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# Practical Application of Multi-Parameter Optimization to Guide Successful Drug Discovery

**Guiding Optimal Compound Design and Development, March 19th 2015**

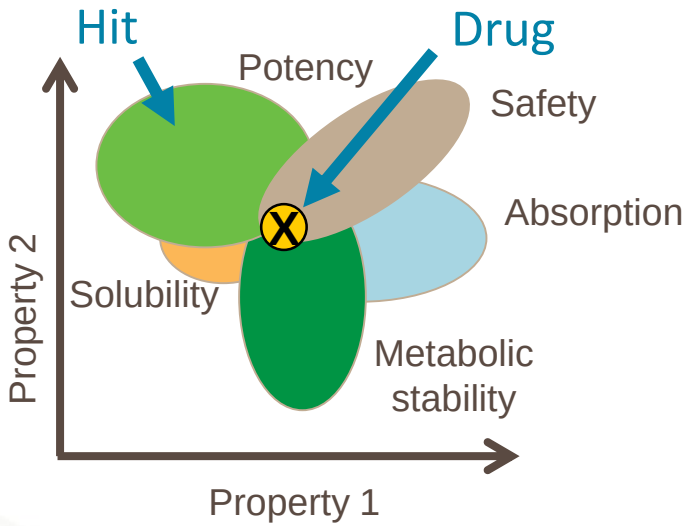
**Matthew Segall, CEO, Optibrium Ltd.**

# Overview

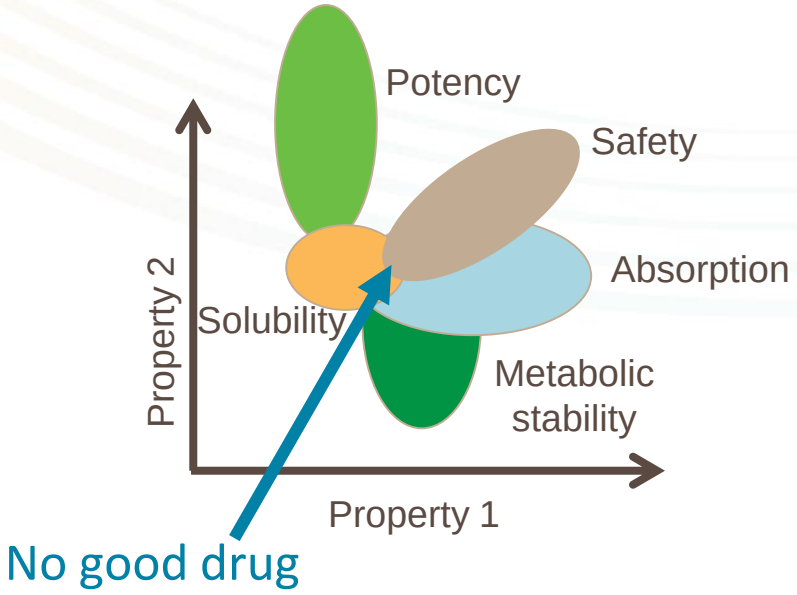
- Multi-parameter optimisation (MPO) in drug discovery
- Practical application of MPO
- Case Study: balancing properties in lead optimisation
- Tailoring property profiles to a project objective
- Example: Properties for CNS drugs
- Conclusions

# Multi-Parameter Optimization
## The objectives

- 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**



# Rules of Thumb
## 'Drug-like' Properties

- The most famous – Lipinski's Rule-of-Five for oral absorption

| | |
|---|---|
| **logP<5** | **MW<500** |
| **HBD<5** | **HBA<10** |

- Many other have been proposed, e.g. Hughes *et al.** explored risk of adverse outcomes in *in vivo* toleration studies

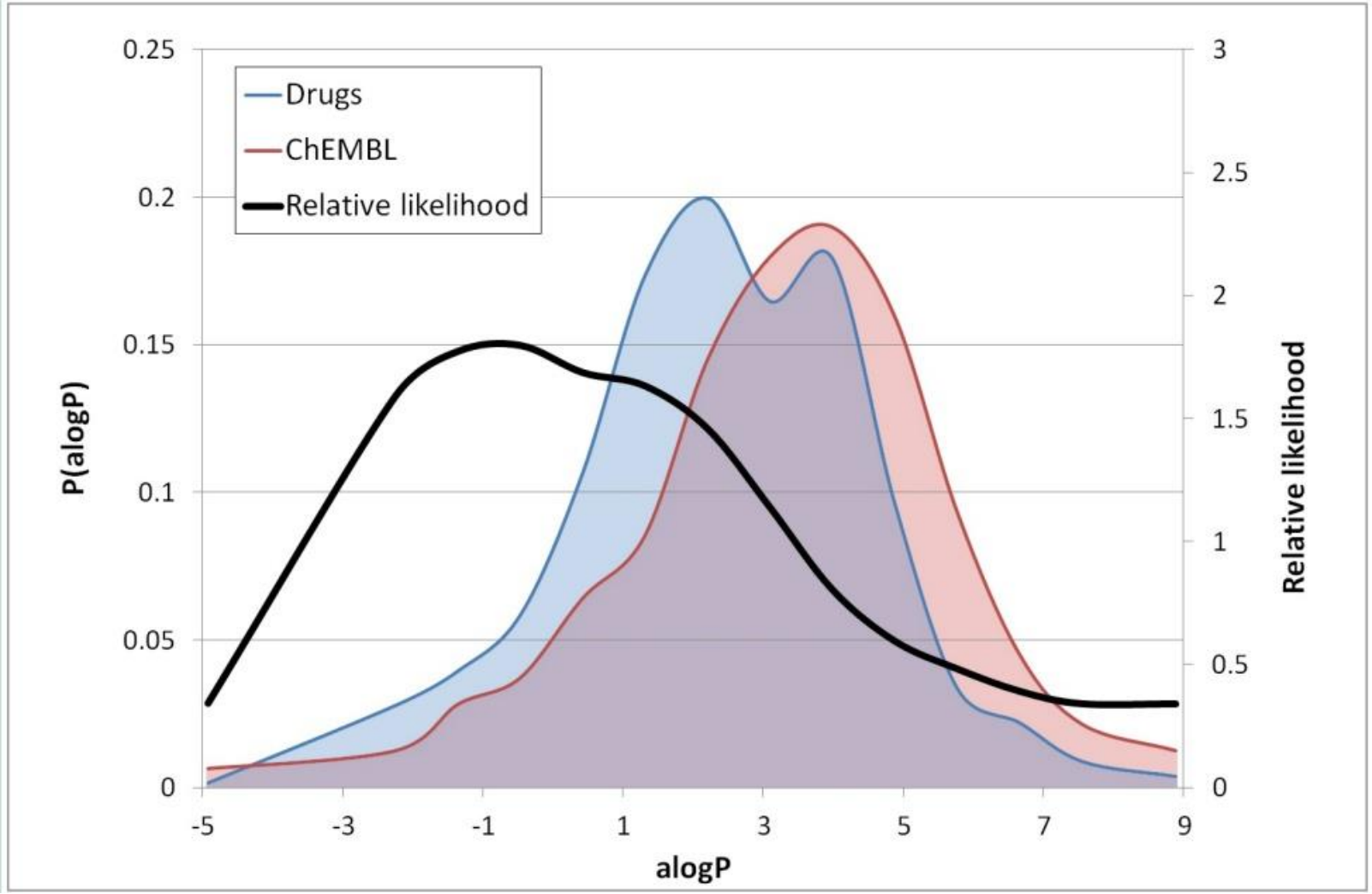
| | |
|---|---|
| **logP<3** | **TPSA>75 Å$^2$** |

- Simple, easy to apply and interpret
- But need to be aware of limitations:
  - Rules tailored to specific objectives
  - Simple parameters do not have strong correlations with outcome



