Functional Annotation of PATRIC using Gene Ontology

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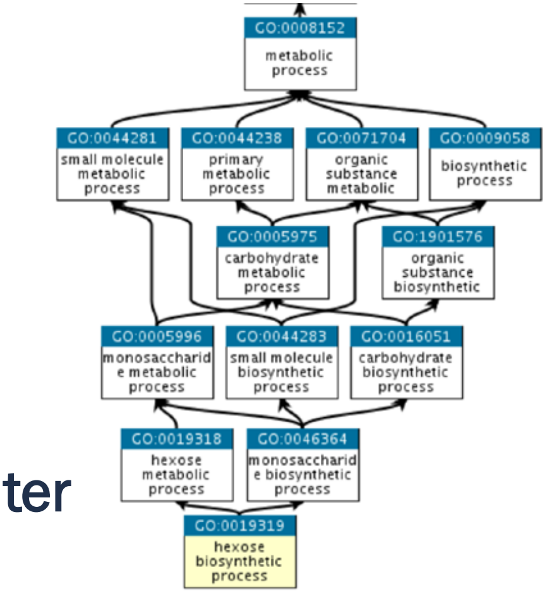
Background

Gene Ontology (GO)

- A network of biological classes that describe the current best interpretation of the "universe" of biology
- A directed acyclic graph representation of protein function separated into three aspects:
  - Molecular Function
  - Cellular Component
  - Biological Processes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small molecule biosynthetic process
GO:0016051
carbohydrate biosynthetic process
GO:0019318
hexose metabolic process
GO:0046364
monosaccharide biosynthetic process
GO:0019319
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PATRIC

- PAthosystems Resource Integration Center
- Database for functional annotation of bacterial and viral genomes used commonly in infectious disease and antibiotic resistance research.
- Proteins/coding sequences are poorly annotated and not updated with GO terms.

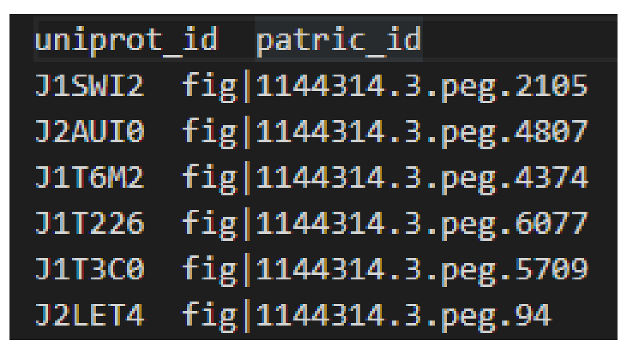
Current Work

Extraction of md5 hashes and IDs from PATRIC

- Use the PATRIC Command Line Interface (CLI) to extract all coding sequences from 459955 bacterial and viral genomes in smaller batches of 250 genomes each.
- Each amino-acid sequence has its own md5 hash that is associated with multiple PATRIC IDs from different bacterial genomes.
- Extract other relational information including genus-specific protein families (PLfams) and cross-genus protein families (PGfams).

Query UniprotKB for GO Terms

- Use md5 hash and the taxonomic identifier from PATRIC to query the UniprotKB database through the SPARQL endpoint.
- Construct a table of link-outs which connect the Uniprot IDs to PATRIC IDs in a many to many relationship.
- Construct a JSONhFasta file that assigns GO Terms to each protein sequence and PATRIC ID in the PATRIC database.



