

A Bayesian Phase I/II Design for Oncology Clinical Trials of Combining Biological Agents

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Outline

- Introduction
- Probability model
- Dose finding algorithm
- Simulation study
- Conclusion

Biological agents

- The paradigm of oncology drug development is expanding from traditional **cytotoxic agents** to novel **biological (or molecularly targeted) agents**.
- Examples of biological agents:
 - **Biospecimens** targeting a specific tumor pathway.
 - **Gene products** aiming for DNA repair.
 - **Immunotherapies** stimulating the immune system to attack a tumor.

Biological agents versus cytotoxic agents

- Cytotoxic agents
 - Toxicity and efficacy are assumed to **monotonically** increase with dose.
 - The goal is to find the **maximum tolerated dose (MTD)**.
- Biological agents
 - The toxicity is usually tolerable within the therapeutic dose range and may plateau at higher dose levels.
 - The dose-efficacy curves often follow a **non-monotonic** pattern.
 - The goal is to find the **optimal biological dose (OBD)**, defined as the dose yielding the most desirable treatment effect.

Drug-combination Trials

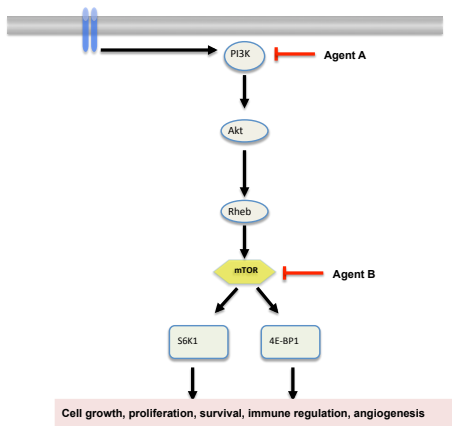
- Treating patients with a combination of agents is becoming common in cancer clinical trials.
- Most existing drug-combination trial designs concern cytotoxic agents (e.g., Thall et al., 2003; Wang and Ivanova, 2005; Yin and Yuan, 2009), thus are not applicable to the trials combining biological agents.
- **A phase I/II trial design is imperative** for biological agent combination trials because of non-monotonic dose-efficacy and -toxicity relationship.

Motivating trial

- A lymphoma trial combining two novel biological agents to target two components in the PI3K/AKT/mTOR signaling pathway.
 - Agent A is a PI3K kinase inhibitor.
 - Agent B inhibits mTOR kinase downstream in the pathway.
- 4 doses of agent A combined with 4 doses of agent B.
- Goal: to find the **biologically optimal dose combination (BODC)**, defined as the dose combination with the highest efficacy and tolerable toxicity.

Motivating trial

Targeting PI3K/AKT/mTOR signaling Pathways in Lymphoma



Proposed design

We propose a **phase I/II trial design** to identify the BODC.

- A **change-line model** is used to reflect the property that the dose-toxicity surface of the combinational agents may plateau at higher dose levels.
- A **logistic model with quadratic terms** is used to accommodate the possible non-monotonic pattern for the dose-efficacy relationship.
- We devise a **novel adaptive dose-finding algorithm** to encourage sufficient exploration of the two-dimensional dose space.

Notation

- Consider a trial of combinational biological agents
 - J doses of agent A: $a_1 < a_2 < \dots < a_J$
 - K doses of agent B: $b_1 < b_2 < \dots < b_K$
 - (a_j, b_k) : combination of dose a_j and dose b_k
 - p_{jk} and q_{jk} denote the toxicity and efficacy probabilities of dose combination (a_j, b_k)
- Goal: identify the BODC in the $J \times K$ dose matrix.

