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Relative Drug Likelihood: Going beyond 'Drug-Likeness'

ACS Fall National Meeting, August 23rd 2012
Matthew Segall, Iskander Yusof

Overview

- ‘Drug-Like’ Properties
- Quantitative Estimate of Drug-Likeness (Bickerton *et al.*)
  - Multi-parameter Optimization
  - Desirability Functions
- Beyond ‘Drug-like’: Relative Drug Likelihood
- Results
- Conclusion

‘Drug-like’ Properties

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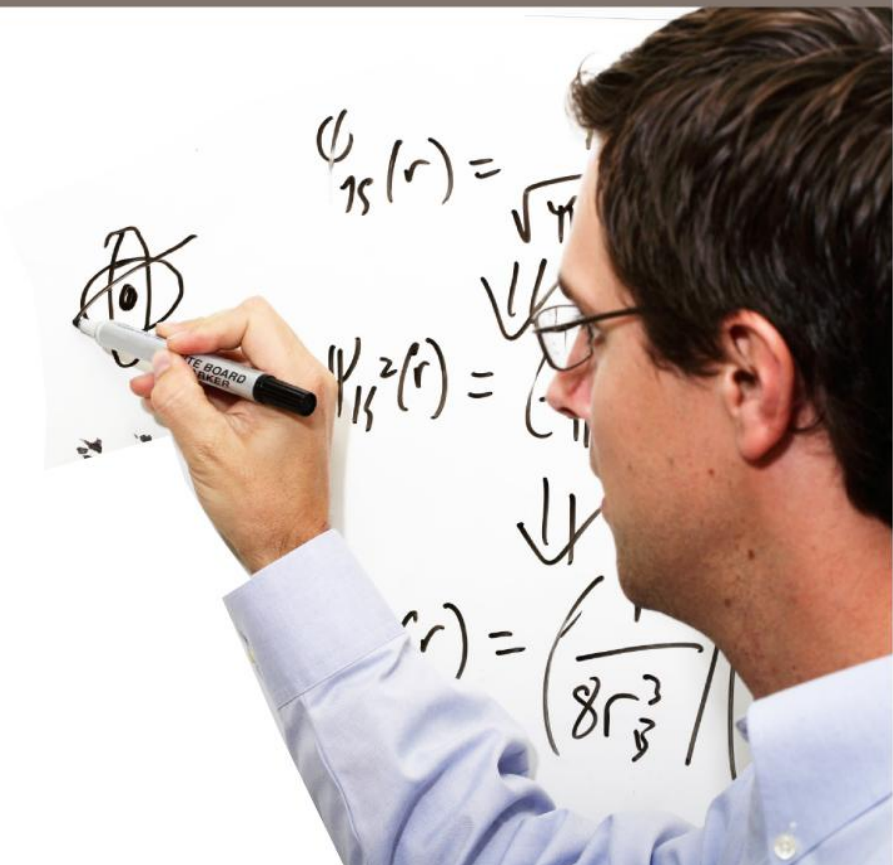

Drug-like Properties
Background

- Rules for simple compound characteristics that drugs have in common
- Original and most influential: Lipinski's Rule of Five

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

- Many others have been proposed, e.g.:
  - Rotatable bonds
  - Aromatic rings
  - Polar surface area
  - Fraction of sp3 carbons

Drug-like Properties
Strengths and Weaknesses

- Strengths
  - Easy to understand and apply
  - Compounds with ‘non drug-like’ properties lie in regions of property space with poor precedence
  - Good guide to avoid potential pitfalls
- Weaknesses
  - Simple characteristics are only weakly predictive of biological properties
  - Binary pass/fail rules
  - Tendency to apply over-rigorously (is MW of 501 worse than 499?)
  - Rules apply only to objective for which they were determined (most commonly oral bioavailability)
  - Many are derived only from analysis of drugs, i.e. what makes drugs similar

Quantitative Estimate of Drug-Likeness (QED)

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

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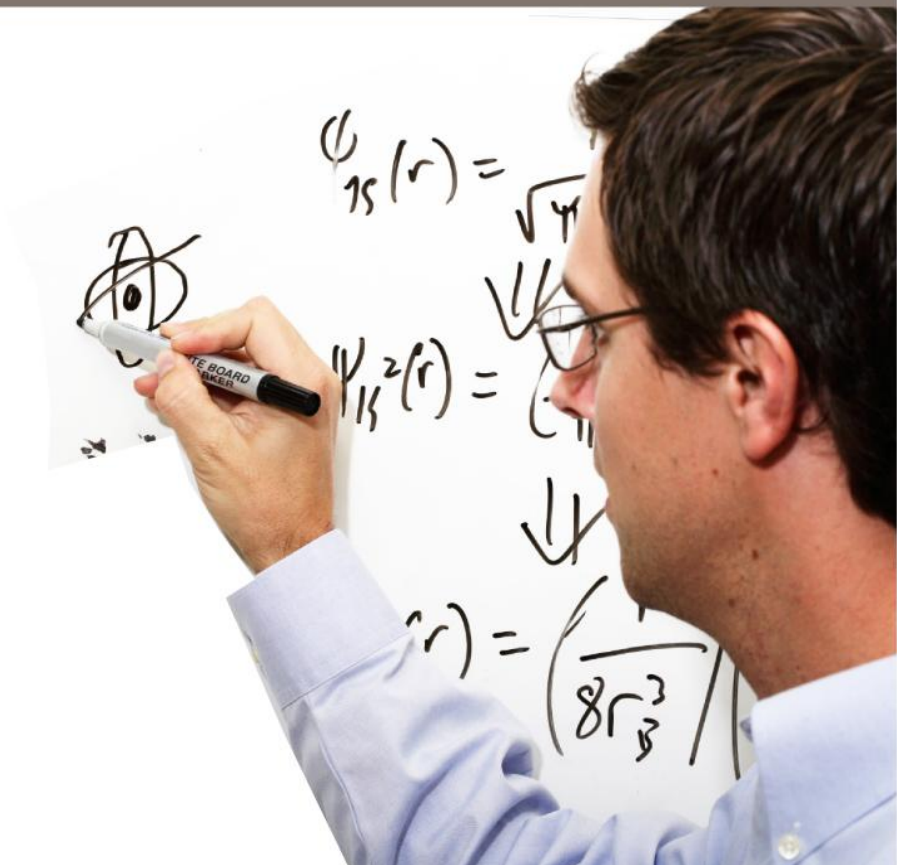
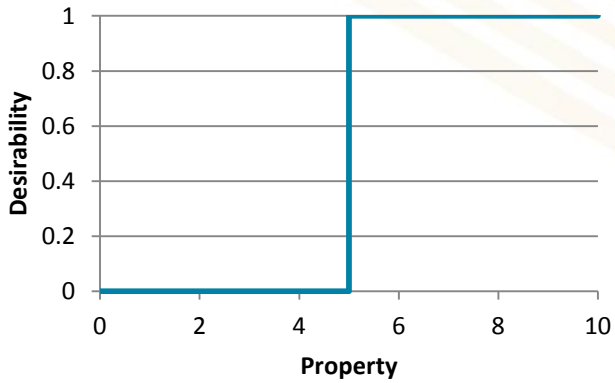


Multi-Parameter Optimization
Desirability Functions

- Combine values of multiple characteristics into single measure of ‘quality’ of a compound*

- Desirability functions relate property values to how ‘desirable’ the outcome



Simple filter: >5

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

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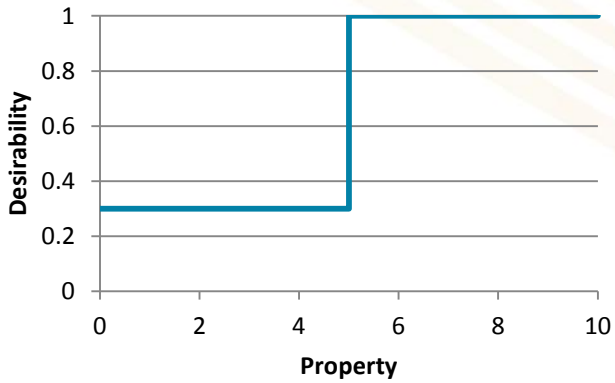

Desired value: >5

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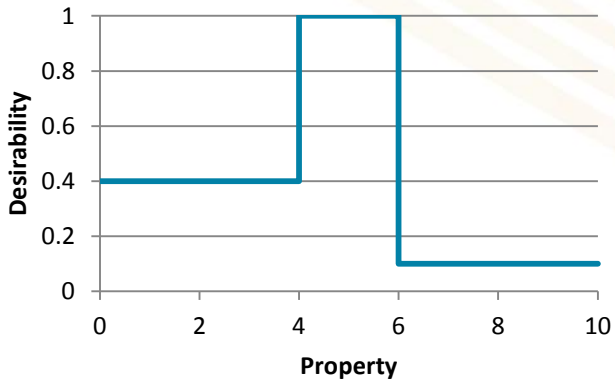

