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Overcoming psychological barriers to good decision-making in drug discovery

Keystone Symposium, Addressing the Challenges of Drug Discovery
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Overview

- Drug discovery productivity
  - The challenge of decision-making in drug discovery
  - The human factor – cognitive biases
  - Comparison with Evidence-Based Medicine (EBM)
- Common cognitive biases
  - Confirmation bias
  - Poor calibration
  - Availability bias
  - Excess focus on certainty
- Conclusion
  - Guiding decisions to overcome biases

Drug Discovery Productivity

- Facts and figures abound for the decrease in productivity of pharmaceutical R&D
- Some debate – is this because:
  - We've become less efficient at discovering NCEs, or
  - All the 'low-hanging' fruit have been discovered?
- In either case, improving productivity would be a good thing!

Challenges of Decision-Making in Drug Discovery

- Importance of multiple, sometimes conflicting, criteria to the success of a potential drug molecule
  - Different degrees of importance of properties
- Lots of data
  - Potentially large numbers of compounds
  - Multiple properties
- Uncertain information
  - Variability/error in data or predictions
  - *In silico* predictions, *in vitro* assays and *in vivo* models are only approximations of the ultimate human target
- Long time scales
  - Difficult to learn from mistakes (individual or organisation)

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 4 common biases*
  - Confirmation bias
  - Poor calibration
  - Availability bias
  - Excess focus on certainty
- Contrast drug discovery with Evidence Based Medicine

*Kahneman & Tversky, On the psychology of prediction. Psychological review, 1973, **80**, 237-257

Confirmation Bias

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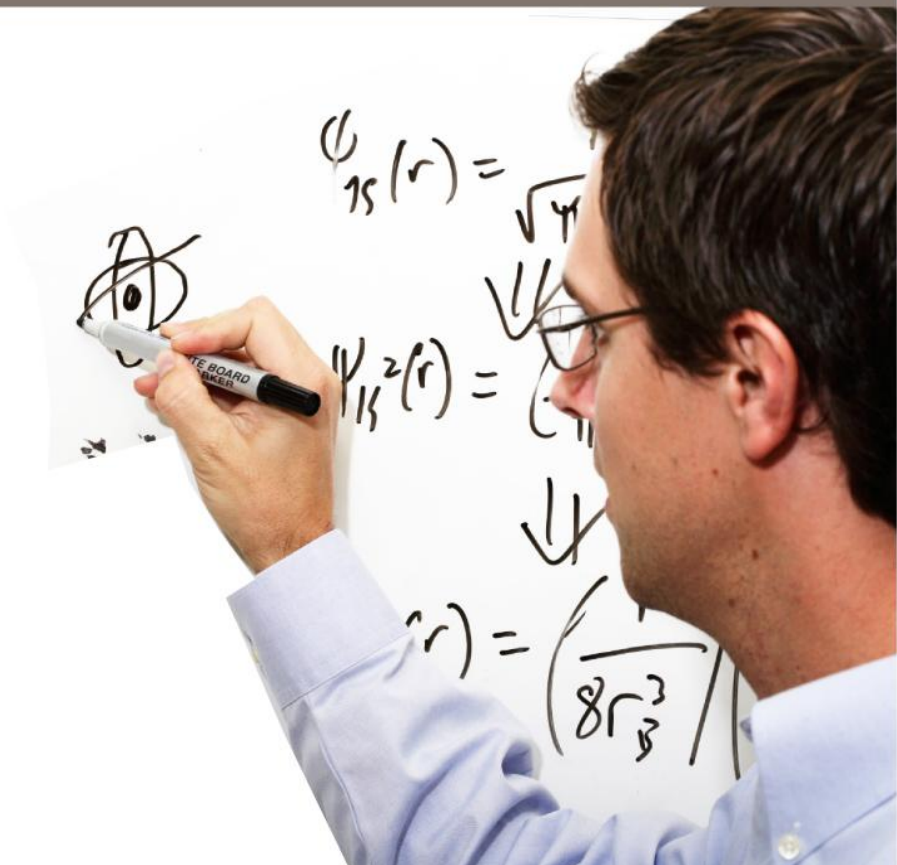

Confirmation Bias

- 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) Quarterly Journal of Experimental 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) Diagnostic Error in Internal Medicine. *Arch. Intern. Med*. 165, 1493-1499