* Hughes *et al.*, Bioorg Med. Chem. Lett. (2008) **18** p. 4875

# Likelihood of Finding a Drug vs. logP





Yusof and Segall, Drug Discov. Today (2013) **18** p. 659

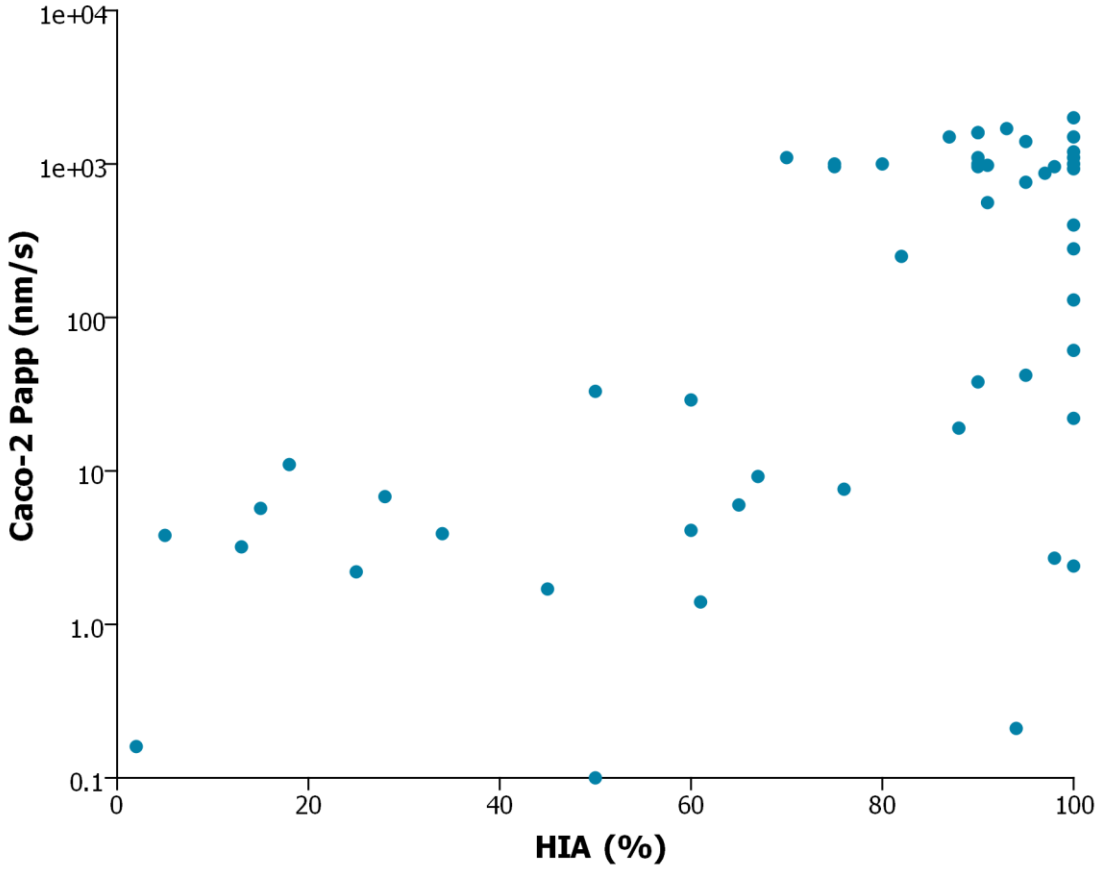
# Ligand Efficiency Indices

- Combine multiple parameters into single metric for optimisation
  - E.g. Ligand Efficiency, $LE = \frac{RT \times pIC_{50}}{N_H} = \frac{1.4 \times pIC_{50}}{N_H}$
- Poor Ligand Lipophilicity Efficiency (LLE) has been shown to increase risk of safety issues*
  - LLE = $pIC_{50}$ – logP
- (Usually) Easy to interpret – only have to monitor one parameter
- Similar limitations to rules of thumb
  - Single non-potency property often has low correlation with outcome
  - Often tailored to specific objective



* Edwards *et al.* (2010) Ann. Rep. Med. Chem **45** p. 381

# Relevance of Experimental Data
## E.g. Caco-2 vs Human Intestinal Absorption*



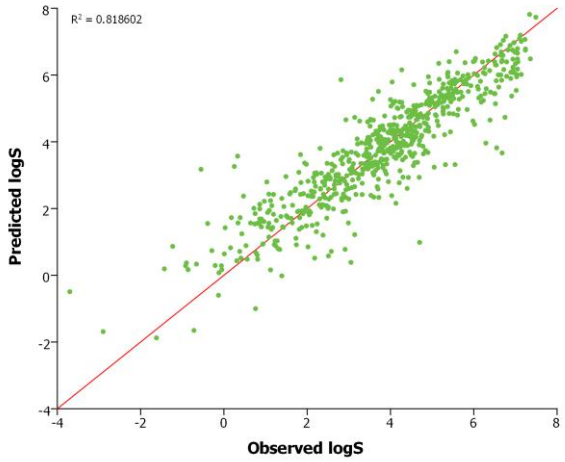



* Irvine *et al.* J. Pharm. Sci. (1999) **88** p. 28

# Uncertainty in Data

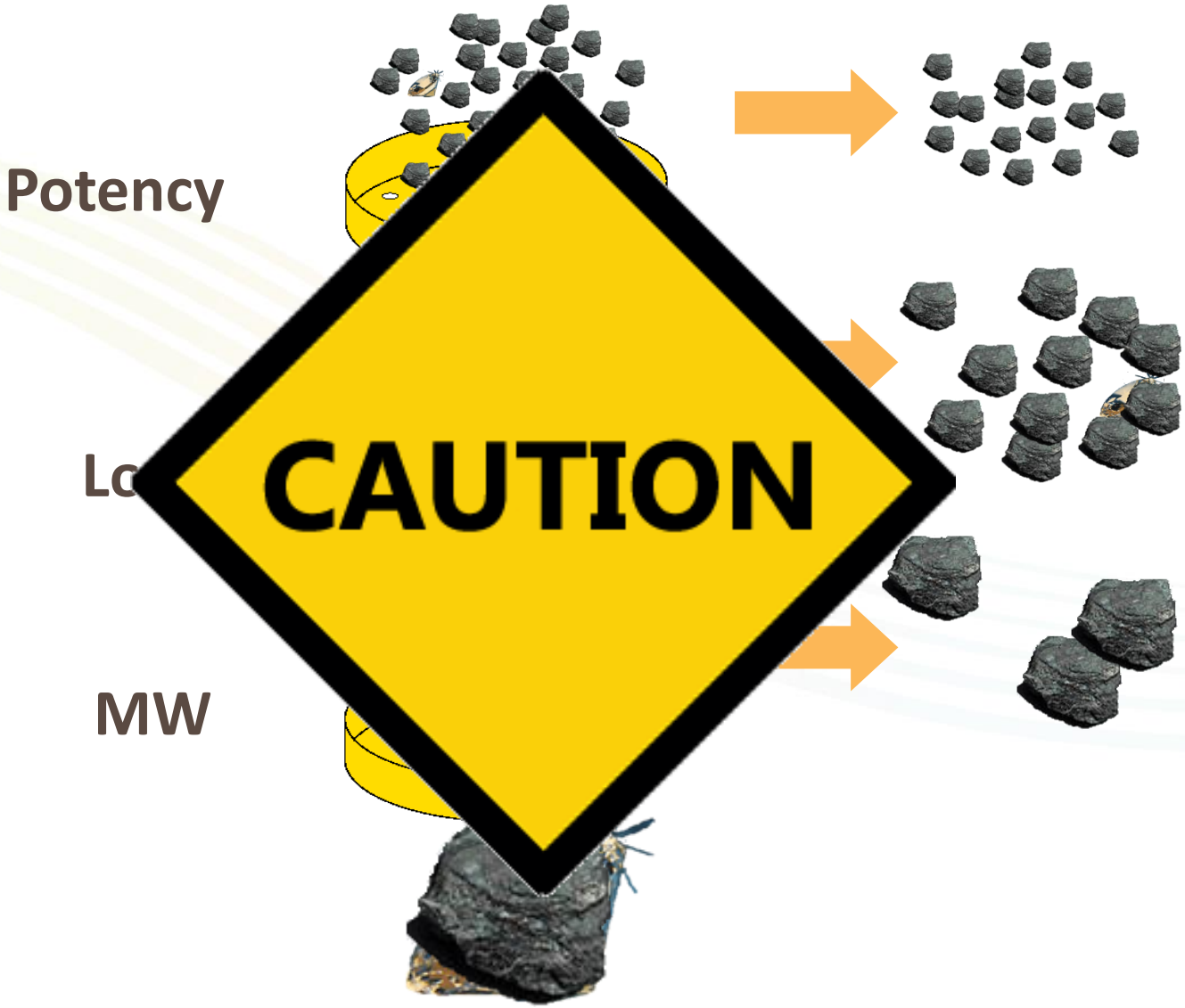
- Experimental variability
  - Single measurements: assay variability
  - Multiple replicates: mean and standard error
- Statistical uncertainty in predictions
  - E.g. Solubility (logS)

$R^2$=0.82
RMSE = 0.8 log units




- Uncertainties combine in efficiency metrics, e.g. LLE
  - $\sigma_{LLE} = \sqrt{\sigma_{pK_i}^2 + \sigma_{logP}^2}$