Range: 4-6

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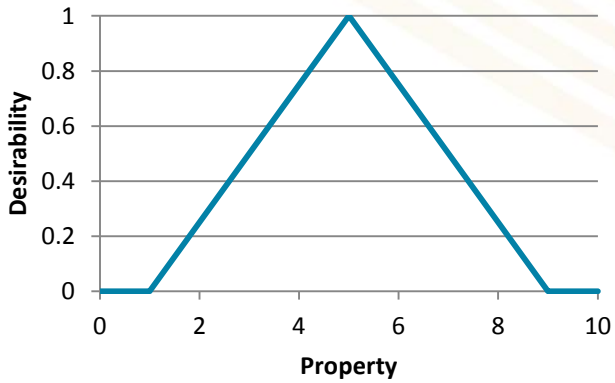

Ideal value: 5

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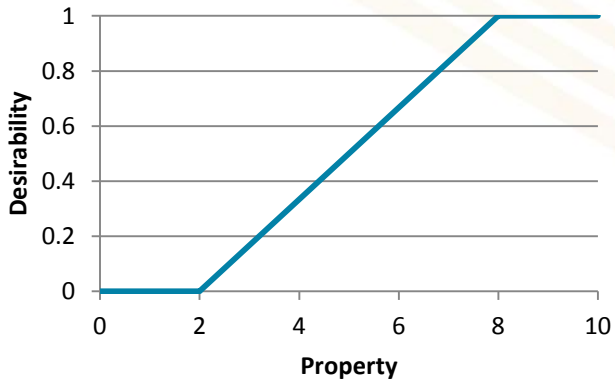

Trend: >8

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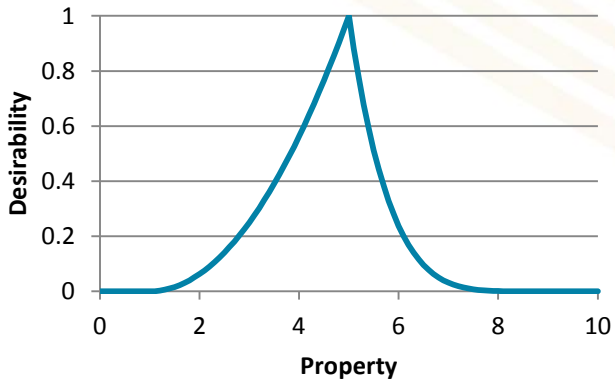


Non-linear, ideal value: 5 (Derringer Function)

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

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

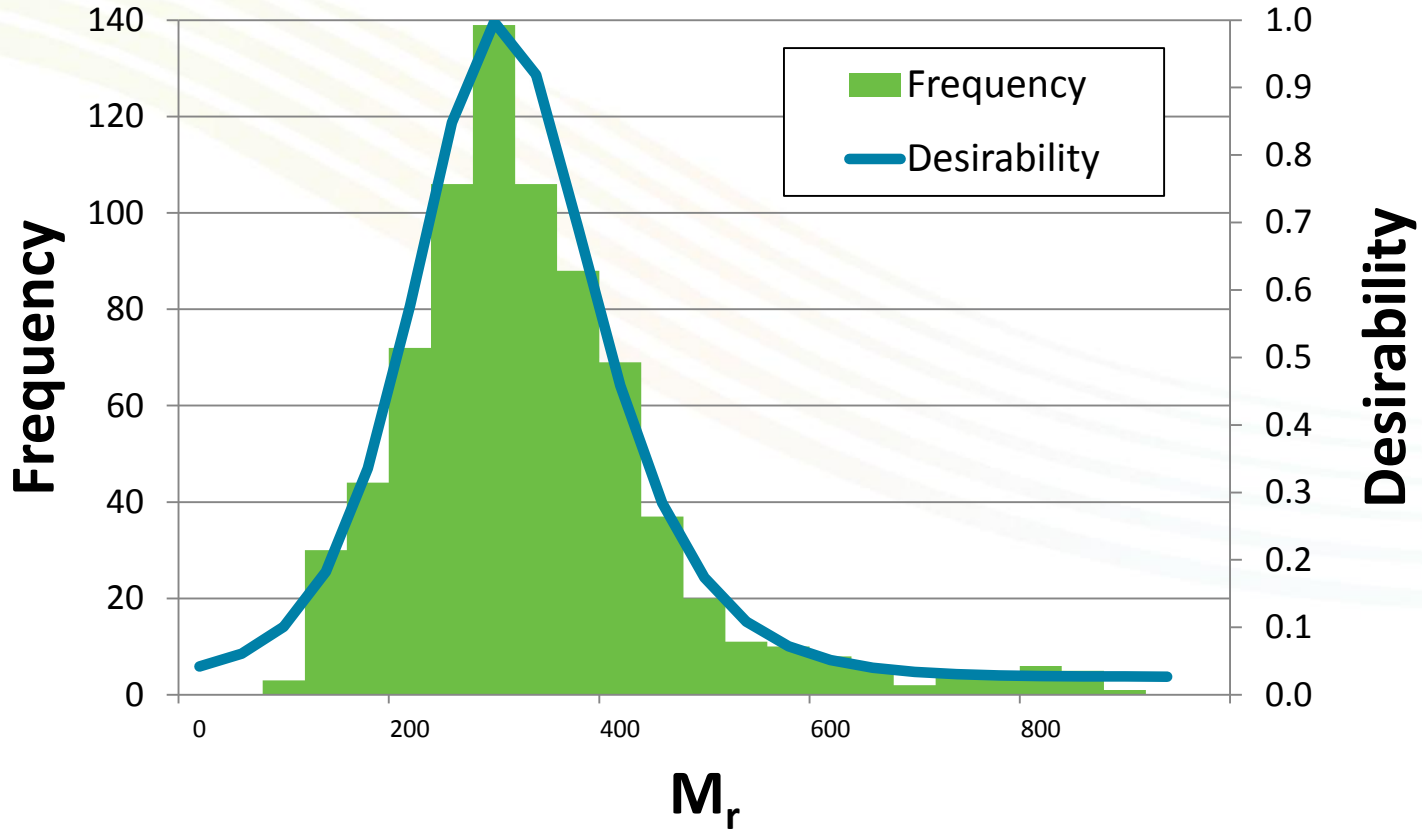
QED*

- Combine values for 8 characteristics
  - Molecular weight (M_r)
  - Lipophilicity (alogP)
  - Number of hydrogen bond donors (HBD)
  - Number of hydrogen bond acceptors (HBA)
  - Polar surface area (PSA)
  - Number of rotatable bonds (ROTB)
  - Number of aromatic rings (AROM)
  - Count of alerts for undesirable substructures (ALERT)

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

QED*

- For each characteristic a desirability function was fitted to distribution for a set of 771 **oral** drugs



