Stochastic Programming Models and Algorithms for Pharmaceutical R&D Planning

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Exogenous and Endogenous Uncertainty in Stochastic Programming
Outline

- Introduction
- Theoretical Properties
- Solution Algorithms
- Extensions
- Applications
Problem Statement

Given:
- Portfolio of products $i \in I = \{1, 2, \ldots\}$ in the R&D pipeline; revenue function if successful
- Clinical trials $j \in J = \{\text{PI, PII, PIII}\}$ for each drug: duration, cost, resource requirements, success probability
- Limited resources $r \in R$; availability & cost

Decisions:
- Product selection & timing of trials to maximize the expected net present value (ENPV) of the R&D pipeline

Uncertainty Sources

Types of uncertainty
- Market: competition & patent issues
- Technical: clinical trial outcome, duration, cost, and resource requirements

Trial outcome uncertainty most important: if a single trial fails, previous investment is wasted

Scenarios

Outcome of trial $(i,j)$: uncertain parameter $\xi_{ij}$ from $\Omega_{ij}=\{F,P\}$

Outcome of drug $i$: $\xi_i$ from $\Omega_i=\{\text{PI-F, PII-F, PIII-F, PIII-P}\}$

Reklaitis, Pekny et al.; Grossmann et al.; Maranas et al.; Solak et al.
Multi-stage Stochastic Programming Formulation

Variables:

- \( X_{ijts} = 1 \) if trial \((i,j)\) starts in stage \(t\) in scenario \(s\)
- \( Y_{ijts} = 1 \) if trial \((i,j)\) is finished by stage \(t\) in scenario \(s\)
- \( Z_{ijts} = 1 \) if trial \((i,j)\) is idle in stage \(t\) in scenario \(s\)

Variable definition:

- \( Y_{i,j,t,s} = X_{i,j,t-1,s} + X_{i,j,t-\tau_{ij},s} \), \( \forall i, j, t, s \)
- \( Z_{ijts} = X_{ij,t-1,s} + X_{i,j,-t-\tau_{ij},s} - X_{ijts} \), \( \forall i, j, t, s \)

Sequencing:

\[ \sum_{t' \leq t} X_{ijt's} \leq Y_{i,j,t-1,s}, \forall i, j \in \{PII, PIII\}, t, s \]

Resource constraints:

\[ \sum_{t} \sum_{j} \sum_{t' > t-\tau_{ij}} \rho_{ijr} X_{ijt's} \leq \rho_r^{\max}, \forall r, t, s \]

Objective:

\[ \max ENPV = \sum_{s} p_s (Rv_s - Cst_s) \]
Endogenous Observation of Uncertainty

Clinical trials planning: We (i.e. the optimization) determine when scenarios become distinguishable.

**Example:**
Drugs D1 & D2 have to undergo PIII

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Trial Outcome</th>
<th>Initial</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>s=1</td>
<td>1) Pass</td>
<td>Pass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pass</td>
<td>Fail</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Fail</td>
<td>Pass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fail</td>
<td>Fail</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Solution 1: No trial
- Solution 2: D1 trial at t=1
- Solution 3: D1 trial at t=1, D2 trial at t=2
- Solution 4: D2 trial at t=1, D1 trial at t=2

**Exogenous Uncertainty with Endogenous Observation**

- **Dynamic** scenario tree: \( t^{s,s'} \) is unknown
- **Non-anticipativity:** \( \{ t < t^{s,s'} \} \Rightarrow x_{ts} = x_{ts'} \ \forall t, s, s' \) (2)
- **Transformation to MIP constraint:** \(-y_{tss'} \leq x_{ts} - x_{ts'} \leq y_{tss'}, \ \forall s, s', t > 1\)

- \(O(TS^2)\) new variables
- \(O(MTS^2) = O(IJT(4^I)^2)\) inequalities; cannot be used to eliminate variables & constraints
- T=6, I=3 \(\rightarrow\) 73,728; I=4 \(\rightarrow\) 1,572,864

Pflug (1990); Jonsbraten et al. (1998); Grossmann et al. (2006, 2008); Van Hentenryck et al. (2006, 2008)
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### Modeling of Non-anticipativity

