ProteinLigandBenchmarks Documentation

plbenchmark

Sep 02, 2022

CONTENTS:

CHAPTER

ONE

INSTALLING THE PROTEIN LIGAND BENCHMARK SET

The Protein Ligand Benchmark Set is currently only installable from source.

1.1 Installation from Source

The repository uses git-lfs (large file storage) for the storage of all the data file. Ideally git-lfs is installed first before cloning the repository.

```
conda create -n plbenchmark python=3.7 git-lfs
conda activate plbenchmark
git lfs clone https://github.com/openforcefield/protein-ligand-benchmark.git
cd protein-ligand-benchmark
conda env update --file environment.yml
pip install -e .
```

CHAPTER

TWO

EXAMPLE NOTEBOOK: PROTEIN-LIGAND-BENCHMARK

2.1 Related Publication

The preprint on "Best practices for constructing, preparing, and evaluating protein-ligand binding affinity benchmarks" provides accompanying information to this benchmark dataset and how to use it for alchemical free energy calculations. For any suggestions of improvements please raise an issue in its GitHub repository.

[1]:
```
from plbenchmark import targets
from IPython.core.display import HTML
```

```
Warning: Unable to load toolkit 'OpenEye Toolkit'. The Open Force Field Toolkit does not␣
↪require the OpenEye Toolkits, and can use RDKit/AmberTools instead. However, if you␣
↪have a valid license for the OpenEye Toolkits, consider installing them for faster␣
↪performance and additional file format support: https://docs.eyesopen.com/toolkits/
↪python/quickstart-python/linuxosx.html OpenEye offers free Toolkit licenses for␣
↪academics: https://www.eyesopen.com/academic-licensing
```

2.2 Get the whole set of targets in the dataset

[2]:
```
# it is initialized from the `plbenchmark/sample_data/targets.yml` file
target_set = targets.TargetSet()
# to see which targets are available, one can get a list of names
target_set.get_names()
```

[2]:
```
['mcl1_sample']
```

The `TargetSet` is a `Dict`, but can be converted to a `pandas.DataFrame` or a `html` string via `TargetSet.get_dataframe(columns=None)` or `TargetSet.get_html(columns=None)`. The default `None` for `columns` means that all columns are printed. One can also define a subset of columns as a `list`:

[3]:
```
HTML(target_set.get_html(columns=['name', 'fullname', 'pdb', 'references', 'numLigands',
↪'minDG', 'maxDG', 'associated_sets']))
```

```
/home/dhahn3/miniconda3/envs/plbenchmark/lib/python3.9/site-packages/pandas/core/dtypes/
↪cast.py:1638: UnitStrippedWarning: The unit of the quantity is stripped when␣
↪downcasting to ndarray.
  result[:] = values
```

[3]:
```
<IPython.core.display.HTML object>
```

A `target` can be accessed with its name in two ways

[4]:
```
mcl1 = target_set['mcl1_sample']
mcl1_2 = target_set.get_target('mcl1_sample')
```

2.3 The `Target` class

contains all the available information about one target of plbenchmark. It also has two member variables, `_ligand_set` and `_edge_set`, which contain the information about the available ligand and edges of the respective target. A `Target` can either be accessed from the `TargetSet` (see cell before) or initialized using its name via

[5]:
```
mcl1 = targets.Target('mcl1_sample')
# The data in the column is stored in a pandas.Series and can be accessed via
mcl1.get_dataframe(columns=None)
```

```
/home/dhahn3/miniconda3/envs/plbenchmark/lib/python3.9/site-packages/pandas/core/dtypes/
↪cast.py:1638: UnitStrippedWarning: The unit of the quantity is stripped when␣
↪downcasting to ndarray.
  result[:] = values
```