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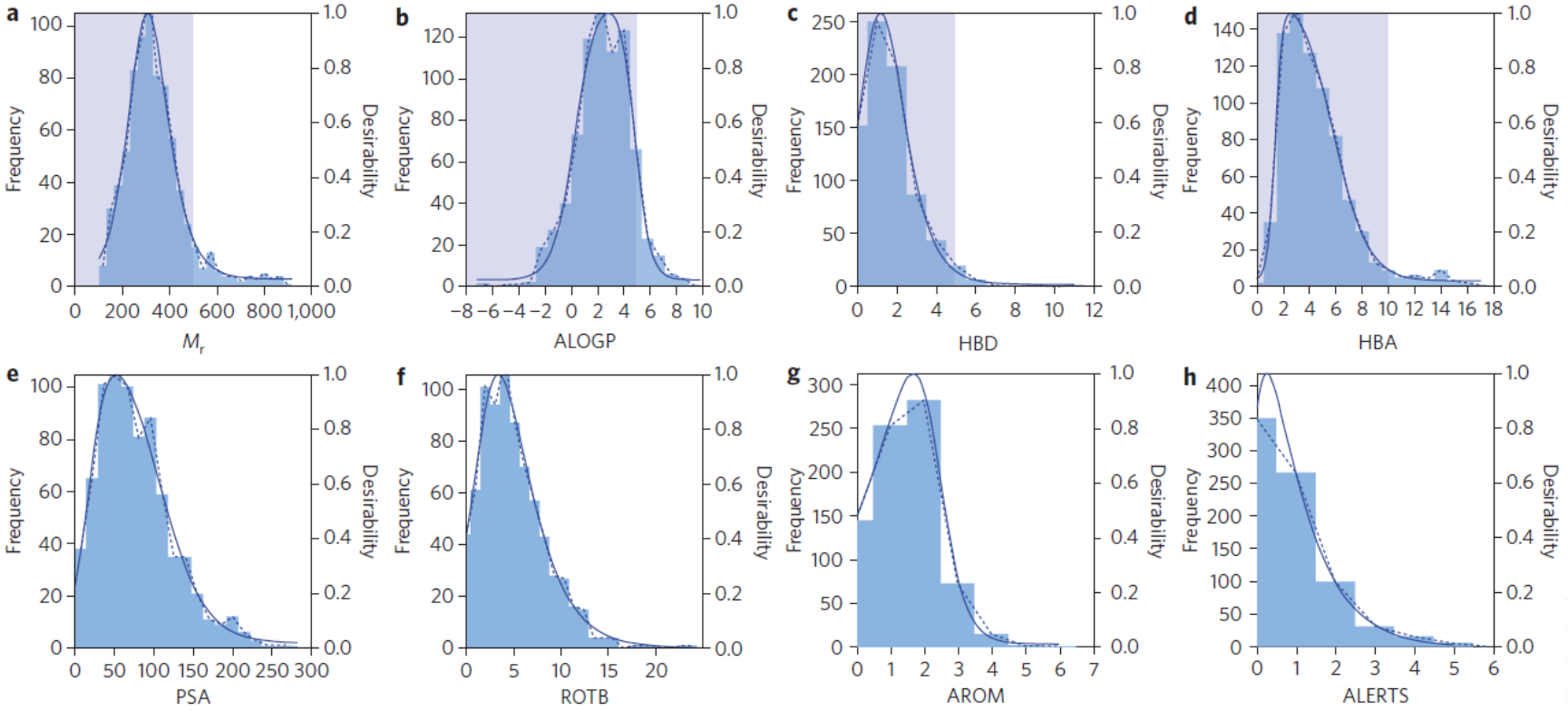
QED*



- The desirabilities for the 8 characteristics are combined using a multiplicative approach:

$$QED_w = \exp\left(\frac{w_{Mr}\ln d_{Mr} + w_{ALOGP}\ln d_{ALOGP} + w_{HBA}\ln d_{HBA} + w_{HBD}\ln d_{HBD} + w_{PSA}\ln d_{PSA} + w_{ROTB}\ln d_{ROTB} + w_{AROM}\ln d_{AROM} + w_{ALERT}\ln d_{ALERT}}{w_{Mr} + w_{ALOGP} + w_{HBA} + w_{HBD} + w_{PSA} + w_{ROTB} + w_{AROM} + w_{ALERT}}\right)$$

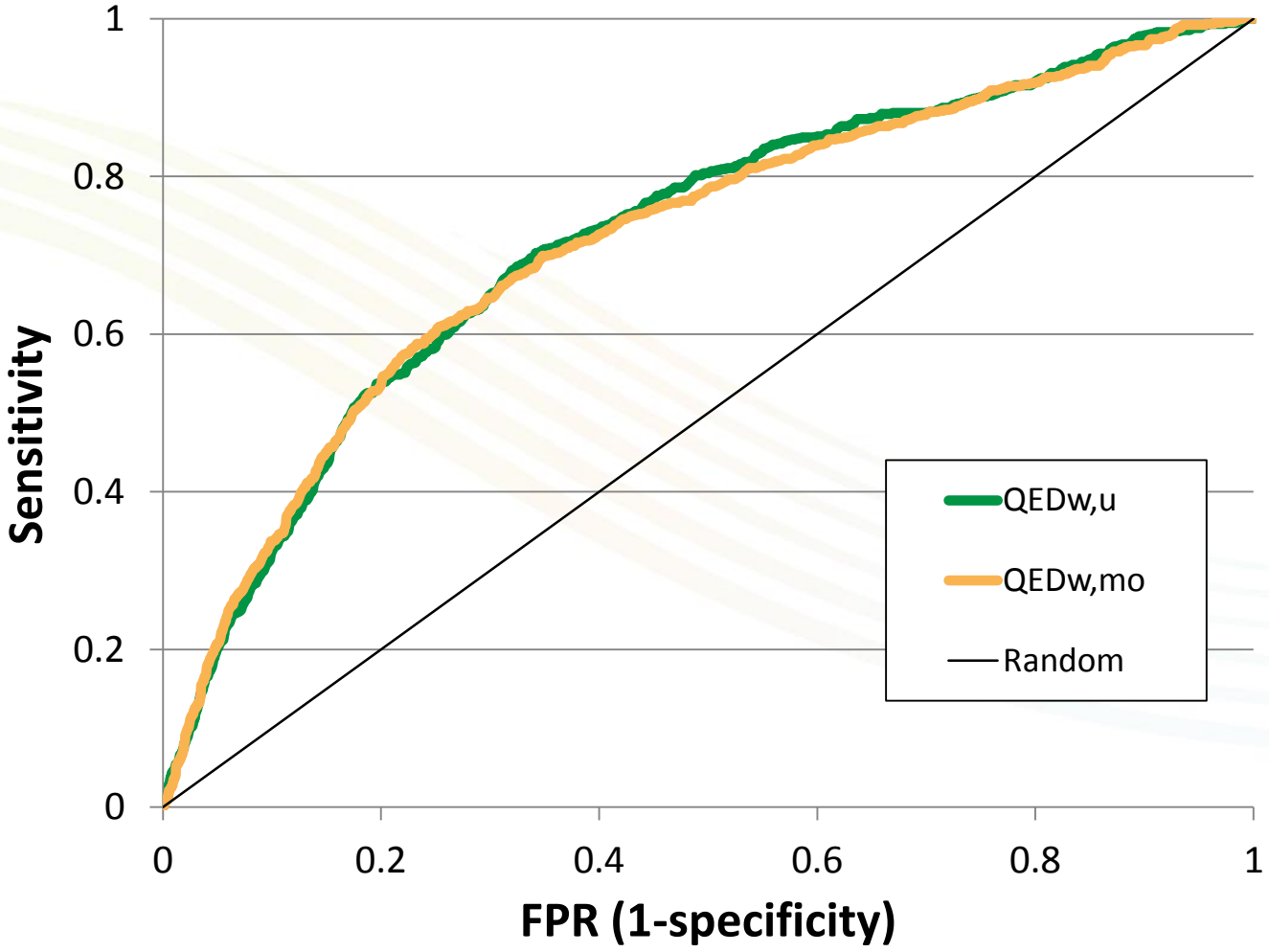
*Bickerton *et al.* Nature Chem. 4, pp. 90-98 (2012)

QED*

- QED avoids the pitfalls of hard cut-offs
  - Provides a single metric for the ‘similarity’ of a compound to known oral drugs
- Bickerton *et al.* showed that QED correlates with chemists’ opinion on ‘beauty’ of compounds
- Benchmarked QED for selection of 771 oral drugs vs. 10,250 compounds from the PDB ligand dictionary
  - N.B. Not a fully independent test set of drugs

