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Comprehensive comparison of automatically generated QSAR models of target potency

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Overview

- Objective
- Data sets
- Automatic QSAR model generation
- Results
  - Summary of model results
  - Comparison of algorithms
  - Comparison of data types
- Conclusion

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Objective

- Large sets of biological data now available in the public domain
- Assess potential for large-scale QSAR modelling of target potency
- Consistently compare different algorithms and data for 2D QSAR modelling

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Data sets

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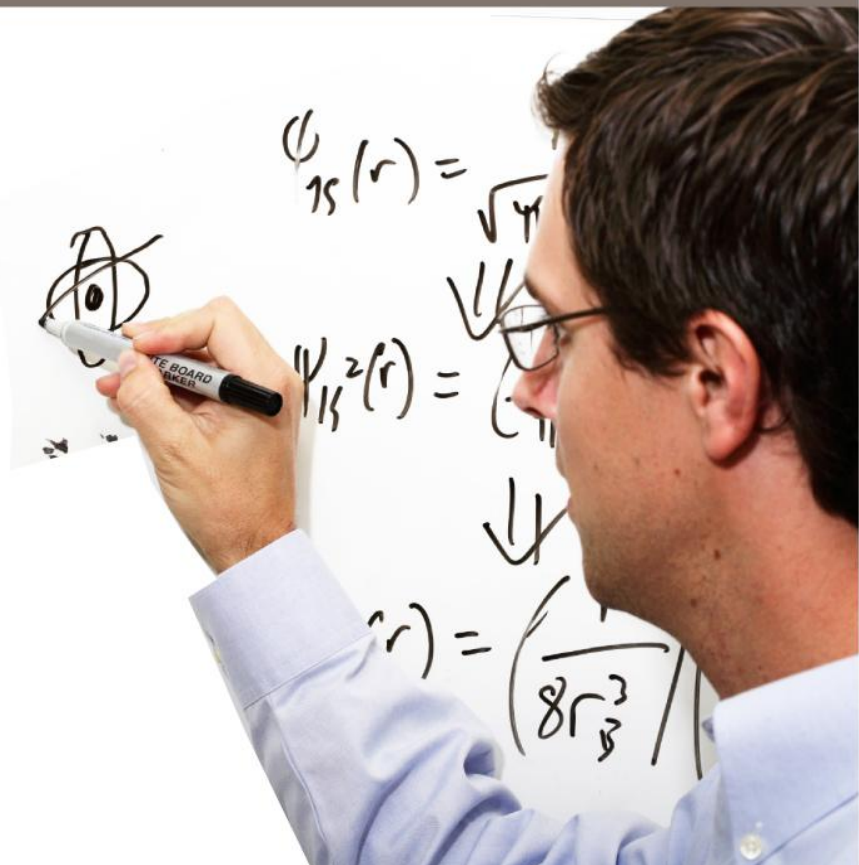

Data sets

- Data obtained from Chembl database
  - https://www.ebi.ac.uk/chembl/
- Data obtained for 67 targets selected from top human drug targets*
- Total of 104 data sets
  - 19 with IC_{50} values only
  - 12 with K_i values only
  - 36 with both IC_{50} and K_i values
- Data set sizes ranged from 29 to 1716 compounds

* Overington *et al.*, Nat. Rev. Drug Discov. 2006, **5**, 993-996

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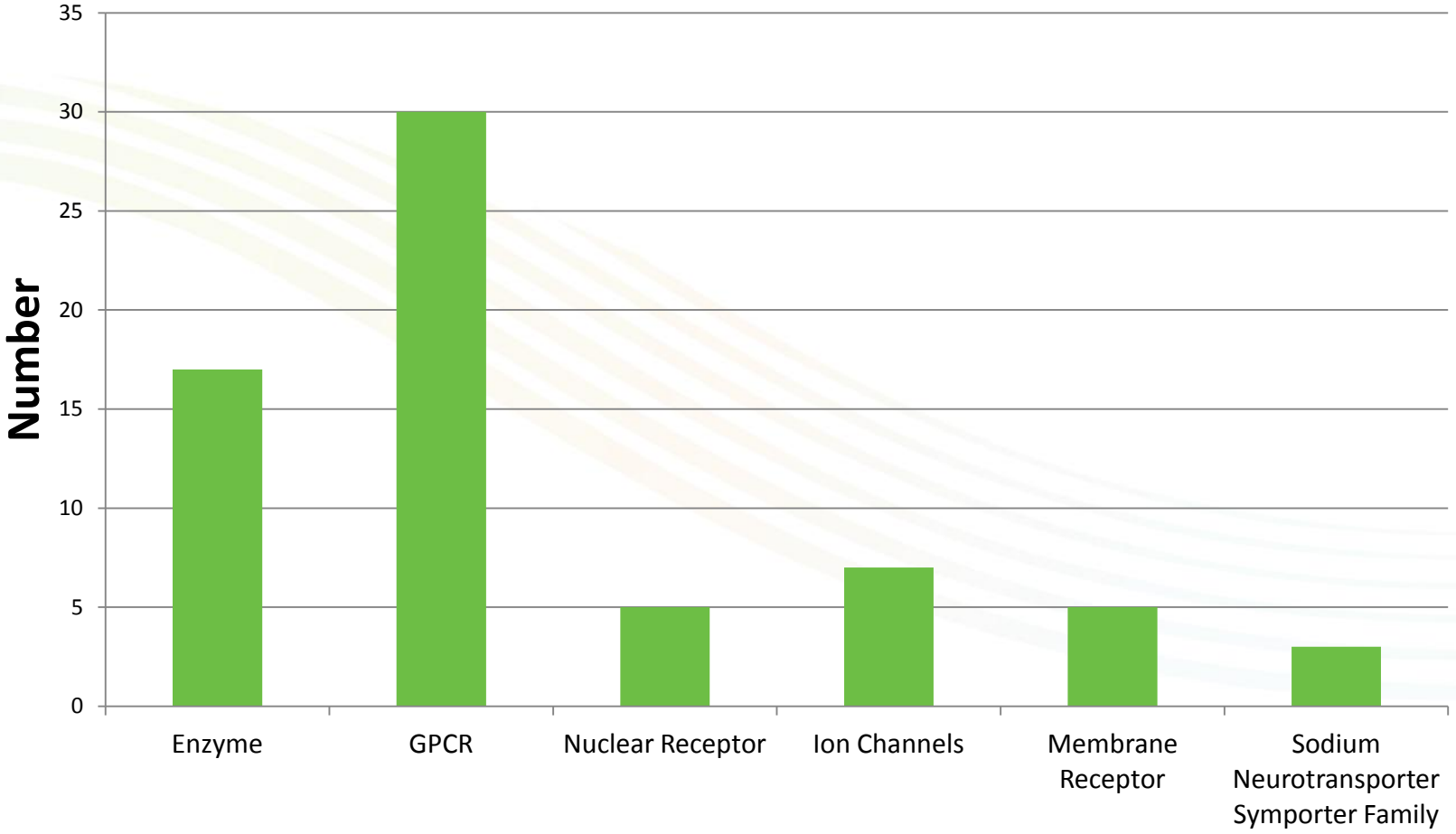
Distribution of Target Classes



