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Introduction to Multi-Parameter Optimization

Prioritizing Compounds with a Balance of Properties

Innovative Lead Optimization and Candidate Selection by *in Silico* Synthesis and ADMET Prediction. December 2nd 2015

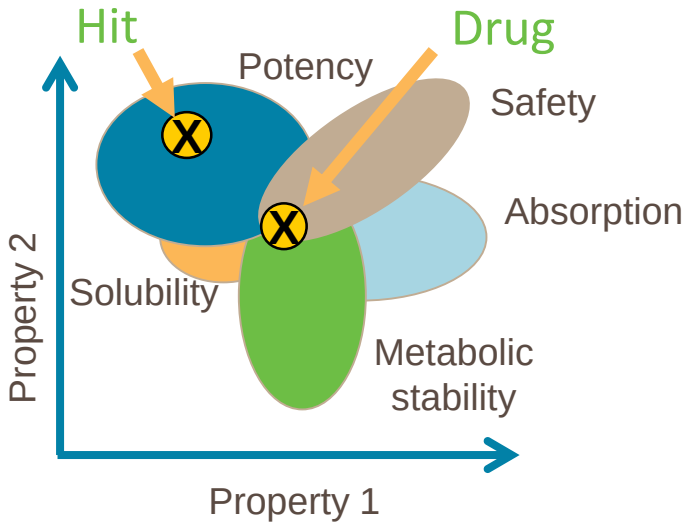
Matthew Segall, CEO, Optibrium Ltd.

Overview

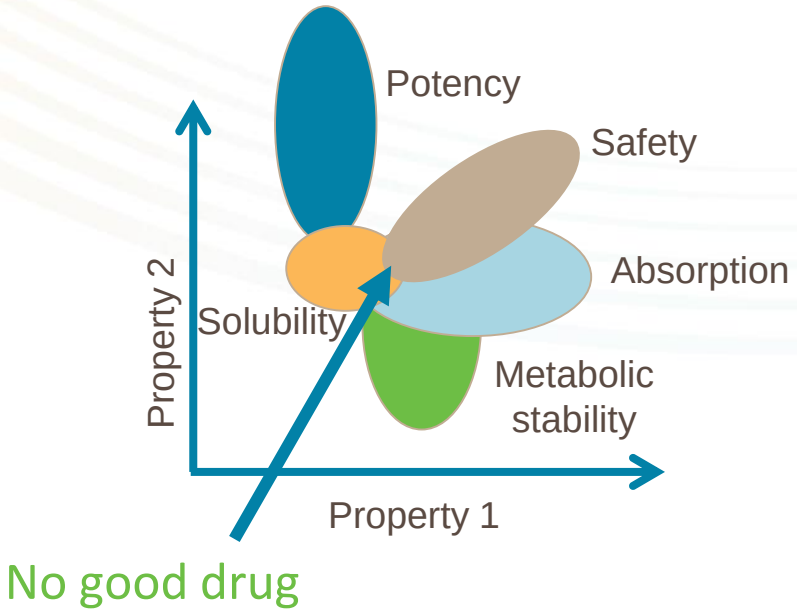
- Introduction: Balancing Properties in Drug Discovery
  - The challenges of multi-parameter optimisation (MPO)
  - Requirements for MPO in drug discovery
- Approaches for Multi-Parameter Optimisation
- Balancing quality and diversity
- Case study
  - Rapid focus in lead optimisation
- Conclusions

The Objectives of Drug Discovery
Multi-parameter optimisation

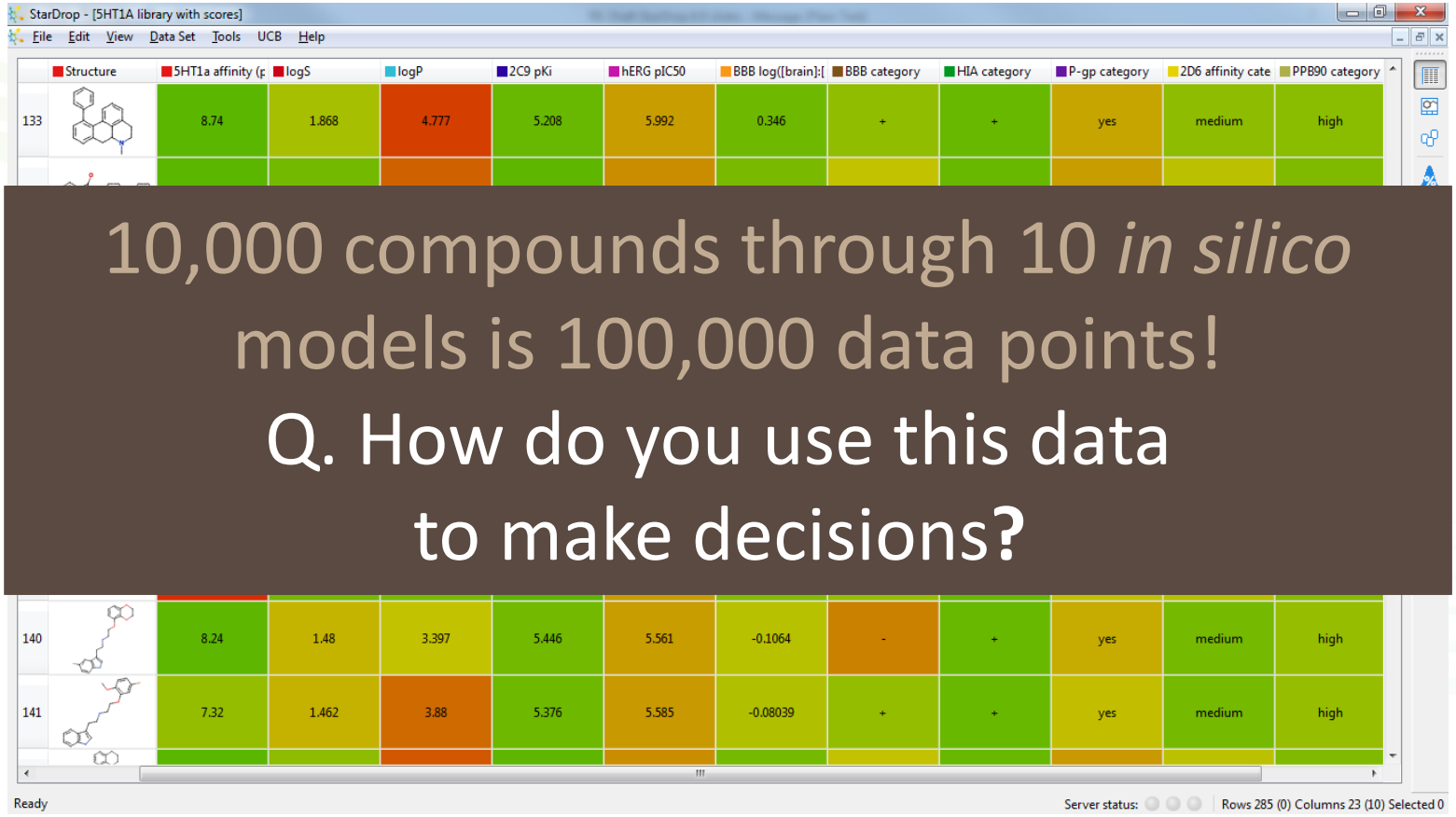
- Identify chemistries with an optimal **balance** of properties



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



Challenge 1: Data overload



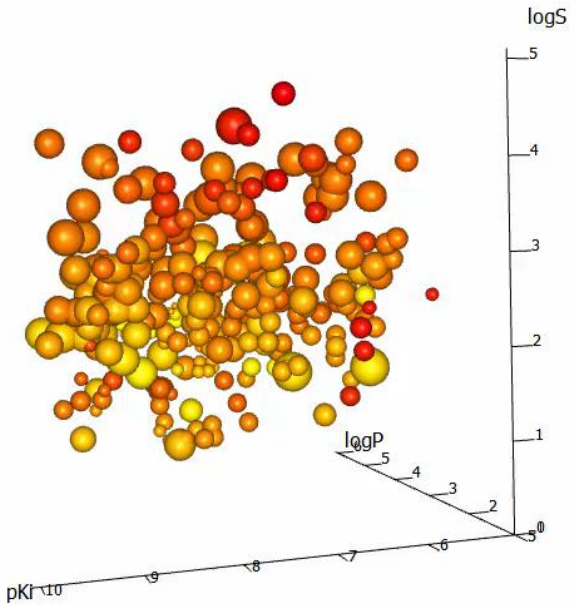
10,000 compounds through 10 *in silico* models is 100,000 data points!

