НИИ физико-химической биологии имени А.Н. Белозерского МГУ,
Научно-исследовательский вычислительный центр МГУ

vsFilt

Новый инструмент структурной фильтрации для виртуального скрининга

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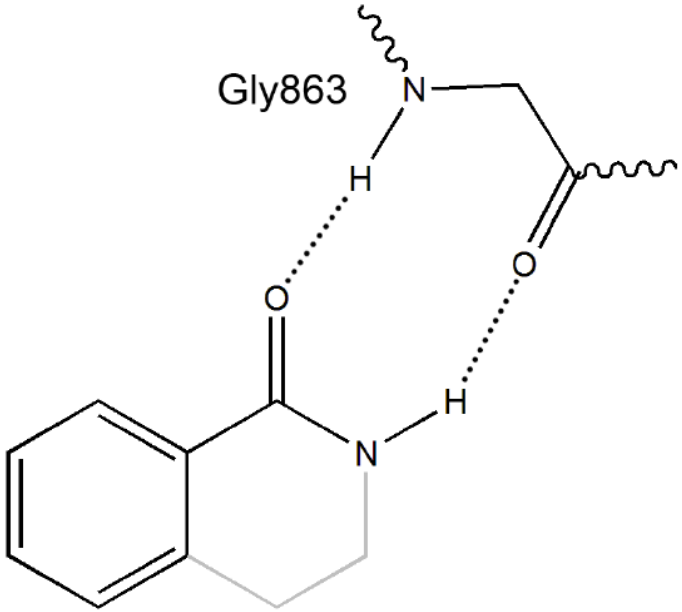
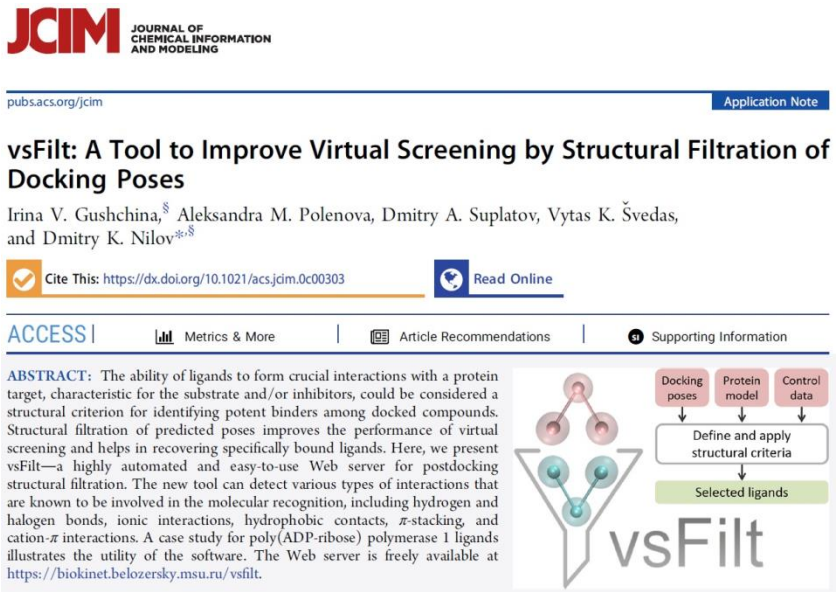
Structural filter is defined by a set of interactions:

- typically observed in available structures of protein−ligand complexes;
- considered to play a crucial role in ligand binding





JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

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vsFilt: A Tool to Improve Virtual Screening by Structural Filtration of Docking Poses

Irina V. Gushchina,[§] Aleksandra M. Polenova, Dmitry A. Suplatov, Vytas K. Švedas, and Dmitry K. Nilov[*,§]

Cite This: https://dx.doi.org/10.1021/acs.jcim.0c00303 Read Online

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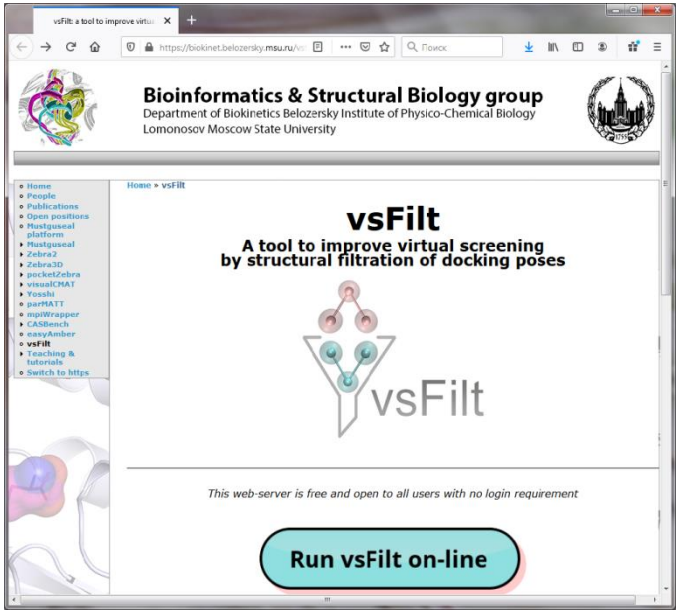
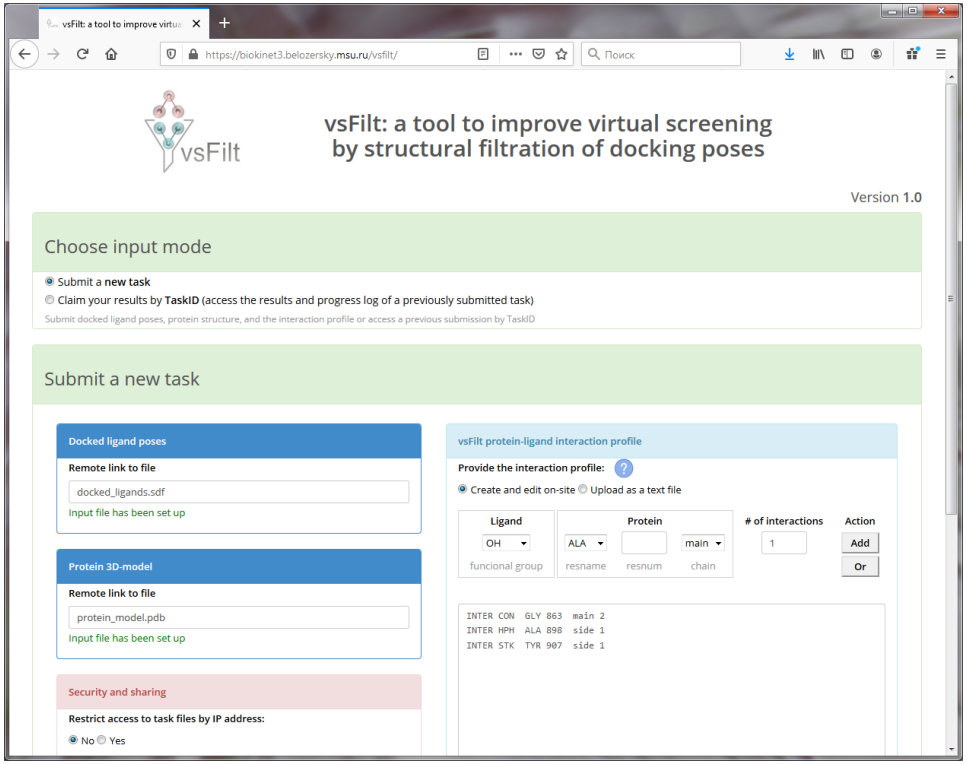
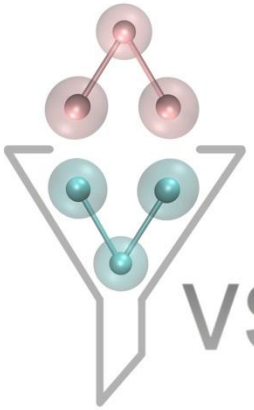
ABSTRACT: The ability of ligands to form crucial interactions with a protein target, characteristic for the substrate and/or inhibitors, could be considered a structural criterion for identifying potent binders among docked compounds. Structural filtration of predicted poses improves the performance of virtual screening and helps in recovering specifically bound ligands. Here, we present vsFilt—a highly automated and easy-to-use Web server for postdocking structural filtration. The new tool can detect various types of interactions that are known to be involved in the molecular recognition, including hydrogen and halogen bonds, ionic interactions, hydrophobic contacts, π-stacking, and cation-π interactions. A case study for poly(ADP-ribose) polymerase 1 ligands illustrates the utility of the software. The Web server is freely available at https://biokinet.belozersky.msu.ru/vsfilt.

