CAPS algorithm

#### Given

- X and Y, two sets of annotating entities,
- RS+, a reference set of confirmed associations between elements of X and Y,
- S<sub>1</sub> to S<sub>n</sub>, n sources of relations between X and protein chains or sequences (CIDs), and between Y and protein chains or sequences,

#### 1. For each datasource S<sub>i</sub>

- Extract X-CID and Y-CID relations (CID: clusters of 100% identical sequences)
- Compute dot product of normalized (X × CID)<sub>i</sub> and (CID × Y)<sub>i</sub> matrices to get the (X × Y)<sub>i</sub> cosine similarity matrix for source S<sub>i</sub>.

#### 2. Aggregate similarity scores of all sources

$$ConfidenceScore_{X_j, Y_k} = \frac{\sum_i^n w_i S(X_j, Y_k)}{\sum_i^n w_i}$$

- Determine sources weights w<sub>i</sub> that maximize AUC in ROC plots using RS positive examples of X-Y associations against background.

#### 3. Determine the threshold confidence score

- Build a set of negative examples RS- (by random shuffling of relations supporting RS+) and build training and test sets of positive and negative examples
- Select confidence score threshold that maximizes F-measure on the training set of positive and negative X-Y associations and evaluate on the test set.

#### 4. (Optional) Calculate P-Values for each association in each source S<sub>i</sub>

- Hypergeometric law + Bonferroni correction
- Categorize the CAPS-inferred associations (Gold: all P-values significant ; Silver: more significant P-values than non significant ones ; Bronze: The rest).

#### Return

- "CAPS-inferred" X-Y associations (score > threshold), score and category.

## CAPS-INFERRED ASSOCIATIONS

### SCOP-CATH

### Pfam-CATH

### SCOP-Pfam

Table 1. CAPS mappings versus InterPro.

| Dataset          | SCOP-CATH Mappings | SCOP SupFam | CATH SupFam | Dataset          | Pfam-CATH Mappings | Pfam Clans/Fam | CATH SupFam | Dataset          | SCOP-Pfam Mappings | SCOP SupFam | Pfam Clans/Fam |
|------------------|--------------------|-------------|-------------|------------------|--------------------|----------------|-------------|------------------|--------------------|-------------|----------------|
| Merged           | 580,763            | 1,851       | 2,604       | Merged           | 1,068,601          | 7,228          | 2,754       | Merged           | 1,004,741          | 2,111       | 7,165          |
| CAPS             | 5,576              | 1,817       | 2,549       | CAPS             | 7,623              | 3,033          | 2,745       | CAPS             | 6,618              | 2,109       | 3,168          |
| InterPro         | 2,856              | 1,637       | 2,231       | InterPro         | 3,573              | 2,008          | 2,494       | InterPro         | 2,100              | 1,537       | 1,752          |
| Common with CAPS | 2,764              | 1,634       | 2,225       | Common with CAPS | 3,494              | 1,998          | 2,489       | Common with CAPS | 2,053              | 1,532       | 1,745          |

Fig1. Distribution according to node degrees (Number of Associations)

