Determining an Optimal Schedule for Pre-mixing Chemotherapy Drugs

Donald Richardson
Research Team

Hassan Abbas, Nursing Student

Jérémy Castaing, PhD Candidate in Industrial and Operations Engineering

Ajaay Chandrasekaran, Computer Science Student

Chhavi Chaudhry, Student in Industrial and Operations Engineering

Amy Cohn, Ph.D., Associate Director, CHEPS

Diane Drago, Patient & Family Advisory Board

Marian Grace Boxer, MD, Patient & Family Advisory Board

Corinne Hardecki, RN, Clinical Care Coordinator

Madalina Jiga, Nursing Student

Pamela Martinez, Student in Industrial and Operations Engineering

Carol McMahon, RN, Nurse Supervisor, Infusion

Matthew Rouhana, Student in Industrial and Operations Engineering
Outline

• Background
  – General Patient Flow
  – Define Premix
  – Goal
  – Motivation
  – Literature

• Problem Description
  – Probabilities of wasting drugs
  – Static Model

• Future Steps
Outline

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• Future Steps
General Patient Pathway (UMCCC)

Overview:

1. Patient Arrives
2. Phlebotomy/ Labs Collected
3. Clinic Appointment
4. Chemotherapy Infusion
5. Pharmacy Preparation
6. Patient Discharged

Patient Flow

Information Flow
What is Pre-mix?

• Anytime you mix a drug before a patient is deemed ready to receive it
  – Generally you don’t pre-mix drugs due to risk in wastage cost
  – Consider the trade off between waste cost and reduced patient waiting time
UMCCC Current Pre-mix Policy

• Will only mix drugs during a fixed window of time before patients arrive
  – 6am-8am

• Have a fixed list of drugs they are willing to mix
  – Based on Cost and common use
Goal

• Reduce patient waiting time

• Best case without pre-mix
  – patient will wait duration of mixing drug (~30-60min)

"This is the pre-pre-pre-waiting room, sir. You have 3 other waiting rooms to wait in before you see the doctor...if it isn't too late in the day."
Motivation

- **Cancer**
  - Second leading cause of death in the U.S.
  - ~1.6 million estimated cases in 2015
  - More than half require Chemotherapy treatment

- **Infusion centers**
  - Increased outpatient demand leads to undesirable outcomes such as:
    - Increased patient waiting times
    - Overworked staff


- Used static (i.e. state-independent) policies
- Much smaller than UMHS
- Analyzed queuing modeling using simulation
- Pre-mixing does prove to have positive outcomes
- Cost associated with patient wait in cancer care
Outline

• Background
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  – Goal
  – Motivation
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• Problem Description
  – Probabilities of wasting drugs
  – Static Model

• Future Steps
  – Introduce Dynamic model
Description of Problem (Static)

• We will also consider having a fixed window for pre-mix

• Assumptions
  – All drugs will last for all patient scheduled that day (most last 12 hours)
  – Only make L drugs at a time
  – All drugs take 30 minutes to make
Probability of Wasting a Drug

• We first say all patients have a probability of $p$ to defer on any given day. Assume we have $n$ patients scheduled to receive the same drug on a given day. We want the probability of wasting each dose we decide to premix.
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Prob(\text{Wasting 1}\text{st dose}) = p^4
$$
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$$Prob(\text{Wasting 1}^{st} \text{ dose}) = p^4$$

$$Prob(\text{Wasting 2}^{nd} \text{ dose}) = \binom{4}{3} p^3 (1 - p) + p^4$$
Probability of Wasting a Drug

- We first say all patients have a probability of $p$ to defer on any given day. Assume we have $m_d$ patients scheduled to receive the same drug on a given day. We want the probability of wasting each dose we decide to premix.

\[
\text{Prob}(\text{Wasting } 1^{st} \text{ dose}) = p^4
\]

\[
\text{Prob}(\text{Wasting } 2^{nd} \text{ dose}) = \binom{4}{3} p^3(1 - p) + p^4
\]

\[
\text{Prob}(\text{Wasting } n^{th} \text{ dose}) = \sum_{i=1}^{n} \binom{m_d}{m_d - i + 1} p^{m_d-i+1} (1 - p)^{i-1}
\]
• The previous formulation considers all patients to have equal probability of deferral. However this could depend on

• age
• sex
• treatment
• type of cancer
• etc.
Let’s now consider the probability of wasting a particular dose given patient $i$ has a probability of deferral $p_i$.

