Inferring contact area heterogeneity from static protein conformations

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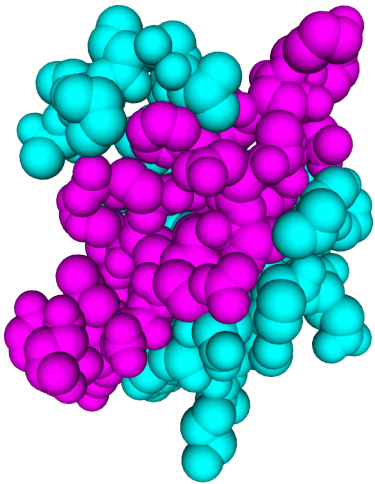


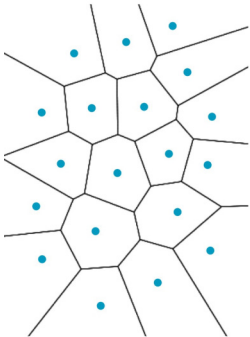
Common problems:

- analyzing how different parts in a molecule interact
- selecting the best model of a multimeric complex

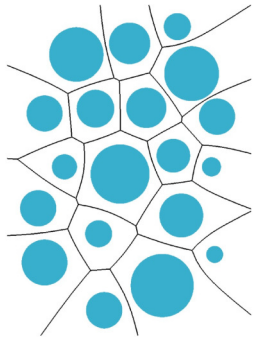
Describing interactions in molecular conformations using the Voronoi tessellation

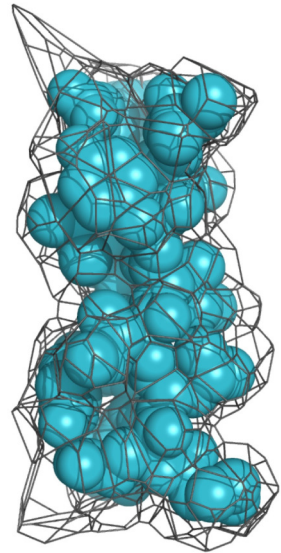
Voronoi diagram of points and balls

"Classic" Voronoi diagram of points



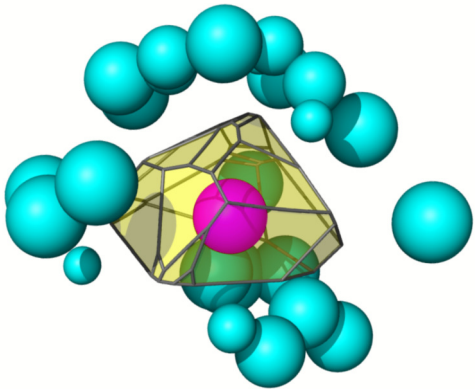
Voronoi diagram of balls



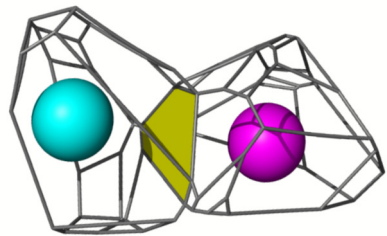


Voronoi tessellation-based analysis of structures

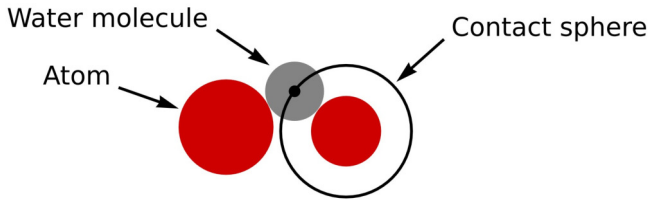
Voronoi cell of an atom surrounded by its neighbors

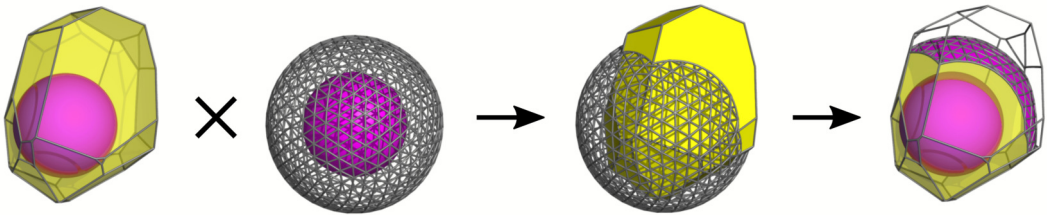


Atom-atom contact surface defined as the face shared by two adjacent Voronoi cells.



