CSM-lig: a web server for assessing and comparing protein-small molecule affinities

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Supplementary Material

1 Figures

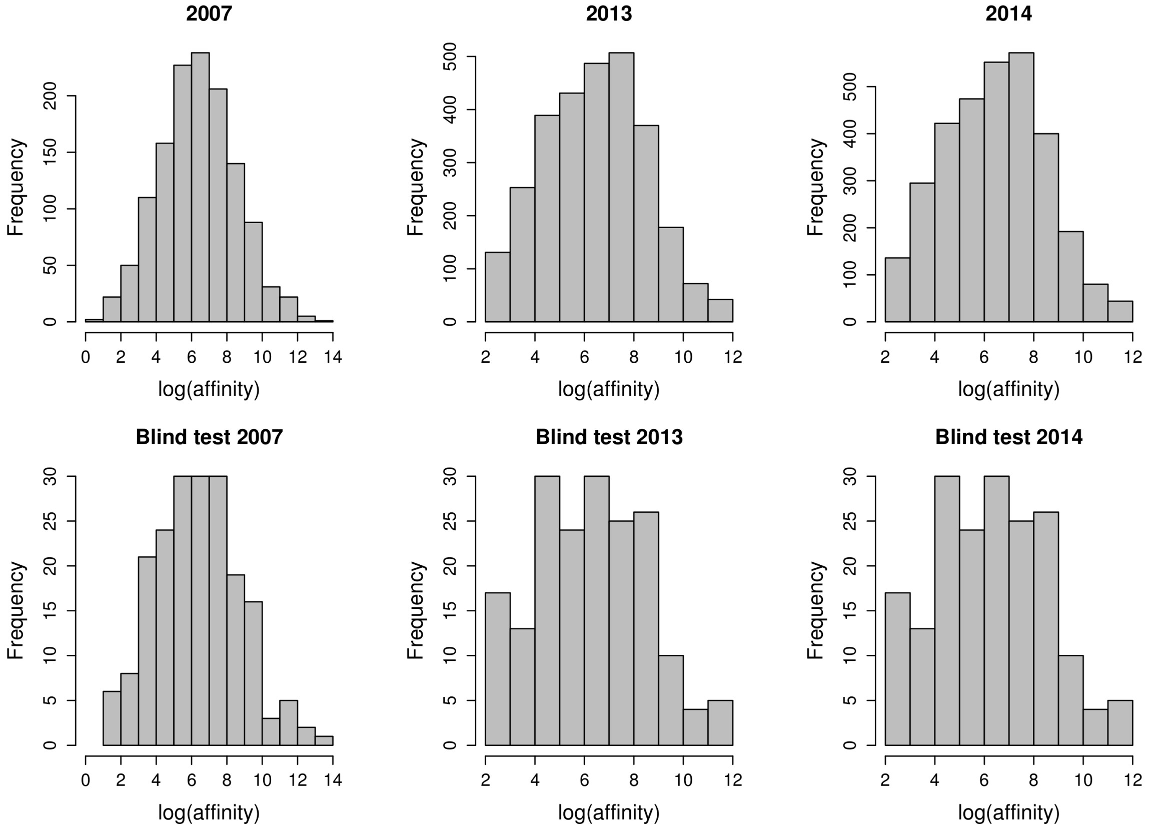

Figure 1: Distribution of experimental affinities for protein-ligand complexes in different PDBbind releases. The distribution of affinities for the blind tests (core sets) are also shown.).

