Maximising compound value by making good decisions: How addressing cognitive biases could improve drug discovery

Matthew Segall, Optibrium Ltd, Cambridge, UK
Andrew Chadwick, Tessella plc., Burton upon Trent, UK

Introduction

People are notoriously poor at making good decisions based on complex, uncertain data when there is a lot at stake. In drug discovery, poor decisions can mean wasting effort in synthesizing and testing compounds that fail or throwing out perfectly good compounds in error, reducing the opportunities to find new, valuable therapies. However, making good decisions in this context is challenging for several reasons: the need to balance multiple, often conflicting criteria for a successful drug; the abundance of data available on many properties; and the uncertainty in the relevance and accuracy of the available data, particularly in early discovery.

Psychological research has demonstrated that reproducible biases affecting human decision-making, known as cognitive biases, threaten objectivity and balance in individual and team decision-making. Drug discovery leaders receive much conflicting advice on possible ways to improve productivity and restore the rate of successful drug launches; however with help to overcome these psychological barriers, better decision-making can enhance R&D performance [1].

We will discuss four of the common biases that have serious implications for decision-making in drug discovery (summarised below). We will suggest approaches for overcoming these, such as strategies adapted from evidence-based medicine and computational tools that seek to guide the decision-making process, encouraging objective consideration of all of the available information and explicit consideration of the impact of uncertainty in drug discovery.

Bias	Drug Discovery Implications
Confirmation bias: self justification or premature closure	• Projects failed too late. • Insufficiently wide search
Availability bias: focus on recent/vivid experiences	• Failure to apply and learn from the 'big picture'
Poor calibration: overconfidence in forecasting	• Too much weight on early screening methods • Incorrectly reject drugs
Excess focus on certainty	• Inefficient use of resources when screening across multiple risk factors

Confirmation Bias

There is a natural optimism in all of us that makes it too easy to believe and latch onto information that tends to confirm our pre-conceptions. For this reason, people have a tendency to look for tests that confirm our hypotheses and it can be very hard to propose, prioritise and act on the tests that could best 'kill' our ideas.

In drug discovery, the implications of this bias are that projects are often failed too late, wasting effort and investment. Conversely, there is a tendency to focus too quickly on a narrow range of compounds where we believe a successful drug will be found, before exploring a sufficiently wide range of options to be confident of finding the optimal chemistry. An example of this is shown in Figure 1, which illustrates the progress of a project that returned repeatedly to the same chemistry in the expectation of finding an optimal compound. Only after progressing almost 200 compounds for detailed *in vitro* studies and approximately 50 compounds for *in vivo* PK studies was an alternative strategy pursued in earnest. More details on this example can be found in [2].

To overcome this bias it is important to balance a focus on 'quality' with exploration of diversity when selecting compounds for progression, mitigating risk and considering alternative chemical series.

Availability Bias

Individuals are biased towards recent, vivid experiences and tend to ignore relevant information on long-run chances of a problem. As an illustration of this, it is believed that more people died on the roads after 9/11, as a result of increased road traffic caused by avoiding airline travel, than in the airplanes deliberately crashed. The many small tragedies are less vivid and available to the individual decision-maker than the one large and vivid event, distorting assessments of relative risk.

In drug discovery, the impact of this bias is that too much emphasis is often given to a recent negative result, even if this is from a method known to be weakly predictive, leading to excess attrition, loss of diversity and missed opportunities to find drugs. An example of the impact of this is shown in Box 1.

One solution to this problem is to provide quantitative analysis of screening options, taking into account the reliability, costs and impact of different strategies. However, in order to provide a truly quantitative analysis, we need to better understand the underlying risks of each factor (known as the 'prior probability') to put these results in the context of the 'big picture'. This is a major challenge and will require a systematic effort across the industry.

