Evaluating models of protein-protein complexes using tessellation-based contact area persistence descriptors derived from conformational ensembles of proteins

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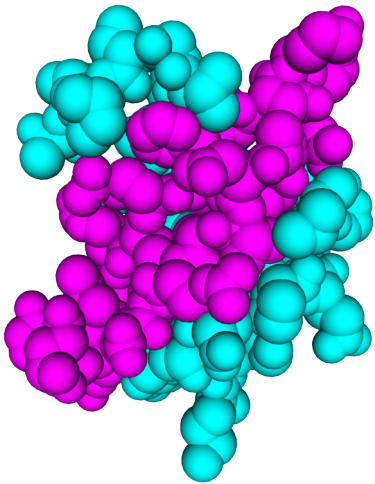
2024-11-14



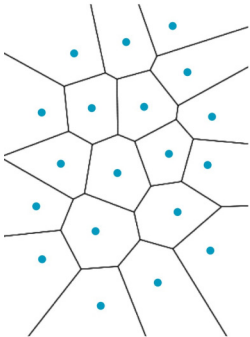
Common problems:

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

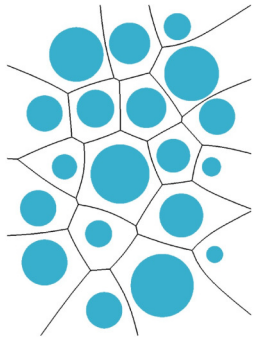
Describing interactions in molecular conformations using the Voronoi tessellation

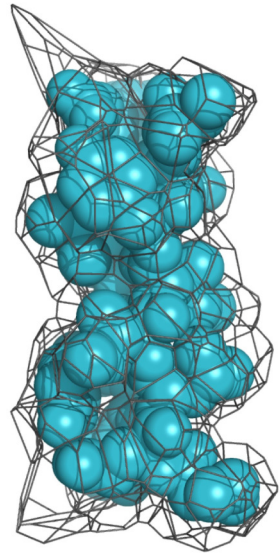
Voronoi diagram of points and balls

"Classic" Voronoi diagram of points



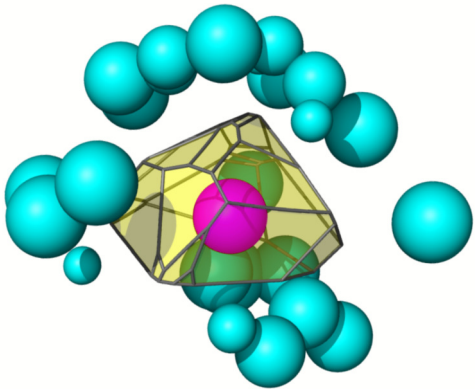
Voronoi diagram of balls



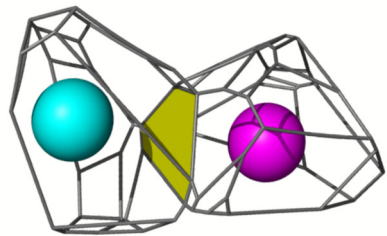


Voronoi tessellation-based analysis of structures

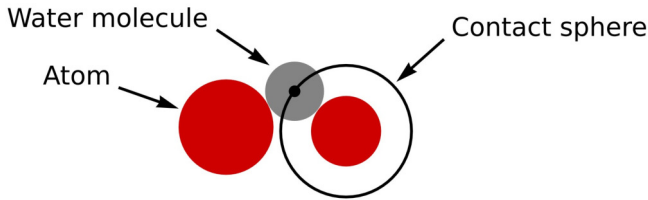
Voronoi cell of an atom surrounded by its neighbors

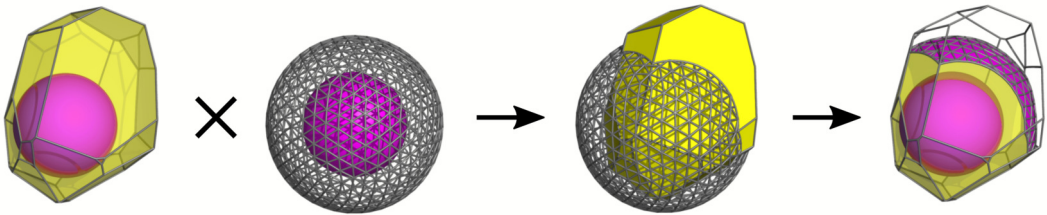


Atom-atom contact surface defined as the face shared by two adjacent Voronoi cells.



