Tutorial of binding affinity prediction by MolAICal and OnionNet model

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1. Introduction

Deep learning model can be used to evaluate binding affinity between ligands and receptors. In this tutorial, OnionNet [1] is introduced to calculate binding affinity of ligands by MolAICal. This example can be for users to know quickly how deep learning predicts binding affinity between ligands and proteins. This tutorial can only run on Linux system. For more detailed MolAICal, please read this paper (https://doi.org/10.1093/bib/bbaa161).

2. Materials

2.1. Software requirement

1) MolAICal: https://molaical.github.io

2.2. Example files

1) All the necessary tutorial files are downloaded from:
https://github.com/MolAICal/tutorials/tree/master/014-bindingaffinityOnionnet

3. Procedure

3.1 Install OnionNet model

Currently, only Linux version of MolAICal is supported.

1) Click and open website: **DownloadModel**
Then go to the folder "AImodels--BindingAffinity--onionnet--linux" in the open website, download a file named "onionnet.tar.gz"

2) Move "onionnet.tar.gz" to the folder "MolAICal-xxx/mtools". Where "MolAICal-xxx" is your decompressed root directory of MolAICal. The folder "mtools" is the targeted directory.

3) Decompress file

```
#> tar -xzvf onionnet.tar.gz
```

And go to folder named OnionNet:

```
#> cd onionnet
```

4) install OnionNet model

```
#> chmod +x install.sh
#> ./install.sh
```

Until now, OnionNet model is installed completely.

3.2 Calculate binding affinity for one complex

3.2.1 Merge one protein and one ligand into a complex file

Open 014-bindingaffinityOnionnet

Then use the below command to prepare complex:
#> molaical.exe -model mergeon -r 1a30_protein.pdb -l 1a30_ligand.mol2.pdb -c 1a30_complex.pdb

Notice: if users do not have pdb format molecular file, they use the command of MolAICal to convert molecules in pdb format. For instance, users have mol2 format file, they can use the below command for format conversion (**Note:** molecule should have correct suffix so that MolAICal can recognize them automatically):
#> molaical.exe -tool format -i ligand.mol2 -o ligand.pdb

3.2.2 Calculate pKx (pKa or pKi) for binding affinity prediction

Put the merged complex files into a file. In this tutorial, this file named "inputlist.dat" contains complex file name. Then, using the below command for pKx calculation:
#> molaical.exe -model onionnet -i inputlist.dat -o results.csv

It will generate a file named results.csv that contains pKx value of one complex. If users want to convert pKx to binding free energy, they can refer to "https://molaical.github.io/tutorial.html" and MolAICal manual which part is involved in "Binding free energy from pKd or pKi".

3.3 Calculate binding affinity for many complexes

3.3.1 Merge many ligands one protein into many complex files

Sometimes, users want to calculate binding affinities of many ligands, under these circumstances, it needs to merge many ligands and one protein into many complex files.

Open 014-bindingaffinityOnionnet/list

Putting all ligand names into a file called "list.txt", in this part, the protein file is named to GCGRNoLigand.pdb. Then use the below command to merge one protein and many ligand flies:
#> molaical.exe -model mergeon -r GCGRNoLigand.pdb -f list.txt

It will produce files named "complex_<you ligand name>.pdb".

3.3.2 Calculate pKx (pKa or pKi) for binding affinity prediction

Put all merged complex files into a file called "complexList.txt", and then using the below command to calculate binding affinity:
#> molaical.exe -model onionnet -i complexList.txt -o results.csv

It will generate a file named results.csv that contains pKx values of many complexes. If users want to convert pKx to binding free energy, they can refer to "https://molaical.github.io/tutorial.html" and MolAICal manual which part is involved in "Binding free energy from pKd or pKi".

Reference

1. Zheng L, Fan J, Mu Y. OnionNet: a Multiple-Layer Intermolecular-Contact-Based Convolutional Neural Network for Protein-Ligand Binding Affinity Prediction. ACS Omega. 2019;4(14):15956-65. Epub 2019/10/09. doi: 10.1021/acsomega.9b01997. PubMed PMID: 31592466; PubMed Central PMCID: PMCPMC6776976.