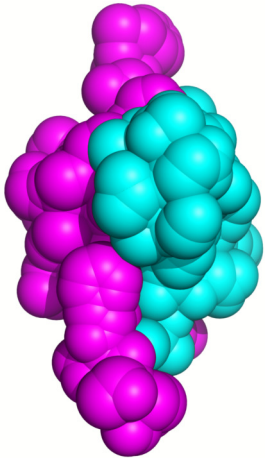
Constrained contacts



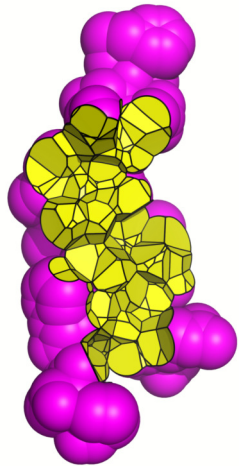


Inter-chain contacts

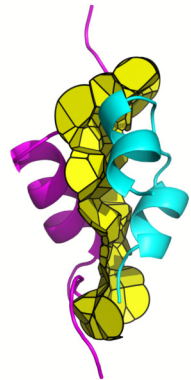
Solvent-accessible surface of an insulin heterodimer PDB:4UNG colored by subunit



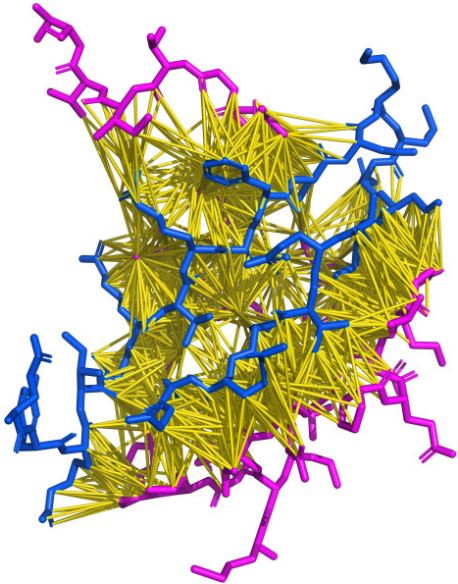
The intersubunit interface shown together with the SAS of one subunit



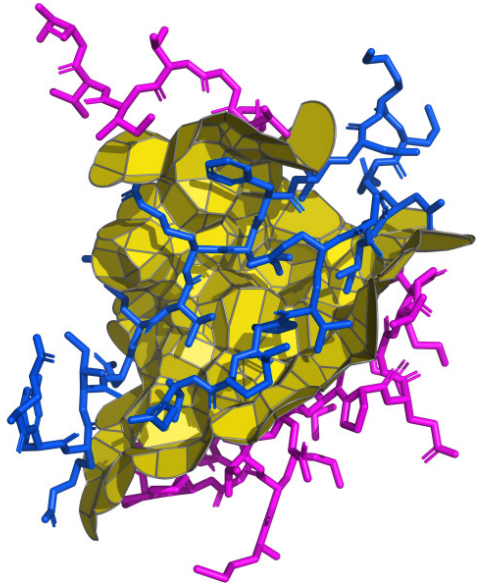
The intersubunit interface shown together with both subunits represented as cartoons



