



A semi-mechanistic dose-finding design in oncology using pharmacokinetic/pharmacodynamic modeling

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Abstract

Background. High failure rates in phase III cancer clinical trials call for more efficient designs of early phase clinical trials. While a number of phase I dose-finding designs exist, the commonly used ones are either algorithmic or empirical model-based, which do not adequately incorporate the mechanisms of the drug actions.

Methods. We propose a new framework for jointly modeling the dose-response relationship, by systematically incorporating the pharmacokinetic (PK) data collected in the trial and the hypothesized mechanisms of the drug effects, via *dynamic* PK/PD modeling, as well as modeling of the relationship between a latent cumulative pharmacologic effect and a binary toxicity outcome. This modeling framework naturally incorporates the information on the impact of dose, schedule and method of administration (e.g., drug formulation and route of administration) on toxicity. The resulting design is an extension of the existing designs that make use of pre-specified summary PK information (such as the area under the concentration-time curve [AUC] or maximum serum concentration [C_{max}]) (e.g., Ursino et al, 2017).

Results. Our simulation studies show, with moderate departure from the hypothesized mechanisms of the drug action, that the performance of the proposed design on average improves upon those of the common designs, including the continual reassessment method (CRM), Bayesian optimal interval (BOIN) design, modified toxicity probability interval (mTPI) method, and a design called PKPOP that models the effect of the AUC on toxicity. In case of considerable departure from the underlying drug effect mechanism, the performance of the design is shown to be comparable with that of the other designs. We illustrate the proposed design by applying it to the setting of a phase I trial of a γ -secretase inhibitor in metastatic or locally advanced solid tumors. We also provide an R package to implement the proposed design.

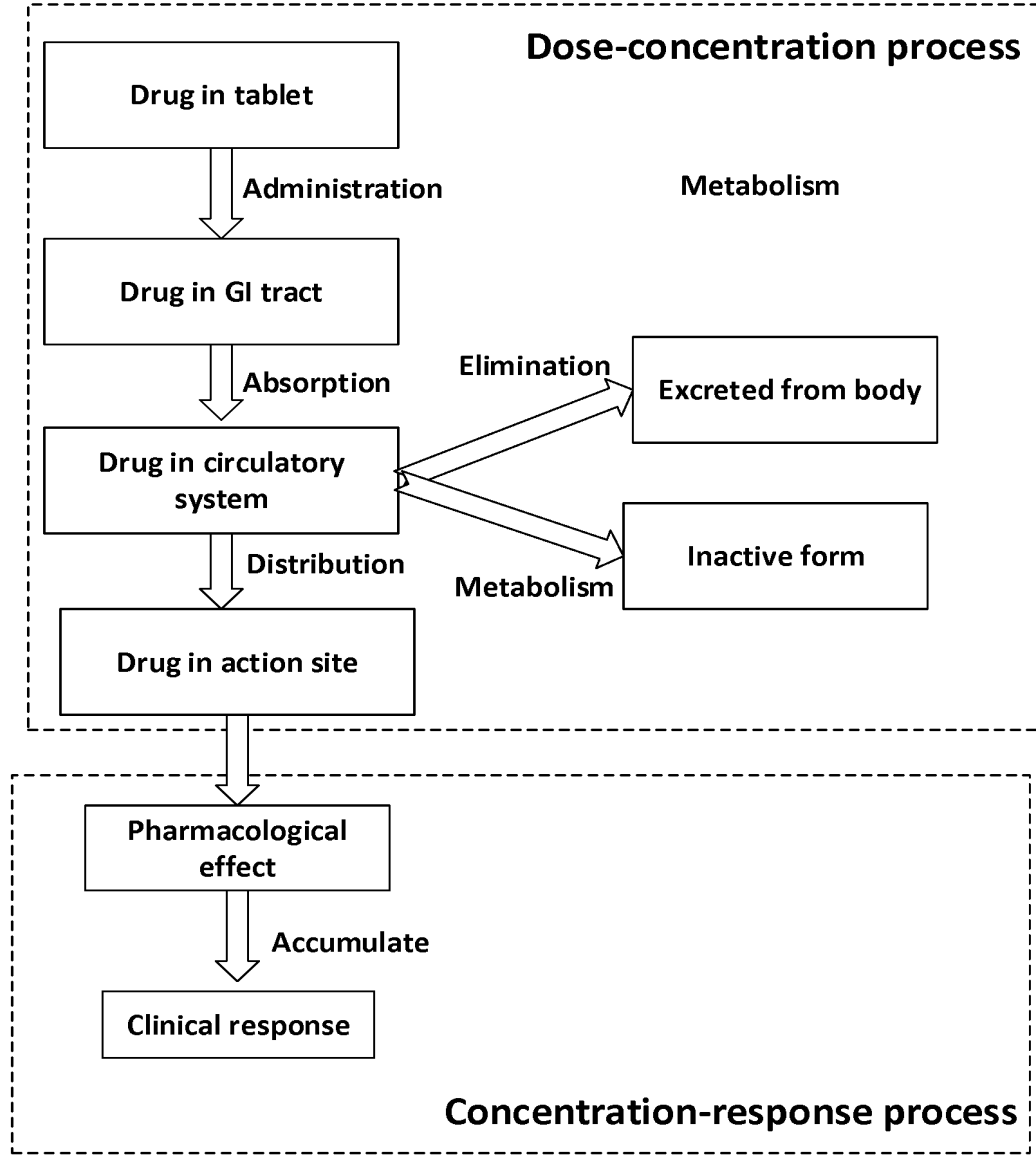
Conclusion. The proposed design and modeling framework appear promising in improving efficiency of dose-finding designs, and have the potential to be extended to a wide variety of early phase clinical trial design settings.