Let’s define a new set $S_d$ which is the total number of patients scheduled to receive drug $d$ for the day. $S_d=\{1,2,\ldots,m_d\}$
• Let’s now consider the probability of wasting a particular dose given patient $i$ has a probability of deferral $p_i$.

• Let’s define a new set $S_d$ which is the total number of patients scheduled to receive drug $d$ for the day. $S_d=\{1,2,...,m_d\}$.

$$\text{Prob( Wasting 1^{st} dose)} = \prod_{i \in S_d} p_i$$
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Let’s define a new set $S_d$ which is the total number of patients scheduled to receive drug d for the day. $S_d=\{1,2,...,m_d\}$.

\[
\text{Prob}(\text{Wasting 1}\text{st dose}) = \prod_{i \in S_d} p_i
\]

\[
\text{Prob}(\text{Wasting 2}\text{nd dose}) = \sum_{i \in S_d} \left[ (1 - p_i) \prod_{j \in S_d \setminus i} (p_j) \right] + \prod_{i \in S_d} p_i
\]
Probability of Wasting a Drug (Cont.)

- Let’s now consider the probability of wasting a particular dose given patient $i$ has a probability of deferral $p_i$.
- Let’s define a new set $S_d$ which is the total number of patients scheduled to receive drug $d$ for the day. $S_d=\{1,2,...,m_d\}$.

\[
\begin{align*}
\text{Prob}(\text{Wasting 1}^{st}\ \text{dose}) &= \prod_{i \in S_d} p_i \\
\text{Prob}(\text{Wasting 2}^{nd}\ \text{dose}) &= \sum_{i \in S_d} \left[ (1 - p_i) \prod_{j \in S_d \setminus i} (p_j) \right] + \prod_{i \in S_d} p_i \\
\text{Prob}(\text{Wasting 3}^{rd}\ \text{dose}) &= \sum_{i \in S_d} \sum_{j \in S_d \setminus i} \left[ (1 - p_i)(1 - p_j) \prod_{k \in S_d \setminus \{i,j\}} p_k \right] + \sum_{i \in S_d} \left[ (1 - p_i) \prod_{j \in S_d \setminus i} (p_j) \right] + \prod_{i \in S_d} p_i
\end{align*}
\]
Probability of Wasting a Drug (Cont.)

• Currently receiving/analyzing data to determine how to best categorize patients

• Current model will only vary the probability of deferral by drug not by patient type
Model Description

Sets

- D: set of drugs d (50 mg of Taxotere)
- T: set of time units (each being 30 min)

Variable

\[ x_{nt}^d = \begin{cases} 
1 & \text{if we mix the nth dose of drug } d \text{ at time } t \\
0 & \text{o.w.} 
\end{cases} \]

\[ y_n^d = \begin{cases} 
1 & \text{if we don’t mix the nth dose of drug } d \\
0 & \text{o.w.} 
\end{cases} \]
Objective

- We first define our Expected Waste cost of a drug with the following:
  \[ E_n^d[waste \ cost] = \sum_{w=1}^{n} c_d P_d(w) \]

- Then we maximize of the difference of Projected Savings – Expected Waste
  \[ \text{maximize} \sum_{d} \sum_{n} \sum_{t} (\Delta_d - E_n^d[waste \ cost]) \times x_{nt}^d \]

Parameters

- \( \Delta_d \): The reward/savings for mixing drug \( d \)
- \( T \): is the total time units for the premix period.
- \( c_d \): cost of drug \( d \)
- \( n[d] \): the number of doses needed for each drug based on the scheduled patients
- \( M \): very large number
Constraints

\[ \sum_{t} x_{nt}^d + y_{n}^d = 1 \quad \forall d, n \] (1)