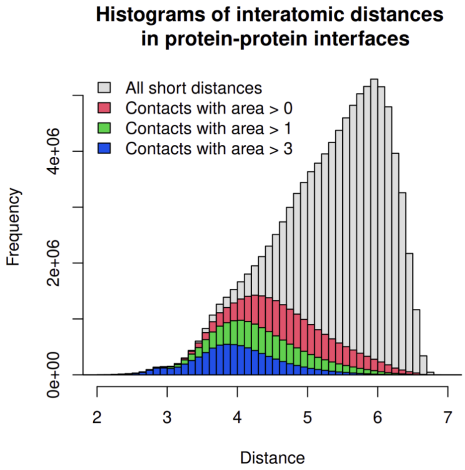
Inter-chain contact areas vs distances

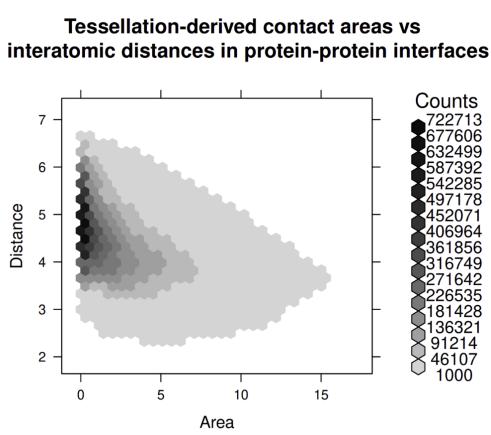


VS



Inter-chain contact areas vs distances, PDB-based statistics

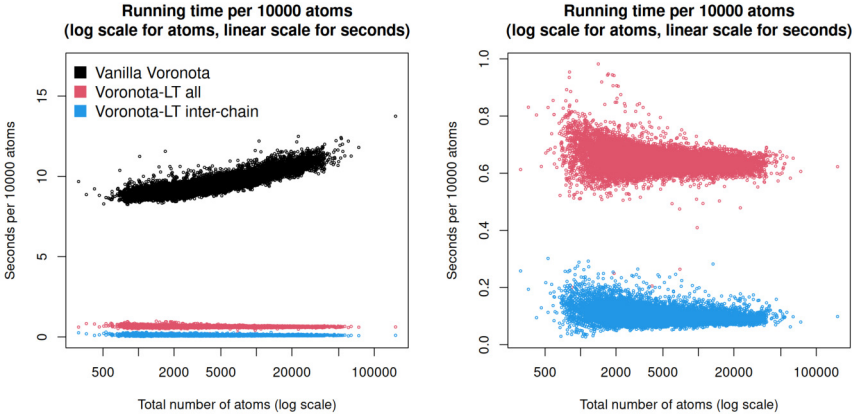




corr(area, distance) ≈ -0.43

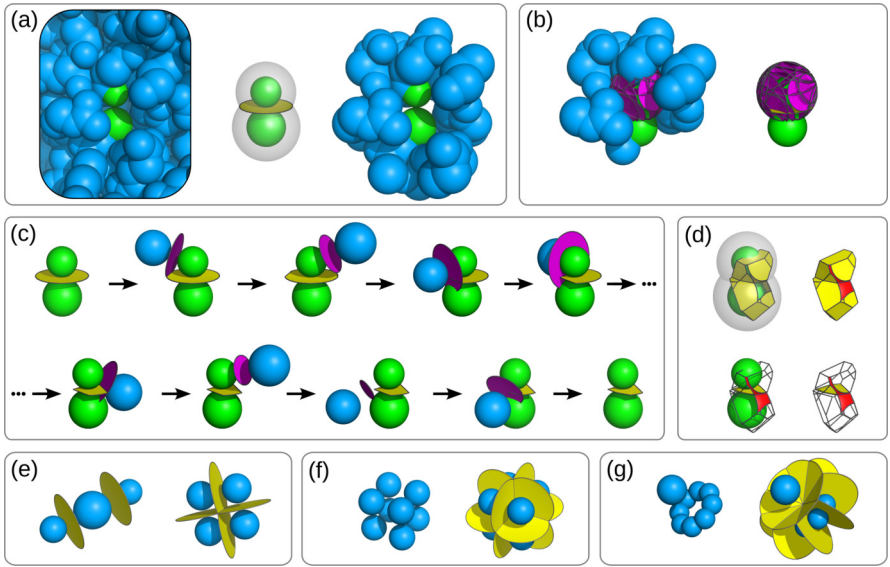
Voronota-LT

Voronota-LT is a new fast software for constructing tessellation-derived atomic contact areas and volumes. It is significantly faster than its predecessor, Voronota:



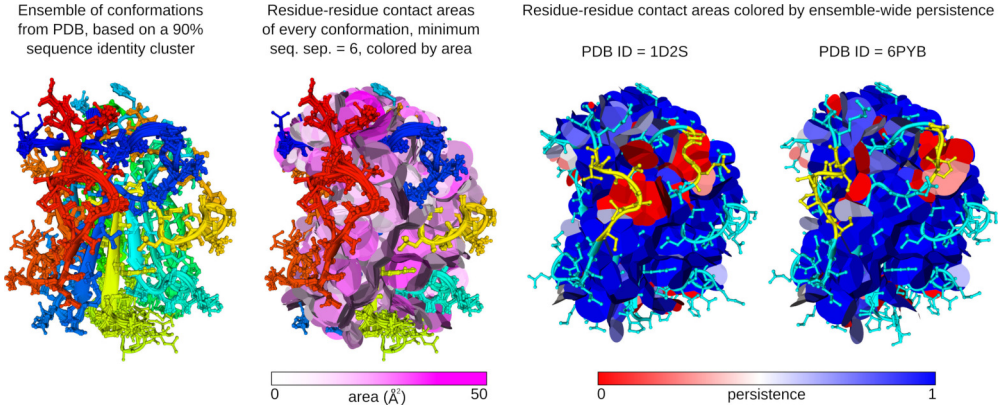
Olechnovic and Grudinin. *Voronota-LT: efficient, flexible and solvent-aware tessellation-based analysis of atomic interactions*. JCC (2025)