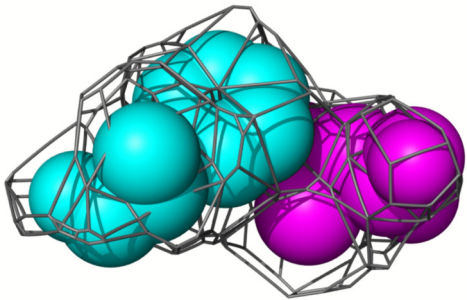
Constrained contacts



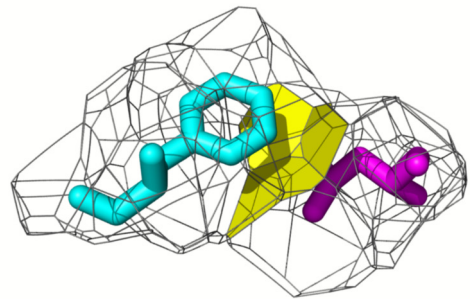


Deriving residue-residue contacts

Voronoi cells of two neighboring residues

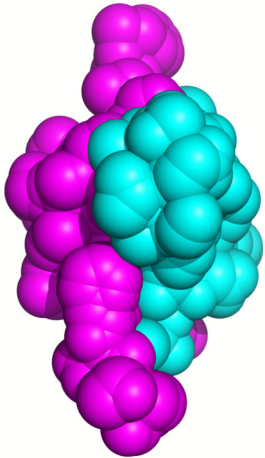


Residue-residue contact surface defined as a union of atom-atom contact surfaces

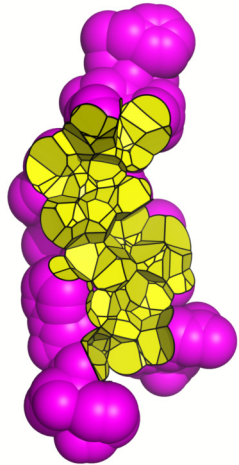


Inter-chain contacts

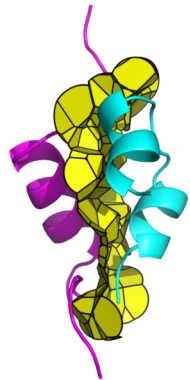
Solvent-accessible surface of an insulin heterodimer PDB:4UNG colored by subunit



The intersubunit interface shown together with the SAS of one subunit

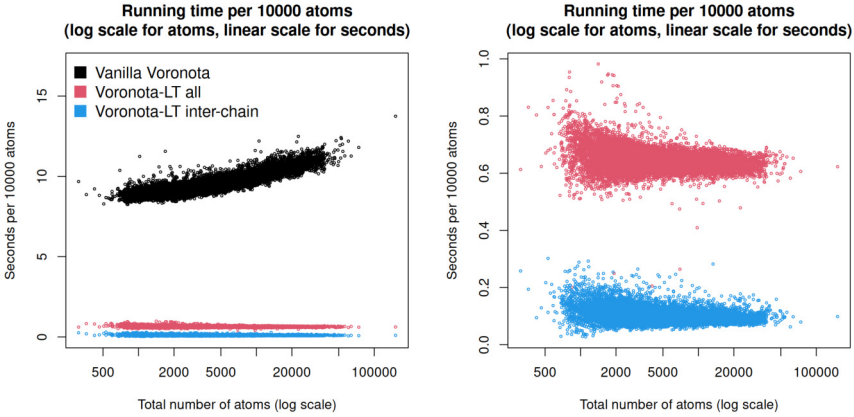


The intersubunit interface shown together with both subunits represented as cartoons



Voronota-LT

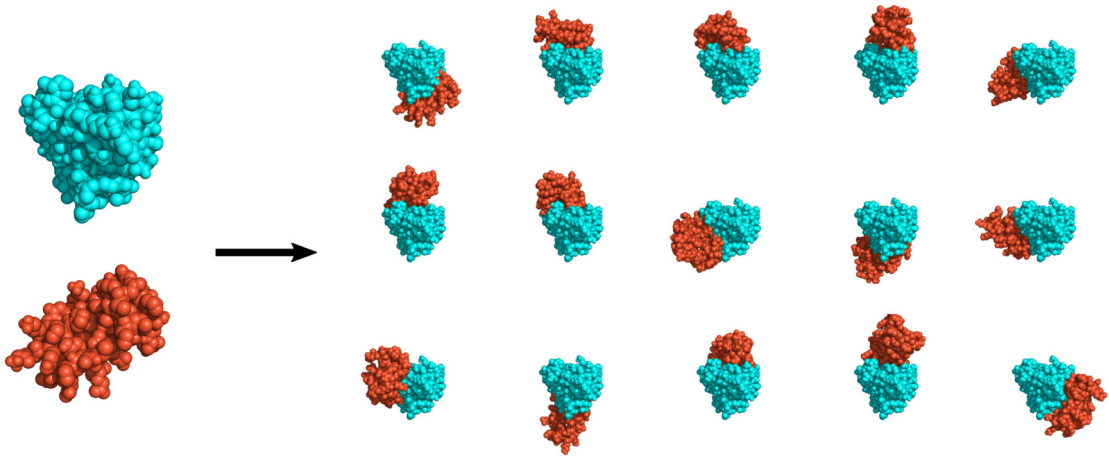
Voronota-LT is a new fast software for constructing tessellation-derived atomic contact areas and volumes. It is significantly faster than its predecessor, Voronota:



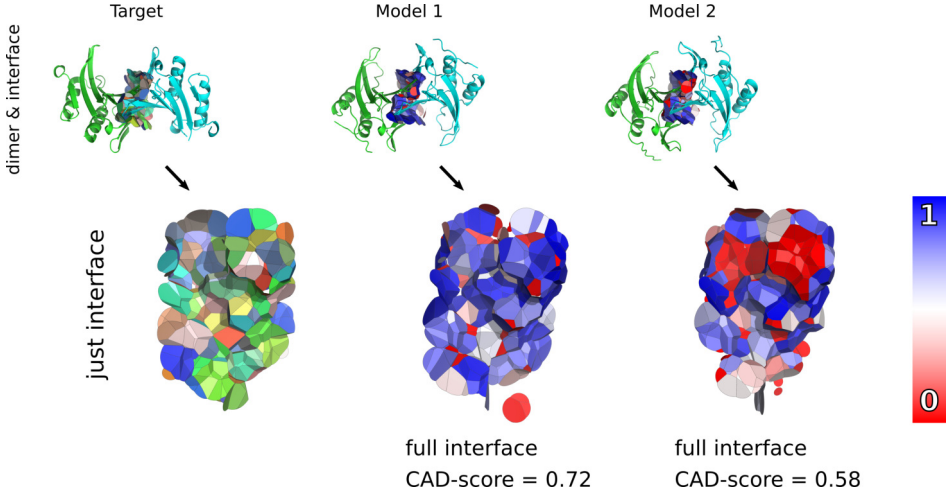
Olechnovic and Grudinin. *Voronota-LT: efficient, flexible and solvent-aware tessellation-based analysis of atomic interactions*. bioRxiv (2024)

Some applications of tessellation-based description of interactions

Same chains can have differently modelled interfaces



Comparing interfaces using CAD-score (Contact Area Difference score)



Olechnovic and Venclovas. *Contact Area-Based Structural Analysis of Proteins and Their Complexes Using CAD-Score*. Methods in Molecular Biology (2020)

Evaluating interfaces with an area-based potential (e.g. VoroMQA)

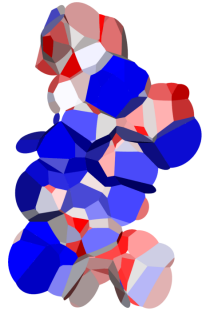
Interface
contact areas

$$\mathrm{E}(a_i, a_j, c_k) = \log \frac{\mathrm{P}_{\mathrm{exp}}(a_i, a_j, c_k)}{\mathrm{P}_{\mathrm{obs}}(a_i, a_j, c_k)} =$$

$$= \log \frac{\mathrm{F}_{\mathrm{exp}}(\mathrm{area}(a_i), \mathrm{area}(a_j), \mathrm{area}(c_k))}{\mathrm{F}_{\mathrm{obs}}(\mathrm{area}(a_i, a_j, c_k))}$$

$$\mathrm{E}_{\mathrm{n}}(\Omega_\phi) = \frac{\sum_{\omega \in \Omega_\phi} \mathrm{E}(\mathrm{type}_\omega) \cdot \mathrm{area}_\omega}{\sum_{\omega \in \Omega_\phi} \mathrm{area}_\omega}$$

Statistical potential
for contact areas

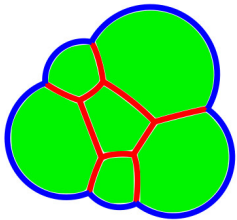


Interface
pseudo-energy

Olechnovic and Venclovas. *VoroMQA: Assessment of protein structure quality using interatomic contact areas*. Proteins (2017)

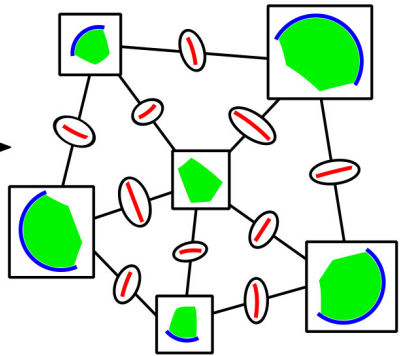
Input interface graph for a graph neural network (e.g. VoroIF-GNN)