[5]:
```
associated_sets                                    [Schrodinger JACS]
comments            hydrophobic interactions contributing to binding
date                                                       2020-08-21
fullname           Induced myeloid leukemia cell differentiation ...
id                                                                99
ligands            [lig_23, lig_26, lig_27, lig_28, lig_29, lig_3...
name                                                     mcl1_sample
netcharge                                                         xx
pdb                                                             4HW3
references         {'calculation': ['10.1021/ja512751q', '10.1021...
numLigands                                                        15
maxDG                                      -6.1 kilocalorie / mole
minDG                                      -9.0 kilocalorie / mole
std(DG)                                     0.9 kilocalorie / mole
calculation        REP1http://dx.doi.org/10.1021/ja512751qREP2Wan...
pdblinks           REP1http://www.rcsb.org/structure/4HW3REP24HW3...
dtype: object
```

Access to the `EdgeSet` and `LigandSet` in different formats is achieved by

[6]:
```
mcl1_ligands = mcl1.get_ligand_set()
mcl1_ligands_df = mcl1.get_ligand_set_dataframe()
HTML(mcl1.get_ligand_set_html(columns = ['name', 'ROMol', 'measurement',
↪'DerivedMeasurement']))
```

[6]:
```
<IPython.core.display.HTML object>
```

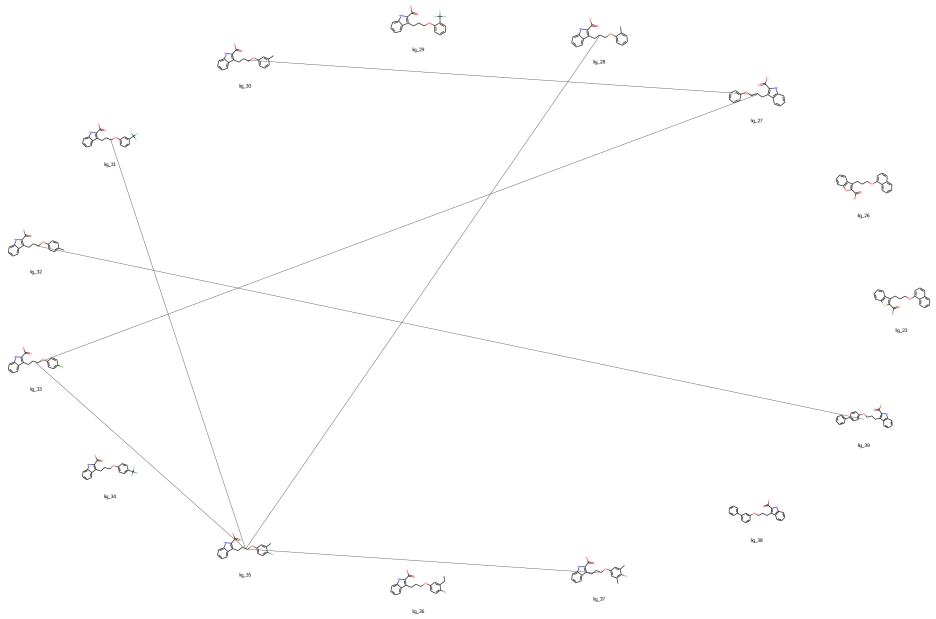
[7]:
```
mcl1_edges = mcl1.get_edge_set()
mcl1_edges_df = mcl1.get_edge_set_dataframe()
HTML(mcl1.get_edge_set_html())
```

```
/home/dhahn3/miniconda3/envs/plbenchmark/lib/python3.9/site-packages/pandas/core/dtypes/
↪cast.py:1638: UnitStrippedWarning: The unit of the quantity is stripped when␣
↪downcasting to ndarray.
  result[:] = values
```

[7]:
```
<IPython.core.display.HTML object>
```

Finally, the set out of ligands and edges can be visualized in a graph:

[8]:
```
graph = mcl1.get_graph()
```



nbsphinx-code-borderwhite

2.4 The `LigandSet` and `Ligand` class

The `LigandSet` consists of a `Dict` of `Ligands` which are availabe for one target. It is accessible via `Target.get_ligand_set()`, but can also be initialized directly.

