Nonparametric Overdose Control for Dose Finding in Drug-Combination Trials

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Joint work with R. Lin and G. Yin
Phase I Trial Design

- A first experimentation of a new drug in human being.
- To find a safe and potentially effective dose for future Phase II/III trials.
- Trials are typically small (20–100 patients).
- In oncology, we seek the highest possible dose level subject to dose-limiting toxicity (DLT) constraints.
- This is known as the maximum tolerated dose (MTD).
- Methods are often based on a monotonicity assumption.
- The target toxicity rate is typically between 20% to 40%.
Why Are Drugs Combined?

- Compared with single-agent treatments, combination therapies may lead to synergistic treatment effects.
- To target tumor cells with differing drug susceptibilities.
- To achieve higher dose intensities with nonoverlapping toxicities.
Challenges in Drug-Combination Trials

- Compared with the single-agent study, the dimension of the dose searching space for a multiple-agent trial increases multiplicatively.

- Drug combinations may exhibit synergistic or antagonistic effects, such that the toxicity order of dose combinations cannot be fully determined a priori.

- As multiple MTD combinations may exist in a drug-combination trial, the exploration of the entire space may be hindered by being trapped in some local regions.
Drug B

Drug A
Multi-Agent NOC

- We extend the single-agent nonparametric overdose control (NOC) design (Lin and Yin, 2016) to drug-combination trials.
- Consider a two-dimensional trial, where $J$ dose levels of drug A and $K$ dose levels of drug B are combined.
- We propose $J \times K$ models in a nonparametric way,

\[ M_{j,k} : \begin{cases} \vert p_{j',k'} - \phi \vert \leq \epsilon, & (j', k') = (j, k), \\ \vert p_{j',k'} - \phi \vert > \epsilon, & (j', k') \neq (j, k), \end{cases} \quad j = 1, \ldots, J; k = 1, \ldots, K, \]

that is, model $M_{j,k}$ indicates that dose level $(j, k)$ is the MTD combination.
Under each model $M_{j,k}$, a joint uniform prior distribution for $\mathbf{p} = (p_{1,1}, \ldots, p_{1,K}, p_{2,1}, \ldots, p_{2,K}, \ldots, p_{J,1}, \ldots, p_{J,K})^T$

$$
\begin{cases}
    p_{j',k'} | M_{j,k} \sim \text{Unif}(\phi - \epsilon, \phi + \epsilon), & (j', k') = (j, k), \\
    p_{j',k'} | \mathbf{p}_{-(j',k')}, M_{j,k} \sim \text{Unif}((l_{j',k'}, u_{j',k'})) \\
    \cap \{(p_{\text{min}}, \phi - \epsilon) \cup (\phi + \epsilon, p_{\text{max}})\}, & (j', k') \neq (j, k),
\end{cases}
$$

where $\mathbf{p}_{-(j',k')} = \mathbf{p} \setminus p_{j',k'}$ (the vector $\mathbf{p}$ excluding $p_{j',k'}$), and

$$
l_{j',k'} = \max(p_{j'-1,k'} I(j' > j), p_{j',k'-1} I(k' > k)),
$$

$$
u_{j',k'} = \min(1 - (1 - p_{j'+1,k'}) I(j' < j), 1 - (1 - p_{j',k'+1}) I(k' < k)).$$
Joint Prior Distribution

• Let $p_{\text{min}}$ and $p_{\text{max}}$ be the lower and upper bounds of the prior distribution respectively, with $0 \leq p_{\text{min}} < p_{\text{max}} \leq 1$.