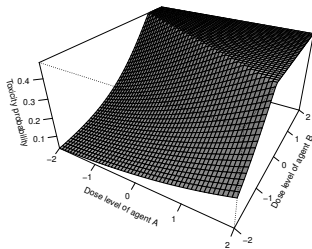
Change-line model for toxicity

We model toxicity probability p_{jk} using a change-line model:

$$\text{logit}(p_{jk}) = (\beta_0 + \beta_1 a_j + \beta_2 b_k) I(\beta_0 + \beta_1 a_j + \beta_2 b_k \leq \omega) + \omega I(\beta_0 + \beta_1 a_j + \beta_2 b_k > \omega)$$

- $I(\cdot)$: indicator function
- $\beta_1 > 0$ and $\beta_2 > 0$ such that p_{jk} initially increases with the doses of A and B
- When it reaches a plateau, the toxicity probability: $e^\omega / (1 + e^\omega)$.
- We did not include an interactive effect for the two agents because the estimation of that needs large sample

Figure : Surface of the toxicity probabilities



Logistic model for efficacy

Assume the efficacy probability q_{jk} follows a logistic model

$$\text{logit}(q_{jk}) = \gamma_0 + \gamma_1 a_j + \gamma_2 b_k + \gamma_3 a_j^2 + \gamma_4 b_k^2$$

- The quadratic terms render the model adequate flexibility to capture the non-monotonic pattern.
- We model the marginal distributions of toxicity and efficacy.
- Joint modeling is possible, but small sample size \rightarrow cannot reliably estimate the correlation parameter.

Likelihood

Suppose that at a certain stage of the trial

- n_{jk} patients are treated at the paired dose (a_j, b_k)
- x_{jk} and y_{jk} patients have experienced toxicity and efficacy, respectively.
- The marginal likelihood for the toxicity data \mathbf{x} is

$$L(\mathbf{x}|\omega, \beta) \propto \prod_{j=1}^J \prod_{k=1}^K p_{jk}^{x_{jk}} (1 - p_{jk})^{n_{jk} - x_{jk}};$$

for the efficacy data \mathbf{y} is

$$L(\mathbf{y}|\gamma) \propto \prod_{j=1}^J \prod_{k=1}^K q_{jk}^{y_{jk}} (1 - q_{jk})^{n_{jk} - y_{jk}}.$$

- The posterior distribution is

$$f(\omega, \beta, \gamma | \mathbf{x}, \mathbf{y}) \propto L(\mathbf{x} | \omega, \beta) L(\mathbf{y} | \gamma) f(\omega) f(\beta) f(\gamma)$$

where $f(\omega)$, $f(\beta)$, and $f(\gamma)$ denote the prior distributions for ω , β , and γ , respectively.

- Vague priors are used:

$$\gamma_0 \sim \text{Cauchy}(0, 10), \quad \gamma_1, \dots, \gamma_4 \sim \text{Cauchy}(0, 2.5). \quad \beta_0 \sim \text{Cauchy}(0, 10), \quad \beta_1, \beta_2 \sim \text{Gamma}(0.5, 0.5) \quad \omega \sim N(0, 4)$$

Trial design

Our design is conducted in two stages:

- Stage I (**run in**): We escalate doses along the diagonal to explore the dose-combination space quickly and collect some preliminary data.
- Stage II (**dose finding**): Based on observed efficacy and toxicity data, we continuously update the posterior estimates of toxicity and posterior means of efficacy and assign patients to the most appropriate dose.

Def: dose (a_j, b_k) is deemed safe if $\Pr(p_{jk} < \phi | \mathcal{D}) > \delta$; otherwise toxic.

- ϕ is the target toxicity upper limit and δ is a prespecified safety cutoff.

Stage I: Run-in period

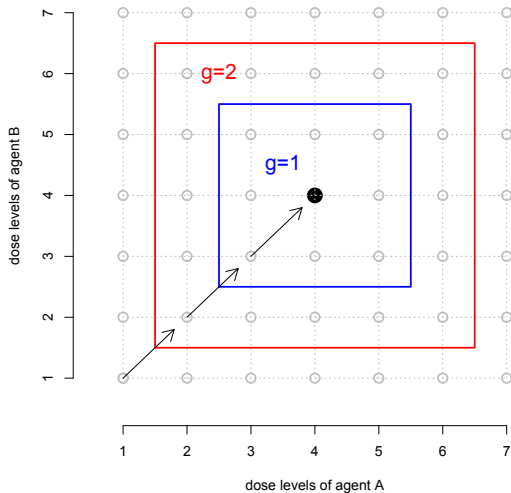
The trial starts with the treatment of the first cohort of patients at the lowest dose (a_1, b_1) .

