FunVar Update

31 March, 2017

Overview

- Developing visualisation tool
  - cath-cluster-web

- Improving accessibility of FunFam alignments
  - Sequence MD5 -> UniProtKB
  - FASTA -> STOCKHOLM

cath-cluster-web

Requirements:

- 3D structural viewer
- Functional annotations
- Sequence alignments

Ideally…

- Use existing web services (CATH, PDBe, UniProtKB)
- Portable, generic, reusable

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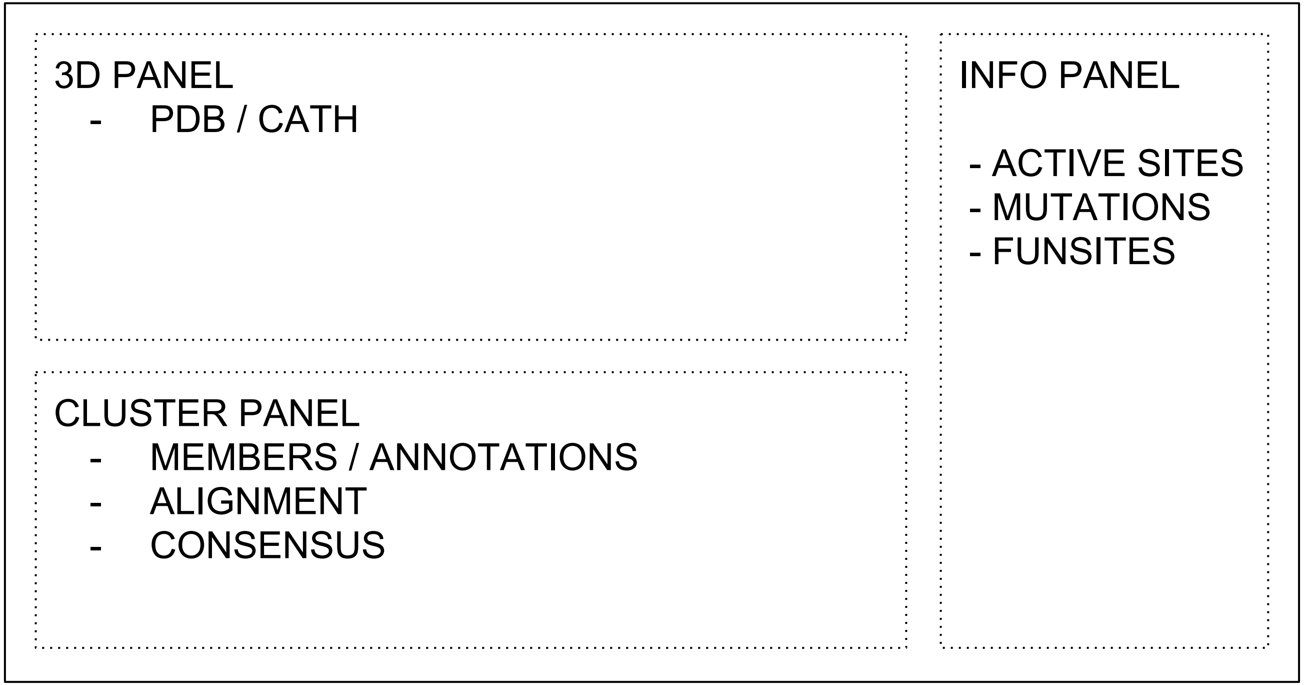

3D PANEL

- PDB / CATH

CLUSTER PANEL

- MEMBERS / ANNOTATIONS
- ALIGNMENT
- CONSENSUS

INFO PANEL

- ACTIVE SITES
- MUTATIONS
- FUNSITES

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Issues:

- Combining existing components
  - 3D viewer, MSA viewer, Tree
- Combining data sources
  - CATH, PDBe, UniProtKB, EC, GO, ...
- Mapping between coordinate frames
  - sequence/structure
- Dynamic
  - Interaction coordinated across all components

cath-cluster-web

Choosing the right tool...

Use an existing framework to glue all views, data and events together into a single web application.

- Angular, Angular2, ReactJS, Polymer, etc, etc… ?

