Optimal Allocation of Funding in Clinical Trials.

- Alex Cox, Kevin Olding, Piotr Morawiecki, Timothy Peters, Mehar Motala, Robbie Peck (Roche)
Introduction

How can Roche optimally allocate funding across their portfolio?

Clinical trials are expensive

Subject to finite budget constraints

Competitive market environment

Portfolio Theory

Game Theory
Section 1:

Portfolio Theory Approach
Portfolio Theory Approach

• Can be approached as a traditional Knapsack Problem with extra constraints.
• Existing model by Patel & Ankolekar considers maximising the Expected Net Present Value.
• How can we extend this to incorporate risk? Variance.
• If we are able to do so, we can obtain a more comprehensive understanding of budget allocation.
• How to make decisions based on full portfolio and manage the drug pipeline.

N Patel, S Ankolekar, Chapter 11, Optimization of Pharmaceutical R&D Programs and Portfolios
Optimisation Framework

Suppose we have a budget $B$ for $i$ drugs, and $j$ possible design alternatives. Let $b_{ij}$ denote the budget requirement for the $i$th drug with design type $j$. Then the Knapsack problem can be formulated in the following way.

**Maximise**

$$\sum_i \sum_j ENPV_{ij} Z_{ij}$$

Subject to:

$$\sum_i \sum_j b_{ij} Z_{ij} \leq B$$

$$\sum_j Z_{ij} \leq 1, \forall i$$

**Risk Adjustment**

Mean-Variance Optimisation

$$\sum_i \sum_j (ENPV_{ij} - \lambda \sigma_{ij}^2) Z_{ij}$$

Subject to:

$$\sum_i \sum_j b_{ij} Z_{ij} \leq B$$

$$\sum_j Z_{ij} \leq 1, \forall i$$

N. Patel, S. Ankolekar
• The optimisation problem can be solved via backward induction. i.e. we consider all possibilities and work backwards in time, making optimal decisions.

• Consider the case with 3 drugs and 3 trials run.

\[ \text{data} = [[[0,0,0],[10,80,110], [22,104,64], [33,118,71]],
[[0,0,0],[14,34,20], [18,48,25], [24,53,28]],
[[0,0,0],[16,52,35], [24,55,21], [42,70,59]]] \]

[Cost, Expected Return, Variance of returns]
Efficient Frontier

- Boundary beyond which you can’t improve the mean-variance trade off.
- Efficient frontiers allow us to view portfolio at different budget levels.
- Exclude portfolios which do not offer a desirable mean-variance trade off.
• Boundary beyond which you can’t improve the mean variance trade off.
• Efficient frontiers allow us to view portfolio at different budget levels.
• Exclude portfolios which do not offer a desirable mean-variance trade off.
• Additional trials added- do they improve the efficient frontier?
Extensions

• Considering covariance and make decisions which are informed by the level of diversity of the portfolio.
• Try different risk adjusted measures. e.g. utility function, expected shortfall.
• How can industry competition influence budget allocation? Model likelihood of competitors arising with similar products and penalising value function accordingly.
• Apply efficient frontier to manage pipeline.
Section 2:

Game Theory Approach

How to model competitive behaviour
**Strategy:** Choosing the drugs to test in each funding period

**Clinical test phases**
(cost, probability of success, duration)

- Disease 1
- Disease 2
- Disease 3
- Disease 4

- **Players:** Pharmaceutical companies
  (annual budget, available projects)

- **Drugs** (current phase, efficacy)

**Goal of the game:**
Maximise your profit (within given risk constraints)
Player A | Player B | Market value
--- | --- | ---
Drug 1 | Drug 1 | MV = 1
Drug 2 | MV = p
Drug 2 | MV = p

Nash equilibria:
- \( p = 0.5 \)
- \( p = 1 \)

2 pure strategies: Each player chooses different medicine
1 mixed strategy: Each player invests in drug 1 with probability \( 2 \cdot (1 - p) \)

Conclusion 1: In competitive situations there may be no single optimal strategy for the pharmaceutical company. It is heavily dependent on competition strategy.
<table>
<thead>
<tr>
<th>Player A</th>
<th>Player B</th>
<th>Market value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1</td>
<td>Drug 1</td>
<td>MV = 1</td>
</tr>
<tr>
<td>Drug 2</td>
<td>Drug 2</td>
<td>MV = $M_a$</td>
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<tr>
<td></td>
<td></td>
<td>MV = $M_b$</td>
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</tbody>
</table>

**Optimal decision for Player A**

- Invest in drug 1
- Invest in drug 1
- Invest in drug 2
- Invest in drug 1
- Invest in drug 2
- Invest in drug 1
- Mixed strategy
- Invest in drug 2
- Invest in drug 2
- Invest in drug 2

**Conclusion 2:** In some competitive situations competitors’ product market volume has higher importance for our decision than our own.
Monte Carlo Tree Search

Classical portfolio optimisation (e.g. knapsack problem)

Backward propagation

Monte Carlo Tree Search

- Tested numerical methods for finding strategies for portfolio optimisation

- Classical portfolio optimisation (e.g. knapsack problem)
  - Very quick to compute
  - Does not model competitive behaviour

- Backward propagation
  - Always gives an optimal solution
  - Can be used only for very simple toy models

- Monte Carlo Tree Search
  - Can be used in very complex games
  - Often finds a suboptimal solution
Company 1: Disease 1 > Disease 4 > Disease 2
Company 2: Disease 1 > Disease 3 > Disease 4

Based on knowledge of company 1 strategy
Game so far:

Different Strategies

Multiple actions

Different numbers of drugs

Properties of each drug's phases:
  • Cost
  • Probability of success
  • Predicted Effectiveness

Extensions:

Different Time Intervals for phases

Increase investment into phases for increased probability of success

Varying budget system

Constraint on risk when calculating players payoff
Final Conclusions:

**Portfolio Theory Approach**

**Conclusion 1:**
Portfolio optimisation problem can be modelled as a knapsack problem.

**Conclusion 2:**
Efficient frontier analysis can be used to plan the pipeline better.

**Game Theory Approach**

**Conclusion 1:**
At certain situations portfolio optimisation requires modelling of competitor's behaviour.

**Conclusion 2:**
Game theory allowed us to
1) obtain useful heuristics based on toy examples,
2) find optimal solution in complex situations.