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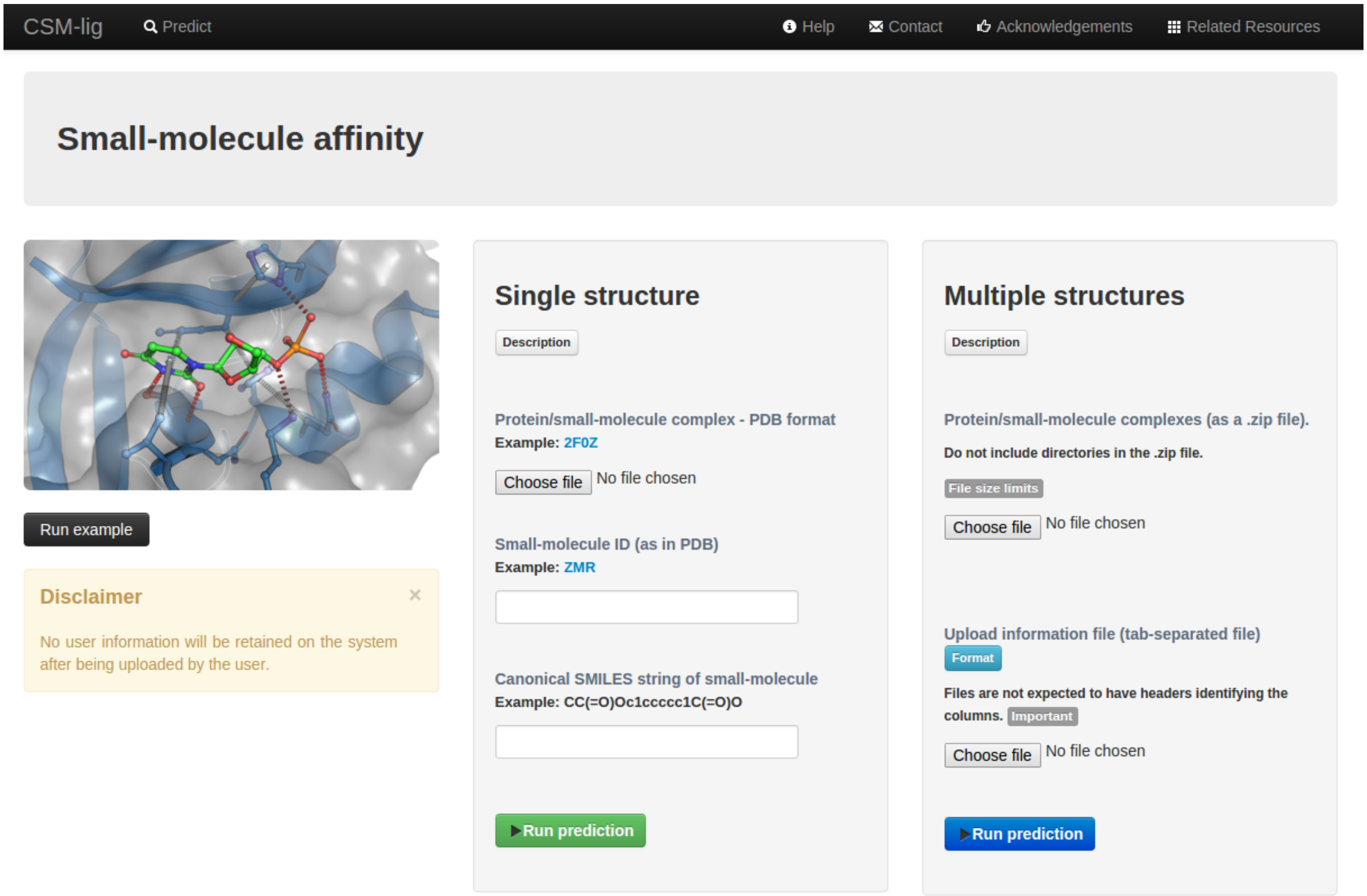

Small-molecule affinity

Disclaimer

No user information will be retained on the system after being uploaded by the user.

Single structure

Protein/small-molecule complex - PDB format
Example: 2F0Z

No file chosen

Small-molecule ID (as in PDB)
Example: ZMR

Canonical SMILES string of small-molecule
Example: CC(=O)Oc1ccccc1C(=O)O

Multiple structures

Protein/small-molecule complexes (as a .zip file).

Do not include directories in the .zip file.

No file chosen

Upload information file (tab-separated file)

Files are not expected to have headers identifying the columns.

No file chosen

Figure 2: CSM-Lig job submission interface. Users have the option to perform CSM-Lig predictions on a single uploaded structure or in multiple structures uploaded in a compressed file.