Gushchina et al. *J. Chem. Inf. Mod.* (2020) 60, 3692-2696

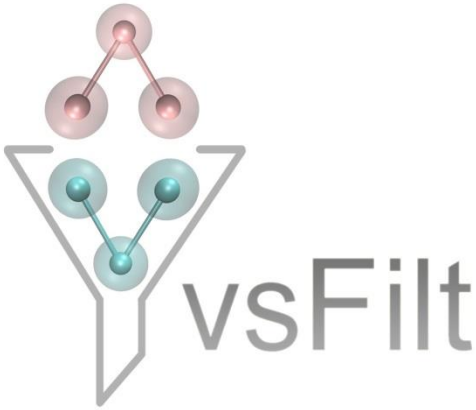
https://biokinet.belozersky.msu.ru/vsfilt







- hydrogen bonds;
- halogen bonds;
- ionic interactions;
- hydrophobic contacts;
- π-stacking;
- cation-π interactions



- hydrogen bonds;
- halogen bonds;
- ionic interactions;
- hydrophobic contacts;
- π-stacking;
- cation-π interactions

Analogs:

- in-house scripts;
- AutoDock/Raccoon (free);
- Schrödinger/Glide (commercial);
- nAPOLI server

vsFilt

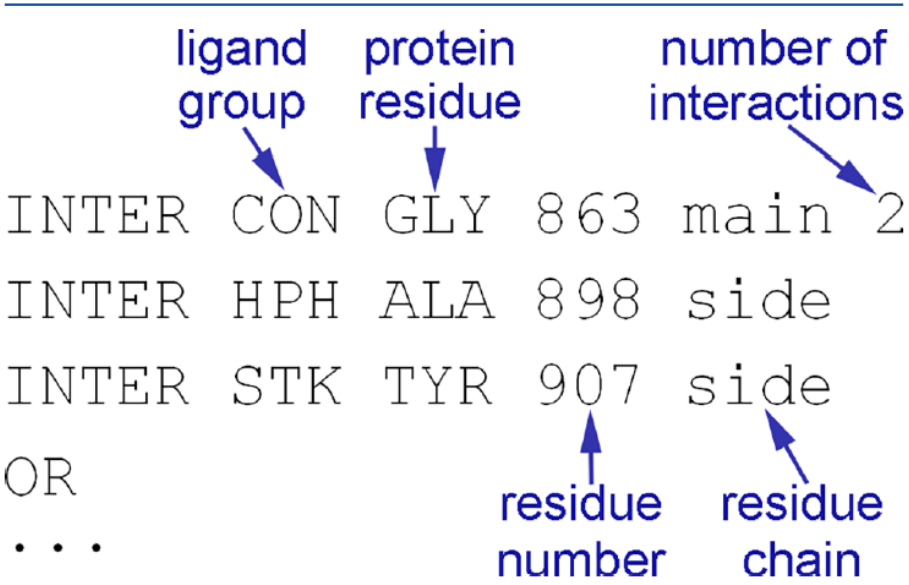


Figure 1. Example of control data used by vsFilt for structural filtration.

vsFilt

- automatically identifies atoms involved in the interaction;
- sets the corresponding criteria for filtering

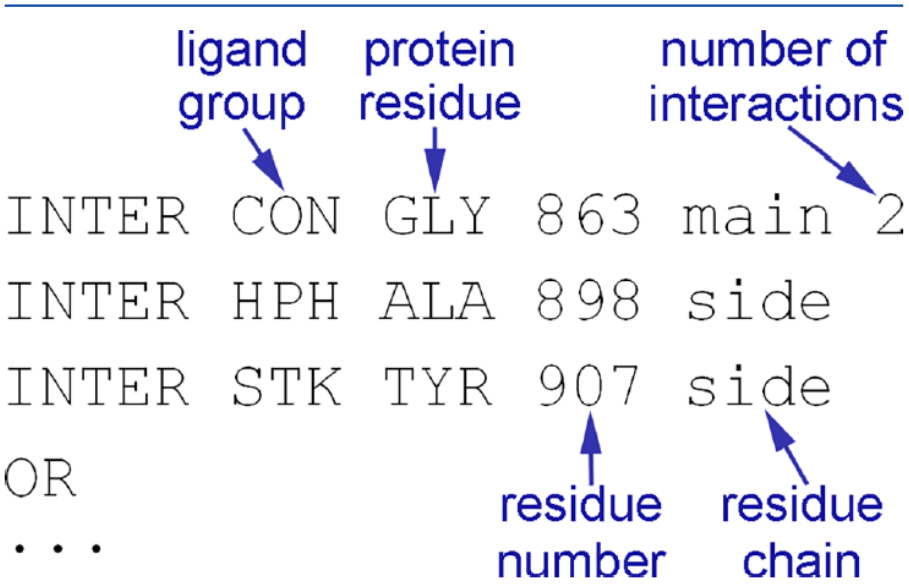
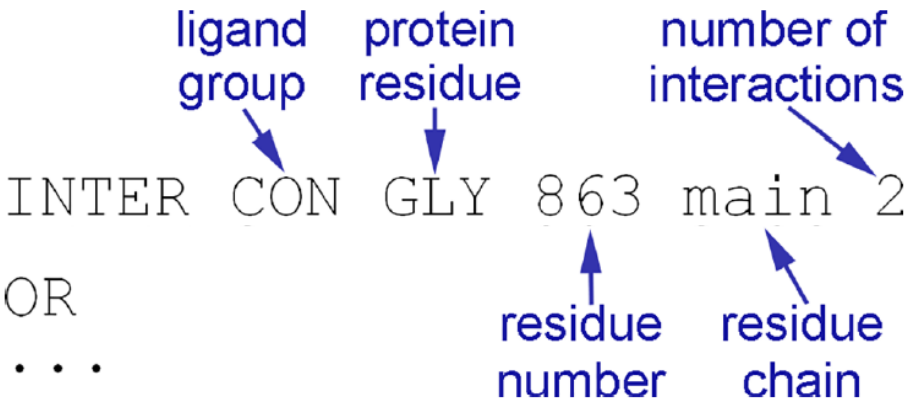


Figure 1. Example of control data used by vsFilt for structural filtration.

vsFilt



- recognizes the type of interaction (H-bonding);
- identifies interacting atoms (H-bond donors and acceptors) and their coordinates;
- applies the corresponding distance and angle criteria for structural filtration

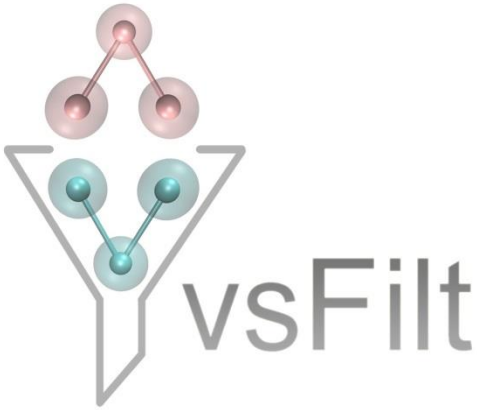
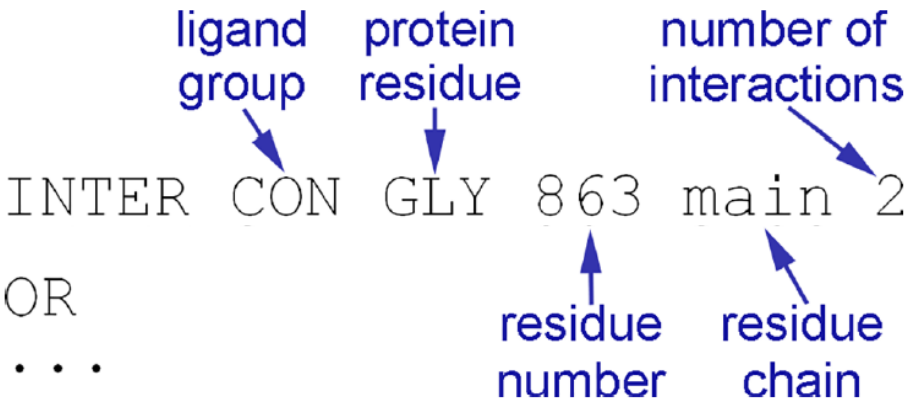


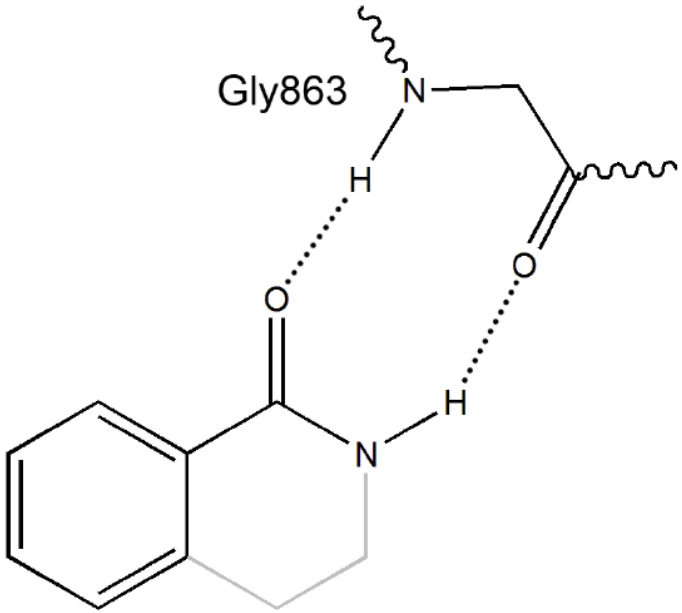
Table 1. Ligand Functional Groups That Can Be Involved in Structural Filtration with vsFilt, and Their Role in the Interaction with Protein

ligand group		interaction
OH	hydroxyl	hb donor/acceptor
CO	carbonyl	hb acceptor
COO	carboxyl	hb acceptor, anion
COOC	ester	hb acceptor
COC	ether	hb acceptor
CON	amide	hb donor/acceptor
NH	amino	hb donor
NAR	N aromatic	hb acceptor
SO3	sulfo	hb acceptor, anion
SO2N	sulfonamide	hb donor/acceptor
DON	hb donor	hb donor
ACC	hb acceptor	hb acceptor
HAL	halo	halo bond donor
HPH	hydrophobic	hydrophobic
STK	aromatic	stacking
PIC	aromatic	cation−π

vsFilt



- available residue names: ALA, ARG, ASN, ASP, CYS, GLN, GLU, GLY, HIS, ILE, LEU, LYS, MET, PHE, PRO, SER, THR, TRP, TYR, VAL, HOH (ordered water molecule), CA2, MG2, and ZN2 (Ca^{2+}, Mg^{2+}, and Zn^{2+} ions);
- main chain/side chain option;
- minimum number of interactions (default = 1) option

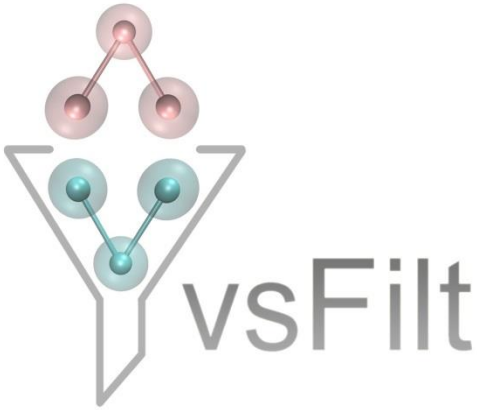


ligand group | protein residue | number of interactions

```
INTER CON GLY 863 main 2
INTER HPH ALA 898 side
INTER STK TYR 907 side
OR
...
```

residue number | residue chain

Figure 1. Example of control data used by vsFilt for structural filtration.

