OptiDose with mrgsolve for efficacy and safety-driven dose optimization

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Multi-objective optimization and OptiDose

Dose optimization, with respect to both efficacy and safety, is a primary objective of drug development and personalized medicine. However, the goals of maximizing efficacy and minimizing toxicity represent inherently conflicting objectives. Increased doses may promote greater efficacy but often come at the cost of increased toxicity. This challenge motivates the specification of a multi-objective optimization problem: to identify dosing strategies that maximize patient benefit by achieving an ideal balance between efficacy and safety.

Control theory provides a mathematical framework for determining how inputs to a dynamic system should be adjusted to achieve a desired state. In a clinical pharmacology context, the drug dose amount, dosing frequency, infusion duration, etc., serve as controllable inputs that can be manipulated to bring a system of pharmacokinetic (PK) and pharmacodynamic (PD) models to a target therapeutic state by minimizing an objective functional (Eq. 1).

$$f_{obj}(\text{Dose}) = f_{efficacy}(\text{Dose}) + f_{safety}(\text{Dose}) \quad (1)$$

where $f_{obj}(\text{Dose})$ represents the objective functional to be minimized by the optimization algorithm, $f_{efficacy}(\text{Dose})$ represents the objective function for the efficacy criteria, and $f_{safety}(\text{Dose})$ represents the objective function for safety criteria.

Recently, the enhanced OptiDose algorithm was introduced to the clinical pharmacology community as a strategy for computing optimal dosing regimens with NONMEM®, given both efficacy and safety criteria [1]. The OptiDose method integrates PK/PD modeling with control theory to provide a quantitative framework for designing and evaluating dosing regimens that maximize clinical utility.

Objectives

The objectives of this work were to: (i) demonstrate the use of mrgsolve in the context of multi-objective dose optimization problems; (ii) build upon the previously published enhanced OptiDose method by incorporating response standardization, penalty weighting, and decision criteria to the optimization problem; and (iii) illustrate the optimization of dosing regimens in a motivating case study using previously published PK/PD models.

Docetaxel in Metastatic Breast Cancer

Docetaxel is a cornerstone of therapy for women with metastatic breast cancer, a condition considered incurable. Accordingly, therapeutic goals vary among patients, with some willing to accept greater toxicity for the chance of improved survival, while others prioritize minimizing adverse effects to preserve quality of life. In the United States, docetaxel is typically administered as a 1-hour infusion at 75-100 mg/m^2 every three weeks (Q3W). For this dosing schedule, myelosuppression is the primary dose-limiting toxicity, with increased incidence of neutropenia at higher doses. To mitigate this toxicity, a weekly dosing (Q1W) schedule of 30-40 mg/m^2 has been proposed and evaluated in multiple Phase 1 and 2 trials. These studies generally report less myelosuppression, though efficacy results are mixed. Accordingly, the 75-100 mg/m^2 Q3W regimen may be considered an "efficacy-prioritizing" regimen, while the 30-40 mg/m^2 Q1W regimen may be a relatively "safety-prioritizing" regimen. However, the quantitative balance between efficacy and safety for these regimens has not been characterized, and the optimal dosing strategy for patients, whose therapeutic goals favor greater efficacy or reduced toxicity, remains undetermined.

Methods

Docetaxel dosing regimen optimizations were performed using previously published population PK and PK/PD models describing the relationship between docetaxel exposure, tumor growth in patients with metastatic breast cancer, and myelosuppression [2, 3]. Dose optimizations were performed across a range of efficacy targets, safety thresholds, dosing frequencies, and relative weights assigned to efficacy-safety priorities. Efficacy and safety endpoints included the sum of longest diameters (SLD) percent change from baseline and absolute neutrophil count (ANC). In all cases, an ANC below 0.5x10^9 cells/L sustained for longer than seven days was incorporated as an additional safety constraint.