Voronota-LT



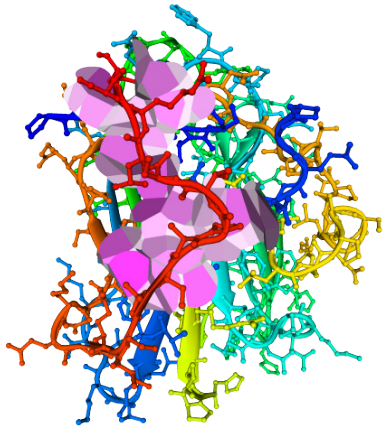
Predicting structural heterogeneity of protein contacts from singular static conformational models

Contact area persistence values for PDB ensembles

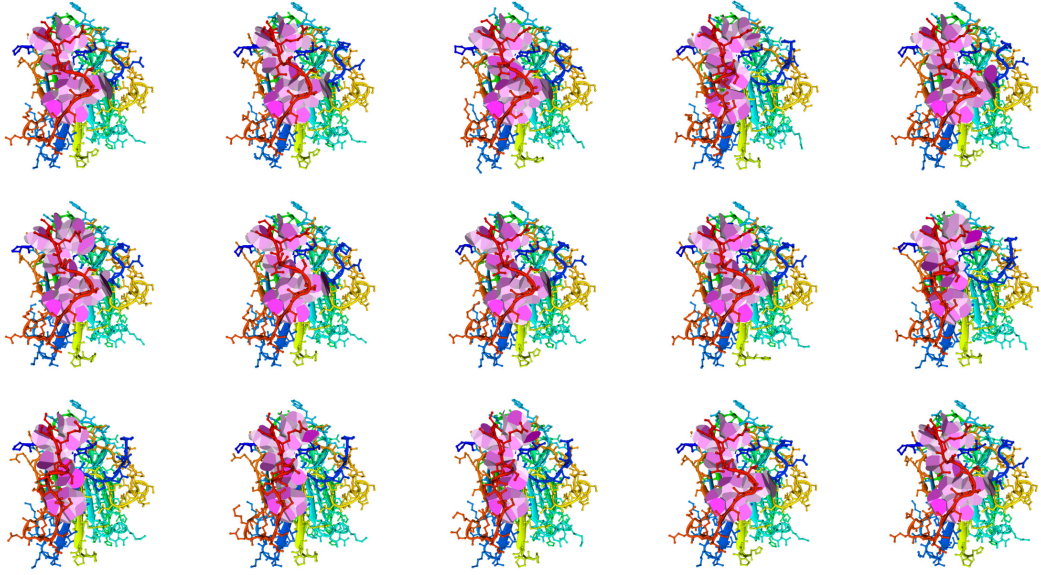


If a contact with ID $\kappa = (\mathrm{residue}_a, \mathrm{residue}_b)$ is present in at least one conformation, and both $\mathrm{residue}_a$ and $\mathrm{residue}_b$ are present in at least two conformations, then $\mathrm{area}_{\min}(\kappa) \geq 0$ and $\mathrm{area}_{\max}(\kappa) > 0$ are available. Then the ensemble-wide contact area persistence is defined as $\mathrm{persistence}(\kappa) = \frac{2 \cdot \mathrm{area}_{\min}(\kappa)}{\mathrm{area}_{\min}(\kappa) + \mathrm{area}_{\max}(\kappa)}$

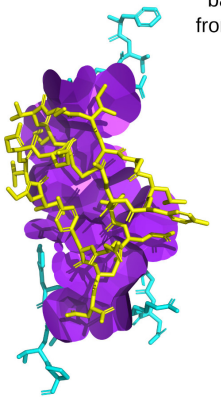
Ensemble contacts for a sub-interface — risky animation



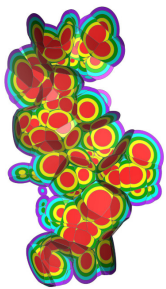
Ensemble contacts for a sub-interface — reliable frames