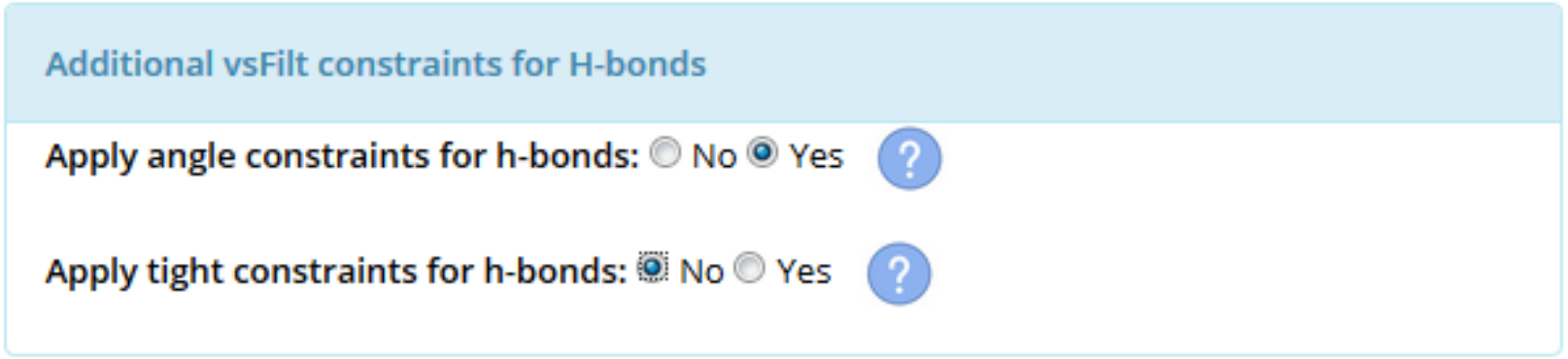


Hydrogen bonds

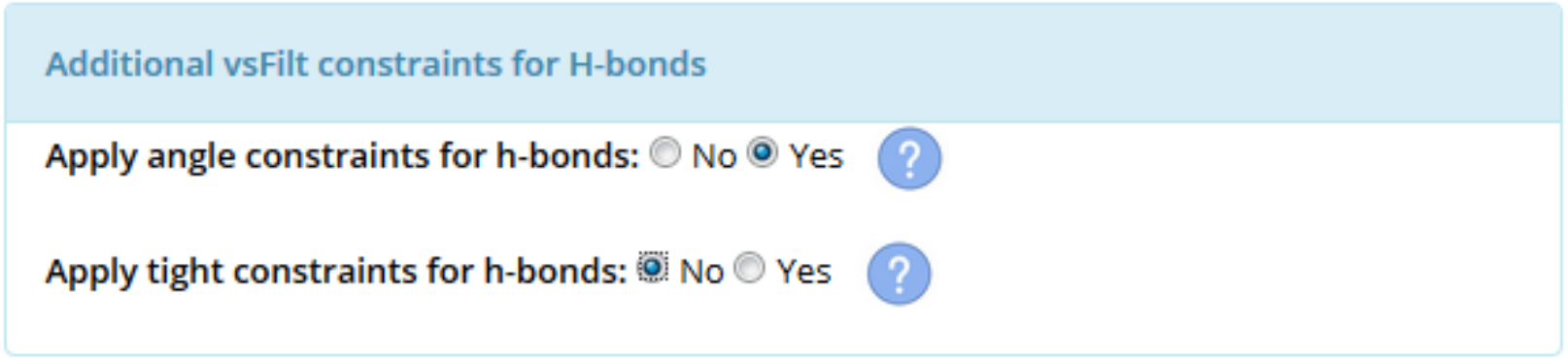
Maximum distances: upper 90% quantiles of H-bond distances obtained from structural database statistics + 0.5 Å

Bissantz et al. *J. Med. Chem.* (2010)

Ligand group		Ligand atom	Protein atom	Max distance, Å
OH	hydroxyl	hb donor O	O:	3.5
			carboxyl O:	3.3
			aromatic N:	3.5
		hb acceptor O	OH:	3.5
			NH:	3.6
CO	carbonyl	hb acceptor O	OH:	3.5
			NH:	3.6
COO	carboxyl	hb acceptor O	OH:	3.3
			NH:	3.5
		anion O	CA2	2.9
			MG2	2.6
			ZN2	2.7
COOC	ester	hb acceptor O	OH:	3.5
			NH:	3.6
COC	ether	hb acceptor O	OH:	3.5
			NH:	3.6
CON	amide	hb donor N	O:	3.6
			carboxyl O:	3.5
			aromatic N:	3.7
		hb acceptor O	OH:	3.5
			NH:	3.6
NH	amino	hb donor N	O:	3.6
			carboxyl O:	3.5
			aromatic N:	3.7
NAR	N aromatic	hb acceptor N	OH:	3.5
			NH:	3.7
SO3	sulfo	hb acceptor O	OH:	3.5
			NH:	3.6
		anion O	CA2	2.9
			MG2	2.6
			ZN2	2.7
SO2N	sulfonamide	hb donor N	O:	3.6
			carboxyl O:	3.5
			aromatic N:	3.7
		hb acceptor O	OH:	3.5
			NH:	3.6



H-bond angles are constrained to be ≥ 130°



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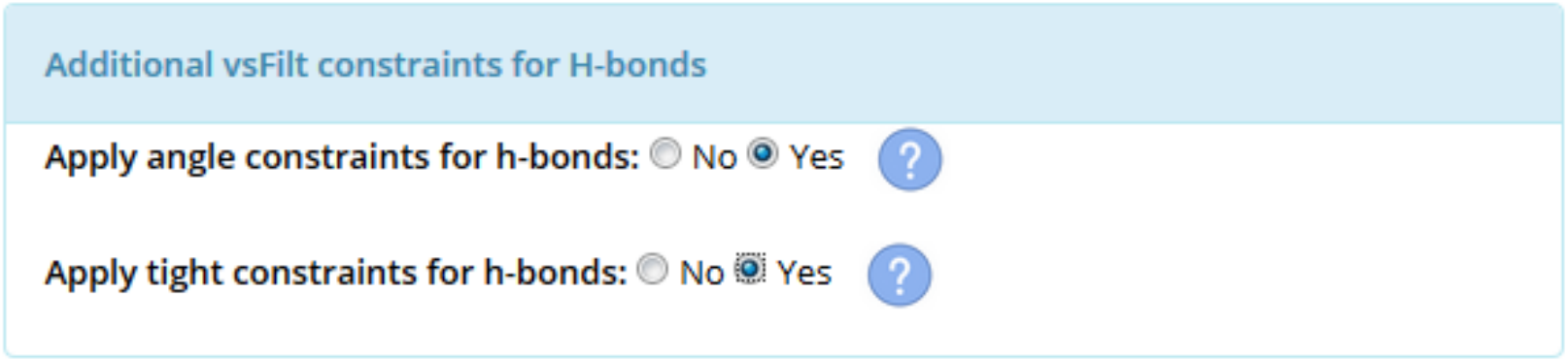
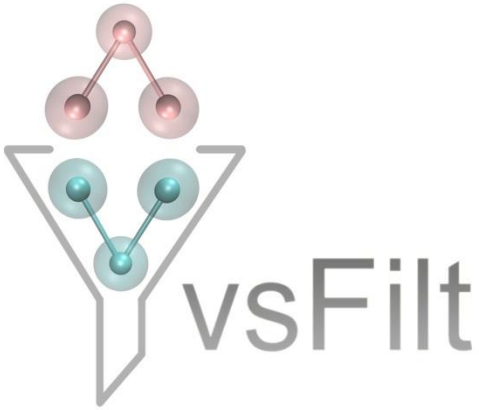


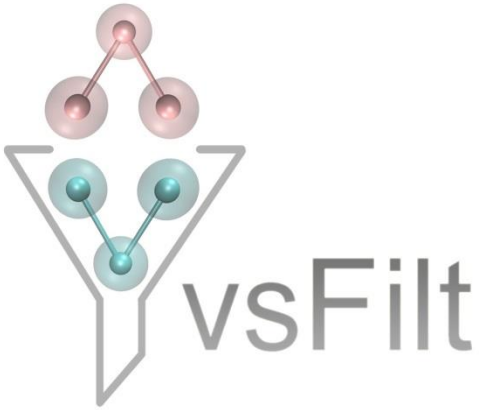
Distance ≤ upper 90% quantile (without 0.5 Å increment), angle ≥ 150°



Hydrogen bonds

DON group can be used as an unspecified H-bond donor and ACC group as an unspecified acceptor:

DON	hb donor	hb donor	O: carboxyl O: aromatic N:	3.5–3.6 3.3–3.5 3.5–3.7
ACC	hb acceptor	hb acceptor	OH: NH:	3.3–3.5 3.5–3.7



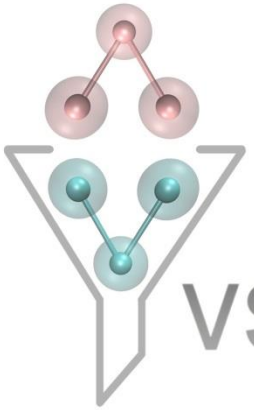
Ionic interactions

Maximum distance: the mean distance obtained from structural database statistics + 0.5 Å