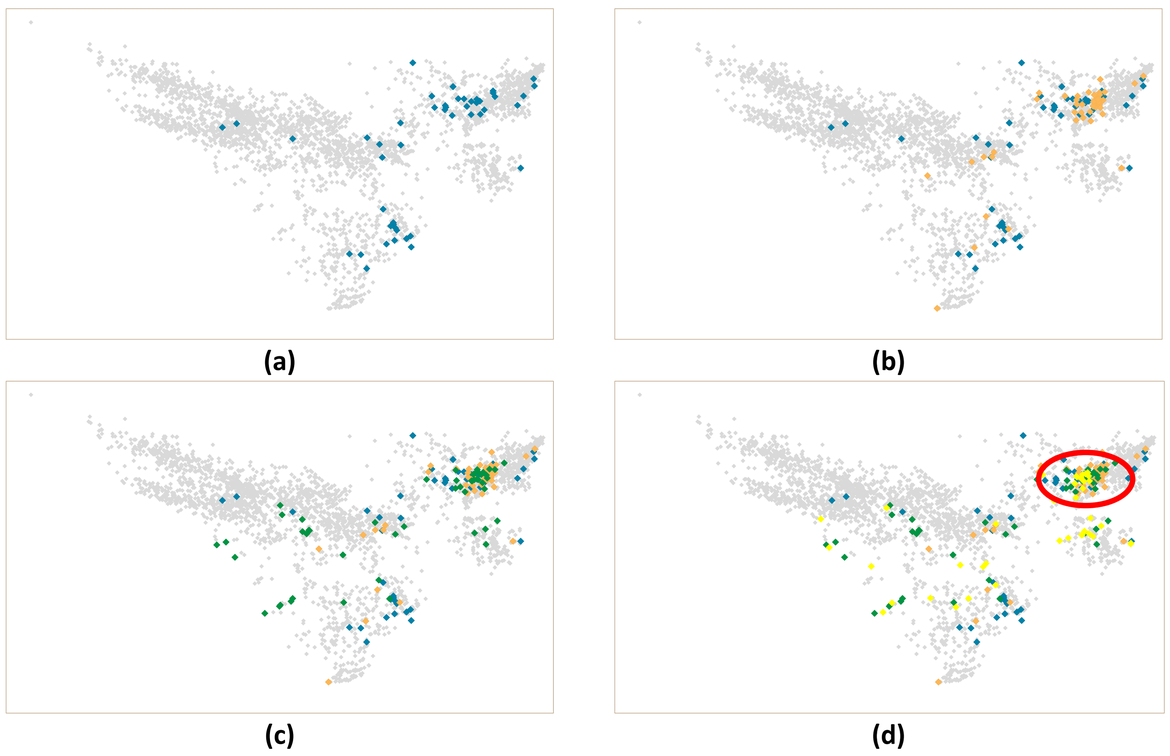

Figure 1. These 'chemical space' maps generated in StarDrop™ [3] illustrate the distribution of compounds selected for progression to secondary studies in a project. Each point represents a compound and the proximity of points indicates their similarity of chemical structure. The grey points illustrate the full diversity of the compounds screened in this project and the coloured points show those for further study in chronological order in the order blue, orange, green and yellow in plots (a) through (d) in groups of approximately 50. The project had difficulty finding a compound with appropriate properties and, in light of this, these maps suggest that too much weight was given to the region circled in plot (d) rather than searching more widely for a satisfactory compound.

Box 1. How well does this assay conserve your options?
You have purchased a series of compounds and 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%

The answer is given below in [4].

Poor Calibration

People tend to be over-confident about their ability to estimate or predict a value. In an experiment in which 1000 people were asked 10 questions (e.g. How long is the Nile river in miles?) for which they were asked to answer by giving a range that they were 90% confident contained the correct answer, only 1% got 9 or 10 out of 10 answers correct!

The impact of this on drug discovery is that risks can be underestimated, leading to late stage, expensive failures while, conversely, inappropriate weight given to early screening results can lead to excess attrition and loss of opportunity.

Getting better at forecasting requires feedback to provide self-awareness of performance. However in R&D the timescales are so long that feedback happens at the organisational, rarely the individual, level. There needs to be a way to use organisation-level learning to help individuals and teams practice in a safe environment where they can get rapid feedback on the impact of their decisions. One approach is to make available interactive simulations that allow the impact of decisions to be explored with visual feedback such as that illustrated in Figure 2.

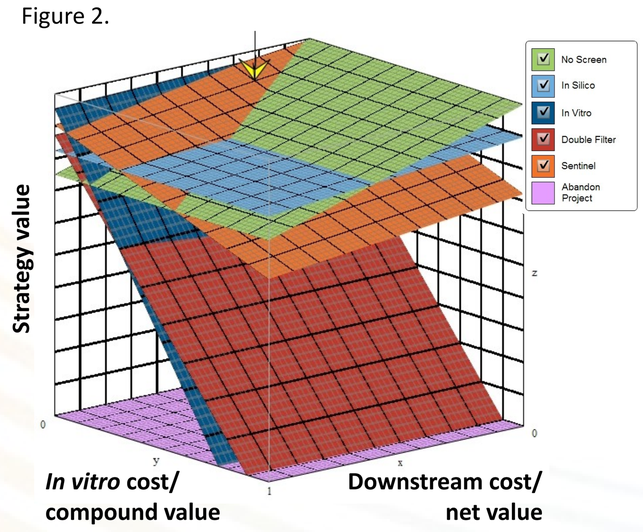

Figure 2. This 'strategy cube' illustrates the value of different screening strategies, combining *in silico* and *in vitro* screening methods for assessing a single risk factor in different ways. The value is indicated on the z-axis; to achieve a value of one would require eliminating all risk at zero cost. The different strategies are represented by different surfaces as indicated in the key; *in silico* – apply *in silico* screen only, *in vitro* – apply *in vitro* screen only, double filter – pass only compounds that pass both *in silico* and *in vitro* screens, sentinel – reject only compounds that fail both *in silico* and *in vitro* screens.

