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Finding and Applying Rules for Successful Drug Discovery

International Symposium on Compound Design Technologies

Matthew Segall, CEO, Optibrium Ltd.

Overview

- Multi-parameter optimisation (MPO) in drug discovery
- Case study: Balancing properties in lead optimization
- Finding multi-parameter rules for drug discovery
- Example application: ‘Drug-like’ properties
- Conclusions

Multi-parameter Optimization in Drug Discovery

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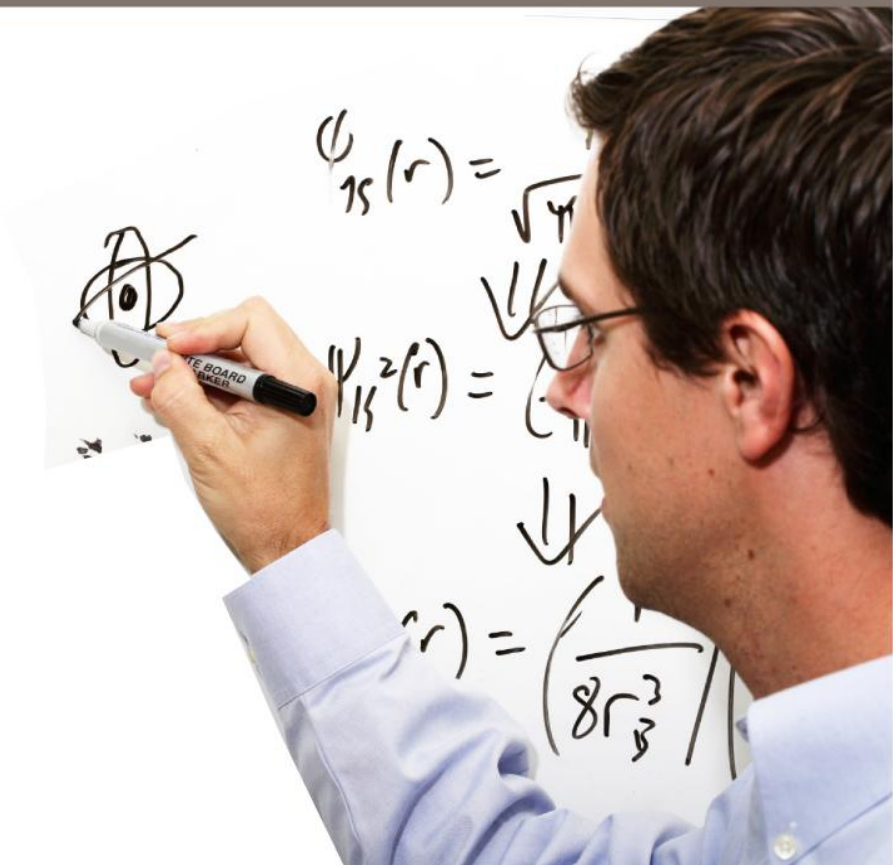
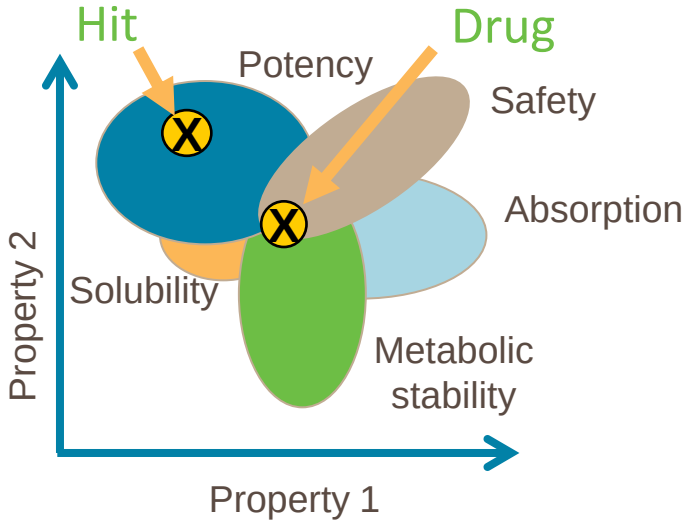
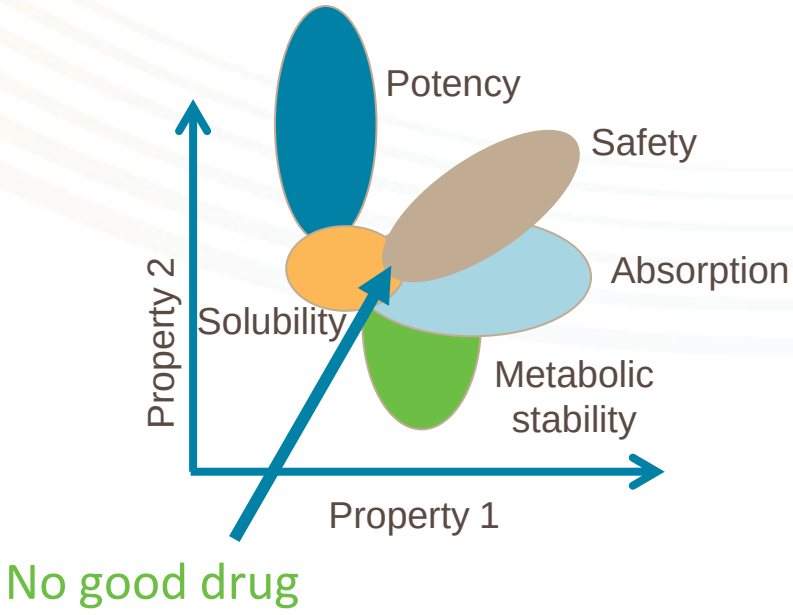