COO	carboxyl	hb acceptor O	OH: NH:	3.3 3.5
		anion O	CA2 MG2 ZN2	2.9 2.6 2.7

SO3	sulfo	hb acceptor O	OH: NH:	3.5 3.6
		anion O	CA2 MG2 ZN2	2.9 2.6 2.7

Zheng et al. *J. Inorg. Biochem.* (2010)

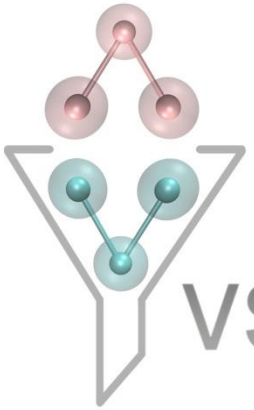


Halogen bonds

Maximum distances: upper 90% quantiles obtained from structural database statistics + 0.5 Å

HAL	halo	Cl	carbonyl O:	3.9
		Br, I	carbonyl O:	4.0

Bissantz et al. *J. Med. Chem.* (2010)

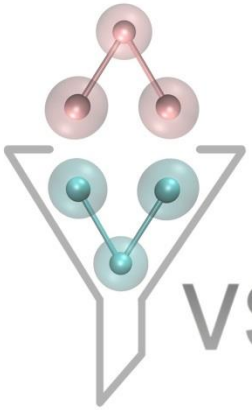


Hydrophobic interactions

Maximum distances: upper 90% quantiles obtained from structural database statistics + 0.5 Å

HPH	hydrophobic	aliphatic C	aliphatic C	4.9
			aromatic C	4.9
		aromatic C	aliphatic C	4.9
			aromatic C	4.3
		F	aliphatic C	4.4
		Cl	aliphatic C	4.8

Bissantz et al. *J. Med. Chem.* (2010)



Stacking interactions

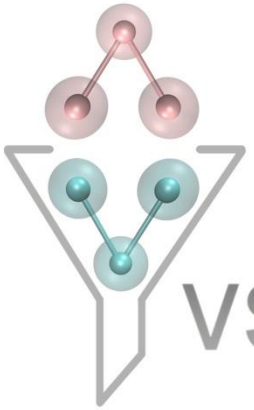
Maximum distance between centroids of stacked rings: ≤ 4. 5 Å

STK	aromatic	centroid*	centroid**	4.5

*Geometric center of ligand aromatic rings

**Geometric center of Phe/Tyr/His/Trp aromatic rings

Gonzalez et al. *J. Phys. Chem.* (2000)



Cation–π Interactions

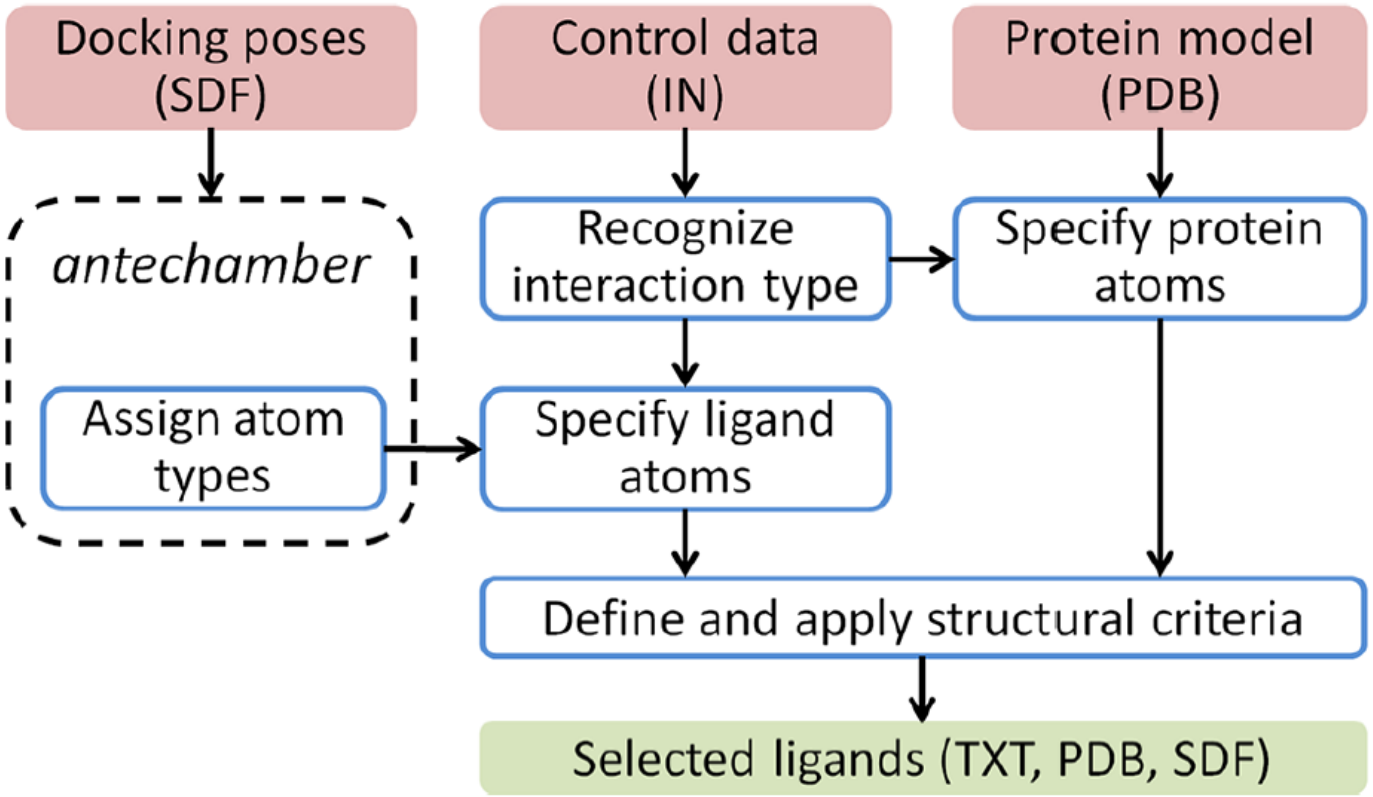
Maximum distances: upper 90% quantiles obtained from structural database statistics + 0.5 Å

PIC	aromatic	aromatic C	guanidinium C	4.5

Bissantz et al. *J. Med. Chem.* (2010)

