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D-optimal designs for parameter estimation for indirect pharmacodynamic response models

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Abstract

This report generates efficient experimental designs (dose, sampling times) for parameter estimation for four basic physiologic indirect pharmacodynamic response (IDR) models. The principles underlying IDR models and their response patterns have been well described. Each IDR model explicitly contains four parameters, k_{in} (production), k_{out} (loss), I_{max}/S_{max} (capacity) and IC_{50}/SC_{50} (sensitivity). The pharmacokinetics of an IV dose of drug described by a monoexponential function of time with two parameters, V and k_{el} is assumed. The random errors in the response variable are assumed to be additive, independent, and normal with zero mean and variance proportional to some power of the mean response. Optimal design theory was used extensively to assess the role of both dose and sampling times. Our designs were generated in *Mathematica* (ADAPT 5 typically produces identical results). G-optimality was used to verify that the generated designs were indeed D-optimal. Such designs are efficient and robust when good prior knowledge of the estimated parameters is available. The efficiency of unconstrained D-optimal designs (4 dose, sampling time pairs) does not improve much when the drug doses are allowed to differ, compared with constrained single dose designs (4 sampling times) with one maximal feasible dose. Also, explored were efficiencies of alternative study designs and results from parameter misspecification. This analysis substantiates the importance of larger doses yielding greater certainty in parameter estimation in pharmacodynamics.

Keywords

Pharmacodynamics; D-optimal design; Indirect response models; Parameter estimation

Introduction

Indirect response models (IDR), which have a logical mechanistic basis, can account for time-delays for many kinds of responses and are widely applicable in clinical pharmacology. These models characterize the pharmacodynamics of drugs that act by mechanisms such as inhibition or stimulation of the production or dissipation of factors controlling the measured response [1–3]. The three initial publications on IDR models [1–3] have been referenced 274, 141 and 48 times, respectively, up to May, 2009. The IDR models have been applied to describe effects of many classes of drugs [2]. Each of the four basic pharmacodynamic models relates response to time through a nonlinear differential equation. Two of these models assume an inhibition process, while the two other models assume a stimulation process. The commonly used sigmoid function (Hill function) usually controlled by plasma drug concentrations connects the pharmacokinetics and pharmacology.

D-optimal design theory underlies a popular statistical experimental design approach that is applicable to any nonlinear (or linear) model, and generates efficient designs for parameter estimation [4]. The D-optimality criterion minimizes the volume of the linearized region of estimated parameters in the parameter space; it is the determinant of the variance–covariance matrix of the parameter estimates. Usually the number of D-optimal design points is equal to the number of estimable parameters. Generally, for nonlinear models, D-optimal design points depend on the true values of the estimated parameters. Therefore, one needs to know the parameters fairly well in order to generate useful D-optimal designs. D-efficiency is the ratio of the D-optimality objective function for a candidate design divided by the power of the D-optimality objective function for the true D-optimal design. The reciprocal of the D-efficiency can be thought of as a factor by which any given design should be replicated in order to achieve the precision of parameter estimates equal to that of the D-optimal design. For example, two replicates of a design with a D-efficiency of 0.5 are needed to achieve the same precision as that of the D-optimal design. A good exposition of the theory can be found [4].

The field of Pharmacokinetic and Pharmacodynamic (PK/PD) modeling is one of the major biomedical disciplines which has integrated D-optimal (and other lettered-optimal) design theory into both general modeling methodology and specific PK/PD applications [5–11]. This methodology has been advanced in recent years to encompass challenging modeling complexities, such as multivariate response pharmacokinetic models [11] and simultaneous design on both dose and sampling times [7]. The current report seeks to further “extend the envelope” of optimal design methodology and application in PK/PD with a study of D-optimal designs for the class of ubiquitous, differential-equation-based, IDR models. The designs described in this paper are not intuitively obvious. Although many of the designs can be generated with common software packages, such as ADAPT, this is not true for the more complex cases. This paper emphasizes the reduction of complex perfectly D-optimal designs for both dose and sampling times, to simpler pseudo-D-optimal designs with practical and efficient constraints on dose.