The Objectives of Drug Discovery
Multi-parameter optimisation

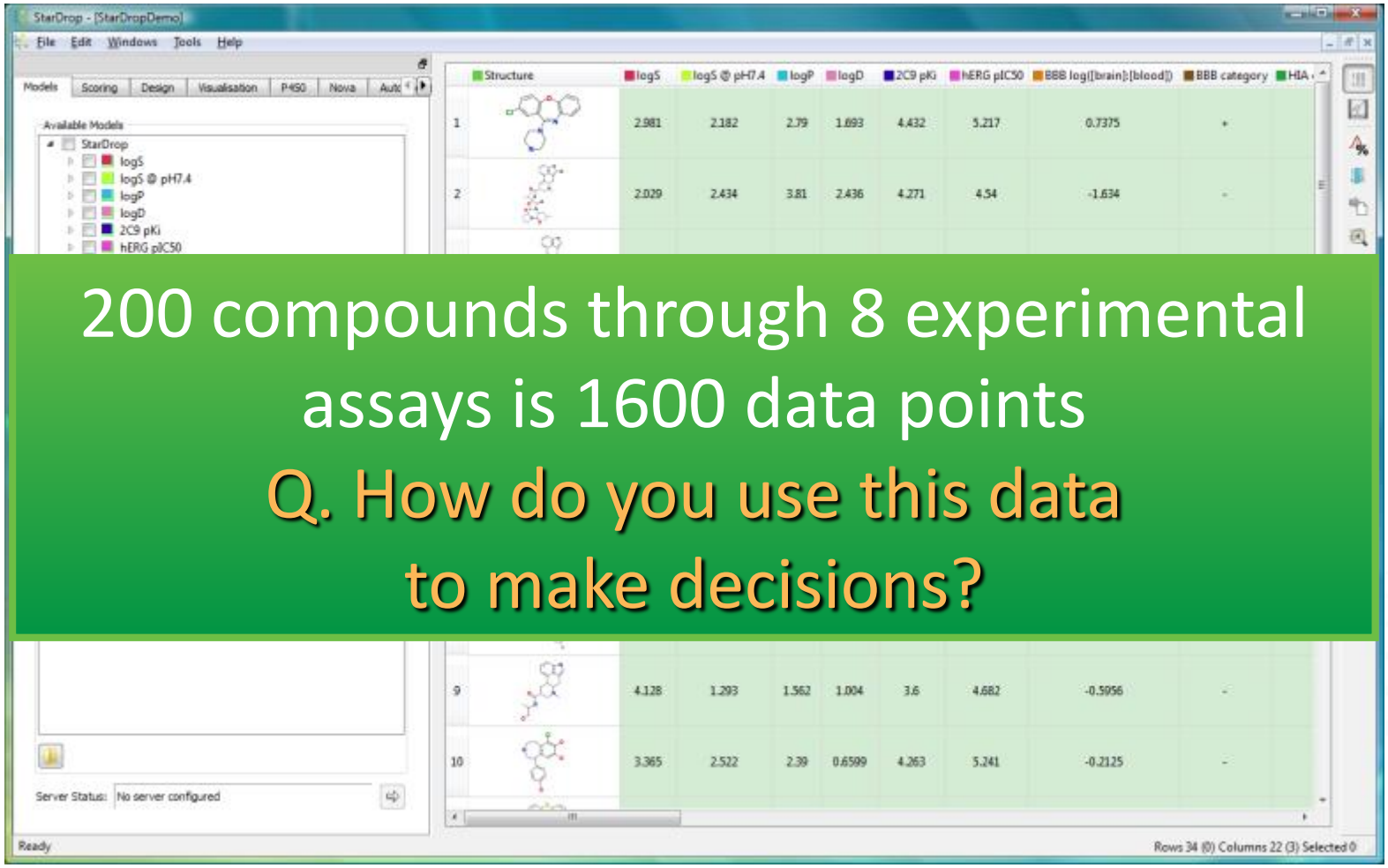
- Identify chemistries with an optimal **balance** of properties



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



The Challenge



200 compounds through 8 experimental assays is 1600 data points

Q. How do you use this data to make decisions?

Requirements for MPO in Drug Discovery

- Interpretable
  - Easy to understand compound priority and how to improve compounds' chances of success
- Flexibility
  - Define criteria depending on therapeutic objectives of project
- Weighting
  - Take into account relative importance of different endpoints to success of project
- Uncertainty
  - Take uncertainty into account, avoid missed opportunities

Approaches for MPO

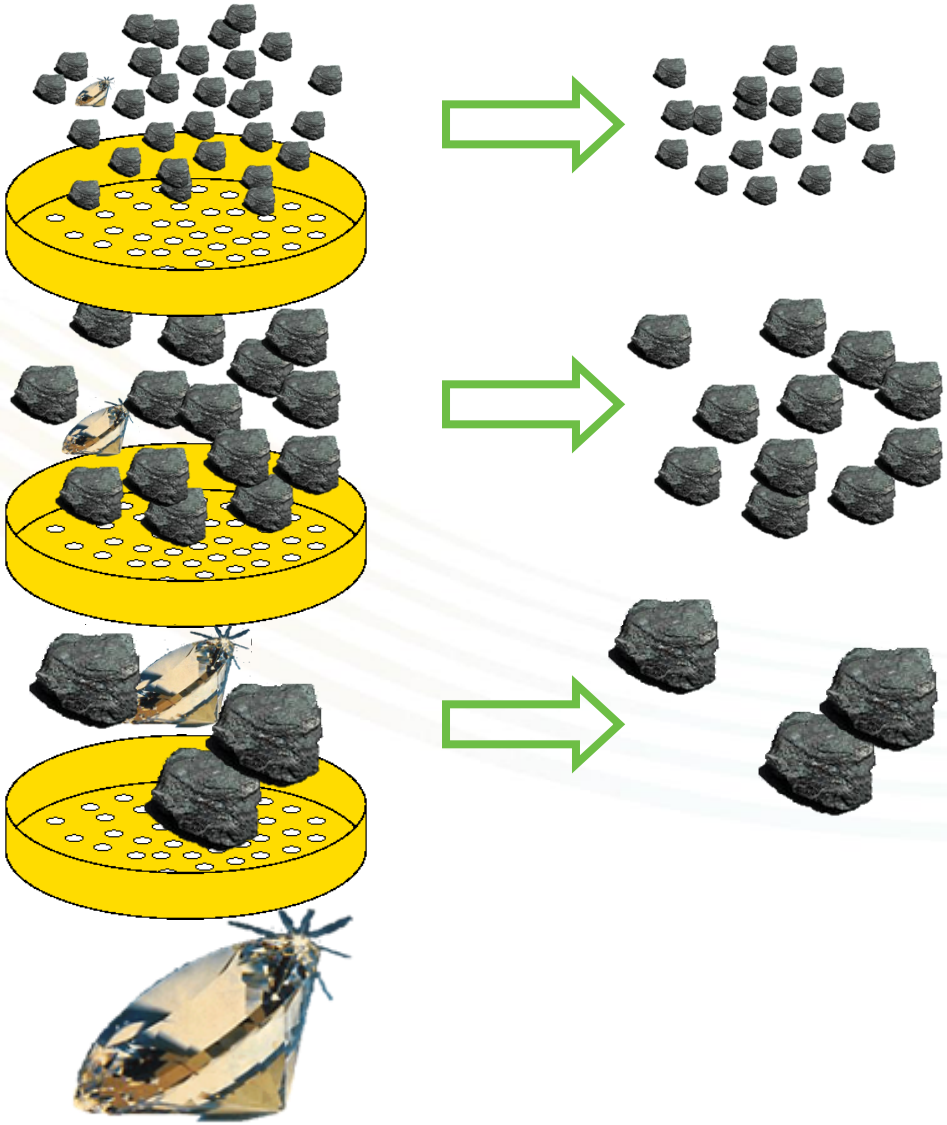
- Many methods have been applied for MPO in drug discovery
  - Rules-of-thumb
  - **Filtering**
  - Calculated metrics
  - Pareto optimisation
  - Desirability functions
  - **Probabilistic scoring**
- For a detailed review, please see:
  - M.D. Segall Curr. Pharm. Des. **18**(9) pp. 1292-1310 (2012)
  - Download from http://bit.ly/1140lS1

