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Methods of utilizing baseline values for indirect response models

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Abstract

This study derives and assesses modified equations for Indirect Response Models (IDR) for normalizing data for baseline values (R_0) and evaluates different methods of utilizing baseline information. Pharmacodynamic response equations for the four basic IDR models were adjusted to reflect a ratio to, a change from (e.g., subtraction), or percent change relative to baseline. The original and modified IDR equations were fitted individually to simulated data sets and compared for recovery of true parameter values. Handling of baseline values was investigated using: estimation (E), fixing at the starting value (F1), and fixing at an average of starting and returning values of response profiles (F2). The performance of each method was evaluated using simulated data with variability under various scenarios of different doses, numbers of data points, type of IDR model, and degree of residual errors. The median error and inter-quartile range relative to true values were used as indicators of bias and precision for each method. Applying IDR models to normalized data required modifications in writing differential equations and initial conditions. Use of an observed/baseline ratio led to parameter estimates of $k_{in} = k_{out}$ and inability to detect differences in k_{in} values for groups with different R_0 , whereas the modified equations recovered the true values. An increase in variability increased the %Bias and %Imprecision for each R_0 fitting method and was more pronounced for 'F1'. The overall performance of 'F2' was as good as that of 'E' and better than 'F1'. The %Bias in estimation of parameters SC_{50} (IC_{50}) and k_{out} followed the same trend, whereas use of 'F1' or 'F2' resulted in the least bias for S_{max} (I_{max}). The IDR equations need modifications to directly assess baseline-normalized data. In general, Method 'E' resulted in lesser bias and better precision compared to 'F1'. With rich datasets including sufficient information on the return to baseline, Method 'F2' is reasonable. Method 'E' offers no significant advantage over 'F1' with datasets lacking information on the return to baseline phase. Handling baseline responses properly is an essential aspect of applying pharmacodynamic models.

Keywords

Indirect response models; Turnover models; Baseline responses; Pharmacodynamics; Modeling and simulation

Introduction

In general, pharmacokinetic (PK) data with endogenous substances and pharmacodynamic (PD) responses have baseline values that should be measured before drug administration and this baseline data may reveal some physiological information that can be further utilized during characterization of drug effects. When analyzing PK and PD data, therefore, it is recommended to use experimental data without any modifications (i.e., baseline normalization). Potential bias can occur in use of baseline subtraction during estimation of some PK parameters (e.g., AUC and $t_{1/2}$) [1] in the analysis of endogenous substances and in resolving pharmacologic/PD parameters [2, 3].

When comparing observed data among patients or between groups, however, often due to differing baselines, normalization of the data relative to their baseline becomes an option to visualize differences. The common forms of normalization include a ratio to and subtraction of subsequent measurements from the baseline, thereby generating the same starting value of 1 or 0 for all response profiles. While the baseline-normalized data would aid comparison of apparent drug-related differences between groups or individuals, the basic properties and variation of individual baselines are no longer taken into consideration as a determinant of drug responses.

For indirect response models, the initial or baseline value (R_0) is a dependent variable that is determined by a ratio of k_{in} (zero-order production rate constant) and k_{out} (first-order loss rate constant). When a data set with an observed/baseline ratio is fitted to the basic IDR models, the parameter estimates will always result in $k_{in} = k_{out}$ due to having the initial condition for differential equations of 1 in such data. This is of particular concern when interpreting and comparing the meaning of system-related parameters, k_{in} and k_{out} , between studies or patients. Higher baselines generate a larger net response (AUC of response) and the baseline data may reveal important sources of variation of drug response [4]. Further, the parameter estimates obtained from the normalized data may not have the same meaning as ones from the original data.

In addition, analyses with IDR and other models offers an option whether to estimate R_0 as a model parameter or to fix R_0 to an initial measurement. When the baseline is known, fixing R_0 provides an advantage by reducing the number of parameters to be estimated. However, for most experimental data the true baseline is usually not known and the baseline value is often taken from the first observation at time zero. As the baseline data is also subject to error, fixing the baseline would carry this uncertainty onto all subsequent measurements which may, in turn, lead to biased estimation of other parameters.

In this report, we provide modified equations for IDR models for baseline-normalized data to include baseline information and demonstrate the resulting concerns if data are fitted without such adjustments. Handling of the baseline parameter (e.g., fixation or estimation) was examined for IDR models and influences on estimation of model parameters were assessed using individualized fittings of simulated data for various study designs. A literature search was performed to reveal the frequency and type of baseline normalization practiced for IDR models.

