Improving Agricultural Systems with Stochastic Optimization

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Themes

• Agricultural systems naturally include many uncertainties and potential for optimizing systems

• Even simple systems with a small number of alternatives can yield solutions that differ structurally from any single scenario solution (and from any combination of scenario solutions)

• Optimization can particularly add to systems with learning from delayed observations
Outline

• Overall model structure
• A problem for a farmer
• Model value concepts and generalizations
• Learning from trials with observation delay
• Impact in a healthcare example
• Conclusions
The Farmer Problem

Total area: 500 acres

Corn?  |  Beets?  
-------|--------
Wheat? |        

Decision: How much to plant of each crop?
Farm Parameters

• Livestock requirements
  – 200 Tons of wheat
  – 240 Tons of corn

• Prices
  – Wheat: $170/ton to sell/ $238/ton to buy
  – Corn: $150/ton to sell/ $210/ton to buy
  – Beets: $36/ton up to 6000 ton (quota); $10/ton if over

• Planting costs
  – Wheat: $150/acre; Corn: $230/acre; Beets: $260/acre

• Yields (means)
  – Wheat: 2.5 tons/acre; Corn: 3 tons/acre; Beets: 20 tons/acre
Deterministic Farmer’s Problem

• Formulation

Min $150x_1 + 230x_2 + 260x_3$
  $+ 238a_1 - 170v_1 + 210a_2 - 150v_2 - 36v_3 - 10v_4$

s.t. $x_1 + x_2 + x_3 \leq 500$ (acres)

$2.5x_1 + a_1 - v_1 = 200$ (wheat)

$3x_2 + a_2 - v_2 = 240$ (corn)

$20x_3 - v_3 - v_4 = 0$ (beets)

$v_3 \leq 6000$ (quota)

$x_1, x_2, x_3, a_1, a_2, v_1, v_2, v_3, v_4 \geq 0$

Note: 5 constraints => 5 basic variables

SOLUTION: WHEAT  CORN  BEETS

ACRES ($x_i$) = 120  80  300

YIELD = 300  240  6000

PROFIT = $118,600 per season

2 Constraints – No Slack
Adding Uncertainty

• **Key Parameter: Yield Uncertainty**
  – While planting the field, the farmer does not know how much each field will yield because of weather, pests, seed variation, etc.

• **Alternatives:**
  – Ignore the variation (i.e., use mean estimates)
  – Try *scenario analysis*:
    See what is best for each possible outcome.
Scenario Analysis

- Random Factor: *Weather*
  - Yield variations: +/- 20% of the mean

- Scenario Approach
  - A - *Optimistic* - Assume +20%
    
    **SOLUTION:** WHEAT  CORN  BEETS
    
    ACRES (xi)= 183  67  250  
    YIELD = 550  240  6000  
    PROFIT= $167,667 per season

  - B - *Pessimistic* - Assume -20%
    
    **SOLUTION:** WHEAT  CORN  BEETS
    
    ACRES (xi)= 100  25  375  
    YIELD = 200  60  6000  
    PROFIT= $59,950  per season

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Scenario Solutions

• We have 5 constraints (acreage, livestock needs (3), high-price beet quota)

• Linear programs have corner (or extreme) point solutions with equal numbers of basic (non-zero) variables and constraints

• We must have 5 basic variables (3 for planting, 1 for beets, then one other)

• Other – slack on livestock need or over-beet quota (so, buy/sell 1 grain or over-beets)
Other Alternative: Stochastic Program to Combine Decisions

- **ASSUME:** Plant without knowing future
  - Suppose each scenario equally likely (prob. = 1/3 each)
  - Place in a single mathematical program (optimization model)
- **GOAL:** maximize expected profits
  - (risk neutral)
- **FORMULATION:**

\[
\min_{x \in X} E[f(x, \xi)]
\]

\[
\begin{align*}
\text{Min} & \quad 150x_1 + 230x_2 + 260x_3 \\
& + \frac{1}{3} \sum_{i=1,3} (238a_{1i} - 170v_{1i} + 210a_{2i} - 150v_{2i} - 36v_{3i} - 10v_{4i}) \\
\text{s.t.} & \quad x_1 + x_2 + x_3 \leq 500 \text{ (acres)} \\
& \quad (1 + 0.2(2-i))2.5x_1 + a_{1i} - v_{1i} = 200 \text{ (wheat)} \\
& \quad (1 + 0.2(2-i))3x_2 + a_{2i} - v_{2i} = 240 \text{ (corn)} \\
& \quad (1 + 0.2(2-i))20x_3 - v_{3i} - v_{4i} = 0 \text{ (beets)} \\
& \quad v_{3i} \leq 6000 \text{ (quota)} \\
& \quad x_1, x_2, x_3, a_{1i}, a_{2i}, v_{1i}, v_{2i}, v_{3i}, v_{4i} \geq 0
\end{align*}
\]
Stochastic Program Setup

