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Advances in multi-parameter optimisation: Targeting the "best" profile for your project's objectives

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Overview

- Multi-parameter optimisation in drug discovery
- Finding the ‘best’ profile for your project’s objective
  - Example: Selection to reduce toxicity risk
- ‘Hard’ vs. ‘soft’ boundaries
  - Example: Selection for CNS indications
- Testing the robustness of your decisions
  - Sensitivity analysis
- Conclusions

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Multi-parameter Optimisation in Drug Discovery

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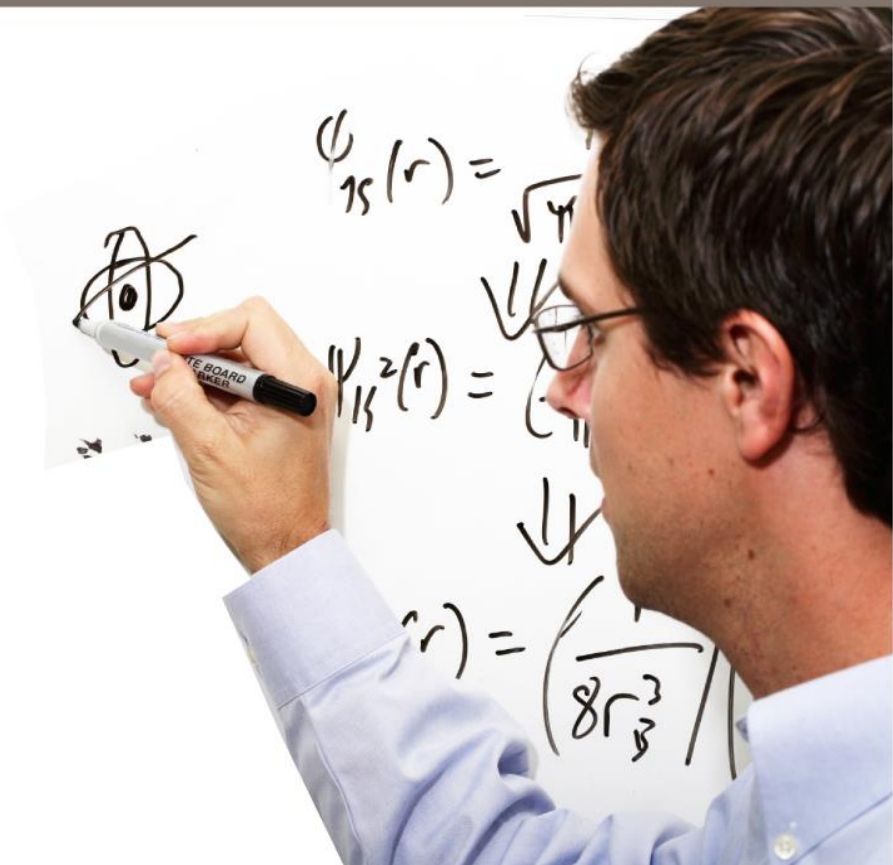
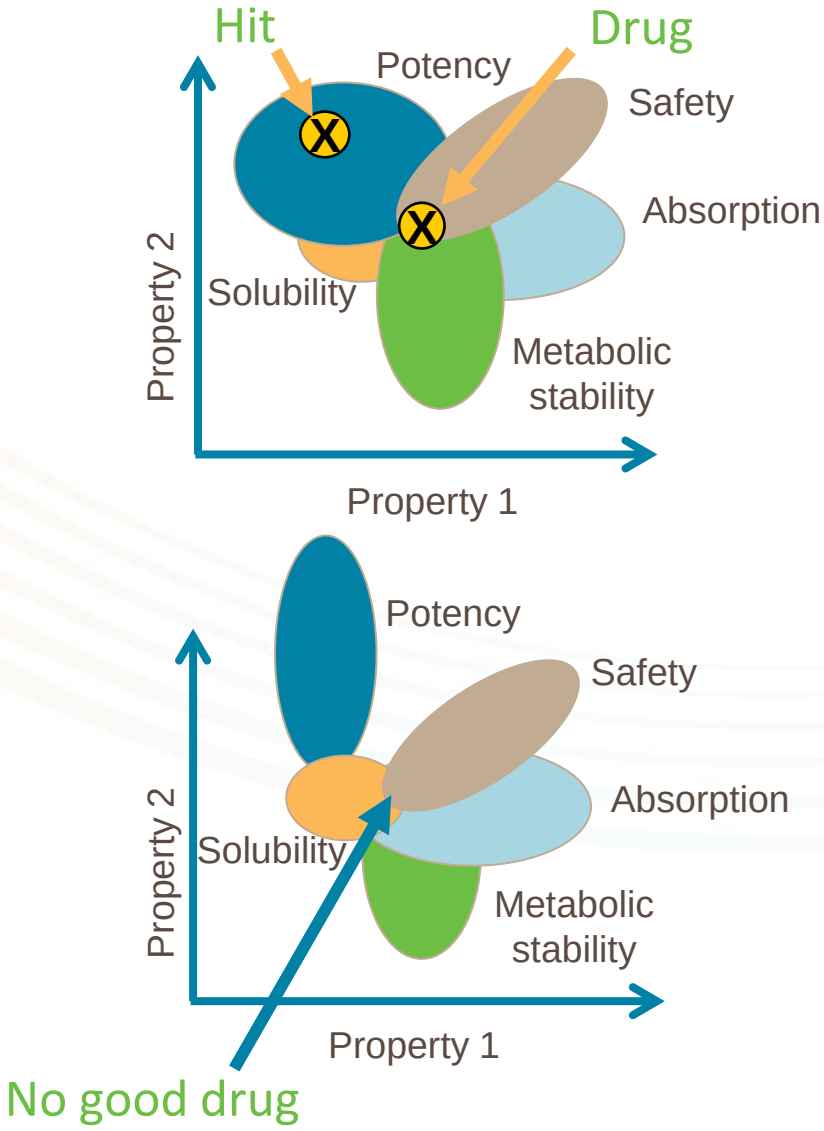


The Objectives
Multi-parameter optimisation

- Identify chemistries with an optimal **balance** of properties

- Quickly identify situations when such a balance is not possible
  - –Fail fast, fail cheap
  - –Only when **confident**



