Shape Matching Service for Structural Biology (SMASB)

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As part of the BioMedBridges project Work Package 9, PDBe (pdbe.org) and STFC (stfc.ac.uk) are setting up a service that will allow users to search and compare volumes derived from structures determined by X-ray crystallography, Electron Microscopy (EM), Electron Tomography (ET) and SAXS. Consequently we aim to arrive at a structural integration of PDB data with EMDB, provide structural annotation for EMDB maps and also link other databases like Uniprot (http://www.uniprot.org), IntAct (http://www.ebi.ac.uk/intact) and GO (http://geneontology.org). Here we discuss potential use cases, volume comparison strategies with some examples, scoring functions and the framework of the service.

Some use cases

Volume *alignments* :
- Derived from different species
- Generated by different experiment types
- Involving conformational variations
- Involving additional components (difference maps)

Structure/Component Annotation :
- *Automated segmentation* of volume (iteratively) into components
- *Fit models* into volumes/segments (PDB and EMDB)
- *Fold identification* by search with known folds

Function Annotation/Interactions:
- Get interaction data (*IntAct*) of components with sufficient linking data
- Get *UniProt* & *GO* annotation/ontology of components with sufficient linking data

Volume matching approaches considered

Density based 6D search :
- **Fast Translational Matching (COLORES)** : Fast Fourier Transform (FFT) driven translational search at each rotation (Chacon and Wriggers, 2002). Cross correlation scores with or without Laplacian filters, are used for matching
- **Fast Rotational Matching (ADP-EM, FRM5D)** : Spherical Harmonics accelerated rotational search at each translation (Garzon et al. 2007, Kovacs et al. 2003). Cross correlation scores with or without Laplacian filters, are used for matching
- **Random Sampling (CHIMERA)**: Randomly sample rotation and translation space (Goddard et al. 2007). An overlap score based on product moments is used for matching.

Reduced representation :
- **Gaussian Mixture Model (GMFIT)**: Linear combination of N 3D gaussian density (Kawabata, 2008). A gaussian overlap metric is used to score the alignment.
- **Point Cloud Matching (MatchPt)** : A self-organizing Topology Representing Network is used to represent volume features as N points (Birmann & Wriggers, 2007). Minimal RMSD or statistical variability measures are used for matching.

Volume pre-processing

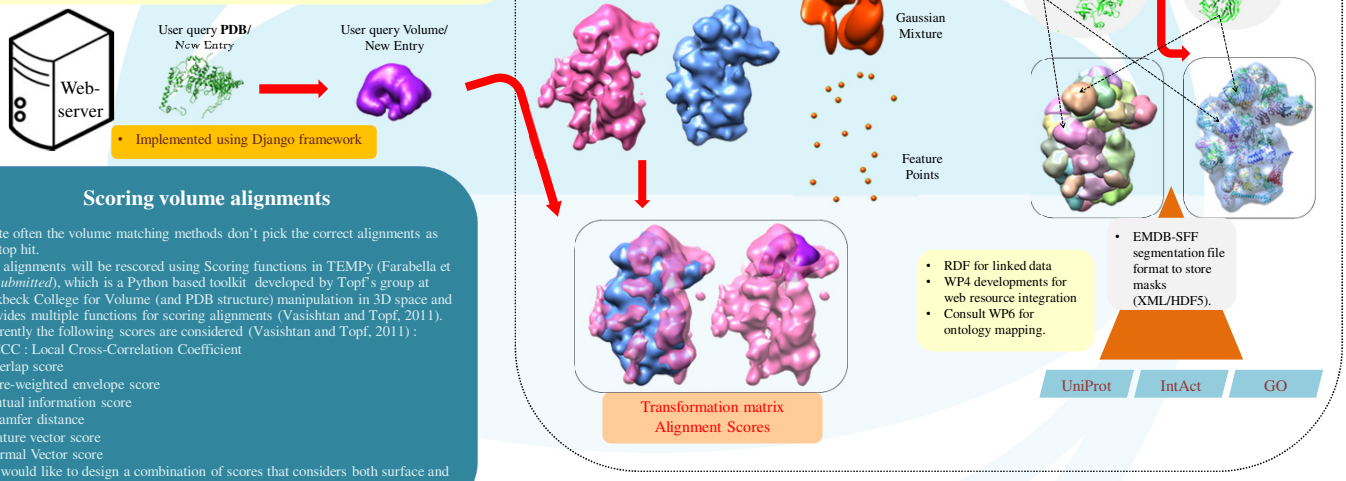
- Volumes of macromolecular complexes determined by EM/ET/SAXS include varying noise levels and the density distributions may differ significantly.
- Contour level determination for the volumes based on the molecular weight, standard deviation of density distribution and levels suggested by authors.
- The background peak is shifted to zero for cases with significant deviations.
- Feature representation (as Gaussian Mixtures and point clouds) is included as part of pre-processing.