# Filtering?



# Practical Application of MPO

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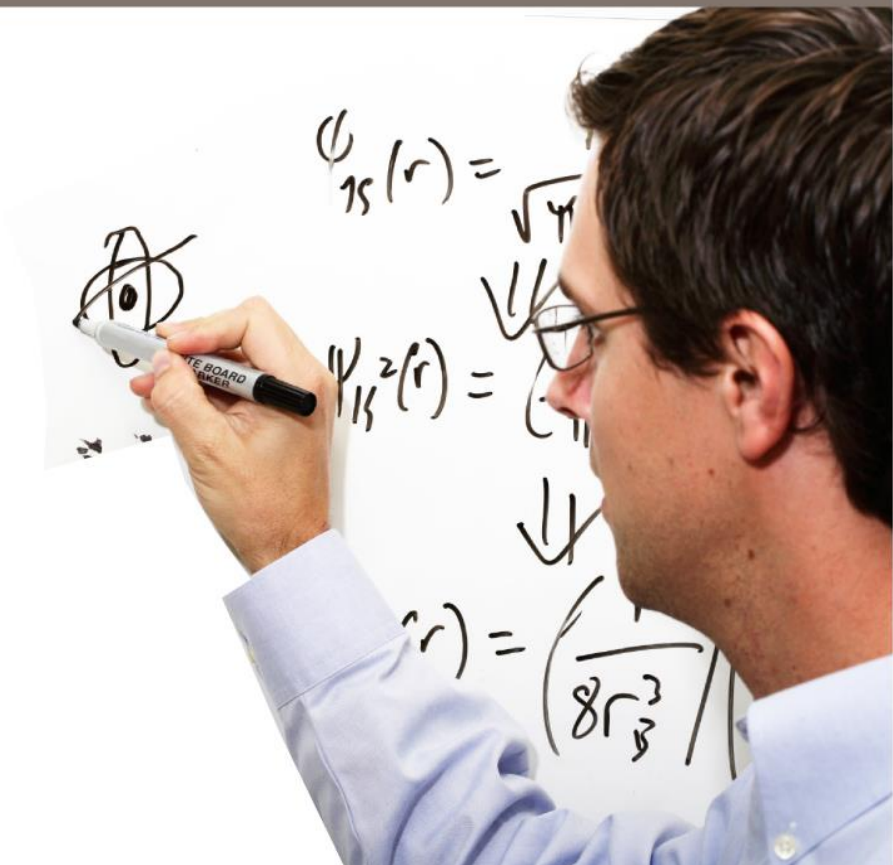
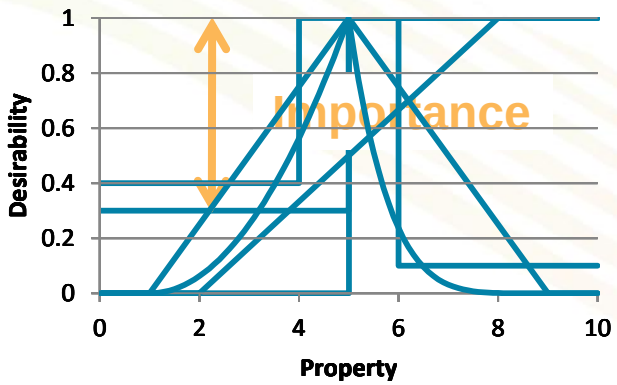


# Accounting for Relevance
## Desirability Functions*

- Avoid ‘hard’ cut-offs
- Relate property values to how ‘desirable’ the outcome

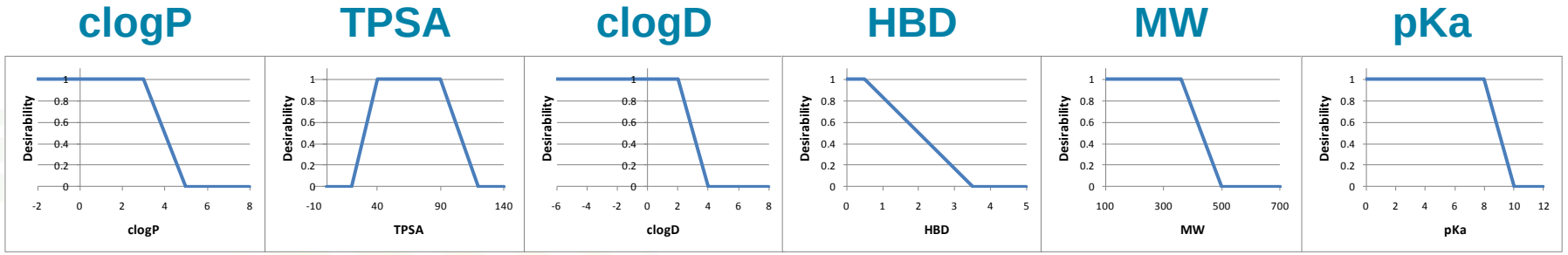



**(Derringer Function)**

- Combine multiple properties into ‘desirability index’
  - Additive: $D = \frac{d_1(Y_1) + d_2(Y_2) + \cdots + d_n(Y_n)}{n}$
  - Multiplicative: $D = (d_1(Y_1) \times d_2(Y_2) \times \ldots \times d_n(Y_n))^{1/n}$


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

# Desirability Functions
## E.g. CNS MPO*



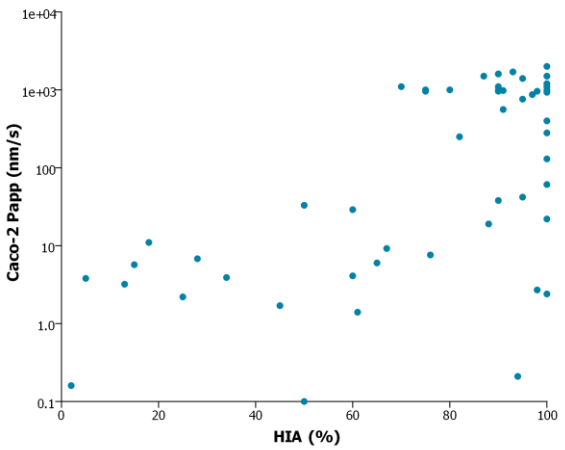

**CNS MPO = sum of desirabilities for each parameter**

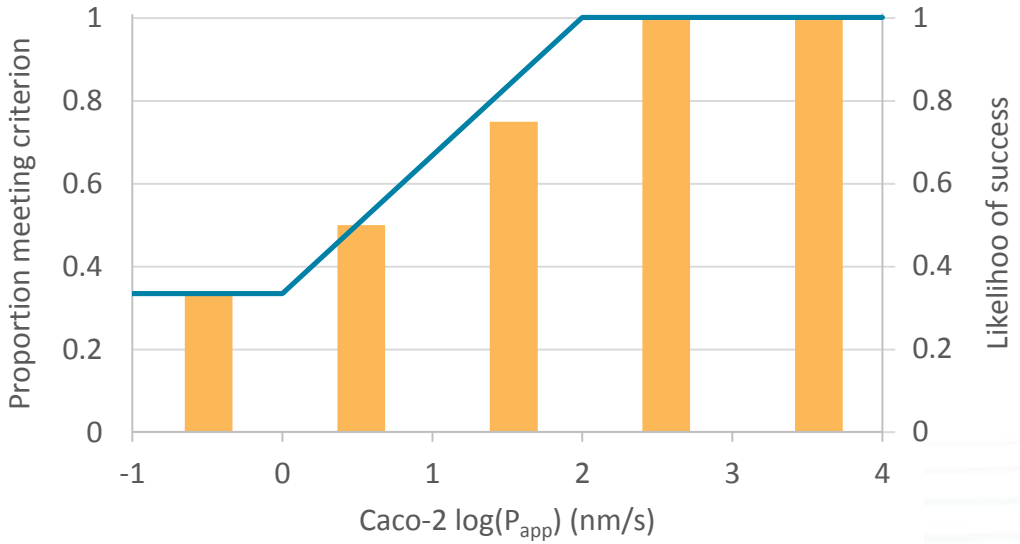
- 74% of marketed CNS drugs achieved CNS MPO > 4 vs. 60% of Pfizer candidates
- Correlations observed between high CNS MPO score and good *in vitro* ADME properties, e.g. MDCK $P_{app}$, HLM stability, P-gp transport