**Example:**
Drugs D1 & D2 have to undergo PIII

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<th>Trial Outcome</th>
<th>S</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pass</td>
<td>1</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pass</td>
<td>2</td>
<td>Fail</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Fail</td>
<td>3</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fail</td>
<td>4</td>
<td>Fail</td>
<td></td>
</tr>
</tbody>
</table>

**Solution 1:**
No trial

**Solution 2:**
D1 trial at $t=1$

**Solution 3:**
D1 trial at $t=1$
D2 trial at $t=2$

**Solution 4:**
D2 trial at $t=1$
D1 trial at $t=2$

---

Scenarios 1 & 2 become distinguishable from 3 & 4 upon completion of (D1, PIII)
Scenarios 1 & 3 become distinguishable from 2 & 4 upon completion of (D2, PIII)

- We want to enforce:

  \[
  \{t < t^{s,s'}\} \Rightarrow \{X_{ijts} = X_{ijts'}, \forall i, j\} \quad \forall t, (s, s') \quad (3)
  \]

- For every pair $(s, s')$, we know the differentiating trial $(i^{s,s'}, j^{s,s'})$

- Pair $(s, s')$ is indistinguishable until the completion of $(i^{s,s'}, j^{s,s'})$; i.e. if $Y_{i^{s,s'}, j^{s,s'}, st} = 0$

- Equation (3) can be re-written:

  \[
  \{Y_{i^{s,s'}, j^{s,s'}, t,s} = 0\} \Rightarrow \{X_{ijts} = X_{ijts'}, \forall i, j\} \quad \forall t, (s, s')
  \]

  \[
  -Y_{i^{s,s'}, j^{s,s'}, t,s} \leq X_{ijts} - X_{ijts'} \leq Y_{i^{s,s'}, j^{s,s'}, t,s} \quad \forall i, j, t, (s, s') \quad (4)
  \]

- No new variables needed; $O(MTS^2)$ constraints

- **Can we reduce the number of non-anticipativity constraints?**
Non-anticipativity Constraints (NACs)

Example

Scenario 1: (D1, PI) fails; (D2, PI) fails.
Scenario 2: (D1, PI) passes, (D1, PII) fails; (D2, PI) fails.
Scenario 3: (D1, PI) and (D1, PII) pass, (D1, PIII) fails; (D2, PI) fails.
Scenario 6: (D1, PI) passes, (D1, PII) fails; (D2, PI) passes, (D2, PII) fails.

Scenarios 1 & 6
Differ in the outcome of (D1, PI) and (D2, PI).
⇒ indistinguishable until (D1, PI) or (D2, PI) completed

Non-anticipativity between scenarios 1 & 6 is enforced via scenario 2 or 5

Scenarios 1 & 3
Differ in the outcome of (D1, PI) (and (D1, PII)?)
⇒ indistinguishable until (D1, PI) (or (D1, PII)?) is completed

Non-anticipativity between scenarios 1 & 3 is enforced via scenario 2
Non-anticipativity Constraints (NACs)

Example

Scenario 1: (D1, PI) fails; (D2, PI) fails.
Scenario 2: (D1, PI) passes, (D1, PII) fails; (D2, PI) fails.
Scenario 3: (D1, PI) and (D1, PII) pass, (D1, PIII) fails; (D2, PI) fails.
Scenario 6: (D1, PI) passes, (D1, PII) fails; (D2, PI) passes, (D2, PII) fails.
Theoretical Properties

Property 1. It is sufficient to express NACs only for pairs of scenarios \((s, s')\) that differ in the outcome of a single drug; i.e., \((s, s')\) does not need to be pairwise constrained if \(\xi_i^s \neq \xi_i^{s'}\) and \(\xi_i^s \neq \xi_i^{s'}\) for any \((i, i') | i \neq i'\).

For a constrained pair \((s, s')\) we will call the drug in which they differ the critical drug and denote it by \(i^{s,s'}\).

Property 2. It is sufficient to express NACs only for pairs of scenarios \((s, s')\) that differ in the outcome of a single trial; i.e., \((s, s')\) does not need to be pairwise constrained if \(\xi_i^s\) and \(\xi_i^{s'}\) are not consecutive elements in \(\Omega_i\).