Approaches for MPO
Filtering

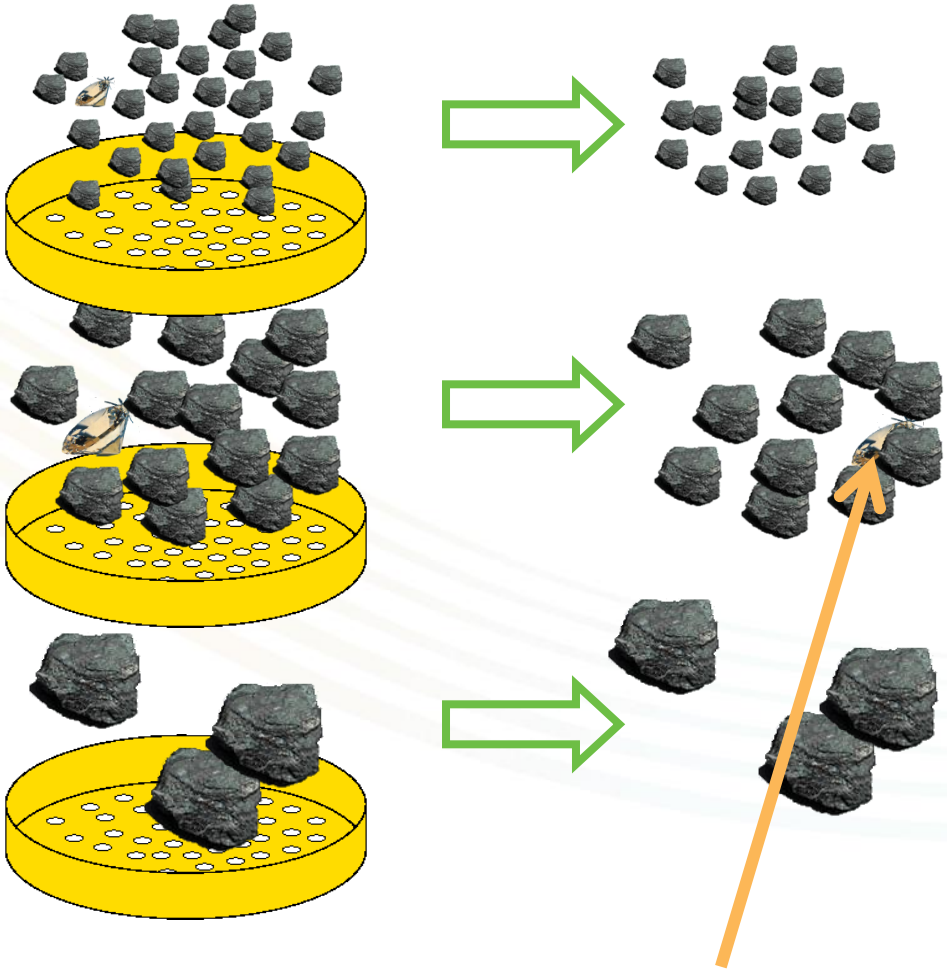
Potency

Absorption

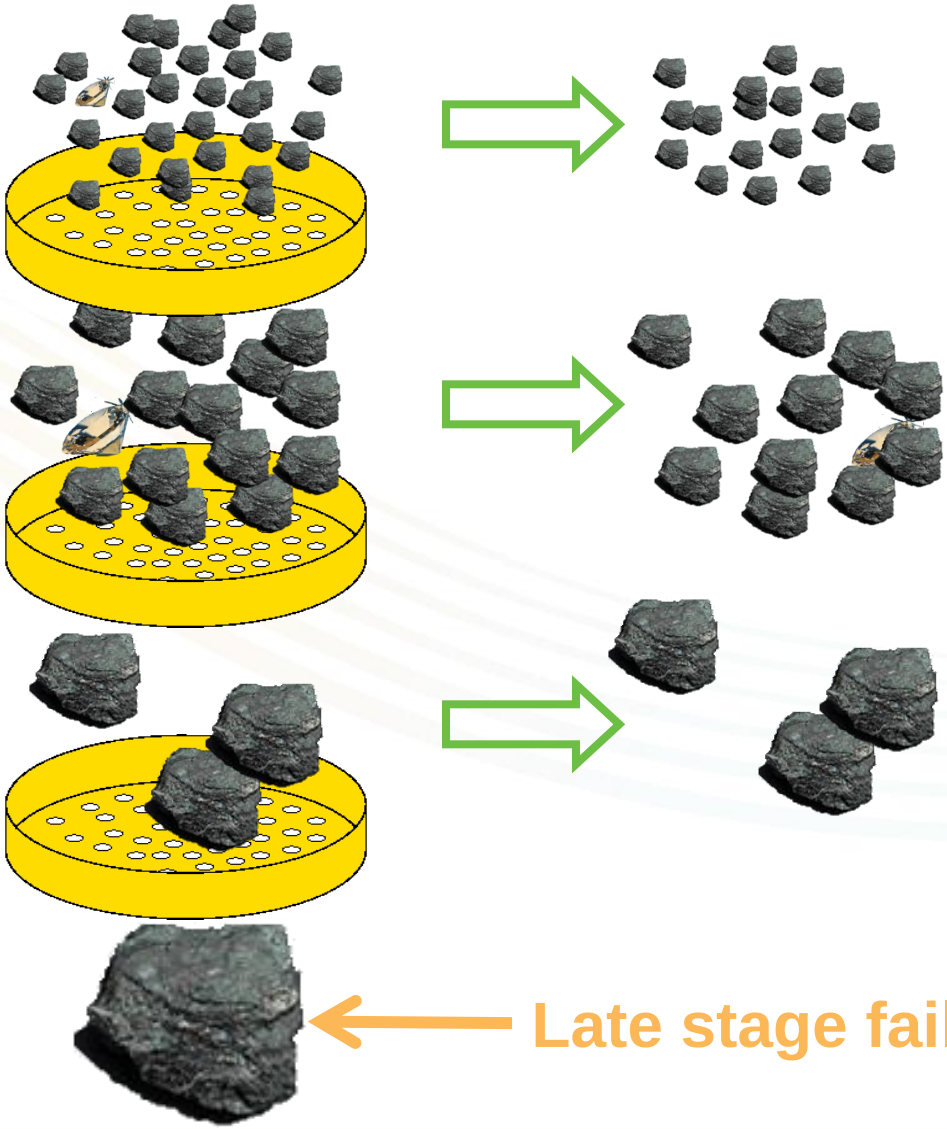
Metabolic Stability



Approaches for MPO
Filtering



Approaches for MPO
Filtering

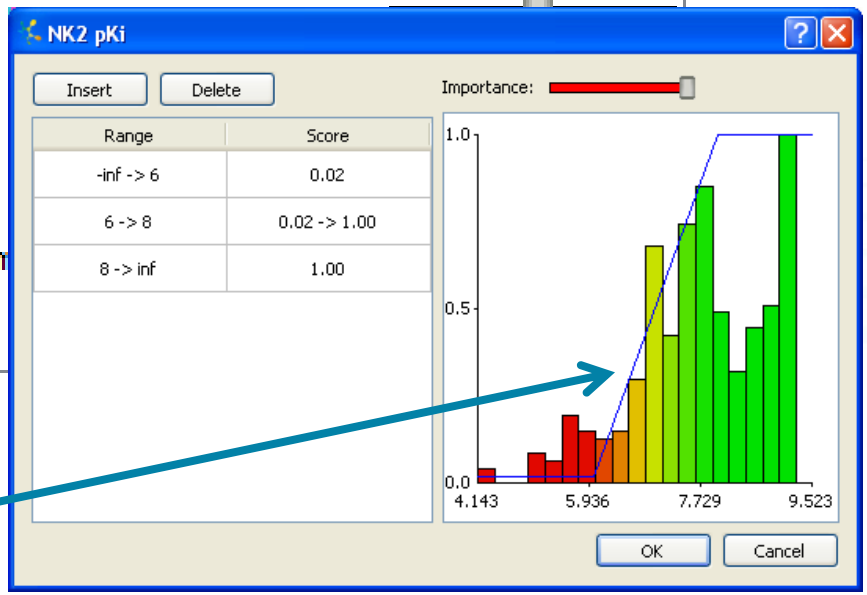


Approaches for MPO
Filtering

10 filters, each 90% accurate:
P( ) even if it exists = 35%

Approaches for MPO
Probabilistic Scoring* – Scoring Profile

Profile	Desired Value	Importance
5HT1a affinity (pKi)	> 7	
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*