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

QED Benchmarking Results



Beyond ‘Drug-like’:
Relative Drug Likelihood

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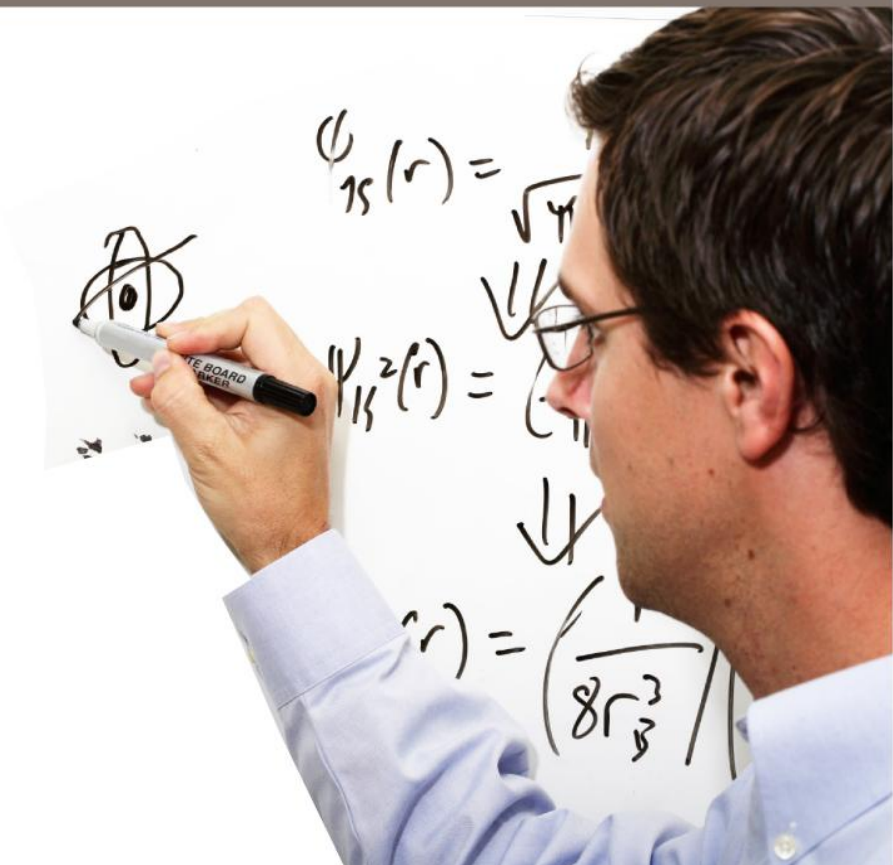
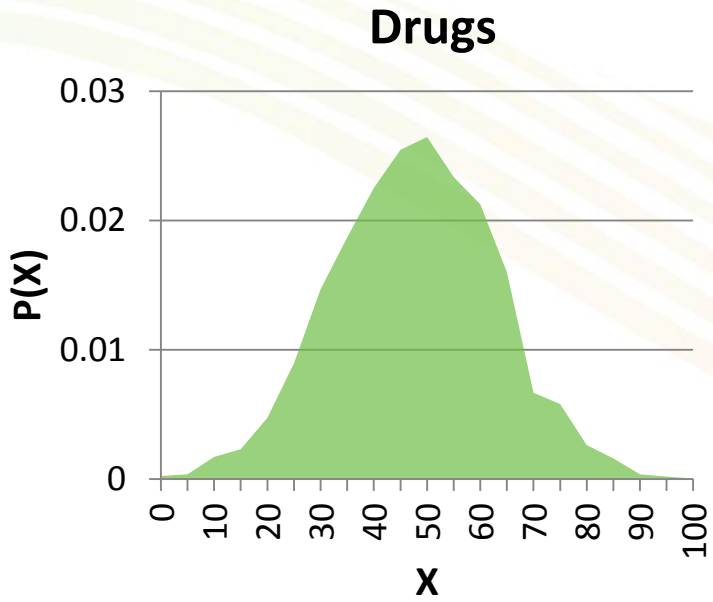
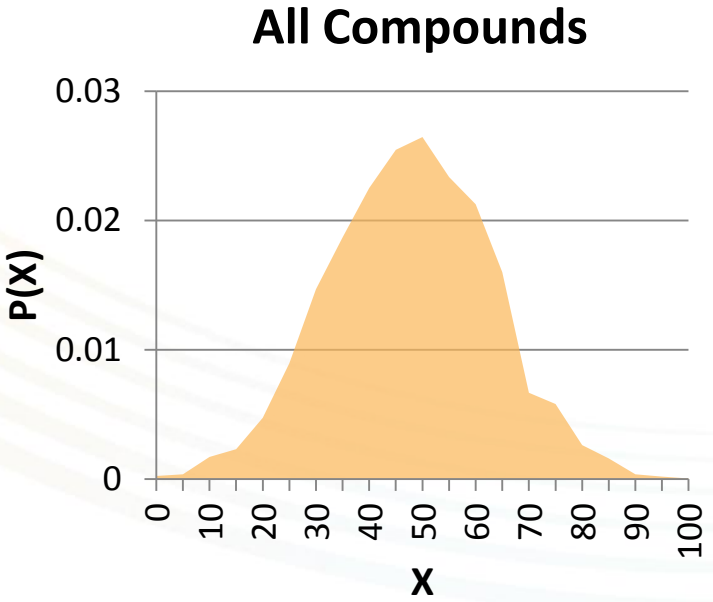


Similarity is Not Enough

- A compound with a characteristic that is ‘similar’ to known drugs does not necessarily have an increased chance of success

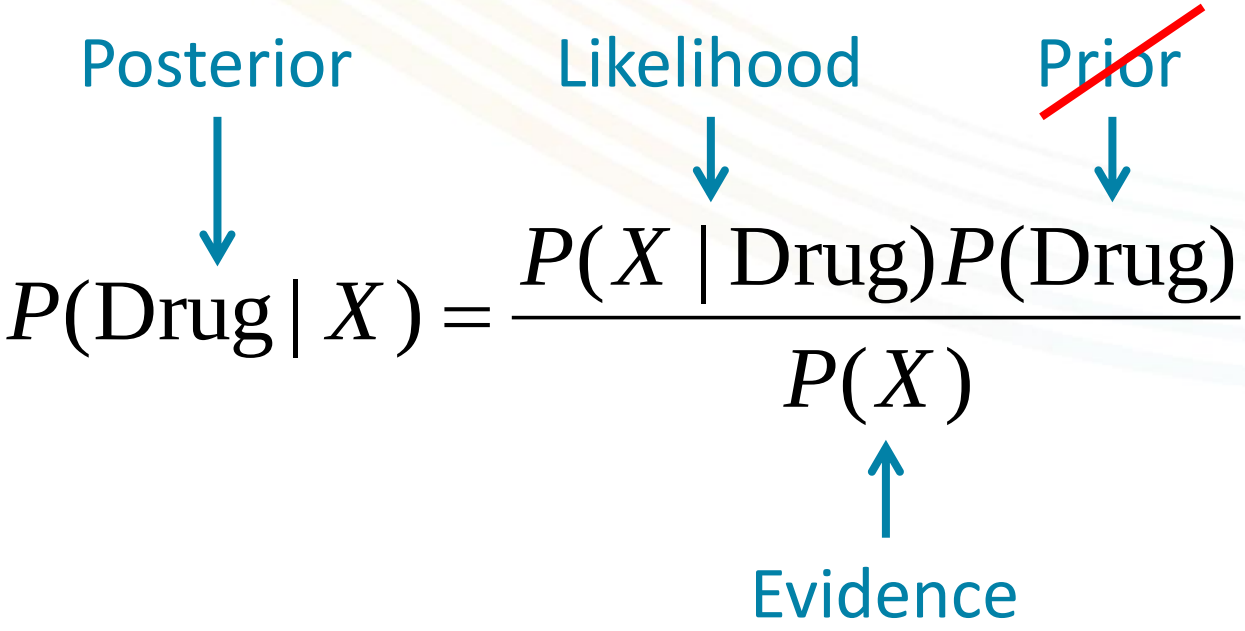




- Some properties distinguish drugs from non-drugs better than others

Relative Drug Likelihood
Bayesian probability theory

- Analysis of characteristics of known drugs gives us P(*X*|Drug)
- We would like to know P(Drug|*X*)
- Bayes' theorem allows us (in principle) to calculate this:



Relative Drug Likelihood
Bayesian probability theory

- Compare with probability compound is not a drug:

$$P(\text{not Drug}\,|\,X) = \frac{P(X\,|\,\text{not Drug})P(\text{not Drug})}{P(X)}$$

- We want to find compounds with high *relative* probability of being drug, so take ratio

$$\frac{P(\text{Drug}\,|\,X)}{P(\text{not Drug}\,|\,X)} = \frac{P(X\,|\,\text{Drug})}{P(X\,|\,\text{not Drug})}\frac{P(\text{Drug})}{P(\text{not Drug})}$$

Constant (v. small)