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

Challenge 1: Data overload

Visualisation is important but not enough…

MolName	Structure	pki 5HT1a affinity	logS	logP	2C9 pKi	hERG pIC50	log(BB)	BBB category	HIA category	P-gp category	2D6 affinity category	PPB category
S1-10		6	3.884	3.322	3.464	5.636	0.8671	-	-	no	medium	high
S1-11		6	3.697	3.44	3.485	5.72	0.7745	-	-	no	very high	high
S1-12		6.6	4.124	3.106	3.677	5.684	0.9036	-	-	no	medium	high
S1-13		9	3.659	3.844	3.558	5.65	0.8504	-	-	no	very high	high
S1-14		6	4.051	2.992	3.369	5.56	0.4056	-	-	no	high	high
S1-15		6.5	2.554	4.38	4.502	6.175	0.6534	-	-	yes	medium	high
S1-16		5.3	3.698	3.892	3.464	5.646	0.6799	-	-	no	medium	high
S1-18		7.96	3.444	4.34	3.558	5.647	0.6568	-	-	no	very high	high
S1-19		6.98	3.927	3.594	3.677	5.677	0.6858	-	-	no	medium	high
S1-20		7.16	3.721	3.487	3.391	5.639	0.2327	-	-	no	very high	high
S1-21		7.54	3.632	3.964	3.485	5.725	0.6016	-	-	no	very high	high

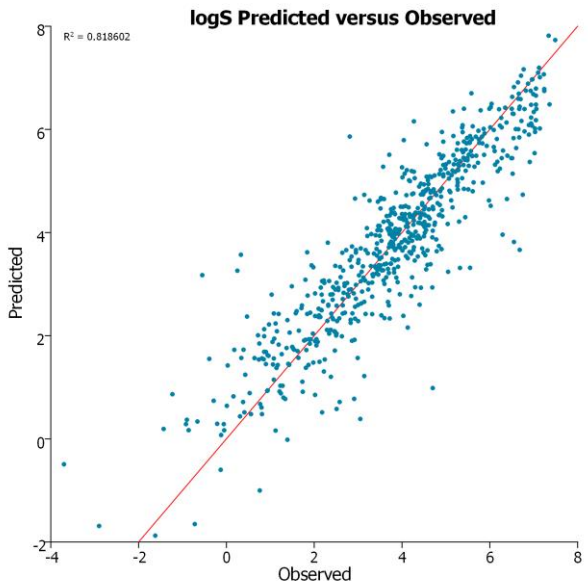


How can you make a confident decision by looking at these?

 *Segall and Champness (2010) GEN, **30** (Sep 1) http://bit.ly/cSx4Tm

Challenge 2: Uncertainty in Data
Statistical

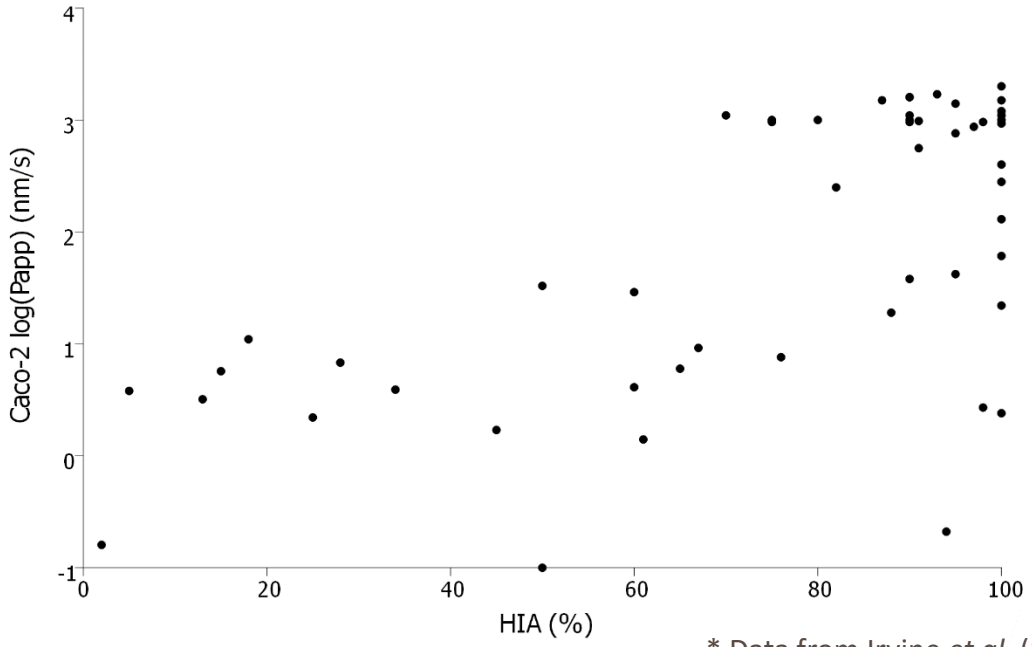
- Experimental variability/error
  - Single measurements: assay variability
    - o pK_i/pIC_{50} ~ 0.3 – 0.7 log units (factor of 2-5 in K_i/IC_{50})
  - Multiple replicates: mean and standard error in mean
- Statistical uncertainty in predictions
  - Standard error of prediction (assessed from validation)
    - o logP ~ 0.4 -0.5 log units
    - o logS ~ 0.7 – 0.8 log units
    - o pK_i ~ 0.9 – 1.0 log units
  - Need to consider domain of applicability



RMSE=0.8 log units

Challenge 2: Uncertainty in Data
Relevance

- All sources of data in drug discovery are **models** of the ultimate human patient
  - *In vivo*, *in vitro* or *in silico*
  - Inference/translation
- For example, Caco-2 permeation (model of absorption)*:



* Data from Irvine *et al.* (1999) J. Pharm. Sci. **88** pp. 28-33

Approaches for MPO in Drug Discovery

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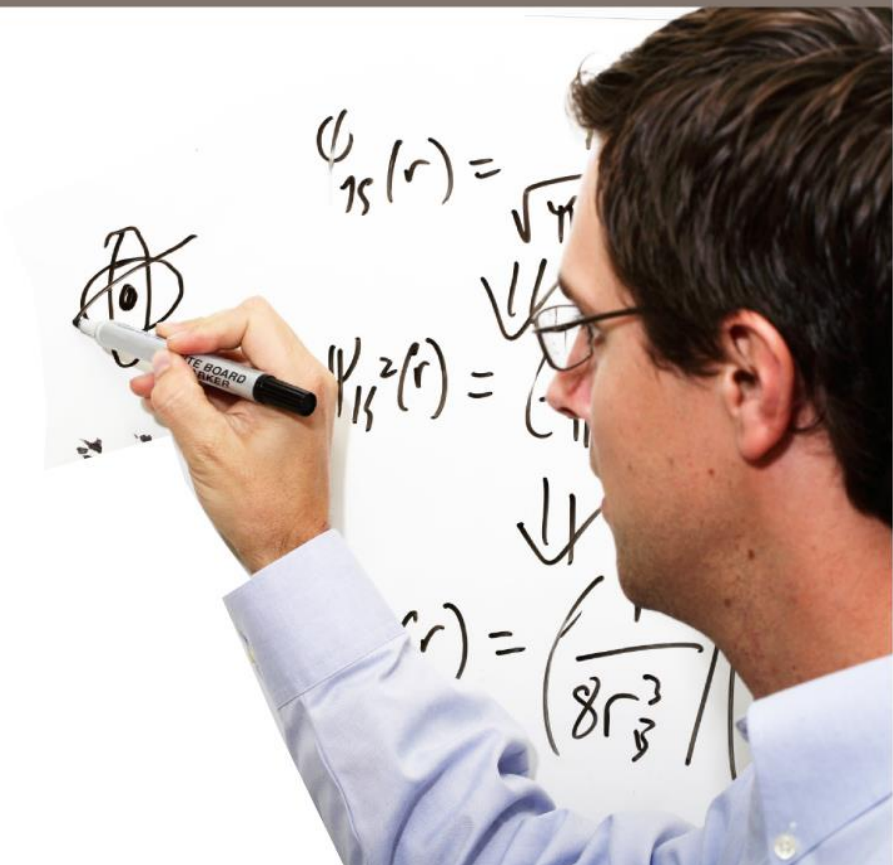