Background

- High failure rates in phase III cancer clinical trials
- Narrow therapeutic index of cancer drugs
- Small sample sizes in early phase trials
- Limitations of existing design approaches
 - Empirically-based dose-response models
 - Two-stage approach to incorporating PK information
 - Use of existing PK summary statistics (AUC, C_{max}, etc.)
 - Failure to link the PD and clinical outcomes
- A motivating phase I trial at MD Anderson**
 - Patients: metastatic or locally advanced solid tumors
 - Study drug: γ -secretase inhibitor
 - Mechanism of drug effect *in vivo*: blocks Notch signaling via γ -secretase inhibition, and delays cancer cell growth
 - Treatment cycle: 28 days
 - Five total doses per cycle: 7, 15, 30, 60, and 120 mg
 - Method of administration: intravenous (IV)
 - Schedule: 4-dosing regimen
 - Goals: characterize DLTs, identify MTD; PK profile
 - Target toxicity: 30%

Approach overview

- Propose a unified joint modeling framework for dose-toxicity relationship to incorporate PK, PD, and a link with clinical outcome (DCEO):
 - Dynamic PK modeling: **D**ose/schedule-**C**oncentration relationship (**DC**)
 - Dynamic PD modeling: **C**oncentration-**P**harmacologic **E**ffect relationship (**CE**)
 - Link between PD and clinical outcome: **C**umulative **P**harmacologic **E**ffect-Clinical **O**utcome relationship (**EO**)
- Data availability:
 - PK data always available in oncology dose-finding trials
 - PD data often available for preliminary efficacy evaluation in phase I, II or I/II trials
 - Potentially relevant PK/PD information from preclinical studies



PK models

- IV administration
 - Drug concentration profile for 1-compartment model:

$$\frac{dc(t)}{dt} = -k_e c(t), c(0) = d/V$$

- Closed-form solution: $c(t) = \frac{d}{V} e^{-k_e t}$
- Based on the superposition principle (Wang and Ouyang, 1998), for repeated administrations, we have:

$$c(t) = \frac{d}{V} e^{-k_e(t-s_k)} I(t > s_k)$$

- Extravenous administration (EV): similarly developable based on solving $c(t)$ and $a(t)$ analytically from a system of two differential equations

PD model

- One of the most commonly used PD models under a steady-state condition is the following sigmoid E_{max}-model:

$$e(t|\phi, \psi) = \frac{E_{max} c(t|\phi)^\gamma}{EC_{50}^\gamma + c(t|\phi)^\gamma},$$

where $e(t|\phi, \psi)$ is the measured (or latent) effect, and ϕ and $\psi = (E_{max}, EC_{50}, \gamma)$ are PK and PD parameters, respectively, with EC_{50} being the concentration that causes 50% of the maximum effect E_{max} .