Relative Drug Likelihood
Bayesian probability theory

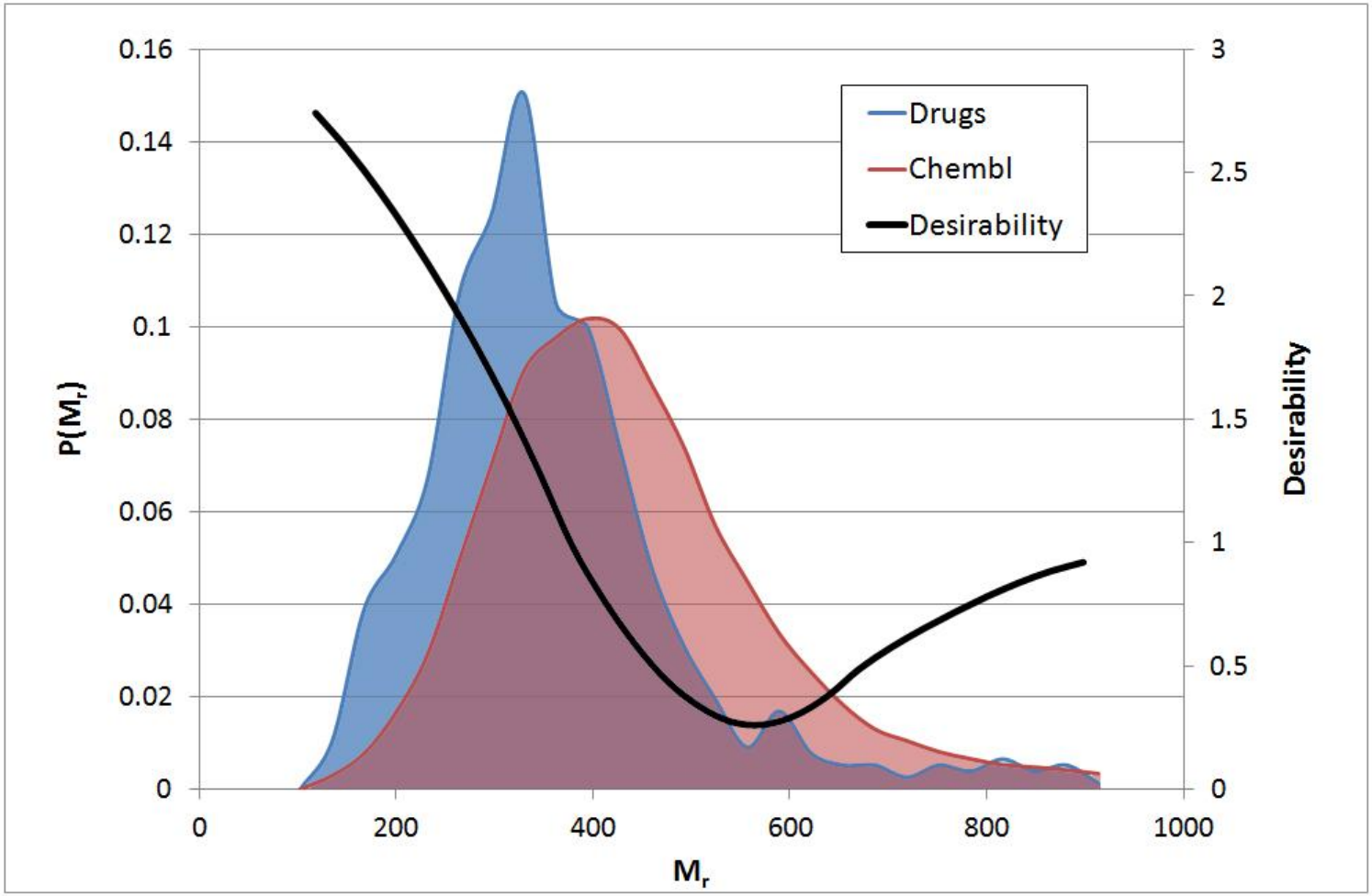
- Therefore, we define the desirability of a value *x* of property *X* as:

$$d(x) = \frac{P(X = x \mid \text{Drug})}{P(X = x \mid \text{not Drug})}$$

- Need to choose appropriate negative set of non-drugs from which we would like to distinguish drugs
  - Choose ChEMBL database* as representative of 'med chem' compounds
  - Trained on random selection of 1000 compounds from ChEMBL and 771 compound **oral** drug set from Bickerton *et al.*

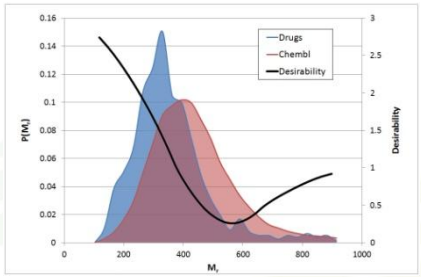
* https://www.ebi.ac.uk/chembldb/

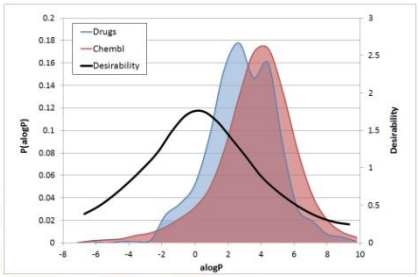
Relative Drug Likelihood
Example – Molecular Weight