For the case shown here, the prior probability for the risk is 20%, the *in silico* method has specificity and sensitivity of 90% and 70% respectively and the *in vitro* method has specificity and sensitivity of 98% and 90% respectively.

An interactive version of this visualisation can be accessed at http://www.tessella.com/screening-strategy-explorer

Excess Focus on Certainty

The final cognitive barrier that we will consider in relation to drug discovery is a curious bias in psychological processing that most of us suffer when considering probabilities. We tend to focus too much on the low-probability, high-impact items - the plane crash, not the car crash - particularly where there are multiple sources of risk, each with different probabilities and impacts. The consequence for drug discovery is likely to be unconscious neglect of some of the parameters when trying to optimise several factors simultaneously to find a high quality drug. For example, if there is 99% chance of activity, which is critical, and 50% chance of good bioavailability, which is fairly important, most people will spend undue effort trying for 100% certainty of activity, when overall, over many projects, increasing the chance of bioavailability to 70% could be worth more.

A solution to this is to use an objective framework to prioritise compounds against the profile of requirements, taking into account both the confidence in the available data and the importance of each factor to the outcome of the project. An example of this is StarDrop™'s probabilistic scoring [5] approach, as illustrated in Figure 3.

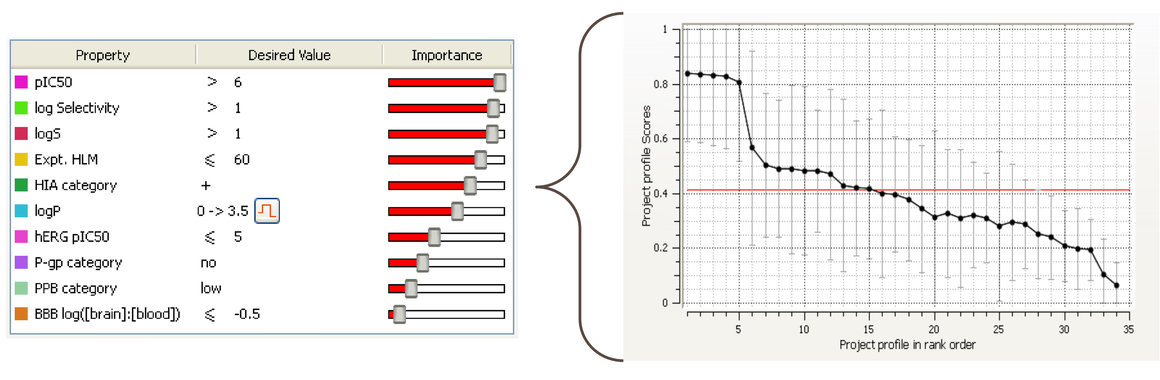

Figure 3. Illustration of a probabilistic approach to multi-parameter optimisation, as implemented in the StarDrop™ software [3] platform. A 'scoring profile' for a project defines the success criteria for predicted and experimental properties, indicating the ideal range for each property value ('Desired Value'), and relative importance (slider bars). The data for each compound, along with the associated experimental or statistical uncertainties, are assessed against this profile to calculate the likelihood of success (score) and overall uncertainty in the score.

Conclusion

Our natural biases can have a negative impact on the decisions we make and the long timescales of the pharmaceutical R&D process make it difficult to learn how to avoid these from personal experience. Guidance can be provided by analysing potential choices and providing feedback to project teams through intuitive visualisation and feedback. Next generation support environments help scientists to manage risk in order to get the most out of their available resources. We think that with corporate and industry experience correctly harnessed through an objective decision-making framework, a team can do much to 'make its own luck'.

Acknowledgements

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References

[1] A. Chadwick and M. Segall Drug Discovery Today, 2010, **15**(13/14), pp. 561-569
[2] M.D. Segall, A.P. Beresford, J.M. Gola, D. Hawksley, M.H. Tarbit. Expert Opin. Drug Metab. Toxicol. 2006 **2**(2), pp. 325-37.
[3] http://www.optibrium.com/stardrop
[4] The answer is (c), approximately 10%. Of 1000 compounds, 108 (990 x 0.1 + 10 x 0.9) would be reported as toxic by the test, of which only 9 really are toxic.
[5] M.D. Segall, E. Champness, O. Obrezanova, C. Leeding. Chem. & Biodiv., **6**(11), pp. 2144 - 2151