For the constrained scenario pair \((s, s')\) we will call the trial in which they differ the critical trial and denote it by \((i^{s,s'}, j^{s,s'})\). The reduced set of scenario pairs that must be constrained will be denoted by \(\Psi\).

Property 3. For a given scenario pair \((s, s') \in \Psi\), uncertainty can be treated as exogenous for \(t < t_{\min}^{s,s'} = \tau_{i^{s,s'}, f(i)} + \ldots + \tau_{i^{s,s'}, j^{s,s'}} + 1\)

Property 4. Decision variables \(X_{i^{s,s'}, f(i)}\) for trials \((i^{s,s'}, f(i^{s,s'})), \ldots, (i^{s,s'}, j^{s,s'})\) in scenarios \(s\) and \(s'\) are identical.

Variables for trial \((i^{s,s'}, j^{s,s'} + 1)\) should not be subject to NACs.

Lemma 1. NACs between \(s\) and \(s'\) for \(t < t_{\min}^{s,s'}\) and for the critical drug can be expressed using:

\[
X_{i^{s,s'}} \sum_{s' \in \mathcal{S}^{s,s'}_{t,s}} p_{s'} - \sum_{s' \in \mathcal{S}^{s,s'}_{t,s}} X_{i^{s,s'}} p_{s'} = 0, \quad \forall s, t > 1, (i, j) \in \mathbf{I} \mathbf{J}_{t,s}
\]

Property 5. Let \(S_t^l = \{s: t^{s,s'} < t, \forall s' \in \}, l \in \mathbf{L}\) be one of the subsets of scenarios that are indistinguishable at stage \(t\). If \(p_s > 0, \forall s \in S_t\), then NACs among scenarios in \(S_t^l\) can be enforced using a single equality.
Formulation Reduction and Tightening

**Reduction in NACs**

![Graph showing reduction in NACs](image)

**Total constraints**

![Graph showing total constraints](image)
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Infinite-horizon Approximations

\[ \max ENPV = \sum_s p_s (R_{v,s} - Cst_s) \]

\[ R_{v,s} = r_{i,s}^{\text{max}} - \gamma^D_i D_i - \gamma^L_i L_i \]

\[ Cst_s = \sum_{i,j,t} c_{ij} c_d X_{ijts}, \quad \forall s \]

\[ \max ENPV = \sum_s p_s (R_{v,s} - Cst_s + FR_{v,s}) \]

\[ FR_{v,s} = \sum_{i \in S'} \sum_j rev_{i}^{\text{open}} f_{ij} Z_{ij|T|s} + \sum_{i \in S'} \sum_{j \in \{P1,P2\}} \sum_{t>T - \tau_j} rev_{i}^{\text{run}} f_{ij+1} X_{ijts}, \quad \forall s \]

Revenue from drugs *idle* at the end of horizon

Revenue from drugs being developed at the end of the horizon
Rolling Horizon with Relaxed Model

**Algorithm**

1. Relax all double inequality NACs for stages greater than stage, $t^*$
2. Solve the model for $T=\{1, 2, \ldots, T\}$; implement the solution for $t = t' \leq t^*$; the current solution defines the scenario tree; a realization of uncertainty defines a path in the tree leading to a node at stage $t'$.
3. For the path (node) of interest, formulate and solve the model with updated information and $T^{new}=\{t'+1, t'+2, \ldots, t'+T\}$

**Remarks**

1. Integrality gap of $M$ is 3-4%;
2. Integrality gap of RM (after removal of NACs for $t > t^*$): 2-3%
3. Reduced model is easy to solve
4. Yields solutions that are *too good* (infeasible) for $t\in\{0, 1, \ldots, T\}$
5. But yields feasible (near) optimal solutions for $t\in\{0, \ldots, t'\}$
- Original Formulation (M): \( \max \{ cx: A^B x \leq b^B, A^* x \leq b^* \} \)
- Reduced Model (RM): \( \max \{ cx: A^B x \leq b^B \} \)
- We remove \textit{essential} constraints
- LP-relaxation of RM (LRM)
- (NAC) check: At each node add violated inequality NACs

\[
\begin{align*}
\text{max } c^T x \\
A^B x &\leq b^B \\
A^* x &\leq b^*
\end{align*}
\]

