A qualitative and quantitative framework to assess the value of QSP modeling in pharmaceutical development.

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Introduction

- What is the value of QSP-style modeling?
- QSP modeling is becoming more prevalent
- QSP uses data from pathway to outcome level to construct plausible hypotheses of biological systems
- QSP models enable extrapolation beyond existing data to prospectively investigate novel questions – Response to a novel target perturbation, identification of patient sub-types, the effects of protocol modifications, etc.
- While practitioners argue that QSP modeling reduces uncertainty and informs decision-making, the value is difficult to conceptualize and quantify
- We lay out a framework for assessing the value of QSP modeling in R&D decision making

Methods

- We apply concepts from the professional discipline of Decision Analysis (DA) to illustrate the economic value of reducing uncertainty
- We use a classic pedagogical problem from DA, the “Party Problem”, to illustrate key concepts and draw analogies to drug development decisions

Conclusions

- DA offers a framework for rationale decision making
- Thinking about drug R&D decisions in DA terms turns ambiguity into defined uncertainty
- The Party Problem illustrates the value of perfect and imperfect information that changes probabilities of uncertain events
- QSP modeling can both refine estimates of the probability of technical success and increase the probability of technical success
- QSP modeling can identify risk mitigation strategies based on better clarity about biology
- At a program level, quantitative elucidation of biological connections reduces risk for current and future projects, and may suggest new alternatives
- Given the potential value of drug R&D projects, the risk reduction benefit of QSP alone far exceeds the costs of QSP modeling
- While most companies do not use formal DA, concepts that can be illustrated by the Party Problem may facilitate better understanding of the value of QSP modeling

References


Anatomy of a Decision: The Party Problem

- This simple decision problem – where to hold a birthday party – illustrates all of the major components of any decision

<table>
<thead>
<tr>
<th>Decision Components</th>
<th>Party Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasible alternatives?</td>
<td>Outside, Inside, Porch</td>
</tr>
<tr>
<td>Relevant uncertainties?</td>
<td>Weather</td>
</tr>
<tr>
<td>Possible outcomes of uncertainty?</td>
<td>Sun, Rain</td>
</tr>
<tr>
<td>Probability of each outcome?</td>
<td>Outside: 100, Inside: 50, Porch: 90</td>
</tr>
<tr>
<td>Value of each outcome for each alternative?</td>
<td>Outside: $160M, Inside: $50M, Porch: $150M</td>
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Once all of this information is clear, risk-adjusted values (eValues) can be calculated by multiplying the value of each outcome by its probability

7 Portable Lessons of the Party Problem

- Structuring the decision in a DA framework means going from ambiguity to defined uncertainty
- You can choose an alternative, not an outcome
- A good decision does not guarantee a good outcome, and a good outcome does not mean you made a good decision
- Uncertainty is a major reason why rationale decision-making is challenging
- A change in outcome probability changes the expected values of the alternatives, and may change the optimal decision
- New information can change outcome probabilities
  - With a perfect weather forecast, you could choose inside if rainy, outside if sunny
  - Your expected value in this case goes up, from $48 to $56. New probabilities computed using Bayesian revision

Drug R&D Problem

- A drug R&D decision is substantially more complex, but has the same basic components

<table>
<thead>
<tr>
<th>Decision Components</th>
<th>R&amp;D Problem</th>
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<tbody>
<tr>
<td>Feasible alternatives?</td>
<td>Pursue target A (first-in-class) OR target B (proven pathway)</td>
</tr>
<tr>
<td>Relevant uncertainties?</td>
<td>Technical &amp; regulatory success</td>
</tr>
<tr>
<td>Possible outcomes of uncertainty?</td>
<td>Success, Failure</td>
</tr>
<tr>
<td>Probability of each outcome?</td>
<td>Target A: 30%, Target B: 60%</td>
</tr>
<tr>
<td>Value (NPV) of each outcome?</td>
<td>Target A: $800M, Target B: $300M</td>
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Results: How QSP Adds Value to R&D Decisions

- Structuring R&D decisions in a DA framework reveals the value of reducing uncertainty
- One way that QSP adds value is as a tool to refine predictions of the probability of success
  - QSP modeling of Targets A and B in the context of disease pathophysiology supports refinement of the assessed probability of success for both targets
  - If the QSP study increases assessed probability of Target A success by even 10%, the expected NPV (eNPV) would be increased by $80M to $215M
- This could change the development decision or increase the likelihood that Target A would become part of the portfolio
- QSP modeling is also routinely used to increase the probability of success by changing the way that a project is conducted, e.g., by:
  - Identifying specific technical risks, which could then be mitigated, increasing probability of success
  - Identifying novel protocol alternatives with a better chance of success
  - Identifying sub-populations most likely to respond to treatment
- Finally, by clarifying biological connections in a disease process, QSP modeling can reduce risk and increase probabilities of success at a program level, and even suggest new alternatives
- While precise quantification of probabilities and eNPVs is challenging, the DA framework reveals significant value in risk reduction