Subject: Dealing with multiple "0% inhibition" results in HTS tests
Posted by Christophe on Thu, 28 Apr 2022 09:25:40 GMT

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Hello everyone

In medicinal chemistry, batches of molecules are tested using high-throughput screening methods constraint with a concentration threshold. For example, the whole batch is used at 1 µM and an efficacy (e.g. % inhibition) is measured at this concentration.

DW allows to calculate a ligand efficiency with these results. This is to be taken with caution as it requires extrapolating a delta G from the % inhibition.

My question: How to deal with molecules that are below their effective concentration (0% inhibition) and for which no ligand efficiency can be calculated? These molecules (more exactly all these zero results) may prevent the calculation of important parameters and/or ruin analyses such as Partial Least Squared Regression for example.
Should one remove all these zeros and retain only the molecules with activity? Is there a reasonable way to code these molecules so that the structural information they carry can still be used in some analyses?
I tried to use categorical variables and it helped for a bit. But does anyone have more experience in this area than I do?
Thanks
Best regards

Subject: Re: Dealing with multiple "0% inhibition" results in HTS tests
Posted by sansun on Tue, 12 Jul 2022 05:14:15 GMT

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Hi

There are many ways by which you can use the structural information of inactive compounds in medicinal chemistry. You can use these molecules to validate your computational models, e.g. QSAR, pharmacophore, docking protocol, machine learning models etc.

e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3438292/

Your model should be able to pick up active molecules while discard inactive ones.

You can also compare physicochemical properties of inactive and active molecules and find out the chemical space in which the probability of finding active molecules may increase for a particular target.

e.g. https://pubs.acs.org/doi/full/10.1021/acsomega.1c00104

I hope it helps!

SS

Subject: Re: Dealing with multiple "0% inhibition" results in HTS tests
Posted by Christophe on Tue, 19 Jul 2022 07:37:17 GMT

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Hi

I didn't check this post for a while.

Thanks for yours helpful comments.

Christophe