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SHREC 2021: Retrieval and classification of protein surfaces equipped with physical and chemical properties

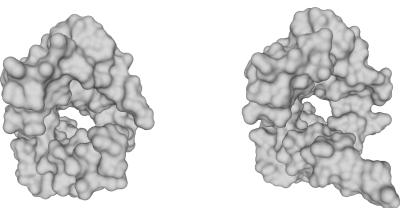
Andrea Raffo, Ulderico Fugacci, Silvia Biasotti, Walter Rocchia, Yonghuai Liu, Ekpo Otu, Reyer Zwiggelaar, David Hunter, Evangelia I. Zacharaki, Eleftheria Psatha, Dimitrios Laskos Gerasimos Arvanitis, Konstantinos Moustakas, Tunde Aderinwale, Charles Christoffer, Woong-Hee Shin, Daisuke Kihara, Andrea Giachetti, Huu-Nghia Nguyen, Tuan-Duy Nguyen, Vinh-Thuyen Nguyen-Truong, Danh Le-Thanh, Hai-Dang Nguyen and Minh-Triet Tran

3D Object Retrieval 2021 (3DOR'21)
POR FSE Liguria 2014-2020

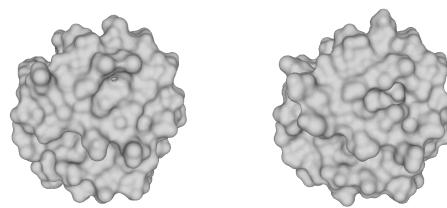
Motivation

Proteins are generally thought to adopt unique structures determined by their amino acid sequences, which are crucial for their functions.

However, proteins are not strictly static objects, but rather populate **ensembles of conformations**.



CALMODULIN-1



THIOREDOXIN

Recognising a protein from an ensemble of geometries can be assumed to mean capturing the **features that are unique** to it. It is preliminary to the definition of a geometry-based notion of similarity, and, subsequently, complementarity, between proteins.

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Special Section on 3DOR 2021
SHREC 2021 Track: Retrieval and classification of protein surfaces equipped with physical and chemical properties

Andrea Ratto^{a,*}, Ulmerico Fugacci^{a,1}, Silvia Biasotti^{a,1}, Walter Rocchia^{b,1}, Yonghui Liu^c, Elsjo Ora^d, Reyer Zwiggelaar^d, Evangelia I. Zacharaki^e, Eleftheria Psathia^e, Dimitrios Laskos^f, Gerasimos Arvanitis^f, Konstantinos Moustakas^f, Tunde Aderinwale^f, Charles Christoffel^f, Woong-Hee Shin^f, Daisuke Kihara^f, Andrea Giachetti^f, Huu-Nghia Nguyen^f, Tuan-Duy Nguyen^f, Vinh-Thuyen Nguyen-Truong^f, Danh Le-Thanh^f, Hai-Dang Nguyen^f, Minh-Triet Tran^f

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ABSTRACT
This paper presents the methods that have participated in the SHREC 2021 contest on retrieval and classification of protein surfaces equipped with physical and chemical properties. The goal of the contest is to verify the capability of different computational approaches to identify different conformations of the same protein, or the presence of common sub-parts, starting from a set of molecular surfaces. We addressed two problems: defining the similarity solely based on the surface geometry or with respect to the presence of common sub-sequences, common sub-parts, common hydrophilicity, and the presence of hydrogen bond donors and acceptors. Retrieval and classification performances, with respect to the single protein or the existence of common sub-sequences, are analyzed according to a number of information retrieval indicators.

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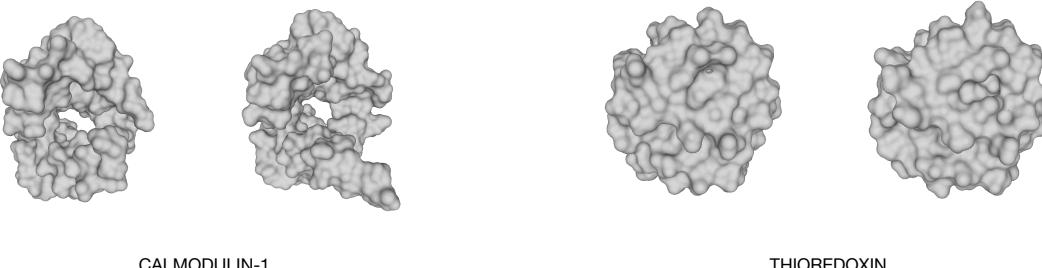
for its function. However, every protein during its time evolution explores a much larger part of the conformational space. The most stable conformations visited by the protein can be experimentally captured by the NMR technique; this is because the hydrogen atoms of the backbone in the atomic model, thus giving less ambiguities in the charge assessment.