Methods

Indirect pharmacodynamic response models

The four basic pharmacodynamic response models are described by [1–3]:

$$\frac{dR(t)}{dt} = k_{in} (1 + H_1(C(t))) - k_{out} (1 + H_2(C(t))) R(t) \quad (1)$$

where k_{in} denotes the zero-order production rate constant; k_{out} is the first-order rate loss constant; $R(t)$ is the pharmacologic response as a function of time, t ; $C(t)$ is the drug concentration at the effect site at time, t . The $H_1(C(t))$ and $H_2(C(t))$ are functions describing drug effects on the production and loss rate for the response according to: Inhibition of k_{in}

$$H_1(C(t)) = -\frac{I_{max}C(t)}{IC_{50}+C(t)} \text{ and } H_2(C(t)) = 0 \quad \text{Model I} \quad (2)$$

Inhibition of k_{out}

$$H_1(C(t)) = 0 \text{ and } H_2(C(t)) = -\frac{I_{max}C(t)}{IC_{50}+C(t)} \quad \text{Model II} \quad (3)$$

Stimulation of k_{in}

$$H_1(C(t)) = \frac{S_{max}C(t)}{SC_{50}+C(t)} \text{ and } H_2(C(t)) = 0 \quad \text{Model III} \quad (4)$$

Stimulation of k_{out}

$$H_1(C(t)) = 0 \text{ and } H_2(C(t)) = \frac{S_{max}C(t)}{SC_{50}+C(t)} \quad \text{Model IV} \quad (5)$$

The parameter I_{max} (S_{max}) expresses the maximum inhibition (stimulation), IC_{50} (SC_{50}) is the drug concentration eliciting 50% of the maximum inhibition (stimulation). The baseline value common for all IDR models is [1–3]:

$$R_0 = \frac{k_{in}}{k_{out}} \quad (6)$$

In Models I–IV, any appropriate pharmacokinetic equation may be used to describe the plasma or effective drug concentration as a function of time. We used a monoexponential PK function:

$$C(t) = \frac{D}{V} e^{-k_{el}t} \quad (7)$$

where D denotes dose of drug, V is the volume of distribution, and k_{el} is the elimination rate constant. Thus, for these models (Eqs. 1–7): R is an output (dependent variable, pharmacologic endpoint); D and t are inputs (independent variables); C is the output for Eq. 7 and an input for Eq. 1; and k_{in} , k_{out} , R_0 , I_{max} , S_{max} , IC_{50} , SC_{50} , V , and k_{el} are all estimable parameters.

Standard response versus time profiles of the four IDR models for three “dose” levels are shown in Figs. 1, 2, 3, and 4. The parameter values used herein are consistent with ones used previously [3]: $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{in} = 9 \text{ units/h}$, $k_{out} = 0.3 \text{ h}^{-1}$, $R_0 = 30 \text{ units}$, $I_{max} = 1$ ($S_{max} = 1$), and IC_{50} or $SC_{50} = 100 \text{ ng/ml}$.

D-optimal designs for the IDR models

In addition to the IDR structural models, we assume that the random errors in the response variable are additive, independent, and identically distributed according to the normal distribution, so that at each point in time the corresponding error is normal with a mean of

zero and variance directly proportional to some power of the response (this is a commonly used power model for the variance), given by [12, 13]:

$$\sigma^2 = \sigma_0^2 R^{2\lambda} \quad (8)$$

where σ^2 is the variance of the observed response, R is the expected value (mean) of the observed response; and σ_0^2 and λ are estimable parameters of the variance model. In the special case when $\lambda = 0$ the variance is constant (homoscedasticity); $\lambda = 0.5$ corresponds to a Poisson counting process; and $\lambda = 1$ provides a constant coefficient of variation.

Our D-optimal designs were generated in *Mathematica*. The results were validated using the ADAPT 5 program [14]. G-optimality was used to verify that the generated designs are indeed D-optimal [4]. The *Mathematica* code is available online. The pharmacokinetic component of the model (Eq. 7), and its associated parameters ($V = 90$ l, $k_{el} = 0.3$ h⁻¹) were fixed, assuming the true model and its true parameters are known without error. Since the PD component (any of Models I–IV) of the combined PK/PD model includes 2 inputs (D , t) and four estimable structural parameters, a true D-optimal design will include 4 (D , t) pairs.

(We will assume that the error variance parameters, σ_0^2 , λ , will not be estimated.) However, this type of design with 4 (D , t) pairs would be impractical, since four separate i.v. injections of drug would have to be given, and all but one sampling time ignored for each injection. Thus, we first examined pseudo-D-optimal designs that constrain the four design points to include the same one dose. We then examined true 4- $(D$, t)-pair D-optimal designs, and subsequently, pseudo-D-optimal designs constrained to include 2 different doses for the 4 (D , t) pairs. Nine scenarios were thus assessed for each IDR model. The “pseudo” label for pseudo-D-optimal designs is dropped hereafter.