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

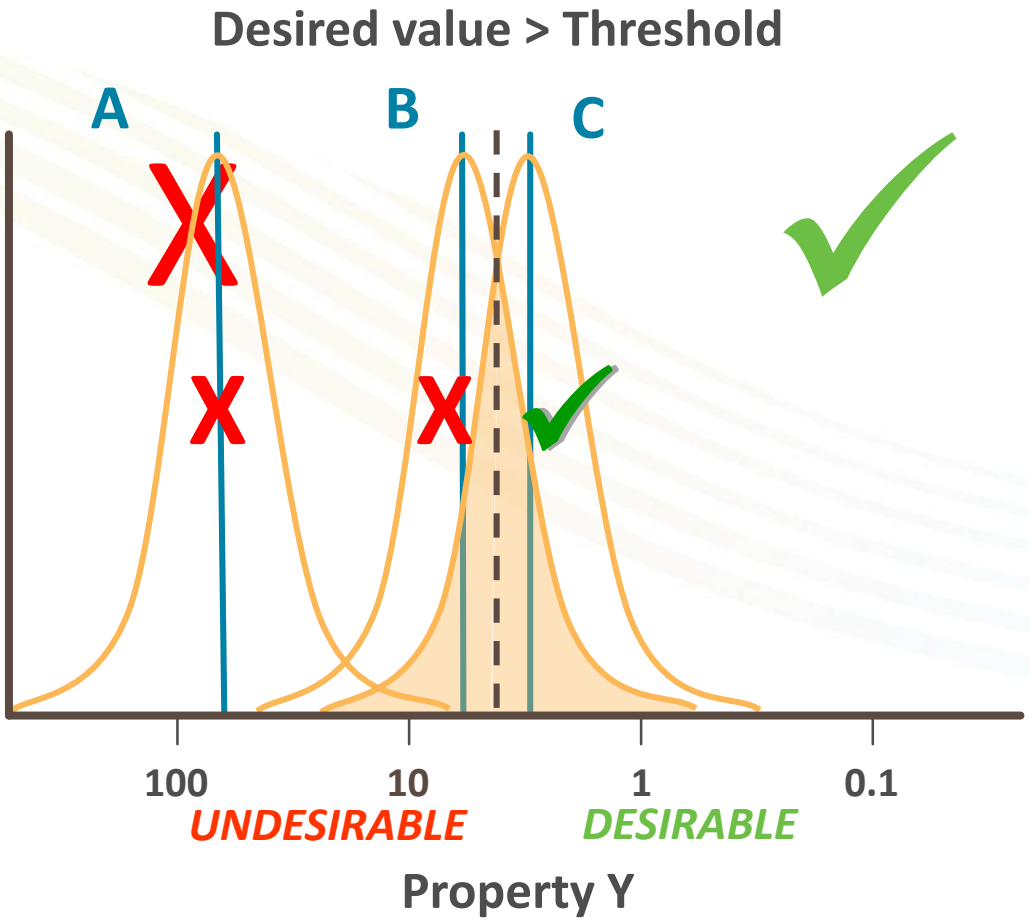
# Desirability Functions
## E.g. Caco-2

- Objective: Human Intestinal Absorption > 50%



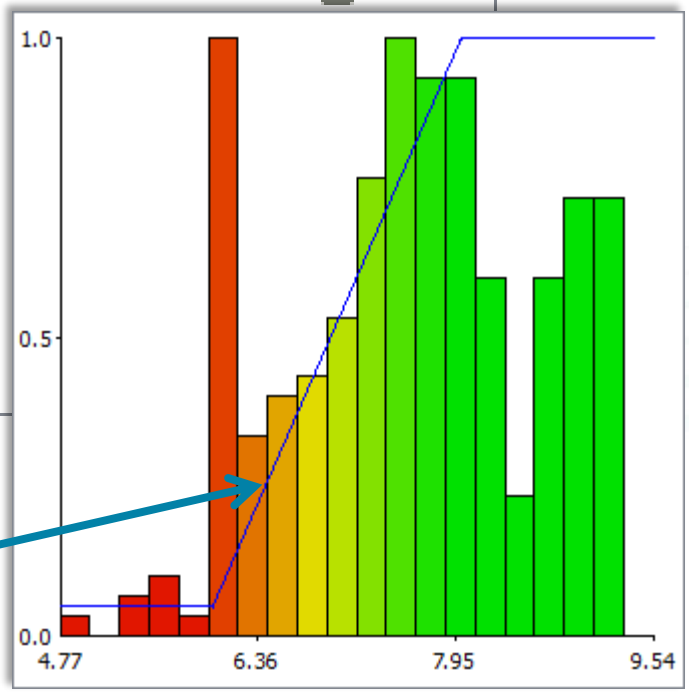



# Taking Uncertainty into Account



# Probabilistic Scoring
## Scoring Profile

| Property | Desired Value | Importance |
|---|---|---|
| 5HT1a affinity (pKi) | 8 -> inf | |
| 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 medium | |
| PPB90 category | low | |




**Desirability function**



Segall *et al.* (2009) Chem. & Biodiv. **6** p. 2144

# Probabilistic Scoring

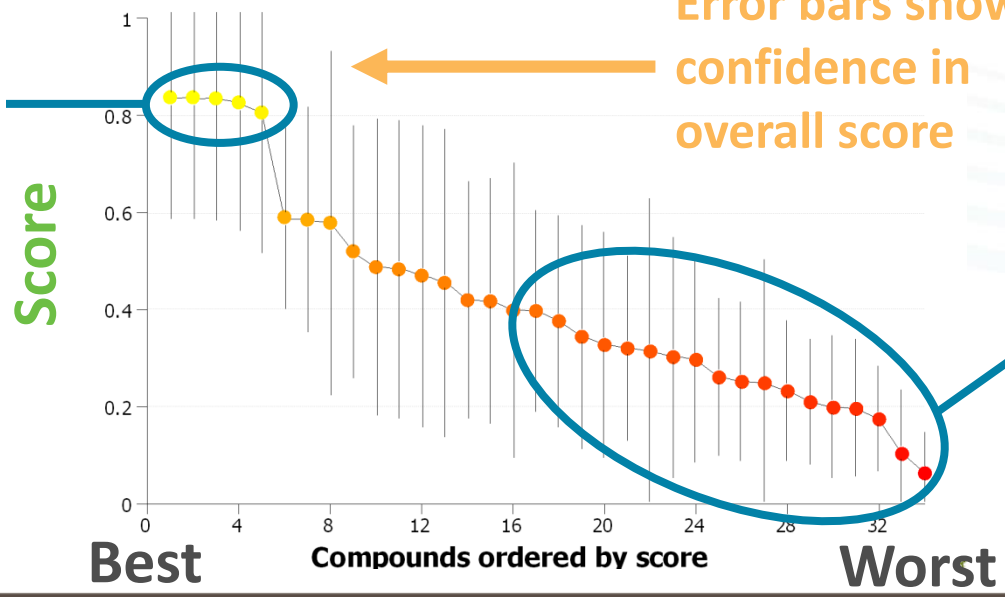
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