[9]:
```
from plbenchmark import ligands
```

[10]:
```
mcl1_ligands = ligands.LigandSet('mcl1_sample')
HTML(mcl1_ligands.get_html())
```

```
/home/dhahn3/miniconda3/envs/plbenchmark/lib/python3.9/site-packages/pandas/core/dtypes/
↪cast.py:1638: UnitStrippedWarning: The unit of the quantity is stripped when␣
↪downcasting to ndarray.
  result[:] = values
```

[10]:
```
<IPython.core.display.HTML object>
```

The `Ligand` classes can be accessed from the `LigandSet` by their name. Each `Ligand` has information about experimental data, references, SMILES string and SDF file path of the docked structure. Additionally, there are functions to derive and process the primary data, which is then added to the `pandas.Series` as a new entry.

[11]:
```
lig_30 = mcl1_ligands['lig_30']
lig_27 = mcl1_ligands.get_ligand('lig_27')
```

2.5 The EdgeSet and Edge class

The EdgeSet contains a dict of Edges which are availabe for one target. It is accessible via Target.get_edge_set(), but can also be initialized directly.

[12]:
```
from plbenchmark import edges
```

[13]:
```
mcl1_edges = edges.EdgeSet('mcl1_sample')
HTML(mcl1_edges.get_html())
```

```
/home/dhahn3/miniconda3/envs/plbenchmark/lib/python3.9/site-packages/pandas/core/dtypes/
↪cast.py:1638: UnitStrippedWarning: The unit of the quantity is stripped when␣
↪downcasting to ndarray.
  result[:] = values
```

[13]:
```
<IPython.core.display.HTML object>
```

[14]:
```
mcl1_edges.keys()
```

[14]:
```
dict_keys(['edge_28_35', 'edge_30_27', 'edge_31_35', 'edge_33_27', 'edge_35_33', 'edge_
↪35_37', 'edge_39_32'])
```

The Edge classes can be accessed from the EdgeSet by their name. They are lightweight and provide only access to a pandas.DataFrame and a Dict:

[15]:
```
edge_30_27 = mcl1_edges.get_edge('edge_30_27')
df = edge_30_27.get_dataframe()
edge_30_27.get_dict()
```

[15]:
```
{'ligand_a': 'lig_30',
 'ligand_b': 'lig_27',
 'name': 'edge_30_27',
 'Mol1': <rdkit.Chem.rdchem.Mol at 0x7f1a3046e8e0>,
 'Smiles1': '[H]c1c(c(c2c(c1[H])C(=C(N2[H])C(=O)[O-
↪])C([H])([H])C([H])([H])C([H])([H])C([H])([H])Oc3c(c(c(c(c3[H])C([H])([H])[H])[H])[H])[H])[H])[H]
↪',
 'Mol2': <rdkit.Chem.rdchem.Mol at 0x7f1a30460700>,
 'Smiles2':
↪'[H]c1c(c(c(c(c1[H])[H])OC([H])([H])C([H])([H])C([H])([H])C2=C(N(c3c2c(c(c(c3[H])[H])[H])[H])[H])C(=O
↪])[H])[H]',
 'exp. DeltaG [kcal/mol]': 1.73 <Unit('kilocalorie / mole')>,
 'exp. Error [kcal/mol]': 0.22 <Unit('kilocalorie / mole')>}
```

[ ]:

CHAPTER

THREE

DATA

3.1 Data file tree and file description

The data is organized as follows:

```
data
├── targets.yml                                # list of all targets and their directories
├── <date>_<target_name_1>                     # directory for target 1
    ├── 00_data                                #     metadata for target 1
        ├── edges.yml                          #         edges/perturbations
        ├── ligands.yml                        #         ligands and activities
        └── target.yml                         #         target
    ├── 01_protein                             #     protein data
        ├── crd                                #         coordinates
            ├── cofactors_crystalwater.pdb     #             cofactors and cyrstal waters
            └── protein.pdb                    #             aminoacid residues
        └── top                                #         topology(s)
            └── amber99sb-star-ildn-mut.ff     #             force field spec.
                ├── cofactors_crystalwater.top#                 Gromacs TOP file of␣
↪cofactors and crystal water
                ├── protein.top                #                 Gromacs TOP file of␣
↪amino acid residues
                └── *.itp                      #                 Gromacs ITP file(s) to␣
↪be included in TOP files
    └── 02_ligands                             #     ligands
    ├── lig_<name_1>                           #          ligand 1
        ├── crd                                #              coordinates
            └── lig_<name_1>.sdf               #                  SDF file
        └── top                                #              topology(s)
            └── openff-1.0.0.offxml            #                  force field spec.
                ├── fflig_<name_1>.itp         #                      Gromacs ITP file :␣
↪atom types
                ├── lig_<name_1>.itp           #                      Gromacs ITP file
                ├── lig_<name_1>.top           #                      Gromacs TOP file
                └── posre_lig_<name_1>.itp     #                      Gromacs ITP file :␣
↪position restraint file
    ├── lig_<name_2>                           #         ligand 2
    ...
    └── 03_hybrid                              #    edges (perturbations)
    ├── edge_<name_1>_<name_2>                 #         edge between ligand 1 and ligand␣
```