Results

D-optimal designs for single-dose IDR models

For each of IDR Models I–IV, the 4 D-optimal points are displayed (PD sampling times) in Figs. 1, 2, 3, and 4, where only single doses of drug are given. The upper sections show the D-optimal sampling times superimposed on the simulated response vs. time curves, and the lower sections showcase the relative positions of the D-optimal design points for the nine scenarios. The parameters held constant are listed in the legend to Fig. 1. The dose level is defined in terms of multiples of $V \cdot IC_{50}$ or $V \cdot SC_{50}$. The three curves in each panel conform to the ratios $D/V \cdot IC_{50} = 1, 10$, and 100 ($D = 9, 90$ and 900). For each curve (dose), we calculated the 4 D-optimal sampling times for 3 different values of λ (from Eq. 8), for a total of 9 sets of D-optimal design points per model. We primarily describe Model I, but the conclusions are generally similar for the other models. Figure 1 reveals that either the zero time or a very late point in time with the response close to the baseline is always one of the four design points. These two types of designs are usually very close in their D-efficiency. A point close to the nadir is another usual D-optimal point. The two other D-optimal points lie on the way down and on the way up the response curve. The points are affected by λ , the power parameter (Eq. 8), so that in designs conforming to larger values of λ the corresponding points are closer to the bottom of the curve. This influence of λ can be seen in the lower section of Fig. 1 in comparing the bottom three display lines.

The influences of changes in D and λ on the patterns of D-optimal sampling times for Models II–IV are shown in Figs. 2, 3, and 4. Similar to the designs for Model I, one D-optimal time is always at or near time zero; one time is near the peak (trough) of the time course; one time is on the up (down) ward curve; and one time is on the down (up) ward

response curve. Increasing λ shifts the D-optimal sampling times towards the trough for Models I and IV and away from the peak for Models II and III.

Six D-optimal designs for Model I (for $k_{out} = 0.3$ or 0.7 , and $D/V/IC_{50} = 1$ or 10 or 100) under the assumption that a single dose is given are listed in Table 1, and one of these D-optimal designs (for $D = 10 \cdot V/IC_{50}$, $k_{out} = 0.3$, $\lambda = 0$) is shown visually in the upper part of Fig. 5. Additionally, we compared the D-optimal sampling times generated by our algorithm implemented in *Mathematica* with the sampling times obtained by the SAMPLE mode of ADAPT 5. Overall, the results were similar.

A number of different single-dose designs, A–F, are compared to the corresponding D-optimal designs by the D-efficiency criterion in Table 2 (for $k_{out} = 0.3$ or 0.7 , and $D/V/IC_{50} = 1$ or 10 or 100). Each of the designs A–F represented in Table 2 was constructed by partitioning intervals on the time axis in a specific logical manner. Intervals were chosen to extend from 0 until the time point (T_{ret}) resulting in a response returning within 2% of R_0 . For example, when $D = 10 \cdot V/IC_{50}$, $\lambda = 0$, $k_{out} = 0.3 \text{ h}^{-1}$, and the other parameters have the standard assumed values, then the mentioned interval is $(0, 26.4)$. For $D = 10 \cdot V/IC_{50}$, $\lambda = 0$, $k_{out} = 0.3 \text{ h}^{-1}$, designs A–F are shown visually in Fig. 5. Design A $(0, 8.80, 17.6, 26.4)$ is evenly spaced containing T_{ret} ; design B $(4.40, 10.26, 16.1, 22.0)$ is evenly spaced not containing T_{ret} ; design C $(0, 5.98, 1.45, 13.6)$ contains 0, time at nadir, time resulting in $0.5 \times R_0$ on the way down, and time resulting in $0.5 \times R_0$ on the way up; design D $(0, 1.99, 3.99, 5.98)$ contains 0, time at nadir, and two evenly spaced points in between; design E $(5.98, 12.8, 19.6, 26.4)$ contains time at nadir, T_{ret} , and two evenly spaced points in between; design F $(2.27, 5.14, 11.6, 26.4)$ is a geometric design (with points evenly spaced on a logarithmic time scale); and the D-optimal design (for $D/V/IC_{50} = 10$, $k_{out} = 0.3$; top design in Fig. 5) is $(1.43, 5.49, 11.8, 24.0)$. Note that Table 2 includes the D-efficiencies for five additional D-optimal designs ($D/V/IC_{50} = 1$, $k_{out} = 0.3$; $D/V/IC_{50} = 1$, $k_{out} = 0.7$; $D/V/IC_{50} = 10$, $k_{out} = 0.7$; $D/V/IC_{50} = 100$, $k_{out} = 0.3$; $D/V/IC_{50} = 100$, $k_{out} = 0.7$), and the not-shown corresponding designs A–F. It can be seen that the designs having higher efficiencies have some of their design points located close to their D-optimal points. Designs C and F (both of which include points close to two of their D-optimal points for all six scenarios), have relatively high efficiencies. Designs are likely to have low efficiencies when they completely miss 3 or more D-optimal points (as, for instance, designs A, D, and E). Note that the geometric design is quite efficient in these examples, and that design C is highly efficient. It appears that the relative spacing of the four design points is also important for D-efficiency.