Requirements for MPO in Drug Discovery

- 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 opportunitites

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)

Rules of Thumb

- 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:
  - Rules tailored to specific objectives – lack of flexibility
  - Risk of too rigid application

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

Rules of Thumb

- How predictive are rules-of-thumb?
  - E.g. Lipinski's RoF applied to 1191 marketed drugs

	RoF result	
	Pass (≤1 RoF Failure)	Fail (>1 RoF Failure)
Oral	709	59
Non-oral	333	90

- Neither specific nor sensitive…

Filtering

Potency

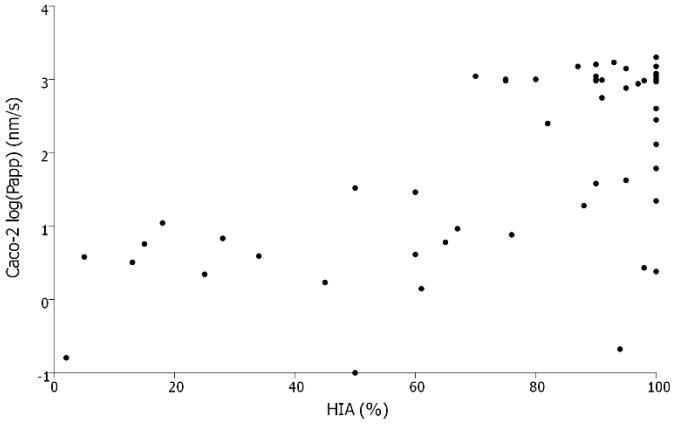
Absorpti

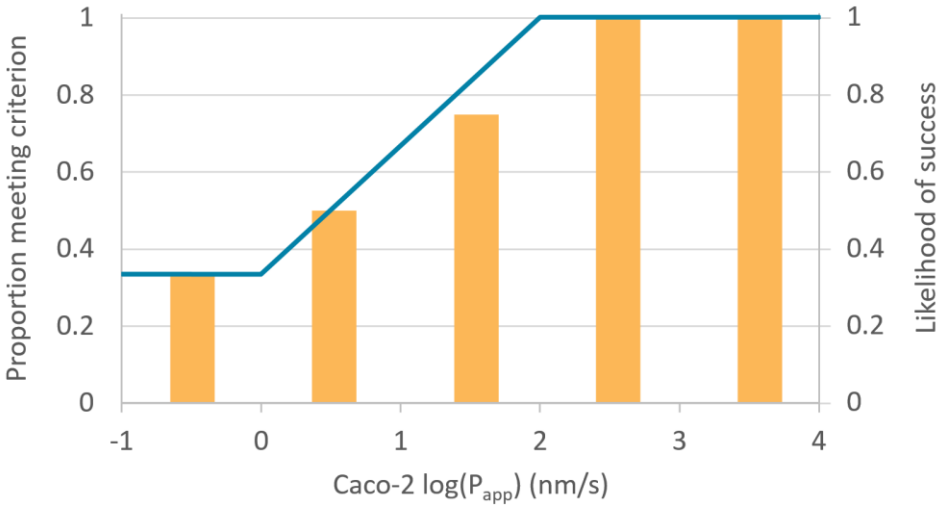
Metabolic Stability

Considering Relevance

What impact does a value have on the ultimate outcome?

- Consider Caco-2 permeation again*
  - Experimental model of human intestinal absorption (HIA)
  - What is chance of a compound achieving HIA > 50%





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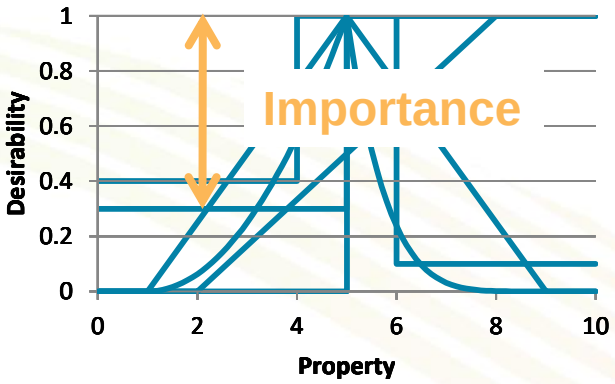
Desirability Functions

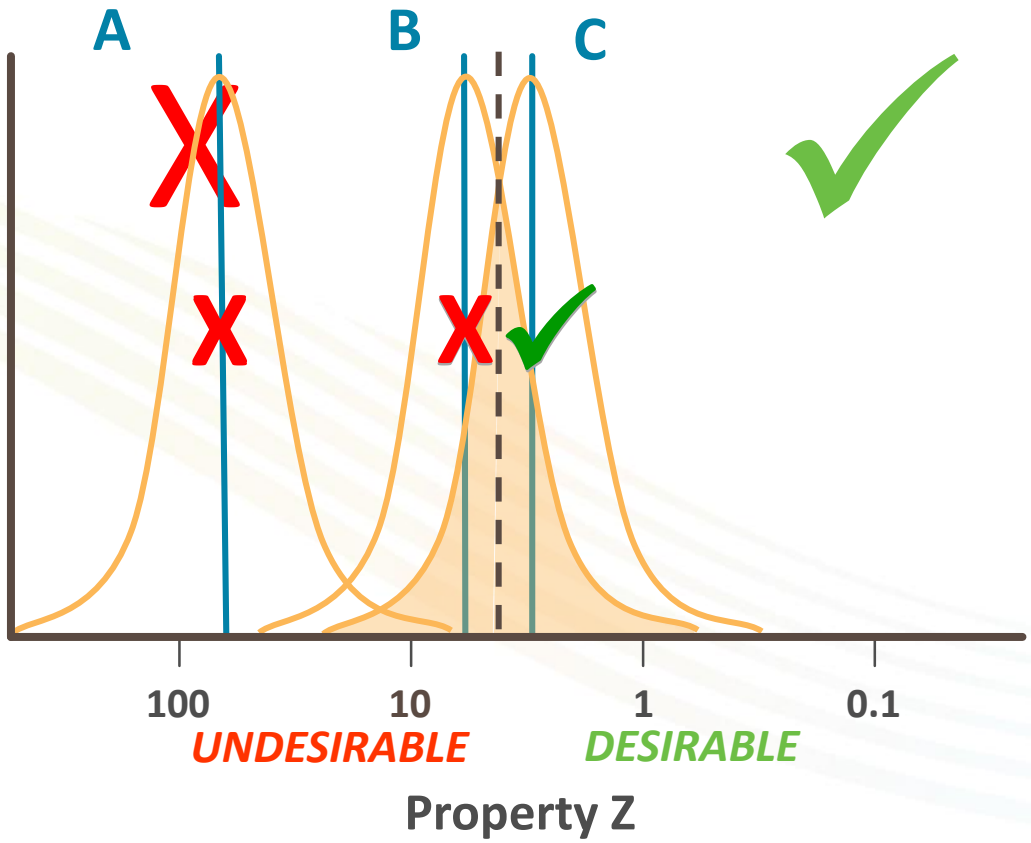
- Relate property values to how ‘desirable’ the outcome



(Derringer Function)