Methods

Modified IDR equations for normalized data by baseline

Derivations of modified IDR equations—The basic IDR model describes a turnover process by which the response variable is controlled by its production and loss. Based on the mechanism of action of the drug, the four IDR models depict inhibition (Models I and II) or

stimulation (Models III and IV) of either production or loss of the response. The rate of the change of the response R with time for IDR models can be described as:

$$\frac{dR}{dt} = k_{in} \cdot (1 + H_1(t)) - k_{out} \cdot (1 + H_2(t)) \cdot R \quad \text{where } R(0) = R_0 \quad (1)$$

where the pharmacologic processes operate according to capacity-limited functions:

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

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

$$\text{Model III: } H_1(t) = \frac{S_{\max} \cdot C(t)}{SC_{50} + C(t)} \quad \text{and} \quad H_2(t) = 0 \quad (2c)$$

$$\text{Model IV: } H_1(t) = 0 \quad \text{and} \quad H_2(t) = \frac{S_{\max} \cdot C(t)}{SC_{50} + C(t)} \quad (2d)$$

where $I_{\max}$ and $S_{\max}$ are the maximum effects, IC_{50} and SC_{50} are drug concentrations producing 50% of maximum effect, and $C(t)$ is the pharmacokinetic function.

When there is no drug present, the baseline is maintained at a steady-state R_0 and is determined by the balance between production rate k_{in} and degradation rate k_{out} :

$$R_0 = \frac{k_{in}}{k_{out}} \quad (3)$$

Derivations of IDR models for normalized data are shown below for three different scenarios where the original data set is computed as: (a) ratio relative to the baseline, (b) change from the baseline (subtraction), and (c) percent change relative to the baseline.

Normalization of data as a ratio—Let a new response variable $\tilde{R}$ reflect a ratio relative to the baseline R_0

$$\tilde{R} = \frac{R}{R_0} \quad (4)$$

Taking derivatives of both sides

$$\frac{d\tilde{R}}{dt} = \frac{1}{R_0} \cdot \frac{dR}{dt} \quad (5)$$

Substituting Eq. 1 for dR/dt and $R = \tilde{R} \cdot R_0$ from Eq. 4 into Eq. 5 yields

$$\frac{d\tilde{R}}{dt} = \frac{1}{R_0} \cdot \left[k_{in} \cdot (1 + H_1(t)) - k_{out} \cdot (1 + H_2(t)) \tilde{R} \cdot R_0 \right] \quad (6)$$

Equation 6 can be rearranged

$$\frac{d\tilde{R}}{dt} = \frac{k_{in}}{R_0} \cdot (1+H_1(t)) - k_{out} \cdot (1+H_2(t)) \cdot \tilde{R} \quad \text{where} \quad \tilde{R}(0)=1 \quad (7)$$

Normalization of data as baseline subtraction—Let a new response variable $\tilde{R}$ reflect a difference from the baseline R_0

$$\tilde{R} = |R - R_0| \quad (8)$$

Take derivatives of both sides

$$\frac{d\tilde{R}}{dt} = \frac{dR}{dt} \quad (9)$$

Substituting Eq. 1 for dR/dt and $R = \tilde{R} + R_0$ from Eq. 8 into Eq. 9 yields

$$\frac{d\tilde{R}}{dt} = k_{in} \cdot (1+H_1(t)) - k_{out} \cdot (1+H_2(t)) \cdot (\tilde{R} + R_0) \quad \text{where} \quad \tilde{R}(0)=0 \quad (10)$$

Alternatively, the normalized data may be fitted to $R - R_0$ with original Eq. 1.

Normalization of data as percent change relative to the baseline—Let a new response variable $\tilde{R}$ reflect percent change relative to baseline R_0

$$\tilde{R} = (|R - R_0|) / R_0 \quad (11)$$

Taking derivatives of both sides

$$\frac{d\tilde{R}}{dt} = \frac{1}{R_0} \cdot \frac{dR}{dt} \quad (12)$$

Substituting Eq. 1 for dR/dt and $R = R_0 \cdot (\tilde{R} + 1)$ from Eq. 11 into Eq. 12 yields

$$\frac{d\tilde{R}}{dt} = \frac{1}{R_0} \cdot \left[k_{in} \cdot (1+H_1(t)) - k_{out} \cdot (1+H_2(t)) \cdot R_0 \cdot (\tilde{R} + 1) \right] \quad (13)$$

Rearranging Eq. 13 gives

$$\frac{d\tilde{R}}{dt} = \frac{k_{in}}{R_0} \cdot (1+H_1(t)) - k_{out} \cdot (1+H_2(t)) \cdot (\tilde{R} + 1) \quad \text{where} \quad \tilde{R}(0)=0 \quad (14)$$

While the initial conditions for the modified IDR Eqs. 7, 10 and 14 become 1 or 0, the relationship between the original baseline R_0 and model parameters k_{in} and k_{out} (i.e., Eq. 3) still holds for these modified equations.