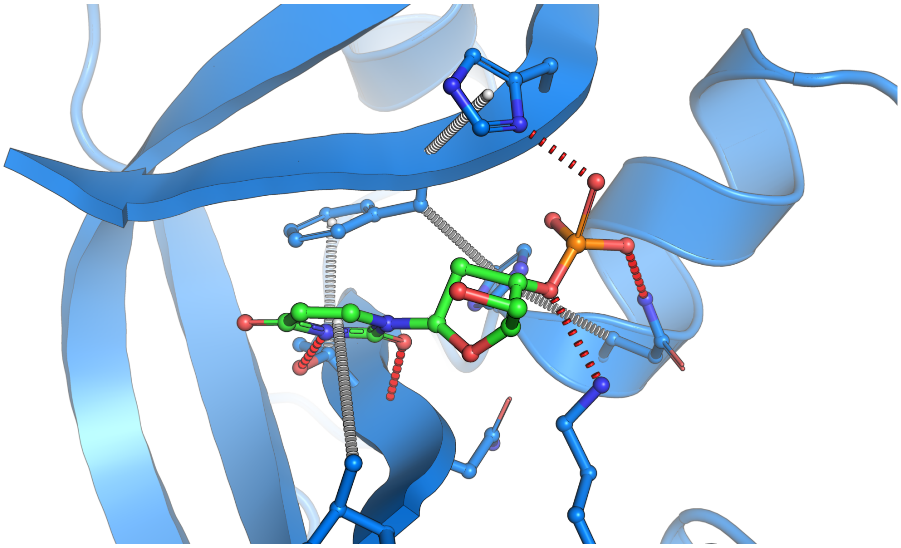

Figure 3: Example of visualization of protein-small molecule interactions generated by Arpeggio (Jubb H and Blundell TL, Unpublished Data) and made available on CSM-Lig. Hydrogen bonds are shown as red dashes and carbon-pi interactions as grey dashes. PDB ID: 1W4P was used.