- Combine multiple properties into ‘desirability index’
  - Additive: $\frac{d_1(X_1)+d_2(X_2)+\cdots+d_n(X_n)}{n}$
  - Multiplicative: $\mathrm{D} = \sqrt[n]{d_1(X_1) \times d_2(X_2) \times \cdots \times d_n(X_n)}$
- Flexible and easy to interpret
  - Clear indication of which properties are poor

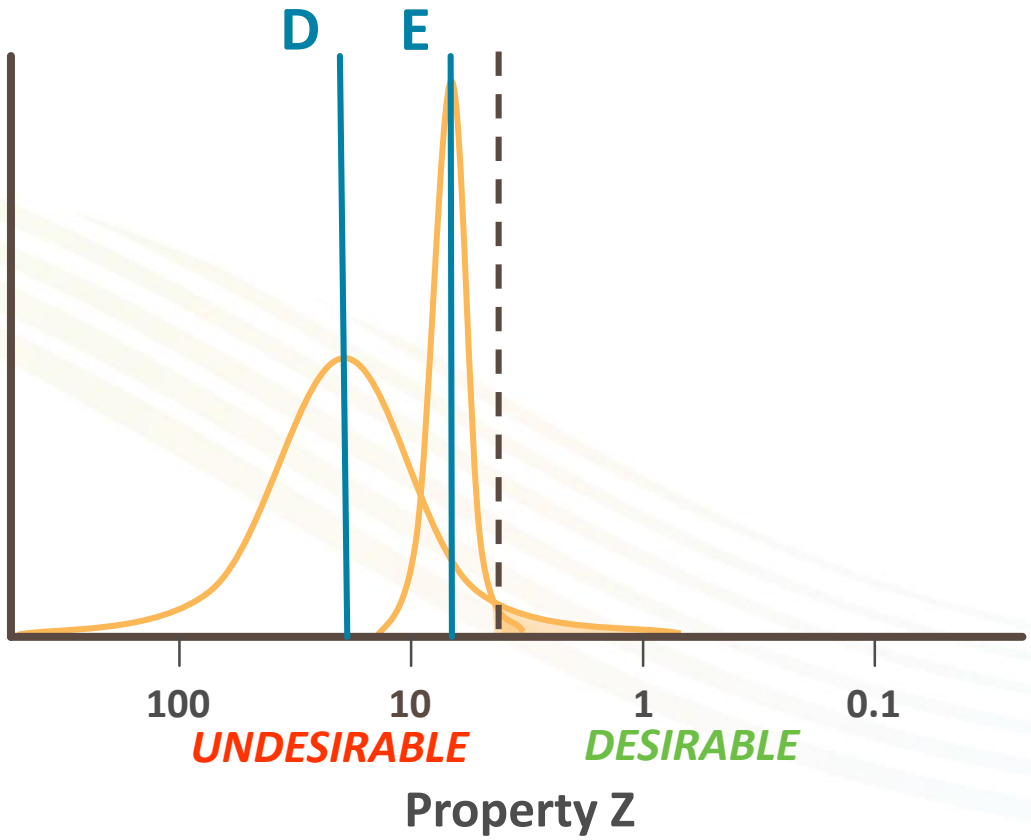
Importance of Uncertainty



- Conclusions:
  - Reject compound A
  - Cannot confidently choose between B and C

 M.D. Segall *et al.* (2006) Expert Opin. Drug. Metab. Toxicol. **2**(2) pp. 325-337

Importance of Uncertainty

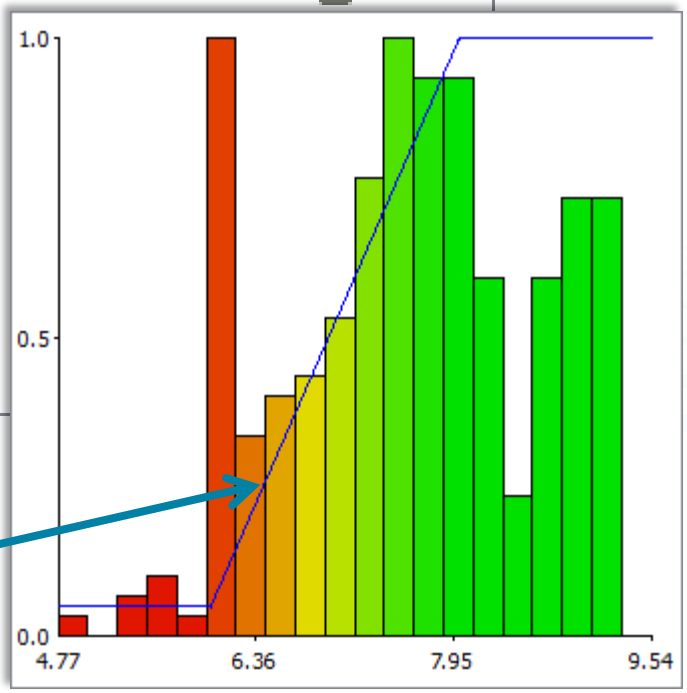


- Conclusion:
  - Compound D has higher probability of success

 M.D. Segall *et al.* (2006) Expert Opin. Drug. Metab. Toxicol. **2**(2) pp. 325-337

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

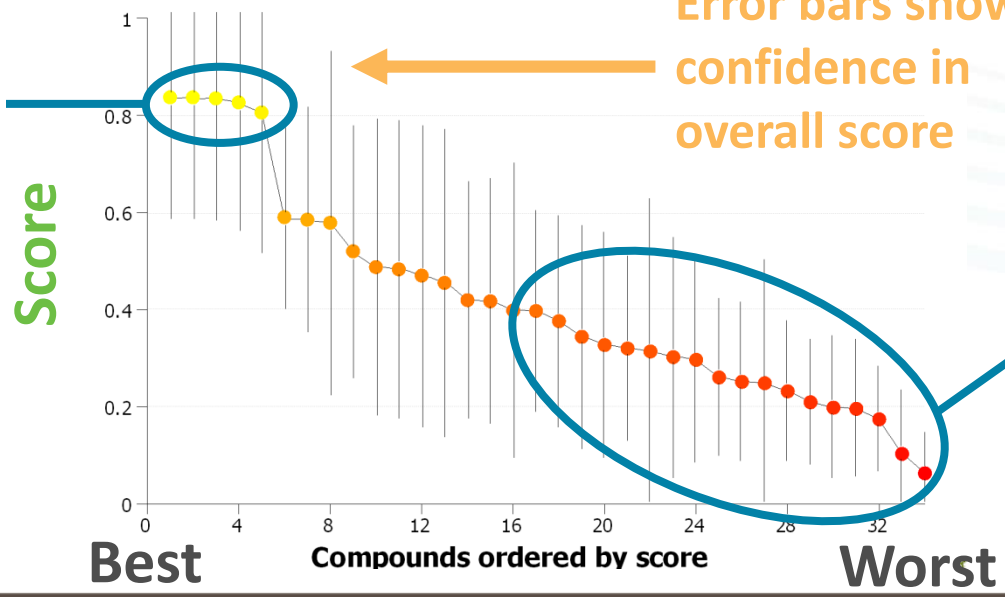
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