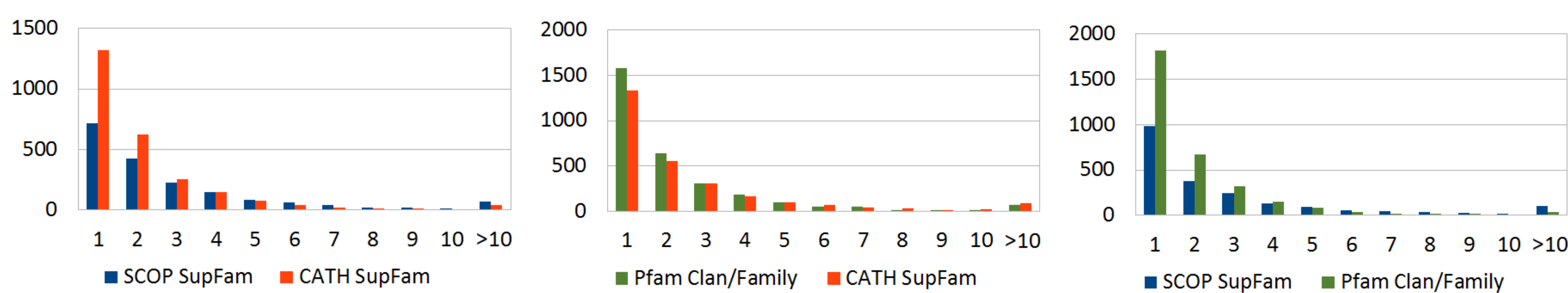
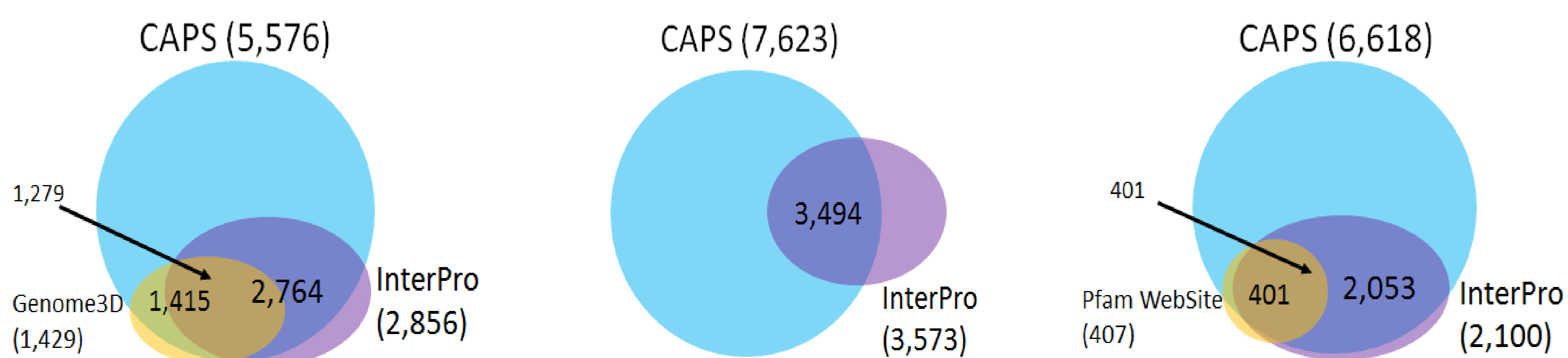
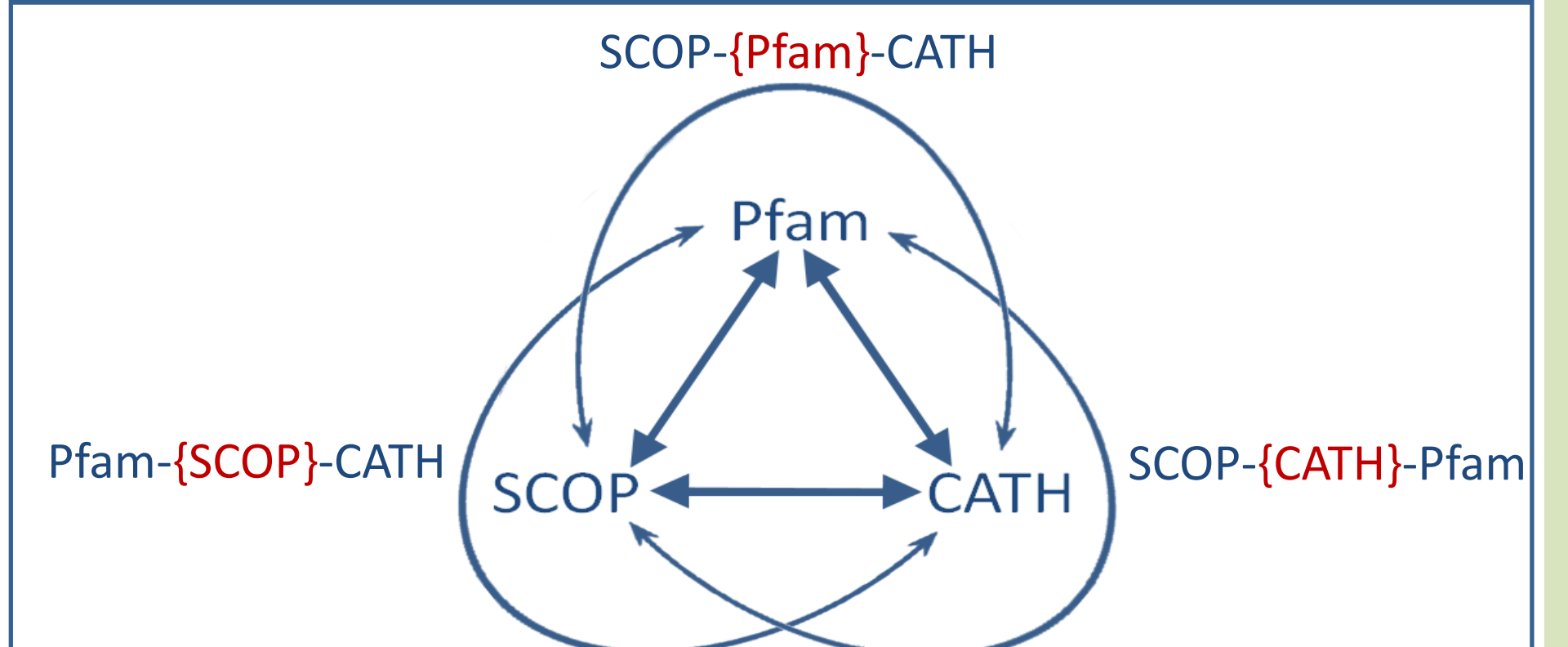