Pharmacodynamic simulations and identification—In order to compare performances of the modified and original IDR equations, simulations were performed to generate PD data using the four IDR models. The pharmacokinetics was described by a linear monoexponential function:

$$C(t) = D/V \cdot e^{-(CL/V) \cdot t} \quad (15)$$

with clearance (CL) = 2.5 and volume (V) = 4 following a single intravenous dose (D) = 10,000. The PK was kept the same for all four IDR models.

Errorless hypothetical PD response profiles were generated using the original IDR equations including two baseline values, $R_0 = 50$ or 80 units. As the baseline parameter is determined by k_{in} and k_{out} (i.e., Eq. 3), two cases were assumed, namely that there was a difference in either k_{in} (Case A) or k_{out} (Case B) for each model. Each response profile contained 13 data points. The sampling times include 4 points selected using the D-optimal sampling design available in the ADAPT V (4) program [5]. This method yields the number of optimal time points matching the number of parameters being sought, and 8 additional ones were chosen to cover the entire response curve. The values used for the PD simulations are listed in Table 1.

The simulated data were then transformed to the three forms of normalized data sets. These transformed data were then fitted to either original or modified IDR equations to evaluate how well the models recovered the true parameter values. All simulations and fittings were performed using ADAPT V (4).

Methods of utilizing baseline information during model fitting with IDR

Simulation of pharmacodynamic data—In order to evaluate different methods of utilizing baseline information (i.e., fixing or estimation) and their influence on other parameter estimates during model fittings with IDR models, errant PD responses were simulated using the IDR equations under various scenarios of different doses, numbers of data points per subject (7, 8, and 13), type of IDR model, and degree of residual errors (RV). The PD parameters used were $S_{max} = 5$ ($I_{max} = 0.8$), $SC_{50} = 4$ ($IC_{50} = 4$), and $k_{out} = 0.4$. The initial conditions for the response curves were set at $R_0 = 50$ units. The IDR III was used to generate PD data sets with 7, 8, or 13 observations following a single intravenous dose input with 10,000. To test the dose-dependence of parameter estimations, a higher dose 100,000 was also used. For IDR Model I, II, and IV, response curves were simulated only for 13 data points at a dose of 10,000. Though these rich datasets cover the entire PD response profiles, they may not closely represent real experimental data seen in general practice. Thus, the number of observations was reduced to have fewer data points in overall response curves ($n = 8$) with less information in the return phase ($n = 7$). Each dataset consisted of 1,000 subjects.

The maximum likelihood objective function was applied with the variance model:

$$Var(Y) = (Intercept + Slope \cdot Y)^2 \quad (16)$$

where Y is the predicted response and $Slope$ (10, 20 or 30%) and $Intercept$ (5 units) are the residual variabilities that were added to the simulated responses to mimic the variability typically observed in practice [6]. The PK function and parameter values were kept the same as previous section with single doses of 10,000 or 100,000.

Analysis of the simulated data—The ADAPT V (4) program was used to estimate model parameters using the original model used for simulation. The refitting of the model

and PD parameter estimation was done using the three approaches that were being compared: estimation of the baseline (E), fixing R_0 at the starting value (F1), and fixing R_0 at an average of starting and returning values of response profiles (F2). The true values of PD parameters used for simulations were provided as initial values for each parameter during fittings. There were no upper limits imposed on the parameter estimates, except for $I_{\max}$, where its upper boundary was set to be 1, and the lower boundary was zero as the ADAPT program constrains model parameters to be positive. The PK parameters were fixed during simulations.