Recognising a protein from an ensemble of geometries corresponding to the different conformations it can assume means capturing the features that are unique to it and a fundamental step from the structural bioinformatics viewpoint. It is preliminary to the definition of a geometry-based notion of similarity, and, subsequently, complementarity, between proteins. From the application standpoint, the identification of characteristic features can point

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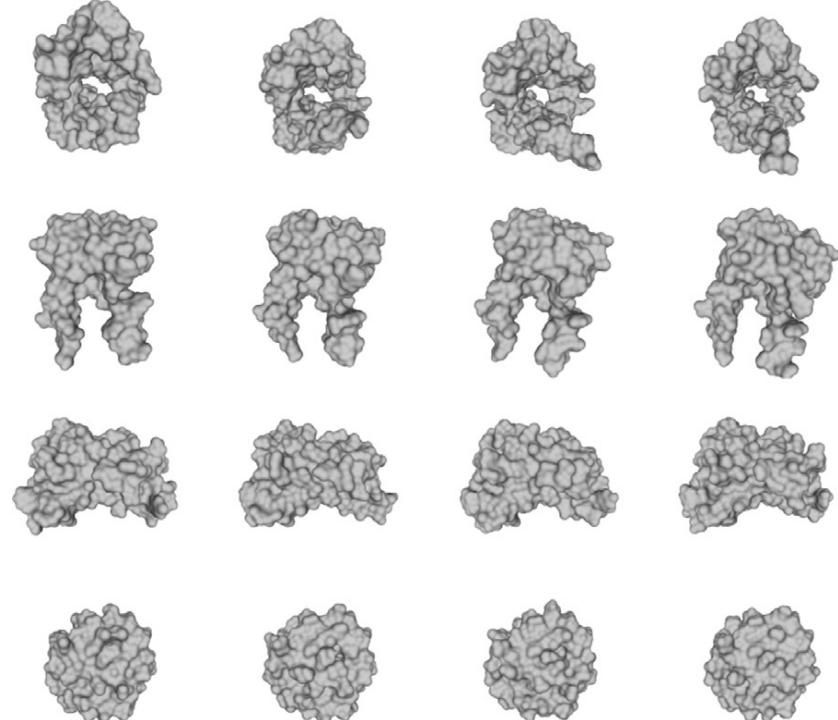
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The benchmark

The dataset

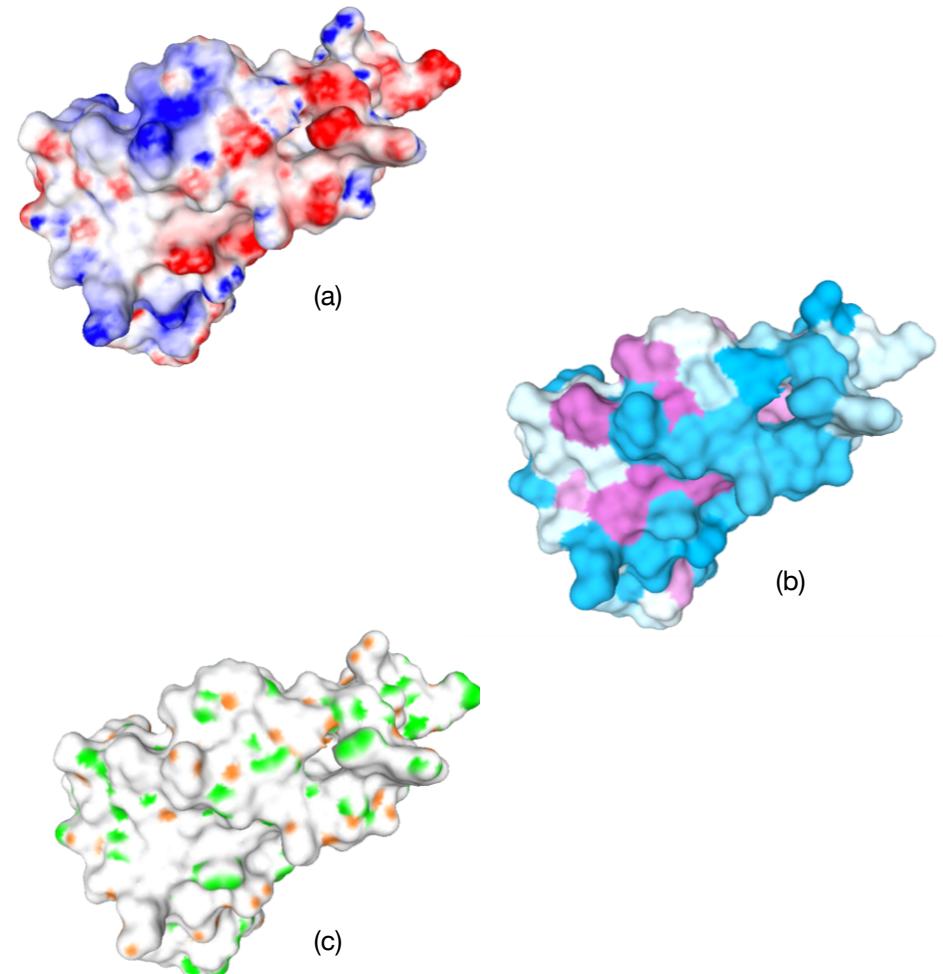
- 5,128 **triangle meshes** of protein surfaces:
 - ★ Available in the OFF¹ format
 - ★ Approximate the Solvent Excluded Surface (SES)
 - ★ Computed by NanoShaper [1]
 - ★ Pre-split: 70% training set, 30% test set
 - For each surface, three physicochemical proteins were approximated at its vertices:
 - (a) Electrostatic potential
 - (b) Hydrophobicity
 - (c) Hydrogen bond donors and acceptors
- Delphi [2,3] ←
Own routines ← {



¹ https://segeval.cs.princeton.edu/public/off_format.html

The dataset

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The ground truth

Evaluation of the results will be based on two ground truths:

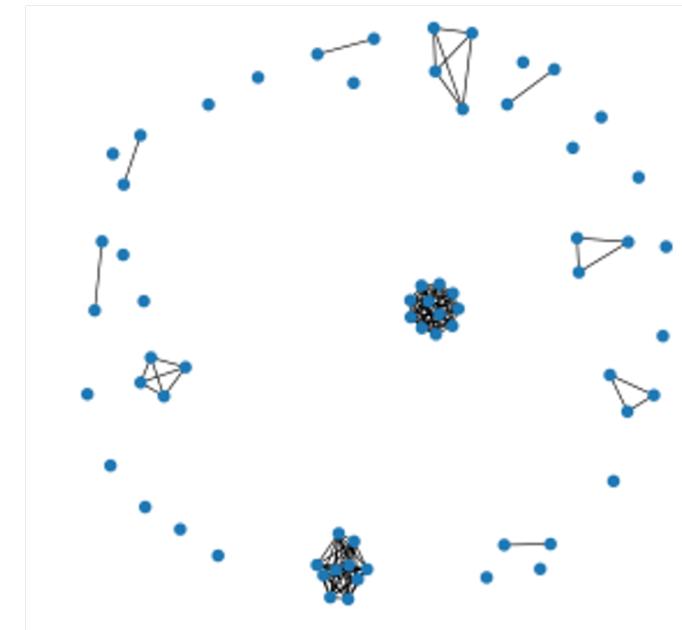
- A 2-level classification of the dataset (**PDB-based classification**)
- A 4-level classification of the dataset (**BLAST-based classification**)

PDB-based classification Two protein surfaces are conformations of the same protein if and only if they refer to the same PDB code.

BLAST-based classification We introduce a less strict classification on the basis of the concept of sequence similarity λ :

- Extremely similar $\longrightarrow 95\% \leq \lambda$ AND at least 50 aligned residuals
- Highly related $\longrightarrow 35\% \leq \lambda < 95\%$ AND at least 50 aligned residuals
- Similar $\longrightarrow 28\% \leq \lambda < 35\%$ AND at least 50 aligned residuals
- Dissimilar $\longrightarrow \lambda < 28\%$ OR less than 50 aligned residuals

Obtained classes are refined for ensuring transitivity.

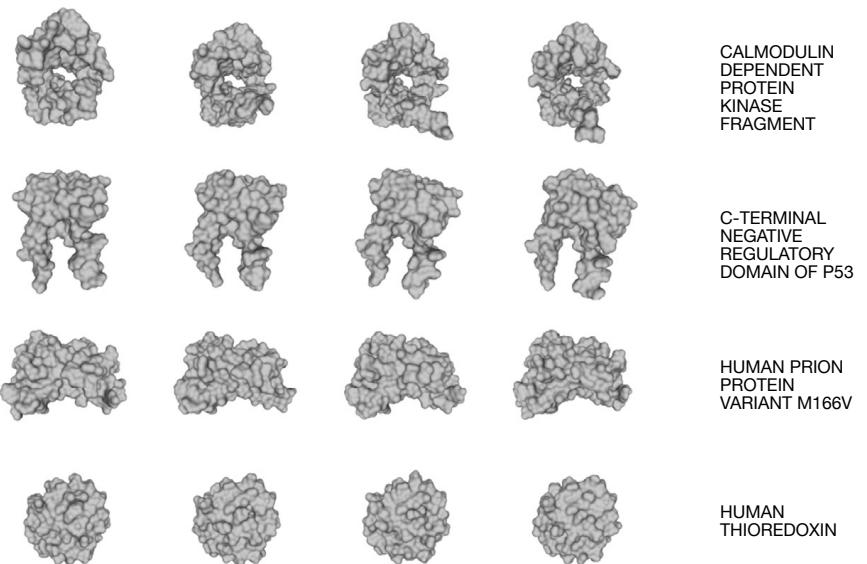


Nodes
↑
PDB-based classes
↑
Connected components
↑
BLAST-based classes

The accuracy measures

- **Retrieval measures:**

- ★ Precision-recall curves and mean Average Precision (mAP)
- ★ First and Second Tiers (1T, 2T)
- ★ Normalized Discounted Cumulated Gain (NDCG)
- ★ Average Dynamic Recall (ADR)