uniprot_id	patric_id
J1SWI2	fig|1144314.3.peg.2105
J2AUI0	fig|1144314.3.peg.4807
J1T6M2	fig|1144314.3.peg.4374
J1T226	fig|1144314.3.peg.6077
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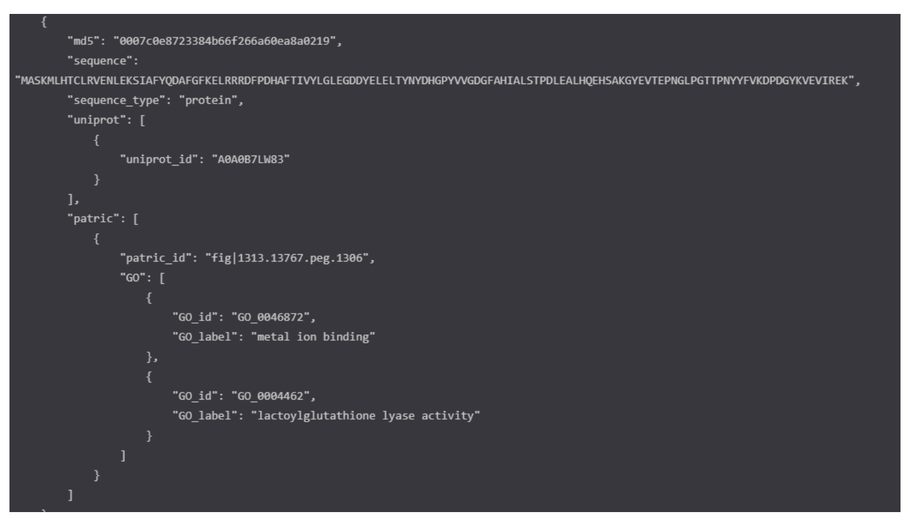
J2LET4	fig|1144314.3.peg.94



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        "sequence":
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                "GO": [
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                        "GO_label": "metal ion binding"
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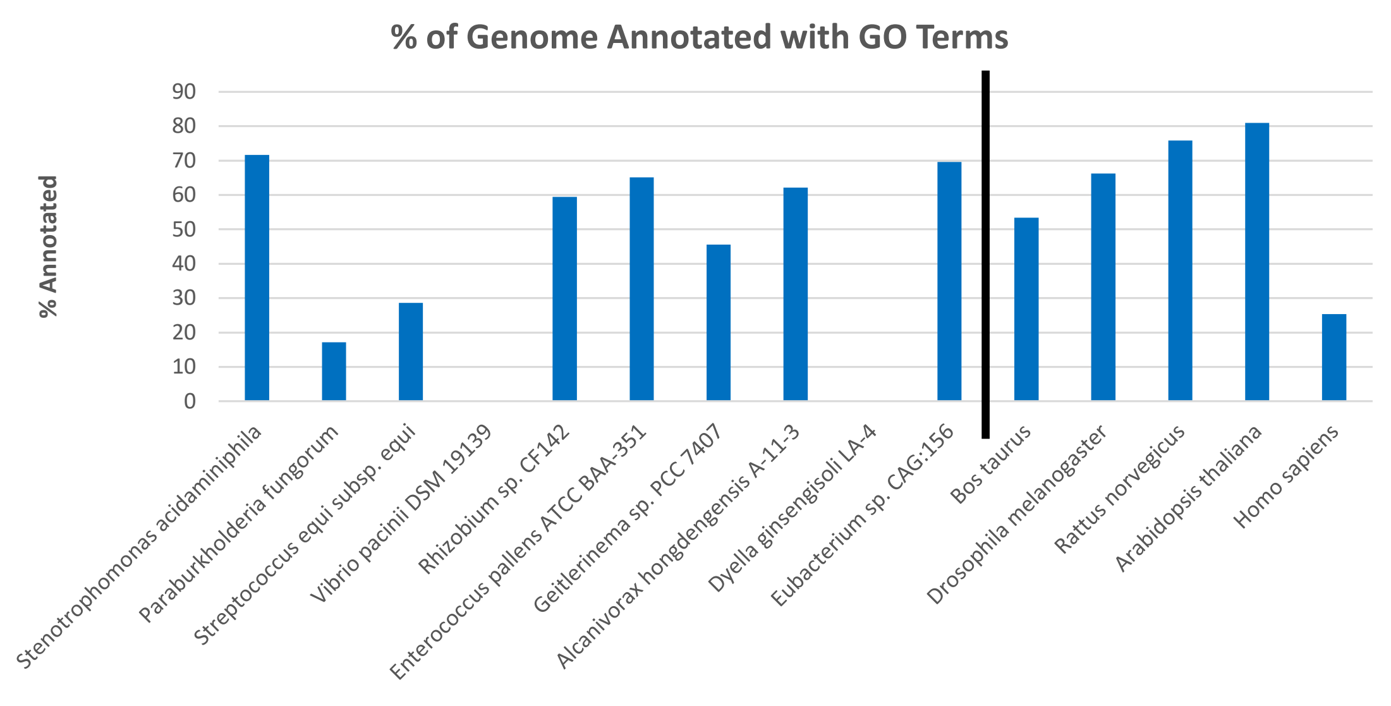

Figure #2. Analysis of PATRIC GO Annotations

Project Goals

Overall Goal: Automated Function Prediction using Gene Ontology

- Predict the GO terms for an unknown coding sequence using the existing network of GO graphs.