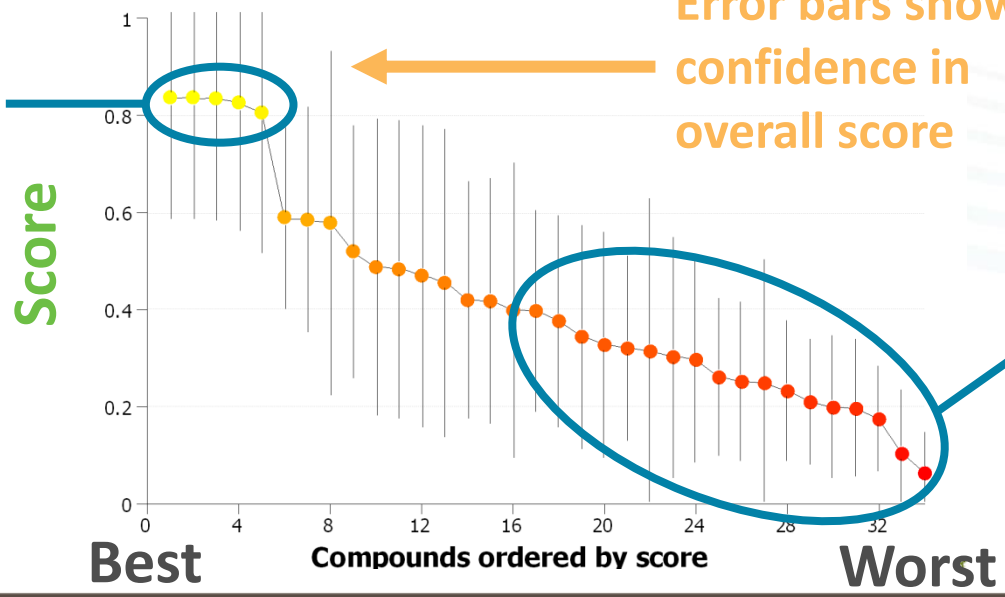
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

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

Data do not separate these as error bars overlap

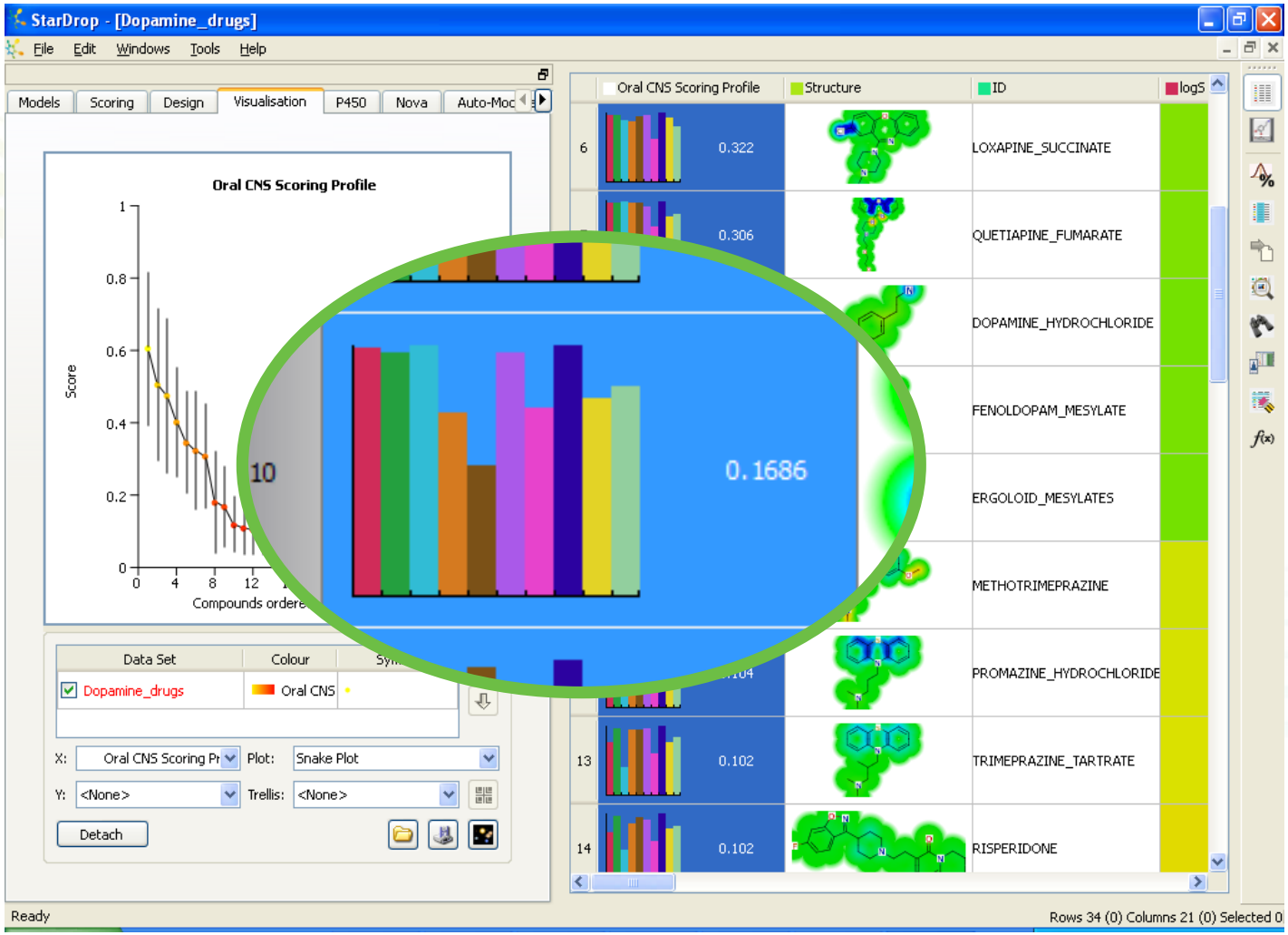
Error bars show confidence in overall score