Confirmation Bias

Example from a drug discovery project

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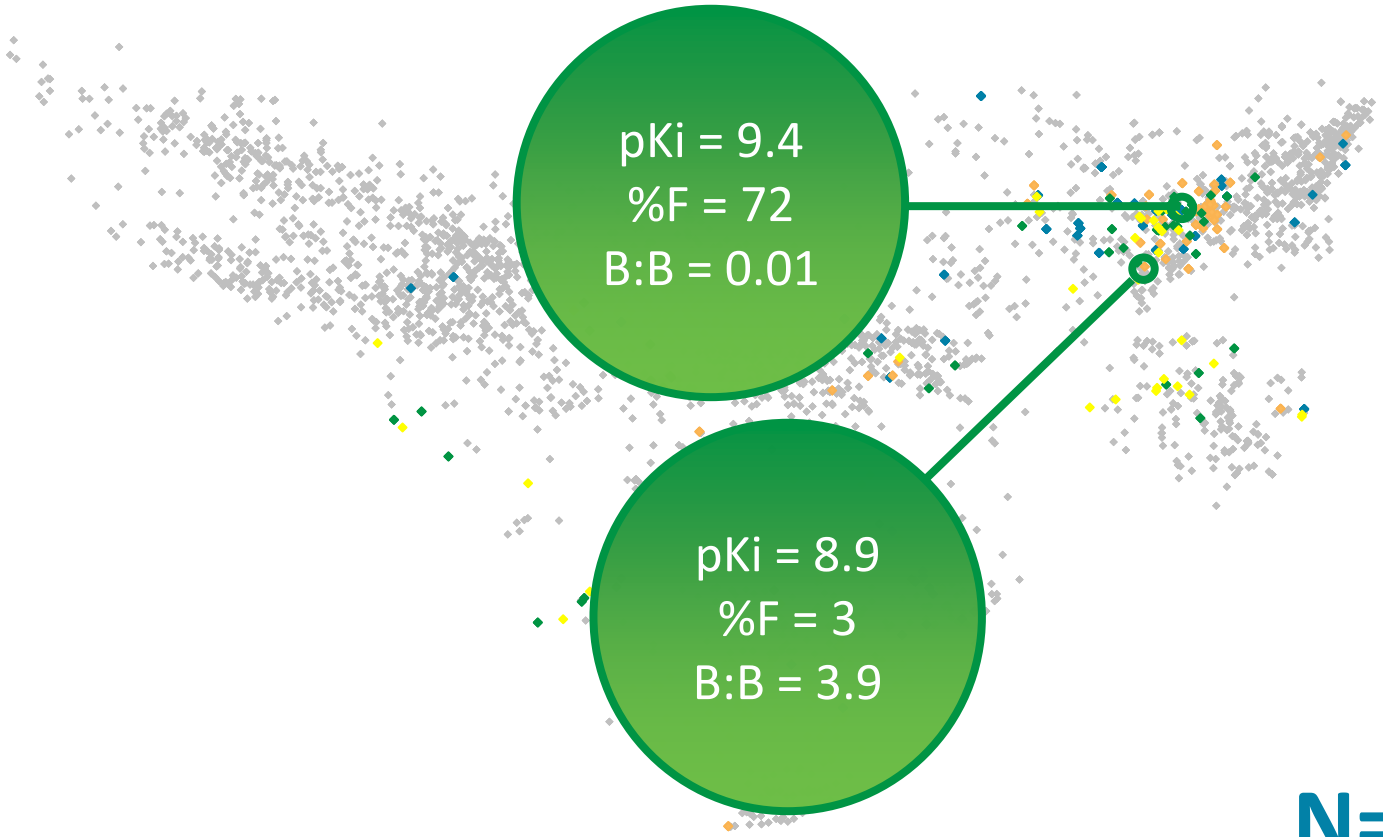
Project chemical space of >3100 compounds.
First 200 progressed, shown in chronological order



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
  - Balance ‘quality’ with diversity when selecting compounds
  - Libraries of evidence-based screening plans with interactive support for modification for different projects and therapeutic areas

Calibration Bias

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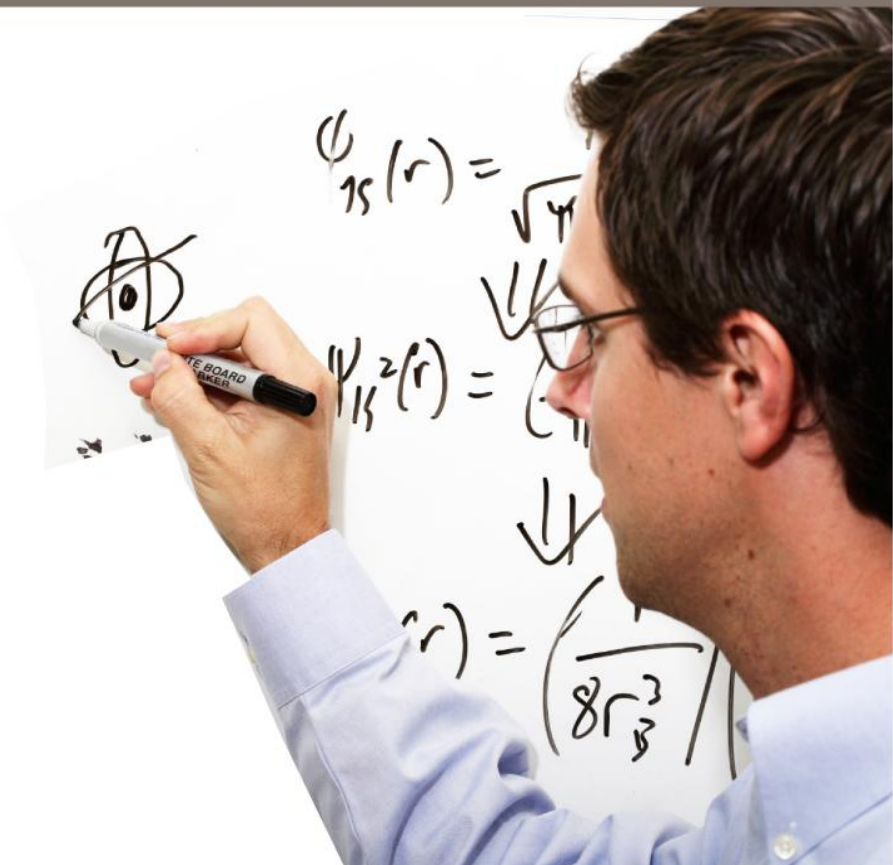

Poor Calibration of Error/Risk

- 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) Improving the Accuracy of Mammography: Volume and Outcome Relationships. *JNCI* 94(5), 369-375