Given the different magnitudes of scale for SLD percent change from baseline and ANC, a min-max standardization technique was applied to each endpoint (Eq. 2):

$$\text{SQD}(x, S) = \left(\frac{\max(0, x)}{S}\right)^2 \quad (2)$$

where SQD represents the scaled quadratic deviation of the endpoint from the target or threshold, x represents the positive deviation of the efficacy or safety parameter from the specified threshold, and S is a scaling factor based on the maximum possible deviation for the response endpoint (e.g., 100% for sum of longest diameters percent change from baseline). This approach effectively balances the contribution of the SLD efficacy and ANC safety endpoints to the dose optimization.

To assess the impact of different patient preferences on the optimized dose, weighting factors were applied to the SLD efficacy and ANC safety objective functions (Eq. 3):

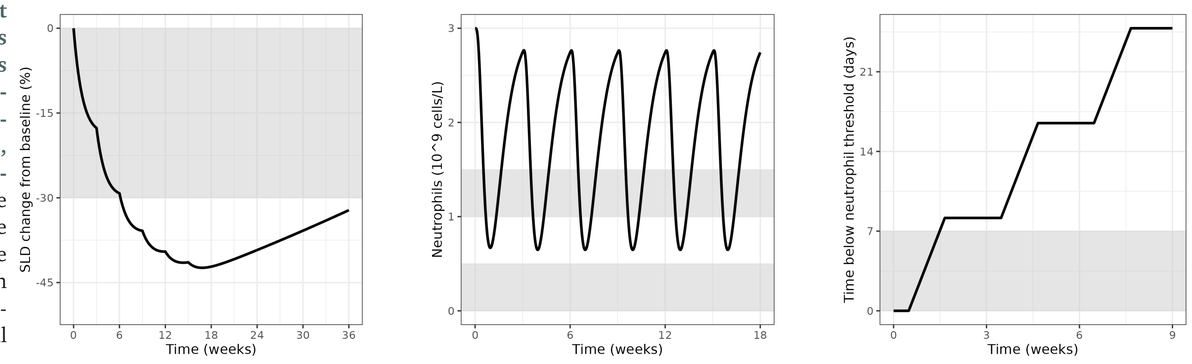
$$f_{obj}(\text{Dose}) = W \cdot f_{efficacy}(\text{Dose}) + (1 - W) \cdot f_{safety}(\text{Dose}) \quad (3)$$

The weight, $W \in [0, 1]$ reflects the relative importance of efficacy versus safety, with higher values prioritizing efficacy and a value of 0.5 giving equal importance to efficacy and safety criteria.

Optimizations were performed for a woman with typical values of model parameters for each of the three published models, with a baseline ANC of 3x10^9 cells/L. All optimizations were performed in R using mrgsolve, an open-source software for simulating from PK/PD and quantitative systems pharmacology models, in combination with the Bound Optimization by Quadratic Approximation algorithm implemented in the minqa R package. Optimized doses were normalized to a body surface area of 1.6 m^2.

Dose optimization must balance diverse efficacy and safety endpoints

Figure 1. The optimal dose must balance efficacy and safety across response endpoints with scales that vary in magnitude and clinical threshold, such as SLD percent change from baseline, ANC, and duration of severe neutropenia. Standardization of response endpoints is essential to balance the contribution of each response to the multi-objective optimization problem. Grey shaded areas highlight ranges of particular clinical relevance.



OptiDose with standardization and penalty weighting in mrgsolve

```
$GLOBAL
// min-max standardization
SQD(x, S) pow(fmax(0.0, x) / S, 2.0);

$DES
[...] ; // PMX model eqs.
DADT(12) = DCP; // Drug AUC

// SLD penalty
SCV = SQD(PCFB - SLDTAR, 100.0);
DADT(13) = sqrt(SCV);

// Neutrophil value penalty
SCVNEUV = SQD(NEUTAR - A(9), BLNEUT);
DADT(14) = sqrt(SCVNEUV);
[...]; // Additional penalty fxs.

$TABLE
// Cost and penalty fx values
CFV=A(12); // Drug AUC
PFV=A(13); // SLD CFB
PFV2=A(14); // Neutrophil depth
[...] ; // Additional penalty fx values.
Y = CFV + W*PFV + (1-W)*PFV2 + PFV3;
```

Figure 2. Implementing OptiDose in mrgsolve: example code for min-max standardization of responses, applying penalty weights, and specifying the objective functional. The optimization algorithm seeks to find the dose that minimizes, Y, the sum of the cost function value and penalty function values.