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Proposed methods

Proposed methods

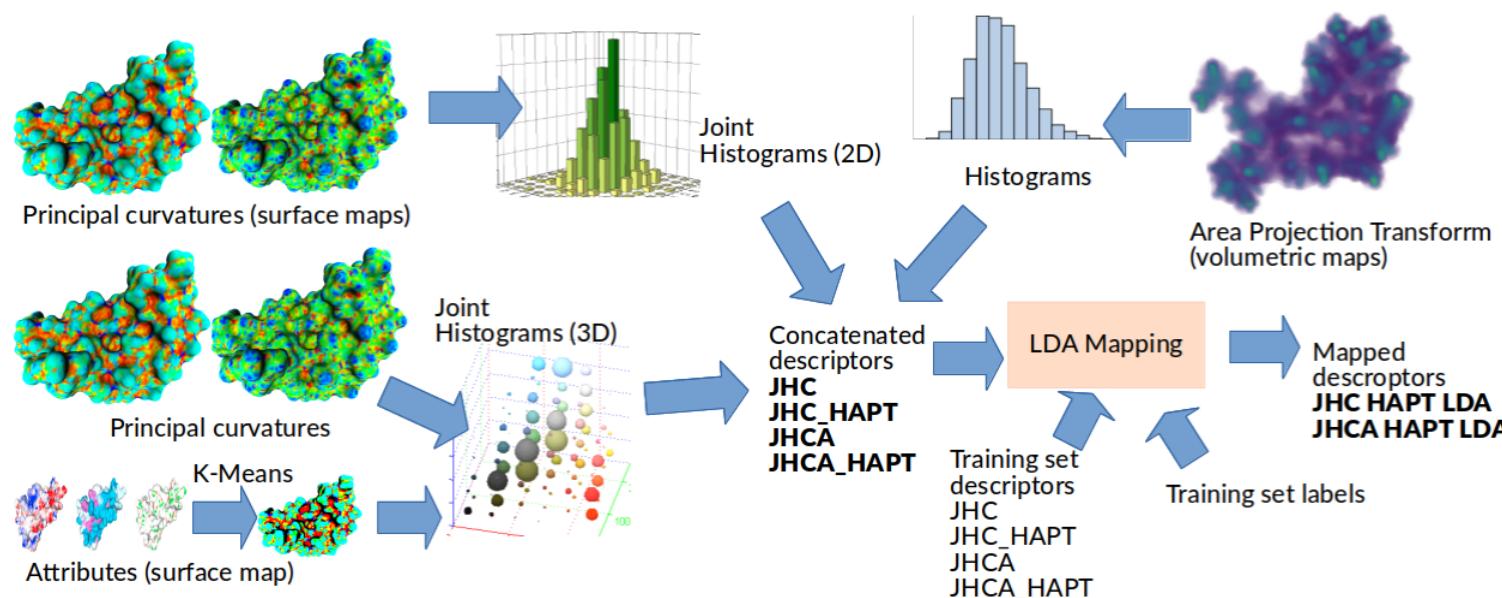
- P1: “**Joint histograms of curvatures, local properties and area projection transform**” by Andrea Giachetti
- P2: “**3D Zernike descriptors**” by Tunde Aderinwale, Charles Christoffer, Woong-Hee Shin, and Daisuke Kihara
- P3: “**Hybrid Augmented Point Pair Signatures and Histogram of Processed Physicochemical Properties of Protein molecules**” by Yonghuai Liu, Ekpo Otu, Reyer Zwiggelaar, and David Hunter
- P4: “**Global and Local Feature fit**” by Evangelia I. Zacharaki, Eleftheria Psatha, Dimitrios Laskos, Gerasimos Arvanitis, and Konstantinos Moustakas
- P5: “**Message-Passing Graph Convolutional Neural Networks (MPGCNNs) and PointNet**” by Huu-Nghia Nguyen, Tuan-Duy Nguyen, Vinh-Thuyen Nguyen-Truong, Danh Le-Thanh, Hai- Dang Nguyen, and Minh-Triet Tran

Two tasks were proposed to the participants, with up to three runs per task:

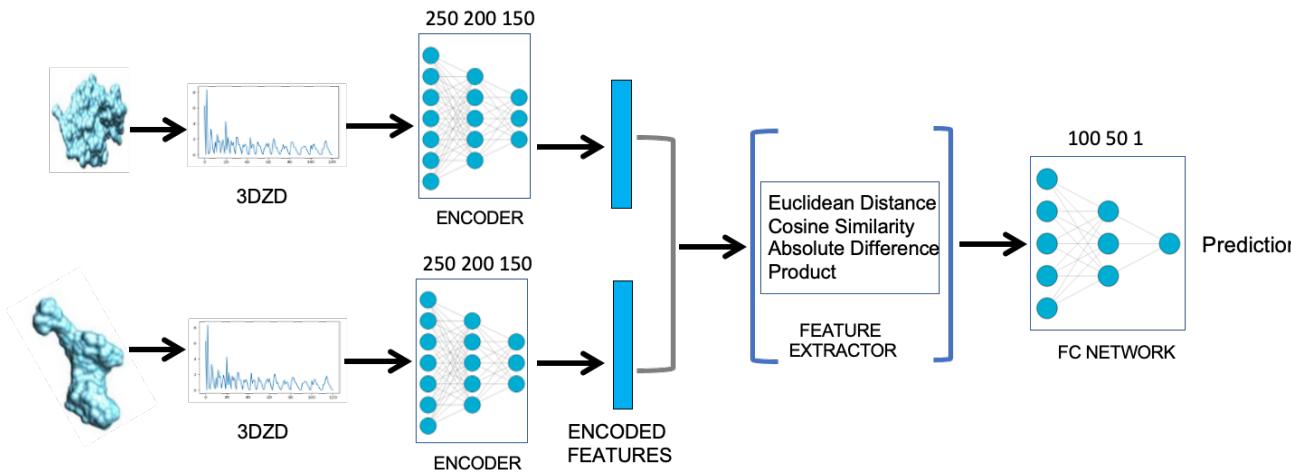
Task A: only the OFF files of the models are to be considered (i.e., only the geometry).
Task B: in addition to the geometry, physicochemical properties are to be considered.