Availability Bias

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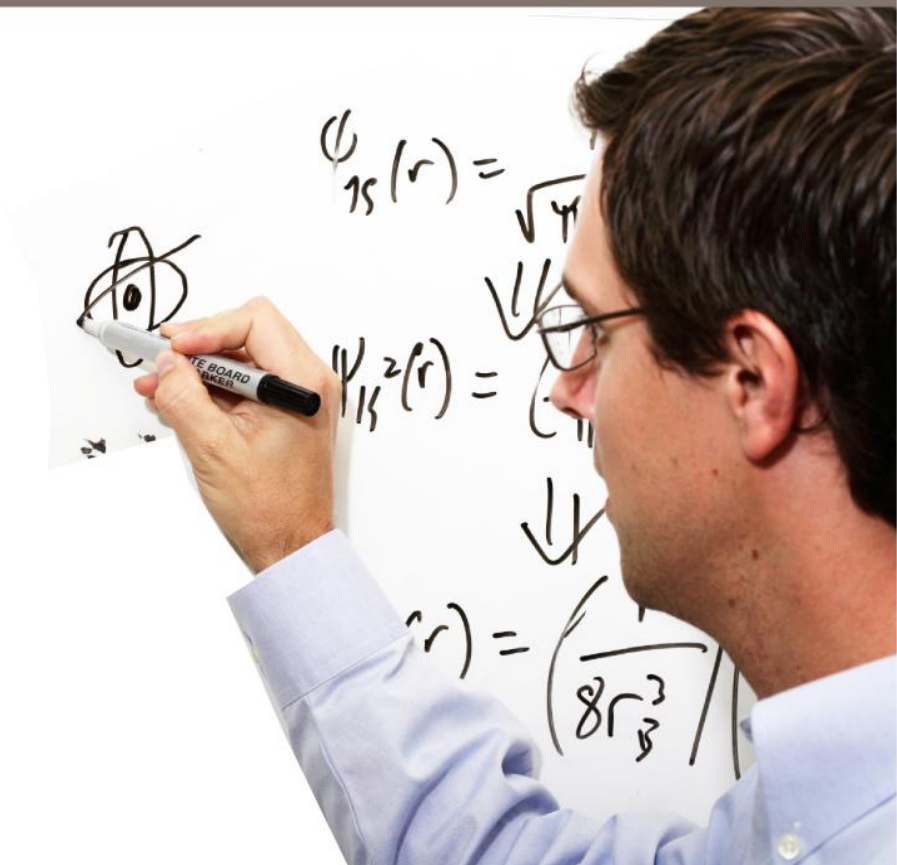


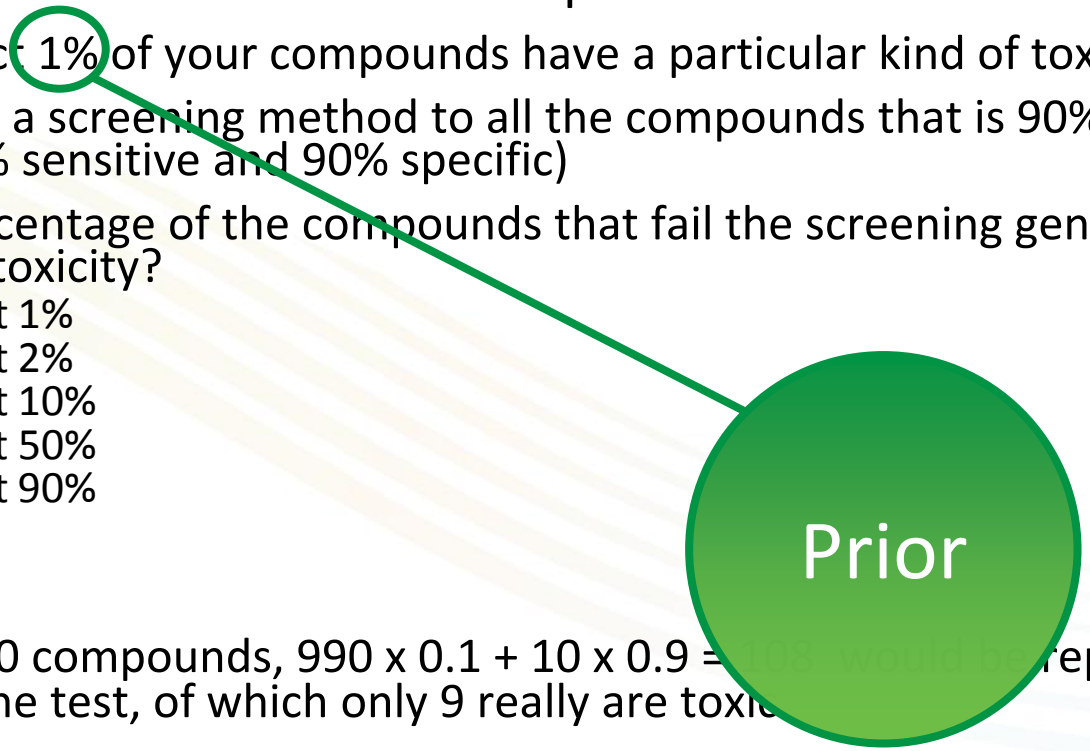
Availability Bias

- 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 = 108 would be reported 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*