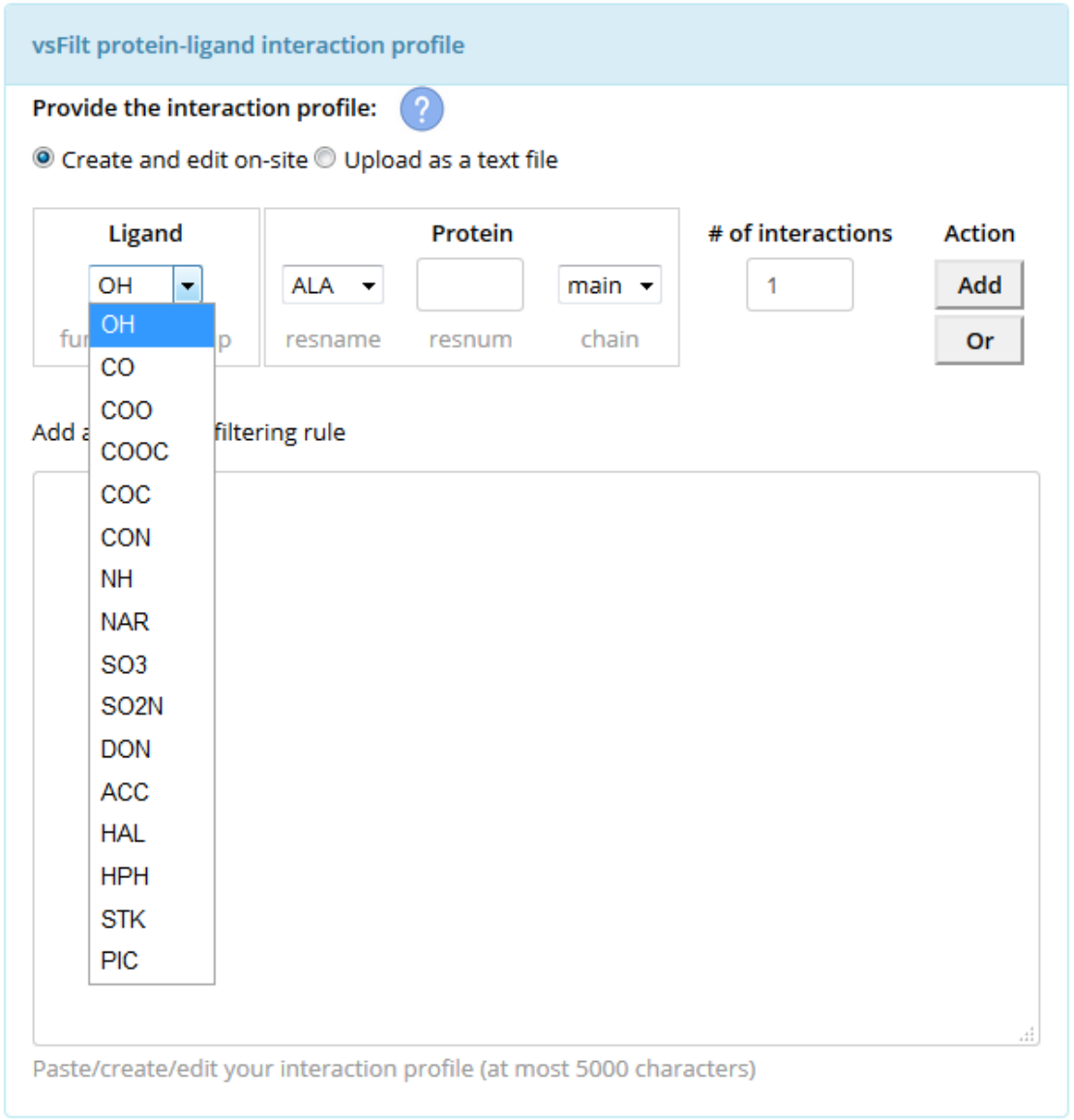
vsFilt

Workflow



vsFilt

https://biokinet.belozersky.msu.ru/vsfilt



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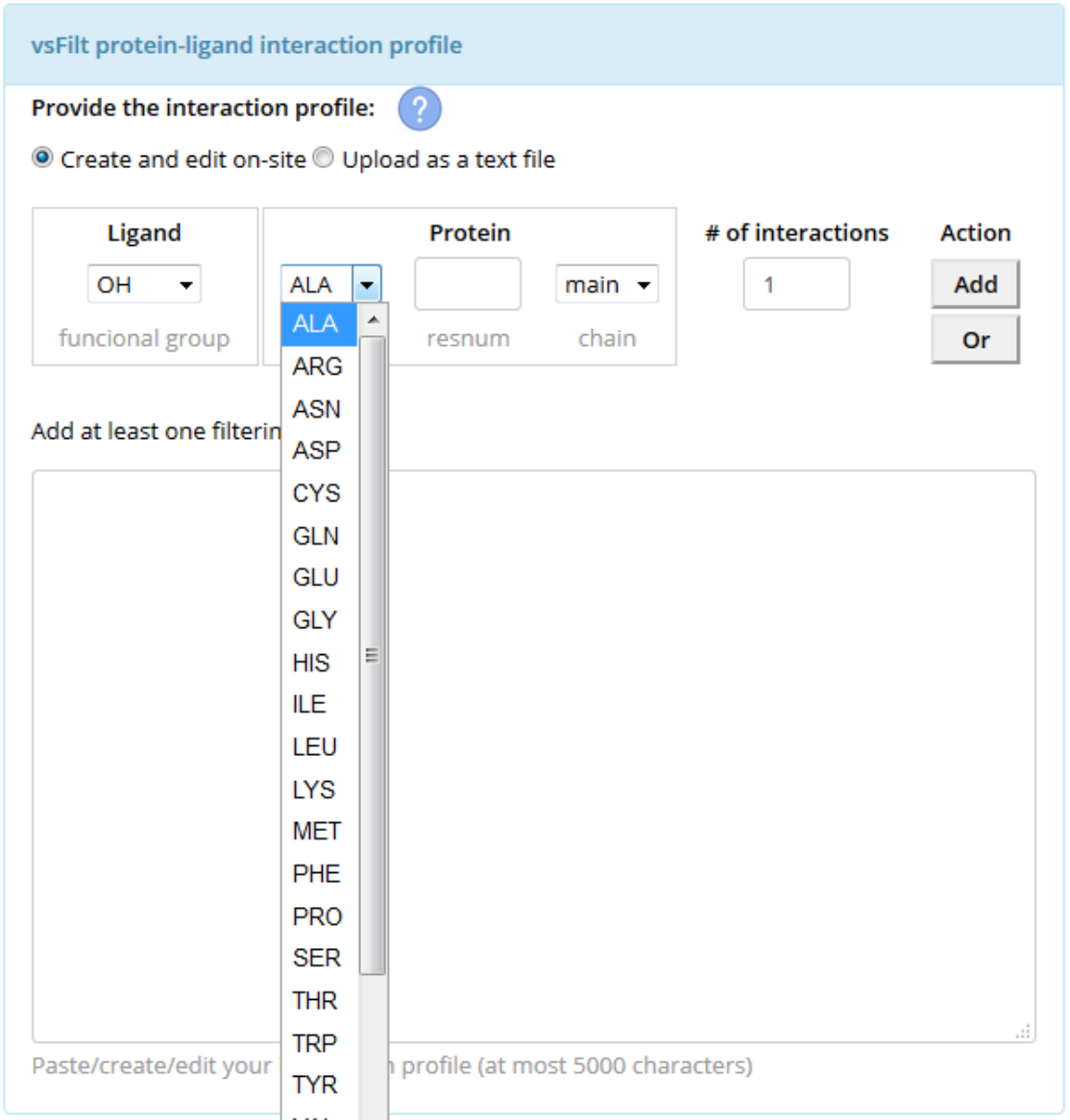

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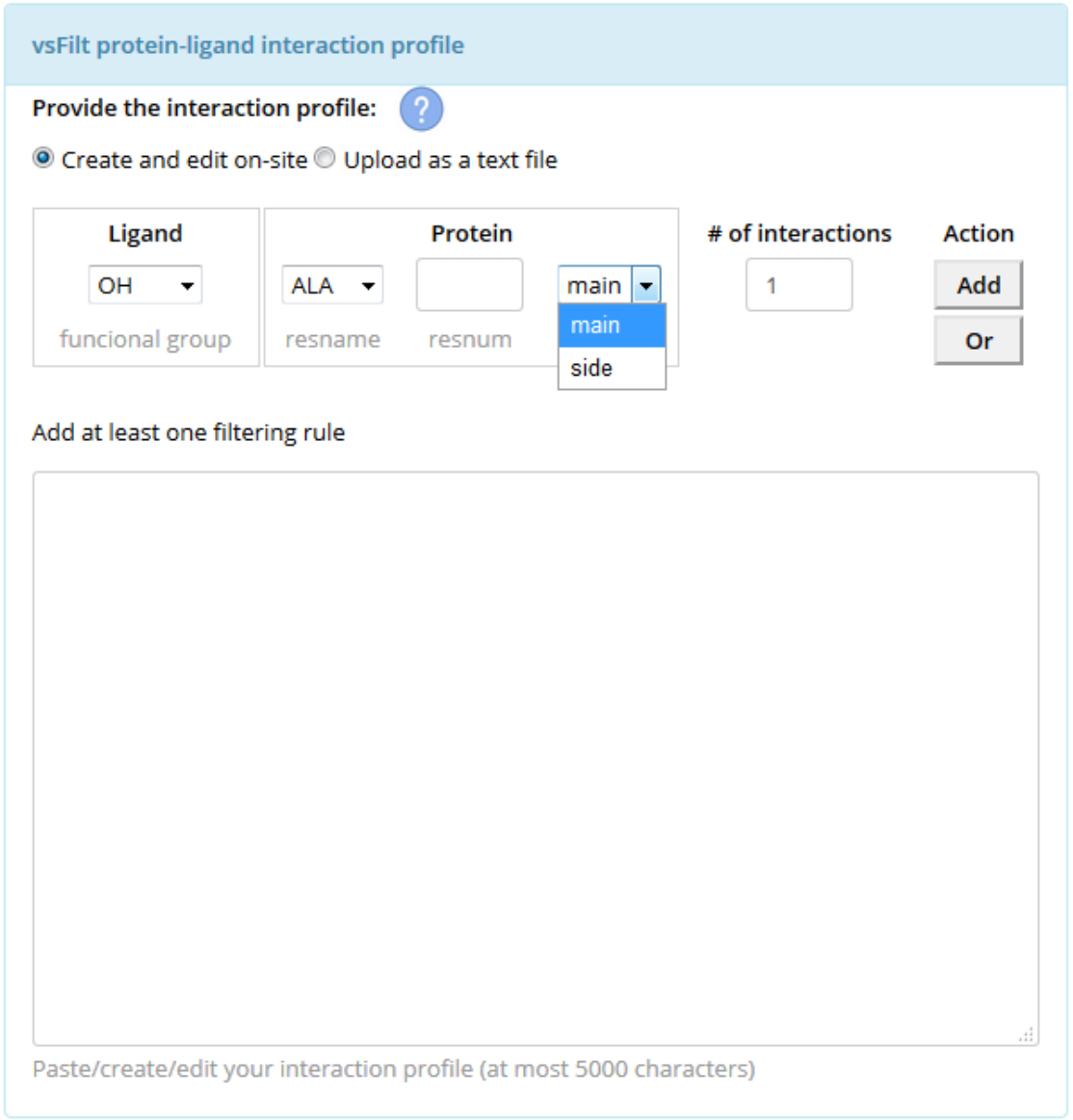