- **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



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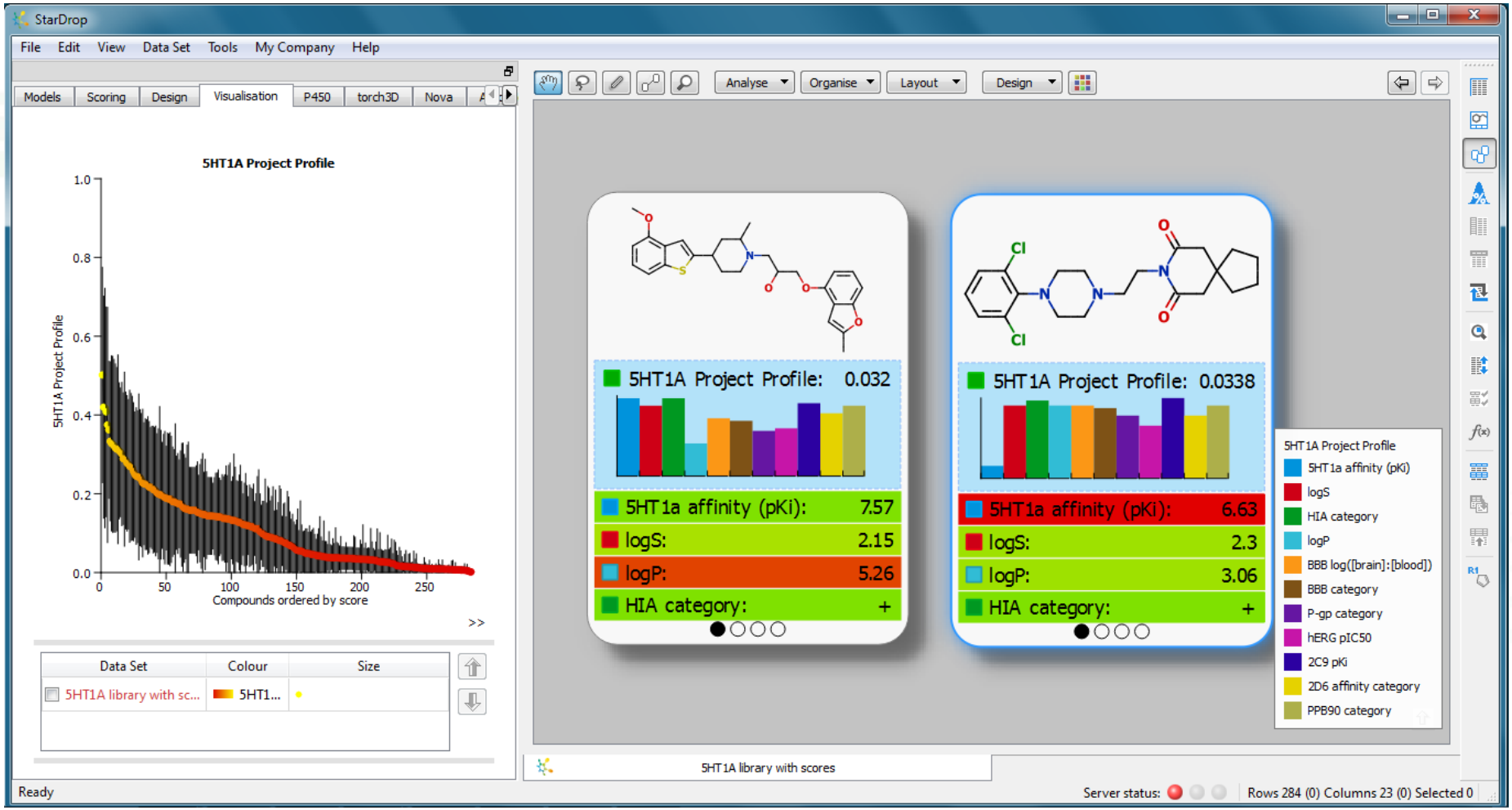
Probabilistic Scoring

Guide redesign to improve chance of success



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Balancing Quality and Diversity