Optimal designs for more than one drug dosage level

It is usually advisable to administer more than a single drug dosage level in PK/PD. Since there are two basic inputs to the system (dose, D and sampling time, t), a D-optimal design should logically consist of four (D, t) pairs. We first assumed that there are no constraints regarding the number of different dosage levels. Each of the D-optimal designs for Models I and III ($k_{out} = 0.3, 0.7$; $\lambda = 0, 0.75, 1.5$) generated under this assumption is represented in Table 3. Each design point is now a (dose, time) pair. It is assumed that the maximal feasible dose, D_{max} , is equal to $100 \cdot V/IC_{50}$. Although, in principle, a D-optimal design may contain four different dose components among the four D-optimal points, it is often not the case. Although 4 different dose levels were allowed, we found that each D-optimal design for Model I displayed in Table 3 contains at most two different doses. Moreover, it is clear from Table 3 that the highest feasible dose plays an important role in these D-optimal designs as, it is used universally in all these designs, often more than once. Interestingly, all the designs corresponding to $k_{out} = 0.7$ use the single largest permissible dose along with the time points identical to the ones used in the D-optimal designs under the single dose constraint when that single dose is the highest feasible one. When $k_{out} = 0.3$, each D-optimal design for

Model I displayed in Table 3 uses one low dose. The low dose increases with an increase in λ .

Eight-point optimal designs which were constrained to only two different permissible dose levels, were also generated. Table 4 displays such designs for Model I ($k_{out} = 0.3, 0.7$; $\lambda = 0, 0.75, 1.5$). Two additional constraints are used to compute these designs: (a) for each of the two doses, the same time points are sampled; and (b) one of the doses is fixed at $100 \cdot V \cdot IC_{50}$, and the other dose is fixed at $10 \cdot V \cdot IC_{50}$, so the ratio of the higher dose to the lower dose is 10. The four points listed in Table 4 for each represented pair (k_{out}, λ) are the four optimal sampling times. Thus, an 8-point design in this case consists of the 8 points obtained by combining each of the two fixed doses with each of the four sampling time points listed in Table 4.

To obtain the optimal designs displayed in Table 5, we relaxed the condition that the ratio of the two doses be held constant at 10. It is assumed that D_{max} ($= 100 \cdot V \cdot IC_{50}$) is the maximal permissible dose. The lowest dose (expressed in the units of $V \cdot IC_{50}$) and the four points in time for each of the described D-optimal designs are listed in Table 5. It turns out that the highest feasible dose, D_{max} , is used in all of these designs as the largest dose. The 8 design points are obtained by combining each of the two doses with each of the 4 time points listed in Table 5.

A few simple observations are in order. A comparison of the time points listed in Tables 4 and 5 to the respective time points listed in Table 1 indicates that the optimal points in time used in the constrained optimal designs with two doses are generally different from the optimal time points used with a single dose, yet often they are not markedly different. While 10 is not the optimal ratio of the two permissible doses when these are used, the respective time points listed in Tables 4 and 5 are close to each other. This is particularly true when λ does not exceed 1.

Eleven different 8-point (dose, sampling time) constrained designs, A1–L1, along with the corresponding 8-point D-optimal design, are listed in Table 6; the D-efficiencies for these 12 designs are given in Table 7. It is assumed that the highest feasible dose, $D_{max} = 100 \cdot V \cdot IC_{50}$ and that $\lambda = 0$. Some of these designs, including the constrained D-optimal design A1 from Table 4, the constrained D-optimal design B1 from Table 5, the constrained D-optimal design F1 from Table 1, and an unconstrained D-optimal design from Table 3, were introduced earlier in this paper. All other designs use, along with the two doses or the single dose listed in Table 6, the sampling times that are evenly spaced either on a linear or a logarithmic scale. The interval range for the times is determined from the response curve for the larger dose used in the design. For some of these designs (C1, G1, I1, L1) the end points of the interval range are included while for the others (D1, H1, K1), they are not included. Design E1 contains T_{ret} and does not contain 0. Tables 6 and 7 merit several important observations:

1. The restriction of using two doses and taking all observations on the two response curves at the same times does not materially reduce the design efficiency. Moreover, an additional restriction that the ratio of the two doses used must be 10 results in a negligible further reduction in the design efficiency. The larger of the two optimal doses is always the largest permissible dose, D_{max} .
2. Some intuitive designs, such as evenly spaced ones, tend not to be highly efficient. The efficiency gets lower when the end points of a time interval are included versus not included. The end points are redundant in their informational content since they reflect the baseline. It is important that the largest permissible dose, D_{max} , be used

as one of the doses in any design. The design efficiency is reduced materially when this is not the case.

3. The geometric design E1 fares quite well in our example.
4. The restriction of using a single dose is not prohibitive as long as it equals the largest permissible dose, D_{max} . D-optimal design F1 for the single dose is highly efficient. Its efficiency is reduced dramatically when only a fraction of D_{max} is used (for example, as in design L1).