- For convenience, notation for the dependence of ϕ on i is suppressed.
- Drug cumulative effect:

$$\eta(t|\tau, \phi, \psi) = \int_0^t e[c(u|\tau, \phi); \psi] du$$

- For 1-compartmental model with IV administration:

$$\eta(t|\tau, \theta') = \int_0^t \frac{E_{max} (\sum_{j=1}^K \frac{d_j}{V} e^{-k_e(u-s_j)} I(u \geq s_j))^\gamma}{ED_{50}^\gamma + (\sum_{j=1}^K \frac{d_j}{V} e^{-k_e(u-s_j)} I(u \geq s_j))^\gamma} du,$$

which has an analytical form, with $\theta' = (\phi, \psi)$.

Link between cumulative pharmacologic effect and toxicity probability

- Basic requirements for a link function $h(\eta)$: 1) $\in [0, 1]$; 2) non-decreasing; 3) $h(0) = 0$; 4) $h(\eta) \rightarrow 1$, if $\eta \rightarrow \infty$.
- We propose a link function $h(\eta) = 1 - e^{-\eta}$
- The resulting toxicity probability within a prespecified time window $[0, t_{ref}]$ for patient i :

$$\pi_{\tau_i, \theta'} = 1 - e^{-\eta(t_{ref}|\tau_i, \theta')},$$

which implies $\eta(t|\tau_i, \theta') = -\log[1 - \pi(\tau_i, \theta')]$.

Sampling models for PK data and clinical outcome

- Recorded concentrations at time t_{ij} : X_{ij}
- DLT for patient i : $Y_i \in \{0, 1\}$
- Sampling models:

$$X_{ij} = c(t_{ij}|\tau_{ij}, \phi_i) + \epsilon_{ij}, \text{ and } p(Y_i = 1) = \pi_{\tau_i, \theta'}$$

where $\epsilon_{ij} \sim N(0, \sigma^2)$, $\phi_i \sim N(\phi, \Sigma)$ with Σ being diagonal for simplicity.

- Vague independent prior distributions: uniform priors over a reasonably large range for PD and log-transformed PK parameters

Posterior inference

- Posterior distribution:

$$p(\theta|\mathcal{D}) \propto L(X, Y|\theta, \tau_i) g(\theta) = L(Y|\theta) L(X|\theta) g(\theta)$$

$$= \prod_i \int \prod_j \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{[x_{ij}-c(t_{ij}|\tau_i, \theta_i)]^2}{2\sigma^2}}$$

$$\times \prod_i (1 - e^{-\int_0^{t_{ref}} e[c(u|\tau_i, \theta_i)] du})^{Y_i} (e^{-\int_0^{t_{ref}} e[c(u|\tau_i, \theta_i)] du})^{1-Y_i} \times \phi(\phi_i; \phi, \Sigma) d\phi_i \times g(\theta),$$

where θ denotes all unknown parameters ($= (\theta', \sigma^2, \Sigma)$), and $g(\theta)$ is the joint prior distribution for θ .

- Posterior MCMC simulation using hyperrectangle slice sampling

Decision rules

- Evaluation by cohorts (with sizes 3 or 2)
- Decision rules in the spirit of the toxicity probability interval (TPI) method (Ji et al, 2007)

Simulation studies

- Simulation settings
 - Nine scenarios
 - 1,000 simulated trials under each scenario
 - In each simulated trial:
 - Sample sizes: 1) N = 30; 2) N = 20
 - Concentration measurement time: (1, 3, 5, 10, 12, 14) hours
 - t_{ref} = 720 hours
 - Inference based on IV + E_{max} model
 - $\epsilon_1 = \epsilon_2 = 0.05$ (for defining equivalence interval), $\delta_1 = 0.04, \delta_2 = 0.06$ (thresholds for terminating the trial or excluding a dose and above)

Notation

- Drug administration time: $s = (s_1, s_2, \dots, s_k)$
- Drug dosage: $d = (d_1, d_2, \dots, d_k)$
- Dose of one administration: d
- Treatment regimen (with fixed method of administration): $\tau = (d, s)$
- Drug concentration in plasma: $c(t)$
- Drug concentration in gastrointestinal tract: $a(t)$ (when orally administered)
- Volume of distribution of the drug in the body: V
- 1st-order elimination rate in 1-compartmental model: k_e
- 1st-order absorption rate in 1-compartmental model: k_a (when applicable)
- Some initial conditions, e.g., $c(0) = d/V$ under IV