- 1 If current dose is safe, escalate the dose along the diagonal. If (a_1, b_1) is deemed toxic, terminate the trial.
- 2 Stage I completes when either current dose is deemed toxic or the highest dose combination is reached. Stage II starts.

g -degree admissible dose set

Assume that the current dose combination is (a_j, b_k) ,

- Define **g -degree neighbors** of (a_j, b_k) , denoted by \mathcal{N}_g , as dose combinations $\{(a_{j'}, b_{k'})\}$ whose dose levels are different from (a_j, b_k) no more than g levels, i.e.,
$$\mathcal{N}_g = \{(a_{j'}, b_{k'}) : |j' - j| \leq g \text{ and } |k' - k| \leq g\}.$$
- Further define a **g -degree admissible dose set** \mathcal{A}_g , which is a subset of the g -degree neighbors \mathcal{N}_g satisfying the pre-specified safety requirement $Pr(p_{j'k'} < \phi_T | \mathcal{D}) > \delta$.

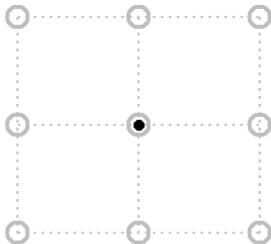


Stage II: Systematic dose finding

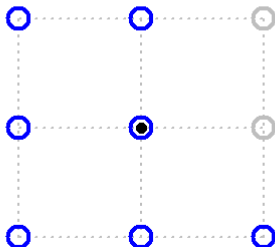
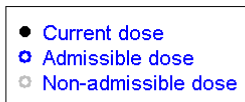
- II1 Based on the observed data, identify \mathcal{A}_{g^*} as the **nonempty set of safe neighbors of (a_j, b_k) with minimum degree g^*** . If \mathcal{A}_{g^*} does not exist (i.e., all experimental doses are deemed toxic), terminate the trial.
- II2 Among the doses in \mathcal{A}_{g^*} , identify the dose (a_{j^*}, b_{k^*}) with the **highest posterior mean of efficacy $\hat{q}_{j^*k^*}$** .

First-degree neighbors of current dose combination, \mathcal{N}_1

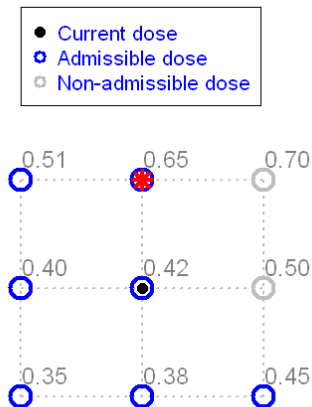
- Current dose
- First-degree neighbors



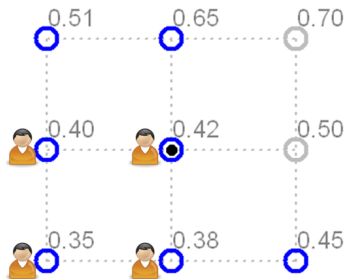
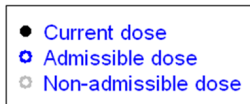
First-degree admissible dose set of current dose combination, \mathcal{A}_1

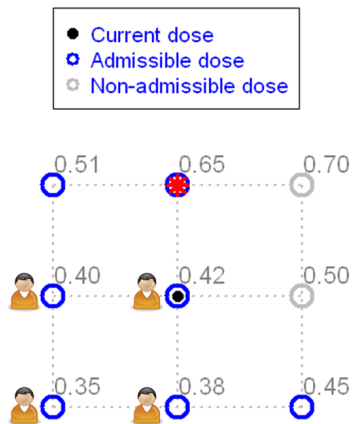


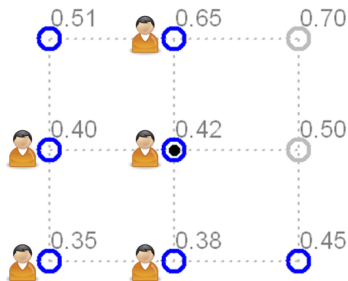
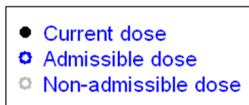
The dose (a_{j^*}, b_{k^*}) with the highest posterior mean of efficacy $\hat{q}_{j^*k^*}$