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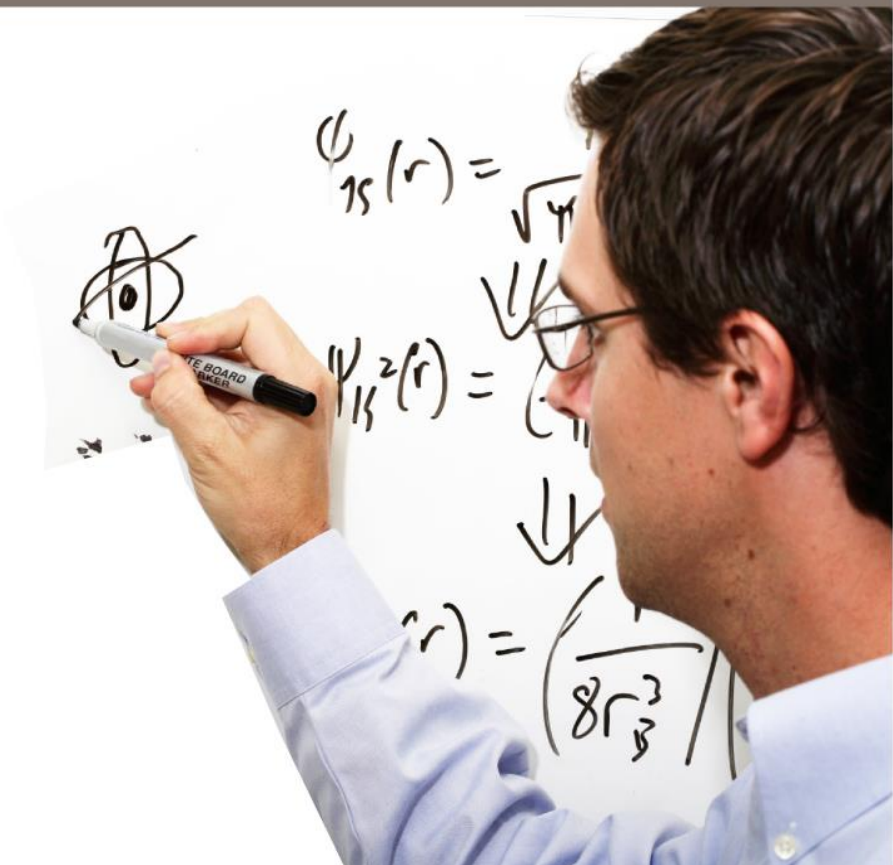
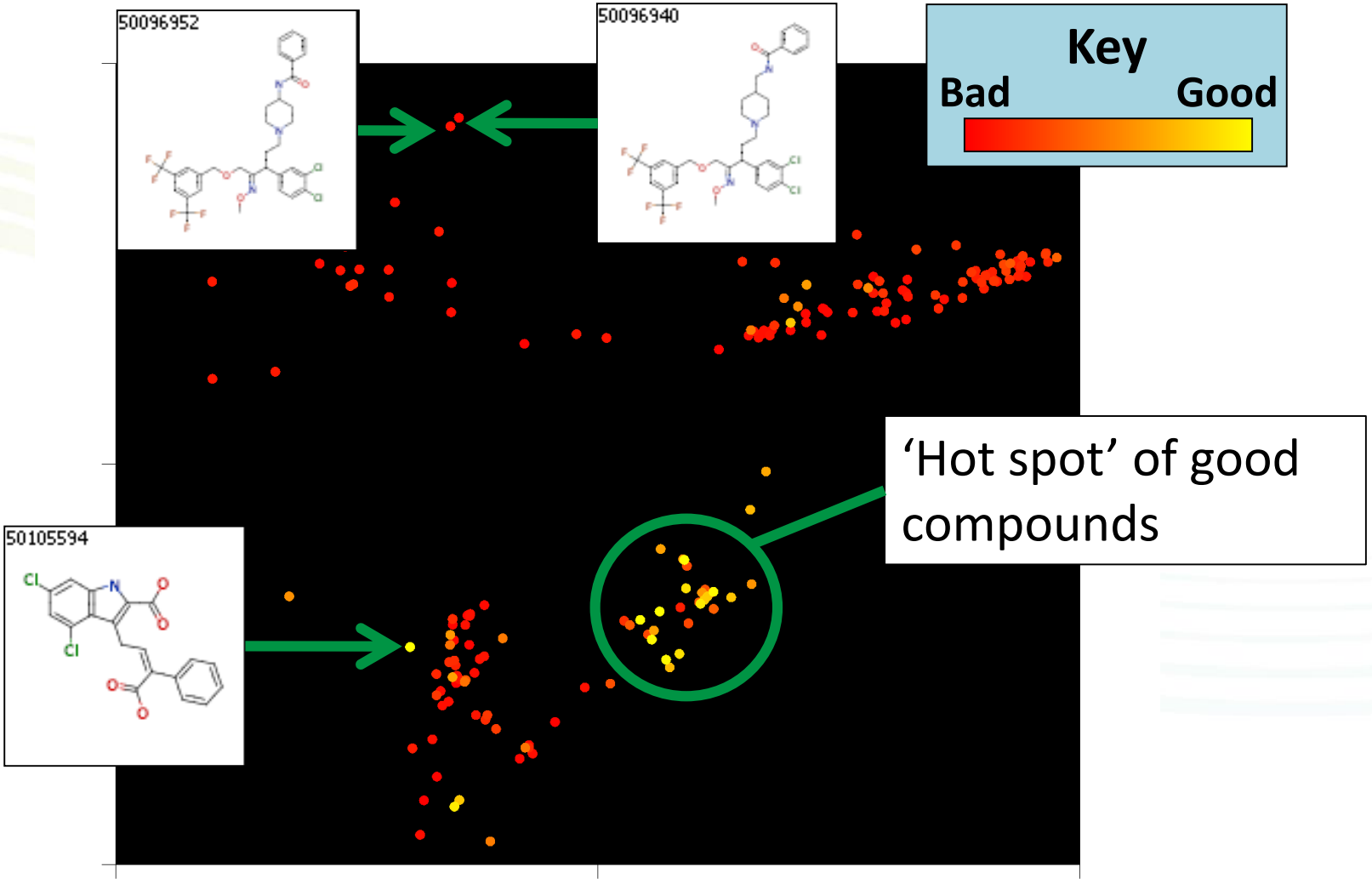
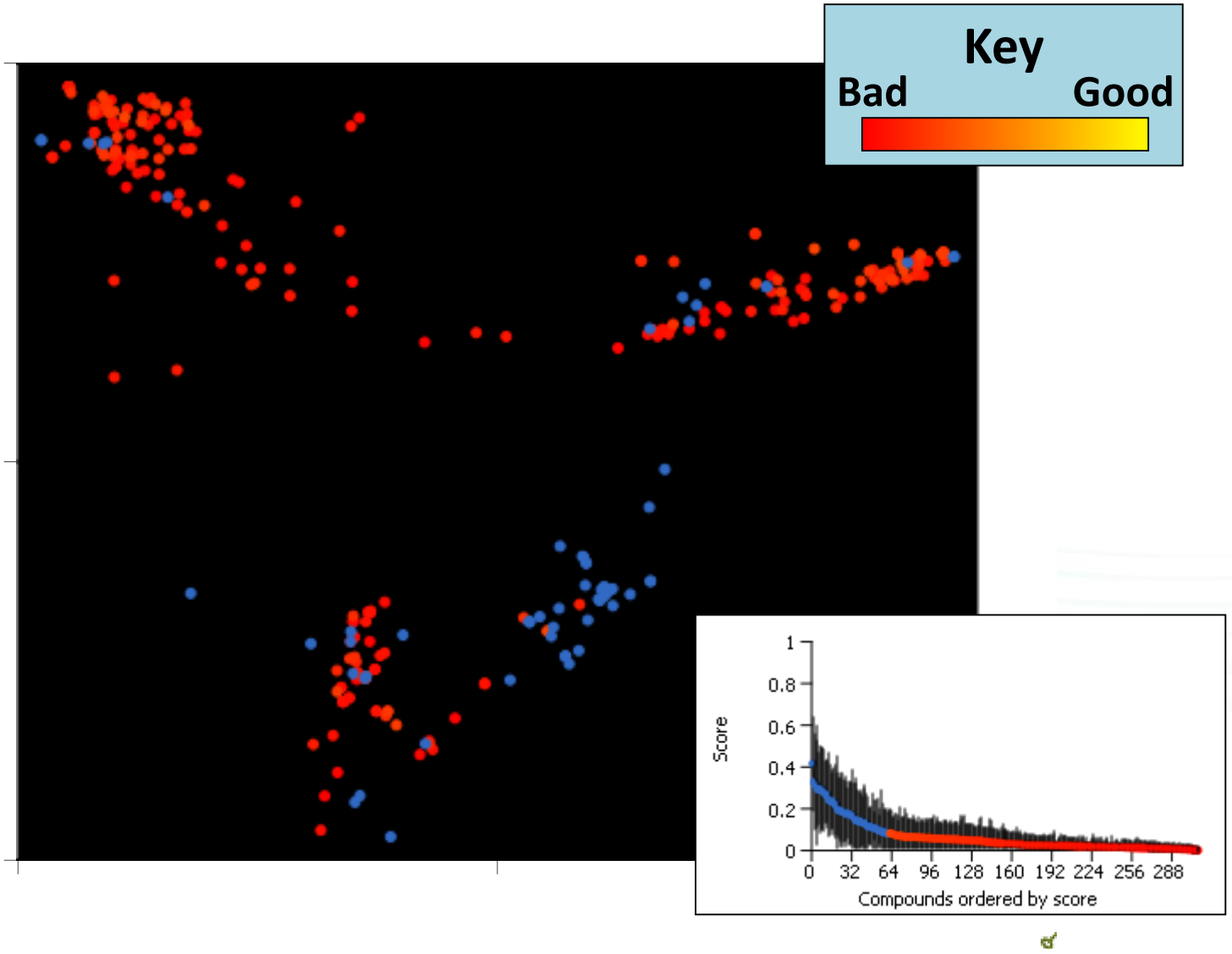