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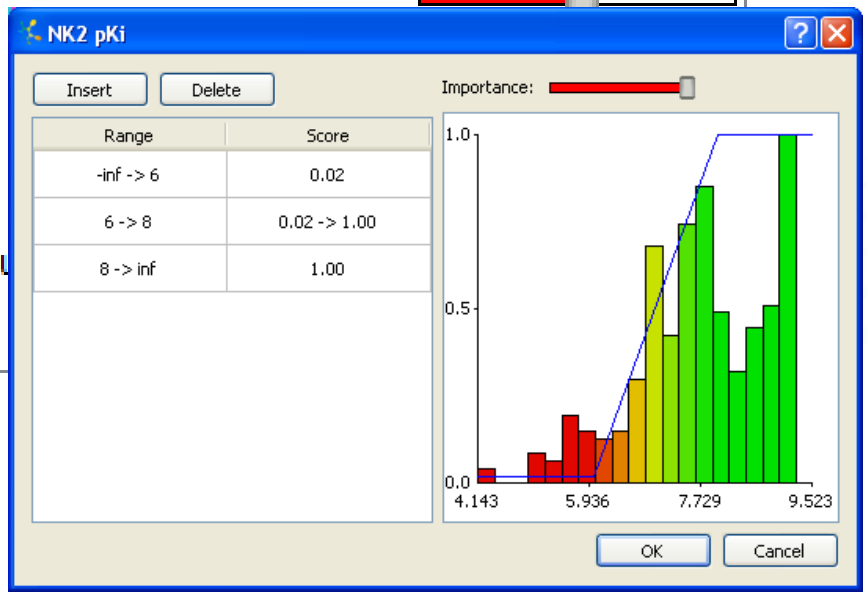
*M.D. Segall Curr. Pharm. Des. **18**(9) pp. 1292-1310 (2012)

Multi-parameter Optimisation
Probabilistic Scoring*

Profile	Desired Value	Importance
logS	⩾ 1	
HIA category	+	
logP	0 -> 3.5	
BBB log([brain]:[blood])	-0.2 -> 1	
BBB category	+	
P-gp category	no	
hERG pIC50	⩽ 5	
2C9 pKi	⩽ 6	
2D6 affinity category	low mediu	
PPB90 category	low	



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*M.D. Segall (2012) Curr. Pharm. Des. **18**(9) pp. 1292-1310

Multi-parameter Optimisation
Probabilistic Scoring*

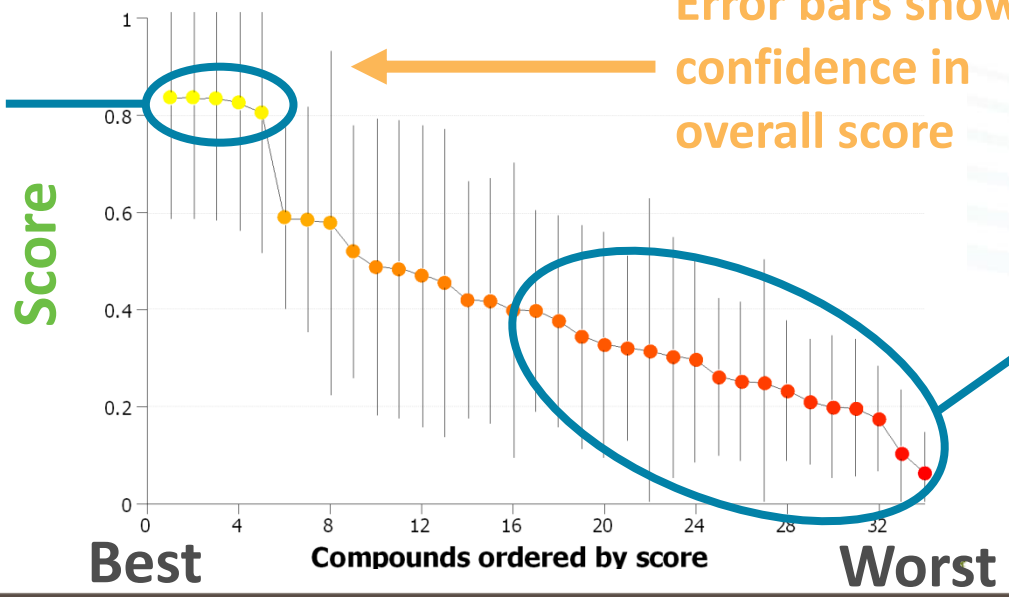
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

- **Score (Likelihood of Success)**
- **Confidence in score**

Data do not separate these as error bars overlap

Error bars show confidence in overall score

Bottom 50% may be rejected with confidence



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Finding the ‘Best’ Profile for your Project Objectives

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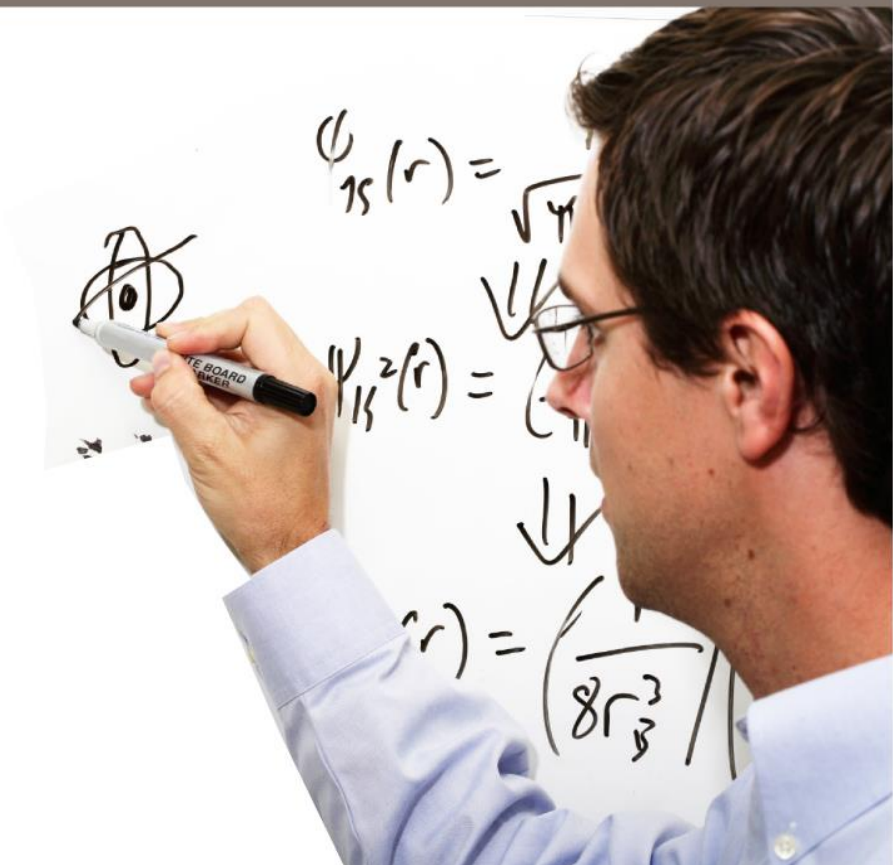

Finding Tailored Profiles
Objectives

- Use existing data to find scoring profiles that identify compounds with improved chance of success
  - Any drug discovery objective, e.g. clinical, PK, toxicity...
  - Once developed, a profile can be applied prospectively to find new compounds
- Identify most important data with which to distinguish between successful and unsuccessful compounds
  - Any data can be used as input, calculated or experimental
- Explore multi-parametric data
  - Consider properties simultaneously, not individually
  - Avoid 'over counting' of correlated factors
- Rules must be interpretable and modifiable
  - Avoid black boxes
  - Synergy between computer and experts

*Patent pending

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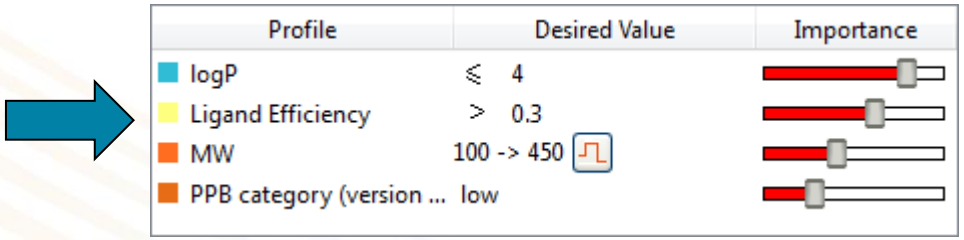
I. Yusof *et al.* (2014) Drug Discov. Today DOI: 10.1016/j.drudis.2014.01.005

What is a Rule?