Since D-optimal designs depend on assumed parameter values, their robustness with respect to parameter misspecification needs to be addressed. Generally, D-optimal designs tend to be quite robust when the discrepancy is not extreme. Some robustness results for single dose D-optimal designs for Model I are presented in Table 8. The single dose used was $D = 100 \cdot V \cdot IC_{50}$. The assumed parameters are: $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $\lambda = 0.75$. The D-efficiencies for the cases in which the true parameter values vary from the assumed ones by exactly a factor of 2, are presented in Table 8. Here the values of k_{in} and k_{out} are paired so that the ratio $R_0 = k_{in}/k_{out}$ is equal to 30. We paired in this way because these parameters are highly correlated (7). Of the 18 different scenarios shown in Table 8, the one ($I_{max} = 1$, $IC_{50} = 1$, $k_{out} = 0.3$, $k_{in} = 9$) resulting in the D-efficiency of 1.0, represents the case where the assumed parameter values are no different from the true parameters. The D-efficiencies of all 18 designs shown in Table 8 suggest that for Model I, D-optimal designs are fairly robust even under appreciable misspecification of true parameter values.

Discussion

This report examines some properties of different designs aimed at an efficient estimation of pharmacodynamic parameters for the four IDR models. Single dose D-optimal designs are both efficient and robust when a good prior knowledge of the estimated parameters is available. The designs incorporating such practical considerations as using only one constrained dose and using two different doses and administering the two doses with the same sampling times, were shown to be highly efficient when compared to 100% efficient unconstrained D-optimal designs. Our study showed that the efficiency of D-optimal designs (4 dose–time pairs) does not improve dramatically when the drug doses used in the 4 design points are allowed to be different, when compared to a constrained single dose design, with one maximal feasible dose. It is essential to use the highest permissible dose in either of these designs, constrained or unconstrained. Moreover, as shown in Table 3, unconstrained D-optimal designs often use the maximal feasible dose with more than one time point. Replicated D-optimal designs may be used when λ (see Eq. 8) needs to be estimated.

We optimized the D-objective function in 1×4 , 2×4 , and 4×4 dimensional dose and sampling time spaces. Consequently, we verified that the most efficient D-optimal designs are those which allow use of the maximal tolerated dose in these models. D-optimal sampling times for IDR models can be determined for regimens of specified doses using software such as ADAPT 5. Simultaneous search for D-optimal dose and sampling times is not supported by ADAPT 5 and it would be difficult to use solely this software to address our objectives.

The D-optimal designs for the IDR models tend to be quite robust. However, since our study used only a limited number of scenarios, with a limited number of sets of parameter values, it is possible that future scenarios may reveal insufficiently robust D-optimal designs. Generating D-optimal design points under the assumption of parameter misspecification and creating a table of their D-efficiencies (similar to Table 8) helps to identify the parameter combinations for which the original D-optimal design would have low efficiency. Often

adding relatively few points to such design will markedly improve its robustness yet not significantly decrease its efficiency.

Another idea widely explored in the literature and aimed at generating both efficient and robust designs is to incorporate uncertainty in the parameters of interest. The ED, EID and API criteria assume prior distributions for the estimated parameters, rather than restricting them to a fixed value [15, 16]. In [9, 10] the corresponding designs are explored in population PK studies. This approach is implemented in such software packages as OSP-Fit by Tod and Roccisani [17], PFIM by Retout et al. [18], and PopED by Foracchia et al. [19].

The role of dose for accuracy of parameter estimates for the four IDR models was explored previously [20] using simulated data. The parameter values were those used throughout this study. Arbitrary “common sense” designs consisting of 7 time points were used with a wide range of single doses. Non-normal and skewed distributions of estimated parameters were reported. The distributions of IC_{50} and SC_{50} estimates had the largest variances of the estimable PD parameters.

D-optimal designs generate a minimal selection of doses and times for recovery of expected parameters for specified models. These serve as ideal starting points in study designs, but such studies usually include intermediary time points in order to assure the reliability of modeling in the face of unexpected variability.

Several practical issues were not included in this paper:

- a. To form a complete PK/PD model, monoexponential PK was employed and it was assumed that the PK parameters are known precisely. Obviously, this assumption is theoretical, and efficient study designs for parameter estimation in a six-parameter PK/PD model should be developed. These designs would naturally have to account for variability in the PK versus PD data. Similar practical issues surround pure PK studies, in which more than one chemical entity is measured simultaneously, such as parent drug and a metabolite.
- b. Efficient study designs for the cases in which a PK model other than the monoexponential one is combined with each of the four IDR models need development.
- c. Impact of different designs (including D-optimal designs) on the distribution of the individual estimated parameters should be further explored.
- d. Designs that estimate the parameters for the error variance models (e.g., σ_0^2 , λ from Eq. 8) are important for many applications.
- e. Designs for model discrimination are desirable. There may exist practical designs that are efficient for both model discrimination and parameter estimation purposes.