Bottom 50% may be rejected with confidence



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

Provide Feedback on Influence of Properties
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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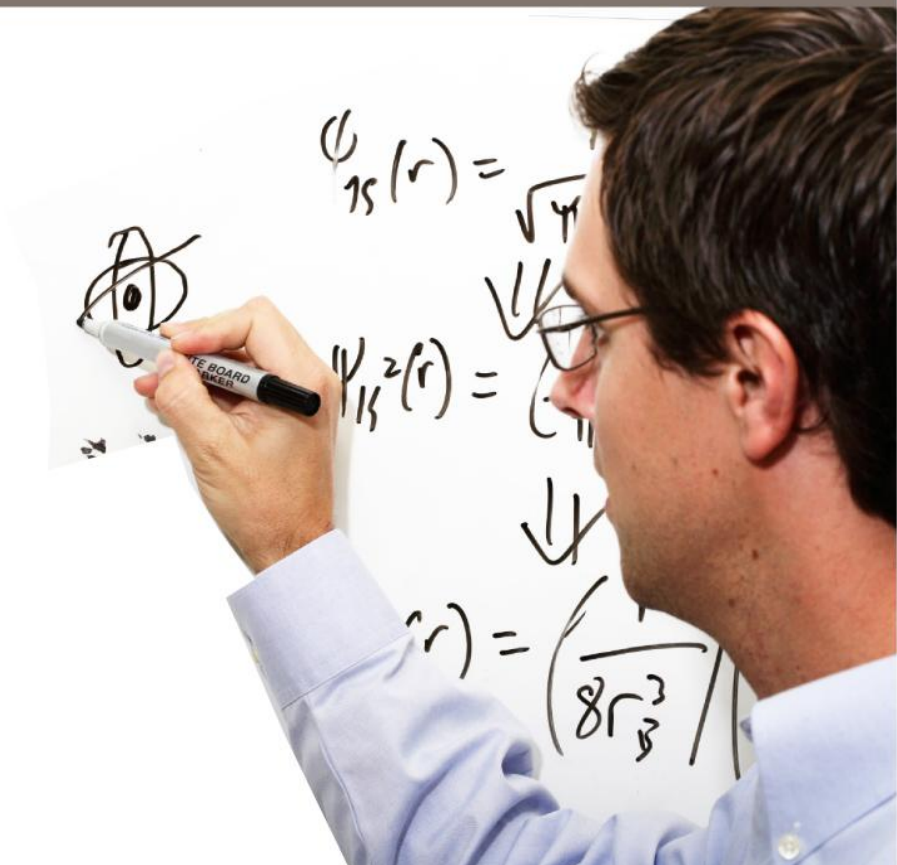

Case Study*
Goal: Orally dosed compound against CV target

- *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
5	XXX540	6.7	1.17
6	XXX160	6.64	1.14
7	XXX572	6.68	1.05
8	XXX104	6.3	1.21
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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)

Finding Multi-Parameter Rules for Drug Discovery

Patent pending

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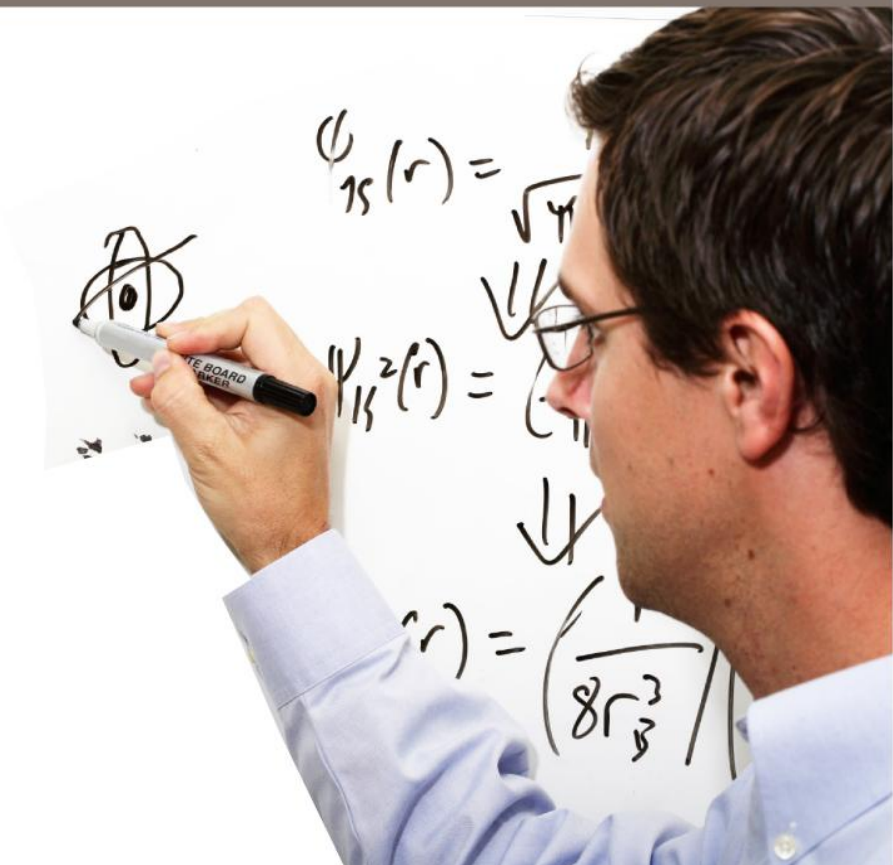


The Next Challenge
How do we choose an appropriate scoring profile?

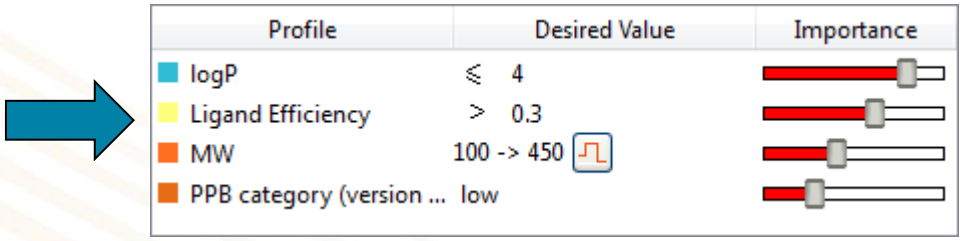
- Traditional methods rely on expert domain knowledge
  - Introduces subjectivity depending on the experience of the scientist
  - Increasing complexity of data
- Use existing data to find scoring profiles that identify compounds with improved chance of success
  - Any drug discovery objective, e.g. 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 complex 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