- A **Rule** is a set of property criteria that in **combination** identify 'good' compounds, e.g.

logP < 4
Ligand efficiency > 0.3
100 < MW < 450
PPB category = low



- For example, Lipinski RoF:

logP<5	MW<500
HBD<5	HBA<10

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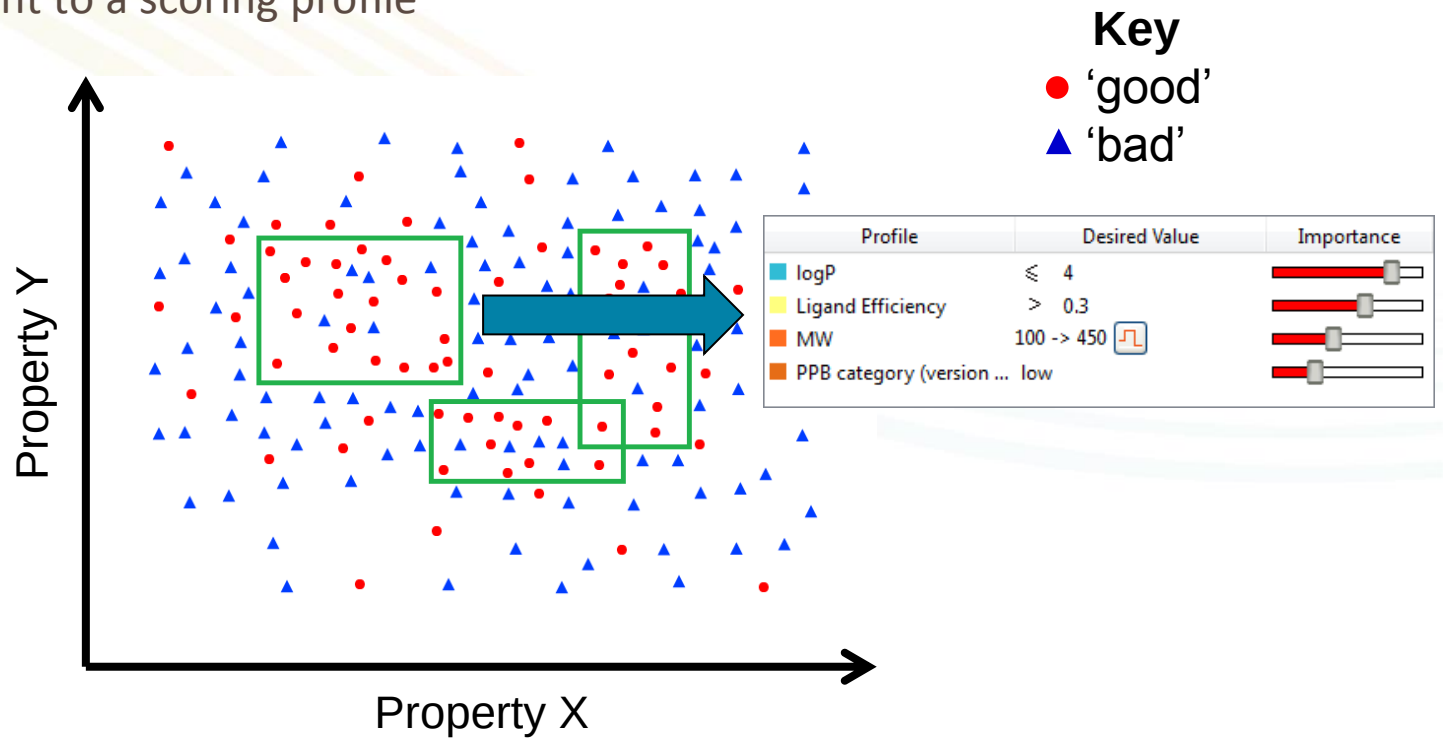
Finding Rules with PRIM

- A **Rule** is a box in multi-dimensional property space containing significantly more ‘good’ than ‘bad’ compounds
  - Use Patient Rule Induction Method (PRIM) by Friedman and Fisher* find rules in multi-dimensional data
  - Equivalent to a scoring profile



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* Friedman & Fisher Stat. and Comp. **9**(2), p. 123 (1999)

Example Application
Finding rules for selection of non-toxic compounds

- *In vitro* assay data from CEREP Bioprint®
  - Percentage inhibition of 185 targets including GPCF, kinase, NR, P450s...
- Drugs labelled as ‘cardiotoxic’, ‘hepatotoxic’ or ‘clean’
  - Based on FDA Adverse Event Reporting System
  - Reporting odds ratio (ROR) of 2.5 or above at System Organ Class level in MeDRA Ontology
  - Cardiotoxicity set: 408 ‘cardiotoxic’ ,66 ‘non-cardiotoxic’
  - Heptotoxicity set: 302 ‘hepatotoxic’ , 168 ‘non-hepatotoxic’
- Data sets divided into training, validation and test sets
  - Ratio 70:15:15

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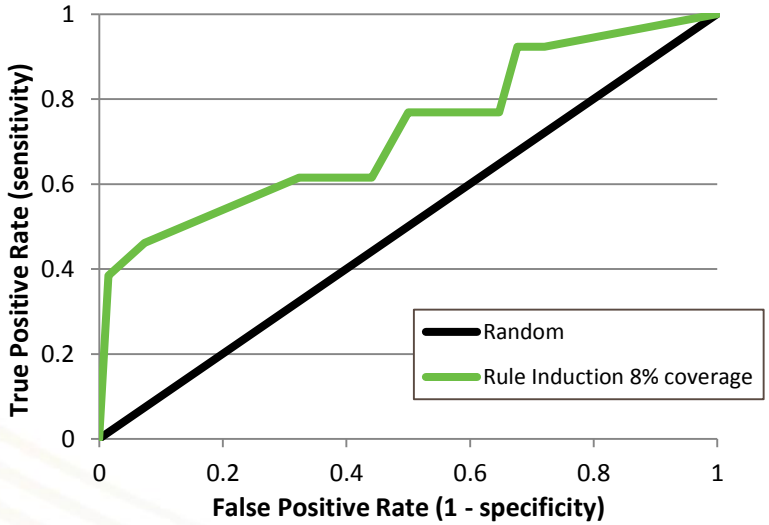
Example Application
Cardiotoxicity results