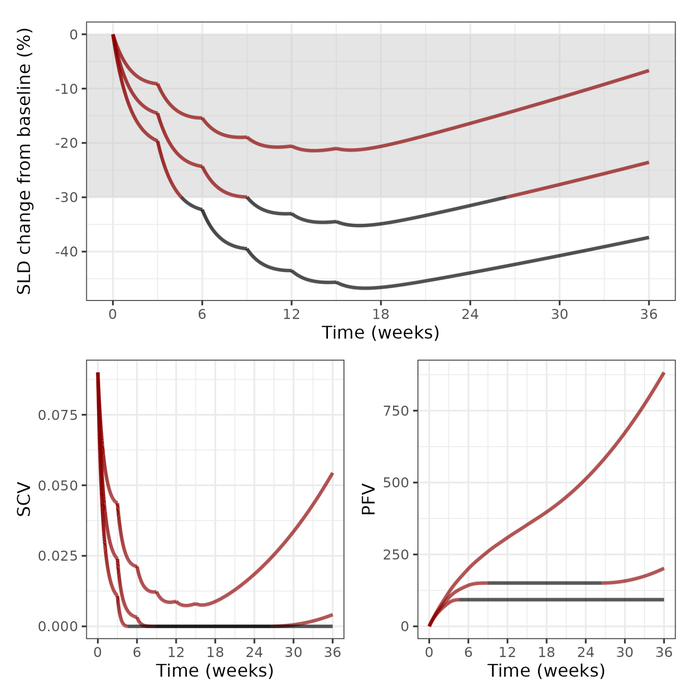


Figure 3. Penalty functions quantify the deviation of the clinical endpoint from the therapeutic target and penalty function values contribute to the objective functional to be minimized. Grey shaded area represents the region where SLD values will be penalized for being below the efficacy target. Red and black color indicates when penalty function is and is not applied, respectively.

Case Study Results: Evaluating Docetaxel Regimens for Metastatic Breast Cancer

Table 1. Evaluation of optimized docetaxel regimens across SLD percent change from baseline efficacy targets and a Grade 2 ANC safety threshold value of 1.5x10^9 cells/L. The current clinical practice regimens are shown for reference. Dose optimization with varying efficacy-safety (E:S) weights is shown; for example, E:S 3:1 indicates efficacy is weighted three times more than safety.

	Current Practice	Optimization				
	Dose (mg/m^2)	ΔSLD Efficacy Target	Neutrophil Safety Threshold (10^9 cells/L)	Dose (mg/m^2) 1:3 E:S	Dose (mg/m^2) 1:1 E:S	Dose (mg/m^2) 3:1 E:S
Q1W	30-40	-30%	1.5	34	40	56
Q2W		-30%	1.5	56	68	95
Q3W	75-100	-30%	1.5	68	84	114
Q4W		-30%	1.5	84	98	150
Q1W	30-40	-10%	1.5	26	33	34
Q2W		-10%	1.5	35	47	52
Q3W	75-100	-10%	1.5	42	56	57
Q4W		-10%	1.5	54	56	58