Simulation scenarios

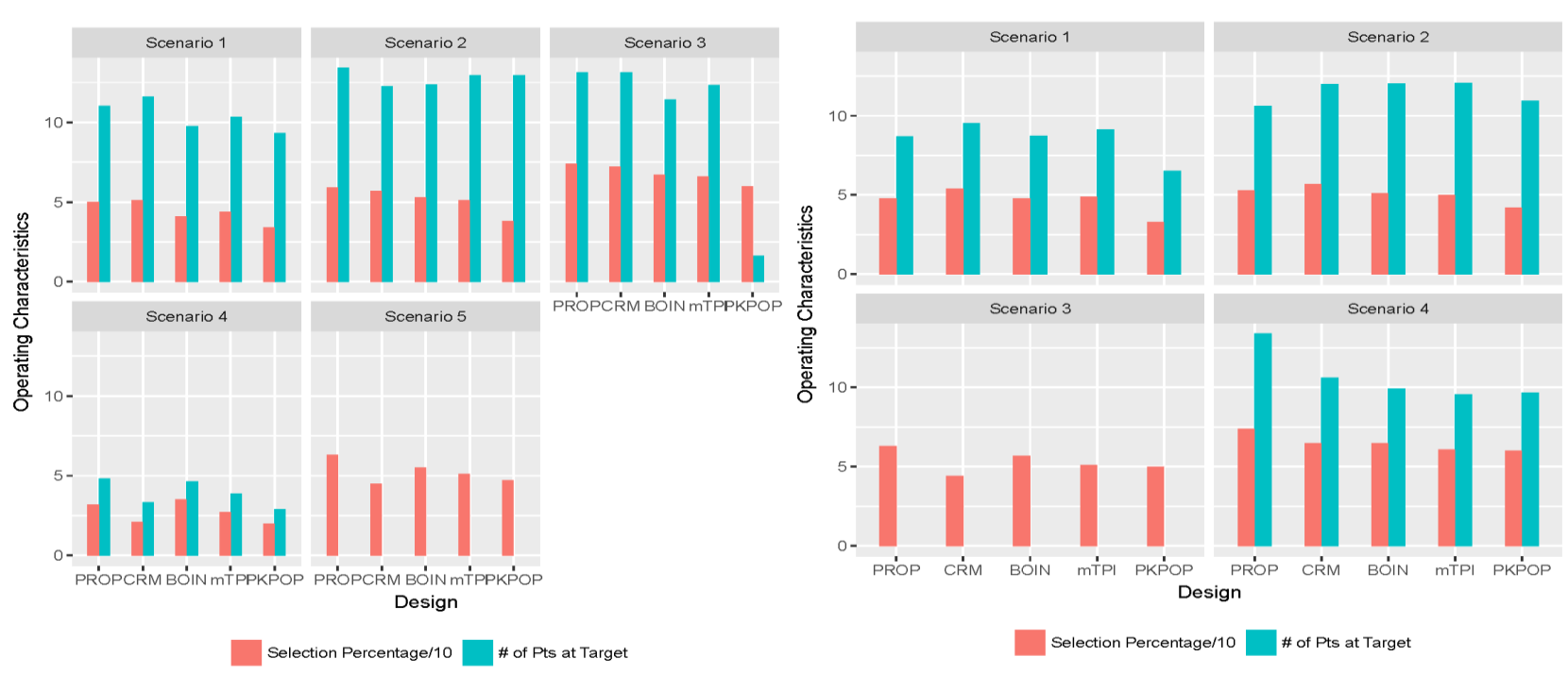
- True PK/PD models based on:
 - IV + 5-parameter logistic (5PL) model (5 scenarios)
 - Ursino et al (2017) (4 scenarios)
- True DLT rates:
 - 0.065 0.157 **0.261** 0.361 0.451
 - 0.167 **0.301** 0.426 0.536 0.627
 - 0.001 0.010 0.094 **0.301** 0.500
 - 0.126 0.166 0.207 0.252 **0.298**
 - 0.419 0.509 0.586 0.656 0.716
 - 0.038 0.079 0.166 **0.303** 0.399
 - 0.158 **0.261** 0.420 0.601 0.697
 - 0.419 0.563 0.725 0.854 0.906
 - 0.019 0.042 0.099 0.202 **0.283**

