optibrium

Overcoming psychological barriers to good decision-making in drug discovery

UK QSAR – 26 April 2017

Matthew Segall - matt.segall@optibrium.com

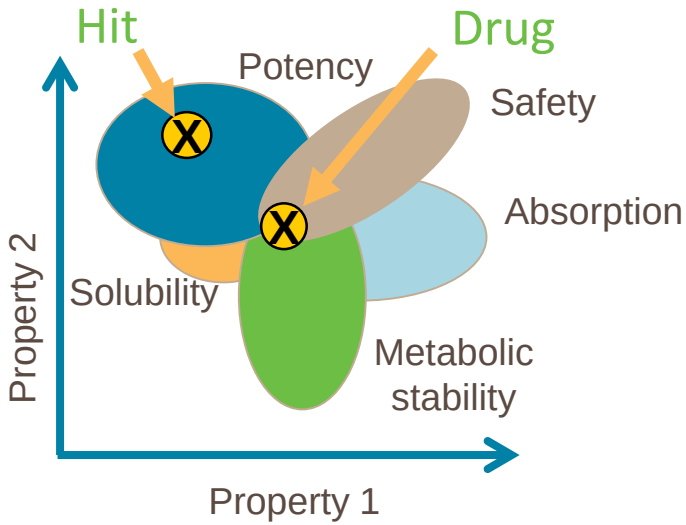
Overview

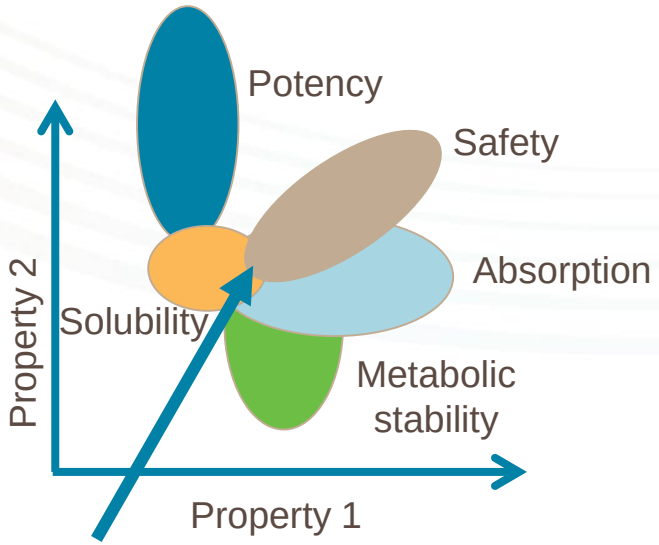
- Challenges of decision-making in drug discovery
- Common cognitive biases
  - Confirmation bias
  - Poor calibration
  - Availability bias
  - Representativeness
  - Excess focus on certainty
- Conclusion
  - Guiding decisions to overcome biases

The Objectives of Drug Discovery
Multi-parameter optimisation

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

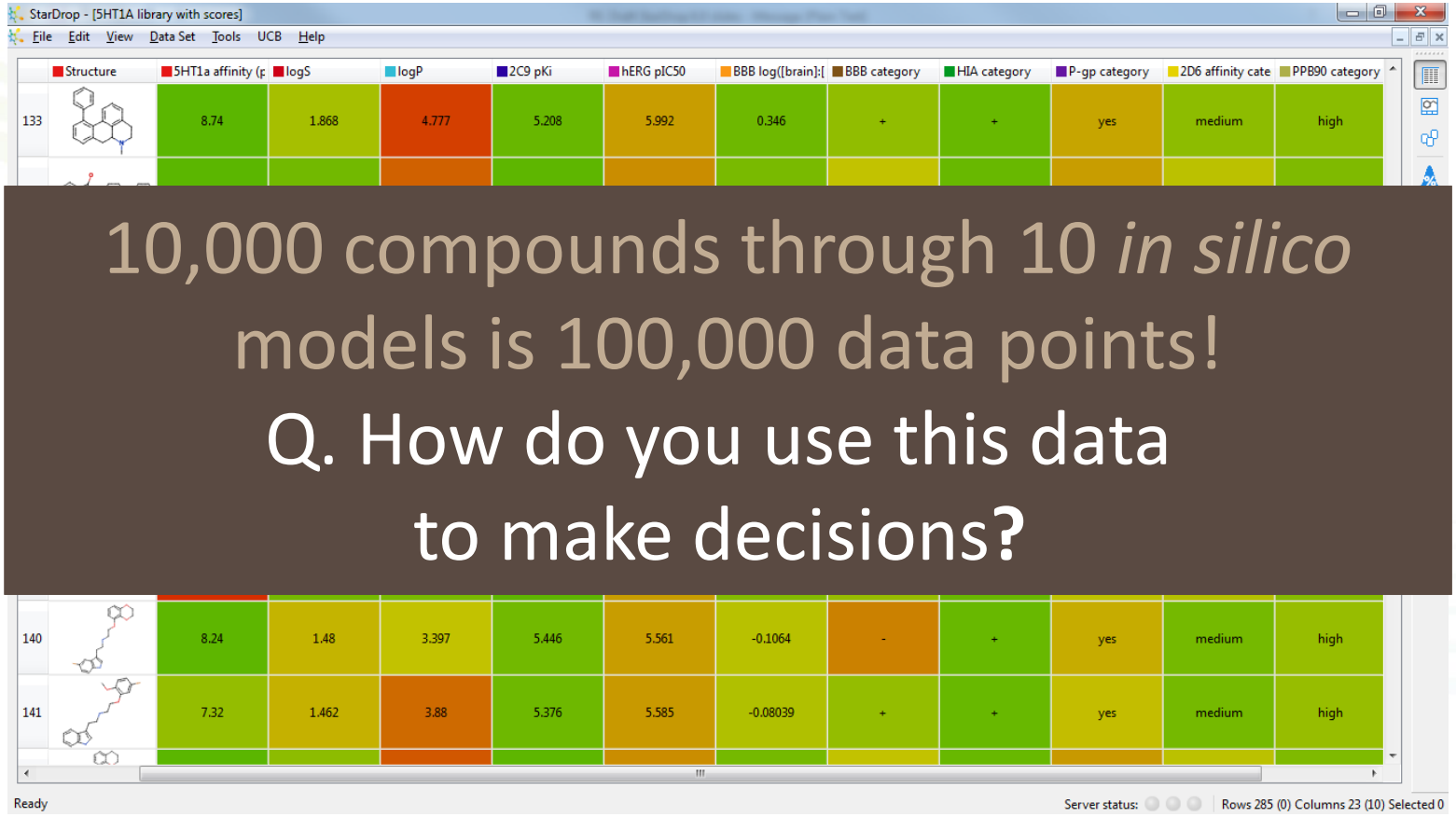
- Quickly identify situations when such a balance is not possible
  - –Fail fast, fail cheap
  - –Only when **confident**
  - –Avoid **missed opportunities**