Relate our auxiliary variable to the decision variable

Parameters

- \( \Delta_d \): The reward/savings for mixing drug \( d \)
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- \( n[d] \): the number of doses needed for each drug based on the scheduled patients
- \( M \): very large number
Constraints

\[ \sum_t x_{nt}^d + y_n^d = 1 \quad \forall d, n \]  

\[ y_n^d \leq y_{n+1}^d \quad \forall d, n = 1..N[d] - 1 \]  

Must make the first dose before making 2\textsuperscript{nd}, 3\textsuperscript{rd}, …

Parameters

- \( \Delta_d \): The reward/savings for mixing drug \( d \)
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Constraints

\[ \sum_{t} x_{nt}^{d} + y_{n}^{d} = 1 \quad \forall d, n \quad (1) \]

\[ y_{n}^{d} \leq y_{n+1}^{d} \quad \forall d, n = 1..N[d] - 1 \quad (2) \]

\[ \sum t x_{nt}^{d} \leq \sum t x_{n+1t}^{d} + M * y_{n+1} \quad \forall n, d \quad (3) \]

**Dose ordering**

**Parameters**

- \( \Delta_d \): The reward/savings for mixing drug \( d \)
- \( T \): is the total time units for the premix period.
- \( c_d \): cost of drug \( d \)
- \( n[d] \): the number of doses needed for each drug based on the scheduled patients
- \( M \): very large number
Constraints

\[ \sum_{t} x_{nt}^d + y_{n}^d = 1 \quad \forall d, n \] (1)

\[ y_{n}^d \leq y_{n+1}^d \quad \forall d, n = 1..N[d] - 1 \] (2)

\[ \sum_{t} tx_{nt}^d \leq \sum_{t} tx_{n+1t}^d + M * y_{n+1} \quad \forall n, d \] (3)

\[ \sum_{d} \sum_{n} x_{nt}^d \leq L \quad \forall t \] (4)

Only make L at a time

Parameters

- \( \Delta_d \): The reward/savings for mixing drug \( d \)
- \( T \): is the total time units for the premix period.
- \( c_d \): cost of drug \( d \)
- \( n[d] \): the number of doses needed for each drug based on the scheduled patients
- \( M \): very large number
Constraints

\[ \sum_{t} x_{nt}^d + y_n^d = 1 \quad \forall d, n \tag{1} \]

\[ y_n^d \leq y_{n+1}^d \quad \forall d, n = 1..N[d] - 1 \tag{2} \]

\[ \sum_{t} tx_{nt}^d \leq \sum_{t} tx_{n+1t}^d + M \cdot y_{n+1} \quad \forall n, d \tag{3} \]

\[ \sum_{d} \sum_{n} x_{nt}^d \leq L \quad \forall t \tag{4} \]

\[ \sum_{t} x_{nt}^d \leq 1 \quad \forall n, d \tag{5} \]

can only make the nth dose of a drug once

Parameters

- \( \Delta_d \): The reward/savings for mixing drug \( d \)
- \( T \): is the total time units for the premix period.
- \( c_d \): cost of drug \( d \)
- \( n[d] \): the number of doses needed for each drug based on the scheduled patients
- \( M \): very large number
Example

- Suppose we have patient scheduled to receive 15 different drugs.
- Each takes 30 min to make

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hang by</th>
<th>Price</th>
<th>Currently pre-mixed</th>
<th>Treatment for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>12 hrs</td>
<td>2.52</td>
<td>Yes</td>
<td>cancer of the ovaries, head, and neck</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>12 hrs</td>
<td>4.10</td>
<td>Yes</td>
<td>cancer in the lungs, ovary, or breast</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>12 hrs</td>
<td>879.00</td>
<td>Yes</td>
<td>leukemia and lymphomas, and nephrotic syndrome.</td>
</tr>
<tr>
<td>Folotyn</td>
<td>12 hrs</td>
<td>4637.21</td>
<td>No</td>
<td>T-cell lymphoma</td>
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<tr>
<td>Adcetris</td>
<td>12 hrs</td>
<td>6516.00</td>
<td>No</td>
<td>Treats Hodgkin's lymphoma and systemic anaplastic large cell lymphoma</td>
</tr>
</tbody>
</table>
Example Scenarios