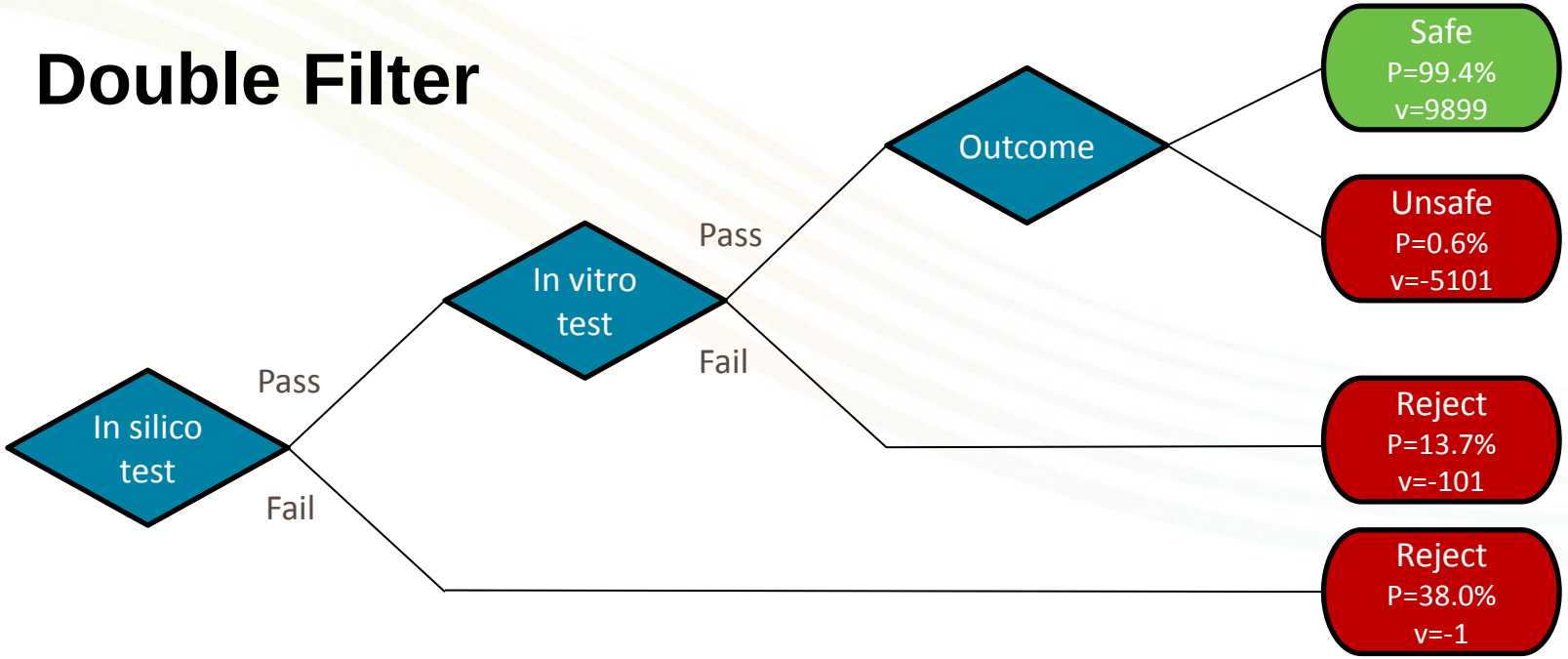
- Two screens for toxicity: *in silico* and *in vitro*
  - *In silico*: cost 1, accuracy 80%
  - *In vitro*: cost 100, accuracy 95%
  - Cost to prove safety 5,000
  - Net value of safe compound 10,000
- 5 Possible screening strategies

*Segall and Chadwick, Making Priors a Priority, 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:

Double Filter

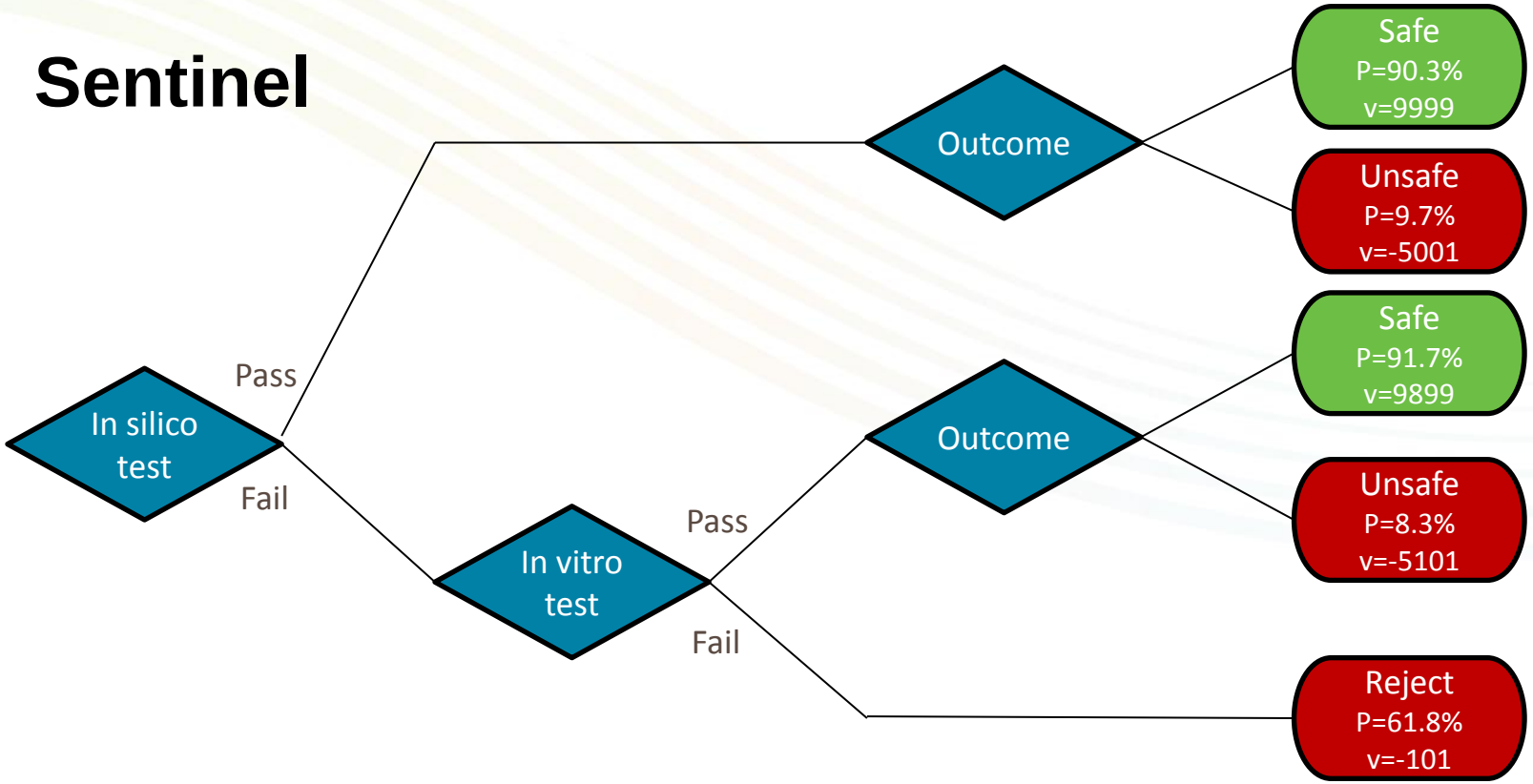


*Segall and Chadwick, Making Priors a Priority, J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

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

Sentinel

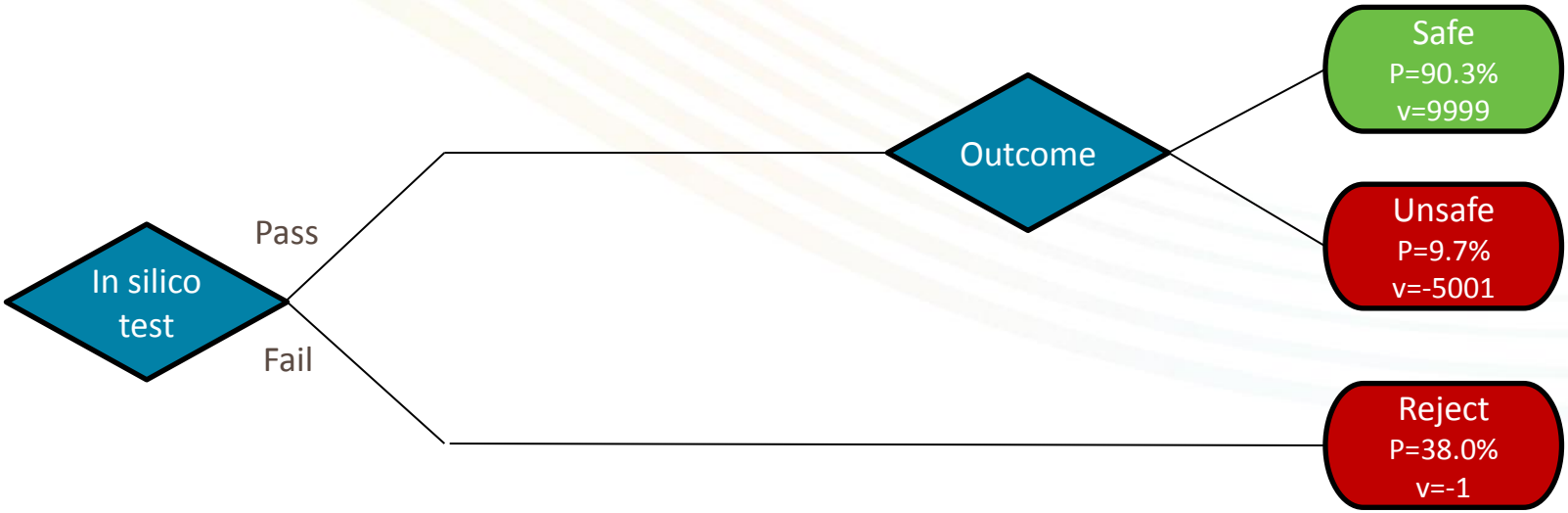


*Segall and Chadwick, Making Priors a Priority, J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

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

***In Silico* Only**

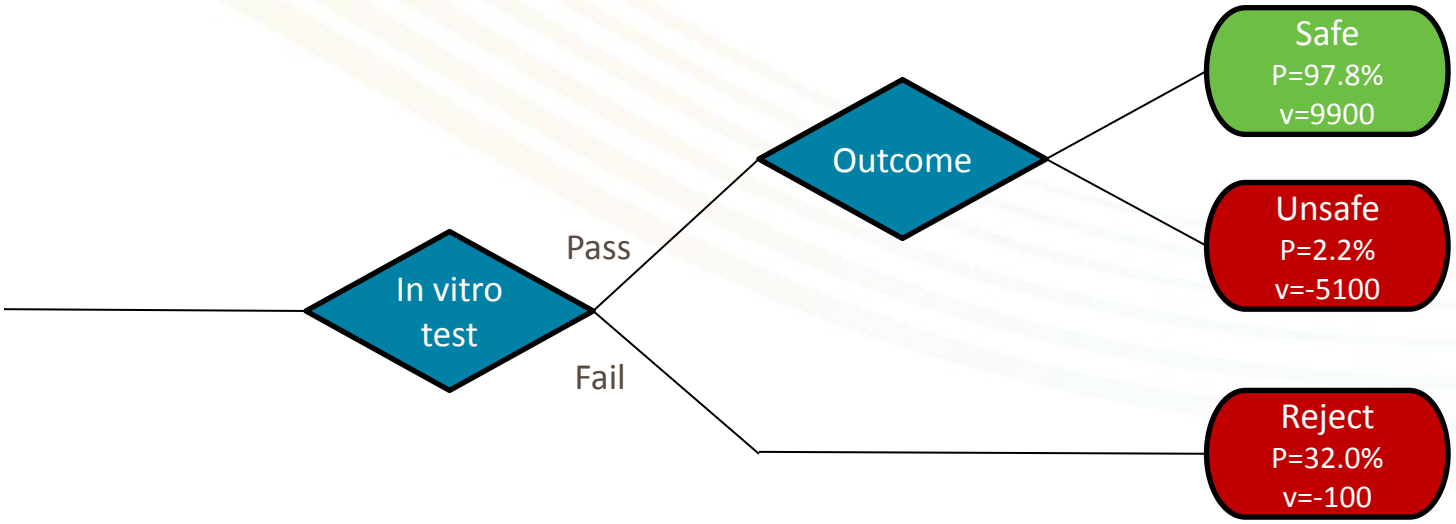


*Segall and Chadwick, Making Priors a Priority, J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