Designs under comparison

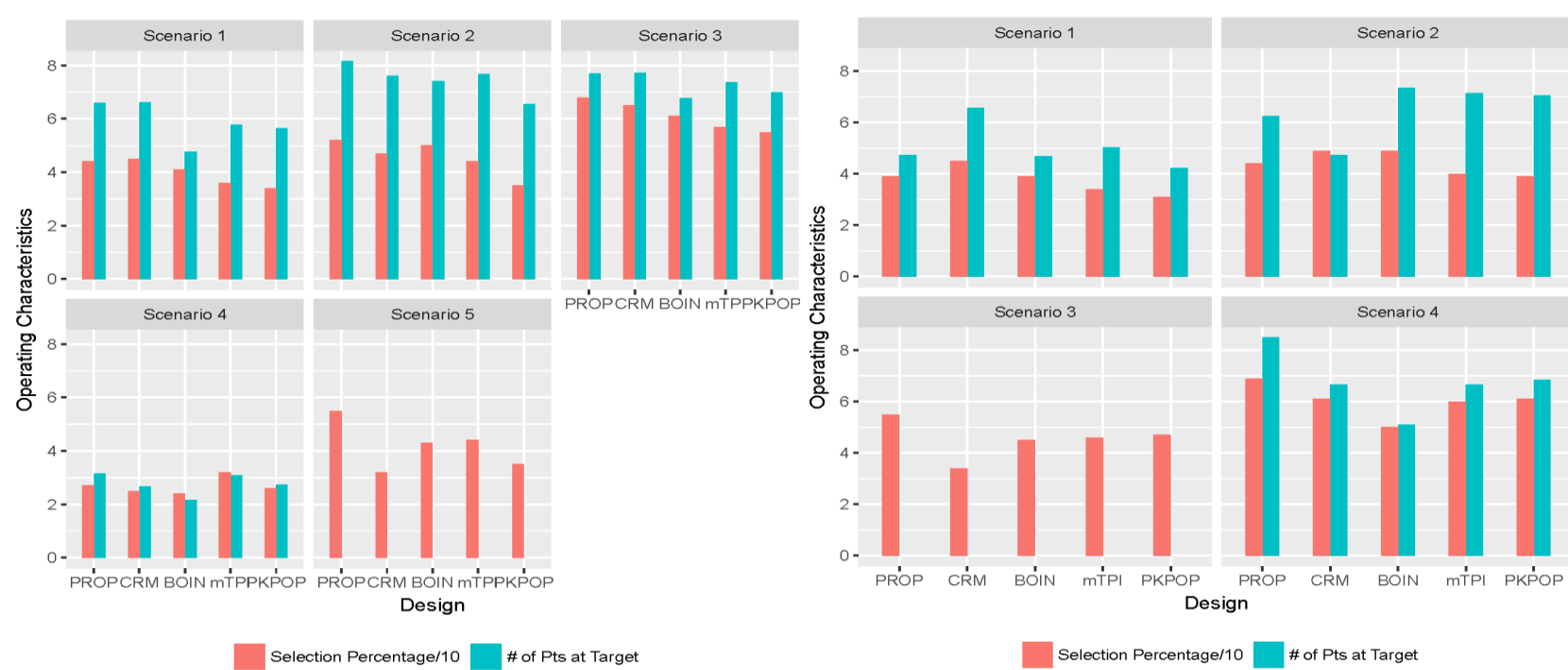
- CRM (O'Quigley, 1990): skeleton selected by the calibration method (Lee & Cheung, 2009)
- mTPI (Ji et al, 2010)
- BOIN (Liu & Yuan, 2015)
- PKPOP of Ursino et al (2017)