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

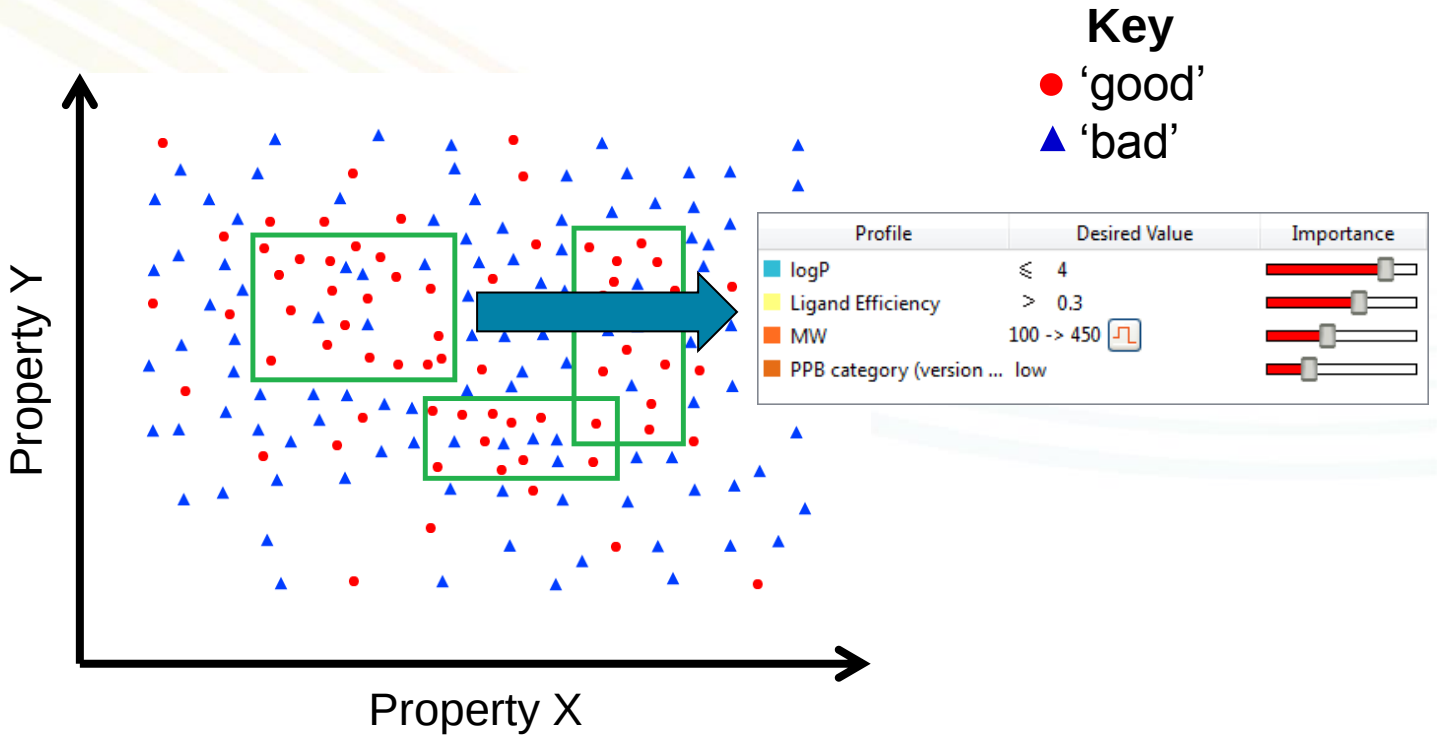


- For example, Lipinski's Rule of Five:

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

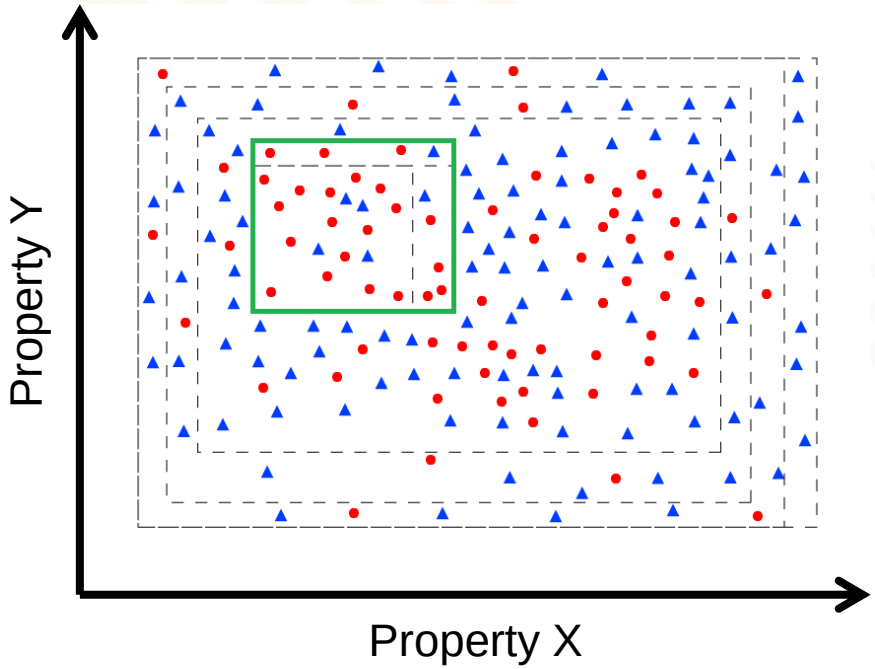
What is a Rule?

- A **Rule** is also a box in multi-dimensional property space containing significantly more ‘good’ than ‘bad’ compounds
  - Each box is equivalent to a scoring profile



Rule Induction with PRIM

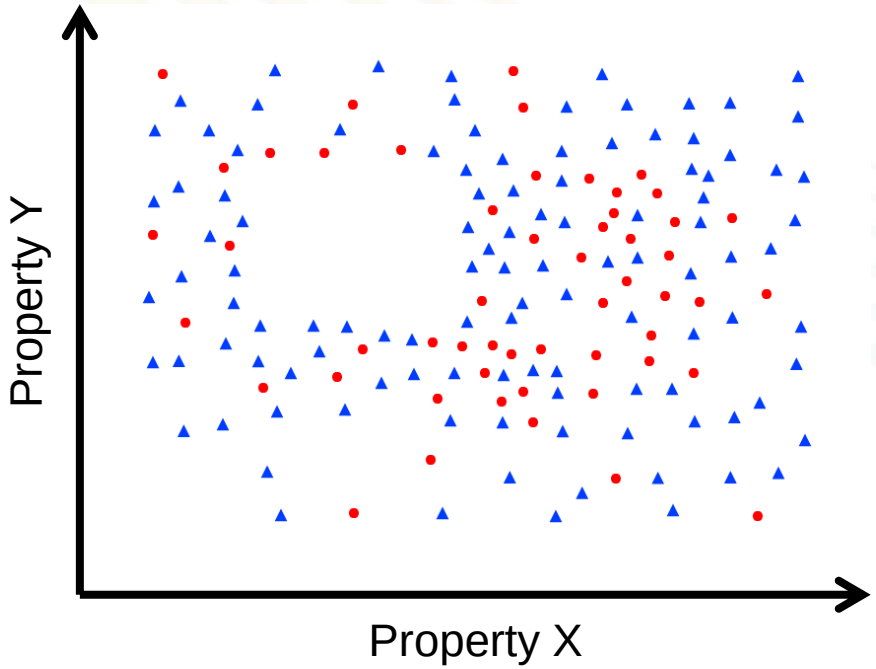
- The Patient Rule Induction Method (PRIM) by Friedman and Fisher* is an effective way to find rules in multi-dimensional data