The bias and precision in the parameter estimates were expressed as (5)

$$\% \text{Bias} = \frac{(\text{Median} - \text{True})}{\text{True}} 100\% \quad (17)$$

$$\% \text{Precision} = \frac{(Q3 - Q1)}{\text{True}} 100\% \quad (18)$$

Since the distribution of the parameters is skewed, medians rather than means were used as a measure of central tendency. Consequently, the mean prediction error was replaced by the median based prediction errors. The $Q1$ and $Q3$ denote the first and third quartiles of the distribution. The relative metric for bias and precision of the individual parameter estimates allowed us to introduce measures of the overall absolute bias and precision as their arithmetic means:

$$\text{Overall absolute bias} = \frac{\sum_{i=1}^{N_p} |\% \text{Bias}_{P_i}|}{N_p} \quad (19)$$

$$\text{Overall absolute precision} = \frac{\sum_{i=1}^{N_p} |\% \text{Precision}_{P_i}|}{N_p} \quad (20)$$

where P_i are individual model parameters, including $S_{\max}$ ($I_{\max}$), SC_{50} (IC_{50}), k_{out} , and R_0 . The number of model parameters estimated (N_p) differs for the fitting methods used depending on whether R_0 was estimated or fixed.

Results

Literature search

A literature search was performed to assess the frequency of normalizing IDR response profiles by baseline values and the types of conversion used. The search was focused by using ‘indirect response models’ and ‘turnover models’ as keywords in PubMed over the time frame of 1995–2008 as well as the references in published papers for the same period of time. A total of 258 research articles were found which performed IDR model fitting of experimental data. Of these, 20 (8%) used a ratio to baseline, 5 (2%) used subtraction of the baseline, and 3 (1%) used percent change relative to baseline. All of these apparently employed the original IDR model equations (Eqs. 1–3) rather than making adjustments for normalization.

Modified IDR equations for baseline-normalized data

The response versus time profiles with two different baseline values (Group I and Group II) were simulated while keeping the values of either k_{in} (Case A) or k_{out} (Case B) parameters constant for the two groups. The original simulated and normalized data from Model III are shown in Fig. 1. When the PD data with the same k_{out} for two groups were normalized as a ratio of their baseline values, the two response curves completely overlapped whereas this was not the case when there is a difference in k_{out} . This also applies to the datasets expressed as relative changes from the baseline. The subtraction method shifted the response curves down to zero baselines from their original baseline values. Expression of the data as absolute or relative changes from the baseline produced a zero baseline. As the PD equations for IDR models require a non-zero baseline, such data were no longer applicable to the IDR models with regular equations due to the relationship k_{in}/k_{out} being equal to zero. For this reason, the measured responses must be transformed as a ratio of observed/baseline if the data are intended to be analyzed using IDR models after normalization.

Table 1 lists the values of PD parameters estimated from baseline-normalized data as a ratio using the original PD equations for IDR models. As expected based on Eq. 3 with $R_0 = 1$, fitting the PD datasets using the regular IDR equations always resulted in parameter estimates of $k_{in} = k_{out}$. In addition, the use of the regular IDR equation was not able to identify a true difference in k_{in} between two groups for Case A whereas it resulted in false detection of a difference in k_{in} for Case B in spite of the same k_{in} for both groups. On the other hand, the modified equations were able to recover all true parameter values for both Cases A (k_{in} difference) and B (k_{out} difference). Regardless of differences in k_{in} and k_{out} , S_{max} and SC_{50} were recovered accurately with both equations. As summarized in Table 1, the same findings applied to all of the IDR Models. Figure 2 provides similar simulations comparing original and ratio-normalized response profiles for the two baseline conditions (Case A and B). Although the original IDR equations were not applicable for the data sets with $R_0 = 0$ resulting from baseline-normalization using baseline subtraction or percent changes from baseline, the modified IDR equations (Eqs. 10, 14) could handle these data and recover the true parameters.

Utilization of baseline information

The simulated mean PD responses for IDR III with different levels of errors (10, 20, and 30%) are shown in Fig. 3. The simulated data sets with 13 time points cover the complete profile depicting the baseline, rising, peak, declining, and return to baseline. Such data sets were generated at two dosages, 10,000 and 100,000. The second sets of simulations have fewer sampling points ($n = 8$) than the previous sets, but ensured the complete return to baseline with later sampling time points. The third sets of simulations have the same sampling time points as ones with 8 observations except for the last sample ($n = 7$), which represents the response profiles with less information for the return to baseline. The last two scenarios were simulated only at a dose of 10,000.