Tessellation-derived interface contacts



Contact surface
Contact-solvent border
Inter-contact border

Interface graph



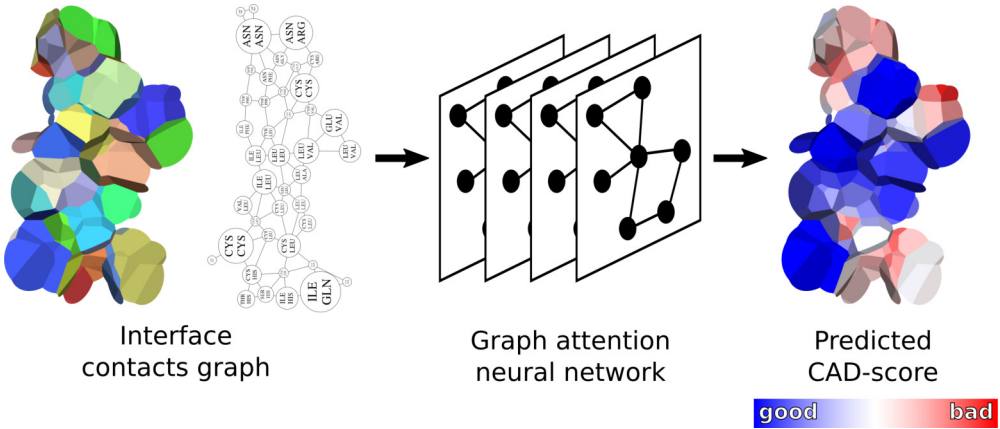
Graph **node** attributes (15 values)

- **Contact surface area**
- **Contact-solvent border length**
- **Sum of inter-contact border lengths**
- **Contact type-dependent descriptors (12 values)**

Graph **edge** attribute (1 value)

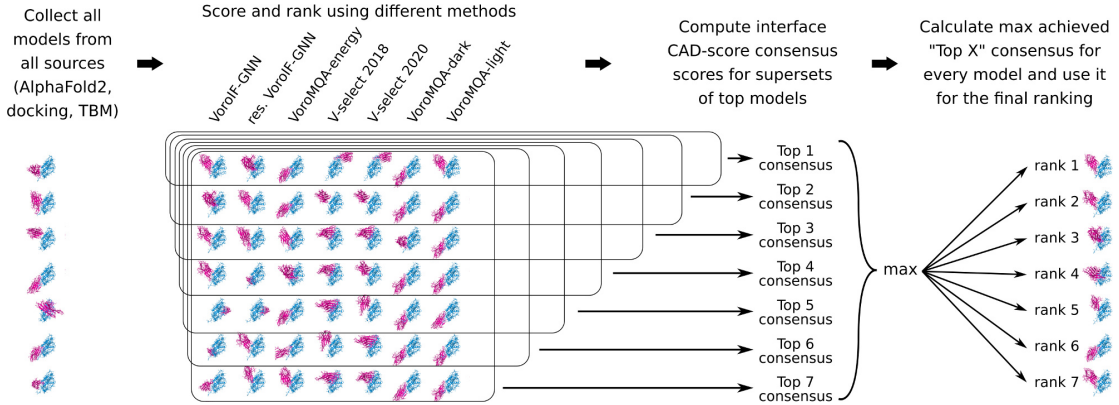
Inter-contact border length

Evaluating interfaces with a graph neural network (e.g. VoroIF-GNN)



Olechnovic and Venclovas. *VoroIF-GNN: Voronoi tessellation-derived protein-protein interface assessment using a graph neural network*. Proteins (2023)

Selecting complex models using VoroIF-jury (a.k.a. FTDMP)

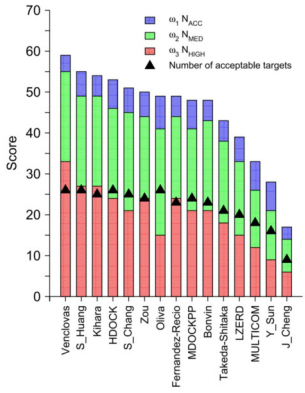


VoroIF-jury was the best-performing multimeric model selector in 2022 CASP and CAPRI double-blind challenges.

CASP15-CAPRI challenge results

Assembly prediction results

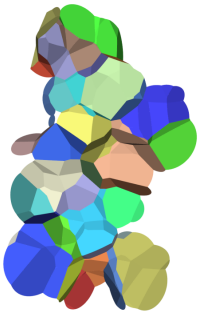
Assembly scoring results



Plots from Lensink et al. (2023) "Impact of AlphaFold on Structure Prediction of Protein Complexes: The CASP15-CAPRI Experiment". Proteins (accepted)

Area-based potential may still be used for testing new ideas

Area-based pairwise interaction potential alone is not the best scoring method, but it may still serve as simple a tool to explore benefits of newer data and descriptors.