Profile	Desired Value	Importance
H2	-0.01 -> 2.02	
5HT1A	⩽ 8.08	
A1	⩽ -0.99	

Set	Mean Improvement (%)	Support (%)
Train	233	9.3
Val	173	10
Test	419	7.4



- Selected only 3 targets from 185
  - Rules 'make sense': Targets identified have known CV side effects
- 5/6 compounds meeting all criteria are non-cardiotoxic (83%)
- 19/20 compounds failing all criteria are cardiotoxic (95%)

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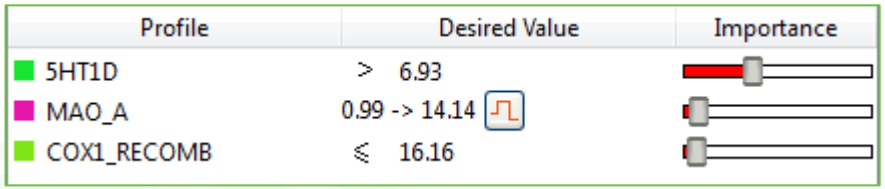
Example Application
Hepatotoxicity results



Set	Mean Improvement (%)	Support (%)
Train	51	12
Val	56	14
Test	39	11

- Rules are (just) statistically significant, but don't 'make sense'
  - Rules appear to be result of noise in small data set
- Large majority of the targets in data set are not known to relate with hepatotoxicity
  - In few examples, e.g. PPARγ there are a statistically insignificant number of inhibitors in the data set
- Non 'black-box' method highlights limitations of data set

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‘Hard’ vs. ‘Soft’ boundaries

Patent pending

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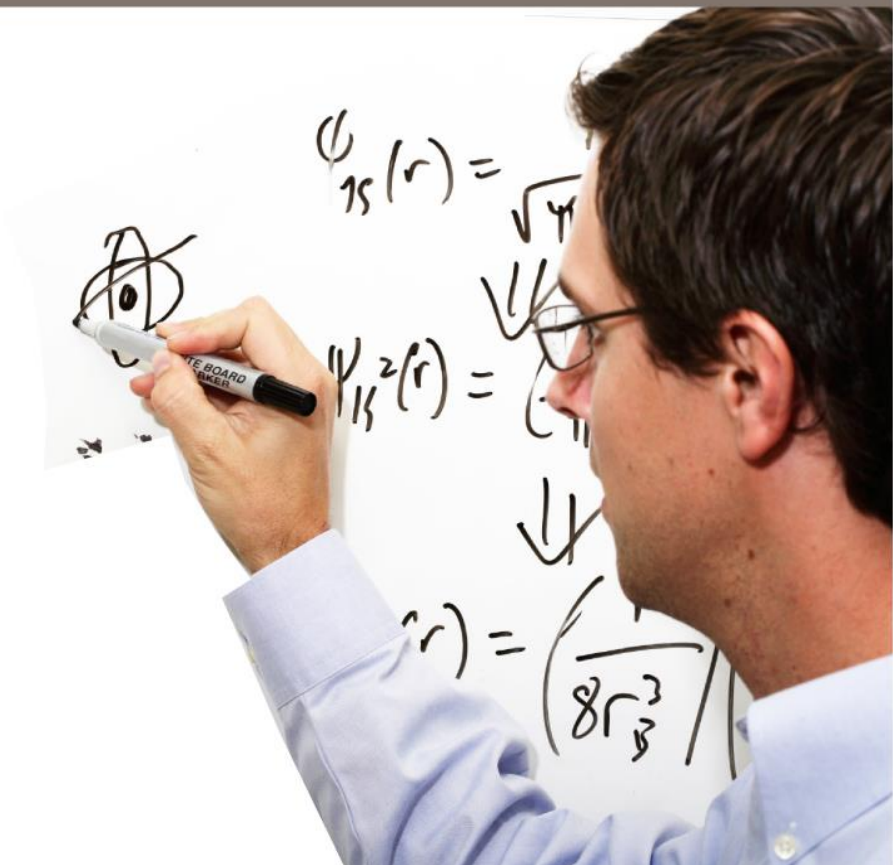
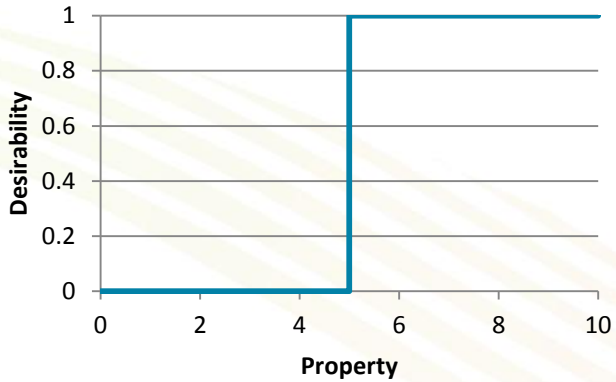


Desirability Functions*

- Relate property values to how ‘desirable’ the outcome



Simple filter: >5

- Avoid hard cut-offs that draw artificially hard distinction between similar compounds

- Add ‘soft’ boundaries to ideal ranges

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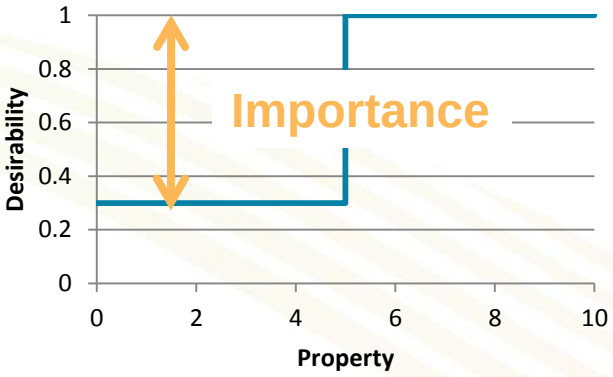
* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Desirability Functions*

- Relate property values to how ‘desirable’ the outcome



Desired value: >5

- Avoid hard cut-offs that draw artificially hard distinction between similar compounds
- Add ‘soft’ boundaries to ideal ranges

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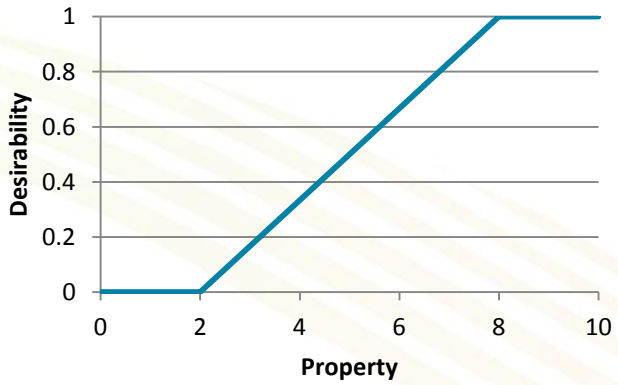
* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Desirability Functions*