After discussion with PDBe dev…

- Angular2 (Google)

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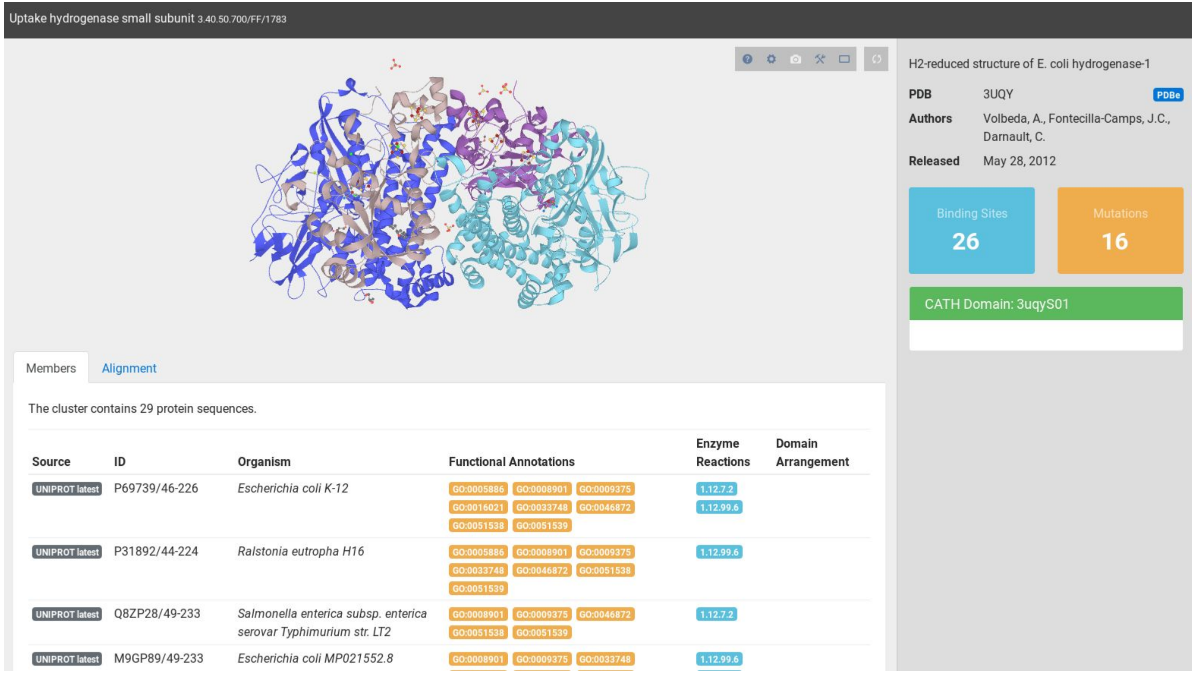

Uptake hydrogenase small subunit 3.40.50.700/FF/1783

H2-reduced structure of E. coli hydrogenase-1

PDB	3UQY
Authors	Volbeda, A., Fontecilla-Camps, J.C., Darnault, C.
Released	May 28, 2012

The cluster contains 29 protein sequences.

Source	ID	Organism	Functional Annotations	Enzyme Reactions	Domain Arrangement
UNIPROT latest	P69739/46-226	*Escherichia coli K-12*	GO:0005886 GO:0008901 GO:0009375 GO:0016021 GO:0033748 GO:0046872 GO:0051538 GO:0051539	1.12.7.2 1.12.99.6	
UNIPROT latest	P31892/44-224	*Ralstonia eutropha H16*	GO:0005886 GO:0008901 GO:0009375 GO:0033748 GO:0046872 GO:0051538 GO:0051539	1.12.99.6	
UNIPROT latest	Q8ZP28/49-233	*Salmonella enterica subsp. enterica serovar Typhimurium str. LT2*	GO:0008901 GO:0009375 GO:0046872 GO:0051538 GO:0051539	1.12.7.2	
UNIPROT latest	M9GP89/49-233	*Escherichia coli MP021552.8*	GO:0008901 GO:0009375 GO:0033748	1.12.99.6	

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Initial data from (FASTA) alignment

- List of members (sequences)
  - Each entity based on unique sequence MD5
- Associated annotations for each member (headers)
  - CATH domains, GO terms, EC terms, UniProtKB accessions, etc
- Alignment

Then use web services to get...