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

In Vitro Only

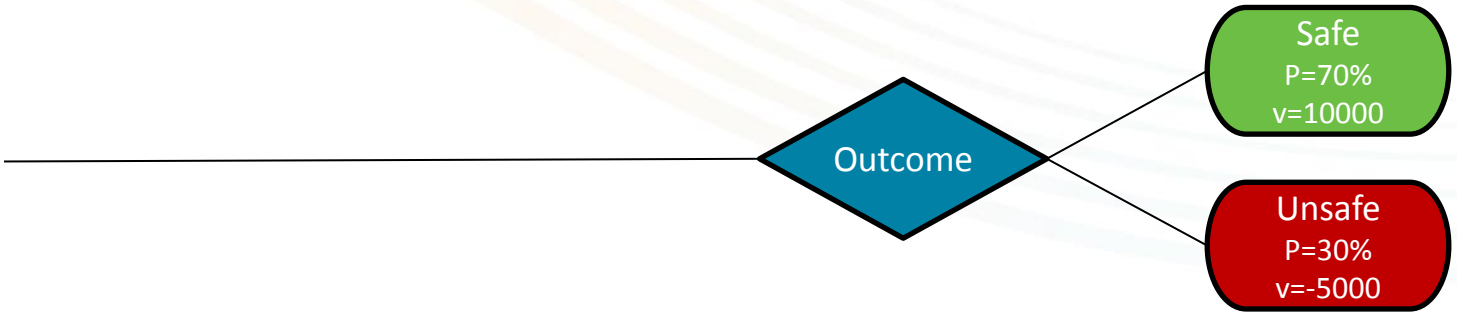


*Segall and Chadwick, Making Priors a Priority, J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

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

No Screen



*Segall and Chadwick, Making Priors a Priority, J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Example Application
Screening Strategy

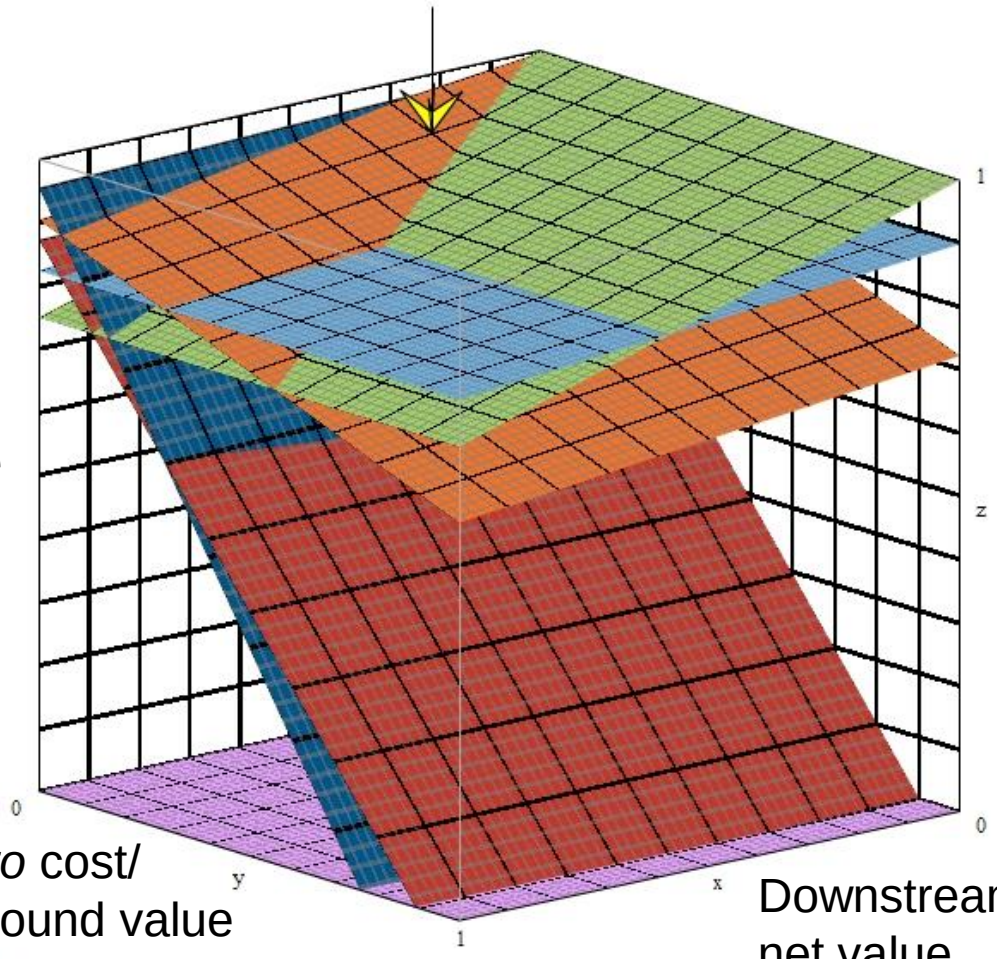
- Parameters:
  - *In silico*: cost 1, accuracy 80%
  - *In vitro*: cost 100, accuracy 95%
  - Cost to confirm safety 5,000; Net value of safe compound 10,000