- Relate property values to how ‘desirable’ the outcome



Trend: >8

- Avoid hard cut-offs that draw artificially hard distinction between similar compounds
- Add ‘soft’ boundaries to ideal ranges

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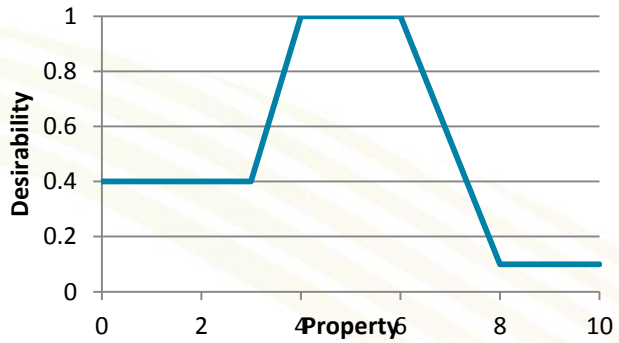
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome



‘Soft’ range: 4-6

- Avoid hard cut-offs that draw artificially hard distinction between similar compounds
- Add ‘soft’ boundaries to ideal ranges

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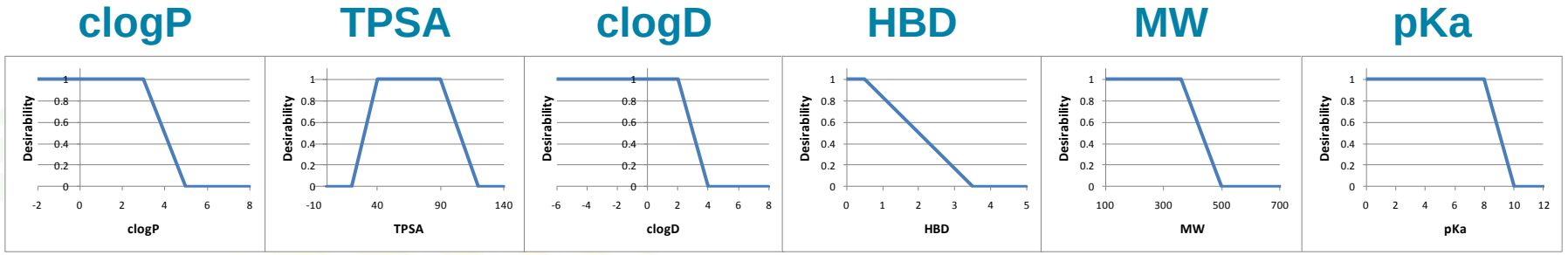
* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Desirability Functions
Example: CNS MPO*



CNS MPO = sum of desirabilities for each parameter

- 74% of marketed CNS drugs achieved CNS MPO > 4 vs. 60% of Pfizer candidates
- Correlations observed between high CNS MPO score and good *in vitro* ADME properties, e.g. MDCK P_{app}, HLM stability, P-gp transport

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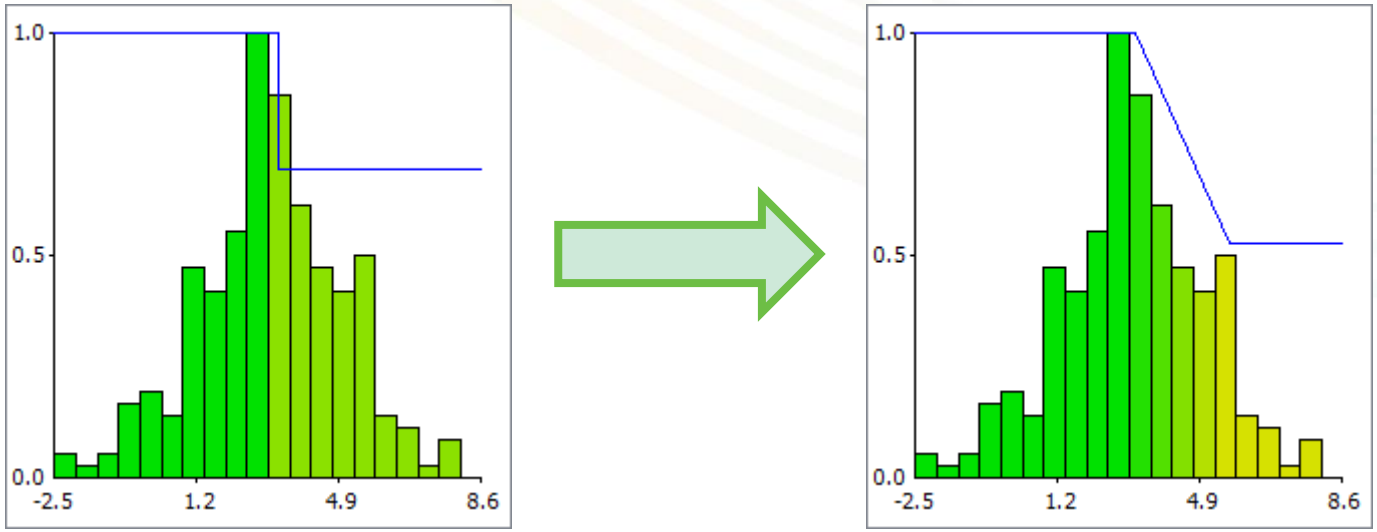
*Wager *et al.* (2010) ACS Chem. Neurosci. **1** p. 435

Determining 'Soft' Box Boundaries

- Box bounds previously only output as hard cut-offs
- Sensitivity analysis of box bounds to data sampling
  - Particularly important for sparse data
  - Incorporate uncertainty into the generated box bounds
  - Cross validation between training/validation sets



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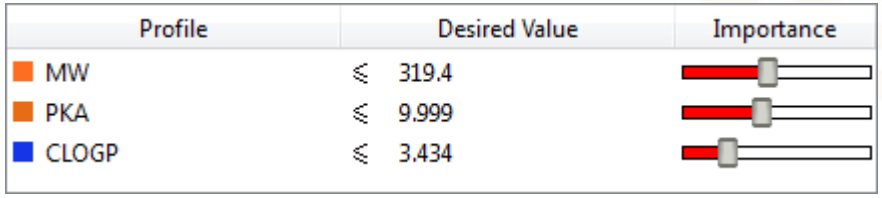
Example Application
CNS Drugs

- Data set of 119 CNS Drugs and 108 Candidates published by Wager *et al.* in CNS MPO paper
- Divided into training, validation and test sets (55:25:20)
- Rule with hard cut-offs:



Set	Mean Improvement (%)	Support (%)
Train	42	28
Val	56	32
Test	47	34

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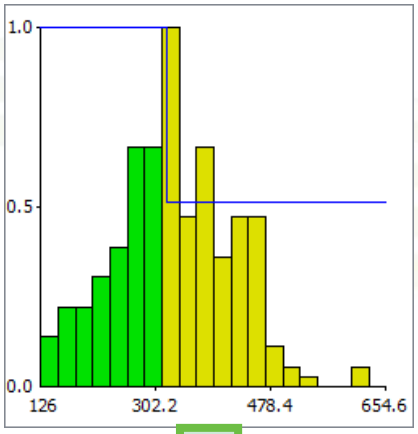
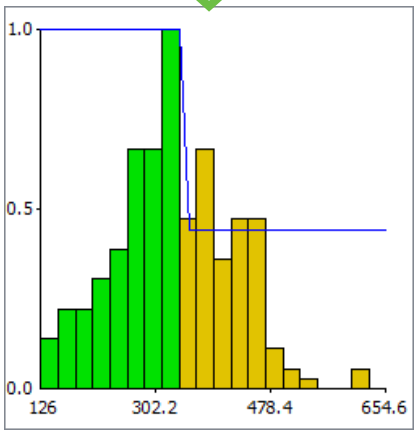
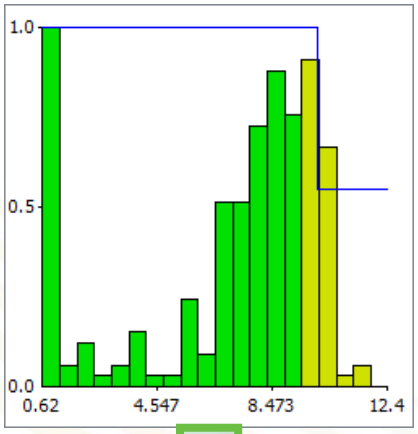
Example Application
CNS Drugs – Introducing 'soft' boundaries

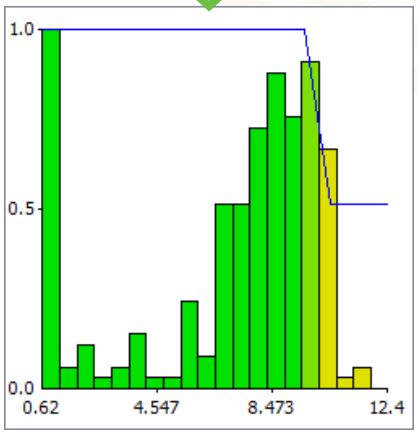
MW



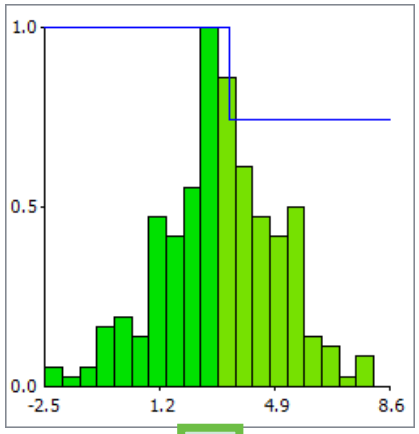


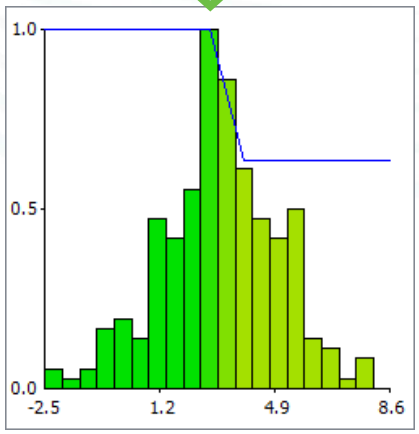
pKa





logP





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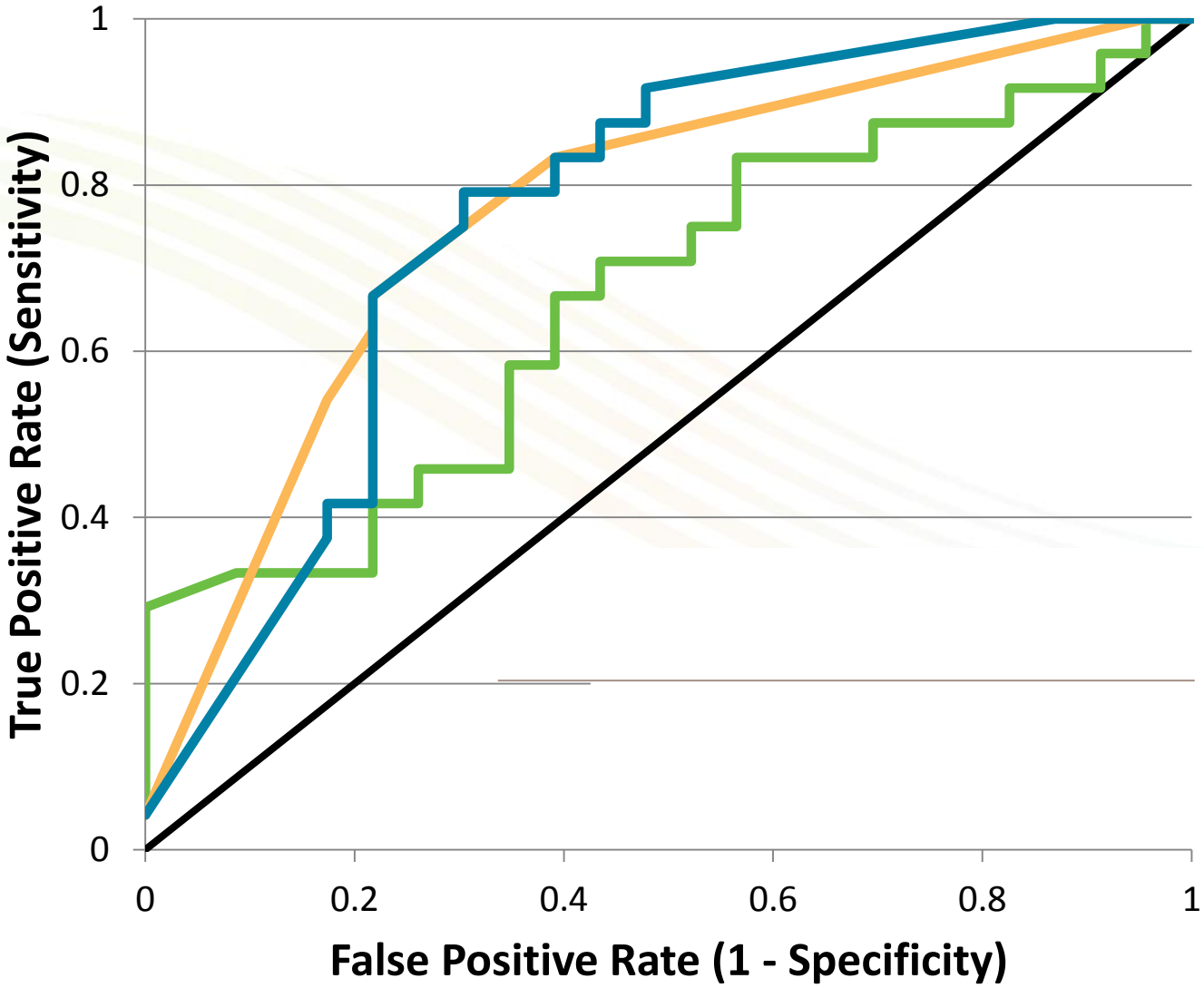
Example Application