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Cleaning the data

- Raw data from Chembl required further cleaning
- Rejected data with confidence <4
- Normalised units
  - Log(K_i) or log(IC_{50}) in nM
- Where multiple values present for the same compound
  - Calculate mean and standard error in mean
  - Reject compound in standard error in mean >0.5 log units
- Generate ‘parent’ structure
  - Remove salts
  - Not able to check structure for each compound (too many data points)

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Automatic QSAR Model Generation

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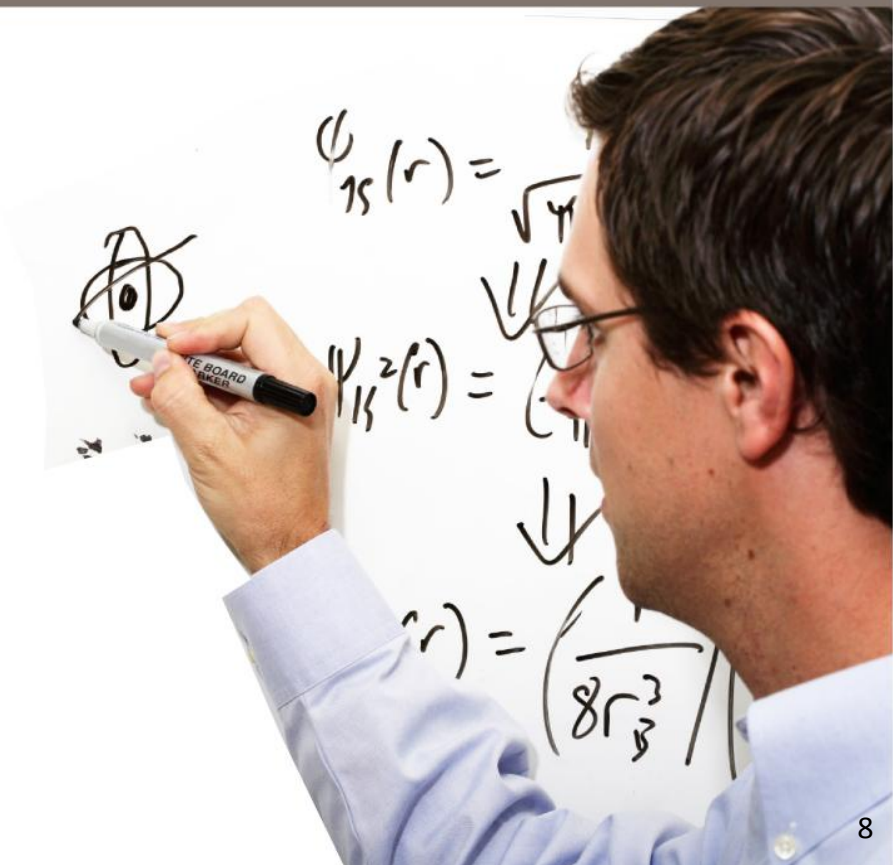
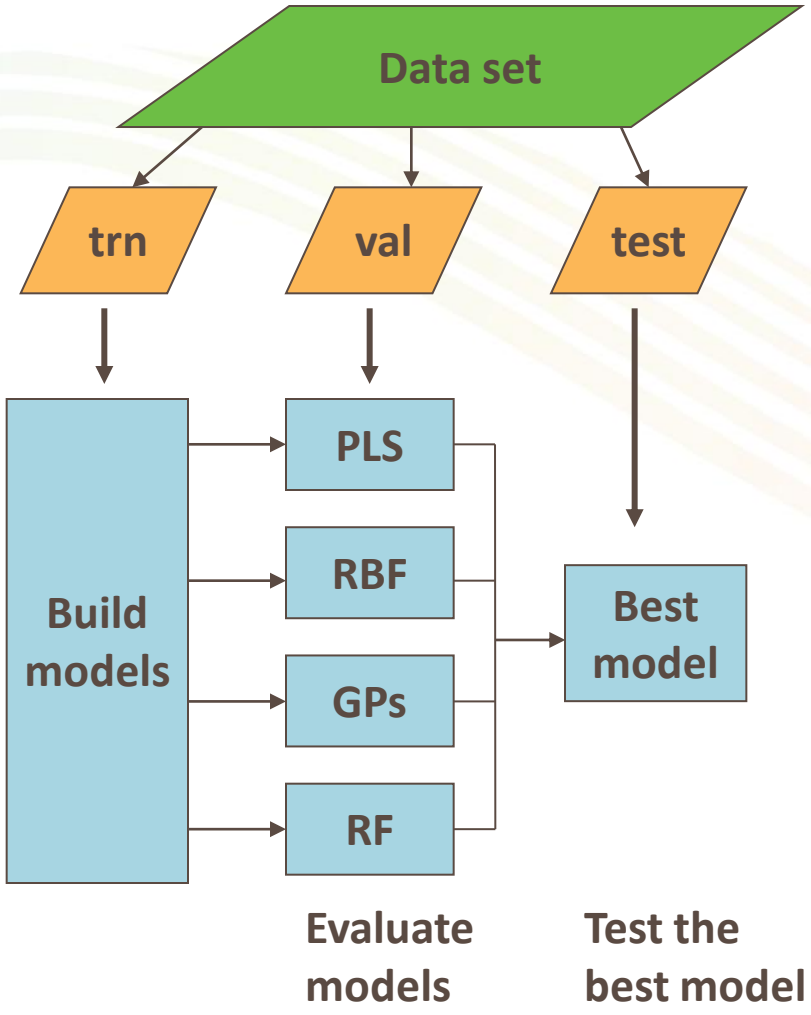


Automatic Model Generation*
StarDrop Auto-Modeller

StarDrop 5
Software that guides you to successful drug discovery

* Obrezanova *et al.* JCAMD 2008, **22**, 431-440



- Split data set
- Calculate descriptors
- Multiple modelling techniques
- Select the best model by performance on the validation set
- Test with an **independent** set

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Data Set Split

- Data set clustered using dbclus algorithm*
  - 2D path-based fingerprints
  - Tanimoto coefficient of 0.7
- Cluster centroids and singletons used as basis for training set
  - Ensure coverage of chemical diversity
- Remaining compounds distributed between subsets
  - Training 70%
  - Validation 15%
  - Test 15%

* Butina, J. Chem. Inf. Comput. Sci. 1999, **39**, 747-750

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Descriptors

- Whole molecule properties
  - logP, TPSA, MW, V_x, flexibility...
- 321 SMARTS descriptors
  - Counts of substructures
- Descriptor preselection
  - Remove count descriptors with <4% occurrence
  - Remove descriptors with standard deviation <0.0005
  - Remove one of pairs with correlation R^2>0.95

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Modelling Methods

- Partial Least Squares (PLS)*
  - Linear model
  - Number of components chosen by cross validation in training set
- Radial Basis Functions (RBF, GA-RBF)
  - Interpolation of training set in descriptor space.

$$y(X) = \sum_{i=1}^{N} w_i \Phi(| X - S_i |)$$

  - Genetic algorithm used to select descriptors in GA-RBF
  - Risk of overtraining for small data sets

* Wold *et al.* The Encyclopedia of Computational Chemistry, Schleyer *et al.* eds, 1999, 1-16

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Modelling Methods II

- Gaussian Processes (GP) *
  - Bayesian approach – infer posterior distribution of functions that fit data
  - **Prediction** = mean of distribution, **uncertainty** = standard deviation
  - Training == learning hyperparameters
    - 6 methods: Fixed, 2DSearch, FVS, RFVS, Opt, Nest
- Random Forests (RF)†
  - Ensemble of random trees (100 trees)
  - **Prediction** = average of output of trees, **uncertainty** = standard deviation