P1: “Joint histograms of curvatures, local properties and area projection transform”

- Use of surface properties (**curvatures+attributes**) combined with joint histograms
- Combined with **volumetric** (symmetry) **features**: Area Projection Transform (Giachetti & Lovato 2012)
- Test of supervised **dimensionality reduction** (Linear Discriminant Analysis)
 - ★ Using training set labels
 - ★ Not effective (different classes)



P2: “3D Zernike descriptors”



	NN	1T	2T
Validation Results			
SHAPE: EXTRACTOR	0.854	0.788	0.442
SHAPE: AVG of (EXTRACTOR&End2End)	0.862	0.785	0.442
SHAPE: AVG of (E2E & EUCLID. of 3DZD)	0.894	0.822	0.447
SHAPE+Phys: EXTRACTOR	0.889	0.858	0.456
SHAPE+Phys: AVG of (EXTRACTOR & EUCLID)	0.899	0.861	0.457
SHAPE+Phys: AVG of (EXTRACTOR&E2E)	0.894	0.870	0.459

- Total number of (training) surfaces provided: 3,585
- Training-validation set split : 80%/20%
- Total number of validation proteins: 717
- Out of $717 \times 716 / 2$ pairs, 10,436 pairs were used for validation

- Shape only: 3ZD for protein surface only
- Shape + Phys: 3D3Z for protein surface and physicochemical properties

P3: “Hybrid Augmented Point Pair Signatures and Histogram of Processed Physicochemical Properties of Protein molecules ”

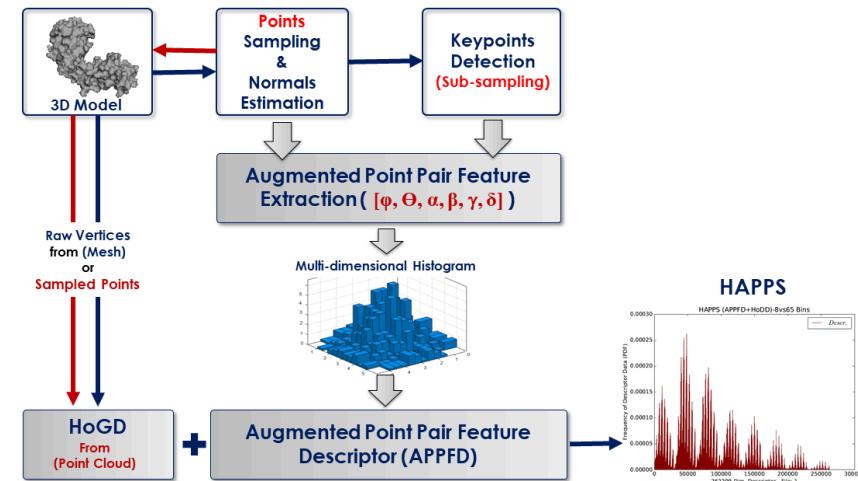
Two separate retrieval strategies for the two different tasks

Task A: Hybrid Augmented Point Pair Signature (HAPPS)

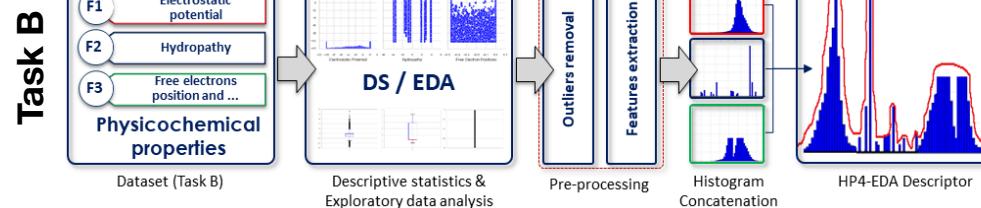
- A 3D geometric shape descriptor combining a collection of normalized vectors between the point of the surface and its centroid with the local geometry around each point

Task B: Histogram of Processed Physicochemical Properties of Protein following an Exploratory Data Analysis (HP4-EDA)

- Strategy based on a descriptive statistics (DS) of the 3D physicochemical variables, following an exploratory data analysis (EDA) of each of them.