• We set $\epsilon = 0.025$, $p_{\text{min}} = 0$ and $p_{\text{max}} = 0.8$ as default values.
\[ p_{2,2} \sim \text{Unif}(\phi - \epsilon, \phi + \epsilon) \]
$p_{1,2} \sim \text{Unif}(p_{\text{min}}, \phi - \epsilon)$

$p_{3,2} \sim \text{Unif}(\phi + \epsilon, p_{\text{max}})$
\[ p_{2,3} \sim \text{Unif}(\phi + \epsilon, p_{\text{max}}) \]

\[ p_{2,1} \sim \text{Unif}(p_{\text{min}}, \phi - \epsilon) \]
\[ p_{1,3} \sim \text{Unif}\left((p_{1,2}, p_{2,3}) \setminus (\phi - \epsilon, \phi + \epsilon)\right) \]

\[ p_{3,1} \sim \text{Unif}\left((p_{2,1}, p_{3,2}) \setminus (\phi - \epsilon, \phi + \epsilon)\right) \]
$p_{3,3} \sim \text{Unif}(\max(p_{2,3}, p_{3,2}), p_{\text{max}})$

$p_{1,1} \sim \text{Unif}(p_{\text{min}}, \min(p_{1,2}, p_{2,1}))$
Posterior Model Probability

- Denote $P(M_{j,k})$ as the prior probability that model $M_{j,k}$ is true, for which we typically use non-informative prior model probabilities, i.e., $P(M_{j,k}) = 1/(JK)$.

- After enrolling the $n$th patient, we can calculate the posterior model probabilities based on the accumulated information $D_n$,

$$P(M_{j,k}|D_n) = \frac{P(D_n|M_{j,k})P(M_{j,k})}{\sum_{j'=1}^{J} \sum_{k'=1}^{K} P(D_n|M_{j',k'})P(M_{j',k'})},$$

where $P(D_n|M_{j,k})$ is the marginal likelihood under model $M_{j,k}$. 
Admissible Regions

- Suppose the current dose combination is \((j_0, k_0)\). Three admissible regions are defined as

\[
R_i = \begin{cases} 
\{(j_0 - 1, k_0), (j_0, k_0 - 1)\}, & \text{if } i = -1 \text{ (De-escalation)}; \\
\{(j_0, k_0)\}, & \text{if } i = 0 \text{ (Retainment)}; \\
\{(j_0 + 1, k_0), (j_0, k_0 + 1)\}, & \text{if } i = 1 \text{ (Escalation)}.
\end{cases}
\]

- In each region \(R_i, i = -1, 0, 1\), we select the most suitable dose combination \((j_i^*, k_i^*)\) such that

\[
(j_i^*, k_i^*) = \arg \max_{(j,k) \in R_i} \Pr(M_{j,k}|D_n).
\]
Multi-Agent Nonparametric Overdose Control Design
To facilitate dose assignment, we define a loss function for action $i$ if the correct action for locating the MTD is $\gamma$,

$$L(i, \gamma) = \alpha(\gamma - i)I(i \leq \gamma) + (1 - \alpha)(i - \gamma)I(i > \gamma),$$

which corresponds to the cost for taking a wrong action.

If we choose $\alpha < 0.5$, the amount of penalty we impose on underdosing ($i \leq \gamma$) is less than that on overdosing ($i > \gamma$).

The normalized posterior probabilities for dose de-escalation, retention and escalation, $q_{-1}$, $q_0$ and $q_1$, are respectively

$$q_i = \frac{\Pr(M_{j_i^*,k_i^*} | D_n)}{\sum_{i=-1,0,1} \Pr(M_{j_i^*,k_i^*} | D_n)}, \quad i = -1, 0, 1.$$
Loss Function

- We can calculate the expected loss with respect to the normalized posterior probabilities $q_i$, 

$$
\bar{L}(i) = \sum_{\gamma=-1,0,1} q_\gamma L(i, \gamma).
$$

(2)

- The next optimal action $i^*$ and the corresponding dose combination $(j_{i^*}, k_{i^*})$ are selected by minimizing $\bar{L}(i)$,

$$
i^* = \arg\min_{i \in \{-1,0,1\}} \bar{L}(i).
$$

(3)
Nevertheless, this overdose control rule can be overly conservative.

We impose a dose-switching rule for selecting the optimal action when the information is sufficiently strong,

$$i^* = \arg \max_{i : q_i > \eta} (q_i),$$

(4)

where $\eta$ is a dose-switching cutoff of the normalized posterior probabilities.

The value of $\eta$ characterizes the amount of information needed for dose switching, and typically, we set $0.5 \leq \eta \leq 1$. 
Let $N$ be the maximum number of patients to be enrolled. When the enrollment is finished, we calculate the posterior probabilities $P(M_{j,k}|D_N)$, $j = 1, \ldots, J$ and $k = 1, \ldots, K$.