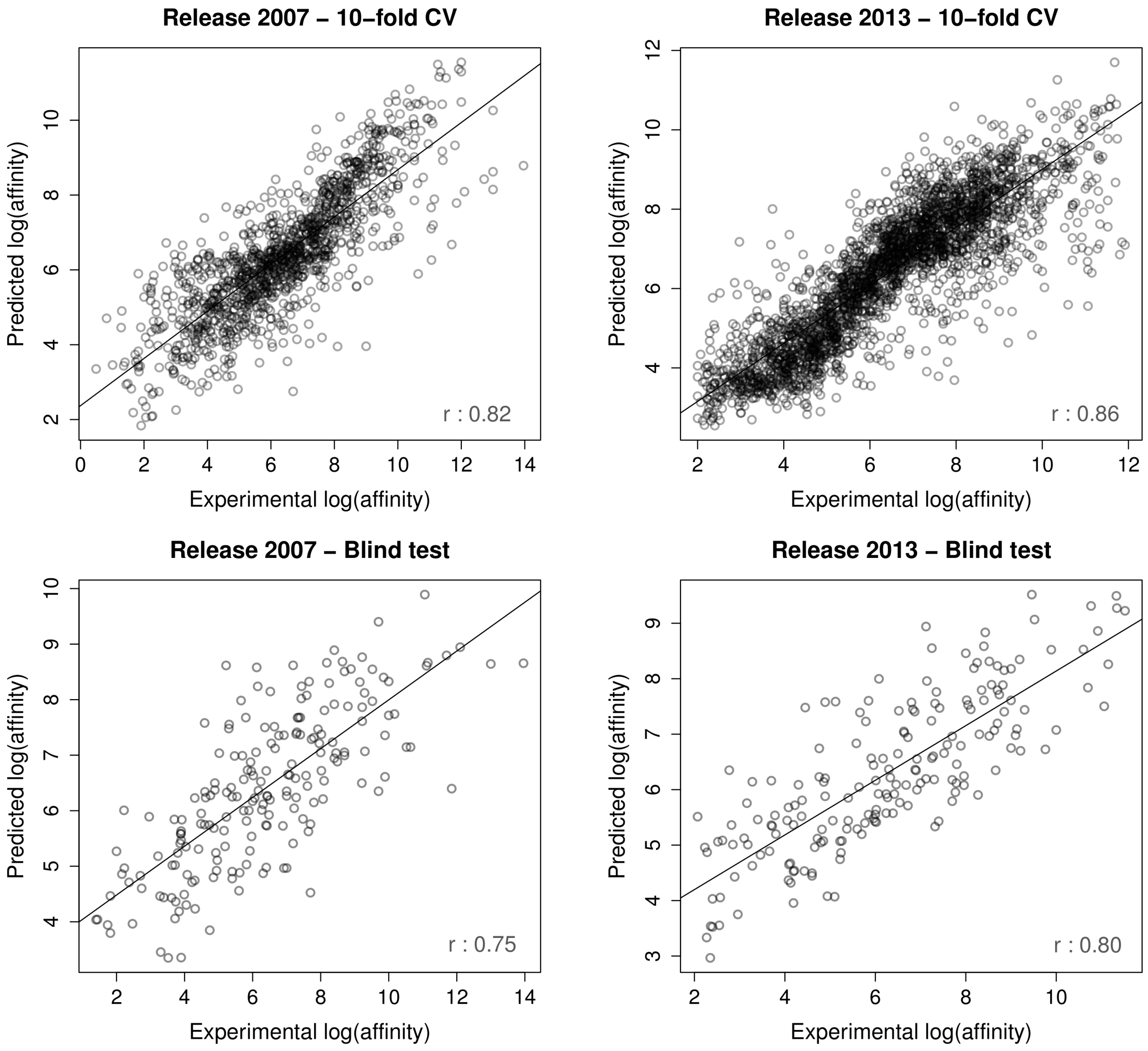

Figure 4: Regression plot between experimental and predicted affinities by CSM-lig on the PDBbind 2007 and 2013 releases. The graph on the top depicts the performance of CSM-lig over 10-fold cross validation, achieving a Pearsons correlation of 0.82 on release 2007 and 0.86 on release 2013. The performance in blind tests for these the 2007 and 2013 releases was 0.75 and 0.80, respectively.

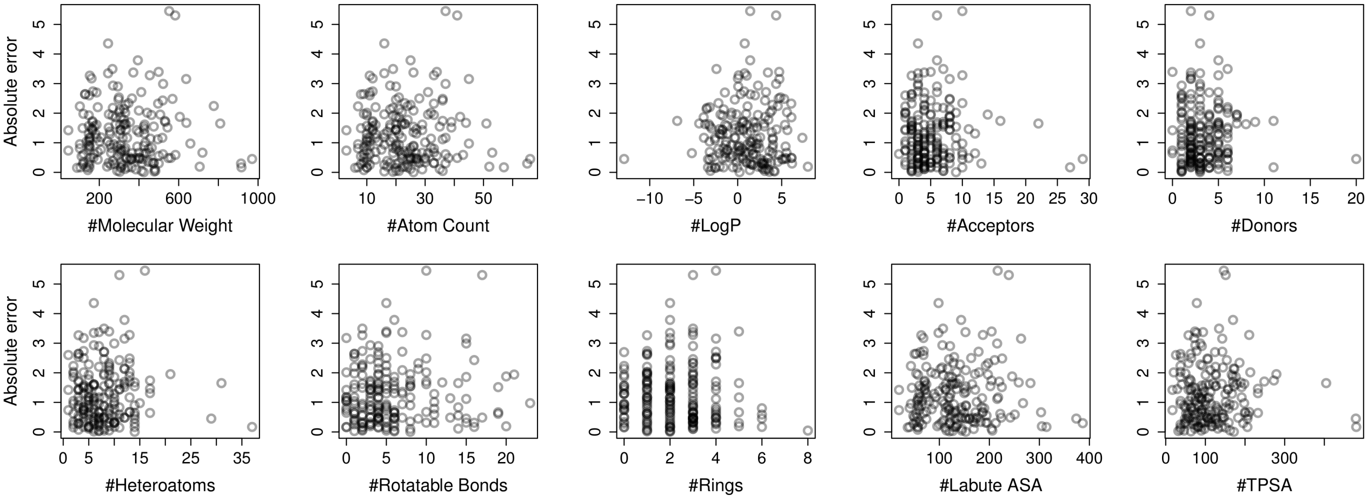

Figure 5: Regression plot between absolute errors of predictions and small-moluce properties on the PDBbind 2007 blind test. No significant correlation has been identified.