No good drug

Challenge 1: Data overload

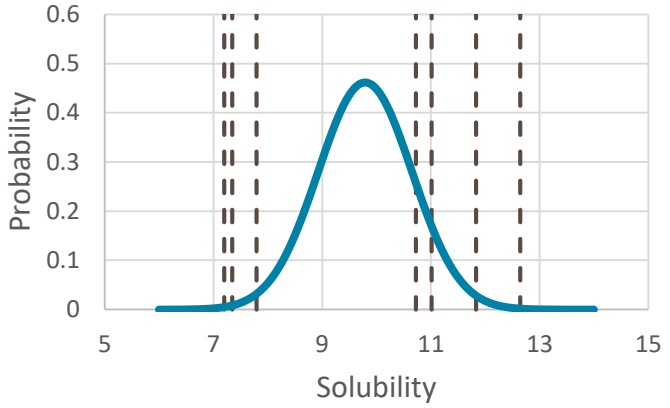


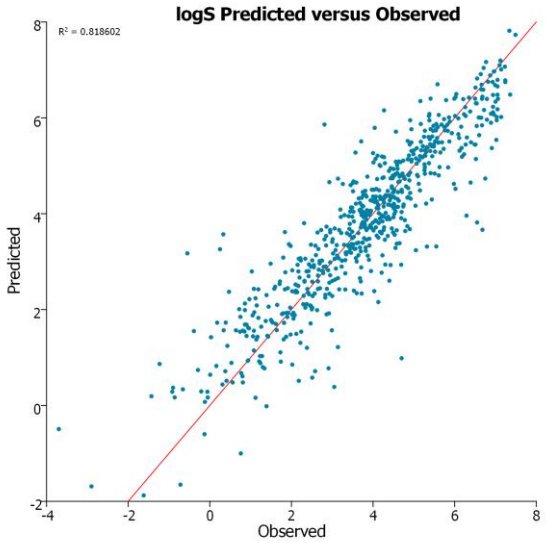
10,000 compounds through 10 *in silico* models is 100,000 data points!

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

Challenge 2: Uncertainty in Data

- 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
    - 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

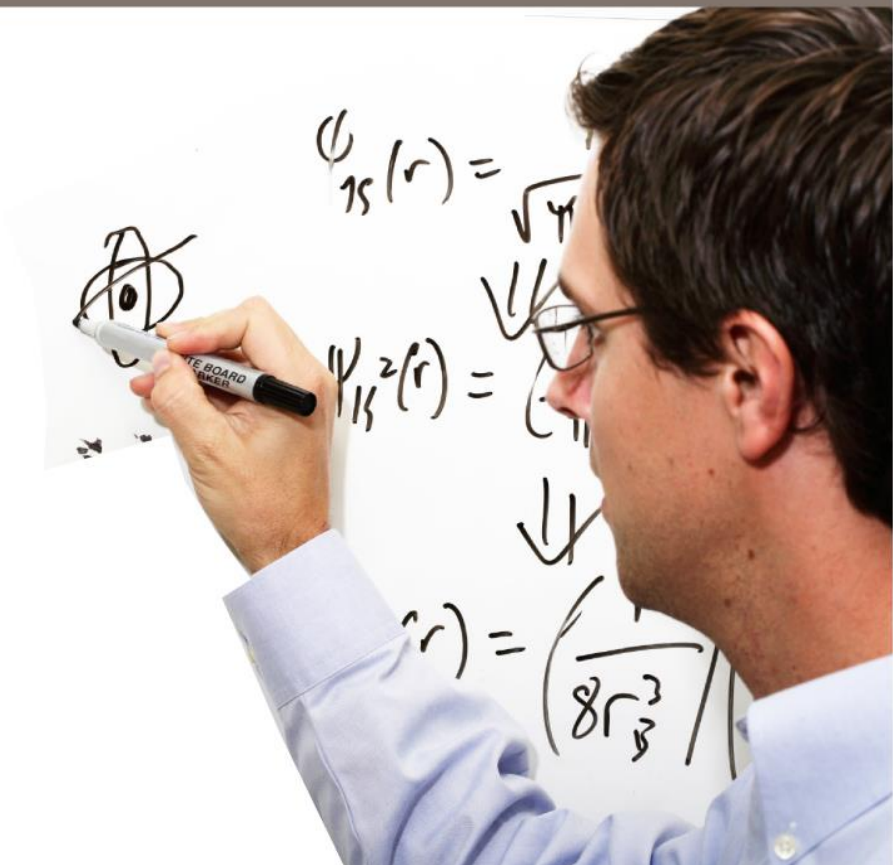
Cognitive Biases
The human factor

- Psychological research shows that people are poor at making complex decisions
  - Particularly involving risk/uncertainty
- System 1 vs. System 2
  - Gut instinct versus rational consideration
- Many examples, but we will focus on 5 common biases*
  - Confirmation bias
  - Poor calibration
  - Availability bias
  - Representativeness
  - Excess focus on certainty
- Contrast drug discovery with Evidence Based Medicine

*Tversky &Kahneman (1974) Science 185 pp. 1124-1131

Confirmation Bias

optibrium



Confirmation Bias

- People tend to look for evidence to support their hypotheses rather than refute them
- Psychological experiment by Peter Cathcart Wason in 1960*
  - The sequence 2, 4, 6 obeys a rule… what is it?
  - To test your hypothesis, you can specify other sequences of three numbers and ask if they obey the unknown rule.
  - When you're confident, you can announce what you think it is.
  - The answer? **Any ascending sequence!**
- Self justification, overconfidence and premature closure

* Wason, P.C. (1960) Quart. J. of Expt. Psychology **12** pp. 129-140

Confirmation Bias
Implications

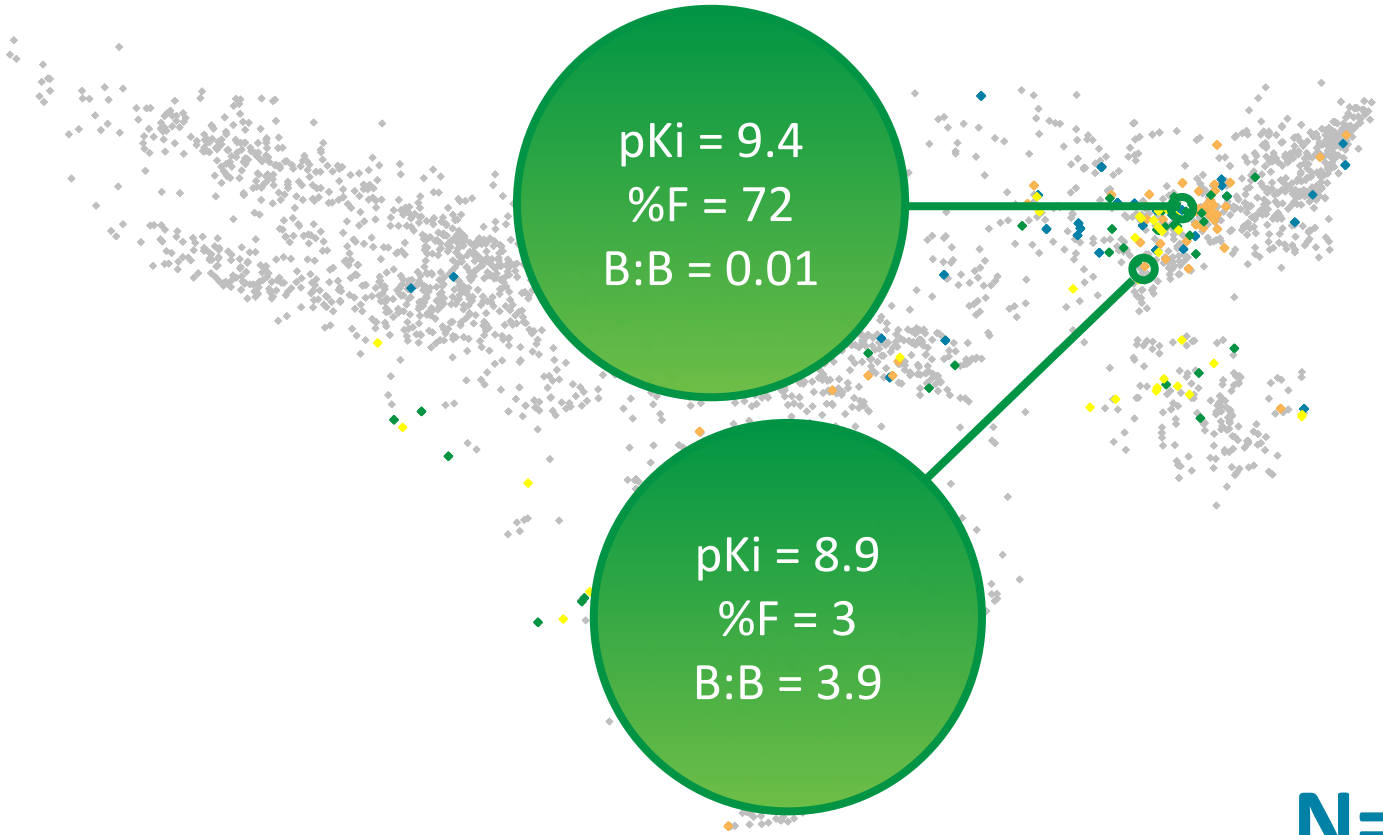
- In medicine: Study of diagnostic error* (90 injuries, including 33 deaths)
  - Cognitive factors contributed to diagnostic error in 74% of cases:
  - “Premature closure, i.e. the failure to continue considering reasonable alternatives after an initial diagnosis was reached, was the single most common cause.”
- In drug discovery:
  - Projects failed too late
  - Insufficiently wide search.