CNS Drugs – Comparison of ROC curves for test set



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Testing the Robustness of Your Decisions

Patent pending

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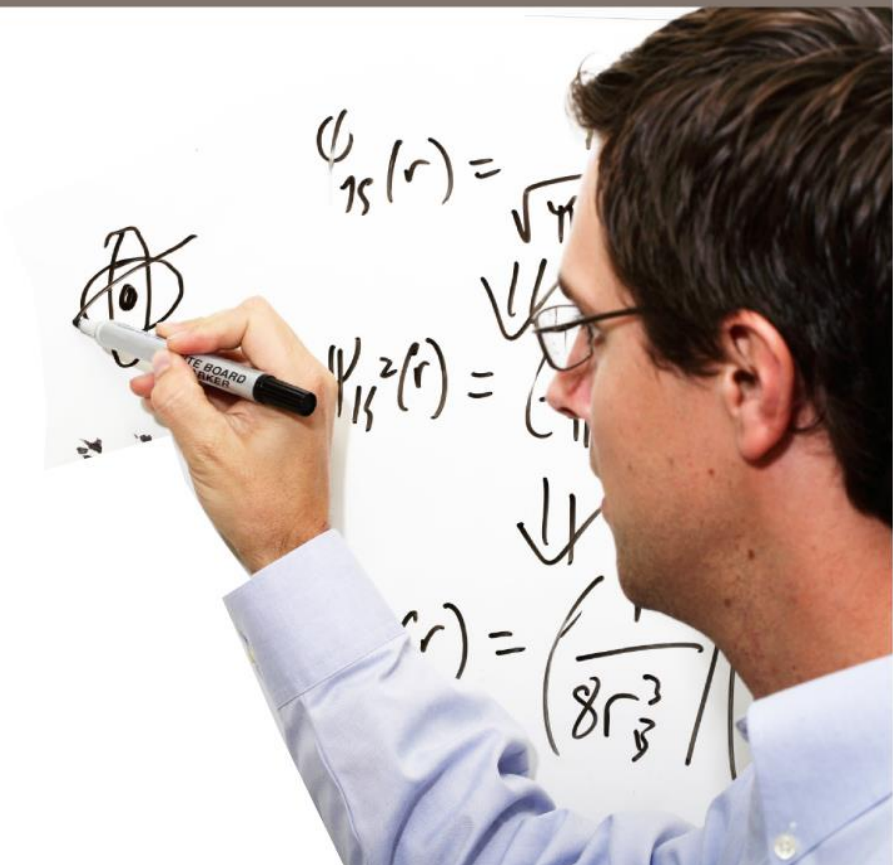

Sensitivity Analysis

- What impact would changing a property criterion have on the *decision* we would make?
  - How large a change is necessary to have a significant impact?
- To which property criteria is compound priority most *sensitive*?
  - Which criteria/importance will, if modified, significantly change the order of compound priority?
- Highlight new avenues for exploration and avoid missed opportunities
- Considerations
  - Need to consider statistical significance of reordering (given uncertainties in scores)
  - Interested in changes to high-ranked compounds. Reordering of rejected compounds is not relevant

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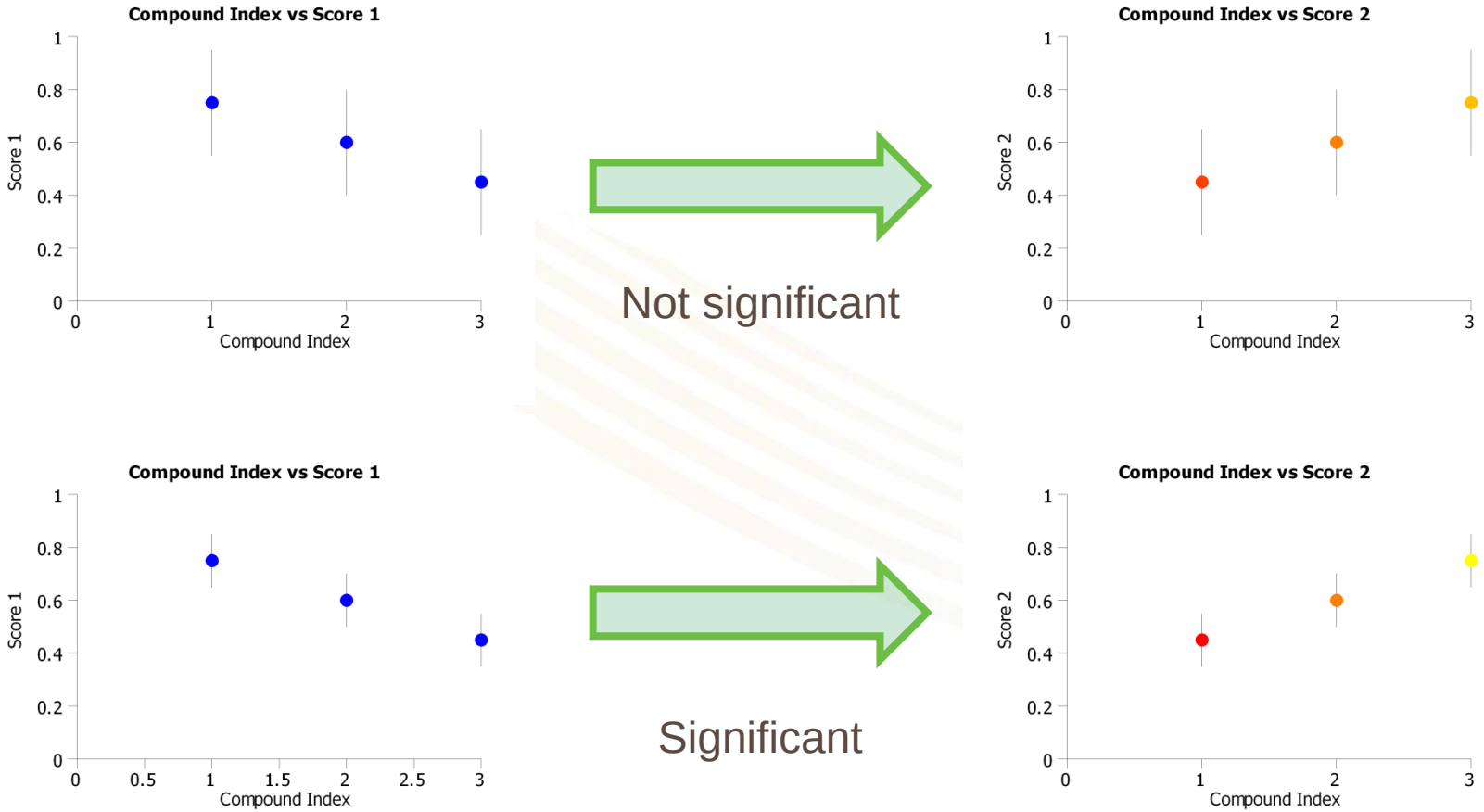
Sensitivity Analysis
Importance of uncertainty