* Obrezanova *et al.* JCIM 2007, **47**,1847-57

† Breiman, L. Machine Learning 2001, **45**, 5-32

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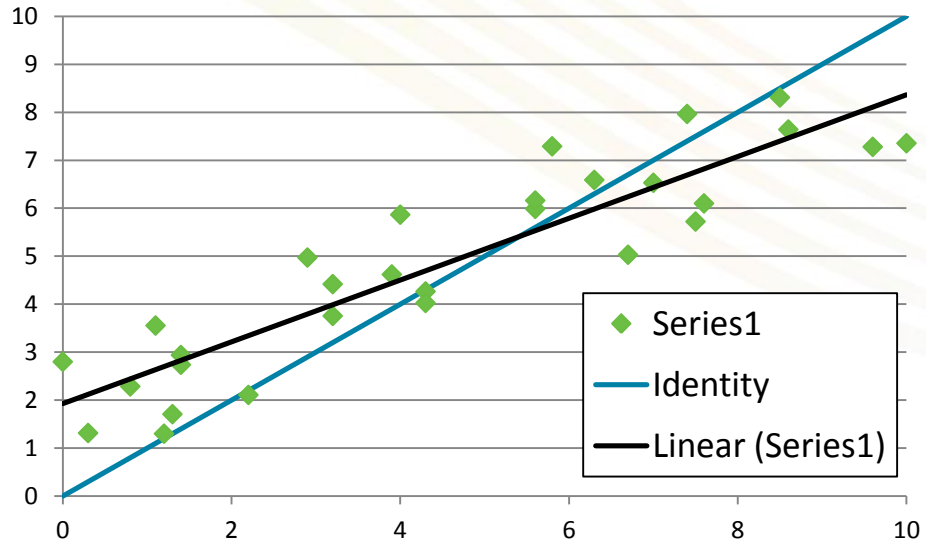
Evaluation of Models

- Coefficient of Determination – $R^2 = 1 - \frac{\sum_{i=1}^{N}(y^{obs} - y^{pred})^2}{\sum_{i=1}^{N}(y^{obs} - \overline{y^{obs}})^2}$
  - Measure of fit to identity line y=x
  - N.B. Not the same as square correlation coefficient r^2_{corr} which is measure of fit to best fit line – R^2 is a stricter test



Best fit line
y= 0.71x + 2.3
r^2_{corr} = 0.86

R^2 = 0.74

- Root mean square error - RMSE

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Assessing Predictive Ability
Domain of Applicability

- The diversity of the training set defines the **chemical space** of the model
- The position of a compound relative to chemical space is reflected in the reported confidence in the prediction

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Results

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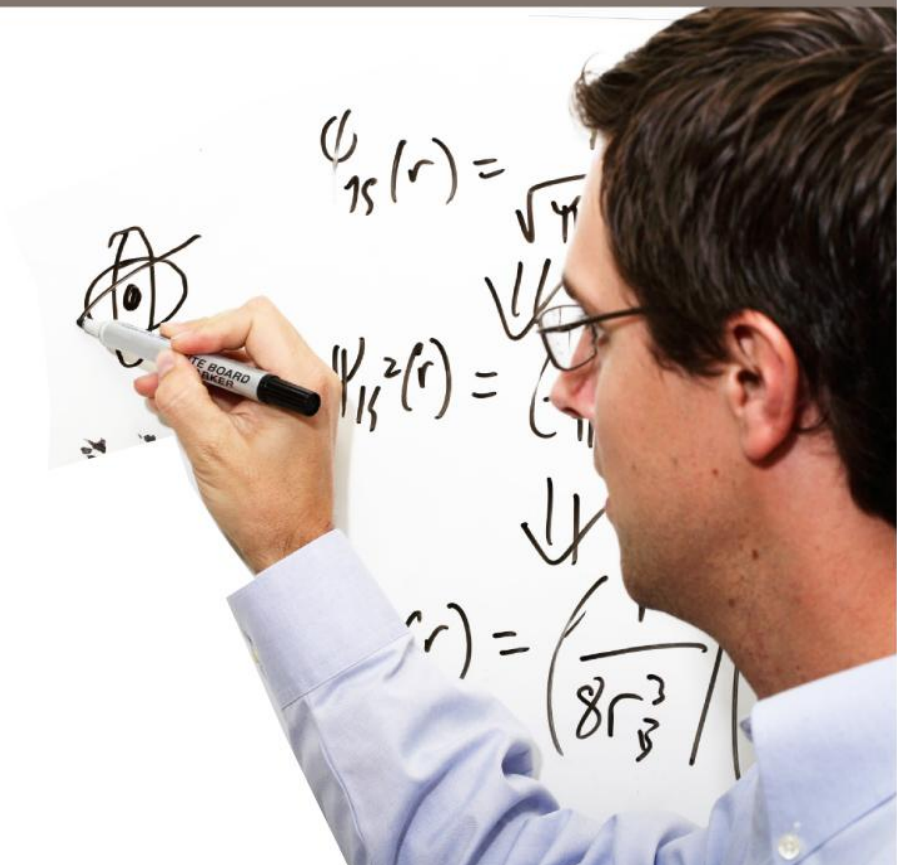
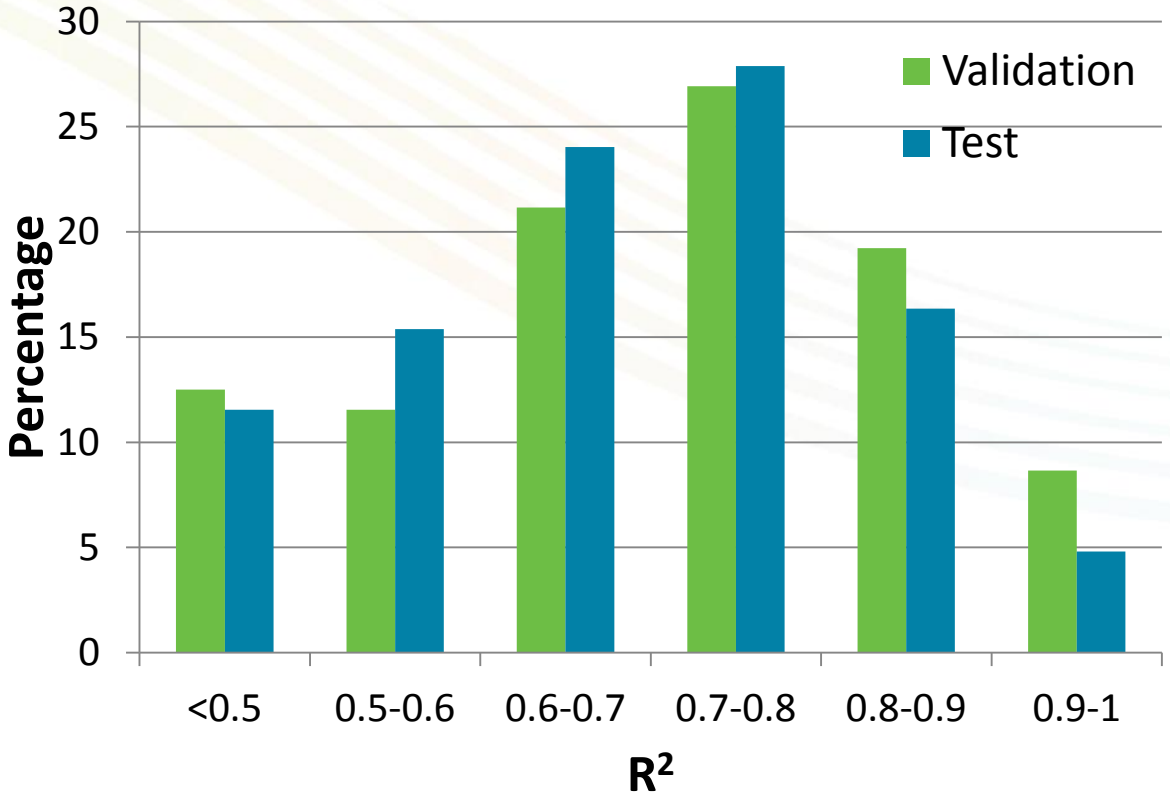