2 Tables

Table 1: List of molecular properties of the small molecule included in the CSM-Lig signatures. Properties were calculated with the Python RDKit library.

Property	Numerical type
Molecular weight	Real
Heavy atoms	Integer
LogP [1]	Real
#Acceptors	Integer
#Donors	Integer
#Heteroatoms	Integer
#Rotatable bonds	Integer
#Rings	Integer
Labute's Approximate Surface Area	Real
Topological Polar Surface Area	Real

Table 2: List of methods used in comparative experiments.

Method/Scoring Function	Reference
RF-Score::Elem-v2	[2]
RF-Score::Elem-v1	[3]
X-Score::HMScore	[4]
DrugScore^{CSD}	[5]
SYBYK::ChemScore	[6]
DS::PLP1	[7]
GOLD::ASP	[8]
SYBYL::G-Score	[9]
DS::LUDI3	[10]
DS::LigScore2	[11]
GlideScore-XP	[12]
DS::PMF	[13]
GOLD::ChemScore	[14]
SYBYL::D-Score	[9]
IMP::RankScore	[15]
DS::Jain	[16]
GOLD::GoldScore	[17]
SYBYL::PMF-Score	[9]
SYBYL::F-Score	[9]

3 CSM-lig Approach

CSM-lig is an efficient machine learning approach for assessing and comparing protein-small molecule affinities from solved structures. The method calculates structural features using the CSM algorithm [18] (called signatures) that together with experimental data are used as evidence to train and test predictive models.

A series of graph-based signatures can be achieved by modelling proteins/small molecule recognition as atomic graphs. The CSM algorithm will then extract distance patterns between its components as described in Algorithm 1.

Algorithm 1 Cutoff Scanning Matrix (CSM) calculation

```
**function** $CSM_{lig}(LigandSet, AtomClass, D_{MIN}, D_{MAX}, D_{STEP})$
    **for all** Ligand $i \in (LigandSet)$ **do**
        $LigandPocket =$ extractLigandPocket($Ligand$)
        $j = 0$
        $distMatrixInter \leftarrow$ calculateAtomicPairwiseDistInter($LigandPocket$)
        **for** $dist \leftarrow D_{MIN}$; **to** $D_{MAX}$; **step** $D_{STEP}$ **do**
            **for all** Class $\in (AtomClass)$ **do**
                $CSM_{lig}[i][j] \leftarrow$ getFrequency($distMatrixInter$, $dist$, $class$)
                $j{+}{+}$
        $distMatrixIntra \leftarrow$ calculateAtomicPairwiseDistIntra($LigandPocket$)
        **for** $dist \leftarrow D_{MIN}$; **to** $D_{MAX}$; **step** $D_{STEP}$ **do**
            **for all** Class $\in (AtomClass)$ **do**
                $CSM_{lig}[i][j] \leftarrow$ getFrequency($distMatrixIntra$, $dist$, $class$)
                $j{+}{+}$
        addLigandProperties($CSM_{lig}[i]$)
    **return** $CSM_{lig}$
**end**
```

The Algorithm receives a set of protein-ligand complexes, a set of atom classes and distance cutoffs (minimum, maximum and a cutoff step). The ligand pockets are extracted and a cummulative distribution of atoms within each distance (based on the cutoff parameters) is calculated per atom class. The distances are calculated separately in two components: intra-pocket distances, which aim to model pocket geometry and physicochemical properties and inter-complex distances, which aim to account for protein-ligand interactions. After this process, a set of ligand properties (Table 1 of Supplementary Material) are calculated and appended to the signatures.

References

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