DM: Decides Now: Plant x acres

Nature: Picks yield

High: DM: How much to buy/sell

Medium: DM: How much to buy/sell

Low: DM: How much to buy/sell
Stochastic Program Solution

• Variables: 3 for x (acres)
  6 for each scenarios for buy/sell (under/over limit for beats)

• Constraints: 1 for acres;
  4 for each scenario

• So, 3+3*6=18 variables; 1+3*4=13 constraints

• Basic variables: 3 for acres, 3 for beets below quote, plus 7 more (2 each scenario plus 1) or **2 tight constraints with no slack**
Stochastic Solution

**SOLUTION:**

<table>
<thead>
<tr>
<th>Crop</th>
<th>Acres ($x_i$)</th>
<th>YIELD (Lo)</th>
<th>YIELD (Mn)</th>
<th>YIELD (Hi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>170</td>
<td>340</td>
<td>425</td>
<td>510</td>
</tr>
<tr>
<td>Corn</td>
<td>80</td>
<td>192</td>
<td>240</td>
<td>288</td>
</tr>
<tr>
<td>Beets</td>
<td>250</td>
<td>4000</td>
<td>5000</td>
<td>6000</td>
</tr>
</tbody>
</table>

**EXPECTED PROFIT = $108,390/season (Recourse Problem (RP))**

**Key Observation:** Two tight (no-slip) constraints in different scenarios (can never happen with single scenario model)

- **Expected Value of Perfect Information**
  - USE expected value with perfect information (wait-and-see) = WS
    
    \[ WS = \frac{1}{3}(166,667 + 118,600 + 59950) = 115,406 \]
  - EVPI = WS - RP = $7,016

- **Value of the Stochastic Solution (VSS)**
  - RP minus expected value of using solution with means (result of ignoring uncertainty) (EMS=$107,240)
  - VSS = RP - EMS = $1,150
Observations

• In the deterministic (single-scenario) linear program, two constraints are binding.

• In the stochastic l.p., two constraints are tight binding but *in different scenarios*.

• *No single-scenario linear program can reproduce the stochastic program solution*.

• *In fact, it is possible that no combination of single-scenario solutions can reproduce the stochastic solution*.

• *The alternative future scenarios create a non-linear adjustment for risk/uncertainty (even without including risk aversion)*.
Generalization: Variety Development

• Suppose the goal is to plant in different locations and different seasons to find the greatest yielding varieties under varying conditions

• Yields may be functions of base values, local conditions, and random variation

• Decisions can represent crop assignments for each location and planting period

• Multiple stages can represent updated probabilities on each variety and sequential planting decisions

• Result is a comprehensive and adaptive optimization model
Variety Design as Clinical Trial Design

• Determining varieties to cross and breed represents a form of multi-armed bandit with multiple correlations

• Designs in this framework should be adaptive to outcomes and continuously represent tradeoffs between exploration and exploitation
Clinical Trial Context*

• Clinical trials of drugs absorb significant resources from the economy (40% of Pharma R&D - $30+ billion)
• Standard (fixed design) studies are inefficient (i.e., do not optimize the use of resource)
• Adaptive designs can make better uses of resources (and be better for patient subjects)
• Fully adaptive designs can be used in multiple settings to save cost and time and improve outcomes

* Ahuja and B (EJOR 2016)
The price of bringing a new drug to market is, on average, $1 billion.