Summary of Validation Results
Coefficient of Determination

- 55% of data sets resulted in models with R^2>0.7 on validation set (50% on test set)
  - 76% with R^2 > 0.6



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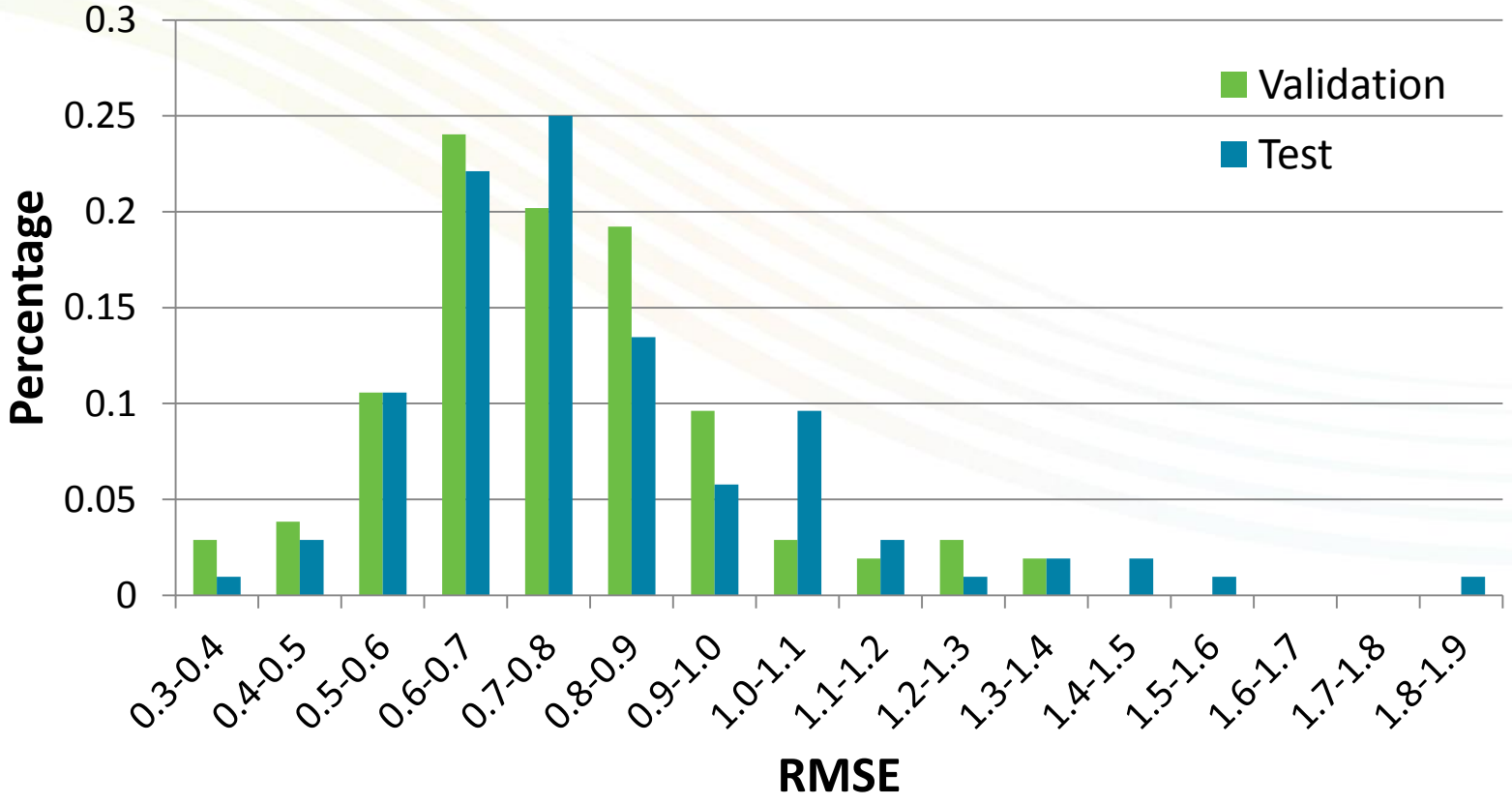
Summary of Validation Results
Root Mean Square Error

- Average RMSE on validation set = 0.76 log units (factor of 5.8)
- Average RMSE on test set = 0.8 log units (factor of 6.3)



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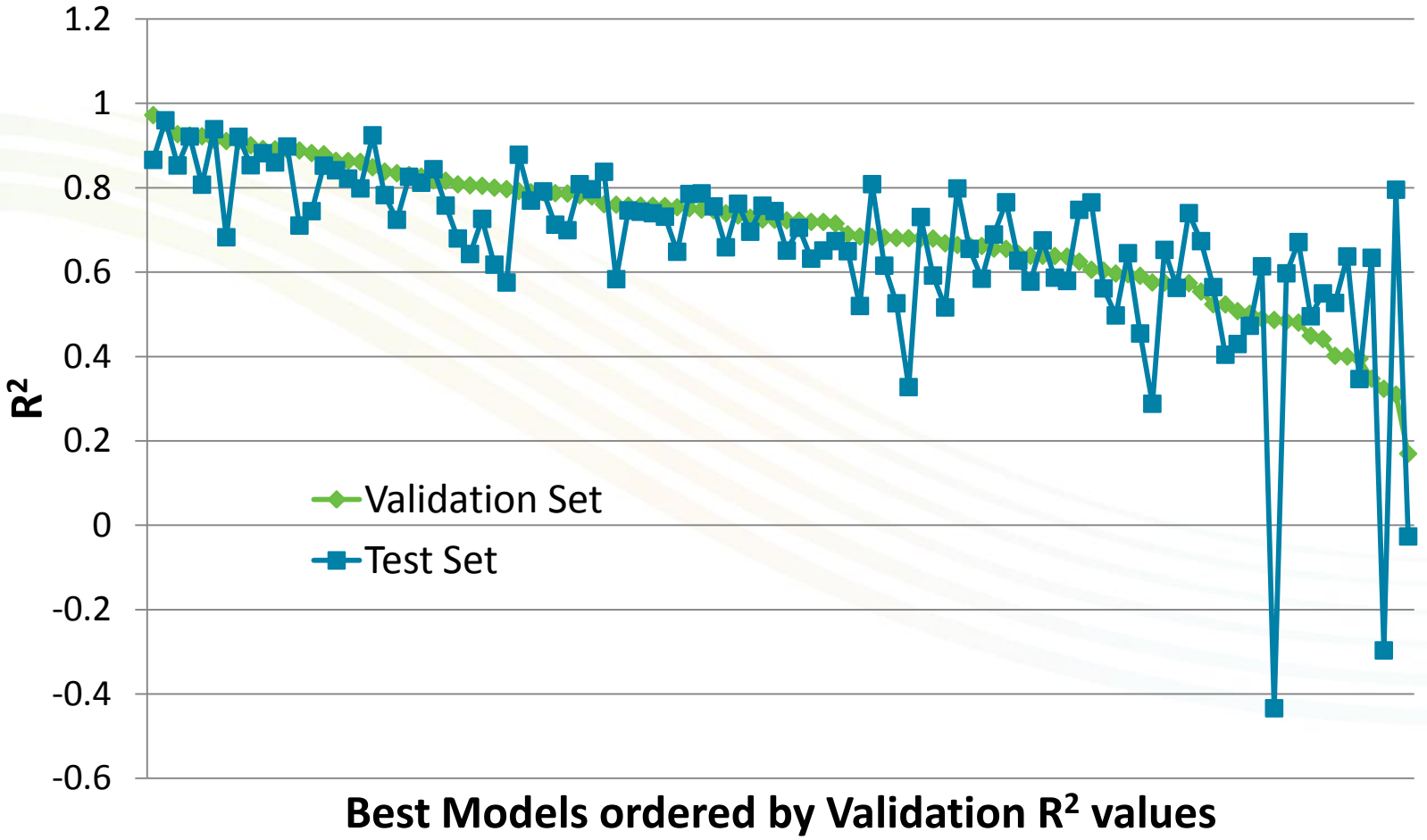
Comparison of Validation & Test Results