*Graber, M.L. et al (2005) Arch. Intern. Med. 165, 1493-1499

Confirmation Bias

Example from a drug discovery project

Project chemical space of >3100 compounds.
First 200 progressed, shown in chronological order



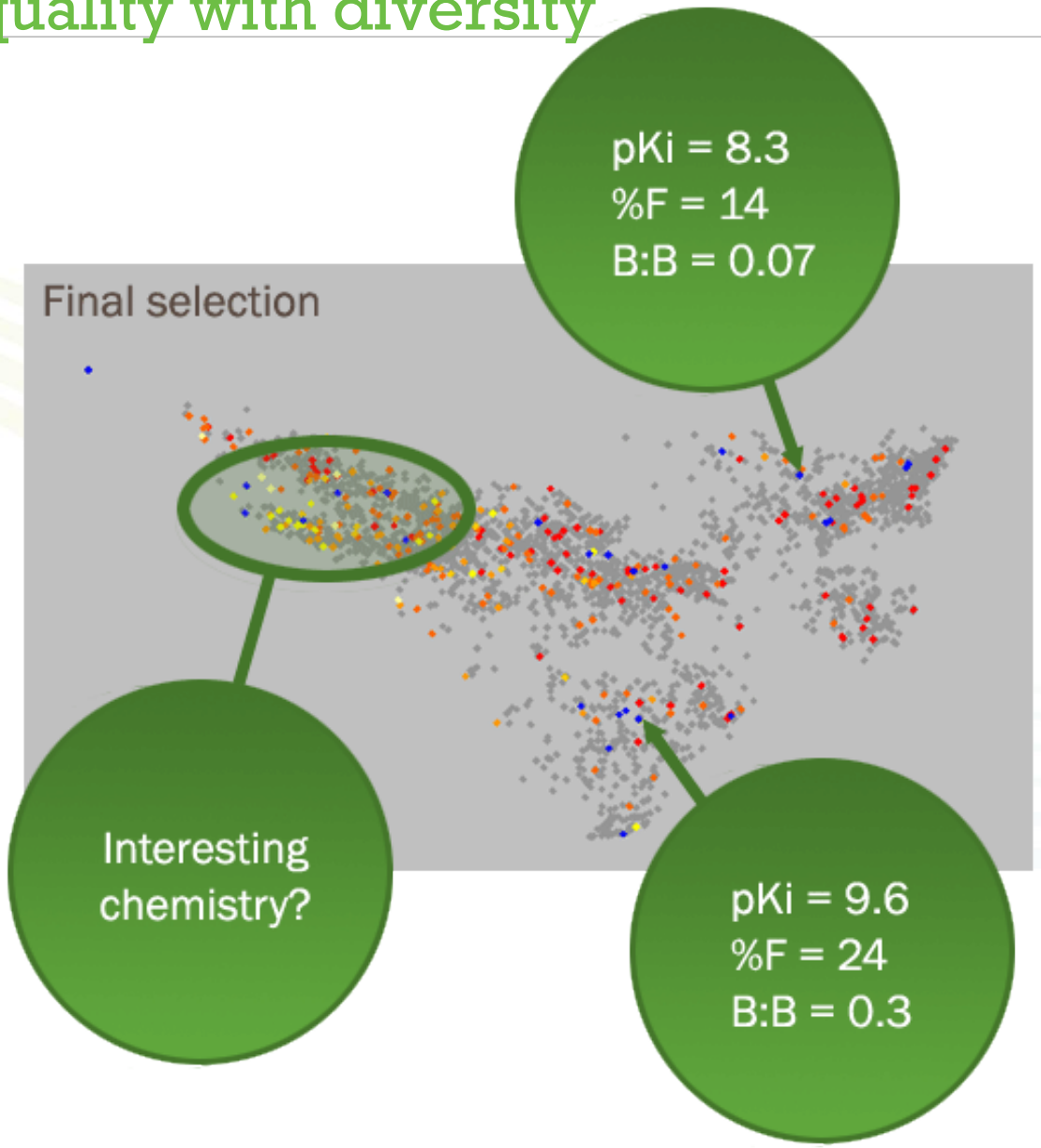
N=200

Confirmation Bias
Possible Solutions

- EBM: Map of Medicine
  - Visualisation of evidence-based pathway for common conditions
  - See http://www.mapofmedicine.com
- Drug discovery
  - Libraries of evidence-based screening plans with interactive support for modification for different projects and therapeutic areas
  - Balance ‘quality’ with diversity when selecting compounds