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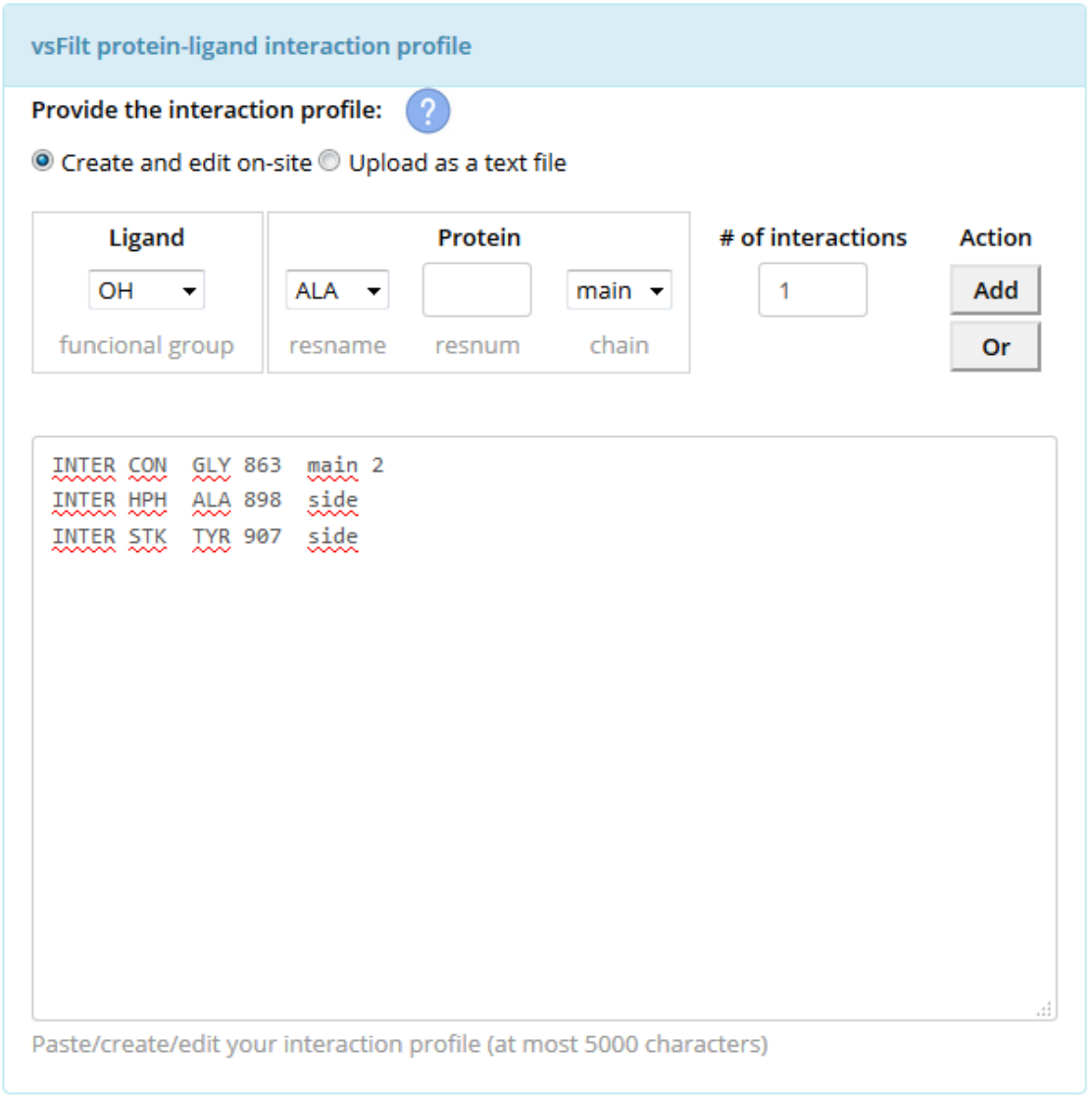
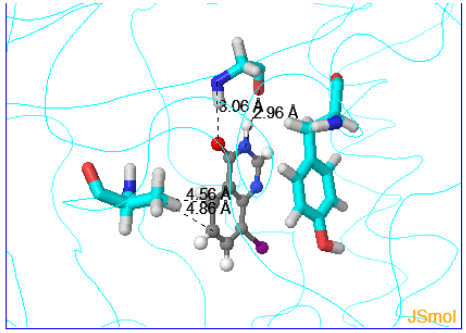


Online analysis

https://biokinet.belozersky.msu.ru/vsfilt

Analysis of the vsFilt results

Basic operations with the 3D-viewer: *Left-click-and-hold* and then *move your mouse* to rotate the structure, *Shift + Left-click-and-hold + Mouse Up/Down* to zoom in and out, *Ctrl + Right-click-and-hold + Mouse Up/Down/Left/Right* to move the structure in the viewer, *Right-click* for more options. Hold mouse pointer over selected amino acid for one second to view the label. Double click on a selected atom to activate the distance/angle measurement feature. For more refer to the *JSMol manual*.
Quick hints: Each ligand and its interactions with the protein residues that comply with the filtering rules can be visualized individually by clicking on the respective checkbox, or loaded all at once by using the buttons **Toggle all ligands** (i.e., all ligands that passed the structural filtration will be shown in the 3D-viewer), **Toggle residues** (i.e., all residues involved in accommodation of ligands that passed the structural filtration will be shown in the 3D-viewer) and **Toggle interactions** (i.e., all interactions will be shown between ligands and residues previously enabled in the 3D-viewer). Click on a "cross" icon (⊗) to hide the info for particular ligand (i.e., row) from the table. To restore all rows use the **Restore all rows** button. To highlight a ligand (row) in the table click on any cell (i.e., this feature can help to work with large tables).



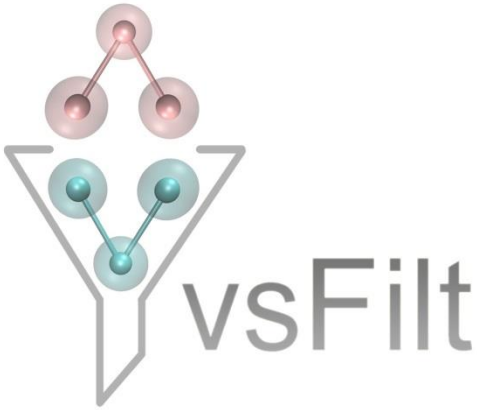
Viewport: *420x300, 840x600, 1260x900, 1680x1200*. **Rendering of *static* image:** *antialias on (slower), antialias off (faster)*. **Rendering of *dynamic* image:** *all features (slower), no antialiasing, no translucency, surfaces dotted, cartoons as trace, geosurfaces as dots, ellipsoids as dots, wireframe only (faster).*

Last action with the 3D-viewer: you have enabled ligand ZINC26894394 ranked #1

Operate PDB Heteatoms: ☐ Show/Hide water ☐ Show/Hide ligands ☐ Show/Hide ions

Operate Ligands: Toggle all ligands | Toggle residues | Toggle interactions | Restore all rows

Show/Hide	Rank	Ligand ID	Score	List of interactions	Hide row
☑	1	ZINC26894394	-9.968	GLY:863 *main* O ··· N *amide* **CON** GLY:863 *main* N ··· O *amide* **CON** ALA:898 *side* CB ··· C *aromatic* **HPH** ALA:898 *side* CB ··· C *aromatic* **HPH** TYR:907 *side* **centroid** ··· **centroid** *aromatic* **STK**	⊗
☐	2	ZINC19522823	-9.364	GLY:863 *main* N ··· O *amide* **CON** GLY:863 *main* N ··· O *amide* **CON** ALA:898 *side* CB ··· C *aliphatic* **HPH** ALA:898 *side* CB ··· C *aliphatic* **HPH** TYR:907 *side* **centroid** ··· **centroid** *aromatic* **STK**	⊗



- free (no login required);
- can be combined with any type of docking software;
- implemented using HTML 5;
- processes an SDF library of up to 150 000 docked ligand poses

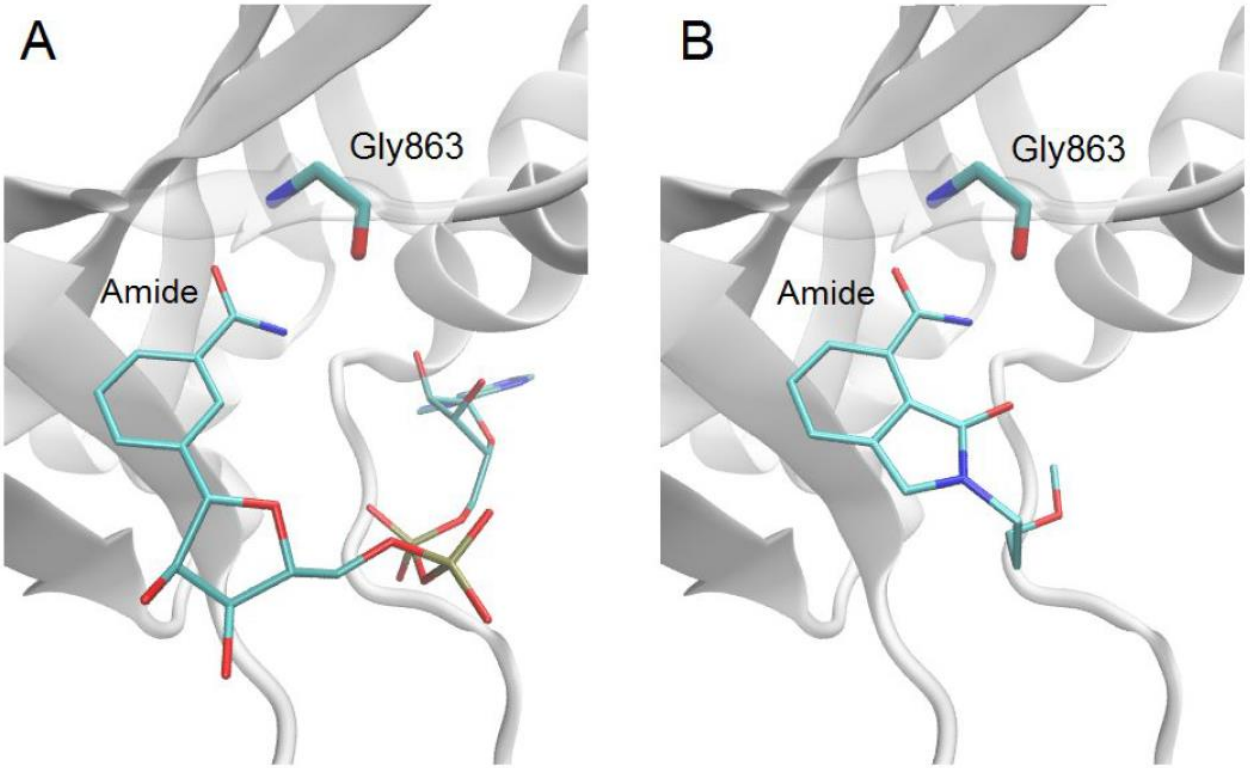
User data is protected by:

- unique access code (TaskID);
- use of HTTPS protocol;
- optional IP/password-based authentication

DEMO mode: ~9000 ligands, takes ~2 min

vsFilt

Illustrative example: PARP ligands



vsFilt

Illustrative example: PARP ligands

- 236 026 compounds containing a benzamide substructure (classical PARP-1 inhibitor scaffold) from the ZINC12 library;
- Docking with Lead Finder;
- Structural filtration with vsFilt