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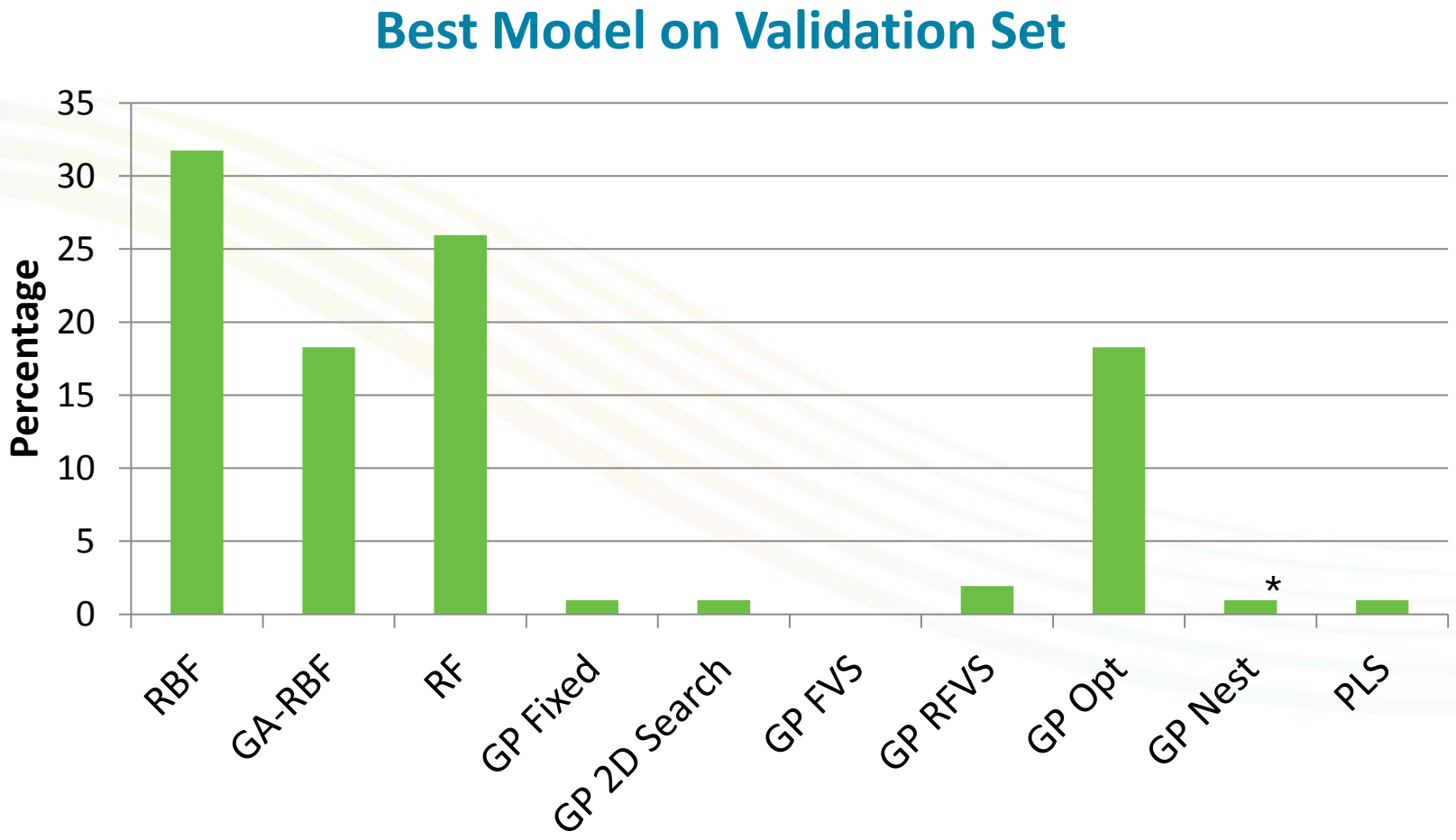
Comparison of Modelling Methods



* GP Nest only applied to 47 smallest data sets.