Visualising 'Chemical Space'
Exploring trends across chemical diversity



Balance Quality Against Diversity
Mitigating risk



Case Study
Rapid Focus in Lead Optimisation

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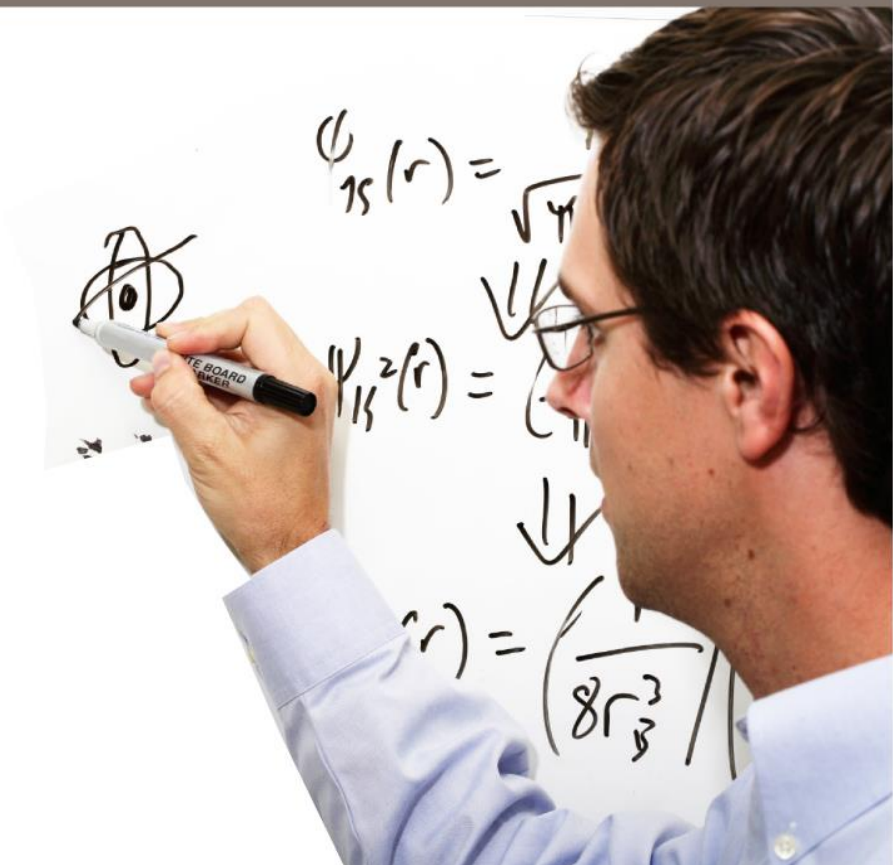
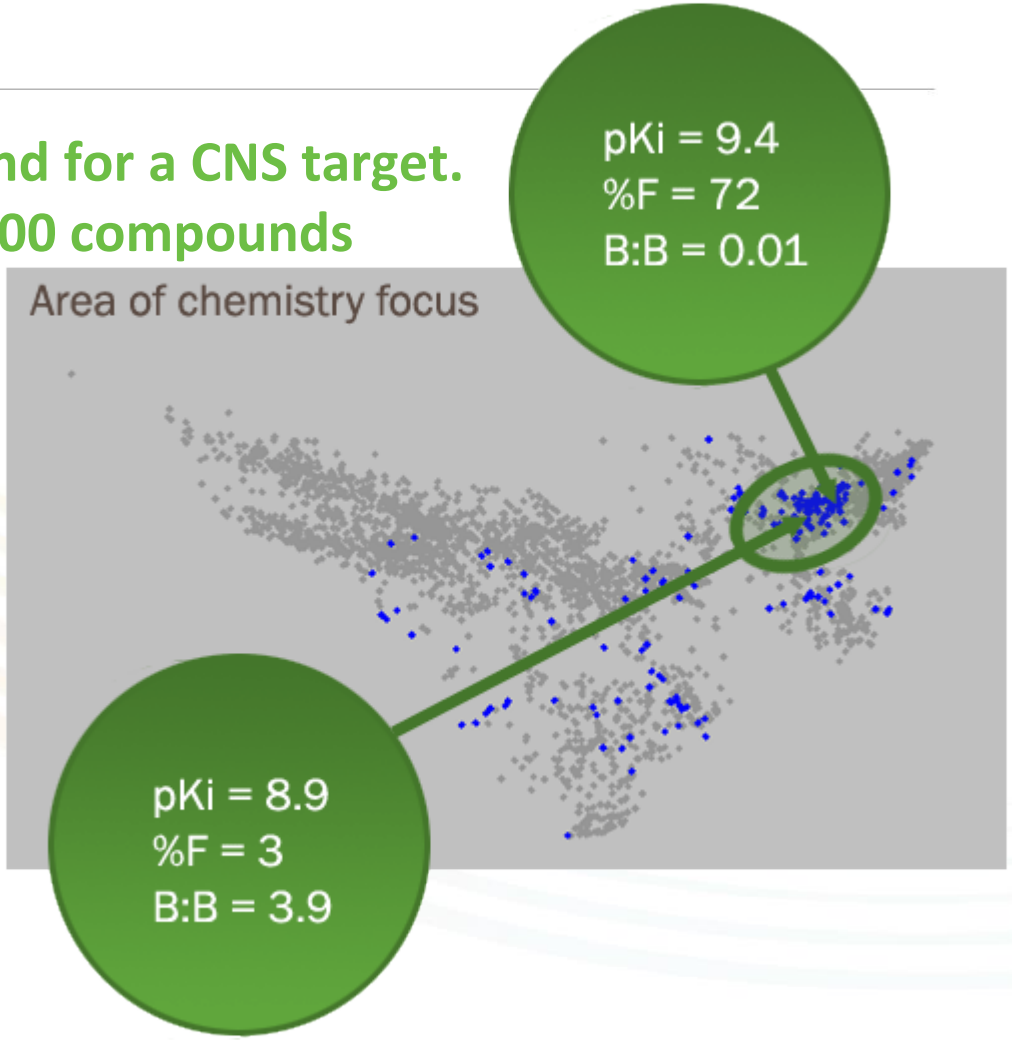


Challenge

Identify orally active compound for a CNS target.
Project 'chemical space' of 3100 compounds



Summary of original project progress

- Focus biased towards one area of chemistry space

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

Challenge

Identify orally active compound for a CNS target.
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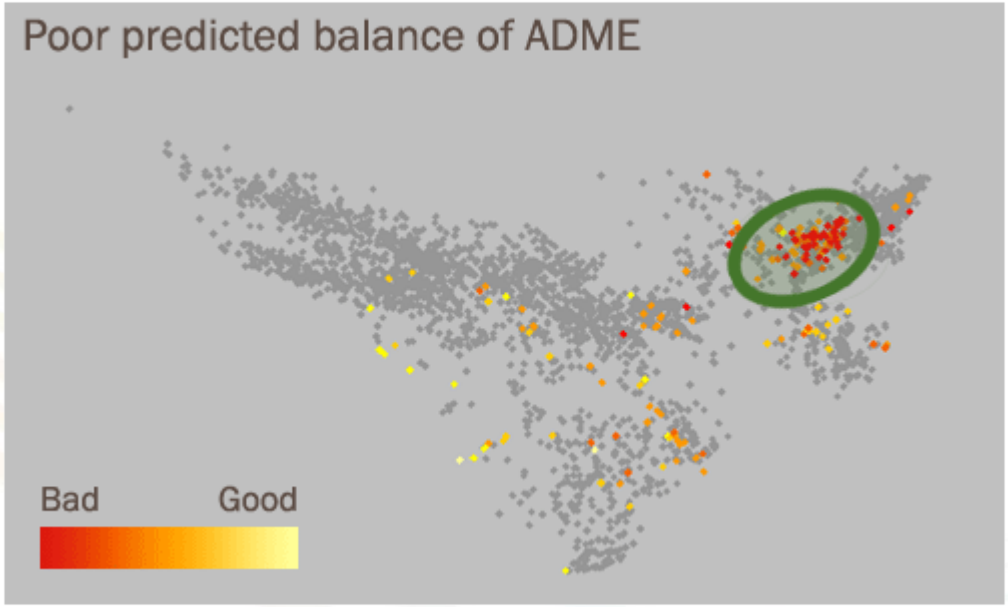


Summary of original project progress

- Focus biased towards one area of chemistry space
- Poor ADME properties

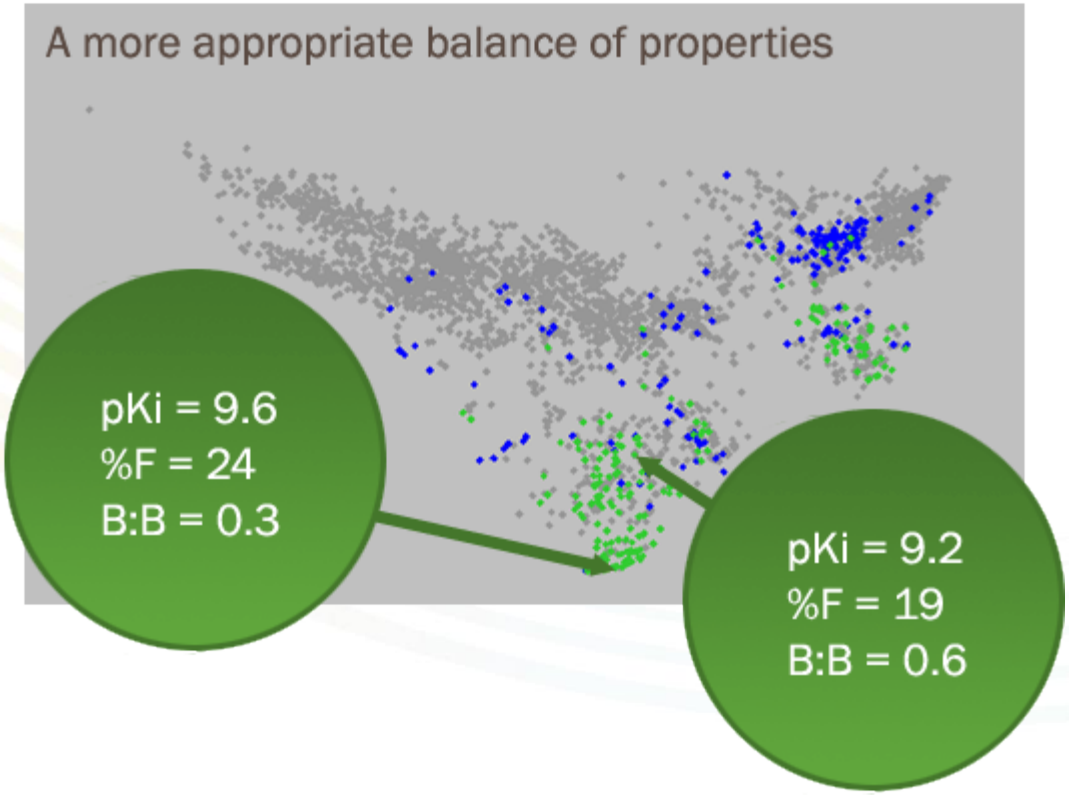
Property	Desired Value	Importance
logS	> 1	
HIA category	+	
BBB log([brain]:[blood])	> -0.5	
logP	⩽ 3.5	
2D6 affinity category	low medium	
2C9 pKi	⩽ 6	
P-gp category	no	