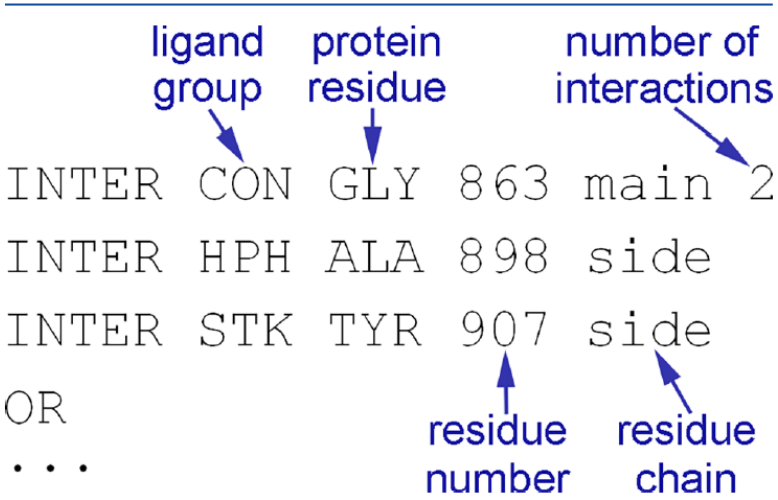
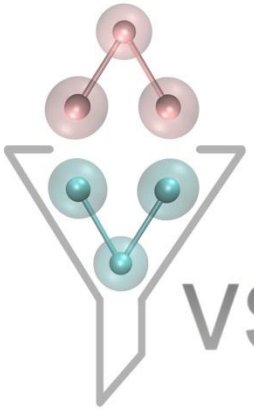


Figure 1. Example of control data used by vsFilt for structural filtration.



Illustrative example: PARP ligands

Table 2. Number of Ligands Selected by vsFilt among 236 026 Benzamide Derivatives by Applying Structural Criteria with "Angle Constraints" and "Tight Constraints" Options

interaction	angle constraints	tight constraints	number of ligands
CON···Gly863	–	–	8814
CON···Gly863	+	–	8199
CON···Gly863	+	+	1857
CON···Gly863 HPH···Ala898 STK···Tyr907	+	+	604 (0.26 %)

vsFilt

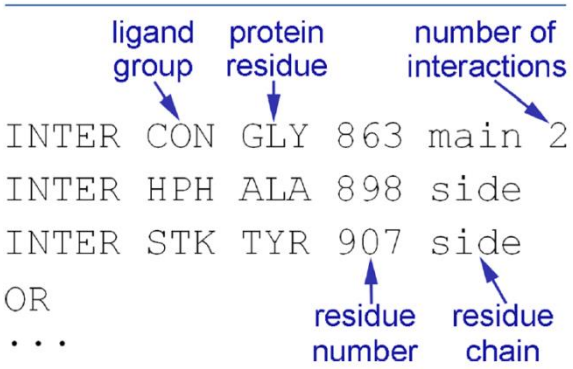
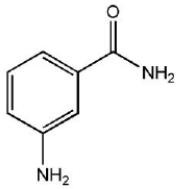
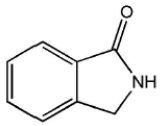
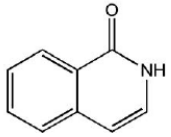
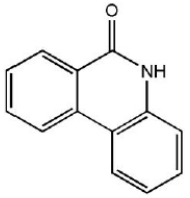
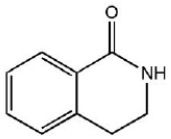
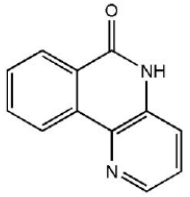
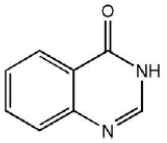
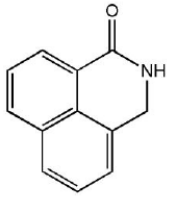


Figure 1. Example of control data used by vsFilt for structural filtration.

Illustrative example: PARP ligands

Scaffold	Number of ligands	Scaffold	Number of ligands
	43		8
	28		6
	8		1
	315		6

vsFilt

Illustrative example: PARP ligands

ligand group | protein residue | number of interactions

```
INTER CON GLY 863 main 2
INTER HPH ALA 898 side
INTER STK TYR 907 side
OR
...
```

residue number | residue chain

Figure 1. Example of control data used by vsFilt for structural filtration.

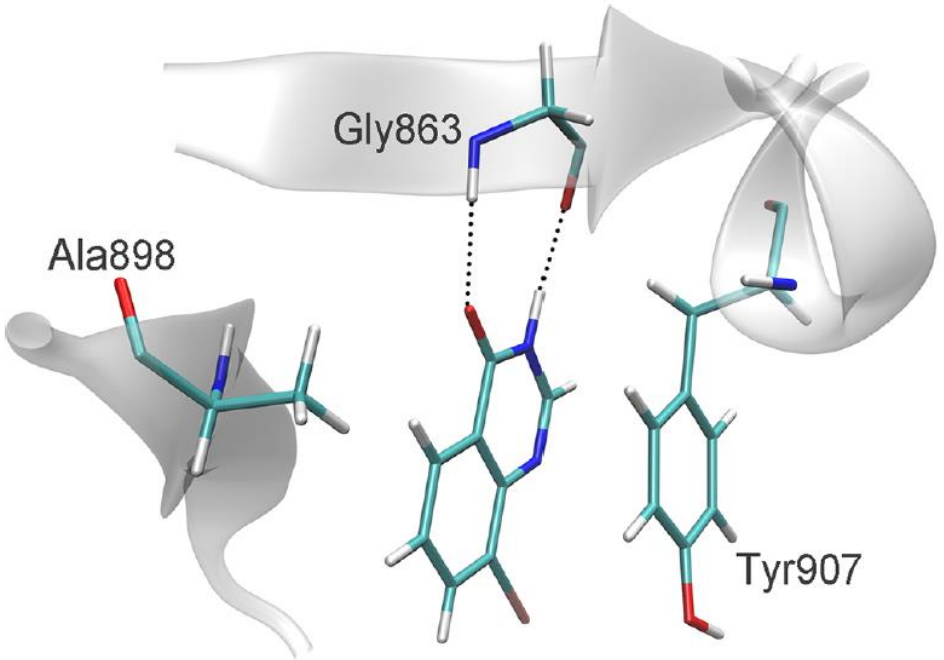
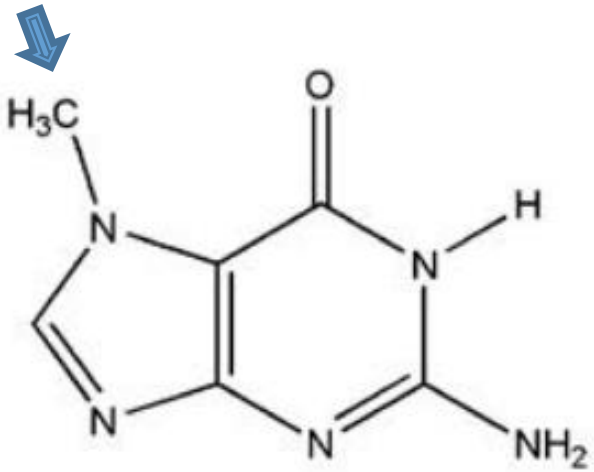


Figure 3. Interactions of ZINC26894394 ligand with the active site residues in the PARP-1 model: H-bonds with Gly863, hydrophobic contact with Ala863, and π-stacking with Tyr907. The ligand pose was selected by vsFilt and visualized using VMD 1.9.2.[26]

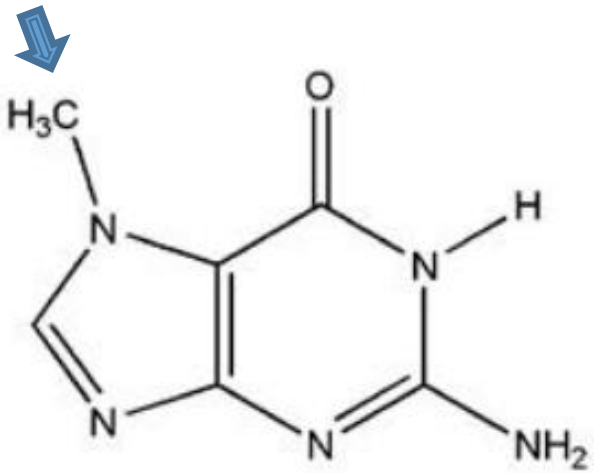
Пример: 7-Метилгуанин (7-МГ):



- Метаболит РНК и ДНК
- В небольшой концентрации обнаруживается в моче
- Не используется для синтеза нуклеотидов и не встраивается в ДНК

Weissmann et al. *J. Biol. Chem.* (1957) 224, 407-422
Kaina et al. *Mutat. Res.* (1983) 108, 279-292
Svoboda et al. *Anal. Biochem.* (2004) 334, 239-250

Пример: 7-Метилгуанин (7-МГ):



- Метаболит РНК и ДНК
- В небольшой концентрации обнаруживается в моче
- Не используется для синтеза нуклеотидов и не встраивается в ДНК
- Ингибитор ПАРП-1

Weissmann et al. *J. Biol. Chem.* (1957) 224, 407-422
Kaina et al. *Mutat. Res.* (1983) 108, 279-292
Svoboda et al. *Anal. Biochem.* (2004) 334, 239-250
Nilov et al. *Int. J. Mol. Sci.* (2020) 21, 2159

Биохимические исследования

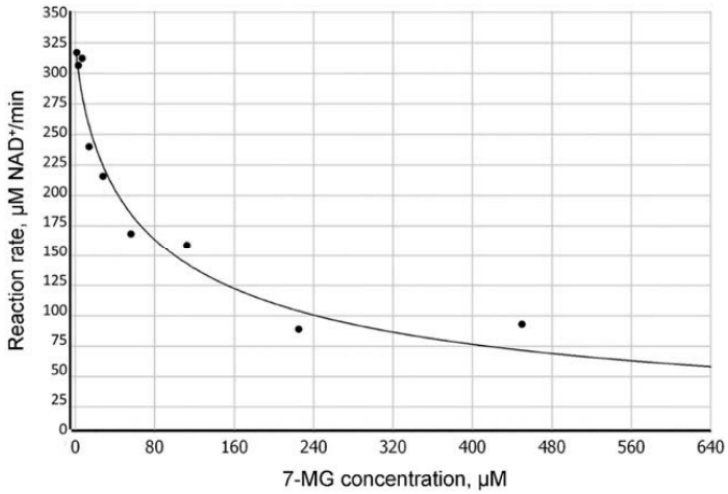
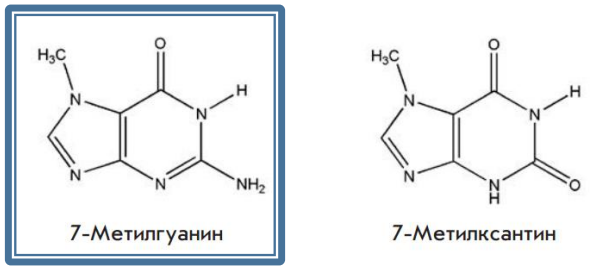


Figure 2. Dependence of the PARP-1-catalyzed reaction rate on the concentration of 7-MG inhibitor determined by fluorescence anisotropy (100 μM NAD^+ concentration).