For those drug combinations $(j, k)$ at which no patient is assigned, we set the corresponding $P(M_{j,k}|D_N) \equiv 0$, i.e., we only select the MTD from the combinations that have been administered in the trial.

The dose combination $(j^*, k^*)$ with the largest value of $P(M_{j^*,k^*}|D_N)$ is selected as the MTD.
Simulation Studies

- We conduct simulation studies to compare the operating characteristics of the MANOC with other existing designs:
  - the two-dimensional Bayesian optimal interval design (2dBOIN) (Lin and Yin, 2016a),
  - the partial ordering CRM (POCRM) (Wages et al., 2011)
  - the two-agent EWOC (TEWOC) (Shi and Yin, 2013).
Simulation Studies

- Twelve different dose–toxicity scenarios are considered.
- The target toxicity probability is set to be $\phi = 0.3$.
- The maximum number of patients is $N = 60$ and the number of patients in each cohort is three.
- In the MANOC design, the tuning parameters are set as $\alpha = 0.35$, $\eta = 0.60$.
- For a fair comparison, no early stopping is allowed for all designs.
<table>
<thead>
<tr>
<th>Dose level</th>
<th>Scenario 1</th>
<th>Agent A</th>
<th>Scenario 2</th>
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<tr>
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<td>0.30</td>
<td>0.42</td>
<td>0.60</td>
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<tr>
<td>3</td>
<td>0.15</td>
<td>0.30</td>
<td>0.45</td>
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<td>2</td>
<td>0.10</td>
<td>0.20</td>
<td><strong>0.30</strong></td>
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<tr>
<td>1</td>
<td>0.08</td>
<td>0.14</td>
<td>0.19</td>
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<tr>
<th>Agent B</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
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<tbody>
<tr>
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<td><strong>0.30</strong></td>
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<td>1</td>
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<td>0.10</td>
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<table>
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<tr>
<th>Scenario 5</th>
<th>Scenario 6</th>
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<tr>
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<tr>
<td>Dose level</td>
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<td>------------</td>
<td>-----</td>
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<tr>
<td><strong>Agent A</strong></td>
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<tr>
<td>Scenario 7</td>
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<td>Scenario 8</td>
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<td>Scenario 9</td>
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<td>Scenario 10</td>
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<tr>
<td><strong>Agent B</strong></td>
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<td>Scenario 12</td>
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<td>Scenario 13</td>
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Note: The values in bold indicate the overdose levels for each agent in each scenario.
Summary Statistics

The first three statistics are related to the accuracy and efficiency of a design, are
- the percentage of selecting the correct MTD
- the percentage of patients allocated to the true MTDs
- the accuracy index ($\mathcal{AI}$), defined as

$$\mathcal{AI} = 1 - JK \left( \sum_{j=1}^{J} \sum_{k=1}^{K} w_{j,k} |p_{j,k} - \phi| \right) / \left( \sum_{j=1}^{J} \sum_{k=1}^{K} |p_{j,k} - \phi| \right),$$

where $w_{j,k}$ is the probability that dose combination $(j, k)$ is selected as the MTD.

It is considered desirable for a design to yield large values of these three statistics.
Summary Statistics

- For the safety aspects, we calculate
  - the percentage of trials selecting overdose combinations as the MTD
  - the percentage of patients allocated to overdose combinations
  - the percentage of patients experiencing the DLT.
- The overdose combinations are the dose pairs with the toxicity probabilities larger than $\phi$.
- A design is considered to be safe and ethical if the values of these three statistics are small.
29 Multi-Agent Nonparametric Overdose Control Design

![Graphs showing performance metrics for different designs.](image-url)
Conclusion

• The MANOC design transforms the two-dimensional dose-finding problem into Bayesian model selection.

• The dose–toxicity relationship is modelled solely based on the partial information of the toxicity order.

• All the information across the entire dose space can be fully integrated for decision making.

• Overdose control is achieved by minimizing an asymmetric loss function, which prevents patients from experiencing excessive toxicities.