Filtering

- The grid spacing and resolution of one map is filtered to match the other, prior to alignment.

- MySQL like relational database.
- XSD schema for representing meta-data
- OpenAstexViewer (http://openastexviewer.net/web) for volume visualization
- Can be provided in RDF format (http://www.ebi.ac.uk/rdf) using D2R (http://d2rq.org/d2r-server)

Database with shapes of EMDB and PDB entries and segmentations

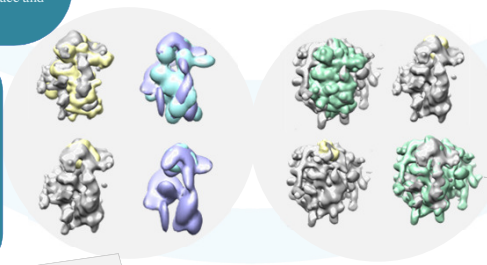


Scoring volume alignments

- Quite often the volume matching methods don't pick the correct alignments as the top hit.
- The alignments will be rescored using Scoring functions in TEMPy (Farabella et al. *submitted*), which is a Python based toolkit developed by Topf's group at Birkbeck College for Volume (and PDB structure) manipulation in 3D space and provides multiple functions for scoring alignments (Vasishtan and Topf, 2011).
- Currently the following scores are considered (Vasishtan and Topf, 2011) :
  - LCCC : Local Cross-Correlation Coefficient
  - Overlap score
  - Core-weighted envelope score
  - Mutual information score
  - Chamfer distance
  - Feature vector score
  - Normal Vector score
- We would like to design a combination of scores that considers both surface and density overlap.

Test set for volume matching methods

- About 50 volumes were selected from each of the four major sample categories from EMDB : Prokaryotic Ribosomes; Eukaryotic Ribosomes; Chaperones ; Viral structures
- The test set involves volumes of different grid sizes, resolutions, sample components and from different research groups.
- Simulated maps derived from PDB structures are also added to each category.
- The test set is publically available at: ftp://ftp.ebi.ac.uk/pub/databases/emtest/PDBeMatch_data/PDBeMatch Data.tar



Examples from sample set

- Viral RNA bound 80S ribosome (EMD-1138, 15Å)
- Viral RNA bound 40S ribosomal subunit (EMD-5527, 17.5 Å)
- 40S ribosomal subunit (EMD-5592, 5Å)
- Simulated 40S maps (PDB ID: 2XZM)
- Simulated maps of sub-complexes (PDB ID : 3J3A, 3 protein complex)

- **Random sampling** search (CHIMERA) is faster than exhaustive search methods. Each alignment takes about 7 mins on a single processor.
- The number of search steps depends on the ratio of volume sizes.
- Except for a 4Å 40S vs (15Å 80S, 17.5Å 40S), correct alignments were obtained in the top 10 hits.

- **Feature (coarse-graining)** based methods are extremely faster than the 6D density search methods. GMFIT takes a few seconds for matching two gaussian mixture models
- The gaussian overlap function used for scoring allows flexibility in matching different resolutions and sizes.
- The number of gaussians chosen to represent a volume is important and it depends on the resolution and size of the volume. Larger number is required to represent maximum features from a high resolution map.
- Search for a smaller component (subcomplex) failed with a constant number of 16 gaussians.
- We plan to automate feature identification and gaussian model generation as part of the pipeline.

- **Exhaustive search** methods (COLORES,ADP-EM) are much slower than Random sampling or Feature based methods. Each alignment takes about 1-2 hours on a single processor.
- Failed cases mainly involved subunit or subcomponent alignments.
- Overall, the exhaustive search methods do not seem to gain largely in the test set, considering the time taken for each run.

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