- 3D structure, known binding sites, mutations, etc

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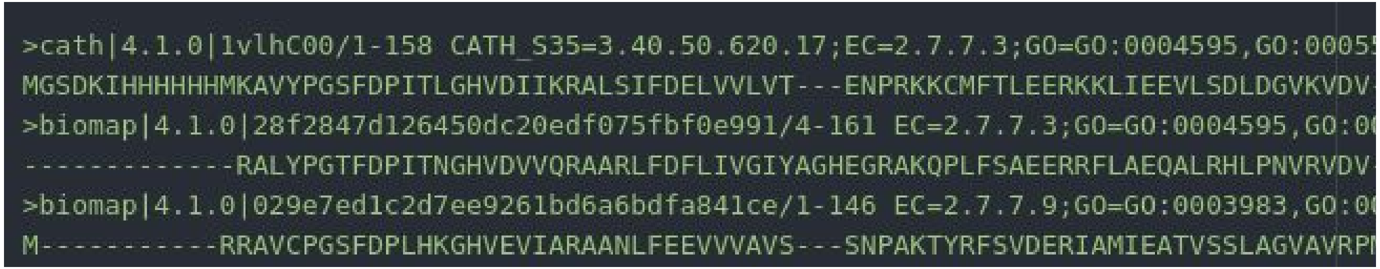
Meta data in FASTA is a hack...

```
> <sequence/structure_id> <annotation;...>
<ALIGNED_AA_SEQUENCE>
```



```
>cath|4.1.0|1vlhC00/1-158 CATH_S35=3.40.50.620.17;EC=2.7.7.3;GO=GO:0004595,GO:0005
MGSDKIHHHHHHMKAVYPGSFDPITLGHVDIIKRALSIFDELVVLVT---ENPRKKCMFTLEERKKLIEEVLSDLDGVKVDV
>biomap|4.1.0|28f2847d126450dc20edf075fbf0e991/4-161 EC=2.7.7.3;GO=GO:0004595,GO:0
-------------RALYPGTFDPITNGHVDVVQRAARLFDFLIVGIYAGHEGRAKQPLFSAEERRFLAEQALRHLPNVRVDV
>biomap|4.1.0|029e7ed1c2d7ee9261bd6a6bdfa841ce/1-146 EC=2.7.7.9;GO=GO:0003983,GO:0
M-----------RRAVCPGSFDPLHKGHVEVIARAANLFEEVVVAVS---SNPAKTYRFSVDERIAMIEATVSSLAGVAVRP
```

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FASTA Pros:

- Simple, easy to parse, alignments already exist

FASTA Cons:

- Forces data into unstructured headers
- No meta data (alignment id, name, date created, etc)
- No consensus information (e.g. scorecons)
- Not easy to map sequence to structure

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Also, problems using sequence MD5s?

Pros: Simple, uses existing mapping

Cons:

- Very specific to CATH-Gene3D
- Annotations are one-to-many-to-many:
  Sequence MD5
   -> one-to-many UniProtKB entries
    -> one-to-many GO/EC/organism entries

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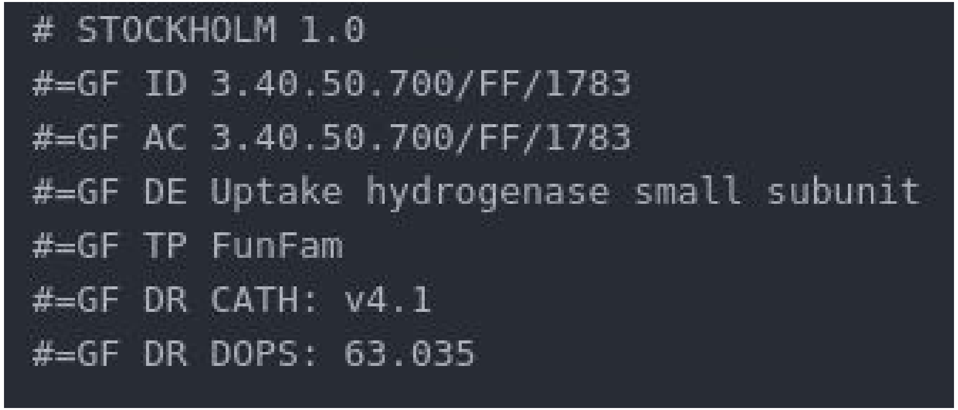
So…