Avoiding Confirmation Bias

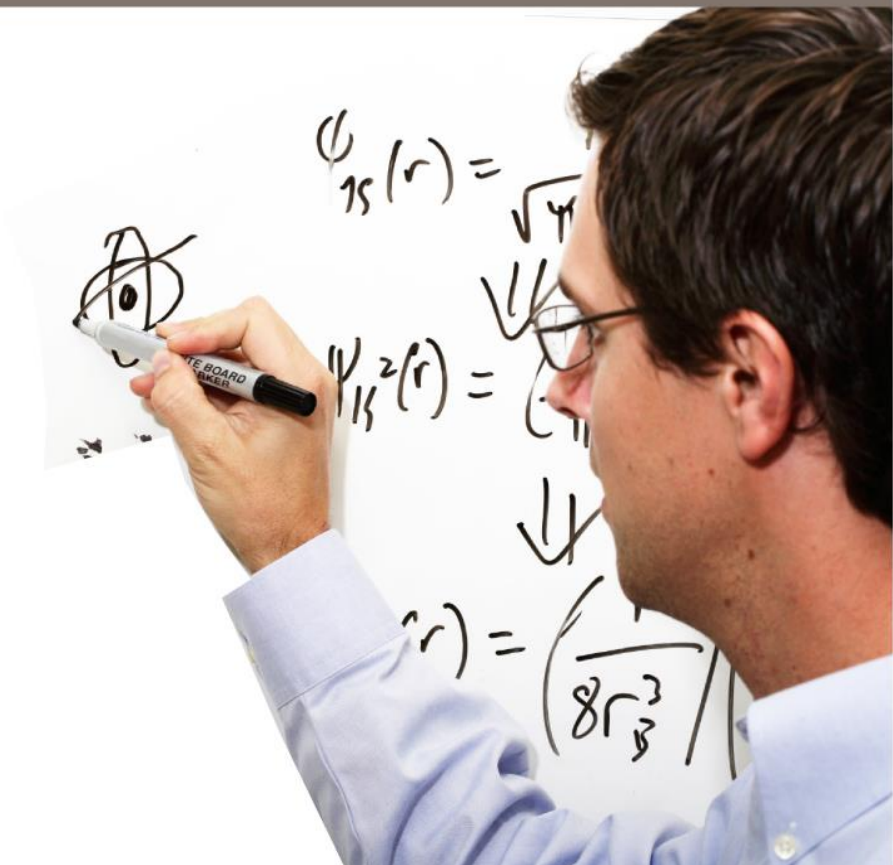
Balance quality with diversity



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

Calibration Bias

optibrium



Poor Calibration of Error/Risk

- People tend to be over-confident about their ability to estimate/predict
  - Asked a group of experienced scientists to estimate the length of the Thames in kilometres.
  - Answer could be any range in which they were 90% confident the correct answer lay.
  - If perfect calibration, expect 90% of ranges would include correct range
  - **Only 20% of answers contained the correct value in the range!**
- In medicine
  - Poor balance of risks of inaction and action (e.g. use of biopsies)
- In drug discovery
  - Underestimate risk – late stage failures
  - Inappropriate weight given to early screening results – excess attrition and loss of opportunity

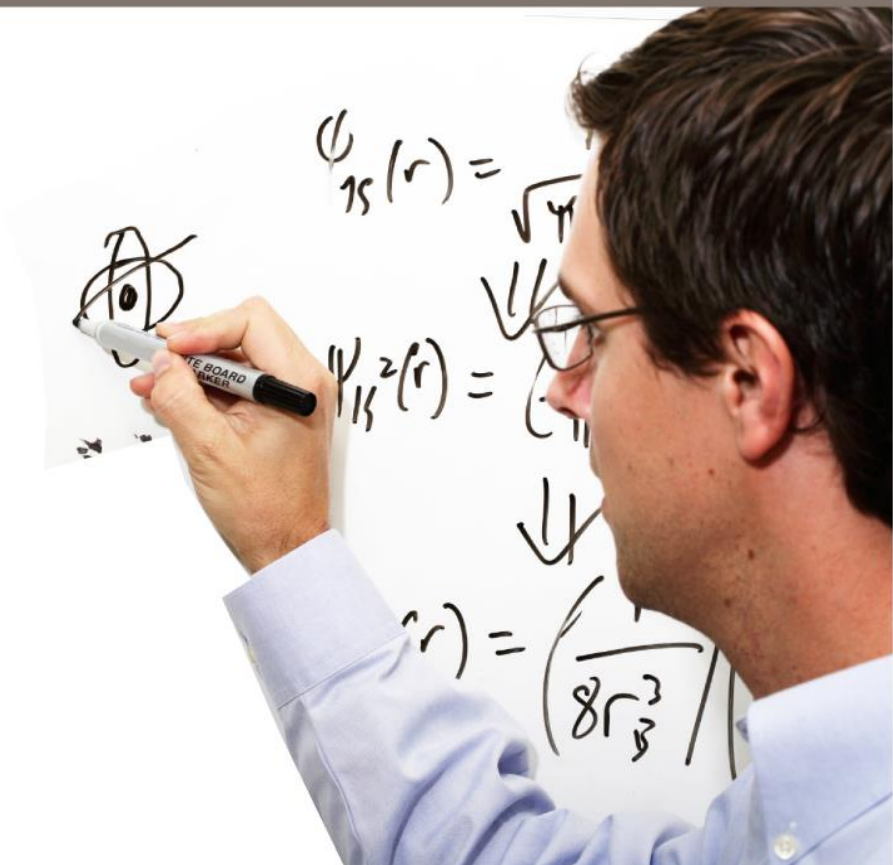
Poor Calibration
Possible Solutions

- EBM
  - For breast cancer radiographic screening in the UK there is a 'round robin' exchange of blinded test cases*
  - “Tracking and reporting critical outcome measures, such as sensitivity, specificity, size and stage of tumours detected, interval cancer rates, and time to recall and diagnosis, have been used in many countries to improve screening performance”
- Drug discovery
  - Training, e.g. anonymised cases for practice and feedback - to take the 'ego' out of decision making

*Esserman, L. et al (2002) JNCI 94(5), 369-375

Availability Bias

optibrium



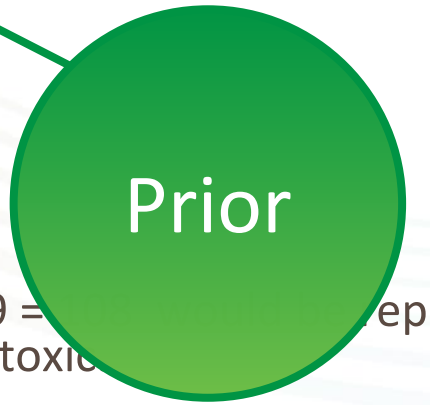
Availability Bias

- People have a tendency to focus on the vivid or recent
  - It has been estimated that following 9/11, over 1,500 additional people were killed in road accidents, due to increased road use as people avoided flying
- In medicine
  - New clinicians have a tendency to consider rare and exotic diseases over more mundane explanations for symptoms – the ‘House’ effect
- In drug discovery
  - Too much emphasis given to faint signs of issues, e.g. toxicity
  - Excess attrition and loss of diversity – opportunity cost

Availability bias

How well does this assay conserve your options?