Current Goals: Improve GO Annotation of Bacterial Genomes

- Update crosslinks between the proteins IDs in the UniprotKB and PATRIC databases.
  - Uniprot KnowledgeBase is the largest repository of protein sequences and annotations. It attempts to gather information from multiple biological databases for centralized access and storage.
  - Current connections between the two databases are outdated and incomplete.
- Annotate PATRIC with GO Terms queried from UniprotKB
- Analyze bacterial annotations for expandable GO Terms that could have more children

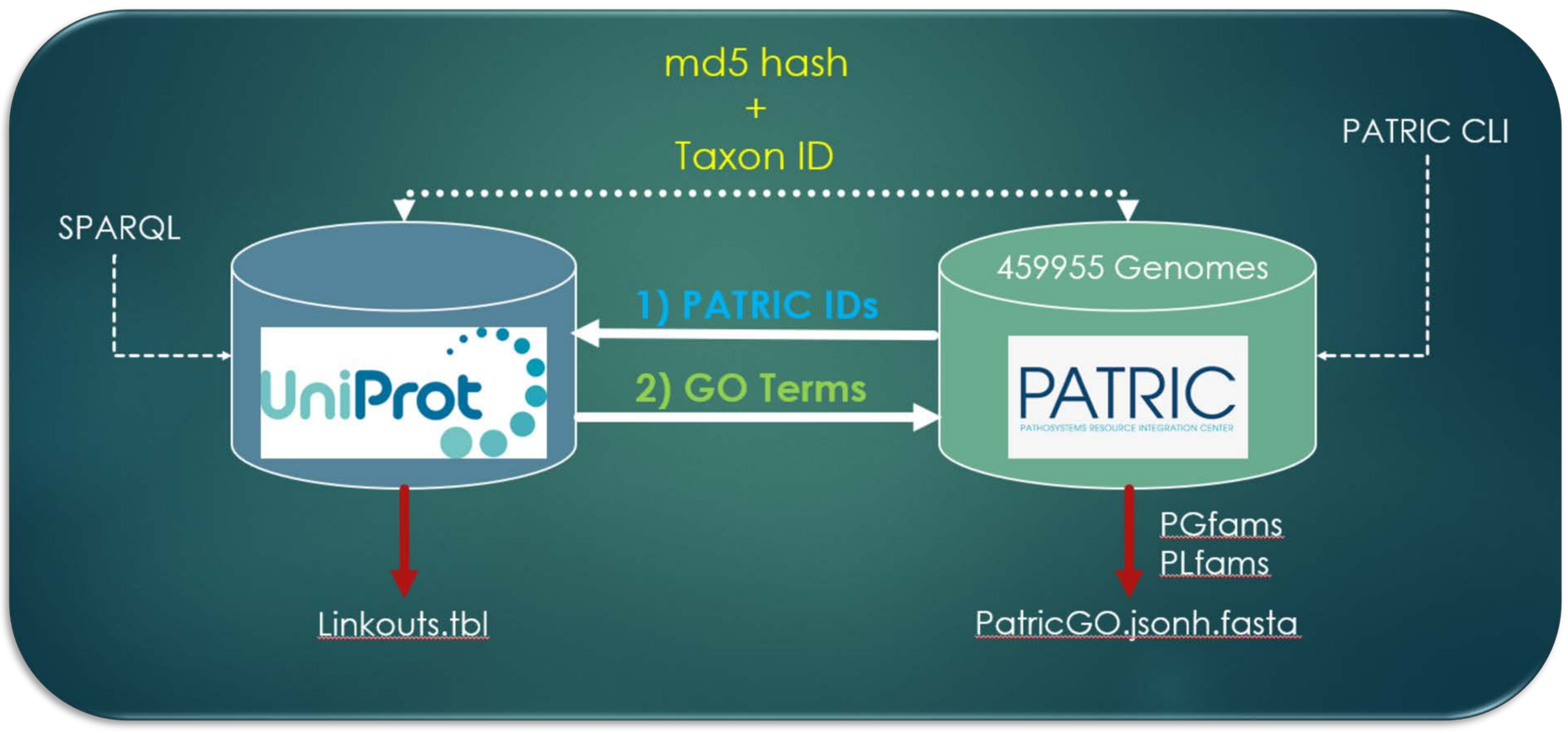

Figure #1. Overall database query structure for updating PATRIC and UniProt.