Fig 2. Intersection between our result (CAPS), InterPro, Genome3D, and Pfam website mappings.



## TRIANGULAR VERIFICATION



|                              | Mappings     | SCOP        | CATH        |
|------------------------------|--------------|-------------|-------------|
| SCOP-CATH                    | 5,576        | 1,817       | 2,549       |
| Common with SCOP-{Pfam}-CATH | <b>5,438</b> | <b>1786</b> | <b>2518</b> |
| 1:1 SCOP-CATH                | 506          | 506         | 506         |
| Common with SCOP-{Pfam}-CATH | 492          | 492         | 492         |
|                              | Mappings     | SCOP        | CATH        |
| Pfam-CATH                    | 7,623        | 3,033       | 2,745       |
| Common with Pfam-{SCOP}-CATH | <b>6,768</b> | <b>2629</b> | <b>2518</b> |
| 1:1 Pfam-CATH                | 457          | 457         | 457         |
| Common with Pfam-{SCOP}-CATH | 393          | 393         | 393         |
|                              | Mappings     | SCOP        | CATH        |
| SCOP-Pfam                    | 6,618        | 2,109       | 3,168       |
| Common with SCOP-{CATH}-Pfam | <b>5,628</b> | 1786        | 2629        |
| 1:1 Pfam-CATH                | 635          | 635         | 635         |
| Common with Pfam-{SCOP}-CATH | 478          | 478         | 478         |

## CONCLUSION

- Over 90% of all associations found, are self-consistent with respect to triangular (SCOP-CATH-Pfam) associations.
- Overall, our approach finds 4 times as many SCOP-CATH superfamily associations than currently exist in Genome3D. These new associations will be beneficial to:
  1. Transfer annotations from one classification scheme to another.
  2. Investigate annotation consistency between different classifications.
- We are currently extending our approach to
  1. Analyze multiple associations in more detail.
  2. Confirm the associations using 3D structure alignment

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