- You have purchased a series of compounds:
  - You expect 1% of your compounds have a particular kind of toxicity
  - You apply a screening method to all the compounds that is 90% reliable (both 90% sensitive and 90% specific)
  - What percentage of the compounds that fail the screening genuinely have the toxicity?
    a) About 1%
    b) About 2%
    c) About 10%
    d) About 50%
    e) About 90%



- Answer?
  - **c)** Of 1000 compounds, 990 x 0.1 + 10 x 0.9 = [illegible] eported as toxic by the test, of which only 9 really are toxic

- Neglect of the prior
  - What are appropriate priors?
  - Calibration bias: not necessarily good at estimating priors

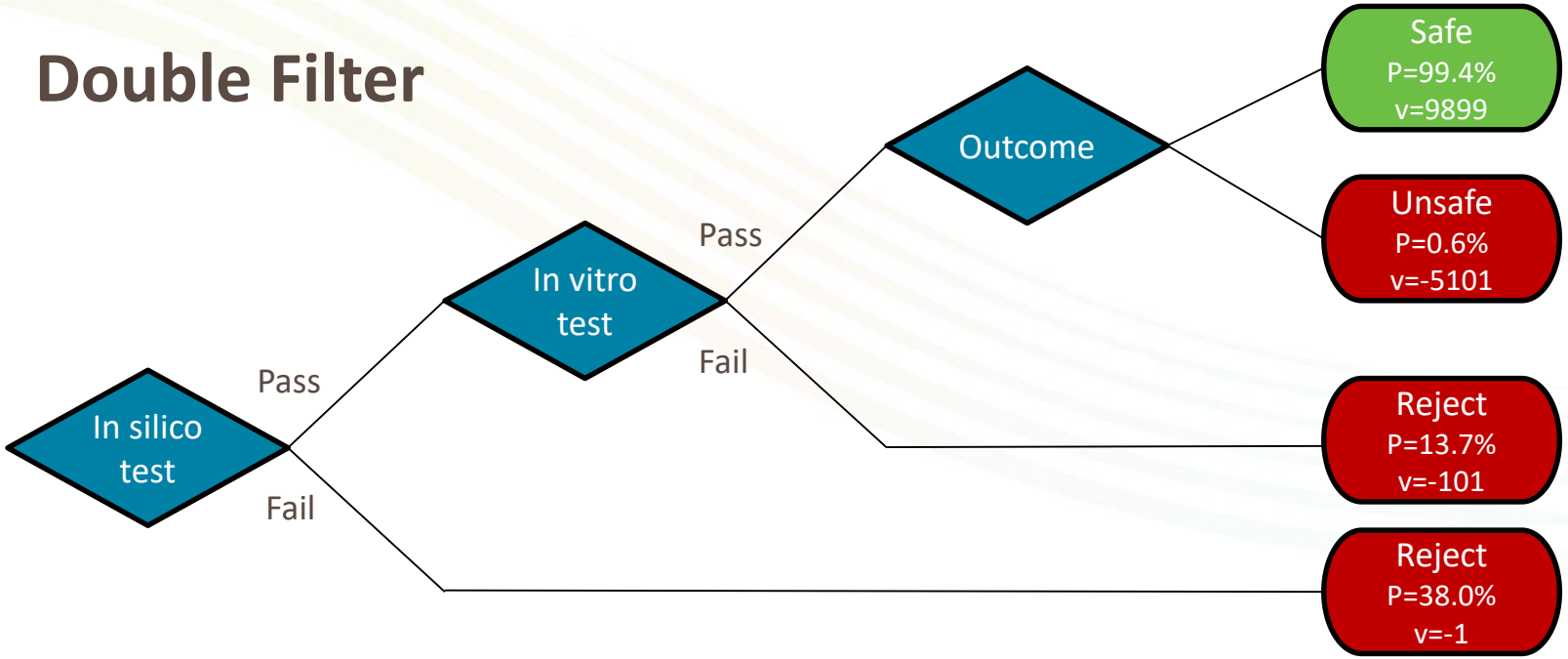
Example Application
Screening Strategy

- Two screens for toxicity: *in silico* and *in vitro*
  - *In silico*: cost 1, accuracy 80%
  - *In vitro*: cost 100, accuracy 95%
  - Cost to prove safety 5,000
  - Net value of safe compound 10,000
- 5 Possible screening strategies

Example Application
Screening Strategy

- Two screens for toxicity: *in silico* and *in vitro*
- 5 Possible screening strategies:

Double Filter

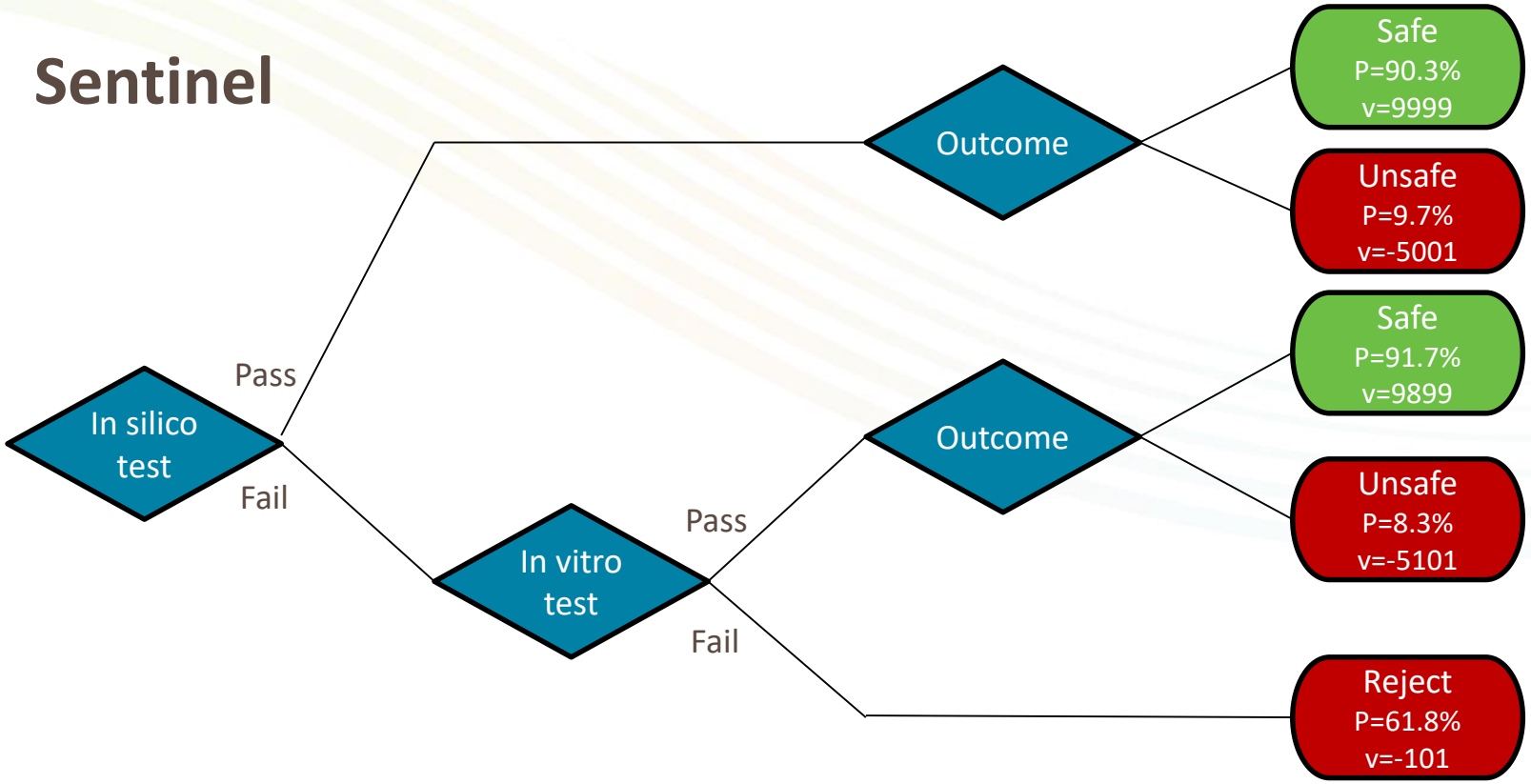


Segall and Chadwick J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

- Two screens for toxicity: *in silico* and *in vitro*
- 5 Possible screening strategies:

Sentinel

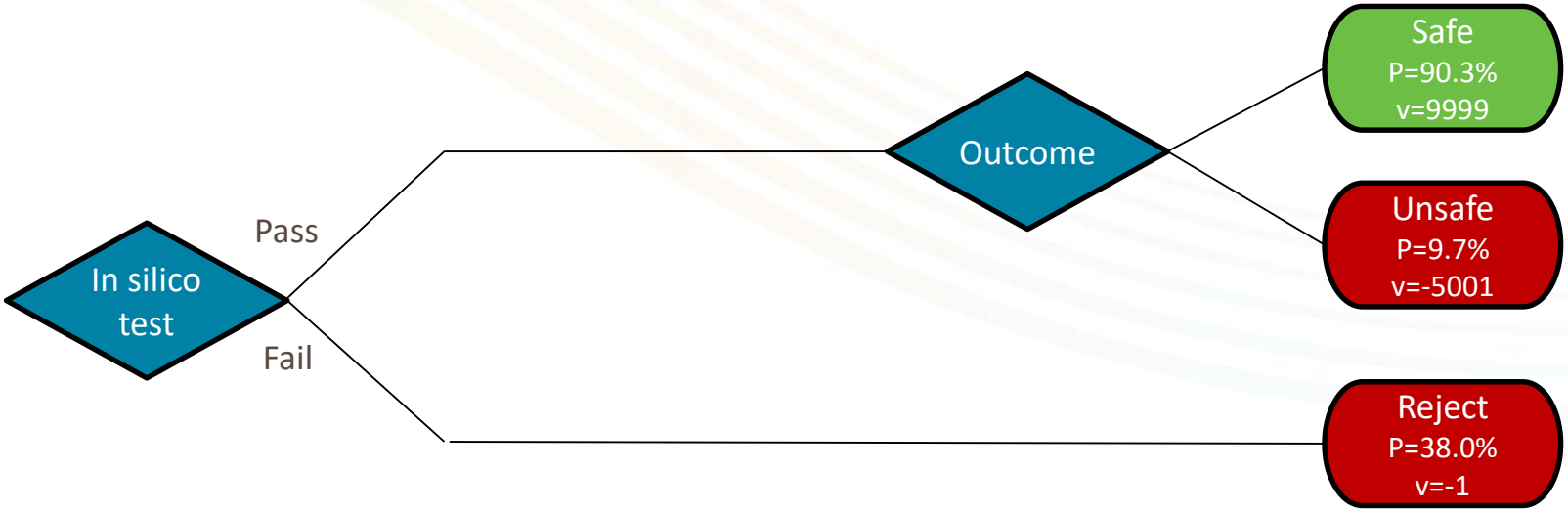


Segall and Chadwick J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

- Two screens for toxicity: *in silico* and *in vitro*
- 5 Possible screening strategies:

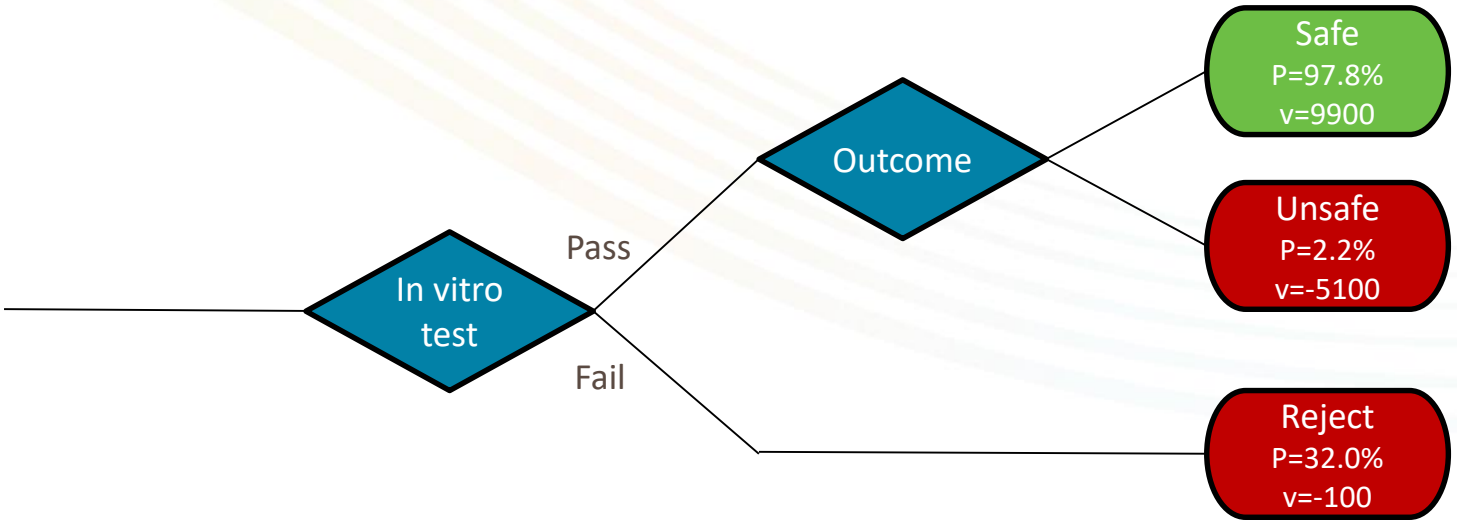
In Silico Only



Example Application
Screening Strategy

- Two screens for toxicity: *in silico* and *in vitro*
- 5 Possible screening strategies:

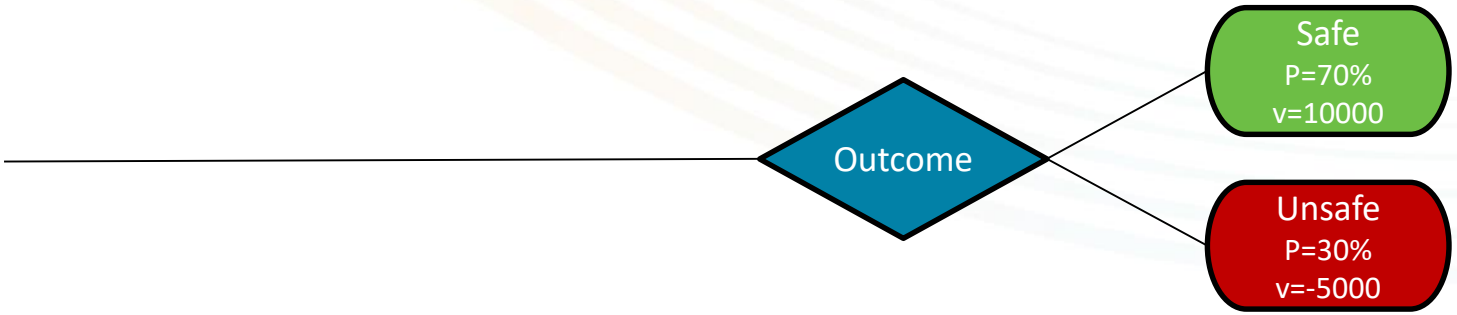
***In Vitro* Only**



Example Application
Screening Strategy

- Two screens for toxicity: *in silico* and *in vitro*
- 5 Possible screening strategies:

No Screen



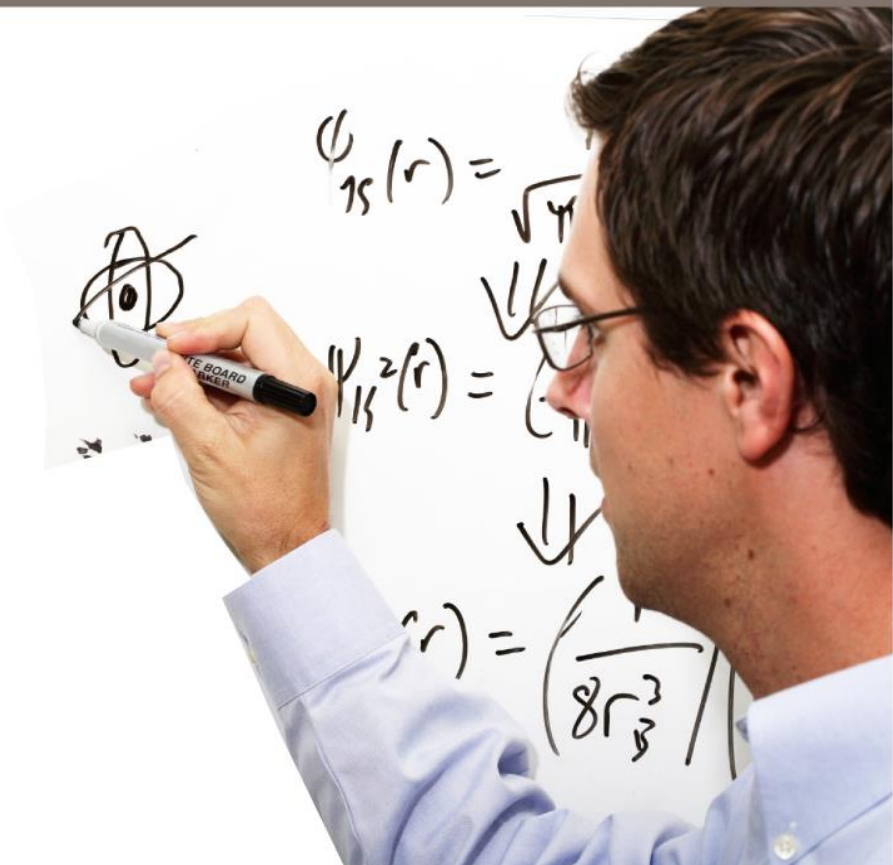
Example Application
Screening Strategy

- Parameters:
  - *In silico*: cost 1, accuracy 80%
  - *In vitro*: cost 100, accuracy 95%
  - Cost to confirm safety 5,000; Net value of safe compound 10,000

Strategy	Value (Prior for risk 30%)	Value (Prior for risk 40%)
Double filter	5242	4483
Sentinel	6531	5415
In silico only	5299	4399
In vitro only	6475	5500
No screen	5500	4000

Representativeness

optibrium



Representativeness

- Which of the following is the most probable description of an oral drug?*
  A. IC_{50} > 10,000 nM
  B. IC_{50} < 1 nM and clogP > 4
  C. IC_{50} = 0.1–1 nM, MW = 450–550, and clogP = 4–6
- **Answer: B** – by definition, B must be at least as probable than C
  - Conjunction fallacy
- People use similarity as a surrogate for prediction
  - Comparison with a stereotype or personal experience
  - Assume that similarity in some aspect(s) implies similarity in others
- Overestimate the accuracy of such a prediction
  - Ignore information on priors

* Shultz ACS Med. Chem Lett. (2014) **5** pp. 2-5

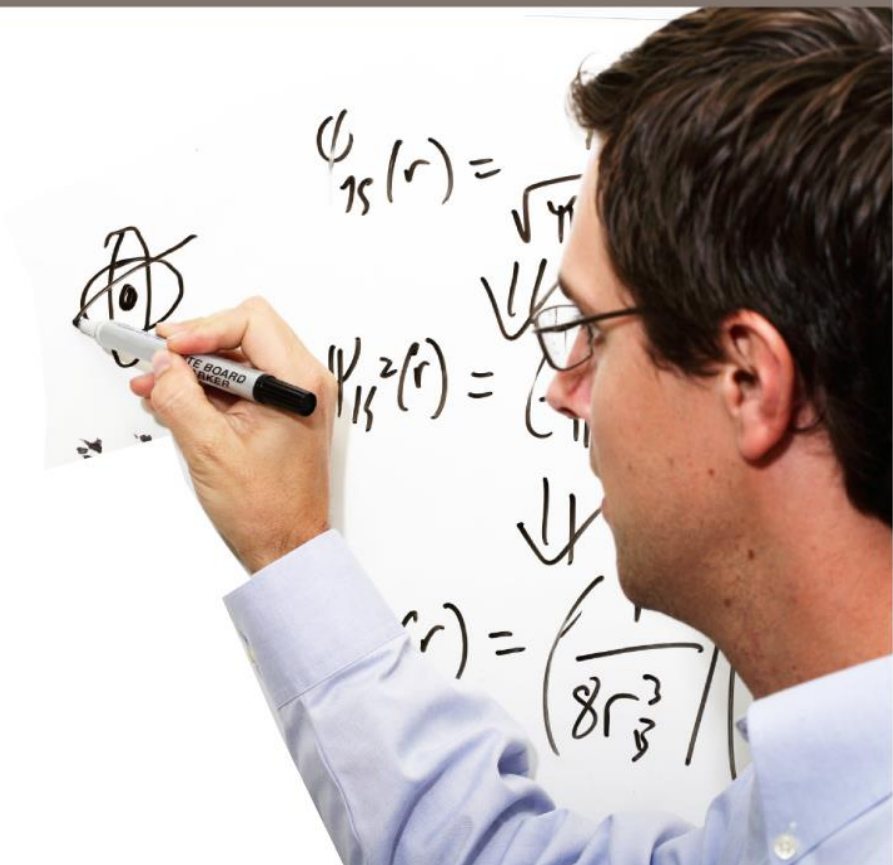
Representativeness
Implications

- In medicine:
  - "Clinicians seem to make diagnoses by comparing patients to typical patients"*
- A drug discovery anecdote…
  - Pharma company considering a partnership for development of a candidate compound for a neglected disease
  - All of the *in vitro* and *in vivo* data meet acceptance criteria for development
  - No cost to the pharma company – external body will fund the project
  - **Outcome:** Project rejected because a senior manager had worked on compounds that "looked like" the candidate and had failed due to toxicity issues

*Garb (1996) Prof. Psyc. Res. & Pract. 27 pp. 272-277

Excess Focus on Certainty

optibrium



Excess Focus on Certainty

- People tend to seek more and more ‘certainty’ even when it adds little value at high cost
- Headlines such as “XXX increases the risk by 50%!”
  - What was the initial risk?
- Human decision-makers are inconsistent in applying the rules they describe if questioned on the basis for their decisions*:
  - “the overwhelming conclusion, including studies of clinical judgment, was that the linear model of the judge’s behaviour outperformed the judge.”