Figures 4 and 5 depict the overall bias and precision of the three methods used to analyze the simulated data for IDR III. For the data sets with 13 observations per subject the bias was least when analyzed by estimating the baseline (Method E) while Method F1 (fixing R_0 at starting value) resulted in the most biased estimation of parameters. When the baseline was fixed to an average of starting and returning response values (Method F2), the overall bias was slightly higher than Method E, but its overall precision was as good as estimation of R_0 . These trends remained the same regardless of the residual errors, but became more noticeable with increasing RV%. As the residual variability increased to 20% and 30%, the bias increased about 2- and 3-fold from the values of 10% random error for Method E and 2.3- and 3.4-fold for Method F2. For overall precision, Method F1 performed worst among

the three methods and this became more apparent with higher residual variability. Similar to the bias, the precision between Methods E and F2 were comparable throughout the various ranges of random errors.

Tables 2 and 3 summarize the bias and precision of individual Model III parameter estimates for the three methods under various conditions. Parameter k_{out} was estimated with the least bias, ranging 2.42–8.84% for all three methods, though Method F1 was the highest in bias. The differences in precision of k_{out} between the methods were insignificant. Interestingly, fixing R_0 to either the starting or average values (Method F1 or F2) led to less biased values of S_{max} compared to the estimation of the baseline. However, more precise estimates of S_{max} were obtained from Method E or F2 over Method F1. The bias and imprecision observed for SC_{50} were the highest among parameters and reflected the same patterns of the overall bias and imprecision from all parameters with Method E being the least followed by Method F2 and F1. This indicates that fitting SC_{50} contributed the most to the overall bias and precision of each method. The lesser performance of Method F1 for estimation of SC_{50} was more pronounced as variability increased. At the higher dose, similar results were observed as with the lower dose. The magnitudes of bias and precision were also similar as before, indicating that the dose used for simulations (i.e., 10,000) was sufficiently high reflecting optimal conditions for resolving IDR parameters.

When fewer samples were collected for PD response profiles ($n = 8$), overall bias increased (i.e., 50–80%) compared to the richer data for all cases, but other findings were unchanged. The imprecision was lowest for Method E and highest for Method F1 and the magnitudes were slightly higher with fewer sampling points as compared to estimations from 13 time points. The bias and precision among individual parameters showed similar trends as seen with 13 observations, but the magnitudes were 1.5–2 times higher for SC_{50} , S_{max} , and R_0 , and 2–4 times for k_{out} than those from more extensive datasets. It appeared that k_{out} and SC_{50} were more affected by having fewer sampling points compared to S_{max} and R_0 .

The datasets with 7 observations have the same sampling scheme as those with 8 samples with the exception of 1 less data point on the return to baseline phase and thus depict less confidence whether the response regained the baseline. Thus, Method F2 was not applicable; only Methods E and F1 were compared for this scenario. The overall bias was slightly lower with Method E as compared to Method F1 at all levels of RV. The parameters were less precisely estimated by fixing R_0 than by its estimation. A multi-fold difference existed in S_{max} values obtained by the two methods. Least bias was observed for k_{out} with Method E and even Method F1 led to negligible bias. The imprecision in estimated parameters was not dependent to a large extent on the method used.

Figure 6 and Tables 4 and 5 provide values of overall bias and precision for simulations with IDR Models I, II, and IV. The findings discussed above for Model III generally apply to all indirect response models with Method E providing least bias and imprecision in fittings.

Discussion

The IDR models have been applied to numerous pharmacodynamic studies of various drugs since introduced by Dayneka et al. [7]. As the basic IDR models are based on a turnover process that maintains the balance between production and loss processes, accurate characterization of the baseline is essential for IDR models not only for better understanding of systems of interest but also for unbiased assessment of drug effects. Whenever possible, therefore, it is highly recommended that original experimental data be used including baseline values rather than normalized data to model drug responses. Once data are normalized by its baseline for any reasons (e.g., illustrative purpose), however, individual

differences in basal conditions between subjects or study groups are lost. Baseline information can be an important factor to adjust individualized dosages [4], to evaluate patient-specific covariates, and to reflect disease status. In addition, since model parameters of the IDR models are interrelated with baseline values, caution is required when interpreting a set of parameter estimates (i.e., k_{in} and k_{out}) obtained from baseline-normalized data. This work illustrates major concerns in use of normalized data in IDR model applications. While baseline normalization is not a frequent practice for handling IDR models, perhaps because of the visibility of the baseline in setting Initial Conditions of differential equations, perusal of pharmacology journals will show that such adjustments are much more commonplace when fitting simple relationships such as the Hill function.