- **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**

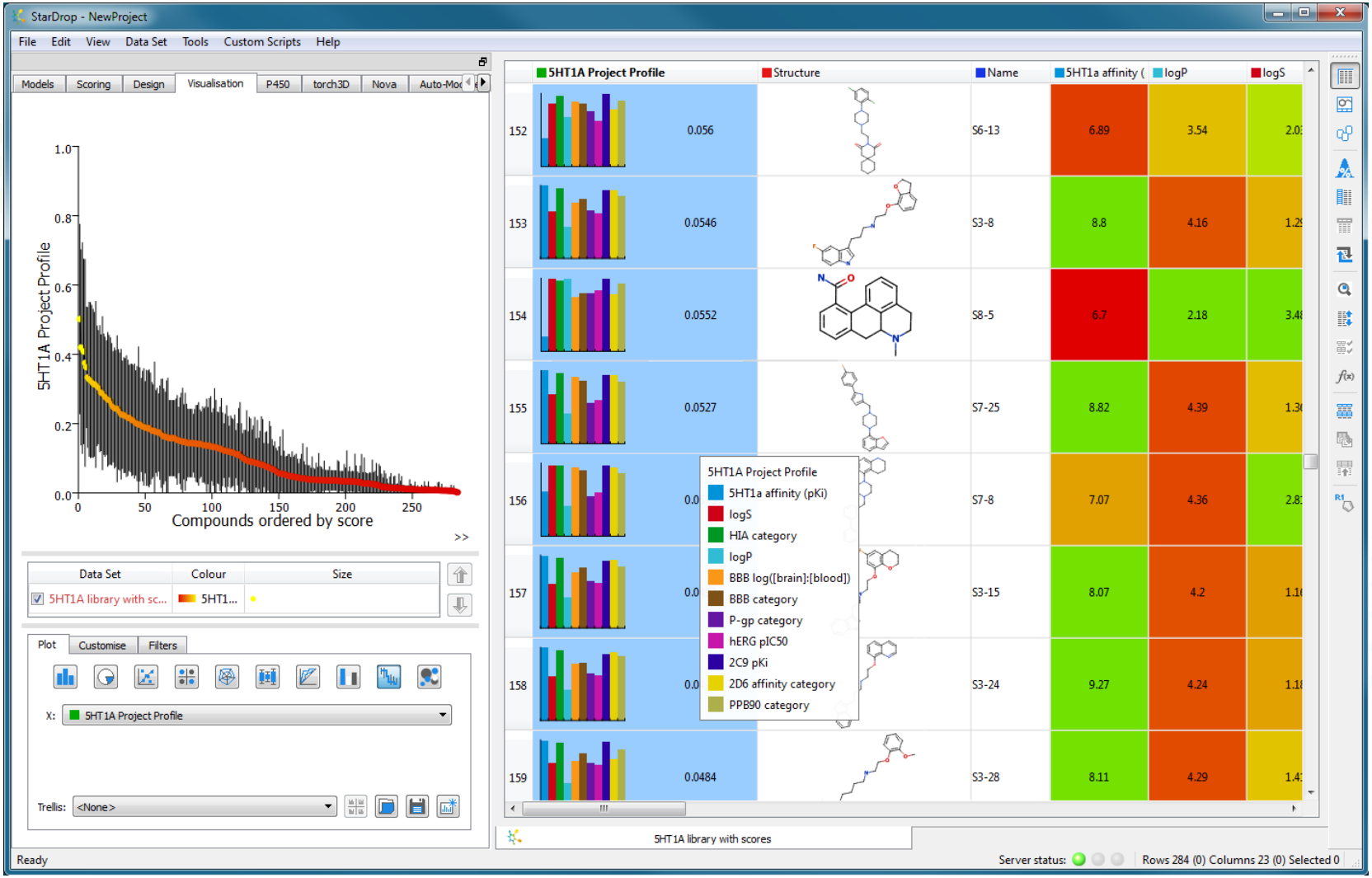





Segall *et al.* (2009) Chem. & Biodiv. **6** p. 2144

# Probabilistic Scoring

## Guide redesign to improve chance of success






Segall *et al.* (2009) Chem. & Biodiv. **6** p. 2144

# Case Study
## Balancing Properties in Lead Optimization

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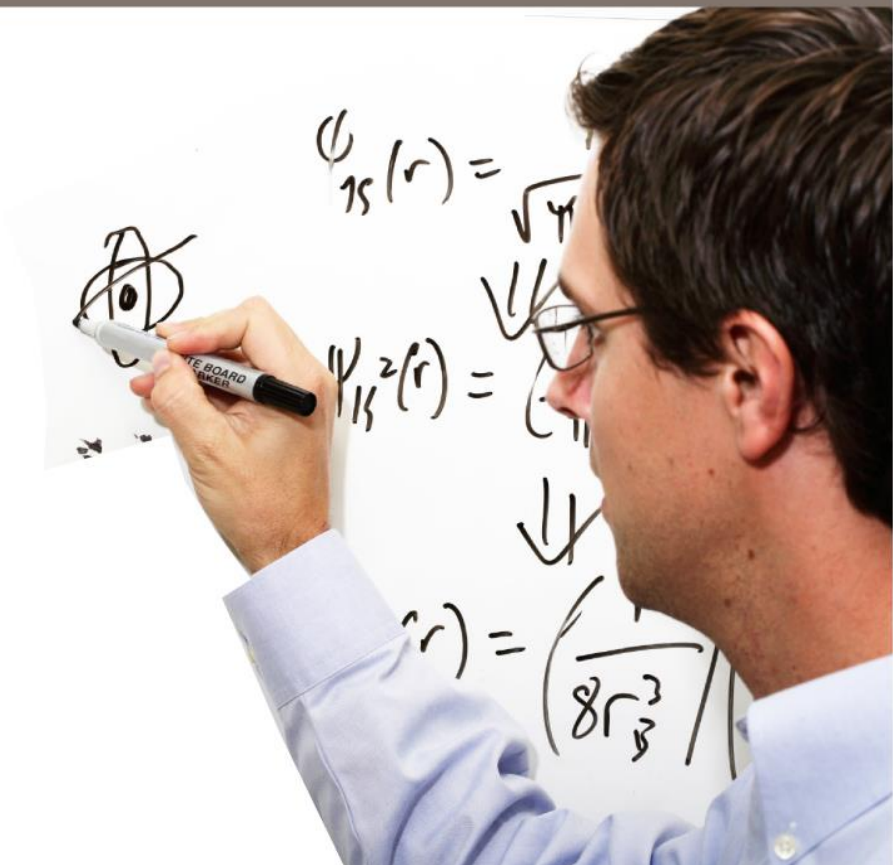

# Case Study*
## Goal: Orally dosed compound against CV target

- *In vitro* data for potency, selectivity, solubility, microsomal stability (human and rat) generated on ~150 compounds
- Original process focused on potency and selectivity, **filtering** compounds that did not meet requirements. Results:
  - Low but prolonged activity after IP dosing
  - No correlation between *in vitro* and *in vivo* potency
  - Problems with solubility and metabolic stability
- Profile for probabilistic scoring:

| Property | Desired Value | Importance |
|---|---|---|
| Selectivity (fold) | > 8 | |
| Potency (uM) | > 6 | |
| Experimental solubility (uM) | > 10 | |
| Experimental HLM (% turnover) | ⩽ 60 | |
| Experimental RLM (% turnover) | ⩽ 60 | |


*Segall *et al.,* Expert Opin. Drug. Metab. Toxicol., **2** pp. 325-37 (2006)

# Comparison of Strategies

**Potency and selectivity**
**No uncertainty - filter**

| | Name | pIC50 | Selectivity (log) |
|---|---|---|---|
| 1 | XXX322 | 6.49 | 1.36 |
| 2 | XXX313 | 6.8 | 1.14 |
| 3 | XXX137 | 6.72 | 1.24 |
| 4 | XXX540 | 6.7 | 1.17 |
| 5 | XXX572 | 6.68 | 1.05 |
| 6 | XXX541 | 6.66 | 0.94 |
| 7 | XXX160 | 6.64 | 1.14 |
| 8 | XXX326 | 6.64 | 1.33 |
| 9 | XXX502 | 6.18 | 1.13 |
| 10 | XXX292 | 6.28 | 1.22 |
| 11 | XXX318 | 6.2 | 1.21 |
| 12 | XXX537 | 6.4 | 0.98 |
| 13 | XXX280 | 6.23 | 1.13 |
| 14 | XXX282 | 6.16 | 0.95 |
| 15 | XXX104 | 6.3 | 1.21 |
| 16 | XXX295 | 6.25 | 0.99 |
| 17 | XXX582 | 6.01 | 1.07 |
| 18 | XXX561 | 6.92 | 0.84 |
| 19 | XXX560 | 6.41 | 0.72 |
| 20 | XXX133 | 6.38 | 0.58 |
| 21 | XXX573 | 6.34 | 0.26 |
| 22 | XXX293 | 6.3 | 0.79 |
| 23 | XXX023 | 6.3 | 0.54 |
| 24 | XXX294 | 6.28 | 0.89 |
| 25 | XXX649 | 6.28 | 0.57 |
| ... | | | |
| 50 | XXX015 | 5.95 | 0.42 |
| 51 | XXX136 | 5.94 | 0.46 |
| 52 | XXX027 | 5.92 | 0.59 |
| 53 | XXX284 | 5.9 | 0.77 |
| 54 | XXX323 | 5.9 | 0.95 |
| 55 | XXX017 | 5.9 | 0.36 |
| 56 | XXX025 | 5.89 | 0.71 |
| 57 | XXX319 | 5.89 | 0.56 |
| 58 | XXX289 | 5.89 | 1.14 |
| 59 | XXX297 | 5.88 | 0.5 |
| 60 | XXX574 | 5.88 | 0.18 |

**Potency and selectivity**
**Consider uncertainty**

| | Name | pIC50 | Selectivity (log) |
|---|---|---|---|
| 1 | XXX326 | 6.64 | 1.33 |
| 2 | XXX137 | 6.72 | 1.24 |
| 3 | XXX322 | 6.49 | 1.36 |
| 4 | XXX313 | 6.8 | 1.14 |
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| 6 | XXX160 | 6.64 | 1.14 |
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| 13 | XXX537 | 6.4 | 0.98 |
| 14 | XXX280 | 6.23 | 1.13 |
| 15 | XXX502 | 6.18 | 1.13 |
| 16 | XXX295 | 6.25 | 0.99 |
| 17 | XXX294 | 6.28 | 0.89 |
| 18 | XXX278 | 6.24 | 0.9 |
| 19 | XXX282 | 6.16 | 0.95 |
| 20 | XXX293 | 6.3 | 0.79 |
| 21 | XXX560 | 6.41 | 0.72 |
| 22 | XXX582 | 6.01 | 1.07 |
| 23 | XXX289 | 5.89 | 1.14 |
| 24 | XXX879 | 6.13 | 0.76 |
| 25 | XXX133 | 6.38 | 0.58 |
| ... | | | |
| 50 | XXX316 | 5.63 | 1.02 |
| 51 | XXX319 | 5.89 | 0.56 |
| 52 | XXX655 | 6.11 | 0.34 |
| 53 | XXX518 | 5.78 | 0.67 |
| 54 | XXX110 | 6.12 | 0.32 |
| 55 | XXX136 | 5.94 | 0.46 |
| 56 | XXX062 | 5.98 | 0.42 |
| 57 | XXX297 | 5.88 | 0.5 |
| 58 | XXX186 | 6.27 | 0.21 |
| 59 | XXX015 | 5.95 | 0.42 |
| 60 | XXX315 | 5.8 | 0.51 |