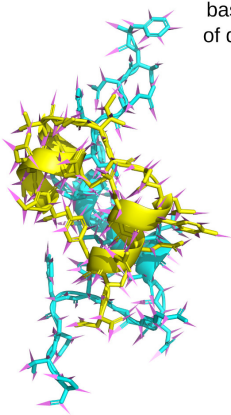


Extended geometry of contacts

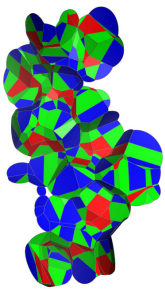


"**Layers**" of contacts based on distances from outer boundaries

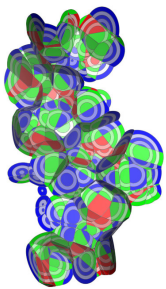




"**Sectors**" of contacts based on halfspaces of directions of atoms

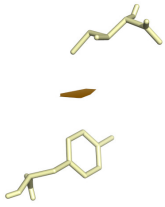


"**Layers**" and "**Sectors**" combined to define multiple geometric contact categories



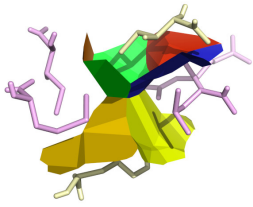
Voronoi contacts block (VCBlock)

Tessellation-derived contact surface between two main residues



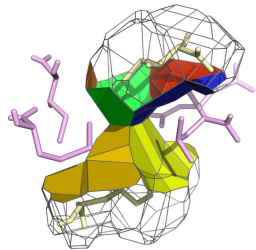
+

Adjacent contacts with shared residues (side residues)



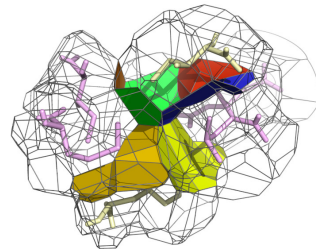
+

Interface of the main residues with the environment

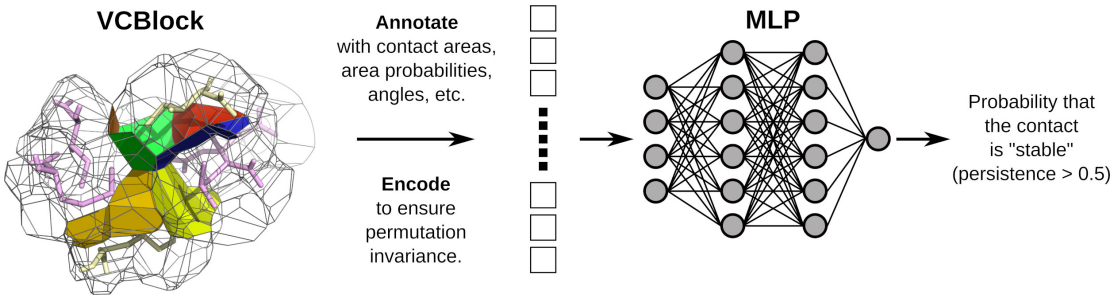


+

Interface of the side residues with the environment

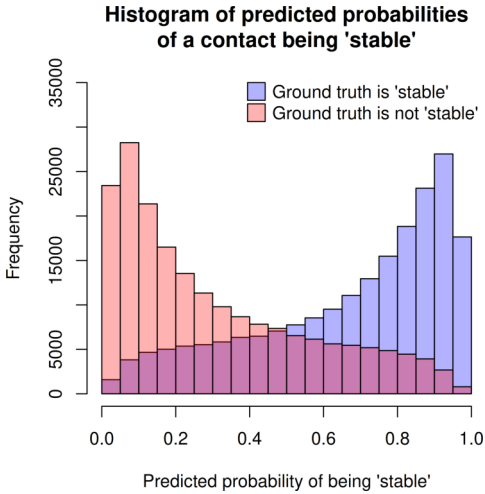


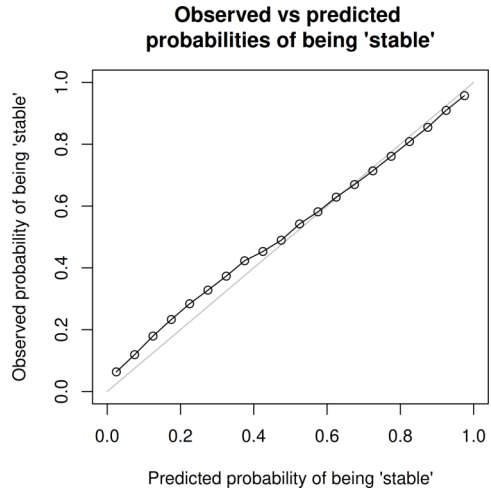
VCBlock-based contacts stability predictor



Current MLP training/validation/testing was done using a set of $\sim 2 \times 10^6$ VCBlocks sampled from $\sim 2 \times 10^4$ protein ensembles collected from PDB. The data split was done respecting the 30% sequence identity-based clustering.