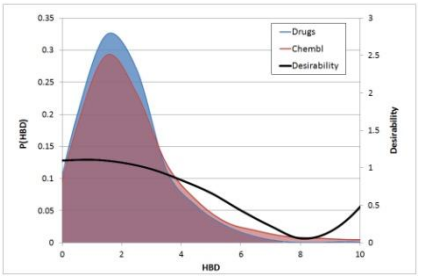


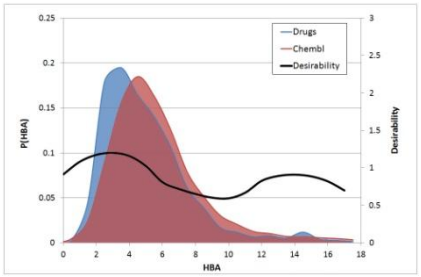
Relative Drug Likelihood

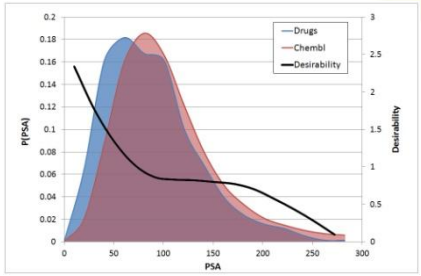
Analysis of 8 properties from QED

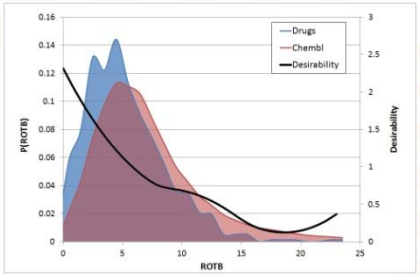


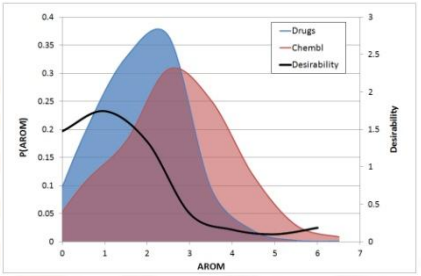


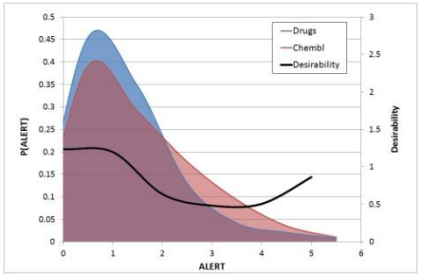






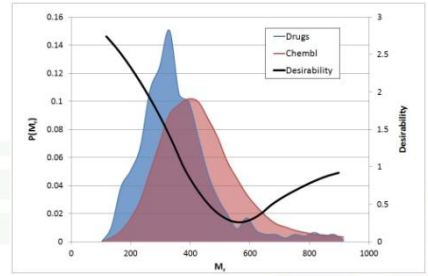


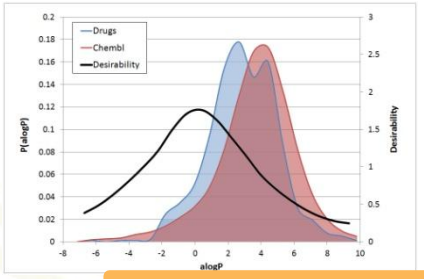


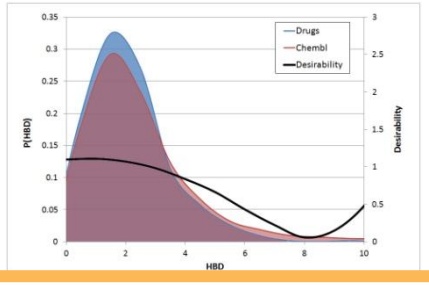


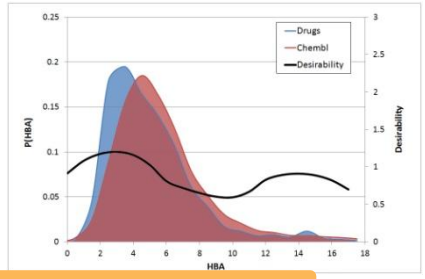
Relative Drug Likelihood

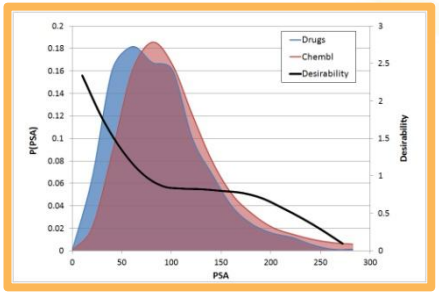
PSA

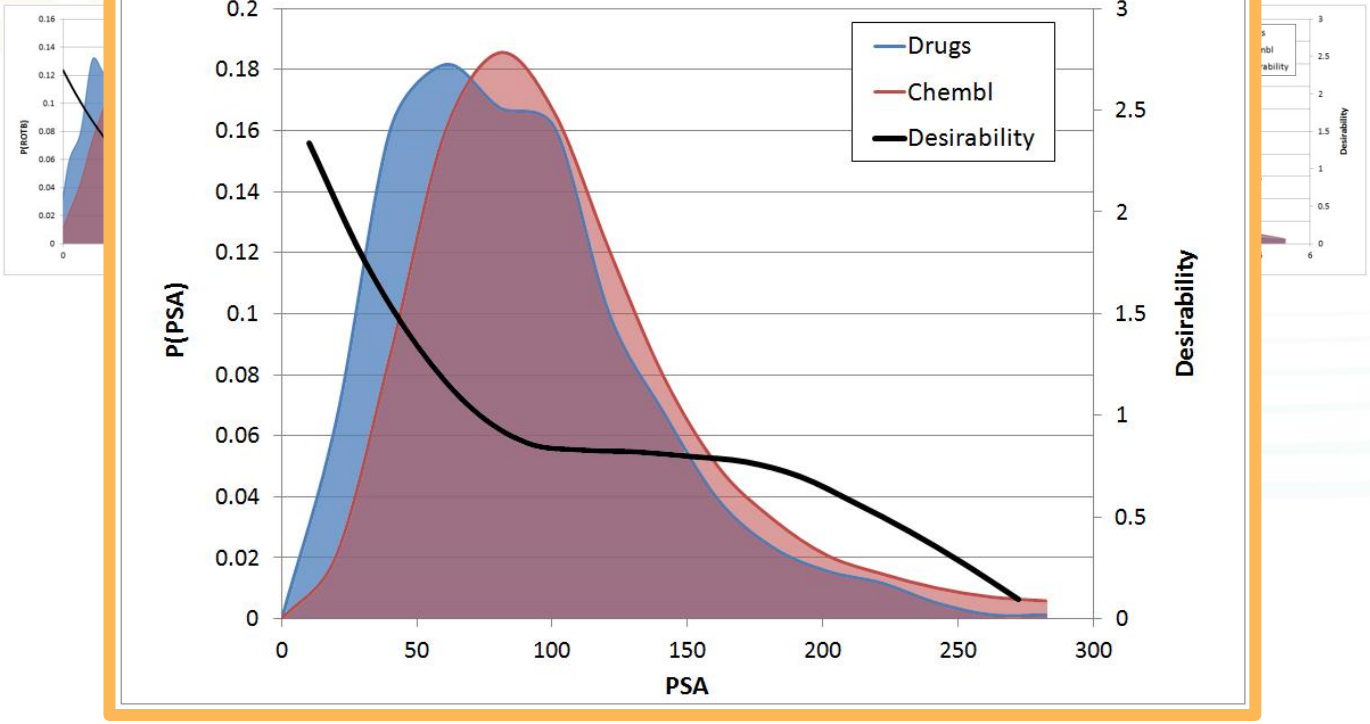




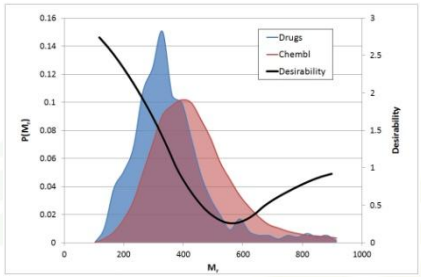


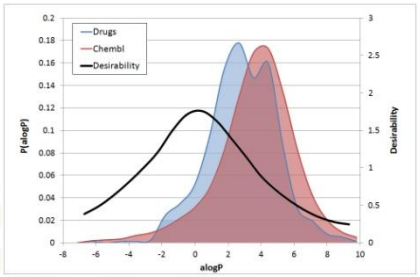


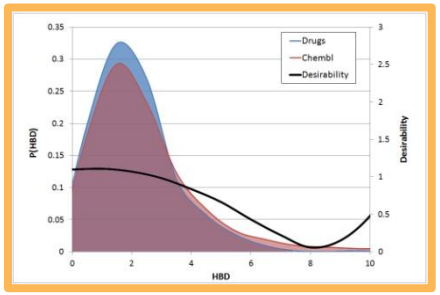


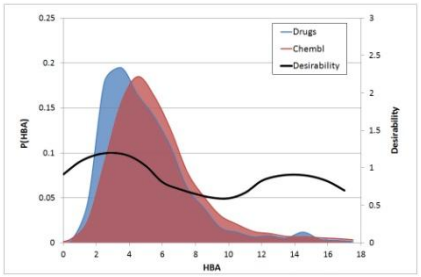


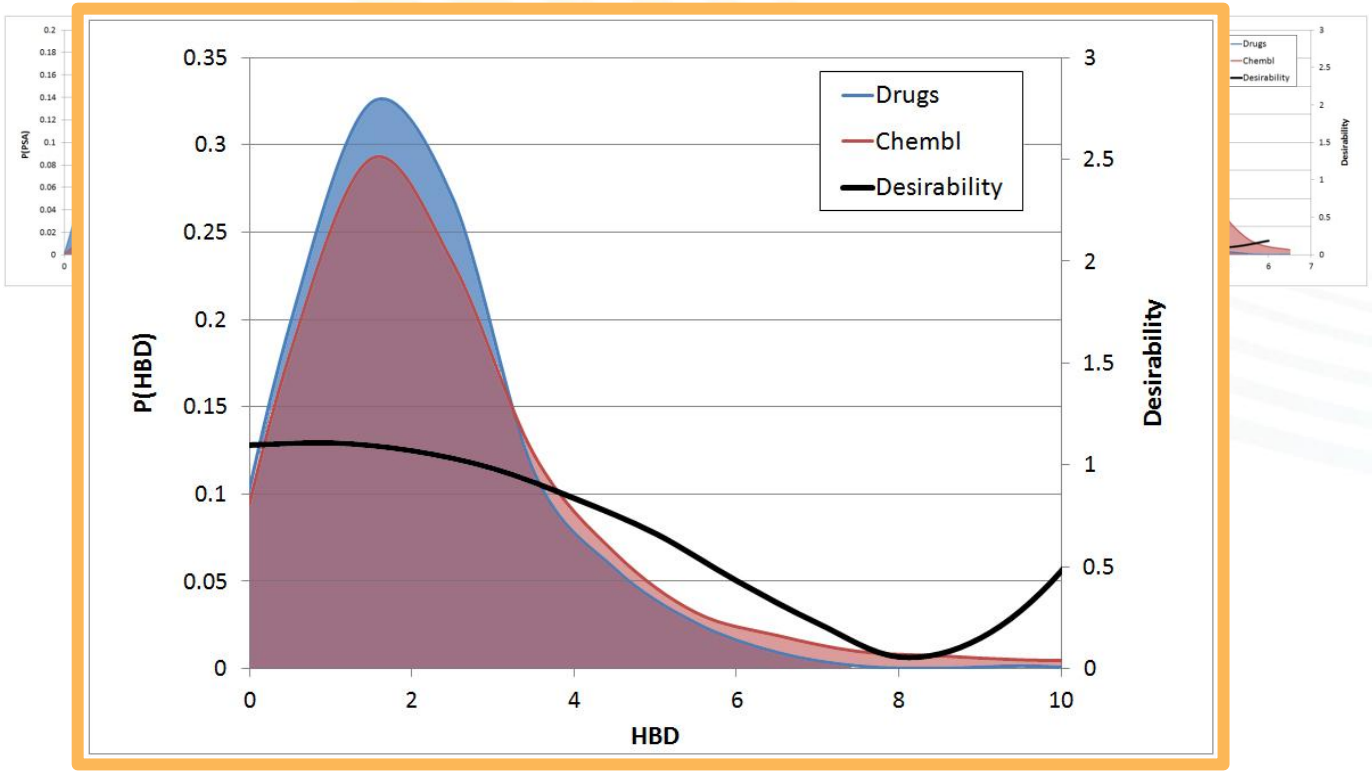
Relative Drug Likelihood
HBA

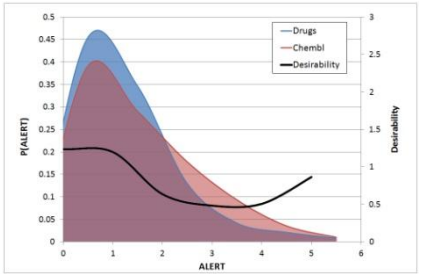












Relative Drug Likelihood

- Combine desirabilities of individual characteristics to give overall Relative Drug Likelihood (RDL)