• Scenario 1
  – Reward: 1 for all drugs
  – Doses: 2 for each drug
  – \( P_d(n) \): \( p=.25 \) for all drugs
Example Scenarios

- **Scenario 1**
  - Reward: 1 for all drugs
  - Doses: 2 for each drug
  - $P_d(n)$: $p=.25$ for all drugs

- **Scenario 2**
  - Reward: 11.67 for all drugs
  - Doses: 2 for each drug
  - $P_d(n)$: inverse to cost of drug ranging from .02 to .30
Example Scenarios

- **Scenario 1**
  - Reward: 1 for all drugs
  - Doses: 2 for each drug
  - $P_d(n)$: $p=.25$ for all drugs

- **Scenario 2**
  - Reward: 11.67 for all drugs
  - Doses: 2 for each drug
  - $P_d(n)$: inverse to cost of drug ranging from .02 to .30

- **Scenario 3**
  - Reward: 11.67 for all drugs
  - Doses: Lower cost drugs only have 1-2 patients scheduled to receive them while higher cost drugs have 3 to 5 patients scheduled to receive them.
  - $P_d(n)$: inverse to cost of drug ranging from .02 to .30
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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<tr>
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<tr>
<td>D</td>
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<tr>
<td>E</td>
<td>$16.56</td>
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<tr>
<td>F</td>
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<td>G</td>
<td>$91.54</td>
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<tr>
<td>H</td>
<td>$155.56</td>
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<tr>
<td>I</td>
<td>$367.02</td>
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<tr>
<td>J</td>
<td>$698.60</td>
</tr>
<tr>
<td>K</td>
<td>$879.00</td>
</tr>
<tr>
<td>L</td>
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</tr>
<tr>
<td>M</td>
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<tr>
<td>N</td>
<td>$4,637.21</td>
</tr>
<tr>
<td>O</td>
<td>$6,516.00</td>
</tr>
<tr>
<td>TOTAL</td>
<td>—</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cost</th>
<th>Scen. 1</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>B</td>
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**Scenario 1**
Objective Value = 3.36
E[Waste] = 1.64

**Scenario 2**
Objective Value = 87.7
E[Waste] = 5.70

**Scenario 3**
Objective Value = 92.23
E[Waste] = 1.17
Outline

• Background
  – General Patient Flow
  – Define Premix
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  – Motivation
  – Literature

• Problem Description
  – Probabilities of wasting drugs
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• Future Steps
Next Steps

- **Static Model**
  - Consider
    - Hang-by time for various drugs
    - Preparation time for various drugs
  - Continue working with data collection to run logistical regression
    - How to categorizes types of patients

- **Dynamic Model**
  - Goal: To find an optimal drug-mixing schedule throughout the day and update as we observe patient deferrals
Thank You!

Contacts
Donald Richardson
donalric@umich.edu
CHEPS
http://cheps.engin.umich.edu
Appendix

• States – 3-dimensional
  – t: Time of day we are making the decision
  – O: List of orders for patients scheduled that day
  – S: Inventory of premixed drugs

• Actions
  – Mix a certain drug or not mix at all: $A = \{ o \in O, \emptyset \}$

• Stages
  – [0,T] in 15 min intervals

• Rewards
  – Expected reward of mixing drug o at time t
Replace with updated version

\[ v(t, O, S) = \max_{o \in O} \left\{ R(o, t) + p(o)v(t', O \setminus o, S \cup \{o\}) + (1 - p(o))v(t', O \setminus o, S) \right\} \]

where:

- \( p(o) \) is the probability of deferral of patient receiving order \( o \)
- \( R(o, t) \) is the expected reward of preparing order \( o \) at time \( t \)
- \( v(t', O', S') \) is the expected reward after we prepared order \( o \).

Work started by Sarah Bach Jeremy Casting
Appendix

- For $|O|$ moderately low
  - Use backward induction

- For $|O|$ otherwise
  - State space blows up!
  - Approximate Dynamic programming