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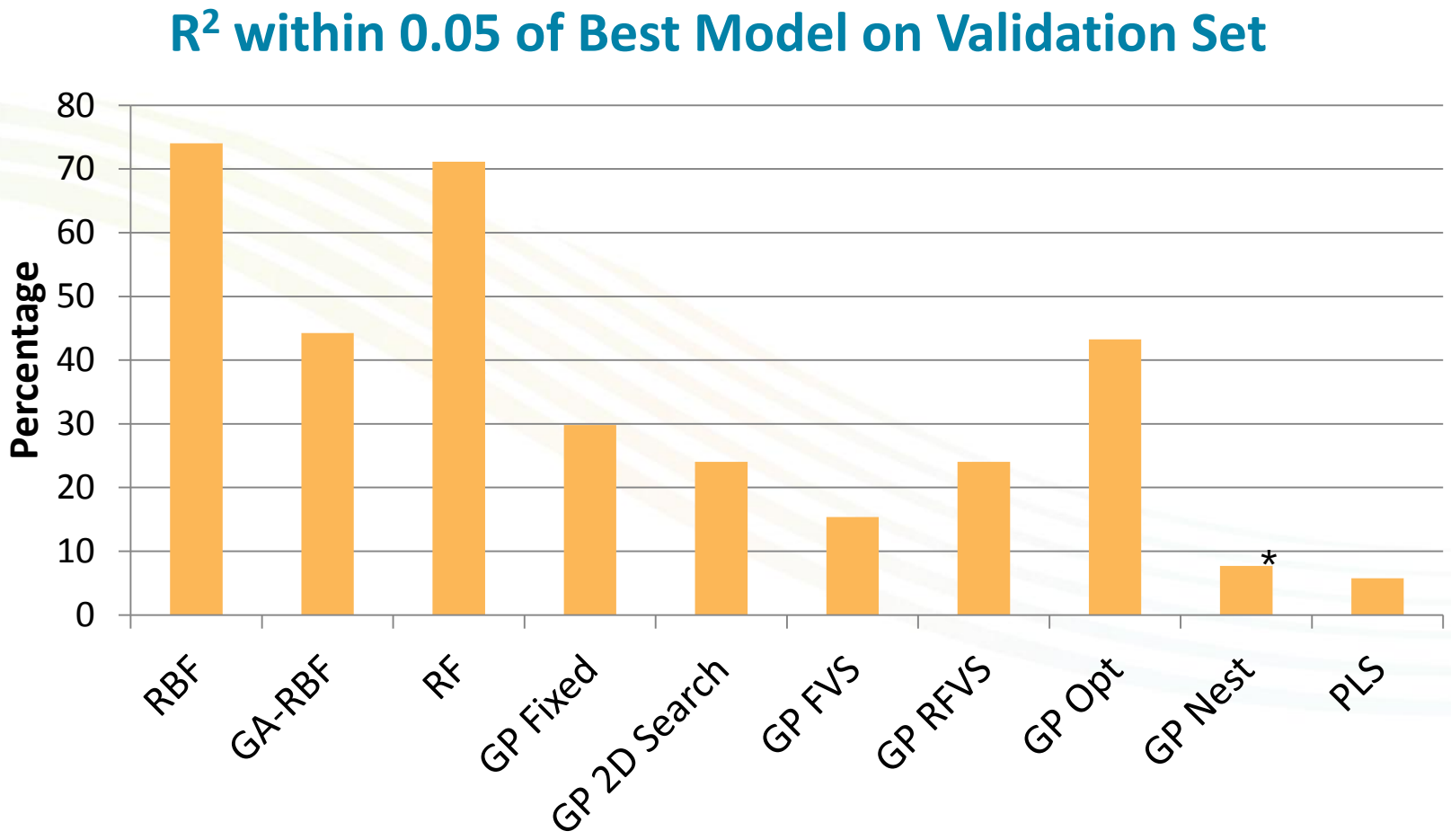
Comparison of Modelling Methods



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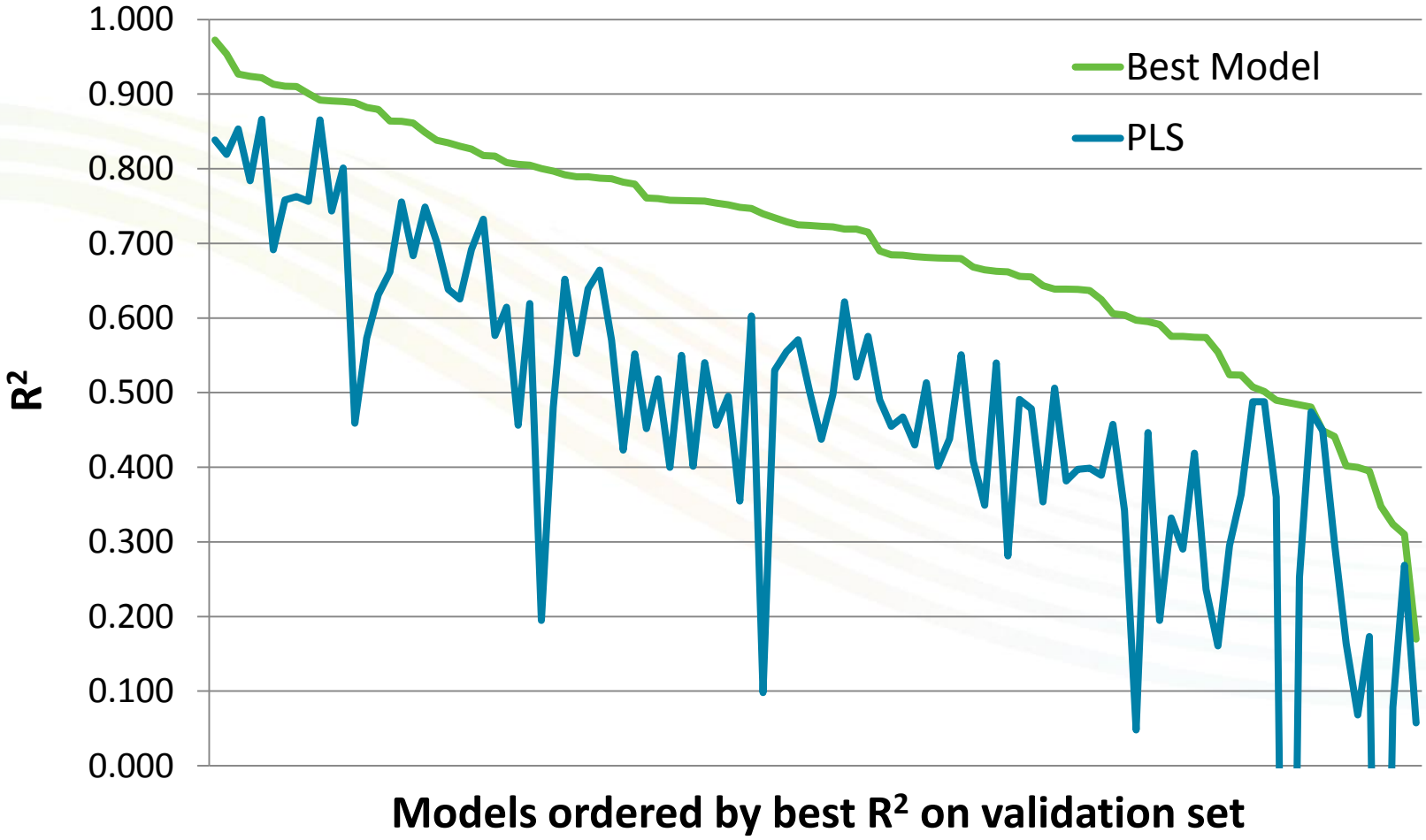
Linear vs Non-linear Models