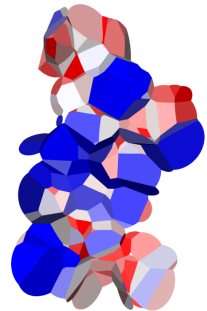
Interface
contact areas

$$\mathrm{E}(a_i, a_j, c_k) = \log \frac{\mathrm{P_{exp}}(a_i, a_j, c_k)}{\mathrm{P_{obs}}(a_i, a_j, c_k)} =$$

$$= \log \frac{\mathrm{F_{exp}}(\mathrm{area}(a_i), \mathrm{area}(a_j), \mathrm{area}(c_k))}{\mathrm{F_{obs}}(\mathrm{area}(a_i, a_j, c_k))}$$

$$\mathrm{E_n}(\Omega_\phi) = \frac{\sum_{\omega \in \Omega_\phi} \mathrm{E}(\mathrm{type}_\omega) \cdot \mathrm{area}_\omega}{\sum_{\omega \in \Omega_\phi} \mathrm{area}_\omega}$$

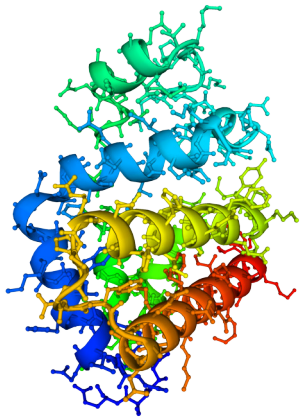
Statistical potential
for contact areas



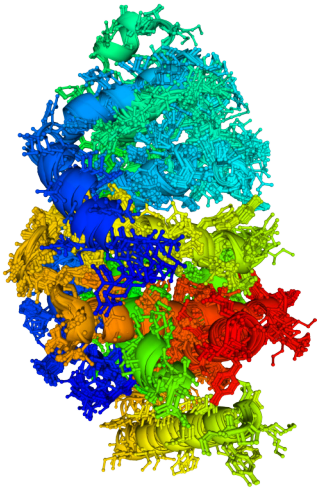
Interface
pseudo-energy

Deriving and using statistics of contact areas from ensembles of conformations

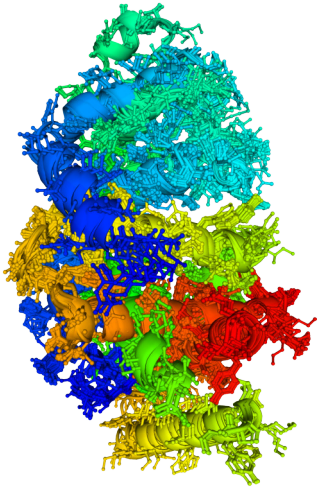
a single conformation



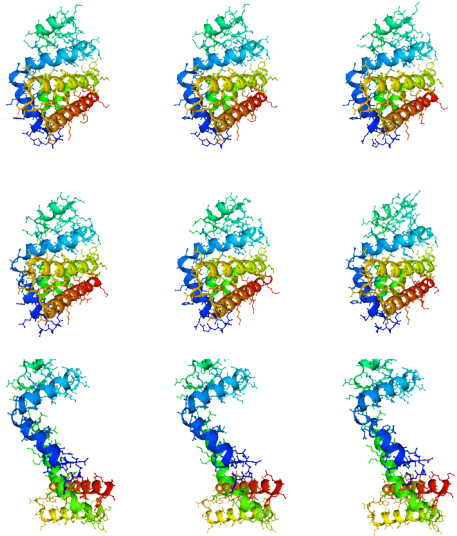
an ensemble of conformations



an ensemble of conformations



the same ensemble of conformations



A dataset of ensembles of conformations from PDB

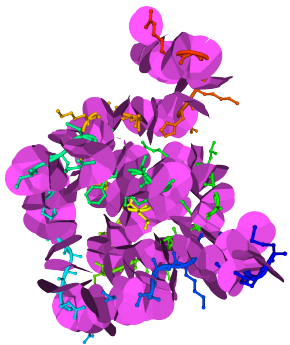
- Collected from the **Protein Data Bank** (PDB), https://www.wwpdb.org/.
- Ensembles formed by clustering chain sequences using **90%** identity.
- We used all **38'807** ensembles that were available.
- Ensembles have very different numbers of chains:
  - the largest ensemble contains **1413** chains
  - **9989** ensembles contain **only two** chains.
- There are **429'945** protein chains in total.

Deriving and using statistics of contact areas from ensembles of conformations

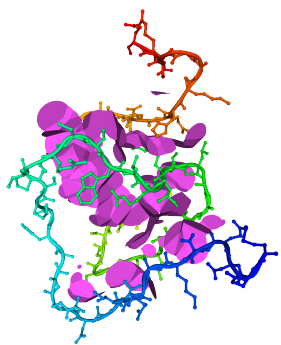
Contacts from a single conformation

A contact type is a tuple *(first atom type, second atom type, contact category)* = (a_1, a_2, c).