Essential constraints

\[
\begin{align*}
\text{LRM-Fractional} \\
\text{LRM-Infeasible} \\
\text{LRM-Fractional after NAC iterations} \\
\text{LRM-Integer} \\
\text{LRM-Integer} / \text{NAC Feasible}
\end{align*}
\]
Branch-and-cut Algorithm

Challenges and Approach

- **Integer solutions may be infeasible**
  - Deactivate heuristics (no good bounds available)
  - Modify bound updating
  - Check against removed NACs

- **Integer nodes can become fractional**
  - Continue branching from integer solutions

- **Standard search strategy inefficient**
  (no *early* good bounds; basis modified due to addition of NACs)
  - Combine best-first (depth<N) and local search

- **Expensive checking for NAC violation**
  - Hybrid cut checking strategy
  - Check at all nodes if node# < N (fewer cut additions)
  - Check only at integer later

Implemented using Xpress-Mosel in Xpress-IVE
### Computational Results

#### Instance characteristics

<table>
<thead>
<tr>
<th>Instance</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7A</th>
<th>7B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>$</td>
<td>I^\text{PI}</td>
<td>/</td>
<td>I^\text{PII}</td>
<td>/</td>
<td>I^\text{PIII}</td>
</tr>
<tr>
<td>Scenarios</td>
<td>144</td>
<td>288</td>
<td>864</td>
<td>2,304</td>
<td>3,456</td>
</tr>
<tr>
<td>Stages</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

#### Constraint Reductions

![Graph showing constraint reductions](image)

#### Computational results

<table>
<thead>
<tr>
<th></th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7A</th>
<th>7B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M0: Properties 1-2</strong></td>
<td>643</td>
<td>927</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>M1: Properties 1-4</strong></td>
<td>448</td>
<td>710</td>
<td>19,826</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>M2: Properties 1-5</strong></td>
<td>419</td>
<td>667</td>
<td>16,429</td>
<td>27,806</td>
<td></td>
</tr>
<tr>
<td><strong>B&amp;C algorithm</strong></td>
<td>323</td>
<td>438</td>
<td>2,781</td>
<td>11,660</td>
<td>28,019</td>
</tr>
</tbody>
</table>

Resource limit: 300,000 CPU sec
Endogenous Uncertainty Observation

Problems with sequential decision-making and endogenous uncertainty observation

- Oilfield planning
- Energy planning for new technologies (learning curves for new technology costs)
- Online fleet management and vehicle routing (decisions to accept customer, locate idle fleet)
- Airline booking systems (allocation of business/economy seats)

Results applicable to a wide range of problems

- **Variable reduction**: SP models where scenarios become distinguishable by a single decision
- **Property 1**: All SP models; effective for endogenous uncertainty observation
- **Property 2**: SP models with *sequential* decision making
- **Property 3**: SP models with timing constraints
- **Property 4**: SP models with *sequential* decision making
- **Property 5**: All SP models with binary decision variables
- **Branch-and-cut**: All SP models with endogenous uncertainty observation
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Integrated Clinical Trial and Resource Planning

**Long planning horizon**
- Outlicensing of drugs successfully passing PI or PII trials
- Expand/contract resources
- Outsourcing (at higher cost)

**New Variables:**
- \( W_{ijt} = 1 \) if drug \( i \) is outsourced at \( t \) after completing trial \( j-1 \)
- \( R^E_{kts} \): Resource expansion/contraction
- \( R^O_{kts} \): Outsourcing

**Idle Drug:**
\[
Z_{ijt} = Z_{ij0} + \sum_{t'=1}^{t-\tau_{ijt}} X_{i,j-1,t',s} - \sum_{t'=1}^{t} (X_{ij't'} + W_{ij't'}), \quad \forall i, j, t, s
\]

**Sequencing:**
\[
\sum_{t' \leq t} X_{ij't'} \leq Y_{i,j-1,t,s}, \quad \forall i, j \in \{PI, PII, PIII\}, t, s
\]

**Resource constraints:**
\[
\sum_{i} \sum_{j} \sum_{t>t'=-\tau_{ij}+1} \rho_{ijk} X_{ij't'} \leq \rho_{r}^{max}, \quad \forall r, t, s
\]
Proposition 6. If variables $X_{ijts}$ and $R_{rts}$ are subject to NACs, then outsourcing decisions $R^0_{rts}$ for $r \in \mathbb{R}^k$ satisfy nonanticipativity in an optimal solution.