Total expense of advancing a new drug from the chemistry stage to the market are as high as $2 billion.
Drug Development and Approval

**DRUG DISCOVERY**

- 10,000 compounds

**Pre-CLINICAL TRIALS**

- Phase I: 20-100 subjects
  - Safety
- Phase II: 100-500 subjects
  - Own Efficacy
- Phase III: 1000-5000 subjects
  - Treatment vs. Control

**FDA Review**

- 1 FDA approved drug

**Manufacturing**

- 2 Years

**Timeframes**

- 5 Years
- 1.5 Years
- 6 Years
- 2 Years
- 2 Years

*Note: The image illustrates the stages of drug development and approval, including drug discovery, pre-clinical trials, clinical trials (Phase I, II, III), FDA review, and manufacturing.*
Traditional Method: Fixed Randomized Design

Advantages
- Well – understood
- Clean way of separating treatments
- When patients need to be followed until end
Compared effectiveness of older vs. newer drugs for treating schizophrenia

Largest, Longest, most comprehensive independent study every conducted

Randomized design, multi-armed trial

1500 patients, $42.6 m, 18 months, multiple sites

Inconclusive → ONLY 26% subjects completed the trial

Treatment of narrowing of a brain artery

Randomized design, two arms

Control arm: Medication alone

Treatment arm: Medication + Stent

451 patients enrolled on a rolling basis (3-4 patients/wk)

Failure: Stroke/Death within 30 days of giving treatment

Actual Failure Rate: 10.2%

Study Is Ended as a Stent Fails to Stop Strokes

By GINA KOLATA
Published: September 7, 2011
Fixed to Adaptive Designs

**Fixed**
- All treatment assignments fixed a priori (i.e., total number of patients to receive each treatment)
- Final analysis based on purely frequentist statistics (i.e., no use of prior information)
- Results set for maintaining Type I (false positive) error rate (with potential for early termination examining Type II (false negative) error rate)

**Adaptive**
- Treatment assignments can vary explicitly according to the results of the trial
- Analysis based on Bayesian model potentially using prior information (and trial observations)
- Allows for frequentist interpretations (but with different analysis since treatment choices no longer independent)
Adaptive Design

Common Adaptive Designs: Consider a SINGLE trial per period or observation (i.e., no delay to observe)

Multi-arm Bandit Formulation
- Reallocation decisions?
- Observation vs. Exploration tradeoff
- Flexible and adapts to each trial response
- Produces quicker results
Adaptive Designs: Long Sequential Trial (Berry)

- Treatments: A (new) and B (existing or placebo)
- Prior: (Expected) probability that A is successful (or better than B) and confidence in that result (e.g., probability is $\frac{1}{2}$ and minimal confidence for uninformed prior)
- Trial: treatment with A or B
- Observation: Result improves or not (success or not)
- Updating: Prior is updated to posterior – probability of success given prior and observation
- GOAL: Use a fixed number N of observations in the most efficient (maximum total number of successes or maximize chance of finding the best treatment) manner
How Much Better is Adaptive?

- Objective: Maximum number of successes (efficient and most humane for human health)
- Prior: A and B both given with uninformative prior with probability $\frac{1}{2}$ of success
- Fixed trials with $N$ patients: $N/2$ successful outcomes expected
- Optimal adaptive trial (observing each patient before next trial): $2N/3$ successes expected (Berry 1978)

Adaptive Advantage: $N=1000$ patients: ~667 successes with adaptive versus 500 successes with fixed (increase of 1/3)

Similar results for number of trials $N$ for outcomes to fixed probability of finding better treatment
Why Not Use (Sequential) Adaptive?

- Requires observation of each patient outcome before the next allocation
  - May be reasonable for small trials with quickly observed results (and many potential treatments, e.g., ISPY-2)
  - Not reasonable for large trials with some delay before outcome can be observed

- Potential resolution: After $K$ observations for a batch of $M$ patients, give all patients ($K+1, \ldots K+M$) the treatment (or treatment probability) that is optimal in sequential adaptive for patient $K$ (out of $N$)
  - Problem: this could lead to many patients receiving the same treatment
Example of Sequential Adaptive Issues

- Consider a trial with three treatments: A, B, and C and two remaining periods (1 and 2)
- M=N/2 observations in each period
- From prior observations, C is slightly preferred => All M trials in period assigned to C
- 1/3 (+\epsilon) chance that C is best

⇒ Exp. Number of trials receiving the best treatment:
  \sim (1/3)(N/2)+(2/3)(N/4)=N/3

Best possible: Give A,B,C to M/3 in first period then all to best:

⇒ Exp. Number given of patients receiving the best treatment:
  \sim (1/3)(N/2)+(N/2)=2N/3
**Sequential Adaptive**

**Stage 1:** All assigned to C

- C succeeds (1/3+)
- C fails (2/3-)

**Stage 2:** All assigned to C

**Stage 2:** Half to A/B
Fully Adaptive

Stage 1: 1/3 to A/B/C

- C succeeds (1/3+)
- B succeeds (1/3-)
- A succeeds (1/3-)

Stage 2:
All assigned to best
Fully Adaptive Advantage

• By anticipating the learning from the first stage, the optimal fully adaptive design can ensure 2 times as many patients receive the best possible treatment

• Challenge: how to find the optimal treatment with large numbers of patients and periods observation
Ahuja/B (2016) Fully Adaptive Effects

- Idea: exploit learning from all trials

With large numbers of trials: up to 100% better (number of successes) than sequential adaptive.