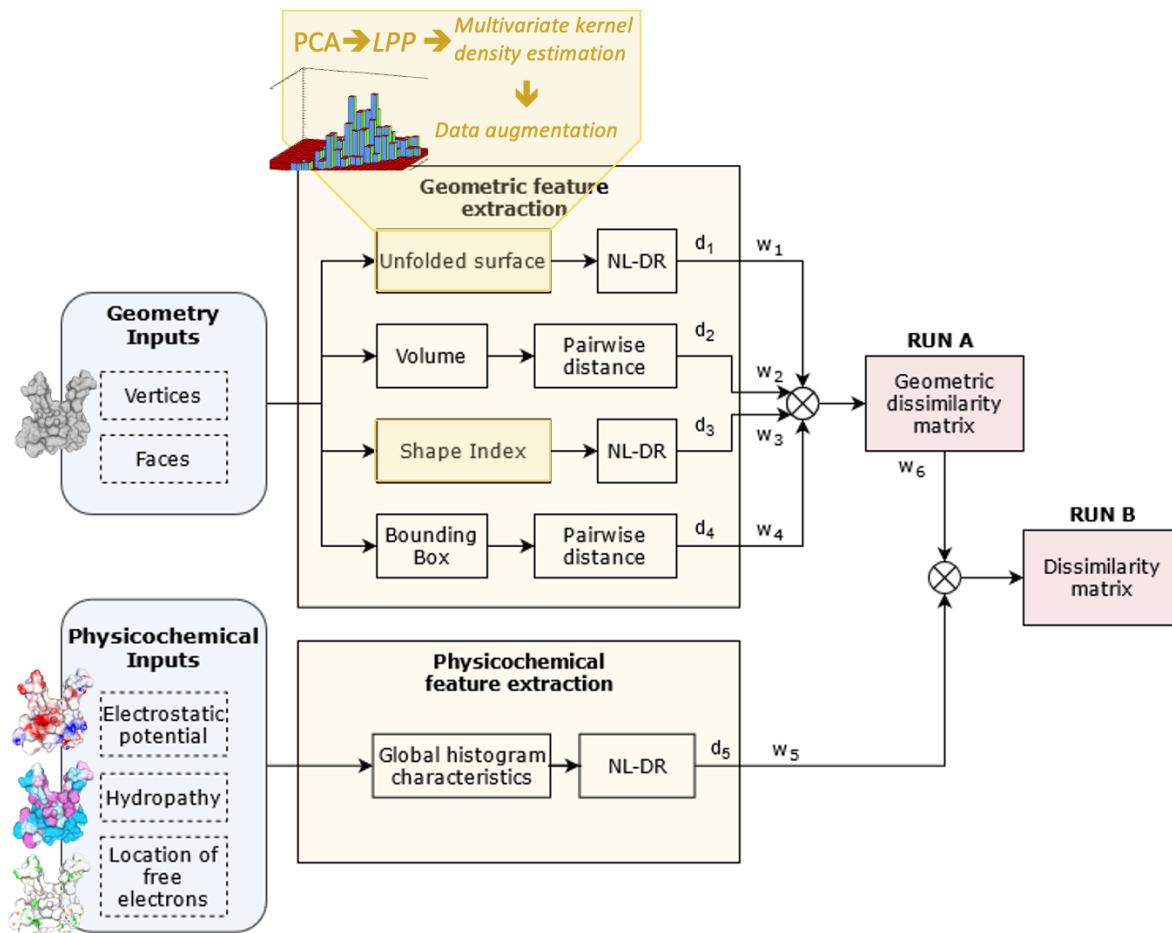


Task A



Task B

P4: “Global and Local Feature fit”



NL-DR : Non-Linear Dimensionality Reduction → tSNE

$$\text{Shape Index} = \frac{2}{\pi} \tan^{-1} \frac{k_1 + k_2}{k_1 - k_2}$$

where k_1, k_2 ($k_1 \geq k_2$) are the principal curvature values

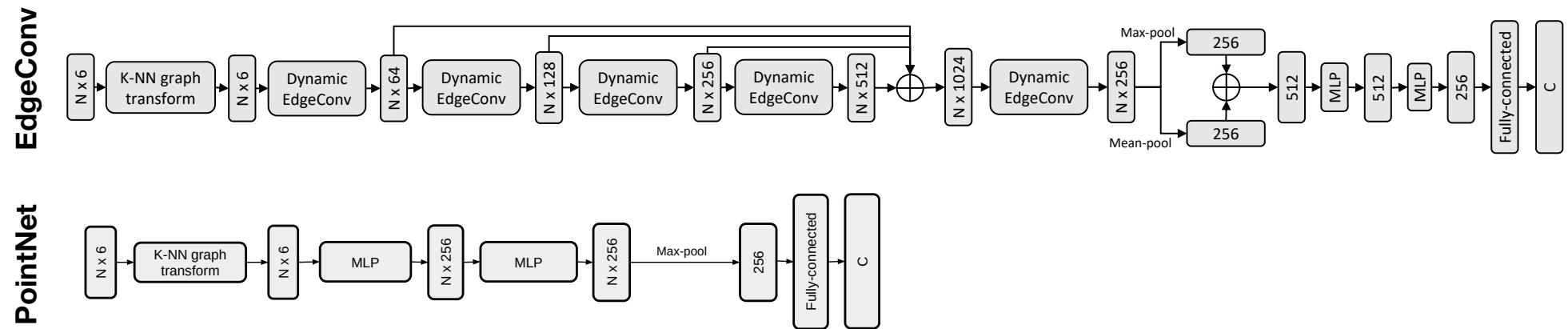
For each of the 3 physicochemical properties:
 global histogram characteristics (mean intensity, standard deviation, mode of histogram, kurtosis, skewness, and energy)

P5: “Message-Passing Graph Convolutional Neural Networks (MPGCNNs) and PointNet ”

Strategy based on the use **graph neural networks (GNNs)**: a deep learning based methods operating on generalized graph domains rather than on Euclidean ones

Two main network architectures have been adopted:

- **EdgeConv.** The module that performs the graph message-passing function is a dynamic variant of edge convolution
- **PointNet.** Two message-passing modules each containing a MLP block that uses ReLU as activation function





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Evaluation and results

Complete analysis
in the paper!