Proposition 7. If variables $X_{ijts}$ and $R_{rts}$ are subject to NACs, then expansion/contraction decisions $R^0_{rts}$ satisfy non-anticipativity in an optimal solution.

Proposition 8. For consumable resources, if variables $X_{ijts}$ are subject to NACs, and $c_n^E > c_{n'}^E, \forall t' > t$, variables $R_{rts}$ satisfy non-anticipativity in an optimal solution.
General Precedences and Shared Tasks

- Process development and capacity planning in parallel with drug development
- Manufacturing facilities, shared among many drugs, built in parallel

General sequencing constraint (modified):

\[
\sum_{t'=1}^{[T]} (|T| - t') X_{ij}'s \leq \sum_{t'=1}^{[T]-\tau_{ik}} (|T| - t' - \tau_{ik}) X_{iks}'s, \quad \forall i, j, k, s \mid (i, k) \in P_{ij}
\]

- Allows successor tasks to remain idle throughout the horizon
- Fewer constraints than standard RCPSP sequencing constraints
- Less tight but computationally equivalent if not better
Other Extensions

- **Probability interdependencies**
  - Results from a clinical trial provide information that can be used in the future
    - Clinical trials are *modified* after results become available
    - Probability of success depends on the order in which drugs are developed
    - MSSP not suited to address this problem
  - Two drugs based on similar compounds/chemistry
    - If one trial fails it is likely that the other will also fail
    - Interdependency given as conditional probability; order of trials is not important
    - Scenario probabilities (modified) can be calculated prior to optimization

- **Other interdependencies**
  - Resource use: reduced resource requirements if two tasks are performed in parallel
  - Revenue: Competitive (complementary) products leading to lower (higher) revenue

- **Risk management**
  - Downside risk
  - Probabilistic constraints
  - Value-at-risk (VaR) and conditional-value-at-risk (CVaR)
    - *Hard* to model because scenarios are not preranked
    - Developed MIP formulation and some tightening constraints
    - Can model VAR/CVaR even if not in the objective
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Example 1

- 3 drugs
- 2 resource types;
- 3-year horizon divided into 12 3-month periods

Decision tree at optimal solution

Gantt charts and resource profiles

Probability density and cumulative distribution of NPV

- Scenarios

- Stages (3-month time periods)

- Decision tree at optimal solution

- Gantt charts and resource profiles

- Probability density and cumulative distribution of NPV
Example 2

- 4 drugs entering PI
- 4-year horizon divided into 8 6-month periods
- Outlicensing

**No risk management**

No risk constraints
ENPV = $366 M
\( p(\text{NPV}<0) = 40\% \)
Risk = $10 M

**Probabilistic:**

\( p(\text{NPV}<0) \leq 20\% \)
ENPV = $322 M
\( p(\text{NPV}<0) = 20\% \)
Risk = $10 M

**Downside risk:**

Risk \( \leq $6 \) M
ENPV = $221 M
\( p(\text{NPV}<0) = 50\% \)
Risk = $6 M

Outlicense at least one drug
Outlicense at least one drug or stop development
Example 3

- Four drugs have to undergo three clinical trials (PI, PII, PIII)
- Multi-stage SP formulation: 8 stages, 256 scenarios

Risk Management Approaches

1. Risk neutral
2. Probabilistic constraints
   \[ p(NPV < 0) \leq 0.2 \]
3. Downside risk
   \[ \sum_s p_s NPV \leq 35M \]
4. Conditional value-at-risk, \( a = 0.05 \)
5. Value-at-risk, \( a = 0.05 \)
Conclusions

- **Modeling methods**
  - No auxiliary binaries to model NACs
  - Resource planning; general precedence constraints
  - Task interdependencies
  - Risk-management methods

- **Theoretical properties for NACs**

- **Novel branch-and-cut algorithm**

- **Methods applicable to a wide range of problems**
  - General stochastic programming problems
  - Problems under endogenous uncertainty observation
  - *Sequential* decision making