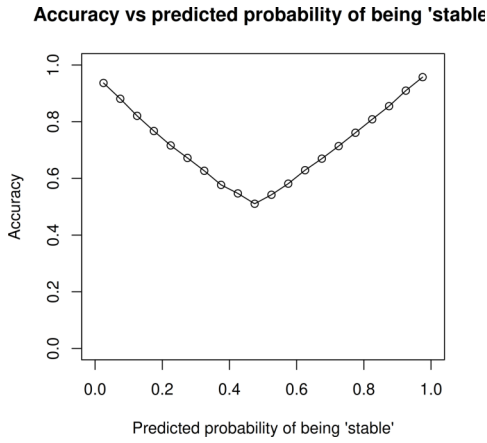
Classifier performance on the testing set



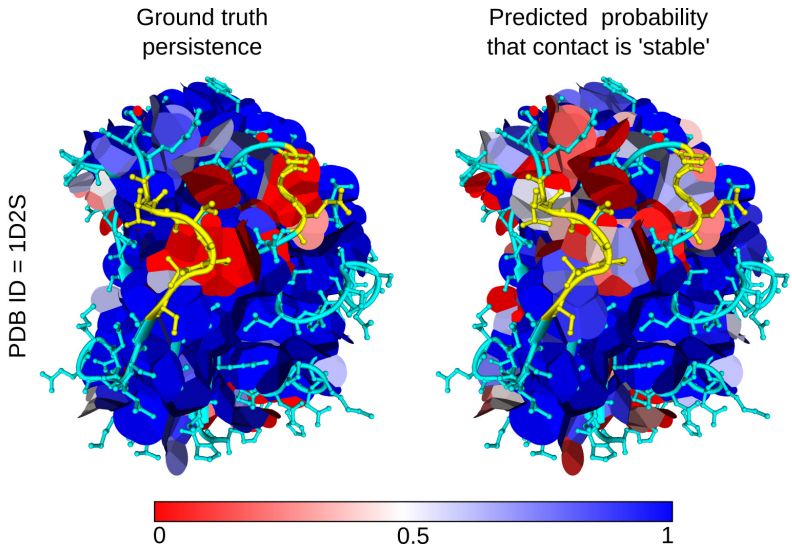


Classifier performance on the testing set

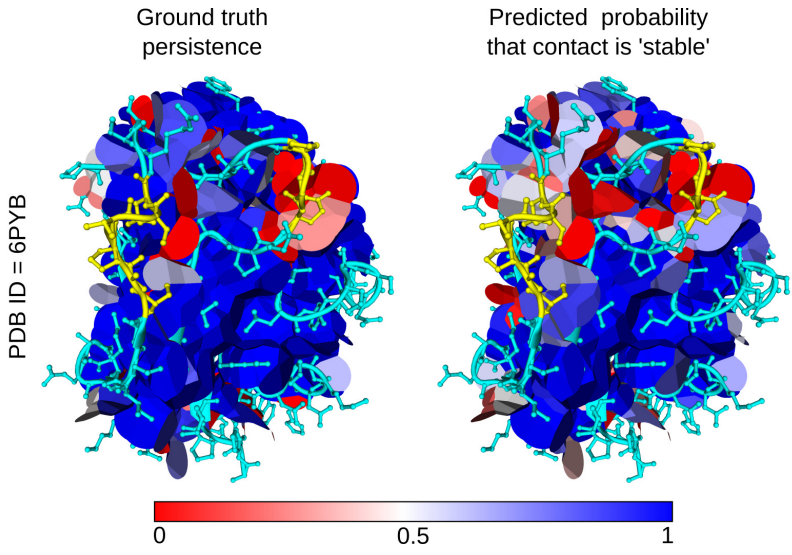
Accuracy ~ 0.78 overall, but extreme values are predicted more accurately



Example of MLP predictions vs ground truth



Example of MLP predictions vs ground truth



VoroMarmotte pseudoenergy

The VoroMarmotte pseudoenergy for a set of contacts K is calculated as follows:

$$E(K) = \sum_{k \in K} \text{area}(k) \cdot \log \frac{P_{\text{predicted}}(k \text{ persists} | k \text{ occurs})}{1 - P_{\text{predicted}}(k \text{ persists} | k \text{ occurs})} \tag{1}$$

We work with probabilities, but there are some relations to physics (constants ommitted):

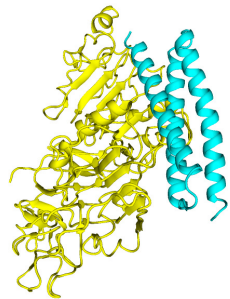
$$\Delta G \sim E(K) \tag{2}$$

Looking at the data from EGFR Protein Design Competition

- `https://foundry.adaptyvbio.com/competition`
- `https://github.com/adaptyvbio/egfr_competition_2`
- There are 400 AF2 structural models of protein-binder complexes, each structure is annotated with experimental binding characterization results and with AF2 scores.
- There are about 50 binders and 350 non-binders.