**All properties**
**Consider uncertainty**

| | Name | pIC50 | Selectivity (log) | Expt. Solubility | Expt. HLM | Expt. RLM |
|---|---|---|---|---|---|---|
| 1 | XXX572 | 6.68 | 1.05 | 136 | 36.5 | 85.6 |
| 2 | XXX518 | 5.78 | 0.67 | 148 | 4.03 | 38 |
| 3 | XXX582 | 6.01 | 1.07 | 132 | 84.1 | 29.9 |
| 4 | XXX295 | 6.25 | 0.99 | 146 | 63 | 77 |
| 5 | XXX321 | 6 | 0.87 | 193 | 55.8 | 71.9 |
| 6 | XXX502 | 6.18 | 1.13 | 127 | 95.6 | 64.6 |
| 7 | XXX292 | 6.28 | 1.22 | 192 | 89 | 88 |
| 8 | XXX274 | 5.81 | 0.89 | 124 | 91.9 | 49.2 |
| 9 | XXX025 | 5.89 | 0.71 | 136 | 54.2 | 77.5 |
| 10 | XXX280 | 6.23 | 1.13 | 165 | 83.6 | 76 |
| 11 | XXX316 | 5.63 | 1.02 | 190 | 57.8 | 78.1 |
| 12 | XXX278 | 6.24 | 0.9 | 144 | 88.9 | 70.8 |
| 13 | XXX294 | 6.28 | 0.89 | 196 | 87 | 92 |
| 14 | XXX282 | 6.16 | 0.95 | 185 | 78.4 | 84.6 |
| 15 | XXX293 | 6.3 | 0.79 | 111 | 97.8 | 81.7 |
| 16 | XXX319 | 5.89 | 0.56 | 178 | 60.3 | 87.9 |
| 17 | XXX284 | 5.9 | 0.77 | 185 | 70 | 71.3 |
| 18 | XXX111 | 5.73 | 0.6 | 116 | 59.9 | 93.9 |
| 19 | XXX289 | 5.89 | 1.14 | 103 | 95.3 | 66.7 |
| 20 | XXX277 | 5.85 | 0.98 | 194 | 91.4 | 83.8 |
| 21 | XXX313 | 6.8 | 1.14 | 8.95 | 71.4 | 53.5 |
| 22 | XXX517 | 5.82 | 0.85 | 137 | 90 | 95.3 |
| 23 | XXX160 | 6.64 | 1.14 | 23.7 | 80.9 | 29.9 |
| 24 | XXX468 | 5.69 | 0.97 | 118 | 82.1 | 87.7 |
| 25 | XXX537 | 6.4 | 0.98 | 6.59 | 75.8 | 47 |

- New series identified with oral bioavailability and efficacy
- New direction for project


*Segall *et al.,* Expert Opin. Drug. Metab. Toxicol., **2** pp. 325-37 (2006)

# Tailoring Profiles to a Project Objective

Patent pending

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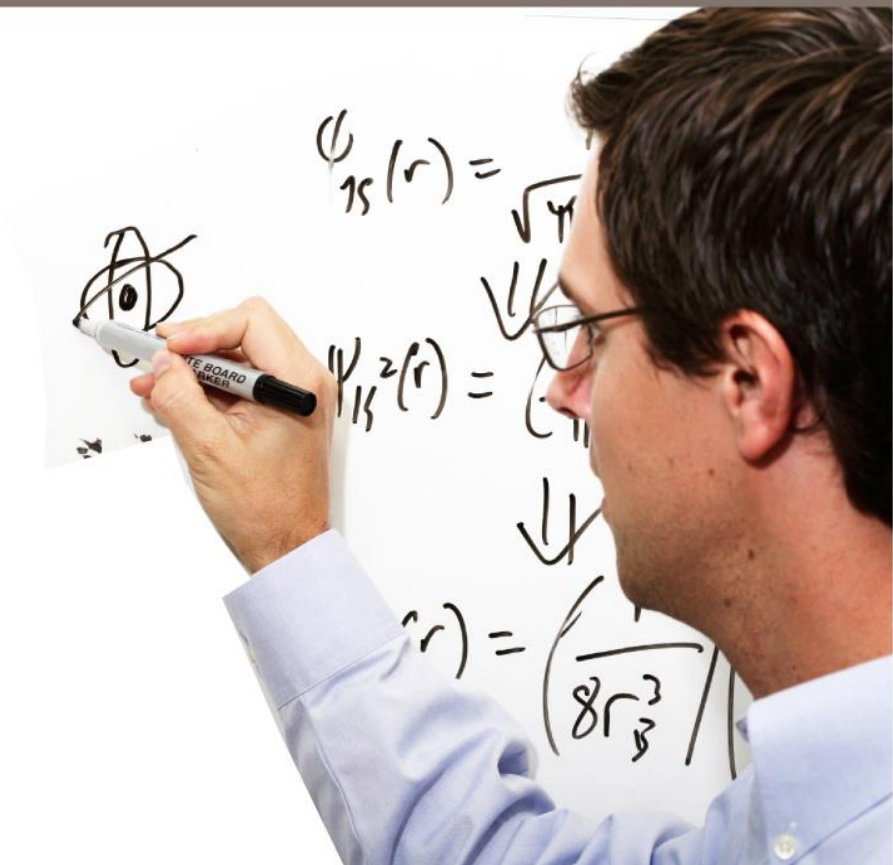
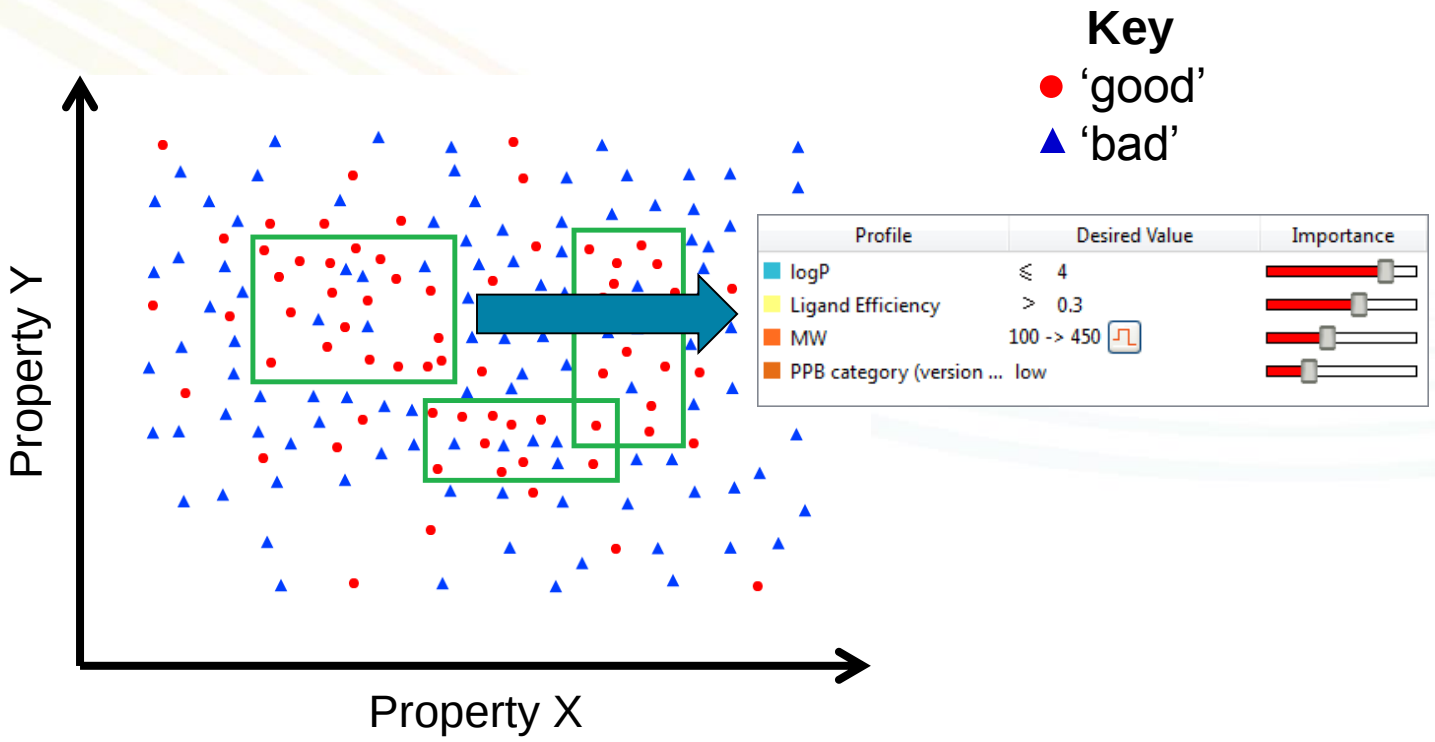