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```
↪2
│   │   └── water                          #             edge in water
│   │       ├── crd                        #                 coordinates
│   │       │   ├── mergedA.pdb            #                     merged conf based on␣
↪coords of ligand 1
│   │       │   ├── mergedB.pdb            #                     merged conf based on␣
↪coords of ligand 2
│   │       │   ├── pairs.dat              #                     atom mapping
│   │       │   └── score.dat              #                     similarity score
│   │       └── top                        #                 topology(s)
│   │           └── openff-1.0.0.offxml    #                     force field spec.
│   │               ├── ffmerged.itp       #                         Gromacs ITP file
│   │               ├── ffMOL.itp          #                         Gromacs ITP file
│   │               └── merged.itp         #                         Gromacs ITP file
│   ...
├── <date>_<target_name_2>                 # directory for target 2
...
```

CHAPTER

FOUR

CONTRIBUTIONS

- **Authors** David Hahn
- **Data Contributors The authors of the following publications, especially Vytautas Gapsys and Christina E. M. Schindler.**
  - V. Gapsys et al., Large scale relative protein ligand binding affinities using non-equilibrium alchemy, Chem. Sci., 2020,11, 1140-1152
  - Christina E. M. Schindler et al., Large-Scale Assessment of Binding Free Energy Calculations in Active Drug Discovery Projects, J. Chem. Inf. Model. 2020, 60, 11, 5457–5474
  - Laura Perez Benito et al., Predicting Activity Cliffs with Free-Energy Perturbation, J. Chem. Theory Comput. 2019, 15, 3, 1884–1895
- **Discussions and Suggestions** Christopher I. Bayly, Marko Breznik, Hannah E. Bruce Macdonald, John D.Chodera, Katharina Meier, Antonia S. J. S. Mey, David L. Mobley, Laura Perez Benito, Gary Tresadern, Gregory L. Warren and all members of the Open Force Field Initiative
- **Code review and discussions** Matt Thompson, Jeffrey Wagner

4.1 Related Publication

The preprint on "Best practices for constructing, preparing, and evaluating protein-ligand binding affinity benchmarks" provides accompanying information to this benchmark dataset and how to use it for alchemical free energy calculations. For any suggestions of improvements please raise an issue in its GitHub repository.

CHAPTER

FIVE

API DOCUMENTATION

5.1 Targets

targets.py Functions and classes for handling the target data.

class plbenchmark.targets.**Target**(*name: str*)

Class to store the data of one target.

add_ligand_data()

Adds data from ligands to plbenchmark.targets.target. Molecule images and the minimum and maximum affinity are added.

Returns
None

find_links()

Processes primary data to have links in the html string of the target data

Returns
None

get_dataframe(*columns=None*)

Access the target data as a pandas.DataFrame

Parameters
cols – list of columns which should be returned in the pandas.DataFrame

Returns
pandas.DataFrame

get_edge_set()

Get plbenchmark:edges:edgeSet associated with the target

Returns
plbenchmark:edges:edgeSet object

get_edge_set_dataframe(*columns=None*)

Get plbenchmark:edges:edgeSet associated with the target as a pandas.DataFrame

Parameters
columns – list of columns which should be returned in the pandas.DataFrame

Returns
plbenchmark:edges:edgeSet object

get_edge_set_html(*columns=None*)

Get `plbenchmark:edges:edgeSet` associated with the target in a html string

Parameters
columns – `list` of edge which should be returned

Returns
html string

get_graph()

Get a graph representation of the ligand perturbations associated with the target in a `matplotlib.figure`

Returns
`matplotlib.figure`

get_ligand_set()

Get `ligandSet` associated with the target

Returns
`plbenchmark.ligands.ligandSet` object

get_ligand_set_dataframe(*columns=None*)

Get `ligandSet` associated with the target in a `pandas.DataFrame`