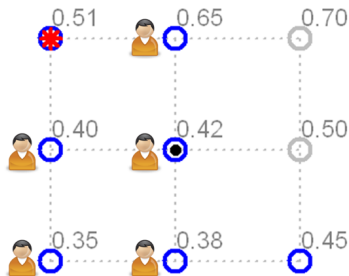
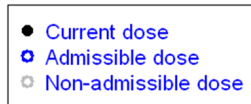


- The commonly used algorithm is to assign the next cohort of patients to (a_{j^*}, b_{k^*}) .
- Problem: this greedy algorithm is easily trapped in locally optimal doses due to
 - small sample size
 - model misspecification
- Solution: a novel dose-finding algorithm to **adaptively encourage the exploration of untried doses**









Stage II: Systematic dose finding

- II3
- 1 If $n_{j^*k^*} = 0$ or $n_{rs} \neq 0$ for all $(a_r, b_s) \in \mathcal{A}_{g^*}$, treat the next cohort at dose (a_{j^*}, b_{k^*}) .
 - 2 Otherwise,
$$\left\{ \begin{array}{l} \text{If } \hat{q}_{j^*k^*} > \left(\frac{N-n}{N}\right)^\alpha \text{ treat the next cohort at } (a_{j^*}, b_{k^*}), \\ \text{If } \hat{q}_{j^*k^*} \leq \left(\frac{N-n}{N}\right)^\alpha \text{ remove dose } (a_{j^*}, b_{k^*}) \text{ from } \mathcal{A}_{g^*} \\ \text{and go to step II2.} \end{array} \right.$$
 - N : prespecified maximum sample size
 - $n = \sum_{j,k} n_{jk}$: the total number of patients treated in the trial
 - α is a known tuning parameter.
- II4 Repeat steps II2-4 until exhaustion of the sample size. Select as the BODC the dose combination with the highest \hat{q}_{jk} among all safe doses.

Simulation setup

- Consider 4 dose levels for each agent:
 - Dose levels of A and B are (0.075, 0.15, 0.225, 0.3) and (0.08, 0.16, 0.24, 0.32), respectively.
- The maximum sample size was 15 cohorts of size 3.
- Set the target toxicity upper limit $\phi = 0.3$ and the safety cutoff $\delta = 0.4$.
- Set the tuning parameter $\alpha = 2$.

Simulation setup

- We compared the proposed design with a greedy design that is otherwise identical except that it uses the greedy dose-assignment rule (i.e., always assign the next cohort to the dose with the highest estimate of efficacy).
- 2000 simulated trials under each scenario.

Simulation results

Table : Scenario 1

Agent B	Agent A Toxicity probability				Agent A Efficacy probability			
	1	2	3	4	1	2	3	4
4	.25	.25	.25	.25	.42	.60	.38	.32
3	.15	.25	.25	.25	.19	.44	.20	.18
2	.10	.25	.25	.25	.12	.29	.15	.10
1	.05	.10	.15	.25	.05	.22	.10	.08

The blue dose is the target BODC.

Simulation results

Table : The selection percentage and the percentage of patients treated at each dose combination (shown as the subscripts) for scenario 1.

		Agent A							
		Proposed design				Greedy design			
B		1	2	3	4	1	2	3	4
4		23.8 _{14.1}	31.0 _{15.9}	10.8 _{9.4}	8.9 _{8.5}	18.2 _{9.5}	21.5 _{10.0}	7.8 _{5.3}	21.8 _{26.5}
3		3.5 _{3.9}	5.5 _{6.0}	1.2 _{6.9}	1.1 _{4.6}	4.5 _{3.0}	4.3 _{3.0}	1.1 _{9.5}	2.2 _{3.2}
2		0.9 _{2.3}	2.7 _{8.1}	0.8 _{3.7}	0.5 _{2.3}	1.2 _{1.6}	4.2 _{11.4}	0.9 _{1.6}	0.6 _{1.9}
1		0.7 _{7.6}	2.1 _{2.8}	1.0 _{2.1}	0.9 _{1.8}	0.5 _{8.4}	2.2 _{1.9}	1.4 _{2.1}	2.1 _{1.2}

The **blue** dose is the target BODC.