Simulation results

- N = 30



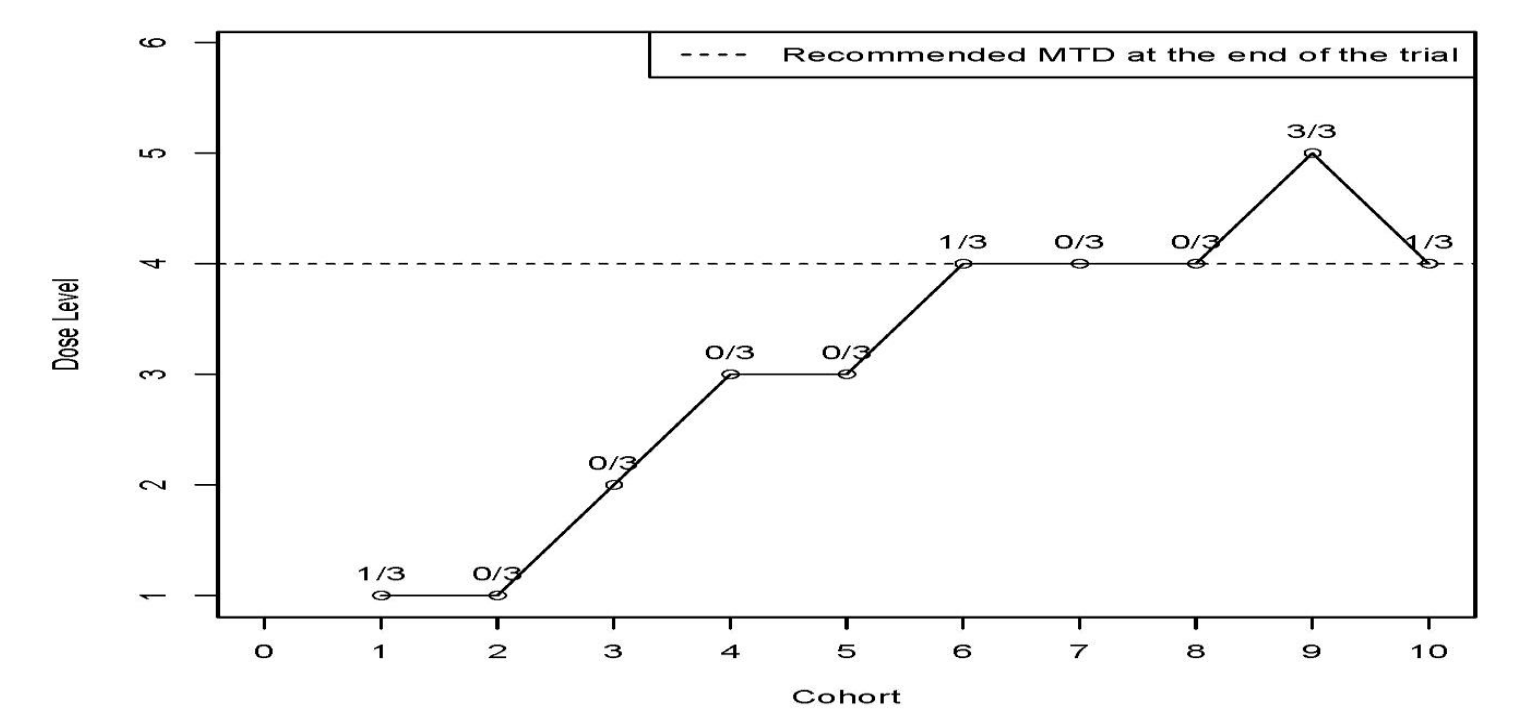
- N = 20



Summary of simulation results

- Improvements in OCs over common phase I designs (in terms of correct MTD selection and number of patients treated at the MTD) when “reasonable” drug mechanisms (especially PK) are exploited
- Comparable OCs with common phase I designs when PK mechanisms are considerably different than assumed
- Better performance than a particular PK summary measure-based design

A hypothetical trial realization



Conclusion

- We propose a new joint modeling framework for the DCEO relationship for phase I dose-finding designs
- The proposed design is feasible and performs well, as compared to common phase I designs and a particular PK summary measure-based design
- An R package is provided at: <https://github.com/esuxiao/PKPDMTD>
- The proposed modeling framework is potentially extendable to various early phase trial design settings, e.g.:
 - Evaluation of drug formulation, route of administration, and delivery system
 - Multiple-schedule dose finding and dose-schedule finding
 - Adaptive schedule insertion
 - (Potentially) complex PK/PD modeling settings characterized by systems of differential equations

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