With 4 trials: up to 8.6% improvement (relative to sequential adaptive) in expected outcomes.
### Gains from Joint Learning

(Uniform starting priors)

<table>
<thead>
<tr>
<th>% improvement in Objective Value</th>
<th>24 observations</th>
<th>48 observations</th>
<th>72 observations</th>
<th>96 observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint vs. Isolated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 patients</td>
<td>0.00%</td>
<td>2.00%</td>
<td>4.00%</td>
<td>6.00%</td>
</tr>
<tr>
<td>3 patients</td>
<td>20.00%</td>
<td>22.00%</td>
<td>24.00%</td>
<td>26.00%</td>
</tr>
<tr>
<td>4 patients</td>
<td>30.00%</td>
<td>28.00%</td>
<td>26.00%</td>
<td>24.00%</td>
</tr>
</tbody>
</table>

| Joint vs. Fixed                 |                |                |                |                |
| 2 patients                      |                |                |                |                |
| 3 patients                      |                |                |                |                |
| 4 patients                      |                |                |                |                |

---

**Joint vs. Isolated**

**Joint vs. Fixed**
Learning Objective

*Equal Allocation* design

- mimic randomized design

**Objective:** Maximize Expected Confidence of finding the better treatment at the end
  - 2 Treatments
  - 2 Outcomes: \{s,f\}
  - 91 sets of starting priors

**Gain from Joint Learning design**

- Only depends on obs.
- Decreases in Obs.

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![Graph showing % improvement in Objective Value vs. Number of Observations](chart.png)
What have we learned so far…

For a given number of patients and time horizon, Joint Learning design yields:

• Higher expected proportion of successes
• Higher learning about the treatment efficacy

To achieve a given level of patient successes or learning, Joint Learning uses:

• Fewer time periods AND/OR fewer trials
Application to a Stent Trial

- Treatment of narrowing of a brain artery
- Randomized design, two arms
  - Control arm: Medication alone
  - Treatment arm: Medication + Stent
- 451 patients enrolled on a rolling basis (3-4 patients/wk)
- Failure: Stroke/Death within 30 days of giving treatment
- Actual Failure Rate: 10.2% (46 deaths)
- Hypothetical Fully Adaptive: 6.4% (29 deaths): 17 fewer lives lost

Question: Can we reduce the failures with adaptive design?
Indications for Fully Adaptive

• Early observations
  – Acute treatments
  – Well-documented intermediate outcomes

• Potential for multiple treatment protocols

• New populations for each period

=> Can include many possible alternatives and interactions as in variety designs
Needs for Full Variety Design Implementations

• Approximation using Approximation Dynamic Programming (ADP) and state space reduction

• Upper and lower bounds on learning to guide action selection

• Efficient Monte Carlo generation using importance sampling

• Markov chain Monte Carlo to allow for non-conjugate priors
Conclusions/Takeaways

• Stochastic optimization models can provide solutions for variety evaluation that are not captured in individual scenario models

• Adaptive trial designs offer potential efficiency for variety design but original sequential adaptive designs are often costly or ineffective

• Fully adaptive trial designs can be implemented for many studies to reduce costs and improve patient outcomes

• Significant opportunities for use of ADP and MCMC to improve the use of bandit models in optimizing selection
Need More evidence?

http://clinicalresearchcartoons.blogspot.com/2012/05/clinical-trials-randomization.html

**Clinical Trials: Randomization**

BY: Shivendra Pal

**MAY I KNOW THE REASON BEHIND GETTING FAVORABLE RESULTS IN THIS CLINICAL TRIAL?**

**RANDOMIZATION..!!! ALL THE INVESTIGATORS WERE RANDOMIZED AT DIFFERENT SITES FOR THIS STUDY....**

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