1. Map all entries via UniProtKB sequences
    a. Expand sequence MD5s to UniProtKB entries
    b. Use existing filter protocols to remove redundant entries

2. Use more structured alignment format
    a. FASTA -> STOCKHOLM (as per Pfam)

STOCKHOLM

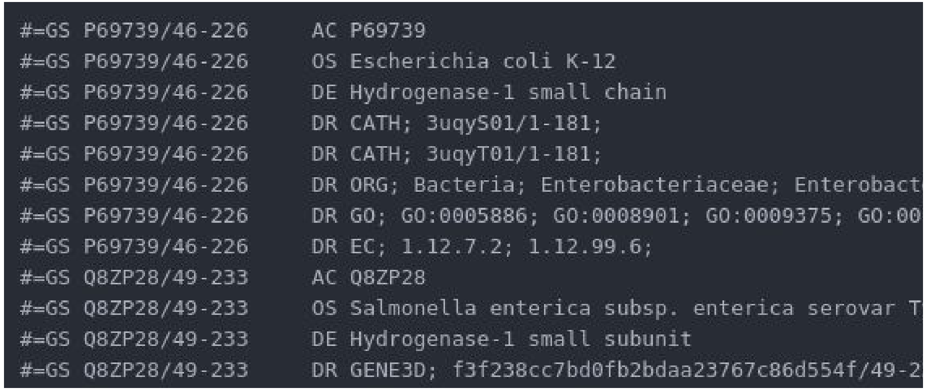
General meta data for the whole alignment...



```
# STOCKHOLM 1.0
#=GF ID 3.40.50.700/FF/1783
#=GF AC 3.40.50.700/FF/1783
#=GF DE Uptake hydrogenase small subunit
#=GF TP FunFam
#=GF DR CATH: v4.1
#=GF DR DOPS: 63.035
```

STOCKHOLM

Individual meta data for each sequence…

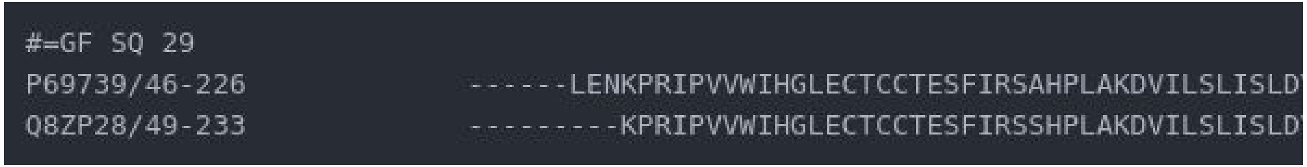


```
#=GS P69739/46-226     AC P69739
#=GS P69739/46-226     OS Escherichia coli K-12
#=GS P69739/46-226     DE Hydrogenase-1 small chain
#=GS P69739/46-226     DR CATH; 3uqyS01/1-181;
#=GS P69739/46-226     DR CATH; 3uqyT01/1-181;
#=GS P69739/46-226     DR ORG; Bacteria; Enterobacteriaceae; Enterobact
#=GS P69739/46-226     DR GO; GO:0005886; GO:0008901; GO:0009375; GO:00
#=GS P69739/46-226     DR EC; 1.12.7.2; 1.12.99.6;
#=GS Q8ZP28/49-233     AC Q8ZP28
#=GS Q8ZP28/49-233     OS Salmonella enterica subsp. enterica serovar T
#=GS Q8ZP28/49-233     DE Hydrogenase-1 small subunit
#=GS Q8ZP28/49-233     DR GENE3D; f3f238cc7bd0fb2bdaa23767c86d554f/49-2
```

CATH entry maps from UniProtKB numbering to PDB residue labels (double-checked against sequence in alignment)