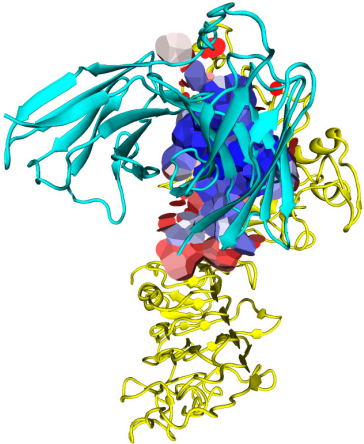
Looking at some examples from EGFR Protein Design Competition

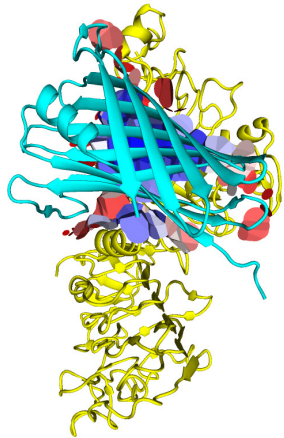
Strong binder (design 1), binder (design 2), non-binder (design 3):

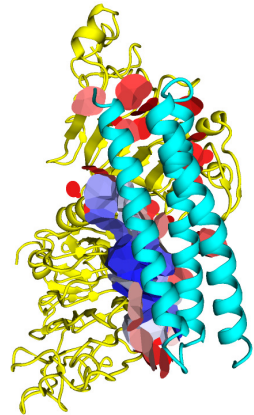


ID	modified	pseudoenergy	area	best_core_pseudoenergy	best_core_area
design1.pdb	no	-1088.83224665428	1311.29595	-1312.60234731125	1165.38884
design2.pdb	no	-483.386123040848	1399.2419	-1047.28512420783	878.30827
design3.pdb	no	-79.5982378233236	1377.05465	-923.84868490561	798.82894