Challenge

Identify orally active compound for a CNS target.
Project 'chemical space' of 3100 compounds

Summary of original project progress

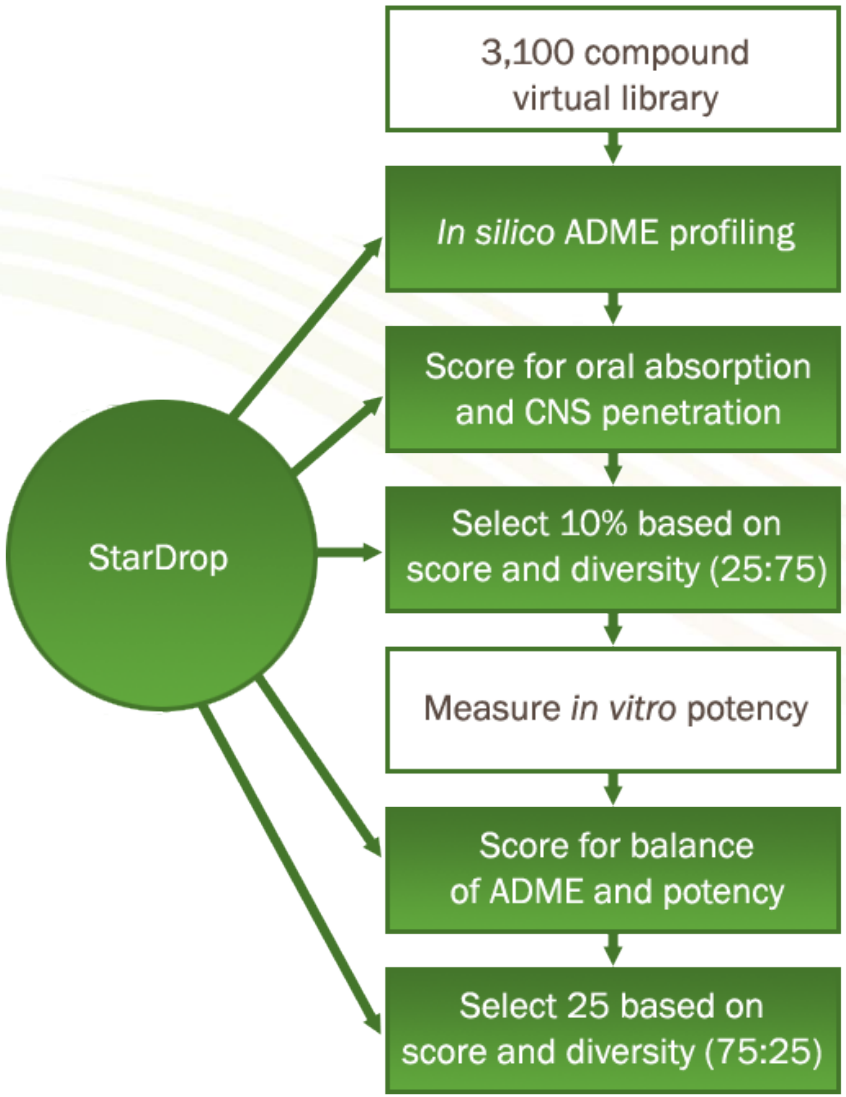
- Focus biased towards one area of chemistry space
- Poor ADME properties
- Follow-up chemistry exploration
- Nowhere obvious to go next!



Cost so far: >**3000** compounds synthesised, **400** compounds tested *in vitro* and **70** compounds tested *in vivo*

StarDrop Process

Select 25 compounds for *in vivo* testing



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BBB log([brain]:[blood])	> -0.5	
logP	⩽ 3.5	
2D6 affinity category	low medium	
2C9 pKi	⩽ 6	
P-gp category	no	

Property	Desired Value	Importance
Potency (pKi)	> 8	
logS	> 1	
HIA category	+	
BBB log([brain]:[blood])	> -0.5	
logP	⩽ 3.5	
2D6 affinity category	low medium	
2C9 pKi	⩽ 6	
P-gp category	no	

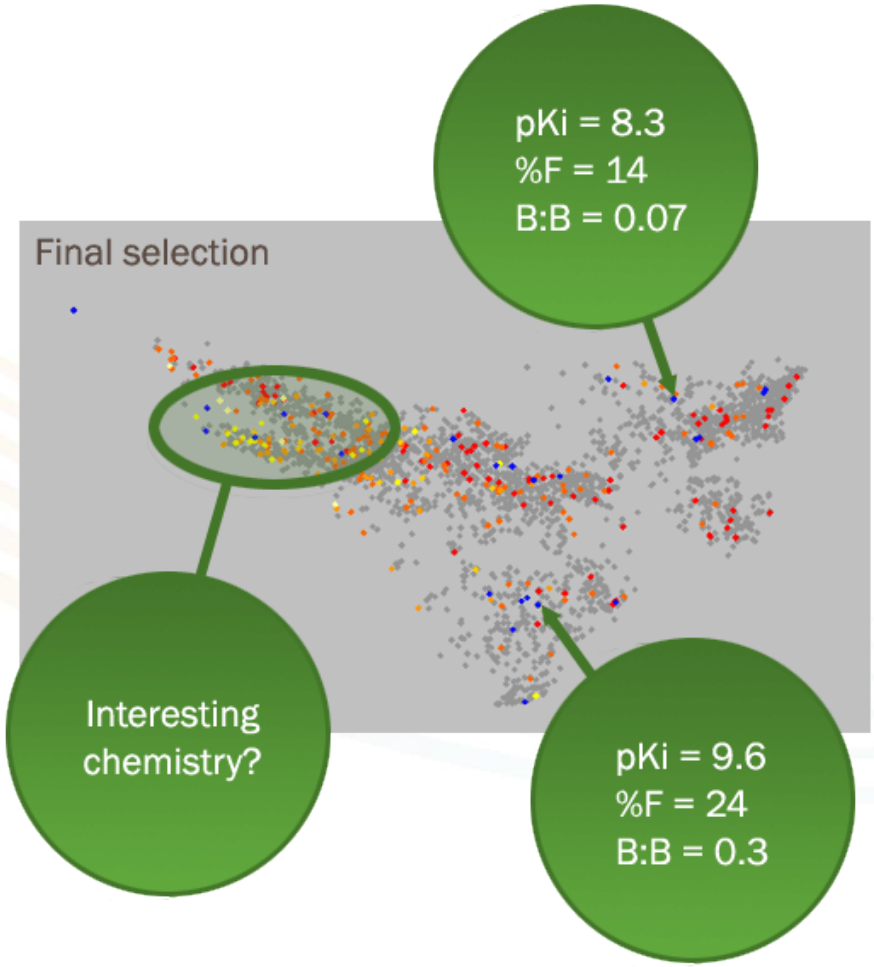
M.D. Segall Curr. Pharm. Des. 18(9) pp. 1292-1310 (2012)

Results

Successfully selected same key compounds identified by the project but with:

- **90%** fewer compounds synthesised
- **90%** less potency screening
- **70%** less *in vivo* testing

In addition, identified a new area of chemistry with good potential!



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
- A ‘balanced’ strategy can dramatically reduce the time and resources required for compound optimisation
- For more details, please see:
  - M.D. Segall Curr. Pharm. Des. **18**(9) pp. 1292-1310 (2012)