Modified Spearman's rank correlation coefficient accounts for uncertainty

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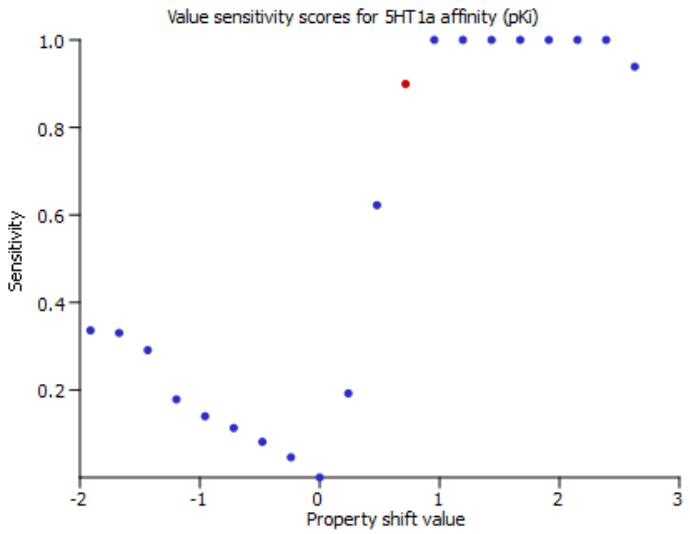
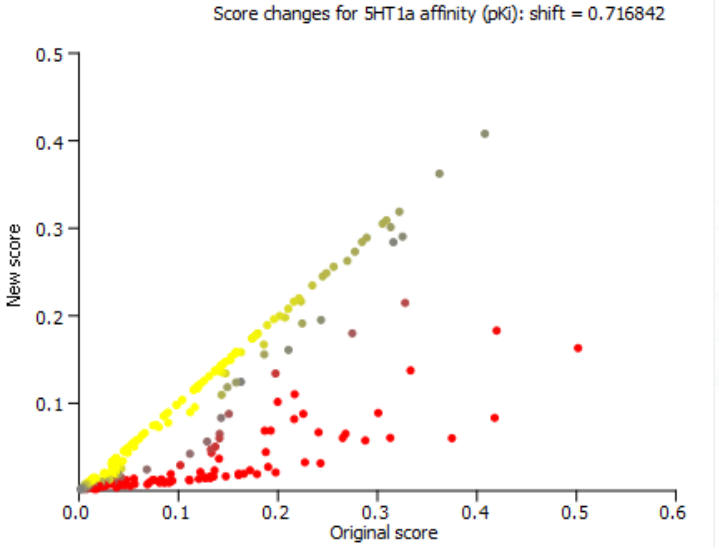
Example Output
Sensitive parameter

What parameters are most sensitive?

	Value Sensitivity	Importance Sensitivity
5HT1a affinity (pKi)	1.000	0.008
logP	0.310	0.096
BBB log([brain]:[blood])	0.249	0.015
hERG pIC50	0.096	0.207
2D6 affinity category	N/A	0.107
BBB category	N/A	0.055
logS	0.040	0.002
		I/A





What magnitude of change has a significant impact?

What compounds are most affected?

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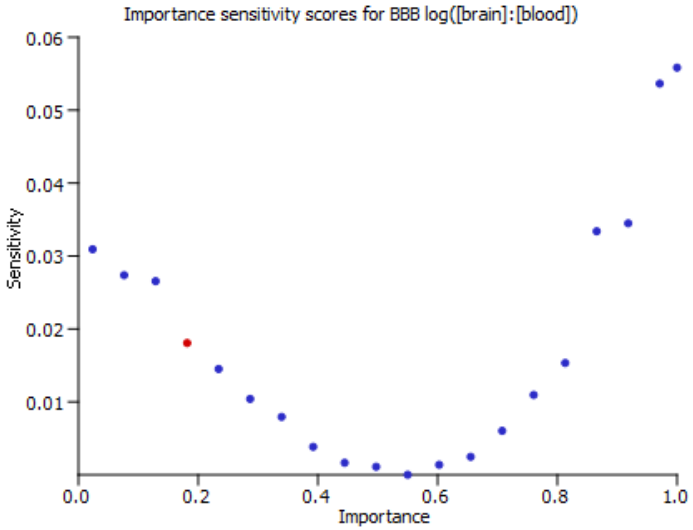
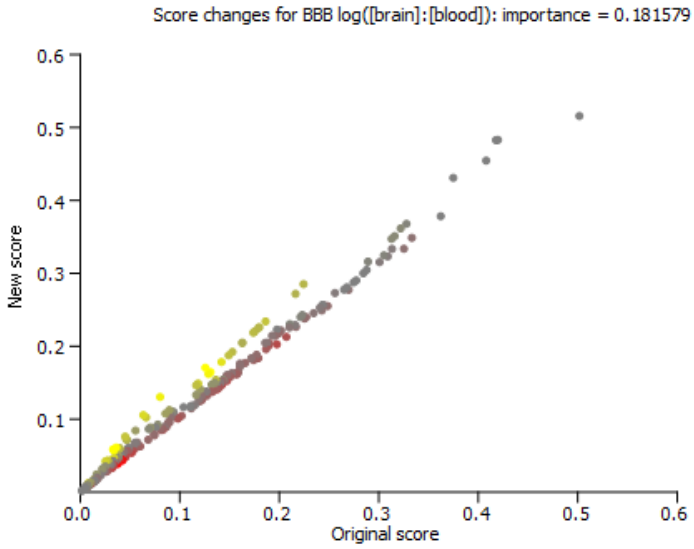
Example Output
Insensitive parameter

What parameters are most sensitive?

	Value Sensitivity	Importance Sensitivity
5HT1a affinity (pKi)	1.000	0.008
logP	0.310	0.096
BBB log([brain]:[blood])	0.249	0.015
hERG pIC50	0.096	0.207
2D6 affinity category	N/A	0.107
BBB category	N/A	0.055
logS	0.040	0.002
	I/A	





What magnitude of change has a significant impact?

What compounds are most affected?

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Conclusion

- Rule induction can generate interpretable parameter scoring profiles tailored project objectives
- 'Soft' boundaries provide more subtle distinctions between compounds
- Sensitivity analysis of scoring criteria is important to avoid missed opportunities due to the criteria we have chosen
- Reference (Rule induction): Yusof *et al.* Drug Discov. Today (2014)
  - 10.1016/j.drudis.2014.01.005
  - www.optibrium.com/community/publications
- See a live demo at Optibrium booth #1516

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