# Finding Tailored Profiles
## Objectives

- 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
- Criteria should interpretable and modifiable
  - Avoid black boxes
  - Synergy between computer and experts

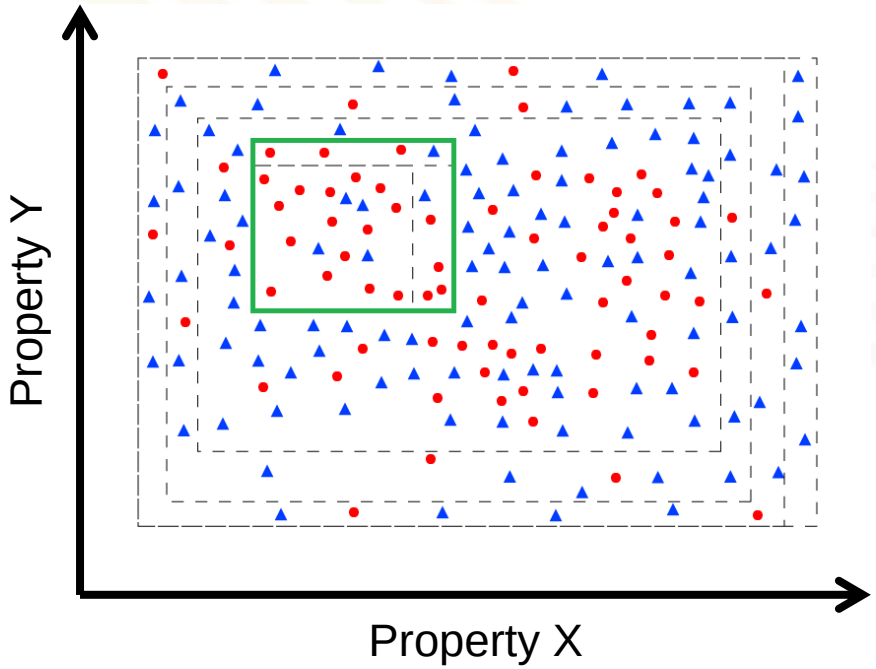
# What is a Rule?

- A **Rule** is a box in multi-dimensional property space containing significantly more ‘good’ than ‘bad’ compounds



# Rule Induction

- 'Rule induction' method identifies multi-parameter regions of property space with higher chance of success
  - Also known as 'bump hunting' because it can find property regions corresponding to small increases in probability distribution



# Example Application
## ‘CNS’ Properties

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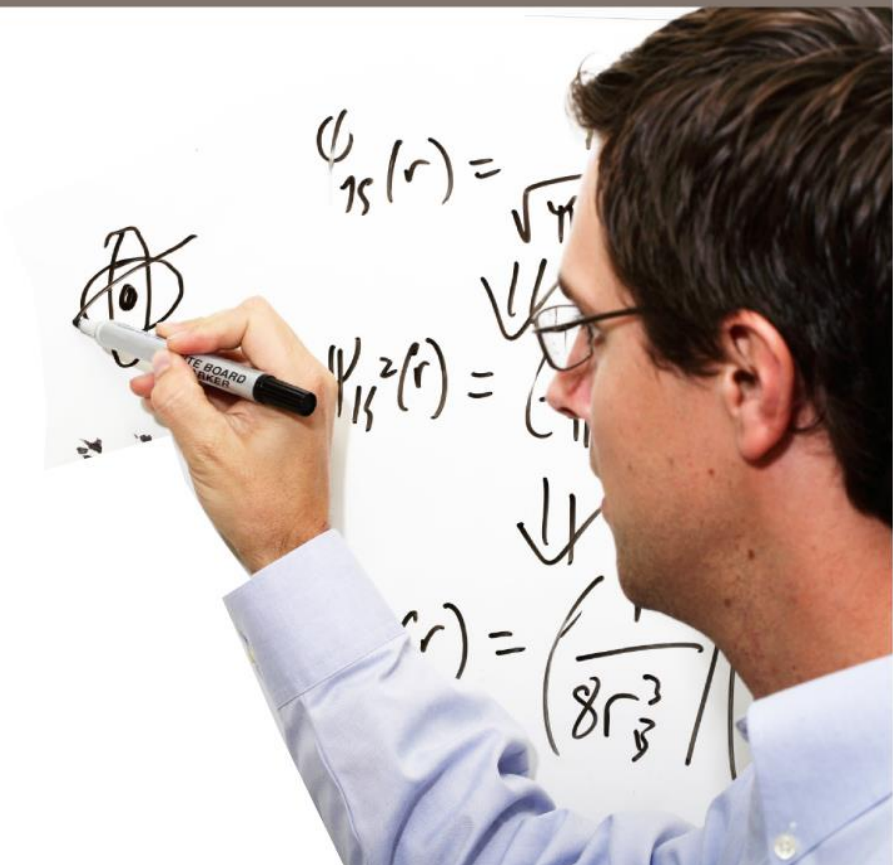
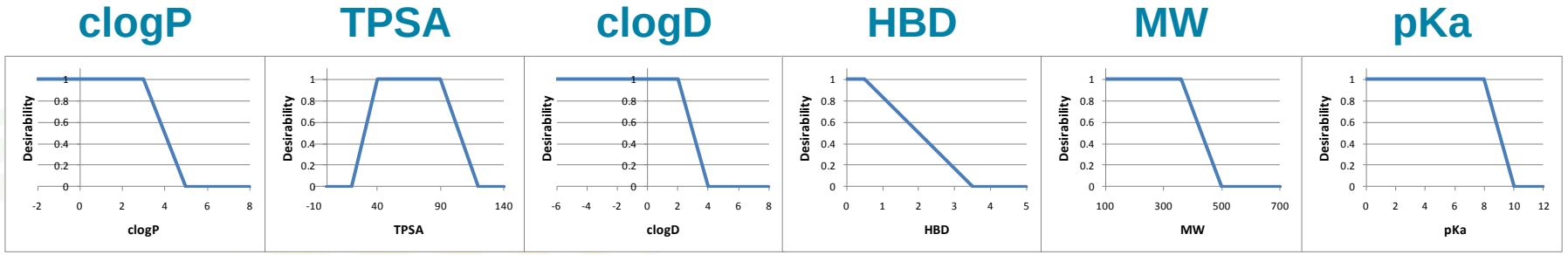


# Desirability Functions
## E.g. CNS MPO*




**CNS MPO = sum of desirabilities for each parameter**

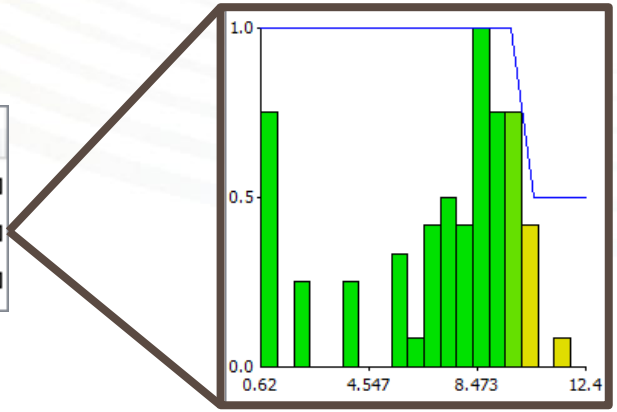
- 74% of marketed CNS drugs achieved CNS MPO > 4 vs. 60% of Pfizer candidates
- Correlations observed between high CNS MPO score and good *in vitro* ADME properties, e.g. MDCK $P_{app}$, HLM stability, P-gp transport


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

# Finding CNS Drugs
## Applying Rule Induction

- Data set of 119 CNS drugs and 108 failed candidates published by Wager *et al.**
- Divided into training and validation sets (70:30)
- Rule derived with 20% minimum coverage:

| Profile | Desired Value | Importance |
|---|---|---|
| MW | -inf -> 312.5 | |
| PKA | -inf -> 9.676 | |
| CLOGP | -inf -> 2.973 | |