Results – PDB-based (2-level) classification

From the classification measures:

- All methods have TNR higher than TPR → more reliable in finding true negatives
- All methods have NPV higher than TPV → more reliable in reporting negatives
- Accuracy is high (always above 95%), but F1-score is a better indicator (classes are unbalanced!)
- Physicochemical properties can bring additional information, but it does NOT always mean an improvement

	Geometry							Geometry and physicochemical properties						
	method	TPR	TNR	PPV	NPV	ACC	F1	method	TPR	TNR	PPV	NPV	ACC	F1
	run 1	0.8373	0.9967	0.8401	0.9973	0.9941	0.8354	run 1	0.9825	0.9997	0.9860	0.9997	0.9994	0.9832
P1: Joint histograms	run 2	0.9475	0.9991	0.9489	0.9992	0.9983	0.9467	run 2	0.9890	0.9999	0.9921	0.9999	0.9998	0.9893
	run 3	0.9274	0.9990	0.9304	0.9988	0.9974	0.9239	run 3	0.5839	0.9885	0.6086	0.9912	0.9807	0.5727
	run 1	0.9145	0.9979	0.9159	0.9984	0.9965	0.9119	run 1	0.9514	0.9989	0.9525	0.9992	0.9981	0.9504
P2: 3D Zernike + ML	run 2	0.8944	0.9975	0.8977	0.9976	0.9954	0.8931	run 2	0.9469	0.9989	0.9470	0.9991	0.9981	0.9460
	run 3	0.9242	0.9983	0.9253	0.9985	0.9969	0.9222	run 3	0.9793	0.9995	0.9819	0.9996	0.9991	0.9791
	run 1	0.9196	0.9985	0.9205	0.9986	0.9971	0.9169	run 1	0.9015	0.9977	0.9037	0.9979	0.9957	0.9007
P3: Point pair signatures	run 2	0.9300	0.9982	0.9333	0.9988	0.9971	0.9276	run 2	0.9216	0.9985	0.9238	0.9987	0.9974	0.9207
	run 3	0.9222	0.9982	0.9258	0.9986	0.9969	0.9199	run 3	0.9015	0.9979	0.9005	0.9985	0.9966	0.8987
	run 1	0.9274	0.9983	0.9284	0.9987	0.9971	0.9262	run 1	0.9410	0.9987	0.9424	0.9990	0.9978	0.9406
P4: Global & Local Fit	run 2	0.9268	0.9983	0.9277	0.9987	0.9971	0.9252	run 2	0.9410	0.9988	0.9422	0.9990	0.9978	0.9409
	run 3	0.9067	0.9979	0.9059	0.9983	0.9963	0.9046	run 3	0.9326	0.9984	0.9336	0.9988	0.9974	0.9323
	run 1	0.7537	0.9944	0.7539	0.9943	0.9892	0.7507	run 1	0.7187	0.9937	0.7215	0.9940	0.9886	0.7160
P5: Graph CNN	run 2	0.4362	0.9870	0.4412	0.9873	0.9754	0.4328							
	run 3	0.7123	0.9927	0.7109	0.9930	0.9868	0.7044							

Complete analysis
in the paper!

Results – BLAST-based (4-level) classification

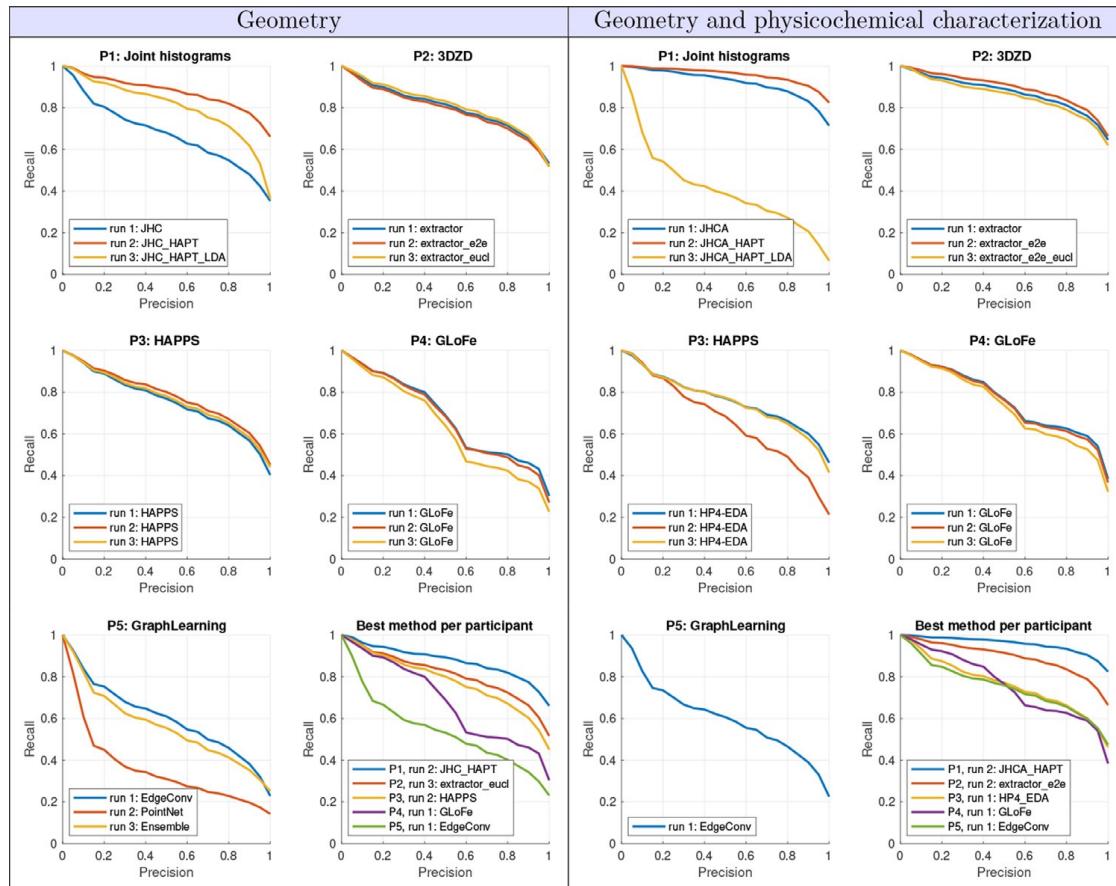
From the classification measures:

- As expected, decreasing the number of classes improves the classification performance
- The improvement takes place despite only PDB-based classification being available to the participants (maybe not surprising, as the number of classes is reduced)

	Geometry							Geometry and physicochemical properties						
	method	TPR	TNR	PPV	NPV	ACC	F1	method	TPR	TNR	PPV	NPV	ACC	F1
	run 1	0.9086	0.9949	0.9082	0.9959	0.9917	0.9069	run 1	0.9961	0.9998	0.9962	1.0000	0.9997	0.9960
P1: Joint histograms	run 2	0.9890	0.9996	0.9891	0.9996	0.9993	0.9888	run 2	0.9981	1.0000	0.9981	1.0000	1.0000	0.9980
	run 3	0.9844	0.9996	0.9869	0.9997	0.9993	0.9840	run 3	0.8529	0.9904	0.8562	0.9931	0.9854	0.8452
	run 1	0.9760	0.9992	0.9766	0.9993	0.9985	0.9758	run 1	0.9929	0.9997	0.9930	0.9999	0.9996	0.9928
P2: 3D Zernike + ML	run 2	0.9728	0.9991	0.9746	0.9991	0.9983	0.9723	run 2	0.9909	0.9998	0.9909	0.9999	0.9997	0.9908
	run 3	0.9767	0.9985	0.9770	0.9989	0.9977	0.9764	run 3	0.9987	0.9999	0.9987	1.0000	0.9999	0.9987
	run 1	0.9689	0.9981	0.9690	0.9985	0.9970	0.9680	run 1	0.9942	0.9996	0.9943	0.9999	0.9995	0.9942
P3: Point pair signatures	run 2	0.9747	0.9980	0.9754	0.9989	0.9972	0.9740	run 2	0.9916	0.9997	0.9921	0.9998	0.9996	0.9916
	run 3	0.9721	0.9987	0.9738	0.9985	0.9976	0.9716	run 3	0.9806	0.9981	0.9809	0.9994	0.9980	0.9803
	run 1	0.9799	0.9987	0.9805	0.9991	0.9980	0.9798	run 1	0.9903	0.9995	0.9909	0.9996	0.9992	0.9904
P4: Global & Local Fit	run 2	0.9793	0.9987	0.9801	0.9990	0.9979	0.9791	run 2	0.9903	0.9995	0.9908	0.9996	0.9991	0.9904
	run 3	0.9734	0.9984	0.9738	0.9987	0.9974	0.9732	run 3	0.9870	0.9993	0.9876	0.9994	0.9988	0.9871
	run 1	0.9209	0.9953	0.9209	0.9958	0.9923	0.9197	run 1	0.9501	0.9975	0.9506	0.9988	0.9968	0.9491
P5: Graph CNN	run 2	0.7168	0.9852	0.7201	0.9853	0.9734	0.7156							
	run 3	0.9047	0.9944	0.9031	0.9953	0.9910	0.9019							

Complete analysis
in the paper!

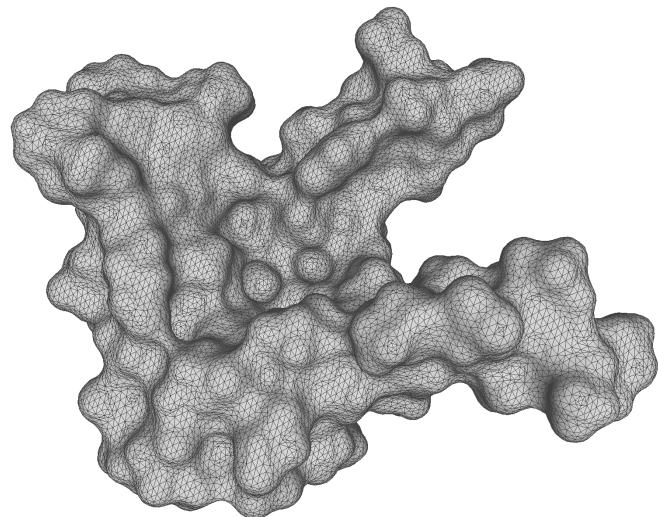
Results – PDB- and BLAST-based classifications



Unexpectedly, the two ground truths have much in common:

- Methods are good but not optimal: highest mAP score is 0.87 (only geometry) and 0.96 (geometry + chemistry) → e.g., P2
- The strong heterogeneity of the class size has influenced prediction accuracy, especially for learning-based methods → e.g., P5
- Physicochemical properties can provide additional information, but one must be careful how to use it → e.g., P1, run 3
- Deep learning does NOT guarantee a better performance (risk to overfit data!) → e.g., P5

Conclusions



- W.r.t. previous contests on protein retrieval, we have taken into account physicochemical properties, provided the participants of a training set and a test set, and proposed different ground truths
- The number of registered teams (8) and of actual participants (5) shows the interest of the community to the problem, despite some difficulties
- The methods present a satisfactory variety in terms of the paradigms nowadays popular

We are underway to apply for the replicability stamp. The benchmark will be available at: <https://github.com/rea1991/SHREC2021>

Thanks for your attention!

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