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

1. Howard, R., & Abbas, A. (2016). *Foundations of Decision Analysis.* Pearson.

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**

Decision Components	Party Problem	
Feasible **alternatives**?	Outside, Inside, Porch	
Relevant **uncertainties**?	Weather	
Possible **outcomes** of uncertainty?	Sun	Rain
Probability of each outcome?	40%	60%
Value of each outcome for each alternative?	Outside: 100 Inside: 40 Porch: 90	Outside: 0 Inside: 50 Porch: 20

- Once all of this information is clear, **risk-adjusted values** (eValues) can be calculated by multiplying the value of each outcome by its probability

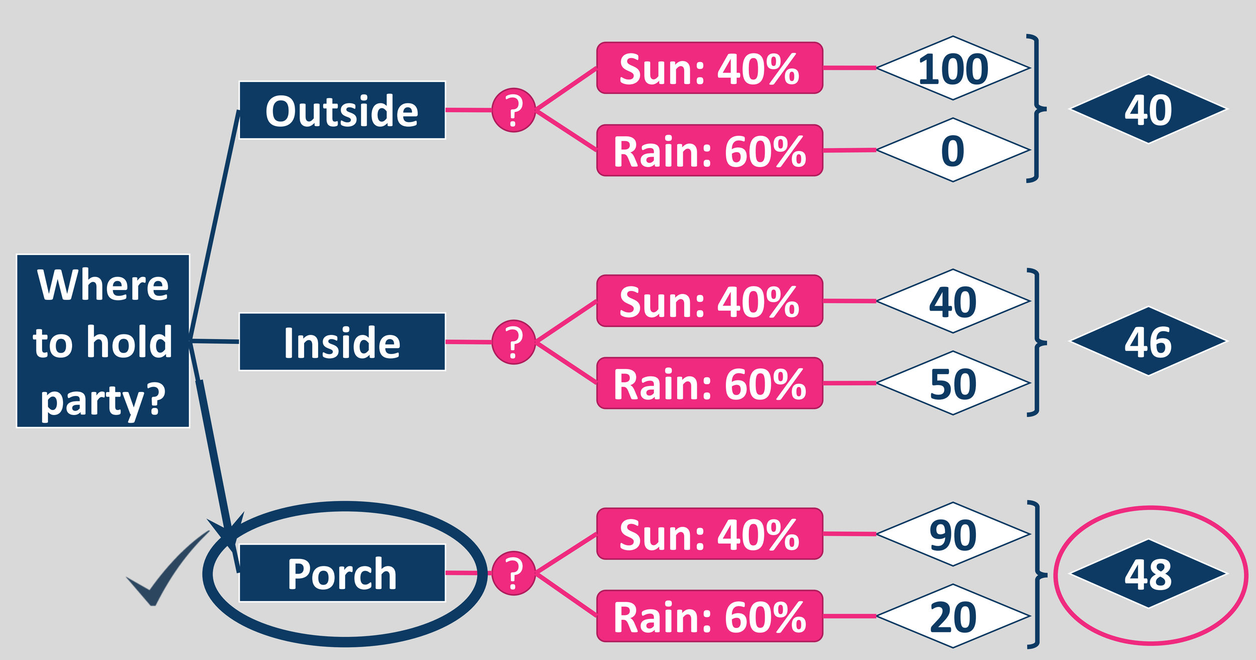

Figure 1. A Decision Tree for the Party Problem.

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 (0.4*90+0.6*20) to 70 (0.4*100 + 0.6*50)
- Even **imperfect information** has value (see Fig. 2)