Many of these general practical issues have been explored by other research groups. For example, practical issues (a), and (c) were investigated by [6]. It was concluded that for designs for PK/PD studies with the same relatively large numbers of samples per individual, neither taking into account issue (a) nor (c) had a material effect on design, but that for frugal designs, in which the number of samples per patient is less than the number of estimated parameters per patient, taking into account issues (a) and (c) may be advantageous. Another specific application [8], addressed issue (e), along with issues (a) and (c). It was concluded that the generated designs were efficient for both parameter estimation and model discrimination. Practical issue (c) has been extensively studied by many groups (e.g., [5, 9, 10]). The ultimate goal for optimal design theory and methodology in PK/PD modeling is to integrate the guidelines extracted from the all relevant studies with all of

these practical issues simultaneously to facilitate the robust and efficient design of any and all future PK/PD studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Three simulated response vs. time curves for Model I conform to the unitless ratio, $D/V/IC_{50} = 1, 10$, and 100 . The PK/PD parameters in the model that were held constant were: $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{in} = 9 \text{ units/h}$, $k_{out} = 0.3 \text{ h}^{-1}$, $I_{max} = 1$, and $IC_{50} = 100 \text{ ng/ml}$. The initial conditions were set at 30 units/l . Circles, squares and triangles represent single-dose D-optimal designs (4 sampling time points) corresponding to the three increasing values of $D/V/IC_{50}$; the symbol sequence in (color, size) from (open, large) to (gray, medium) to (black, small) correspond to λ values of $0, 0.75$, and 1.5 . The bottom part of the figure shows the same design points, but depicts the relative positions in time of the D-optimal points

Fig. 2.

Three response vs. time curves for Model II were simulated, displayed, and labeled with all of the same fixed parameters and conventions as described in the legend for Fig. 1

Fig. 3.

Three response vs. time curves for Model III were simulated, displayed, and labeled with all of the same fixed parameters and conventions as described in the legend for Fig. 1 (except that $S_{max} = 1$, $SC_{50} = 100$ ng/ml)

Fig. 4.

Three response vs. time curves for Model IV were simulated, displayed, and labeled with all of the same fixed parameters and conventions as described in the legend for Fig. 1 (except that $S_{max} = 1$, $SC_{50} = 100$ ng/ml)

Fig. 5.

One D-optimal single-dose design for Model I, corresponding to $D/V/IC_{50} = 10$ and $k_{out} = 0.3$, plus six other non-optimal single-dose designs described in “Methods” section. Each design consists of 4 sampling time points. Here, the fixed parameters include: $V = 90$ l, $IC_{50} = 100$ ng/ml, $k_{el} = 0.3$ h⁻¹, $k_{in} = 1$, $k_{in} = 0.9$ units/h, $I_{max} = 1$, $\lambda = 0$

Table 1

D-optimal sampling times for Model I with a single-dose constraint

k_{out} (h^{-1})	Sampling times		
	$\lambda = 0$	$\lambda = 0.75$	$\lambda = 1.5$
$D/V/IC_{50} = 1$			
0.3	0, 1.93, 6.20, 13.4	0, 2.03, 6.00, 13.0	0, 2.13, 5.90, 12.7
	0, 1.90, 6.22, 13.4	0, 2.01, 6.09, 13.2	N/A
0.7	0, 0.860, 3.07, 7.34	0, 0.960, 3.02, 7.00	0, 1.04, 2.98, 6.68
	0, 0.890, 2.96, 7.27	0, 0.920, 2.99, 7.06	0, 1.05, 3.11, 6.74
$D/V/IC_{50} = 10$			
0.3	1.43, 5.49, 11.8, 24.0	1.93, 5.69, 10.8, 23.1	2.43, 5.69, 9.99, 21.7
	1.43, 5.49, 11.8, 24.0	1.93, 5.66, 10.8, 23.1	2.45, 5.75, 10.0, 21.7
0.7	0, 1.15, 4.51, 10.7	0, 1.66, 4.31, 9.31	0, 2.06, 4.25, 7.97
	0, 1.16, 4.51, 10.7	0, 1.66, 4.33, 9.28	0, 2.06, 4.24, 7.98
$D/V/IC_{50} = 100$			
0.3	2.53, 9.49, 18.5, 40.0	4.13, 9.39, 16.0, 37.7	5.53, 9.39, 13.9, 32.2
	2.55, 9.48, 18.5, 39.1	4.15, 9.41, 16.0, 37.8	5.57, 9.38, 13.9, 32.3
0.7	0, 1.36, 6.80, 17.0	0, 2.76, 6.30, 13.8	0.280, 3.90, 6.24, 10.2
	0, 1.35, 6.86, 17.1	0, 2.80, 6.35, 13.9	0, 3.84, 6.21, 10.2

The parameter values used were $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{in} = 9 \text{ units/h}$, $I_{max} = 1$, and $IC_{50} = 100 \text{ ng/ml}$.