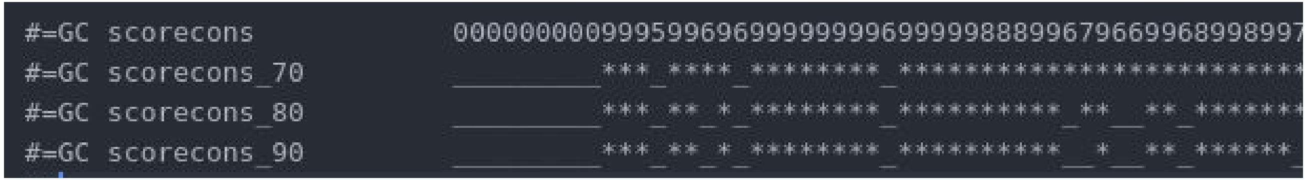
STOCKHOLM

The aligned sequences for each entry



```
#=GF SQ 29
P69739/46-226            ------LENKPRIPVVWIHGLECTCCTESFIRSAHPLAKDVILSLISLD
Q8ZP28/49-233            ---------KPRIPVVWIHGLECTCCTESFIRSSHPLAKDVILSLISLD
```

And consensus information...



```
#=GC scorecons          0000000009995996969999999969999988899679669968998997
#=GC scorecons_70       _________***_****_********_*************************
#=GC scorecons_80       _________***_**_*_********_**********_**__**_*******
#=GC scorecons_90       _________***_**_*_********_**********__*__**_******_
```

STOCKHOLM

Added Bonus:

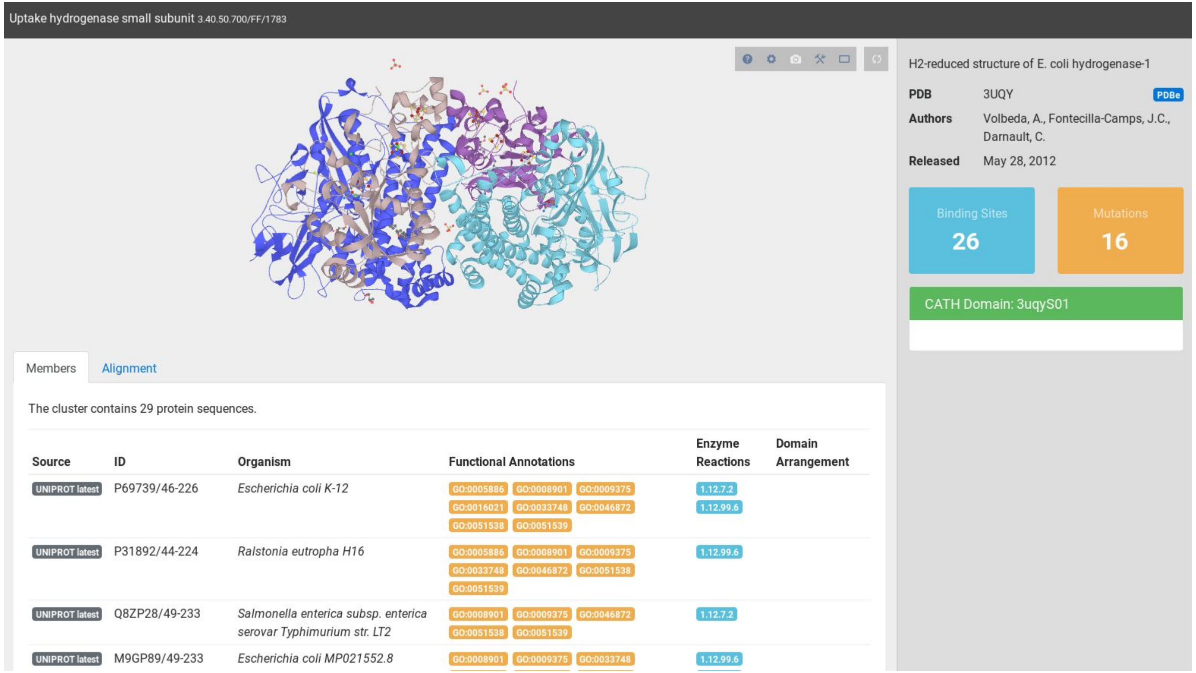
- No need for separate files (names, scorecons, DOPS, etc)
- HMMER uses this as native alignment format
  - Aligning new sequence to this alignment does what you would expect with consensus information (i.e. opens gaps)
  - No need to rerun scorecons

cath-cluster-web

Actions:

- Generate filtered STOCKHOLM alignments for all FunFams (done)
- Integrate STOCKHOLM parser into cath-cluster-web (done)

cath-cluster-web



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