Kinome Feature Database V1.0

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1. Introduction

The Kinome feature database is designed specifically for kinome-wide drug selectivity profiling using the PocketFEATURE program, an application which identifies novel protein-drug interactions by analyzing the similarity between protein pockets[1]. The database contains > 2800 kinase PDB structures available in the Invitrogen kinase panel and the prediction can be complemented by experimental validations.

2. Kinome Feature Database Search

2.1 Requirements

The kinome feature database search is required to be performed under the Mac or Linux computer system with Perl installation and Shell command line access. Please complete SimTK user signup and login before accessing the programs.

2.2 Program Execution

Step 1: Download and unzip the "Kinome_Example.zip" file from the SimTK website (https://simtk.org/projects/kdb). Make sure the scripts, "CompareTwoSetSites.pl" and "Run_Kinome.sh" are placed under the "Kinome_Example/" directory and with executable permission using the following command[2]:

chmod +x ./CompareTwoSetSites.pl

chmod +x ./Run_Kinome.sh

Step 2: For each query kinase inhibitor, identify the corresponding co-crystal structure from the protein data bank (PDB)(http://www.rcsb.org/pdb/home/home.do) and note the kinase PDB_ID, ligand_ID, residue_number. Next, under the "Kinome_Example/InputFiles" directory, create a text file named "inputlist.txt" listing the receptor information in the following order: PDB_ID, ligand_ID, residue_number of ligand separated by tab with one kinase structure per line as shown below:

PDB_ID ligand_ID residue_number

Multiple kinase can be placed in the “inputlist.txt” and searched the kinome database simultaneously.

Step 3: Under the “Kinome_Example/InputFiles” directory, run the following command:

./Kinome_run.sh

The script will search the kinome feature database for the kinase feature vector files (.ff extension) in the “inputlist.txt”. If found, the script will retrieve the corresponding feature vector files and compare them to the kinome feature database. The output of the kinome feature database search will be generated in the file “Kinome_Example/output.txt”. Users can also generate their own feature vector files using the PocketFeature package from the SimTK website (https://simtk.org/projects/pocketfeature).

2.3 Kinome-wide Inhibitor Selectivity Profiling Analysis

Step 1: Here, we present an example by profiling the kinase selectivity of one kinase drug, Sorafenib co-crystalized with B-Raf kinase (PDB ID: 1UWH).

Example output:

Field 1	Field 2	Filed 3	Filed 4	Field 5	Field 6	Field 7	Field 8	Field 9
1UWH_BAX_1723	1A9U_SB2_800	131	12	-4.198	12	-4.198	12	-4.198
…	…	…	…	…	…	…	…	…

Field 1: Query binding site

Field 2: Hit binding site from the kinome feature database search

Field 3: Number of comparable pairs of micro-environments

Field 4: Number of alignment above cutoff: -0.15

Field 5: Score of alignment above cutoff: -0.15

Field 6: Number of alignment above cutoff: -0.2

Field 7: Score of alignment above cutoff: -0.2

Field 8: Number of alignment above cutoff: -0.25

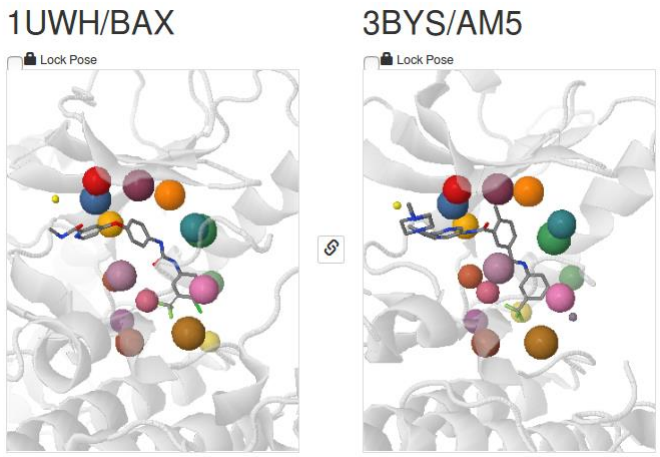
Field 9: Score of similarities above cutoff: -0.25

Step 2: To identified the on and off-target of the query ligand, we recommend initially sorting the PFS values with a cutoff of -0.2 (Field 7). A more negative score indicates a higher structure

similarity between two comparing sites and an increased probability of kinase cross-activities. As shown below, the intended target, B-Raf of Sarafenib (kd=260 nM) was identified with a PFS value of -15. In addition, one off-target LCK at rank 31, (kd=2.7 µM) reported by Karaman *et al.* was also identified with a PFS value of -7.5[3]:

Query: Sorafenib	Target Name	Field 1	Field 2	Field 3	Field 4	Field 5	Field 6	Field 7	Field 8	Field 9
Intended Target	B-RAF	1UWH_BAX_1723	1UWH_BAX_1723	227	25	-15	25	-15	25	-15
Off Target	LCK	1UWH_BAX_1723	3BYS_AM5_1	247	18	-7.501	18	-7.501	16	-7.26

To further visualize the output, structural alignment can be performed using the FeatureViz web-based visualization program (https://simtk.org/projects/feature-viz/). Below is an example output of pocketFEATURE-based structural alignment between B-RAF (PDB: 1UWH) and LCK (PDB: 3BYS). Note that balls of the same color indicate matching protein microenvironment pairs.



3. References

1. Liu, T. & Altman, R.B. Using multiple microenvironments to find similar ligand-binding sites: application to kinase inhibitor binding. *PLoS Comput Biol* **7**, e1002326 (2011).
2. Liu, T. & Altman, R.B. Identifying druggable targets by protein microenvironments matching: application to transcription factors. *CPT Pharmacometrics Syst Pharmacol* **3**, e93 (2014).
3. Karaman, M.W. et al. A quantitative analysis of kinase inhibitor selectivity. *Nat Biotechnol* **26**, 127-132 (2008).