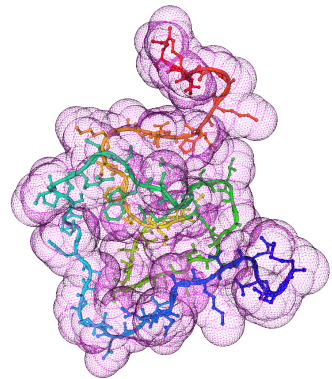
sequence separation <=5



sequence separation >5



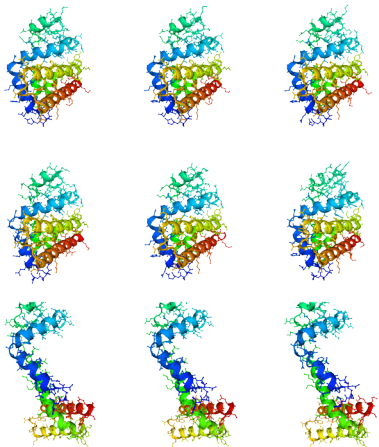
solvent-accessible surface



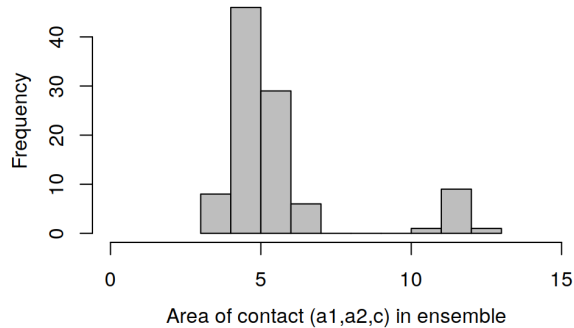
Contacts from a single conformation

Let's look at some 3D animation ...

An ensemble



Distribution of areas of some contact in the ensemble



We summarize a contact type $t = (a_1, a_2, c)$ area distribution in a PDB ensemble with:

- $v^t = \min(\text{observed } t \text{ areas})$
- $u^t = \max(\text{observed } t \text{ areas})$

Areas of contact types from a multiple ensembles of conformations

v^t and u^t values are areas, therefore we can sum them.

For a contact type $t = (a_1, a_2, c)$ we sum the relevant v^t and u^t values from all the available ensembles G to get V^t and U^t sums:

$$V^t = \sum_{g \in G} v^t(g) \tag{1}$$

$$U^t = \sum_{g \in G} u^t(g) \tag{2}$$

We do it for every contact type t from the set of all possible contact types T.

Observed probabilities of areas of contact types

Observed probability estimate of contact area unit of type $t = (a_1, a_2, c)$ to occur:

$$P^t_{\text{obs}}(\text{occur}) = \frac{V^t + U^t}{\sum_{s \in T}(V^s + U^s)} \tag{3}$$

Observed conditional probability estimate of contact area unit to persist:

$$P^t_{\text{obs}}(\text{persist}|\text{occur}) = \frac{2V^t}{V^t + U^t} \tag{4}$$

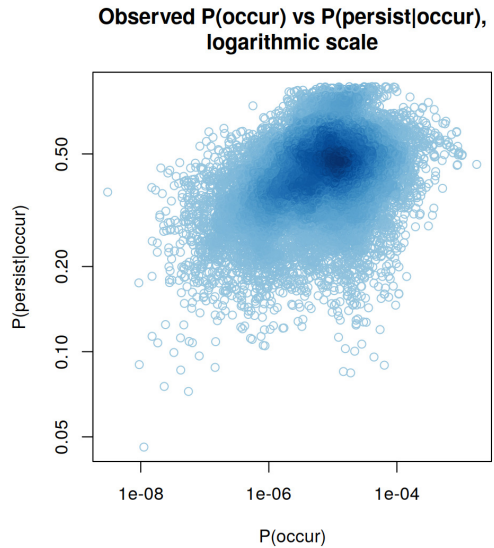
Observed probability estimate of contact area unit to occur and persist:

$$P^t_{\text{obs}}(\text{occur and persist}) = P^t_{\text{obs}}(\text{occur}) \cdot P^t_{\text{obs}}(\text{persist}|\text{occur}) \tag{5}$$

Low correlation between occurence and persistence probabilities

$$\text{corr}(P_{\text{obs}}(\text{occur}), P_{\text{obs}}(\text{persist}|\text{occur})) = 0.11$$

$$\text{corr}(\log P_{\text{obs}}(\text{occur}), \log P_{\text{obs}}(\text{persist}|\text{occur})) = 0.36$$



Expected probabilities of areas of contact types

Expected probability estimate of contact area unit of type $t = (a_1, a_2, c)$ to occur (modeling the situation where there are no atom type-dependent or contact category-dependent effects):

$$P_{\text{exp}}^{t=(a_1,a_2,c)}(\text{occur}) \sim P_{\text{obs}}^{(a_1,*,*)}(\text{occur}) \cdot P_{\text{obs}}^{(*,a_2,*)}(\text{occur}) \cdot P_{\text{obs}}^{(*,*,c)}(\text{occur}) \cdot \tag{6}$$

Expected conditional probability estimate of contact area unit to persist:

$$P_{\text{exp}}^{t}(\text{persist}|\text{occur}) = \frac{2 \cdot \sum_{s \in T} V^s}{\sum_{s \in T}(V^s + U^s)} \tag{7}$$