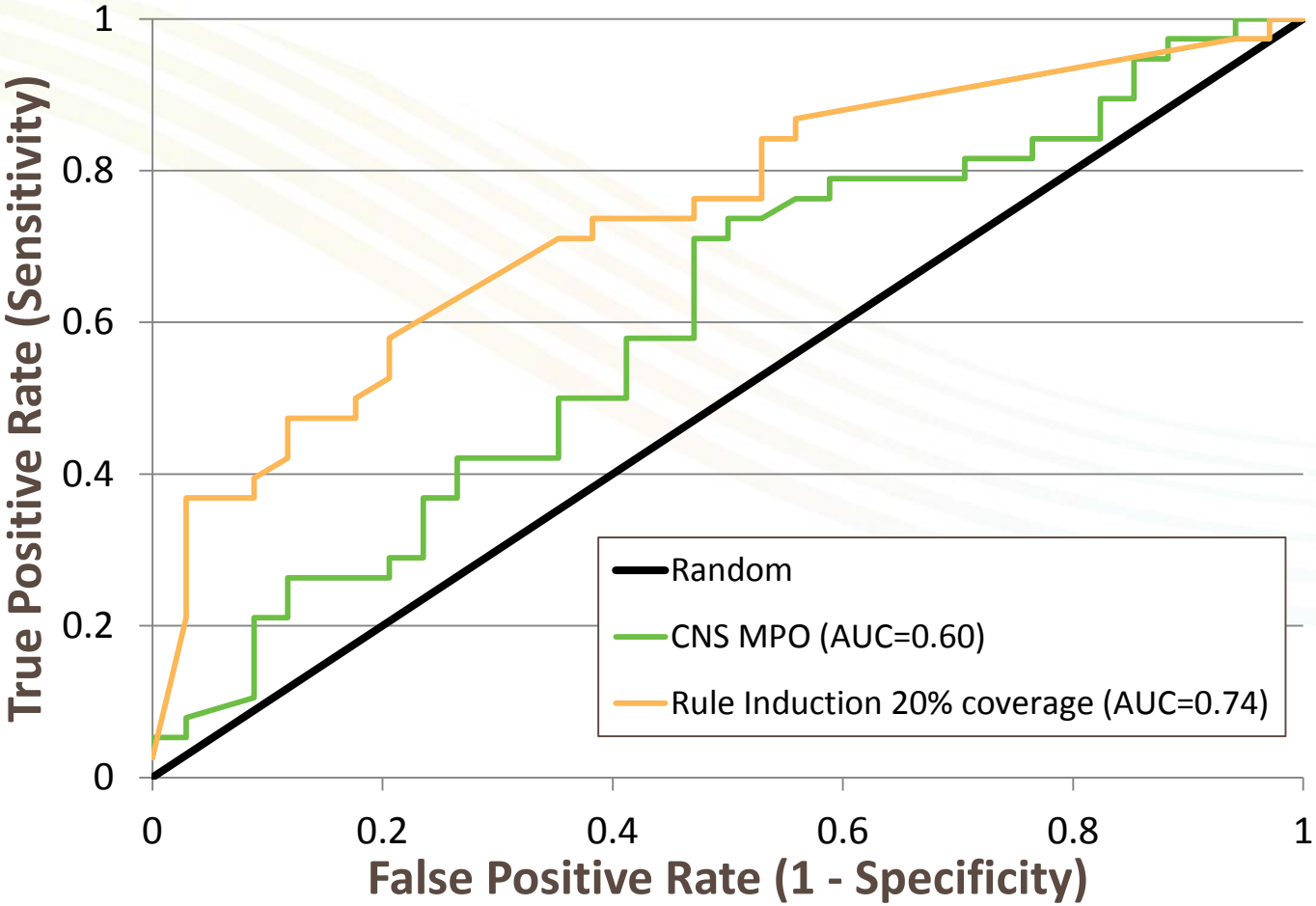

PKA



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

# Finding CNS Drugs
## Validation Results – ROC plot

- 38 CNS drugs and 34 failed candidates from Wager dataset*

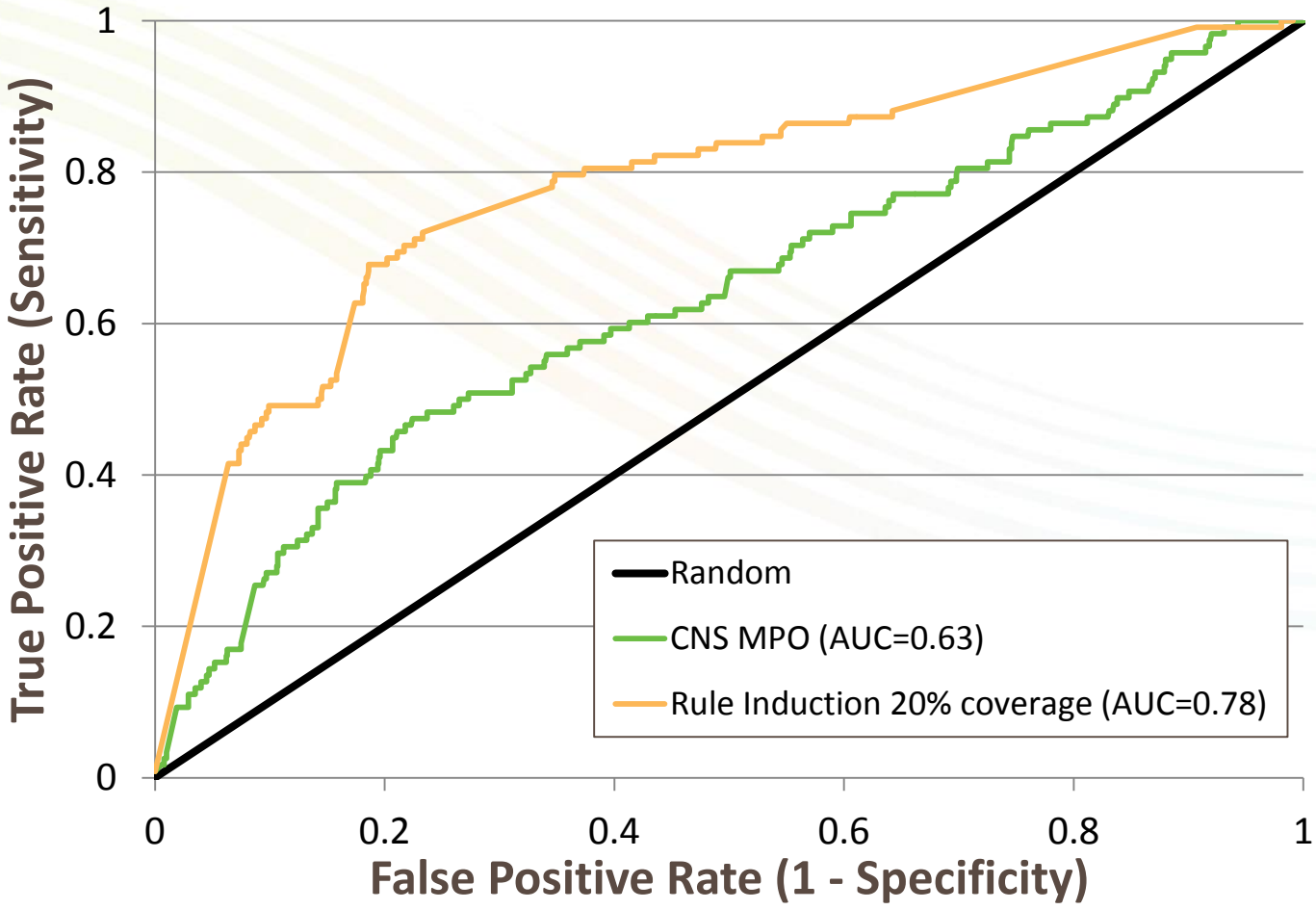




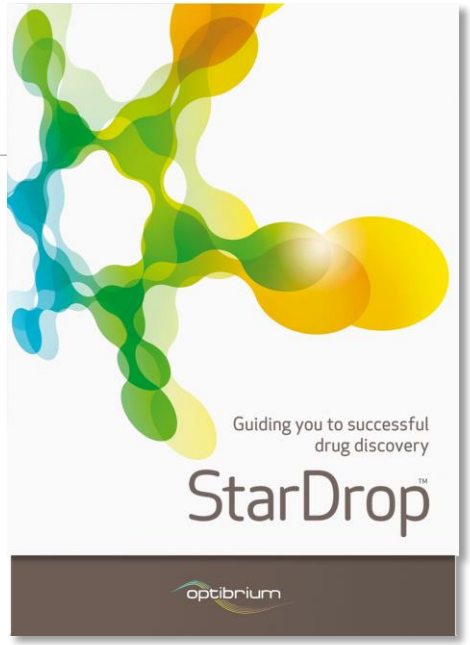

*Wager *et al.* (2010) ACS Chem. Neurosci. **1** p. 435

# Finding CNS Drugs
## A more realistic external test

- 118 (different) CNS drugs and 1000 CNS 'leads' (measured $K_i$ < 1 µM against CNS target) from ChEMBL database



# Conclusion




- MPO is a powerful approach to select and design high quality compounds
  - Quickly target compounds with high chance of success
  - Avoid missed opportunities
- Be aware of the limitations of drug discovery data
  - Relevance
  - Uncertainty
- Tailor property criteria/profile to the objectives of your project
  - 'One size fits all' profile not realistic
  - Rule Induction provides a powerful way to develop tailored profile based on existing data
- Download papers from:
  - www.optibrium.com/community/publications
- For more information: www.optibrium.com

# Acknowledgements


- Tatsu Hashimoto – MIT
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  - Ed Champness
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  - Alex Elliott
  - Sam Dowling
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