The second rows of sampling times were obtained by ADAPT 5

N/A ADAPT 5 did not converge

Table 2

D-efficiencies of single-dose designs (D-optimal, A–F) for Model I

$k_{out} \text{ (h}^{-1}\text{)}$	Design						
	D-optimal	A	B	C	D	E	F
$D/VC_{50} = 1$							
0.3	1.0	0.309	0.362	0.740	0.094	0.437	0.435
0.7	1.0	0.019	0.339	0.963	0.307	0.296	0.675
$D/VC_{50} = 10$							
0.3	1.0	0.252	0.278	0.891	0.394	0.501	0.927
0.7	1.0	0.058	0.289	0.947	0.271	0.156	0.830
$D/VC_{50} = 100$							
0.3	1.0	0.257	0.577	0.974	0.295	0.363	0.687
0.7	1.0	0.119	0.371	0.964	0.180	0.136	0.654

The parameter values used were $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{in} = 9 \text{ units/h}$, $I_{max} = 1$, $IC_{50} = 100 \text{ ng/ml}$, and $\lambda = 0$

Table 3

D-optimal designs for Models I and III, with no dose–time constraint

$k_{out} \text{ (h}^{-1}\text{)}$	$\lambda = 0$	$\lambda = 0.75$	$\lambda = 1.5$
Model I			
0.3	(100, 0), (2.51, 3.55),	(100, 0), (5.62, 5.10),	(100, 0), (15.8, 7.00),
	(100, 7.15), (100, 8.30)	(100, 7.00), (100, 12.8)	(100, 7.30), (100, 10.8)
0.7	(100, 0), (100, 1.36),	(100, 0), (100, 3.00),	(100, 0), (100, 3.80),
	(100, 6.80), (100, 17.0)	(100, 6.40), (100, 13.8)	(100, 6.40), (100, 10.2)
Model III			
0.3	(100, 0), (2.51, 3.50),	(100, 0), (1.00, 2.90),	(100, 0), (100, 0.700),
	(100, 7.20), (100, 18.3)	(100, 6.20), (100, 23.3)	(0.320, 2.40), (50.1, 25.3)
0.7	(100, 0), (100, 1.36),	(100, 0), (2.51, 0.700),	(100, 0), (100, 0.400),
	(100, 6.80), (100, 17.0)	(100, 6.40), (39.8, 17.0)	(0.320, 0.760), (17.8, 17.2)

The parameter values used were $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{in} = 9 \text{ units/h}$, $I_{max} = 1$, and $IC_{50} (SC_{50}) = 100 \text{ ng/ml}$. The maximal feasible dose, D_{max} , is assumed to be equal to $100 \cdot V \cdot IC_{50}$. Each of the 4 optimal design points listed is a pair ($D/V/IC_{50}$, sampling time)

Table 4

D-optimal designs for Model I with constraints

k_{out} (h ⁻¹)	Sampling times		
	$\lambda = 0$	$\lambda = 0.75$	$\lambda = 1.5$
0.3	0, 3.10, 10.5, 10.5 0,	4.80, 8.60, 11.0 0,	6.70, 6.70, 10.7
0.7	0, 1.45, 8.26, 8.26	0, 2.70, 6.42, 6.42 0,	4.20, 4.20, 6.60

Two doses, $D = 100 \cdot V \cdot IC_{50}$ and $D = 10 \cdot V \cdot IC_{50}$, are used with the same sampling times. The parameter values used were $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{in} = 9 \text{ units/h}$, $I_{max} = 1$, and $IC_{50} = 100 \text{ ng/ml}$. Only the D-optimal sampling times are listed. Every D-optimal design presented in the table consists of 8 dose–time pairs, obtained by combining each of the two doses, $100 \cdot V \cdot IC_{50}$ and $10 \cdot V \cdot IC_{50}$, with each of the 4 sampling times given in the table

Table 5

D-optimal designs for Model I with constraints

$k_{out} \text{ (h}^{-1}\text{)}$	$\lambda = 0$	$\lambda = 0.75$	$\lambda = 1.5$
0.3	6.70	15.5	29.0
	0, 3.10, 10.1, 10.1 0,	4.80, 10.0, 10.0	0, 6.30, 9.10, 10.9
0.7	100	100	100
	0, 1.36, 6.8, 17.0	0, 2.76, 6.3, 13.8	0.28, 3.9, 6.24, 10.2

