An Investigation Into Free-Wilson Analysis: Library Design & Lead Optimisation

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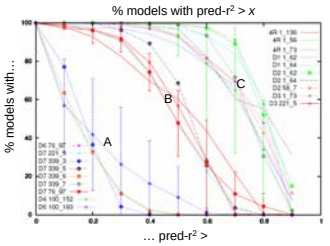
INTRODUCTION: Free-Wilson Analysis[1] (FWA) can be used to help decide if a complete library of combinations of a scaffold and R-groups is required to be synthesised and tested, or if we can cherry pick the (potentially) most desirable compound(s) based on whether the R-groups are shown to be *additive* (have an independent contribution to the property under investigation, regardless of the other R-groups present) or not. Eight data sets, with up to six properties each, were provided by Janssen for this study (right).

CLASSIFYING DATA SETS



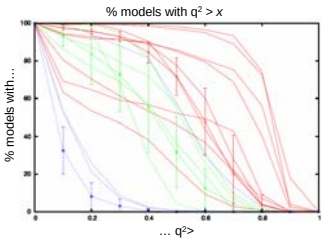
Using pred-r² (left): The data sets can be divided into three categories:

Additive [A] (region C): > 50% of models with pred-r2 >= 0.7

Partially additive [PA] (region B): > 20% of models with pred-r2 >= 0.4 and < 50% with pred-r2 >= 0.6

Non-additive [NA] (region A): < 20% of models with pred-r2 >= 0.4

Using q² (right): When the data sets are classified using q² as opposed to pred-r² the distinction between the data set types is not as well defined – some of the additive (red) and one of the NA (blue) data sets appear to be PA (green). Although the classifications are not as well defined as when using pred-r², the results show that using q² can still be beneficial.

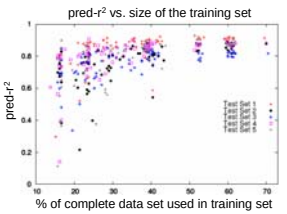


Data Set	Enzyme or Property Type	Number of R_x-Groups	Number of R_y-Groups	Number of Possible Compounds (Complete Data Set)	Percentage of Complete Data Set Available	Minimum Property Value	Maximum Property Value
+4R 1_136	Potassium Channel	7	11	77	70.1	5.05	7.17
+4R 1_56	Sodium Channel	6	16	96	75.0	5.06	7.07
+4R 1_73	Class A GPCR	7	17	119	68.1	6.04	8.98
+D1 1_62	Class A GPCR	14	15	210	84.8	5.01	7.86
+D1 1_64	Class A GPCR	14	15	210	84.8	5.16	8.99
+D2 1_62	Class A GPCR	9	12	108	80.6	5.30	7.86
+D2 1_64	Class A GPCR	9	12	108	80.6	5.52	8.99
+D2 58_7	Class A GPCR	9	12	108	80.6	5.01	7.91
+D3 1_73	Class A GPCR	22	5	110	89.1	5.46	8.98
+D3 221_5	Cellular Metabolism Assay	22	5	110	74.5	12.00	100.00
-D4 100_152	Ion Channel	13	7	91	75.8	5.03	7.98
-D5 100_193	Class A GPCR	7	11	77	70.1	5.07	8.79
#D6 76_97	Ser/Thr Kinase	19	6	114	84.2	6.79	8.90
*D7 221_5	Class A GPCR	12	5	60	70.0	0.00	91.5
*D7 339_3	P450	12	5	60	66.7	12.01	85.26
+D7 339_5	P450	12	5	60	66.7	16.81	110.79
+D7 339_6	P450	12	5	60	66.7	11.35	54.23
+D7 339_7	P450	12	5	60	66.7	3.93	102.75
+D7 76_97	P450	12	5	60	70.0	7.18	8.87

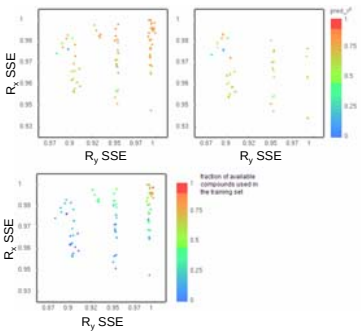
Data sets: The data sets have the following property types: +biological activity, *metabolic stability, -signal transduction, #enzymatic screening.
Each data set was divided into multiple training and test sets in which the distributions of R-groups, numbers of compounds and properties ranges were varied.