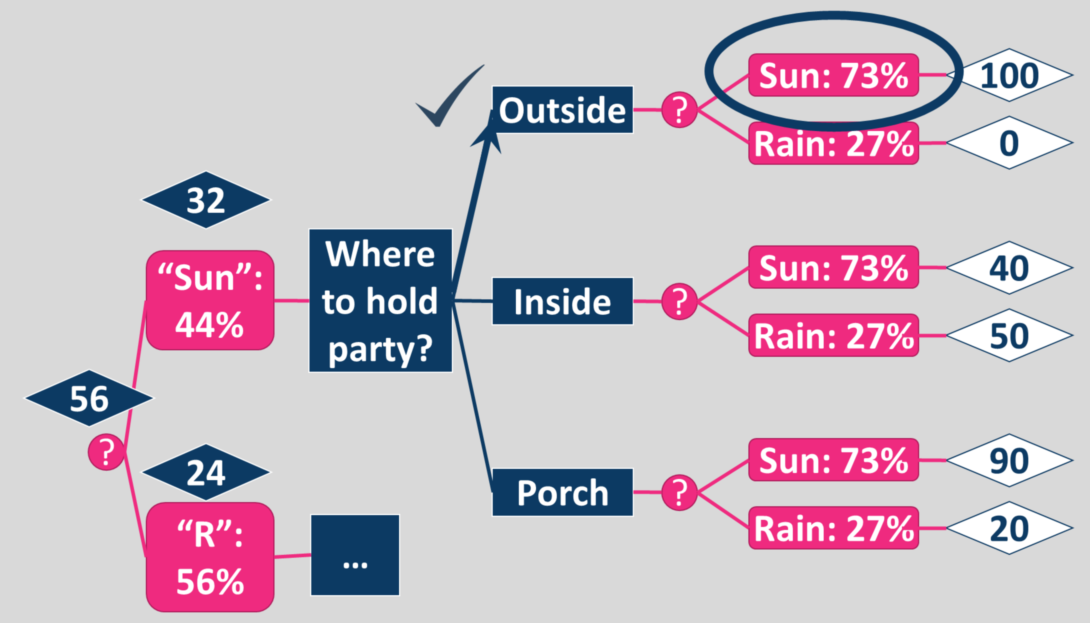

Figure 2. A partial decision tree illustrating the impact of new, imperfect information. A rain detector with 80% sensitivity and specificity would increase the eValue from 48 to 56. New probabilities computed using Bayesian revision.

Drug R&D Problem

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

Decision Components	R&D Problem	
Feasible **alternatives**?	Pursue target A (first-in-class) OR target B (proven pathway)	
Relevant **uncertainties**?	Technical & regulatory success	
Possible **outcomes** of uncertainty?	Success	Failure
Probability of each outcome?	Target A: 30% Target B: 60%	Target A: 70% Target B: 40%
Value (NPV) of each outcome?	Target A: $800M Target B: $300M	Target A: $-150M Target B: $-50M

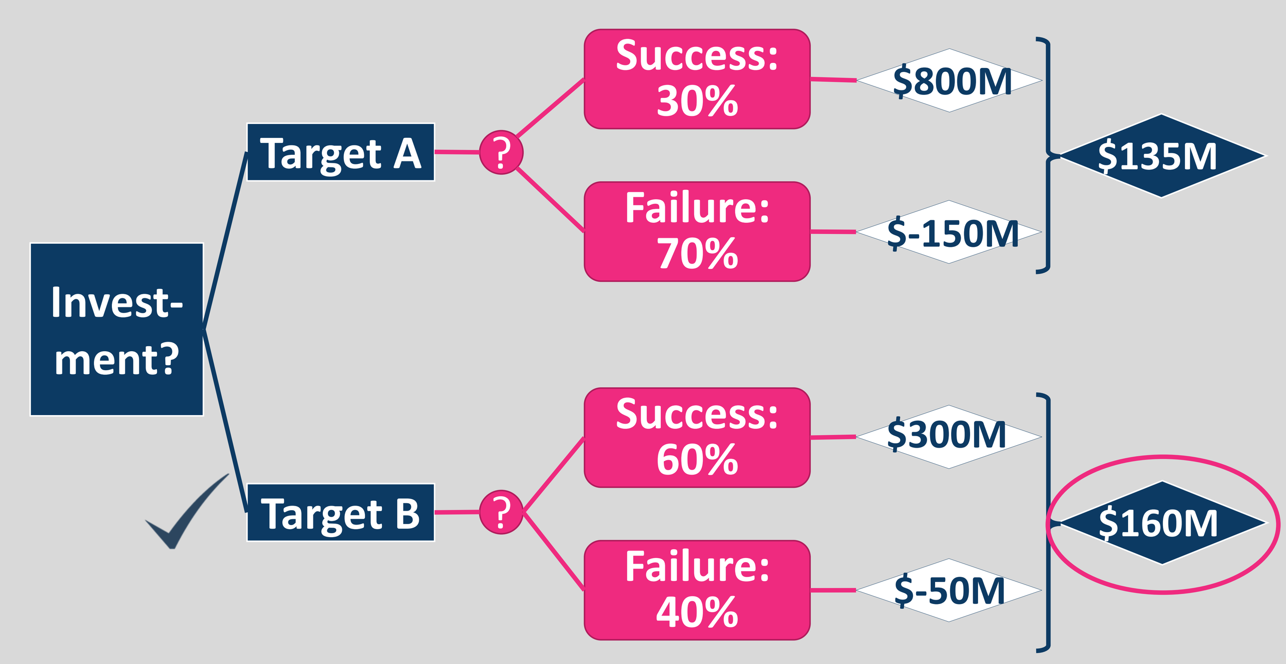

Figure 3. A Decision Tree for an R&D Investment Problem.

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

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