- Multiplicative – analogous to QED

$$\mathrm{RDL} = \exp\left(\frac{1}{n}\sum_{i=1}^{n}\ln(d_i(x_i))\right)$$

Results

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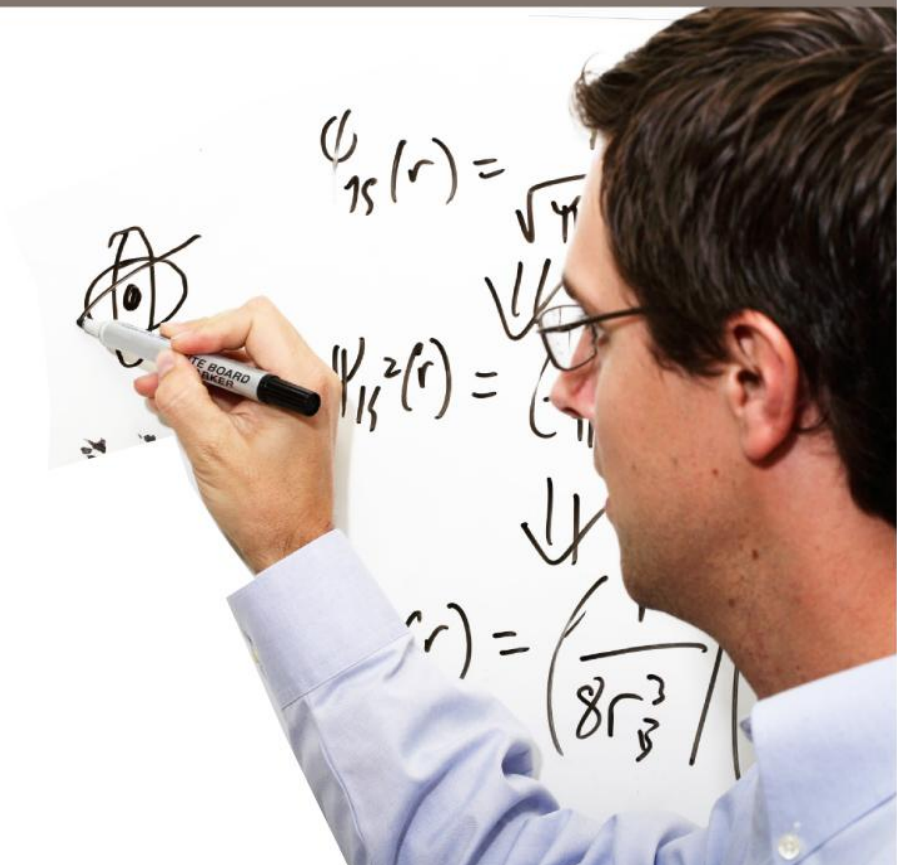
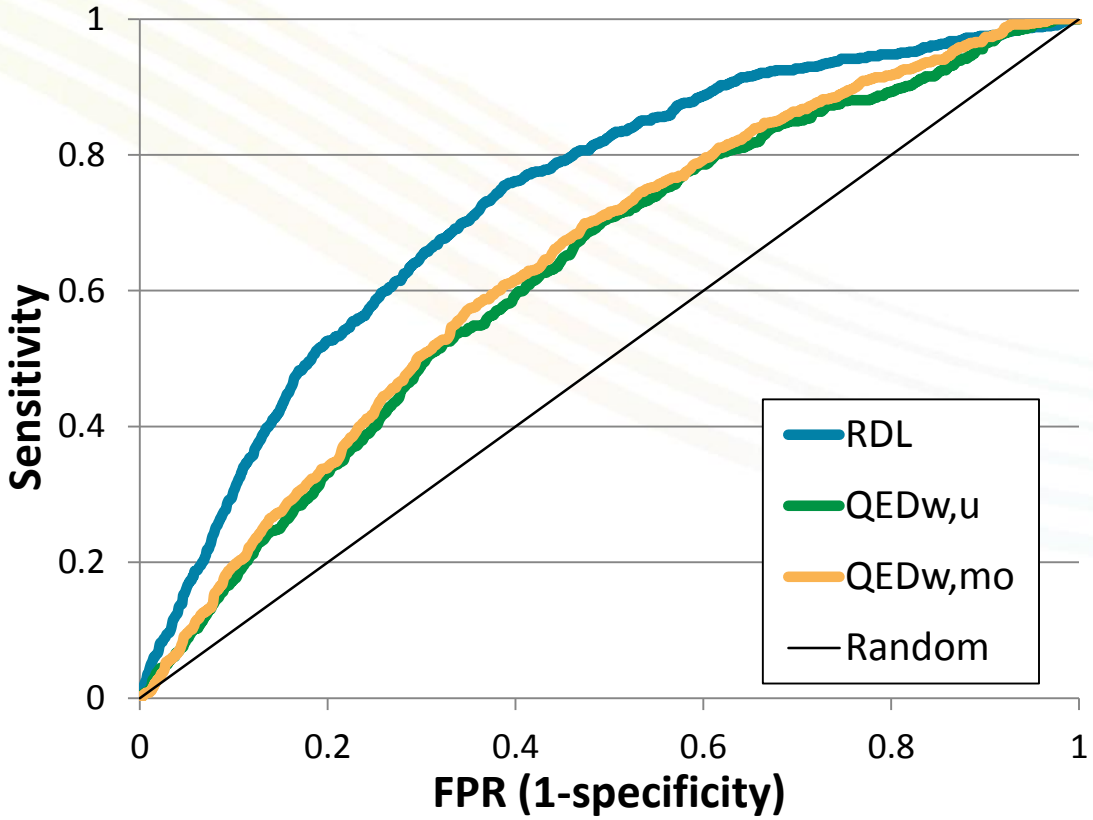


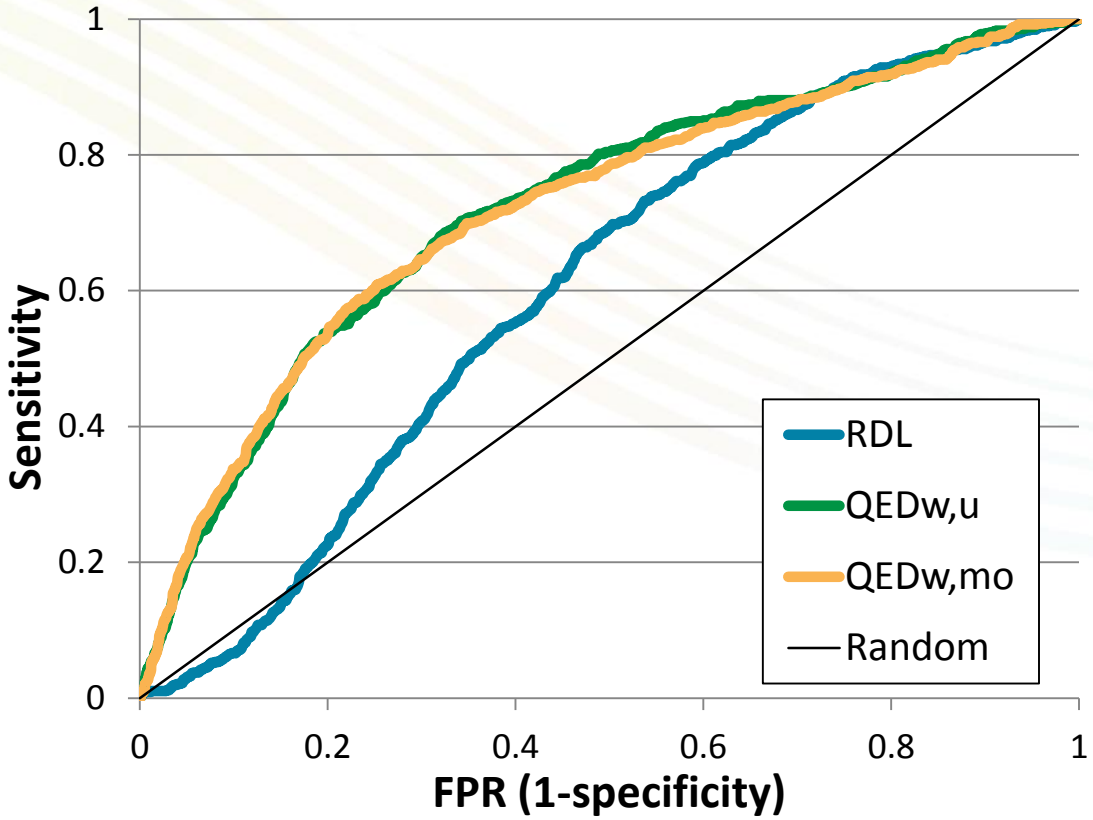
Identifying Drugs
Selecting from 'med chem' compounds