Expected probability estimate of contact area unit to occur and persist:

$$P_{\text{exp}}^{t}(\text{occur and persist}) = P_{\text{exp}}^{t}(\text{occur}) \cdot P_{\text{exp}}^{t}(\text{persist}|\text{occur}) \tag{8}$$

Deriving pseudo-energy coefficient from probality estimates

Pseudo-energy coefficient for a contact area unit of type $t = (a_1, a_2, c)$:

$$E^t \sim \log\left(\frac{P^t_{\text{exp}}(\text{occur and persist})}{P^t_{\text{obs}}(\text{occur and persist})}\right) \tag{9}$$

E^t can be written as a weighted sum (weights to be optimized later):

$$E^t_{\alpha_1,\alpha_2,\alpha_3,\alpha_4,\beta} = \alpha_1 \cdot \log P^t_{\text{obs}}(\text{occur}) + \alpha_2 \cdot \log P^t_{\text{exp}}(\text{occur}) + \tag{10}$$
$$+\alpha_3 \cdot \log P^t_{\text{obs}}(\text{persist}|\text{occur}) + \alpha_4 \cdot \log P^t_{\text{exp}}(\text{persist}|\text{occur}) + \beta$$

Using pseudo-energy to score inter-chain interfaces

A total pseudo-energy score for a set of contacts K is:

$$S_{\alpha_1,\alpha_2,\alpha_3,\alpha_4,\beta}(G) = \sum_{k \in K} \text{area}(k) \cdot E^{\text{type}(k)}_{\alpha_1,\alpha_2,\alpha_3,\alpha_4,\beta} \tag{11}$$

We optimize the weights $(\alpha_1, \alpha_2, \alpha_3, \alpha_4, \beta)$ for the task of selecting best-modelled interfaces.

A dataset of correct and incorrect interfaces

- A non-redundant set of 1567 native heterodimers, selected using PPI3D and downloaded from PDB.
- Each native structure (target) was redocked and a set of models of varying quality was selected (about 15-20 models for a target), for example:

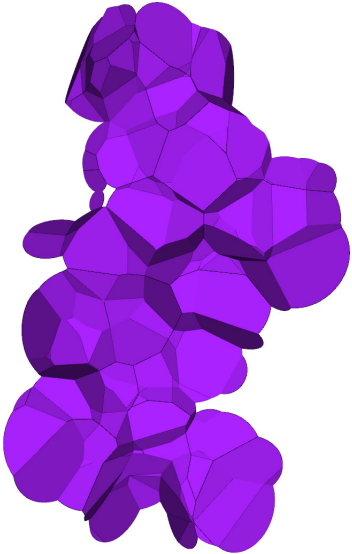
ID	x	y	z	a1	a2	a3	cadscore	site_cadscore
1E50_nat	0	0	0	0	0	0	1	1
1E50_2250	-7	27	4	45	153	90	0.74375	0.87635
1E50_32	-13	25	2	18	153	90	0.63728	0.75543
1E50_2735	-7	28	1	72	162	120	0.53173	0.68644
1E50_15946	-16	26	-2	45	162	120	0.38075	0.55364
1E50_10393	-16	28	5	0	153	90	0.24134	0.47034
1E50_3759	7	29	7	351	117	40	0.13939	0.51889
1E50_17192	24	22	8	315	63	0	0.0386	0.42122
1E50_15006	-13	27	13	342	18	0	0	0.40432
1E50_5533	28	-13	20	0	45	204	0	0.30295
1E50_14280	27	-22	-22	180	126	60	0	0.20266
1E50_532	34	4	-18	207	54	100	0	0.10126
1E50_20368	1	-39	10	324	117	80	0	0.00119
1E50_9297	37	5	-22	261	54	80	0	0

5-fold cross-validation results of selection performance

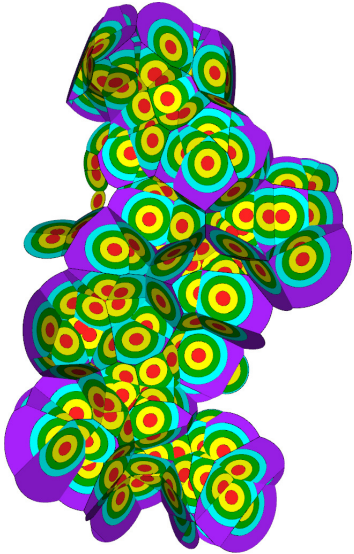
Method	**Components**	**Correct selection rate**	
		mean	**std. deviation**
Ideal selector		1	0
Random		0.07	0.012
Total area		0.05	0.011
Simple pseudo-energy	$P(\text{occur})$	0.70	0.026
	$P(\text{persist}\|\text{occur})$	0.81	0.020
	$P(\text{occur}) \cdot P(\text{persist}\|\text{occur})$	0.83	0.021