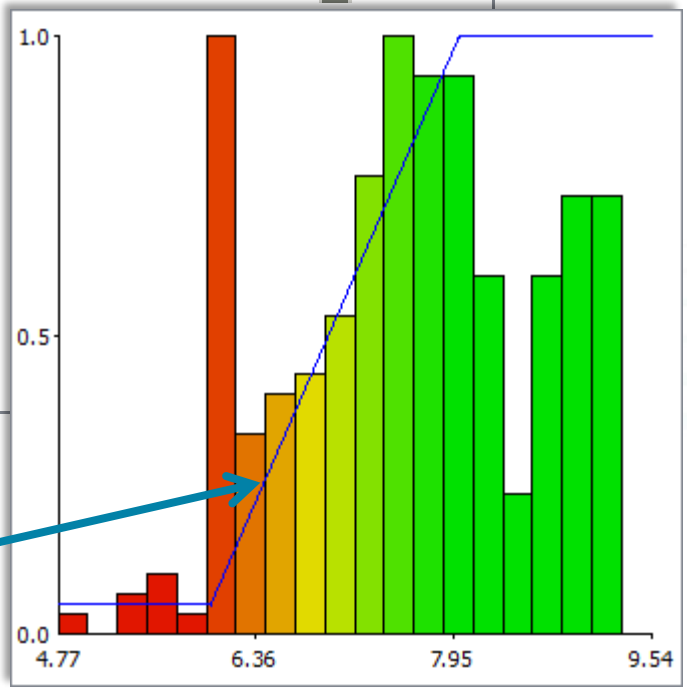
 *Goodwin and Wright Decision Analysis for Management Judgment (3rd ed.), Wiley p. 449-451 (2004)

Excess Focus on Certainty
Implications

- In medicine
  - Clinical guidelines difficult to agree and use
  - Problems reassuring patients.
- In drug discovery
  - Inefficient use of resources when screening across multiple risk factors

Possible Solution
Probabilistic Scoring

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

Possible Solution
Probabilistic Scoring

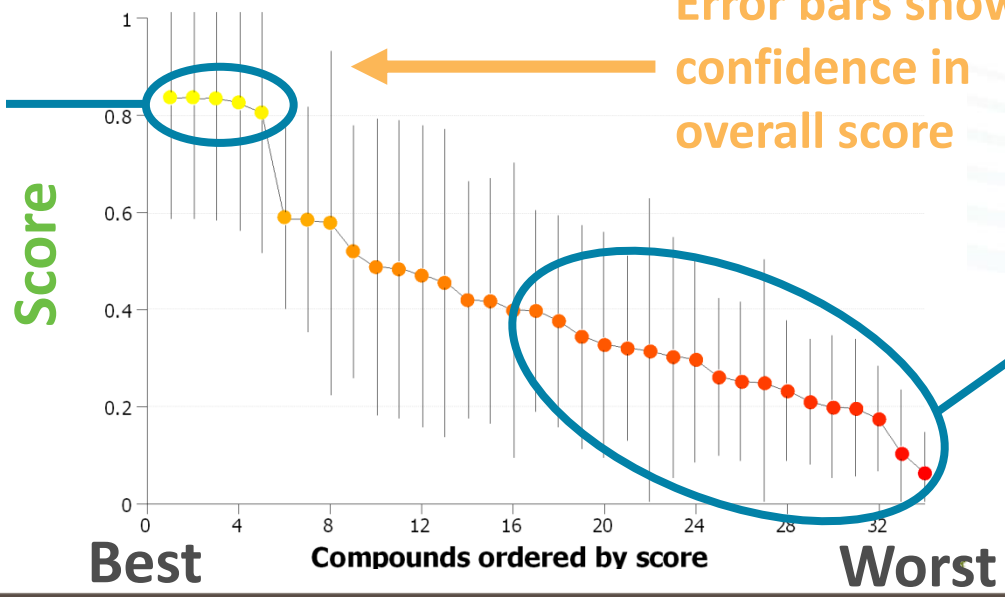
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

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

Data do not separate these as error bars overlap

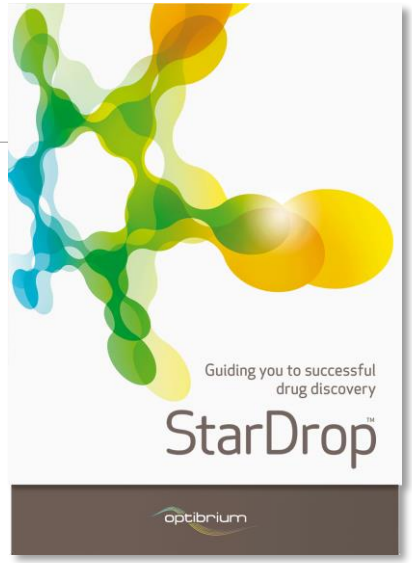
Error bars show confidence in overall score

Bottom 50% may be rejected with confidence



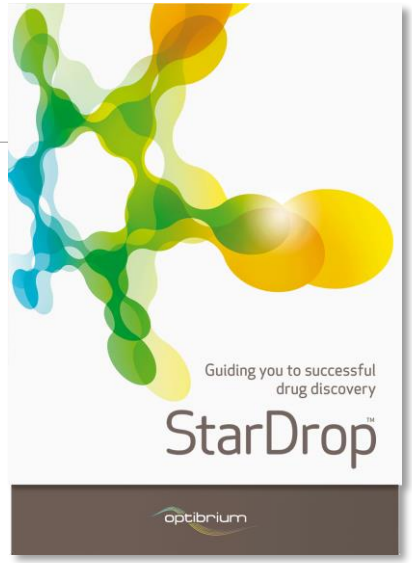
M.D. Segall (2012) Curr. Pharm. Des. **18**(9) pp. 1292-1310

Conclusions



- Drug discovery scientists are human!
- Cognitive biases can be a barrier to good decisions and hence impact drug discovery productivity
- Can be addressed through a combination of training and tools to apply decision-analysis approaches to guide decisions
- A critical issue – priors
  - What are appropriate priors for common drug discovery risks?
  - Need to pool information on priors and method reliability
- Chadwick and Segall, Drug Discov. Today., **15**, 561-569 (2010)
  - (p)reprint: http://bit.ly/2peVoYV

Acknowledgements



- Tessella
  - Andrew Chadwick
  - Rob Rowley
- Optibrium
  - Ed Champness
- Interesting reading
  - Daniel Kahneman (2011) Thinking Fast and Slow
  - Ben Goldacre (2008) Bad Science
  - Dan Gardner (2009) Risk – the science and politics of fear
  - Michael Lewis (2017) The Undoing Project

THURSDAY 18 MAY. 2017, CAMBRIDGE UK

Symposium on Streamlining Drug Discovery

A FREE-TO-ATTEND ONE DAY EVENT

Learn more about:

- Intuitive molecular design and 3D SAR interpretation
- Making the best use of data

When: Thursday, 18 May 2017
Where: University of Cambridge
Maxwell Centre
Cambridge, UK

Speakers include:

- Dr John Overington, Medicines Discovery Catapult
- Dr Matt Segall, Optibrium
- Dr Christel Menet, Confo Therapeutics
- Dr Stuart Frances, Beatson Institute
- Prof Robert Glenn, University of Cambridge
- Dr Martin Swarbrick, CRT
- Dr Lewis Mervin, University of Cambridge
- Dr Ismail Moarefi, CRELUX
- Dr Christian Lemmen, BioSolveIT

Register for free at: www.optibrium.com/events

Organised by:

optibrium

BioSolveIT

药明康德 WuXi AppTec

Lhasa Limited