Any two doses each not exceeding $100 \cdot V \cdot IC_{50}$ are permitted. The same sampling times are used with each of the two doses. The lowest dose expressed in units of $V \cdot IC_{50}$ and the 4 optimal sampling times are listed. The highest feasible dose of $100 \cdot V \cdot IC_{50}$ is used in all of these designs. Every D-optimal design consists of 8 dose–time pairs obtained by combining each of the two doses, $100 \cdot V \cdot IC_{50}$ and the given dose with each of the 4 indicated sampling times

Table 6

Selected 8-point designs for Model I

k_{out} (h ⁻¹)	Study design										
	A1	B1	C1	D1	E1	F1	G1	H1	I1	K1	M1
0.3											
Dose	100, 10	100, 6.70	100, 10	100, 10	100, 10	100	100	100	10, 1	10, 1	(100, 0), (2.51, 3.55)
Time	0, 3.10, 10.5, 10.5	0, 3.10, 10.1, 10.1	0, 11.3, 22.7, 34.0	5.65, 13.2, 20.8, 28.4	2.41, 5.83, 14.1, 34.0	2.53, 9.49, 18.5, 39.6	0, 11.3, 22.7, 34.0	5.65, 13.2, 20.8, 28.4	0, 8.80, 17.6, 26.4	4.50, 10.5, 16.5, 22.5	0, 8.80, 17.6, 26.4
0.7											
Dose	100, 10	100, 100	100, 10	100, 10	100, 10	100	100	100	10, 1	10, 1	(100, 0), (100, 1.36)
Time	0, 1.45, 8.36, 8.36	0, 1.36, 6.8, 17.0	0, 10.3, 20.7, 30.1	5.15, 11.7, 18.3, 25.0	2.34, 5.49, 12.9, 30.1	0, 1.36, 6.80, 17.0	0, 10.3, 20.7, 30.1	5.15, 11.7, 18.3, 25.0	0, 7.50, 15.0, 22.5	3.75, 8.75, 13.8, 18.8	0, 7.50, 15.0, 22.5

The parameter values used were $ke/\equiv 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $k_{12} = 9 \text{ units/h}$, $f_{max} = 1$, and $IC_{50} = 100 \text{ ng/ml}$. The first two numbers in each of the columns A1–E1, I1–K1 are 2 doses followed by 4 sampling times. Each of the two doses is paired with each of the four sampling times to yield an 8-point design. Designs F1–H1, L1 use a single dose listed at the top of each column. The dose is combined with each of the 4 sampling times listed below in that column. Each of the dose–time combinations in F1–H1, L1 is replicated twice, which results in an 8-point design. Column M1 contains 4 dose–time pairs, each replicated twice. The dose is listed first in each dose–time pair. All doses are expressed in units of V/IC_{50}

Table 7

D-efficiencies for some 8-point designs for Model I

$k_{out}(h^{-1})$	Study design										
	A1	B1	C1	D1	E1	F1	G1	H1	I1	K1	M1
0.3	0.89	0.90	0.41	0.69	0.76	0.84	0.56	0.67	0.18	0.44	0.28
0.7	0.96	1.0	0.16	0.45	0.76	1.0	0.49	0.73	0.07	0.35	0.45

The parameter values used were $k_{el}=0.3\text{ h}^{-1}$, $V=90\text{ l}$, $k_{in}=9\text{ units/h}$, $I_{max}=1$, and $IC_{50}=100\text{ ng/ml}$.

The designs A1–M1 are given in Table 6

Table 8

D-efficiencies for Model I under parameter misspecification

k_{out}, k_{in}	I_{max}, IC_{50}					
	1, 2	1, 0.5	1, 1	0.5, 1	0.5, 0.5	0.5, 2
0.6, 18	0.81	0.95	0.91	0.92	0.92	0.83
0.3, 9	0.85	0.91	1	0.98	0.88	0.84
0.15, 4.5	0.66	0.82	0.83	0.78	0.76	0.63

The parameter values held constant were $k_{el} = 0.3 \text{ h}^{-1}$, $V = 90 \text{ l}$, $\lambda = 0.75$. The changed parameters were k_{in} (units/h), k_{out} (h^{-1}), I_{max} (no units), and IC_{50} (ng/ml). A single dose, $D = 10 \cdot V \cdot IC_{50}$, was used with 4 sampling times (1.93, 5.69, 10.8, 23.1) listed in Table 1, which makes for a single-dose D-optimal design obtained using the assumed parameters, $k_{in} = 9 \text{ units/h}$, $k_{out} = 0.3 \text{ h}^{-1}$, $I_{max} = 1$, and $IC_{50} = 1 \text{ ng/ml}$. The D-efficiencies of this design are given for the 18 sets of the true values of I_{max} , IC_{50} , and k_{in} , k_{out} .