Simulation results

Table : Scenario 2

Agent B	Agent A Toxicity probability				Agent A Efficacy probability			
	1	2	3	4	1	2	3	4
4	.25	.25	.25	.25	.10	.29	.29	.42
3	.15	.25	.25	.25	.25	.35	.43	.60
2	.10	.25	.25	.25	.12	.24	.32	.39
1	.05	.10	.15	.25	.05	.14	.28	.32

The blue dose is the target BODC.

Simulation results

Table : The selection percentage and the percentage of patients treated at each dose combination (shown as the subscripts) for scenario 2.

Agent	Agent A							
	Proposed design				Greedy design			
B	1	2	3	4	1	2	3	4
4	1.6 _{2.1}	3.2 _{3.2}	4.1 _{6.4}	17.0 _{13.7}	2.5 _{1.6}	3.1 _{2.3}	3.9 _{3.7}	30.1 _{32.0}
3	2.5 _{2.1}	2.8 _{4.3}	7.1 _{9.2}	33.1_{18.5}	2.4 _{2.3}	3.1 _{2.3}	9.0 _{13.9}	17.9_{9.3}
2	0.7 _{1.6}	1.5 _{7.8}	3.4 _{5.3}	9.6 _{8.5}	0.8 _{0.9}	1.1 _{9.0}	3.0 _{2.6}	8.2 _{5.1}
1	0.3 _{7.3}	0.8 _{1.6}	2.5 _{2.7}	6.0 _{5.7}	0.1 _{7.7}	0.6 _{0.9}	2.2 _{2.3}	7.1 _{3.9}

The **blue** dose is the target BODC.

Simulation results

Table : Scenario 3

Agent	Agent A							
	Toxicity probability				Efficacy probability			
B	1	2	3	4	1	2	3	4
4	.17	.25	.45	.55	.60	.35	.32	.28
3	.12	.16	.25	.43	.42	.30	.28	.25
2	.08	.10	.19	.22	.35	.28	.22	.20
1	.05	.08	.12	.18	.25	.23	.19	.16

The **blue** dose is the target BODC.

Simulation results

Table : The selection percentage and the percentage of patients treated at each dose combination (shown as the subscripts) for scenario 3.

		Agent A							
		Proposed design				Greedy design			
B		1	2	3	4	1	2	3	4
4		46.3 _{18.9}	6.8 _{5.5}	3.4 _{5.2}	1.3 _{6.1}	39.1 _{13.8}	7.1 _{5.2}	3.3 _{3.6}	0.9 _{9.8}
3		7.8 _{5.5}	2.7 _{5.0}	3.1 _{8.6}	2.2 _{4.5}	7.3 _{3.9}	2.6 _{2.9}	3.5 _{13.2}	2.9 _{3.9}
2		5.3 _{5.0}	1.9 _{8.2}	1.5 _{4.5}	3.1 _{3.4}	3.9 _{2.7}	3.0 _{12.0}	1.8 _{2.5}	3.9 _{3.6}
1		5.5 _{10.2}	2.3 _{3.6}	1.7 _{2.7}	2.9 _{3.0}	8.6 _{16.1}	2.5 _{2.0}	2.5 _{1.8}	4.9 _{2.9}

The **blue** dose is the target BODC.

Conclusions

- Our proposed design explicitly accounts for the unique features of the biological agents, i.e., dose-efficacy and -toxicity relationships may take non-monotonic patterns.
- The proposed design adaptively encourages dose exploration in the two-dimensional dose space.
- Our design identifies the BODC with substantially higher selection percentage and allocates more patients to the target dose combination than the greedy design.
- In the case that efficacy plateaus, a similar change-line model can be used.

Reference

- Cai, C., Yuan, Y. and Ji, Y. (2014) A Bayesian Phase I/II Design for Oncology Clinical Trials of Combining Biological Agents. *Journal of the Royal Statistical Society: Series C*, **63**, 159-173.

Thank you !