- 771 drug 'test' set from Bickerton *et al.* vs. >650k compounds from ChEMBL (independent of training set)



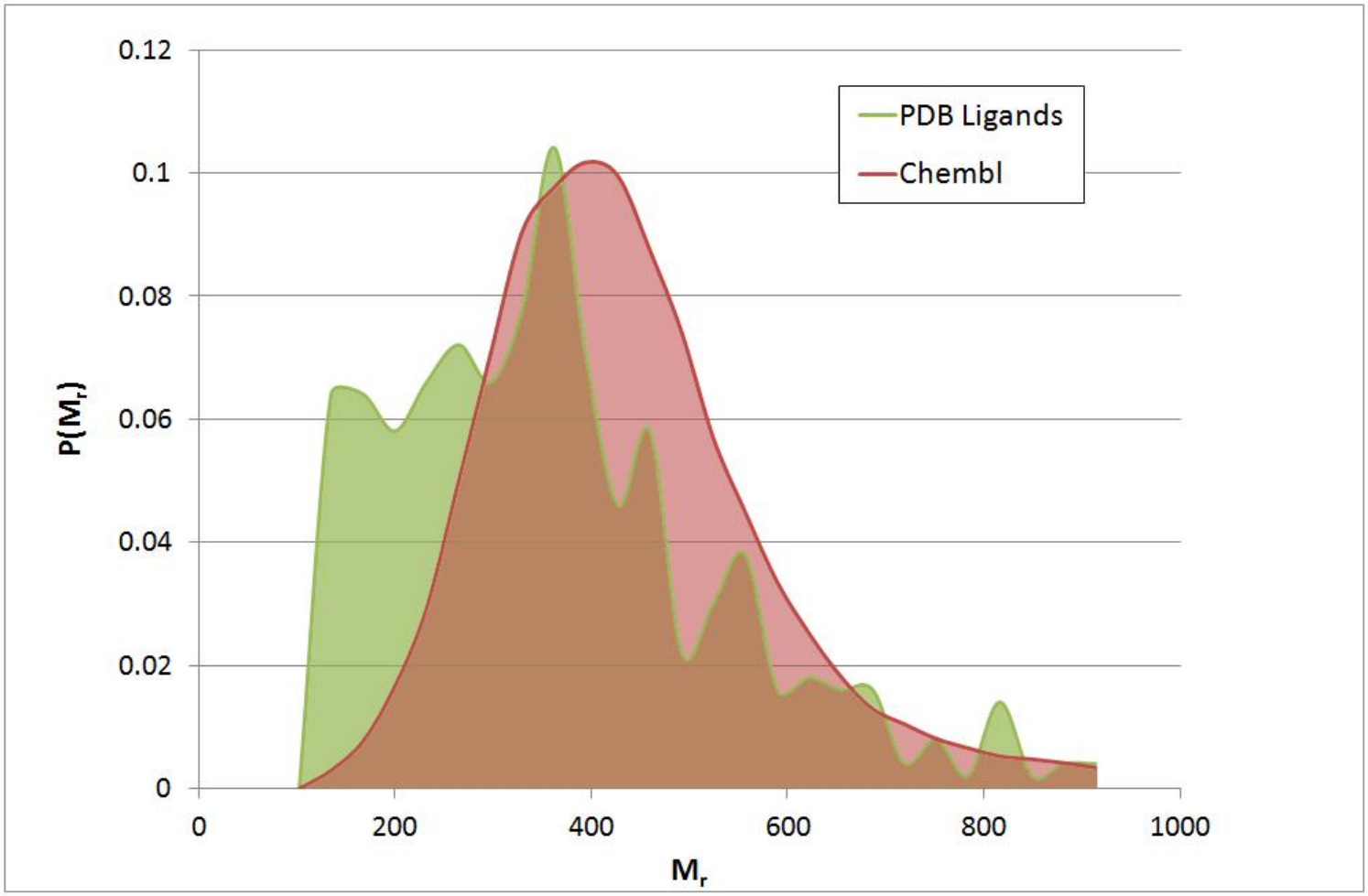
Identifying Drugs
Selecting from PDB ligand dictionary

- 771 drug 'test' set from Bickerton *et al.* vs. 10,250 compounds from the PDB ligand dictionary



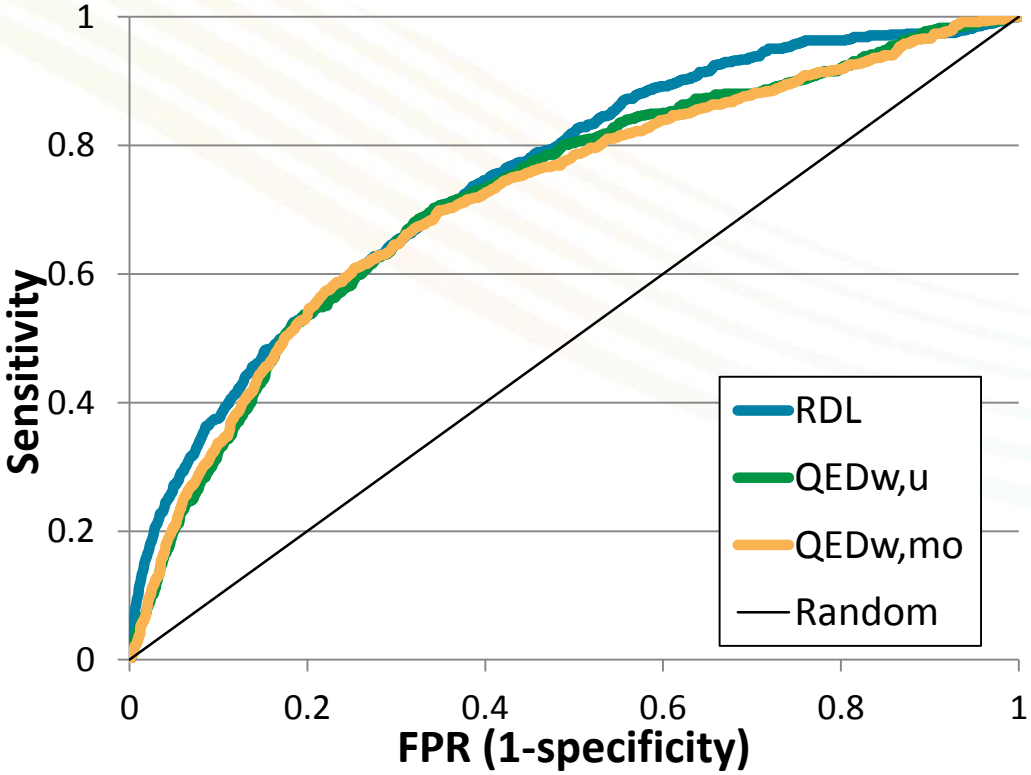
Comparing PDB Ligands with ChEMBL

Molecular weight distribution



Identifying Drugs
Selecting from PDB ligand dictionary

- PDB ligand dictionary is not representative of med chem compounds
- Retrain RDL using 500 compound 'negative' set from PDB ligand dictionary
- 771 drug 'test' set from Bickerton *et al.* vs. 9.750 compounds from the PDB ligand dictionary



Conclusions

- Binary rules for selection of compounds are risky
  - Filters may throw away valuable opportunities
- The criteria to accurately identify good compounds depend on the population from which we are selecting
  - We have used ChEMBL as representative of 'med chem' compounds
  - ChEMBL is already biased by med chemists experience, so RDL shows added value over medicinal chemistry 'instincts'
- Could be applied to different therapeutic classes
- Having a good RDL (or QED etc.) is not a guarantee of success
  - *Relative* drug likelihood
  - Remember the very small constant we ignored (P(Drug)/P(not Drug))
  - A compound with good 'drug-like' characteristics may fail for a large number of reasons
- Preprint and scripts to calculate RDL yourself can be downloaded from:
  - www.optibrium.com/community

Acknowledgements

- Optibrium team
  - Ed Champness
  - Chris Leeding
  - James Chisholm
  - Nick Foster
  - Hector Garcia
- Helpful comments from many others
  - Andrew Hopkins
  - Richard Bickerton
  - Stephen Smith