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

Rule Induction with PRIM

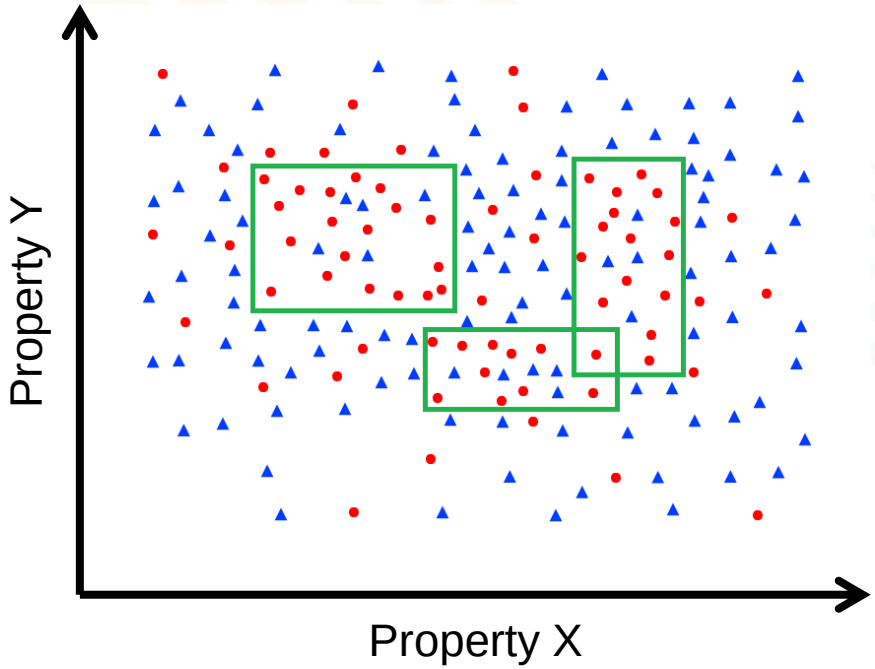
- After finding one box, we remove the box's compounds from the dataset and repeat



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

Rule Induction with PRIM

- The result is a series of boxes, each corresponding to an individual rule or scoring profile



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

Example Application
‘Drug-like’ Properties

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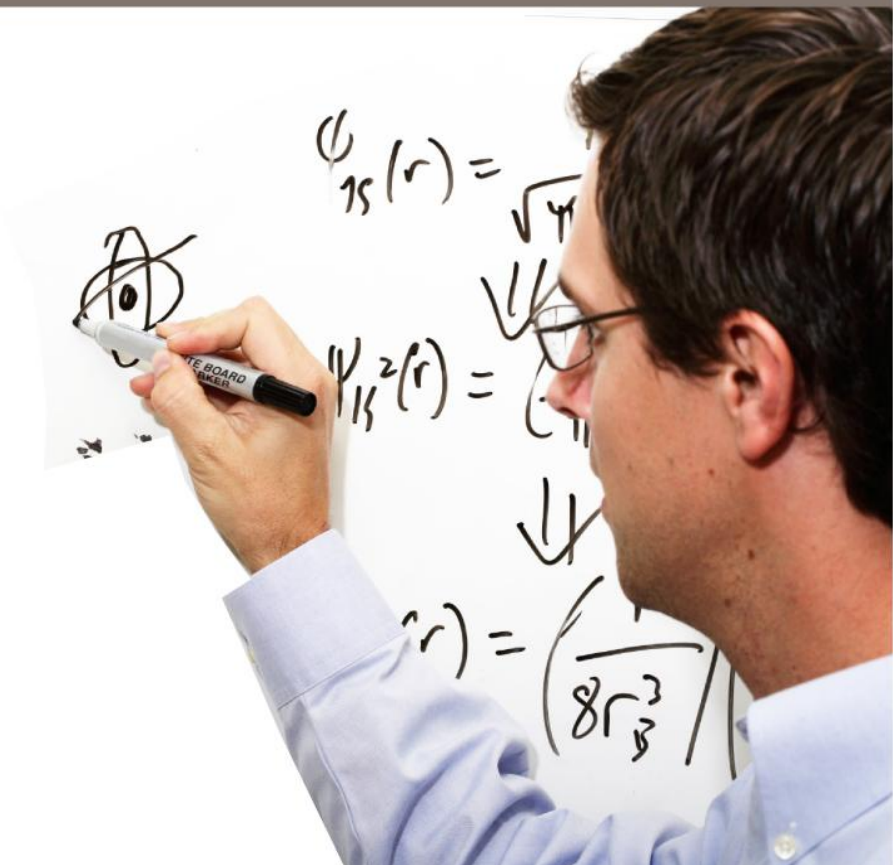
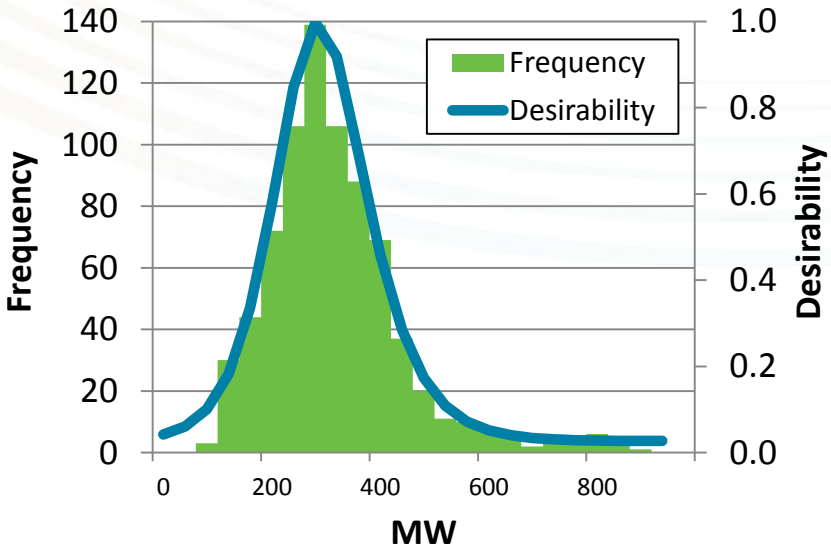


Example: Drug-Like Properties
Quantitative Estimate of Drug-likeness*

- Quantitative Estimate of Drug-Likeness (QED)*
  - Published method we will use for comparison
  - Measure of **similarity** to known oral drugs
- Combine values for 8 properties:

MW	logP	HBD	HBA
PSA	ROTB	AROM	ALERT

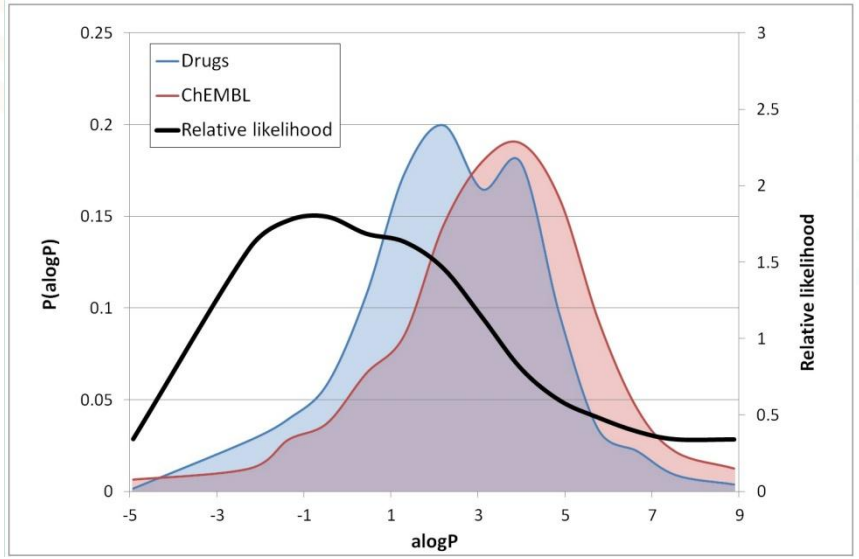
- For each individual property desirability function fitted to distribution for 771 **oral** drugs
- QED calculated as geometric mean of **individual** desirabilities