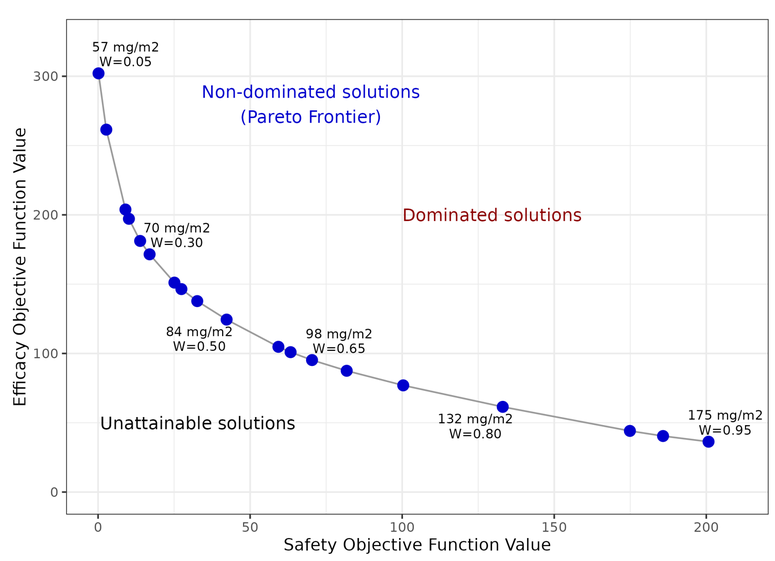


Figure 4. Pareto frontier for Q3W regimens targeting a -30% SLD change from baseline and a Grade 2 ANC safety threshold. The Pareto frontier represents optimized regimens where efficacy cannot be improved without compromising safety and vice versa. W values represent the weight of efficacy in the optimization.

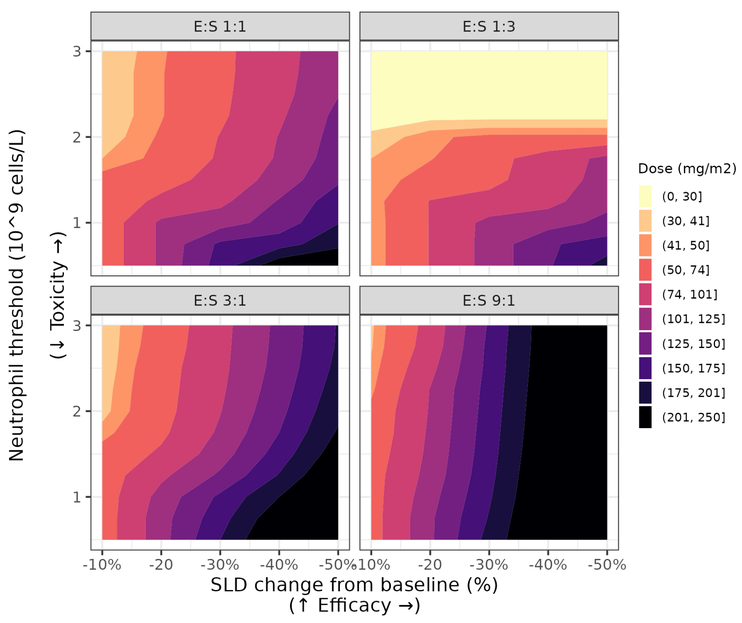


Figure 5. Relationship between safety threshold, efficacy target, and optimized Q3W dose. Dose optimizations with varying E:S weights are shown.

Conclusions and Future Directions

The OptiDose method offers a robust, quantitative approach for optimizing dosing regimens. This work extended the enhanced OptiDose method by standardizing response outcomes, incorporating efficacy-safety weighting, and demonstrating efficient dose optimization with mrgsolve and optimization algorithms available in R. Future work will extend these methods to patient populations, alternative optimization algorithms, and formal frameworks for specifying efficacy-safety priorities.

References and MetrumRG Publications

[1] Bachmann, F., Koch, G., Bauer, R.J., Steffens, B., Szinnai, G., Pfister, M. and Schropp, J. Computing optimal drug dosing regarding efficacy and safety: the enhanced OptiDose method in NONMEM. *J. Pharmacokinet. Pharmacodyn.* **51** (2024):919–934.

[2] SM, K., SS, L., BC, B., AL, Q. and LE, F. Tumor growth inhibition modeling of individual lesion dynamics and interorgan variability in HER2-negative breast cancer patients treated with docetaxel. *CPT Pharmacometrics Syst Pharmacol.* (2021).

[3] Friberg, L.E., Henningsson, A., Maas, H., Nguyen, L. and Karlsson, M.O. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. *J. Clin. Oncol.* **20** (2002):4713–4721.

Presented at the American College of Clinical Pharmacology Annual Meeting; 14 September - 16 September 2025