TRAINING SET ATTRIBUTES (Using D1 1_64)

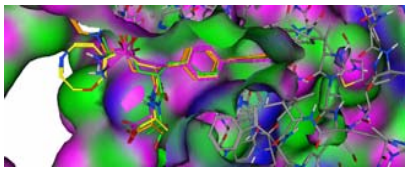
Property Range: There is no correlation with the property range and the predictive ability of a model. FWA assumes the R-groups have an independent contribution to the property. It is possible that different combinations of R-groups can lead to the same property value. If the data set is additive, FWA should be able to deduce the contribution of each R-group, as long as there are enough occurrences of the R-group in the training set, regardless of the property range of the training set.



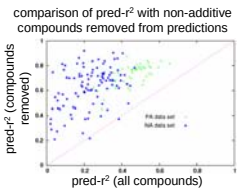
Training Set Size: In an additive case, we can see that 30% of a complete data set is enough for a successful FWA. In this study a training set with 100% of the compounds is not possible as compounds have been removed from the data set to form the test sets.



Distribution of R-groups (measured by the Scaled Shannon Entropy [SSE]): All the data sets which show signs of additivity show a trend for pred-r² to increase as the SSE increases for the R_x/R_y-group distribution in the training set. The trends in the top left of the three plots can be attributed to the relationship of the SSE of the R-groups with the number of compounds in the training set (bottom of the three plots). If we look at just the small training sets (top right of the three), we can see there is no correlation between the distribution of R-groups and the predictive ability of a model.

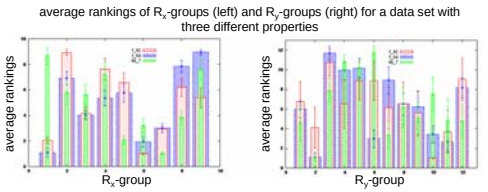


USING COEFFICIENTS



Analysis of Coefficients (left): The additive data sets have a higher number of good correlations between the coefficients of various models compared to those for the PA and NA data sets. Can we use this information to deduce which R-groups are non-additive? First unstable R-groups (those who's rank varied wildly if the R-groups were ranked according to their coefficients for the models of the various training sets) were identified. Next, compounds with these R-groups were omitted from predictions. Improvements are seen in the predictive ability of the models for a NA and a PA when the same training sets are used to create the models but non-additive R-groups are omitted.

R-Group Profiling (below): The profiles show that R_{x1} should be least active with target 58_7. The table (right) shows this to be true. R_{x7} and R_{y2}, according to the profile, should give a compound with an order of activity of 58_7 > 1_64 > 1_62. This compound does have a low activity with 1_62 and a high activity with 58_7, but also has a high activity with 1_64. This could be because the R_{y2} group has more influence on activity in reality; it has a higher contribution than R_{x7}, but only for target 1_64. The qualitative analysis provided by this study may also be complemented with a quantitative assessment based on the coefficients for each R-group.



activity values for a selection of compounds of data set D2

R_x-Group	R_y-Group	1_62	1_64	58_7
X1	Y1	6.74	8.06	5.64
X1	Y2	6.68	8.94	5.98
X1	Y6	6.76	8.61	5.01
X1	Y7	6.96	7.69	6.06
X1	Y9	6.81	7.77	5.77

R_x-Group	R_y-Group	1_62	1_64	58_7
X1	Y8	6.79	8.06	5.59
X1	Y10	7.77	8.84	5.10
X1	Y11	6.85	8.55	5.17
X1	Y12	6.81	7.78	5.23
X7	Y2	6.88	8.42	7.91

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References
1. Free, S. M. J. and Wilson, J. W., J. Med. Chem., 1964. **7**: p. 395-399.

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CONCLUSION:
- It is possible to identify data sets which are additive by FWA using q².
- The distribution of R-groups along with the property range of the training set have no effect on the predictive ability of a model.
- 30% of compounds of an additive data set are required for predictions.
- The correlation of coefficients between various training sets can be used to deduce which R-groups are additive, and which are not.
- The use of R-Group Profiling can help select compounds which can fulfil various property requirements, as long as the data set shows signs of additivity with the various properties.