- Конкурентный ингибитор
- $K_i \approx 10$ мкМ



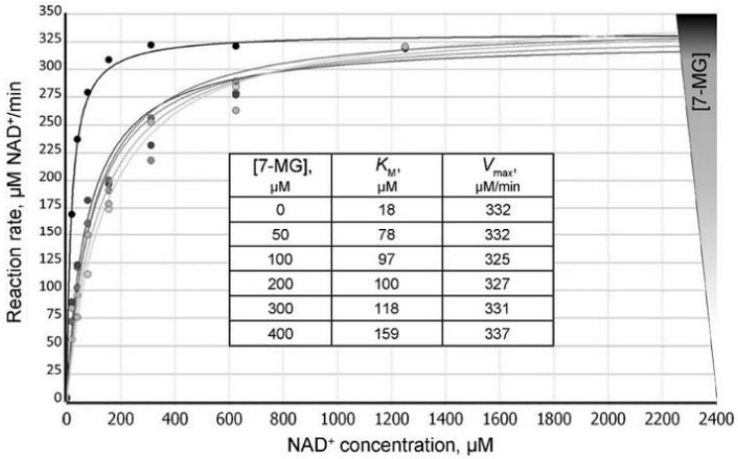


Figure 3. Dependence of the PARP-1-catalyzed reaction rate on the NAD^+ concentration at different concentrations of 7-MG added to the reaction mixture. Insert: calculated K_M^{app} values increase with increasing 7-MG concentrations, thus demonstrating the competitive inhibition mechanism.

Молекулярное моделирование

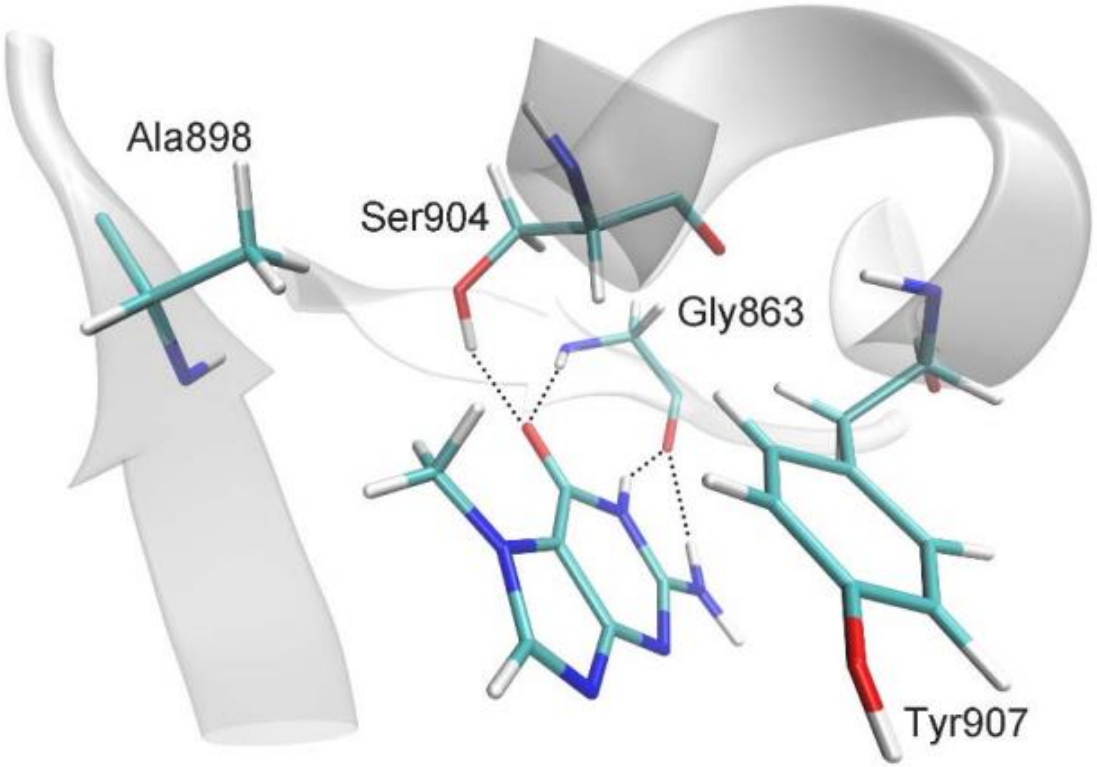


Figure 1. Interactions of 7-MG molecule in the PARP-1 active site revealed by MD simulation: hydrogen bonds with Gly863 and Ser904, π-stacking of purine rings with Tyr907, and hydrophobic contact between the 7-MG methyl group and Ala898.

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Nilov et al. *Int. J. Mol. Sci.* (2020) 21, 2159
Manasaryan et al. *Cancers* (2021) 12, 1201

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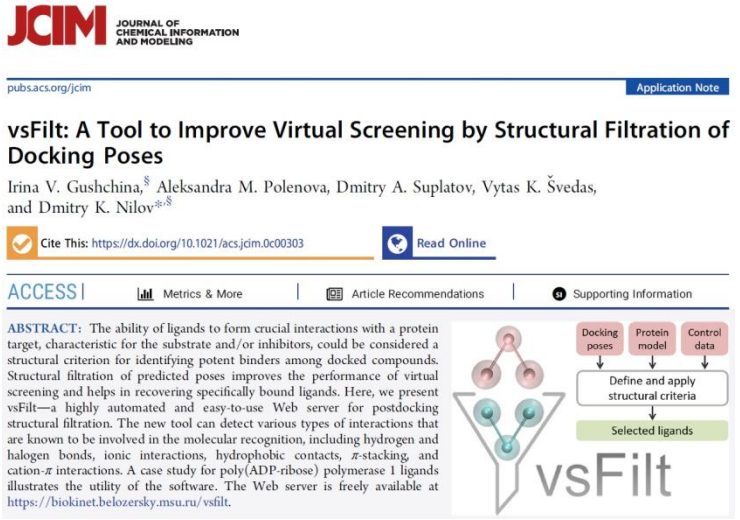
РФФИ

Gushchina et al. *J. Chem. Inf. Mod.* (2020) 60, 3692-2696


JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim Application Note

vsFilt: A Tool to Improve Virtual Screening by Structural Filtration of Docking Poses

Irina V. Gushchina,[§] Aleksandra M. Polenova, Dmitry A. Suplatov, Vytas K. Švedas, and Dmitry K. Nilov[*,§]

Cite This: https://dx.doi.org/10.1021/acs.jcim.0c00303 Read Online

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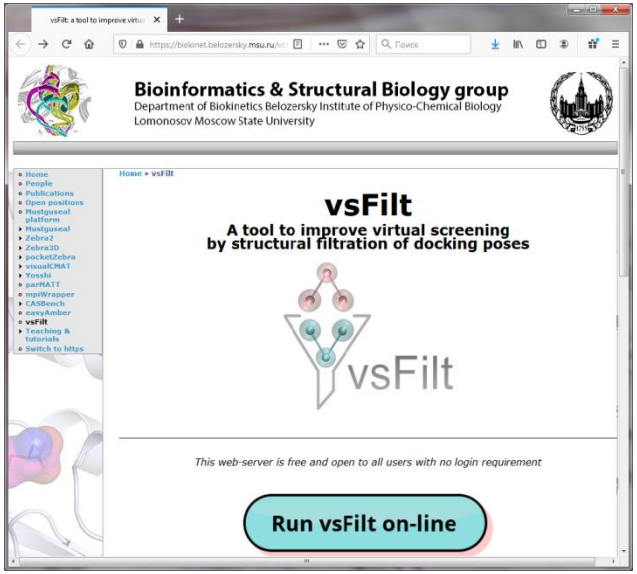
ABSTRACT: The ability of ligands to form crucial interactions with a protein target, characteristic for the substrate and/or inhibitors, could be considered a structural criterion for identifying potent binders among docked compounds. Structural filtration of predicted poses improves the performance of virtual screening and helps in recovering specifically bound ligands. Here, we present vsFilt—a highly automated and easy-to-use Web server for postdocking structural filtration. The new tool can detect various types of interactions that are known to be involved in the molecular recognition, including hydrogen and halogen bonds, ionic interactions, hydrophobic contacts, π-stacking, and cation-π interactions. A case study for poly(ADP-ribose) polymerase 1 ligands illustrates the utility of the software. The Web server is freely available at https://biokinet.belozersky.msu.ru/vsfilt.

https://biokinet.belozersky.msu.ru/vsfilt



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