Parameters
columns – `list` of columns which should be returned in the `pandas.DataFrame`

Returns
`pandas.DataFrame`

get_ligand_set_html(*columns=None*)

Get `ligandSet` associated with the target in a html string

Parameters
columns – list of columns which should be returned

Returns
html string

get_name()

Access the name of the target.

Returns
name as a string

class plbenchmark.targets.**TargetSet**(**arg*, ***kw*)

Class inherited from dict to store all available targets in plbenchmark.

get_dataframe(*columns=None*)

Convert targetSet class to `pandas.DataFrame`

Parameters
columns – `list` of columns which should be returned in the `pandas.DataFrame`

Returns
`pandas.DataFrame`

get_html(*columns=None*)

Access the `plbenchmark:targets:targetSet` as a HTML string

Parameters
cols – `list` of columns which should be returned in the `pandas.DataFrame`

Returns
HTML string

`get_names()`

Get a list of available target names

Returns
`list` of strings

`get_target(name)`

Accesses one target of the targetSet

Parameters
name – string name of the target

Returns
`plbenchmark.targets.target` class

`plbenchmark.targets.get_target_data_path(target)`

Gets the file path of the target data

Parameters
target – string with target name

Returns
list of directories (have to be joined with '/' to get the file path relative to the plbenchmark repository)

`plbenchmark.targets.get_target_dir(target)`

Gets the directory name of the target

Parameters
target – string with target name

Returns
string with directory name

`plbenchmark.targets.set_data_dir(path='/home/docs/checkouts/readthedocs.org/user_builds/plbenchmarks/checkouts/latest/plb`

Gets the directory name of the target

Parameters
path – string with path to data directory

5.2 Ligands

ligands.py Functions and classes for handling the ligand data.

`class plbenchmark.ligands.Ligand(d: dict, target: Optional[str] = None)`

Store and convert the data of one ligand in a `pandas.Series`.

`add_mol_to_frame()`

Adds a image file of the ligand to the `pandas.Dataframe`

Returns
None

`derive_observables(derived_type='dg', destination='DerivedMeasurement', out_unit=None)`

Derive observables from (stored) primary data, which is then stored in the `pandas.DataFrame`

Parameters

- **derived_type** – type of derived observable, can be any of 'dg' 'ki', 'ic50' or 'pic50'
- **destination** – string with column name for 'pandas.DataFrame' where the derived observable should be stored.
- **out_unit** – unit of type `pint` unit of derived coordinate

Returns
None

find_links()

Processes primary data to have links in the html string of the ligand data

Returns
None

get_coordinate_file_path()

Get file path relative to the plbenchmark repository of the SDF coordinate file of the docked ligand

Returns
file path as string

get_dataframe(*columns=None*)

Access the ligand data as a `pandas.Dataframe`

Parameters
columns – list of columns which should be returned in the `pandas.Dataframe`

Returns
`pandas.Dataframe`

get_html(*columns=None*)

Access the ligand as a HTML string

Parameters
columns – list of columns which should be returned in the `pandas.Dataframe`

Returns
HTML string

get_image()

Creates a molecule image.

Returns
`PIL.Image` object

get_molecule()

Get molecule object with coordinates of the docked ligand

Returns
file path as string

get_name()

Access the name of the ligand.

Returns
name: string

class plbenchmark.ligands.**LigandSet**(*target*, **arg*, ***kw*)

Class inherited from dict to store all available ligands of one target.

`get_dataframe`(*columns=None*)

Access the `ligandSet` as a `pandas.Dataframe`

Parameters
columns – `list` of columns which should be returned in the `pandas.Dataframe`

Returns
`pandas.Dataframe`

`get_html`(*columns=None*)

Access the `plbenchmark:ligands.ligandSet` as a HTML string

Parameters
columns – `list` of columns which should be returned in the `pandas.Dataframe`

Returns