Future Work

Resolve Issues with Larger Query Sizes

- Both databases are extremely large and expensive to query leading to memory errors and faulty server endpoints.
  - Extracting a single batch of 250 genomes using PATRIC CLI takes 40 min.
  - Querying those 250 genomes for GO Terms through Uniprot's SPARQL endpoint takes more than 20 hours.
- Proposed solution is to locally download the entire Uniprot database to avoid queries to remote servers.

Construct Automated Function Prediction Model for Bacterial Proteins

- Index through the JSONhFasta file to obtain sequences and GO graphs.
- Use DIAMOND, an all-to-all BLAST tool, to find clusters of similar sequences and create a weighted network of GO graphs.
- Determine the distribution of each possible GO Term in the network.
- Predict the probability for a new protein sequence to have a set of GO Terms based on the existing distribution of GO Terms and network of protein sequences.

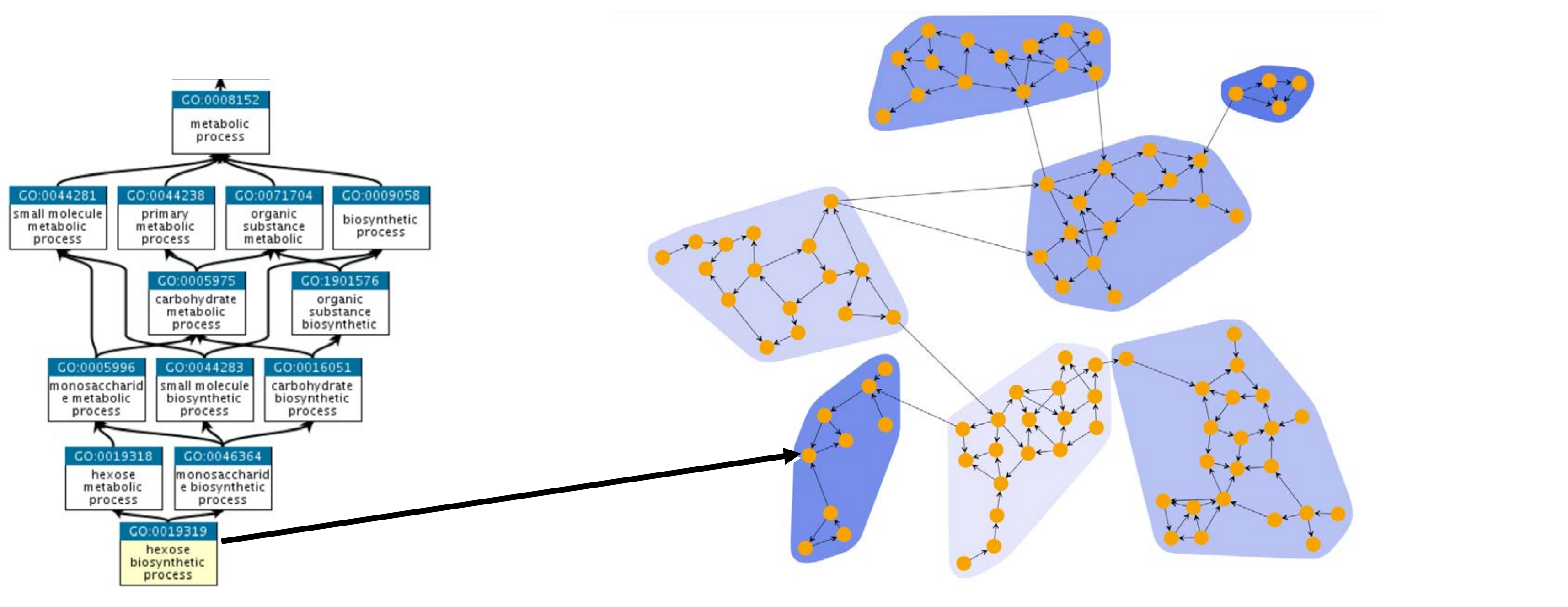
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Figure #3. Automated function prediction model using a combination of DIAMOND and Gene Ontology

References

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