Looking at some examples from EGFR Protein Design Competition

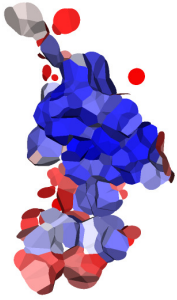


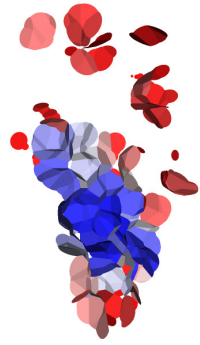




https://github.com/kliment-olechnovic/voromarmotte-app

Looking at some examples from EGFR Protein Design Competition

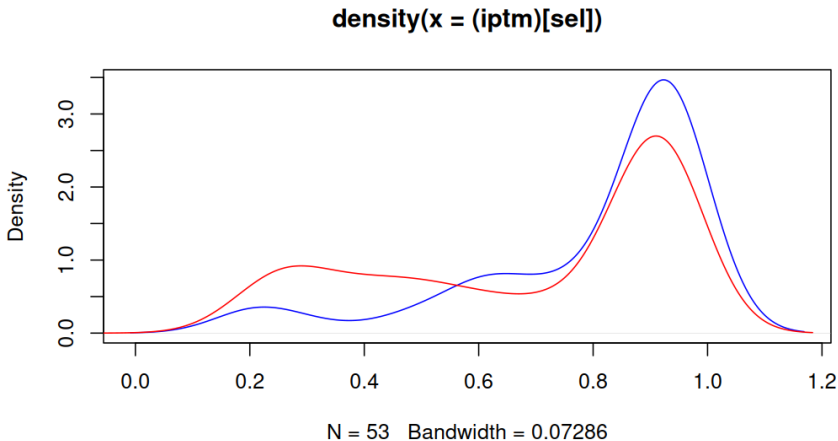




https://github.com/kliment-olechnovic/voromarmotte-app

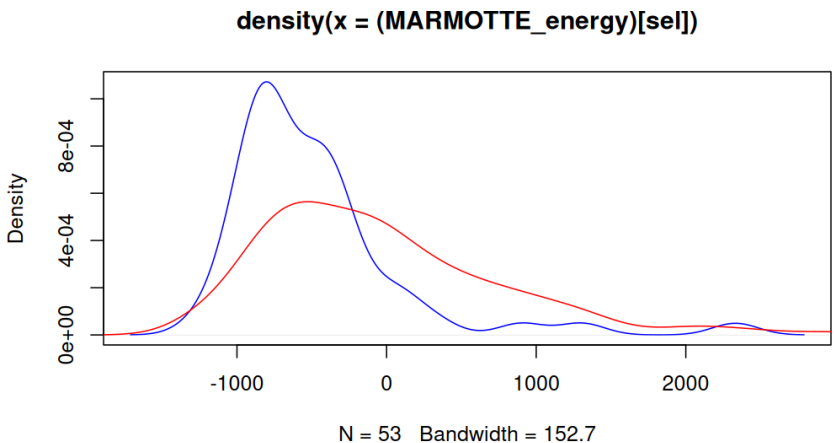
Scores for binders and non-binders

Empirical densities of AF2 ipTM scores for binders and non-binders:



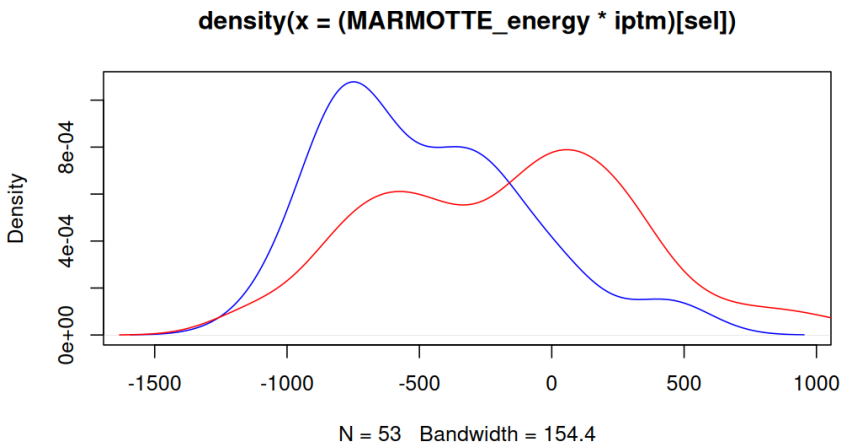
Scores for binders and non-binders

Empirical densities of VoroMarmotte pseudoenergies for binders and non-binders:



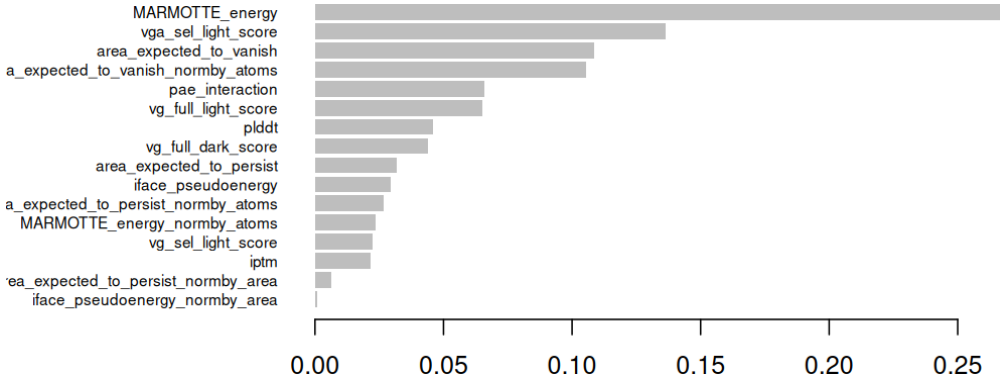
Scores for binders and non-binders

Empirical densities of naive combo-scores for binders and non-binders:



XGBoost analysis of importance of scores

An XGBoost-based binder/non-binder classifier was trained and cross-validated using various scores in input, the reported most important features were:



The classifier performance on test data is low, balanced accuracy is about 0.65.

Final remarks (Oasis-like)

Definitely:

- Tessellation-derived contact area descriptors can be used to collect information about contact stability from ensembles of conformations in PDB.
- The Voronoi Contacts Block can be used to predict stability of contacts in an ensemble.

Maybe:

- The predicted stability of contacts can be used to select better binders.
- The tessellation-based methodology for scoring interfaces can be used for protein design-related tasks.

Thanks

Thank you!

CNRS Laboratoire Jean Kuntzmann:

- Sergei Grudinin
- The GruLab Team (https://grulab.imag.fr)

Useful links:

- https://www.voronota.com
- https://www.kliment.lt
- https://www.bioinformatics.lt

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