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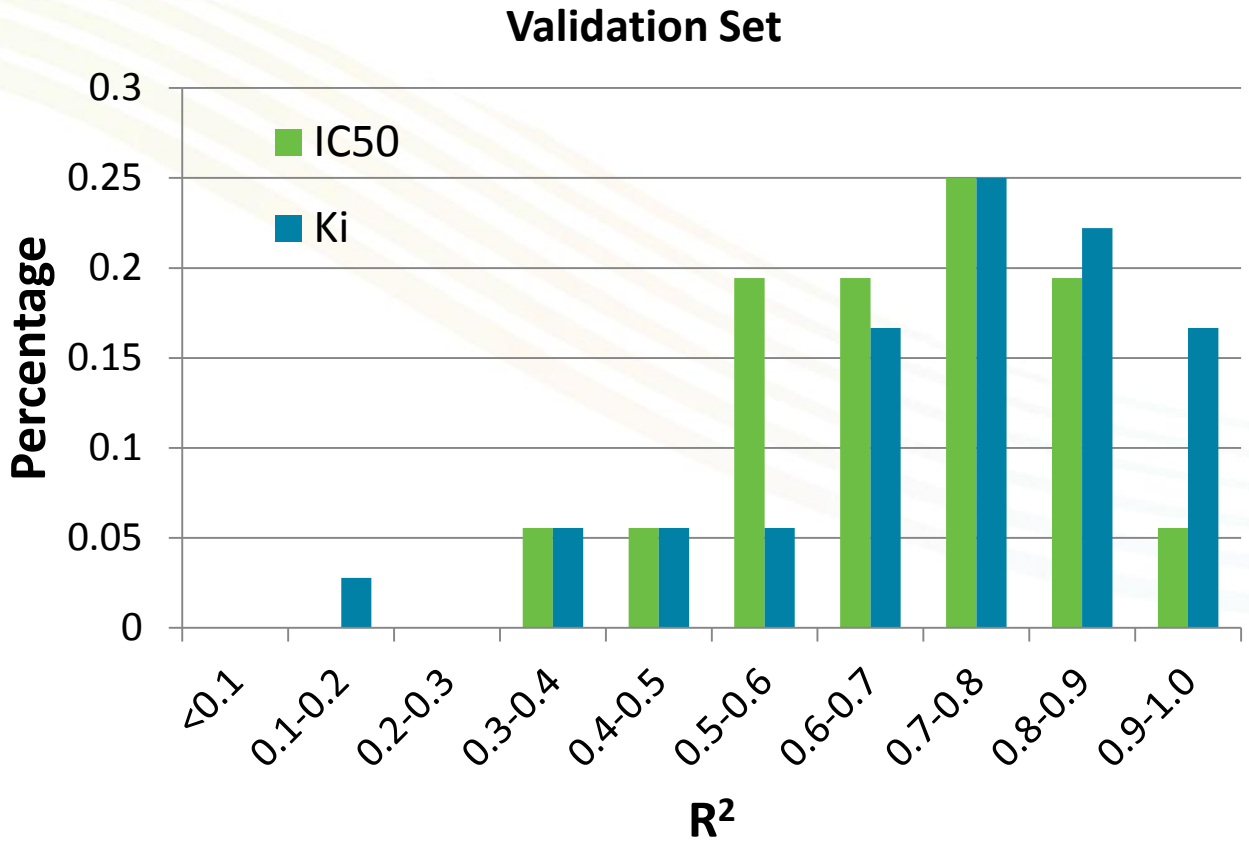
Comparison of Data Types
IC_{50} vs K_i

- Mean validation set R^2: IC_{50} = 0.69, K_i = 0.72



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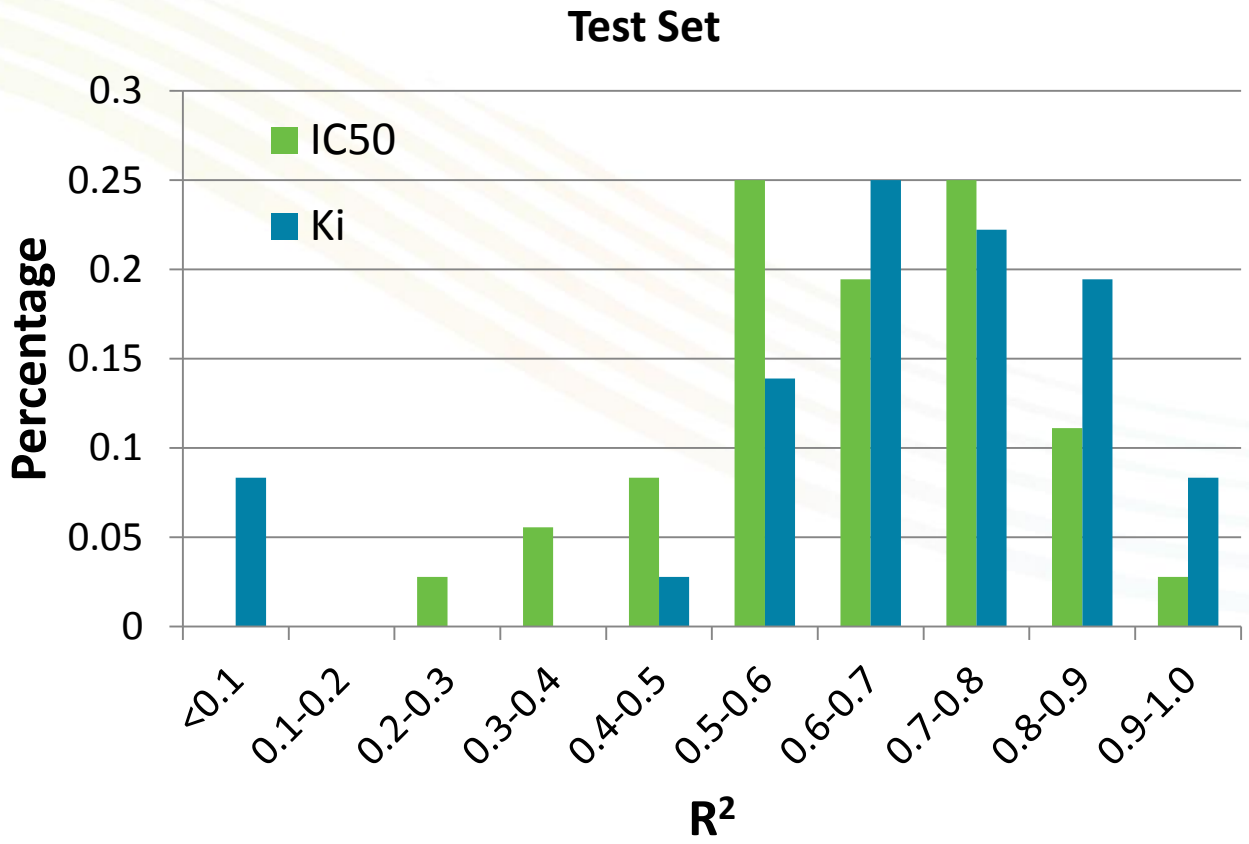
Comparison of Data Types
IC_{50} vs K_i