HTML string

`get_ligand`(*name*)

Accesses one ligand of the `ligandSet`

Parameters
name – string name of the ligand

Returns
`plbenchmark.ligands.ligand` class

`get_list`()

Returns list of ligands

Returns
`list` of ligand names

`get_molecules`()

Returns a `dict` with names as keys and values as py:class:*openforcefield:topology:Molecule* objects

Returns
`dict`

5.3 Edges

edges.py Functions and classes for handling the perturbation edges.

`class` `plbenchmark.edges.Edge`(*d: dict*)

Store and convert the data of one perturbation (“edge”) in a `pandas.Series`.

Parameters
d – `dict` with the edge data

Returns
None

`add_ligand_data`(*ligand_set*)

Adds data from ligands to `edge`. Molecule images and the affinity difference are added.

Parameters
ligand_set – `plbenchmark:ligands:ligandSet` class of the same target

Returns
None

get_dataframe(*columns=None*)

Access the edge data as a pandas.DataFrame

Parameters
cols – list of columns which should be returned in the pandas.DataFrame

Returns
pandas.DataFrame

get_dict()

Access the edge data as a dict which contains the name of the edge as key and the names of the two ligands as list.

Returns
dict

get_name()

Access the name of the edge.

Returns
name as string

class plbenchmark.edges.**EdgeSet**(*target*, **arg*, ***kw*)

Class inherited from dict to store all available edges of one target.

get_dataframe(*columns=None*)

Access the plbenchmark:edges.edgeSet as a pandas.DataFrame

Parameters
cols – list of columns which should be returned in the pandas.DataFrame

Returns
pandas.DataFrame

get_dict()

Access the plbenchmark:edges.edgeSet as a dict which contains the name of the edges as key and the names of the two ligands in a list as items.

Returns
dict

get_edge(*name*)

Accesses one edge of the plbenchmark.edges.edgeSet

Parameters
name – string name of the edge

Returns
plbenchmark:edges:edge class

get_html(*columns=None*)

Access the plbenchmark:edges.edgeSet as a HTML string

Parameters
cols – list of columns which should be returned in the pandas.DataFrame

Returns
HTML string

5.4 Utils

utils.py Contains utility functions

plbenchmark.utils.**convert_error**(*error_value*, *value*, *original_type*, *final_type*, *temperature=300.0*, *out_unit=None*)

Converts an experimental value into another derived quantity with specified unit.

Parameters

- **error_value** – float, error of val, numerical value
- **value** – float, numerical value
- **original_type** – string, code for the original observable. Can be *dg*, *ki*, *ic50*, *pic50*
- **final_type** – string, code for the desired derived quantity. Can be *dg*, *ki*, *ic50*, *pic50*
- **temperature** – float, temperature in kelvin
- **out_unit** – unit of type `pint`, output unit of final_type, needs to fit to the requested final_type

Returns
`pint.Quantity` with desired unit

plbenchmark.utils.**convert_value**(*value*, *original_type*, *final_type*, *temperature=300.0*, *out_unit=None*)

Converts an experimental value into another derived quantity with specified unit.

Parameters

- **value** – float, numerical value
- **original_type** – string, code for the original observable. Can be *dg*, *ki*, *ic50*, *pic50*
- **final_type** – string, code for the desired derived quantity. Can be *dg*, *ki*, *ic50*, *pic50*
- **temperature** – float, temperature in kelvin
- **out_unit** – unit of type `pint`, output unit of final_type, needs to fit to the requested final_type

Returns
`pint.Quantity` with desired unit

plbenchmark.utils.**find_doi_url**(*doi*)

Finds the links to a digital object identifier (doi).

Parameters
doi – string

Returns
string compiled string including the urls to the publication

plbenchmark.utils.**find_pdb_url**(*pdb*)

Finds the links to a pdb or a list of pdb codes.

Parameters
pdb – string or list of strings

Returns
string compiled string including the urls to the pdb entries

CHAPTER

SIX

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