Analyzing Patterns of Computational Similarity between Kinase Ligands

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Background and Overview

Background

Protein kinases are relevant to a large number of human pathologies, including cancer, immune disorders, and infectious diseases. Protein Kinases have been classified into several different groups (a.k.a. "families"). These classifications are based on sequence similarity, evolutionary conservation, and known functions.

The similarity property principle (SPP), has been enormously influential in the realm of medicinal chemistry [2]. According to the SPP, structurally-similar compounds often exhibit similar properties. Among these properties is biological activity, such that similar compounds often demonstrate similar activity.

This work investigates whether ligands which are active within a particular kinase group are more similar to one another than kinase ligands generally.

Why is this important?

- Relevant to drug discovery research
- If there is a relationship between kinase group and ligand similarity, then it may be informative to look at the ligands of related kinases (i.e., those belonging to the same group)
- There may not be much information on a particular protein target, but related and more well-studied proteins could potentially be informative

Methodology Overview

The set of active ligands and their relationship to specific kinase proteins/groups was determined using data from single protein target binding assays in the ChEMBL database [3].

- Assay/ligand selection based on Pharos [1]
- Remove assays where target was a variant/mutant
- Filtered out PAINS compounds
- Molecular weight of ligand must fall between [200, 900] Da

The criteria above resulted in a dataset with the folllowing properties:

Variable	Value
N. Protein Targets	423
N. Assays	73,487
N. Assay-Ligand Pairs	38,622
N. Unique Ligands	9,995

Ligands are considered active within a Kinase group if they were identified as an active within an assay targeting a protein belonging to the group.

After determining the set of ligands and their group relationship(s), Morgan fingerprints were computed using RDKit. Tanimoto similarity coefficients were then computed between these 2D fingerprints.

Results

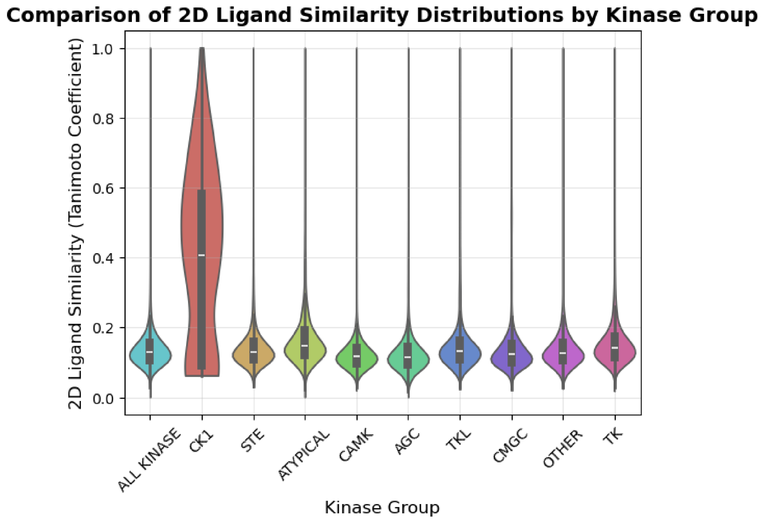

Figure 1. Comparison of 2D structural similarity distributions by kinase group

Kinase Group	N. Ligands	Group Median	Comparison Median	p-value
CK1	13	0.407	0.129	3.10e-11
STE	425	0.131	0.129	2.48e-169
ATYPICAL	357	0.149	0.129	< 5e-324
CAMK	597	0.117	0.130	1.0
AGC	809	0.116	0.131	1.0
TKL	810	0.133	0.129	< 5e-324
CMGC	1275	0.122	0.130	1.0
OTHER	727	0.127	0.129	1.0
TK	5347	0.140	0.121	< 5e-324

Table 1. Table showing comparisons of similarity distributions per kinase group. Shown p-values are calculated from a Mann-Whitney U-test testing whether the distribution of similarity values within the group is stochastically greater than the distribution of other similarity values. A Bonferroni correction was applied to all p-values. Note that p-values of $< 5e-324$ are due to the reported p-value being 0, so the smallest absolute positive float greater than 0 was reported.

Discussion

Limitations

- Only considered Morgan fingerprints + Tanimoto coefficients when measuring "similarity" of ligands
- Methodology does not account for differences in assay conditions
- Data gathered from ChEMBL may not reflect global trends

Conclusions

Overall, this study found no clear relationship between kinase group and 2D ligand similarity.

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