- Mean test set R^2: IC_{50} = 0.64, K_i = 0.65



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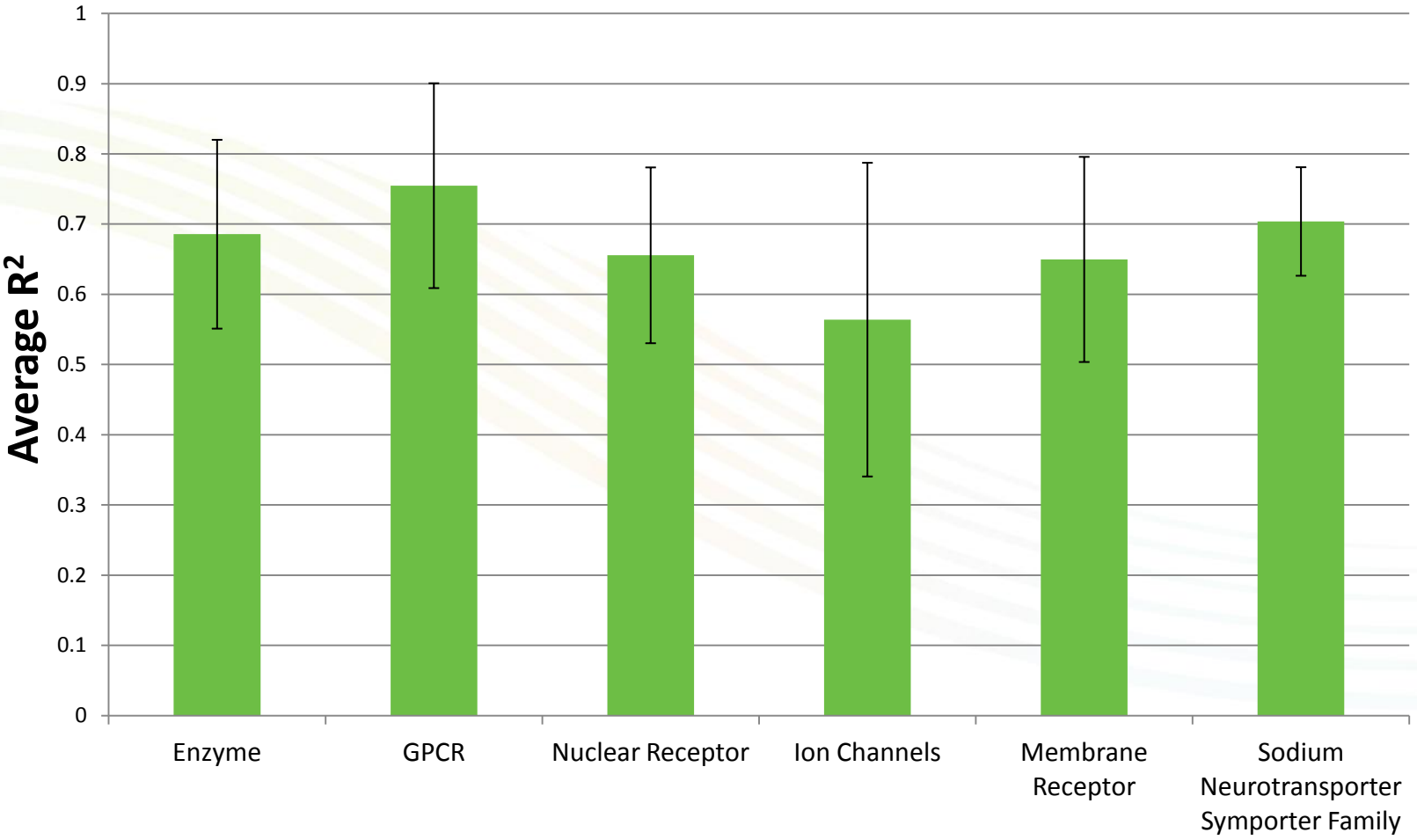
Comparison of Target Classes



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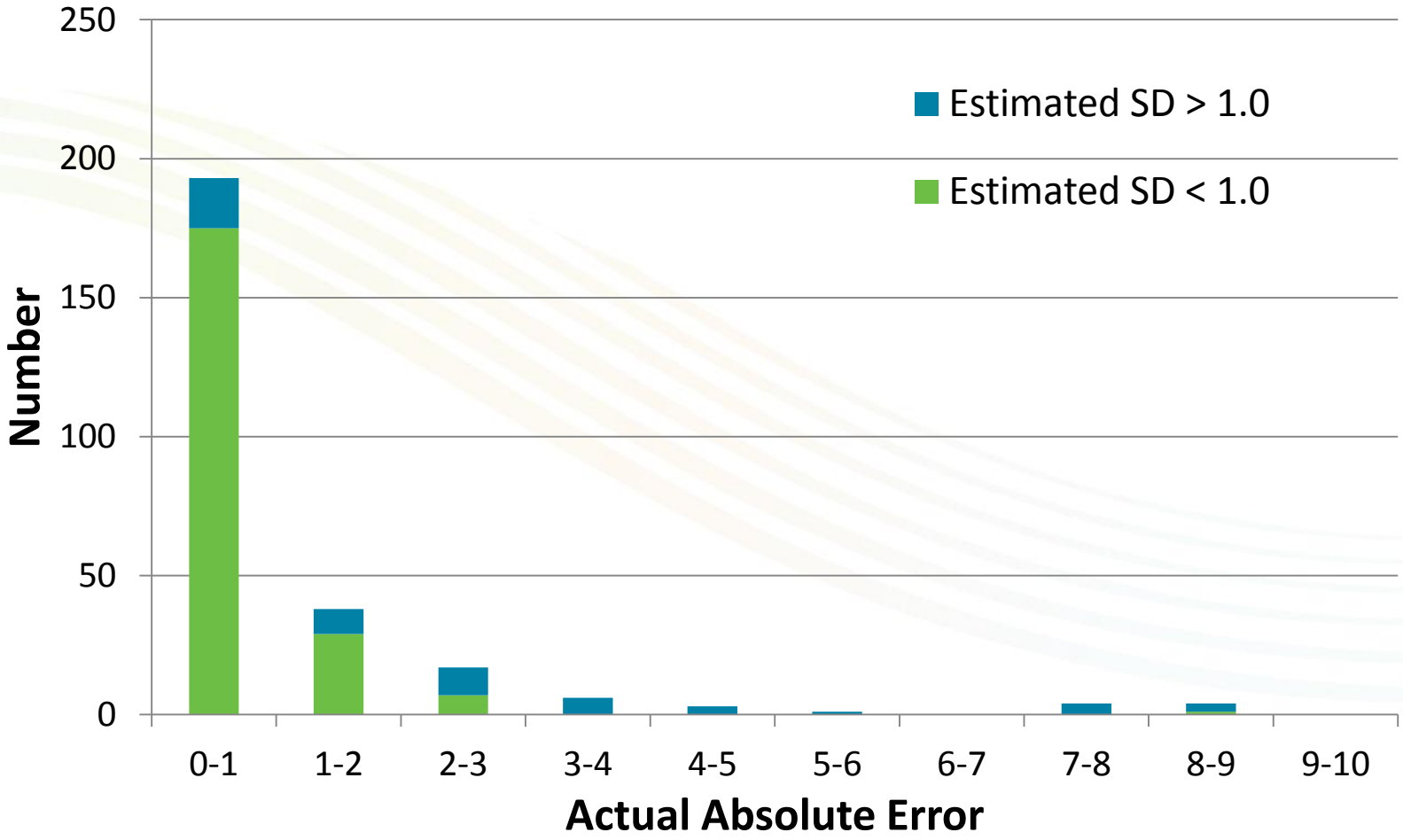
Identification of Low Confidence Predictions

GP Opt Model of Alpha 1a Adrenergic Recept.



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Conclusions

StarDrop™5
Software that guides you to successful drug discovery

- Built 104 2D QSAR models of target activity using StarDrop Auto-Modeller and public domain data sets
  - Consistent descriptors, set splits and validation
  - 9 methods based on 4 algorithms
- Achieved $R^2 > 0.7$ for 55% of data sets
- Linear models (PLS) consistently performed worse than non-linear
  - RBF and RF most often best
- Possible applications
  - Activity profiling – identify potential for off-target interactions
  - Compound repurposing
  - Virtual screening?
- Future work: Other descriptors including 3D
- All models and data sets will be available soon on the Optibrium on-line community
  - **www.optibrium.com/community**
  - If you would like to be notified when they are available please email me: **matt.segall@optibrium.com**

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