Introducing layered contacts

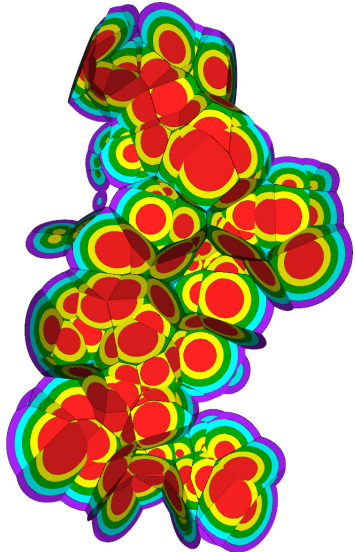
Simple contacts



Layered contacts v1



Layered contacts v2



Introducing layered contacts

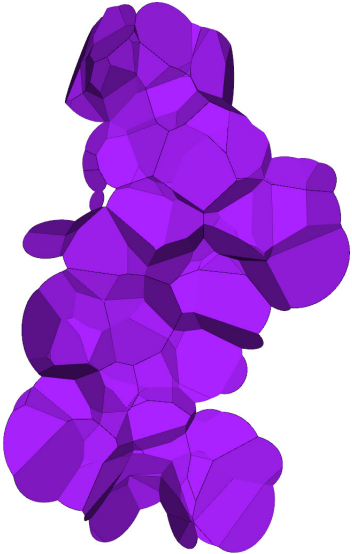
Let's look at some 3D animation ...

5-fold cross-validation results of selection performance

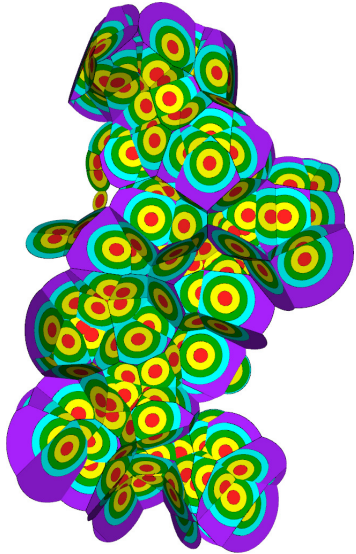
Method	Components	Correct selection rate	
		mean	std. deviation
Ideal selector		1	0
Random		0.07	0.012
Total area		0.05	0.011
Simple pseudo-energy	$P(\text{occur})$	0.70	0.026
	$P(\text{persist}\|\text{occur})$	0.81	0.020
	$P(\text{occur}) \cdot P(\text{persist}\|\text{occur})$	0.83	0.021
Layered (v1) pseudo-energy, layers weighted samely	$P(\text{occur})$	0.75	0.020
	$P(\text{persist}\|\text{occur})$	0.88	0.009
	$P(\text{occur}) \cdot P(\text{persist}\|\text{occur})$	0.91	0.008

Layered contacts

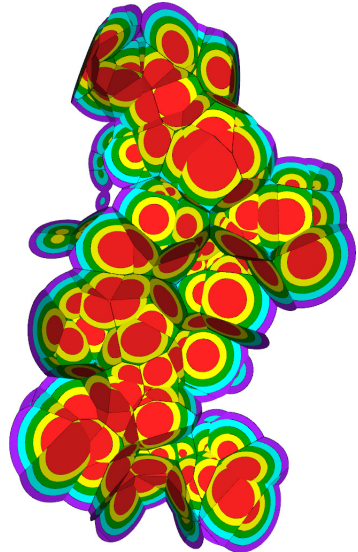
Simple contacts



Layered contacts v1



Layered contacts v2



5-fold cross-validation results of selection performance

Method	Components	Correct selection rate	
		mean	std. deviation
Ideal selector		1	0
Random		0.07	0.012
Total area		0.05	0.011
Simple pseudo-energy	$P(\text{occur})$	0.70	0.026
	$P(\text{persist}\|\text{occur})$	0.81	0.020
	$P(\text{occur}) \cdot P(\text{persist}\|\text{occur})$	0.83	0.021
Layered (v1) pseudo-energy, layers weighted samely	$P(\text{occur})$	0.75	0.020
	$P(\text{persist}\|\text{occur})$	0.88	0.009
	$P(\text{occur}) \cdot P(\text{persist}\|\text{occur})$	0.91	0.008
Layered (v2) pseudo-energy, layers weighted differently	$P(\text{occur})$	0.88	0.010
	$P(\text{persist}\|\text{occur})$	0.97	0.011
	$P(\text{occur}) \cdot P(\text{persist}\|\text{occur})$	0.97	0.010

Conclusions

- Tessellation-derived contact area descriptors can be used to collect information about contact stability from ensembles of conformations in PDB.
- The information about contact stability can improve scoring of protein-protein interfaces.
- Subdivinding tessellation-derived contacts into layers provides an improved description of protein-protein interfaces, making the contact stability information even more useful.
- The presented new contact descriptors can be used in more sophisticated ML methods, e.g. VoroIF-GNN

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

Funded by the European Union