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

*Segall and Chadwick, Making Priors a Priority, J. Comp.-Aided Mol. Des., 24, 957-960, (2010)

Possible Solutions
Quantitative Analysis of Screening Options

Strategy value



In vitro cost/
compound value

Downstream cost/
net value

For an interactive example visit http://www.tessella.com/screening-strategy-explorer

Excess Focus on Certainty

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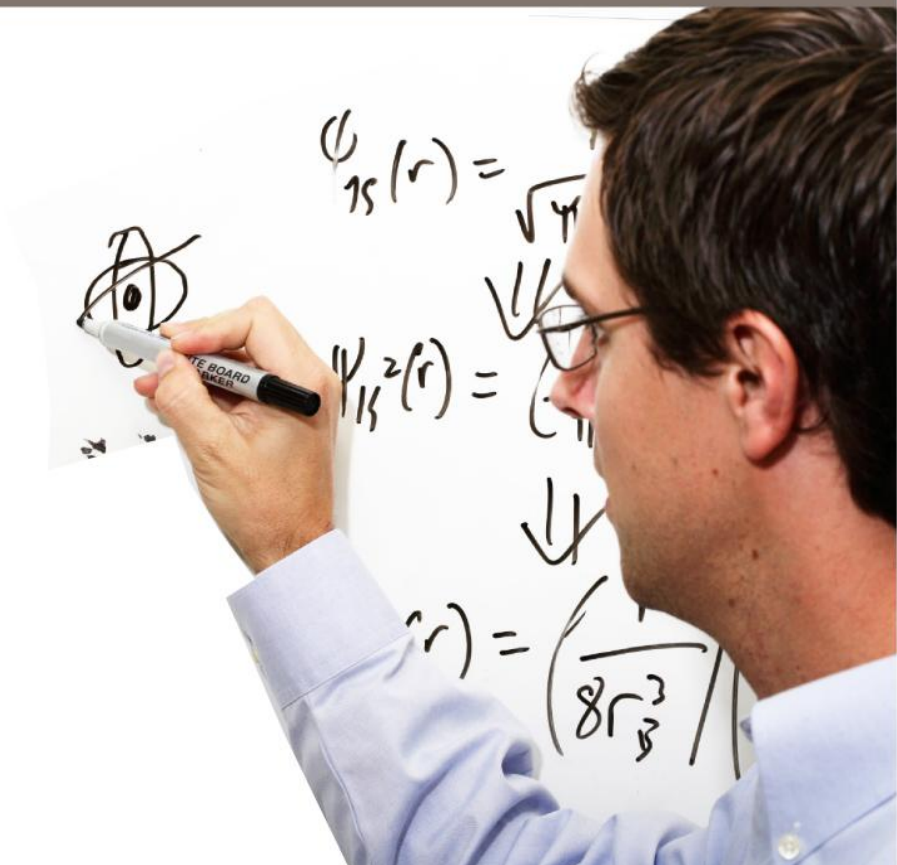


Excess Focus on Certainty

- 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)