*Bickerton *et al.* Nature Chem. 4, pp. 90-98 (2012)

Example: Drug-Like Properties
Relative Drug Likelihood*

- Relative Drug Likelihood (RDL)*
  - Another published method also for comparison
  - What makes a drug **different** from non-drug med. chem. compounds?
- Compare characteristics of 771 **oral** drugs with 1000 randomly selected non-drugs from ChEMBL database
  - What property values increase likelihood of compound being an oral drug?
- Used same 8 properties as QED
- RDL calculated as geometric mean of **individual** likelihoods



*Yusof and Segall, Drug Discov. Today 18, pp. 659-666 (2013)

Example: Drug-Like Properties
Rule Induction

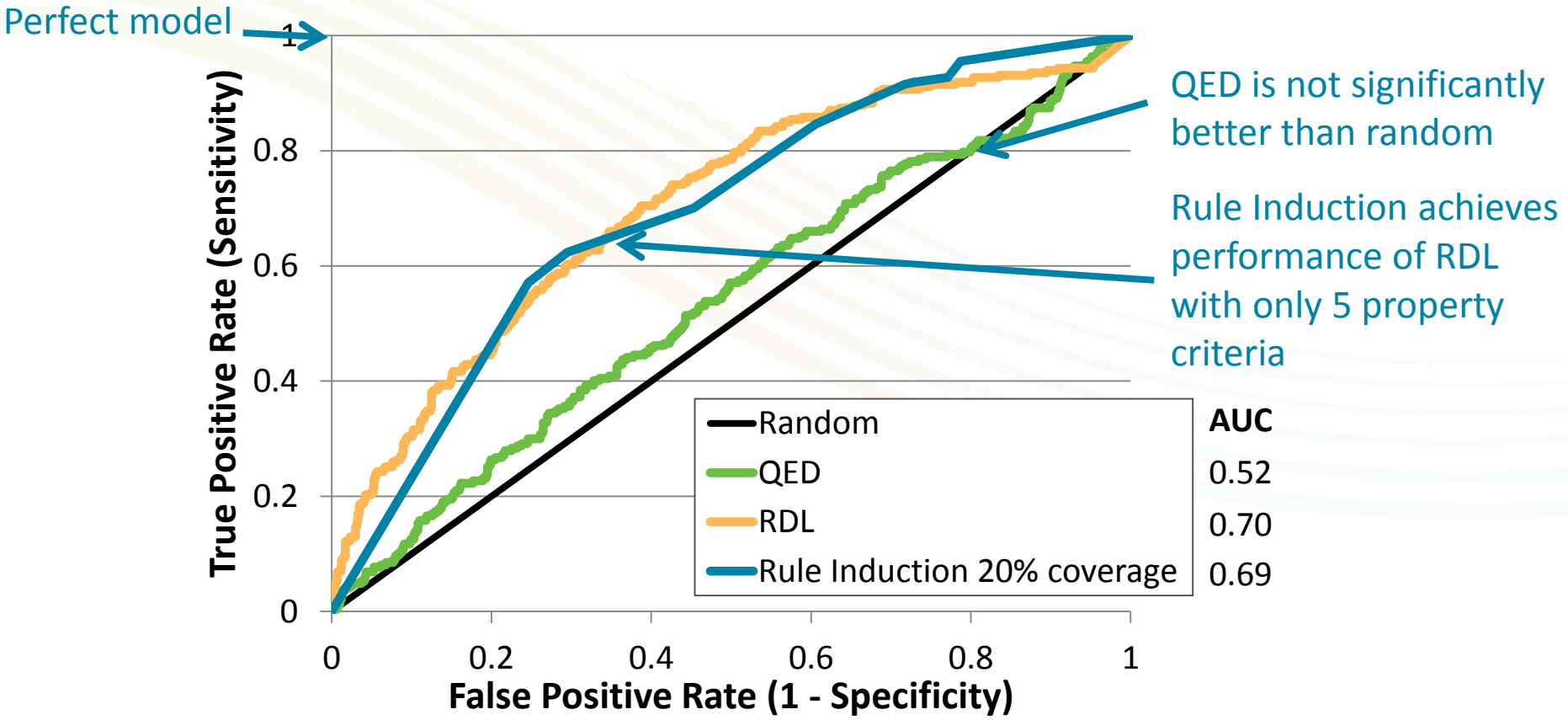
- Rule induction applied to data set of 771 **oral** drugs and 1000 randomly selected non-drugs from ChEMBL
  - Random split 70:30 training:validation sets
- Used same 8 properties as QED and RDL as inputs
- 2 Rules:

Profile	Desired Value	Importance
Rule 1		
MW	⩽ 444.855	
AROM	⩽ 1.01	
ALERTS	⩽ 1.01	

Profile	Desired Value	Importance
Rule 2		
ROTB	⩽ 4.04	
ALOGP	⩽ 2.727	

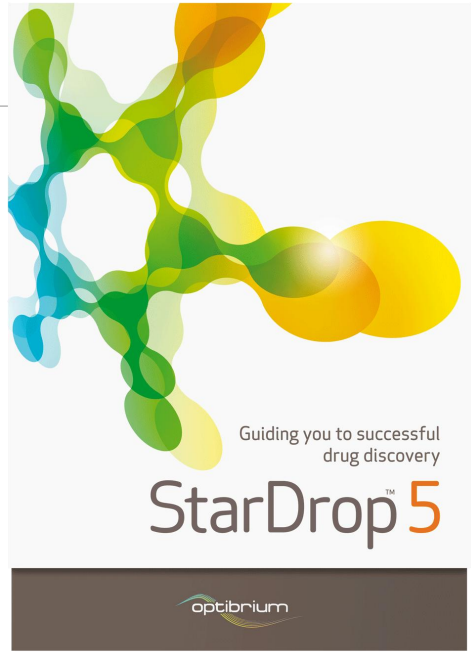
Example: Drug-Like Properties
Results: ROC plot

- Applied to **independent** test set of 247 oral drugs and 1000 compounds randomly selected from ChEMBL



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

Conclusion



- MPO is a powerful approach to select and design compounds with a high chance of success
  - Focus quickly on high quality compounds
- Rule Induction helps to guide the development of scoring profiles to select compounds for a drug discovery objective
  - Apply to any objective
  - Use experimental or calculated data
  - Not black box – synergy between computer and expert
- Identify most important data to guide selection of successful compounds
  - Optimise screening strategy and prioritise experimental resources
- Download papers from:
  - www.optibrium.com/community/publications
- For more information: www.optibrium.com

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