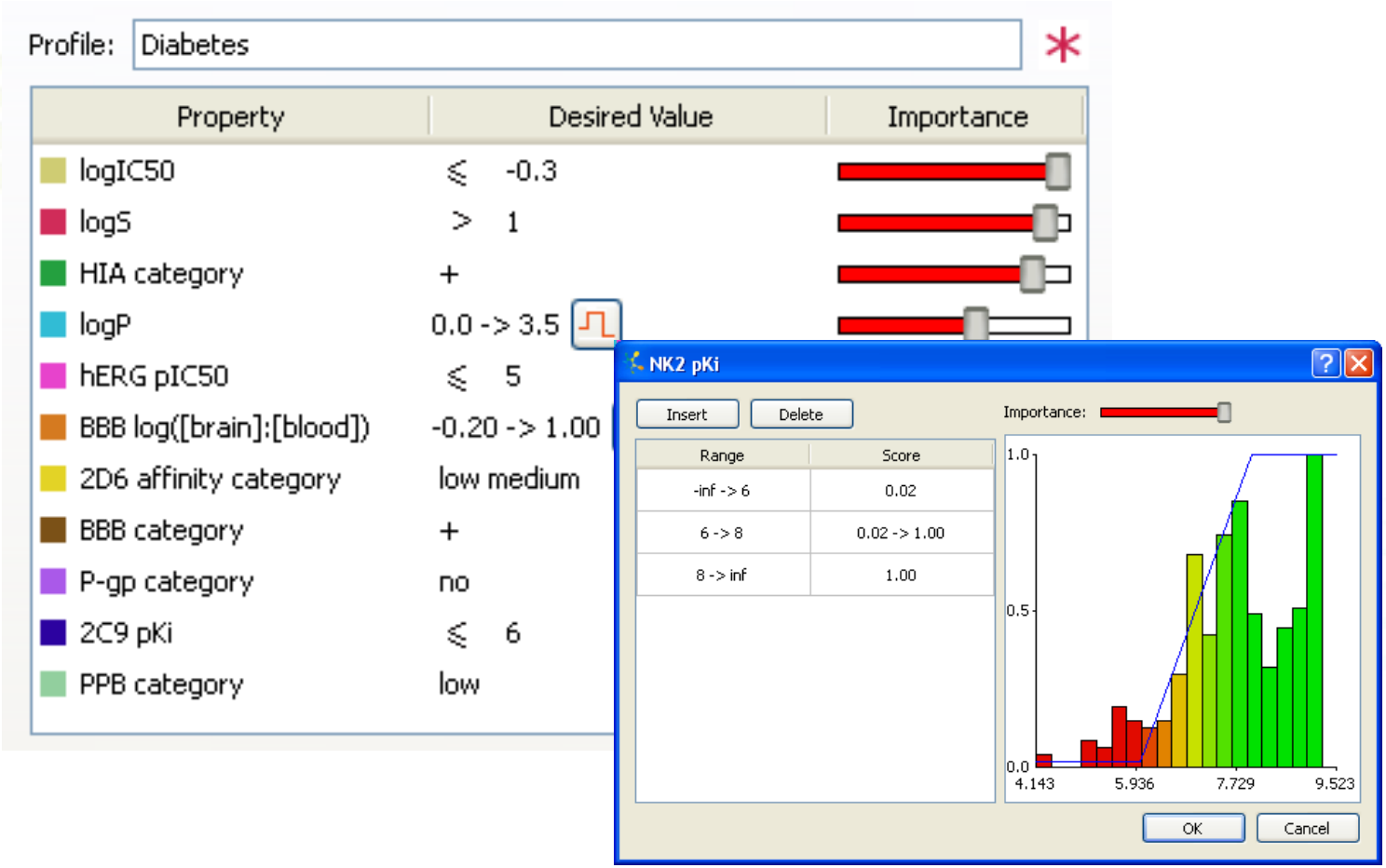
Excess Focus on Certainty
Implications

- 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
Multi-parameter optimisation*

StarDrop 5
Software that guides you to successful drug discovery

- E.g. Probabilistic scoring



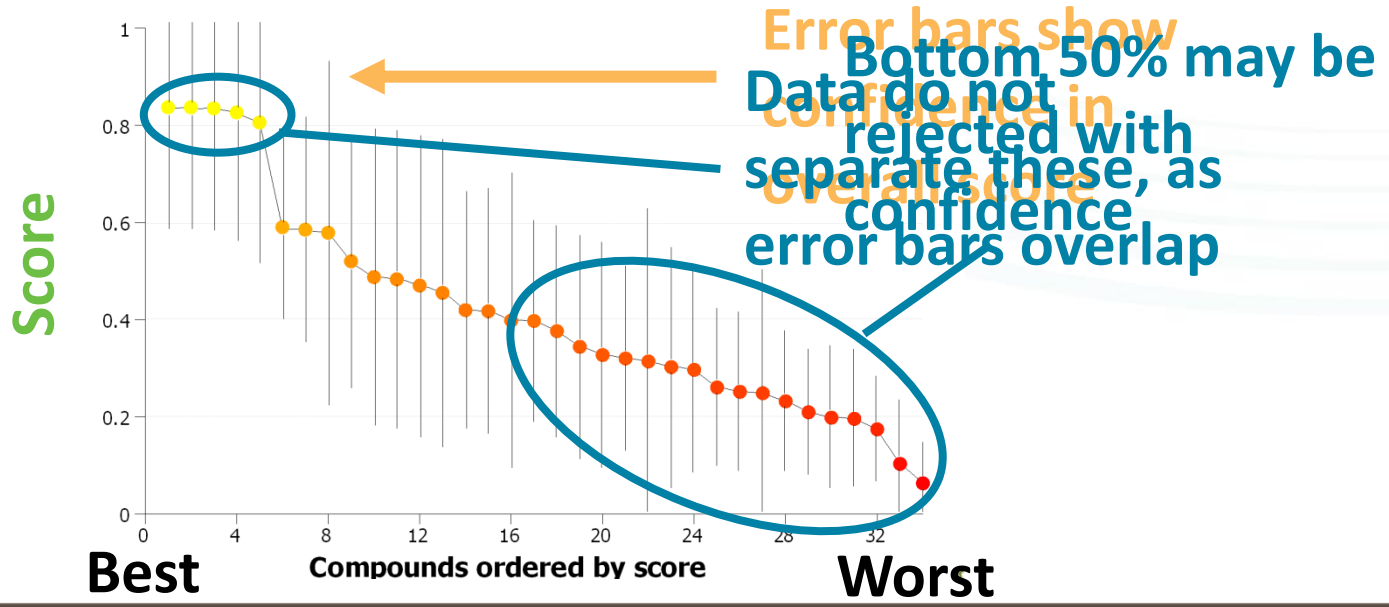
*Segall, Multi-Parameter Optimization..., Curr. Pharm. Des., **18**, 1292-1310(2012)

Possible Solution
Multi-parameter optimisation

StarDrop™5
Software that guides you to successful drug discovery

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

- Score (Likelihood of Success)
- Confidence in score



Illustrative Example*

StarDrop™5
Software that guides you to successful drug discovery

- *In vitro* data being generated
  - Potency
  - Selectivity
  - Solubility
  - Microsomal stability (rat and human: RLM and HLM)
- 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

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

Comparison of Strategies

StarDrop™5
Software that guides you to successful drug discovery

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
9	XXX292	6.28	1.22
10	XXX541	6.66	0.94
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12	XXX318	6.2	1.21
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

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, Overcoming psychological barriers to good discovery decisions. Drug Discov. Today., **15**, 561-569 (2010)

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  - Andrew Chadwick - Andrew.Chadwick@tessella.com
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  - James Chisholm
- Interesting light reading
  - Ben Goldacre (2008) “Bad Science”, Fourth Estate (paperback)
  - Dan Gardner (2009) “Risk – the science and politics of fear”, Virgin Publishing (paperback)

Anchoring*

- Question: Estimate the percentage of African nations that are members of the United Nations.
- First spin a wheel to generate random number between 1 and 100 and ask if estimate was higher or lower
- If random number was 10: Median estimate 25%
- If random number was 65: Median estimate was 45%

*Tversky &Kahneman, Judgment under Uncertainty: Heuristics and Biases. *Science*, **185**, 1124-1131 (1974)