Applying normalized data as ratios in IDR models always led to the value of k_{in} the same as k_{out} , though their units are different, and such models would behave as if operating by a single system parameter, either k_{in} or k_{out} . As far as a single response profile is concerned, the consequence may not be noticeable. However problems can arise when parameter estimates are compared among individuals or study groups. Our study shows that application of IDR models to baseline normalized data affects estimation of parameter k_{in} , but not k_{out} . However, estimation of drug-specific potency and efficacy parameters were not affected by normalization. Baseline normalized profiles always returned to values of k_{in} normalized relative to their baseline, thereby yielding response profiles that completely overlap between two groups with different R_0 as long as k_{out} is same for both groups. This is consistent with the observations from Sun and Jusko [4] that net IDR response was proportional to baseline when they assumed k_{out} to be same for all profiles. It is worthwhile to note that this trend only applies to data sets without any physiological limits. Yao et al. [8] showed that PD profiles with physiological limits do not overlap each other when normalized for baseline and their net response is not proportional to the baseline.

When normalized data were fitted to IDR models with the original equations, a true difference was not identified when two groups originally had different values of k_{in} . On the other hand, detection of a false difference in k_{in} was noticed when a true difference existed in k_{out} but not in k_{in} . These findings clearly demonstrate that caution is needed when one wishes to correlate individual parameter estimates to patient specific covariates or physiological variables. In order to avoid such bias, we derived modified PD equations for IDR models that can be applied to different forms of baseline-normalized data, including a ratio and baseline subtraction. The modified IDR model equations were able to recover true values of all parameters and true differences in model parameters between two groups were resolved from the normalized data. This simple adjustment allows for original baseline information, otherwise being lost, being reflected onto characterization of pharmacodynamic responses.

When IDR models have been applied to baseline-normalized data, it is commonly found that the PD data were converted to a ratio rather than formats of baseline subtraction or relative changes. This would be due to the fact that the latter produce response profiles starting from zero, which invalidates IDR model application (i.e., $k_{in}/k_{out} = 0$). However, the modified IDR model Eqs. 10 and 14 could still be utilized regardless of such baseline-normalization without losing the properties of the basic IDR models. This can be useful, for example, when assessing induction of proinflammatory cytokines such as tumor necrosis factor- α (TNF α) and IL-6 in experimentally induced inflammatory animal models, where these substances are not present or are below the assay detection level in the normal state, but when there is a trigger, their concentrations rise. Gozzi et al. [9] adapted a turn-on/off model for k_{in} to reflect induction of TNF α in control and disease animals.

In this study, we assumed that the baseline remains constant during the course of study. In cases where the baseline is gradually changing over time (e.g., disease progression) or following a circadian rhythm, baseline normalization is particularly inappropriate. Under these circumstances the baseline relationship $R_0 = k_{in}/k_{out}$ is no longer constant and thus special consideration is needed to characterize such changes using placebo or control groups. Post et al. [10] adapted time-dependent k_{in} or k_{out} processes to represent disease progression, thereby producing gradual changes in baselines over time. Krzyzanski et al. [11] and Chakraborty et al. [12] employed a periodic time-dependent production rate $k_{in}(t)$ and first-order loss constant $k_{out}(t)$ to represent circadian rhythms in IDR model application to cortisol dynamics.

Baseline normalization implies that the baseline is not estimated but fixed to a specific value. This reduces the number of model parameters to be estimated. Having fewer model parameters may offer some advantages, including a less complex model, reduction in uncertainty of other parameter estimates, faster computational times, and fewer time points in analysis of data. The benefits are offset by disadvantages such as bias from a possibly inaccurate baseline value and less freedom in parameter estimation. While modelers may have debated as to whether the baseline should be estimated or fixed, previous studies have not formally assessed how each approach would impact estimation of other model parameters. We compared overall performance of two methods of handling the baseline parameter, estimation versus fixation, using simulated IDR response profiles under various study designs, mainly including different levels of residual errors and numbers of sampling points.

If the baseline is not estimated, it is not uncommon to find the baseline parameter fixed to initial values recorded before treatment is given [13]. Since a true baseline is generally not known in experimental settings and baseline observations also contain measurement variability, fixing the baseline results in those errors being propagated onto subsequent measurements and leading to biased parameter estimation. Dansirikul et al. [3] discussed different ways of modeling baseline responses while taking into consideration between- and within-individual variability and demonstrated how those errors could impact overall performances of models. Their findings also support that baseline normalization by the observed baseline value (their method B4) yields more biased and imprecise estimation of parameters than the estimation methods (their methods B1–B3). It can be noted that a population modeling approach provides an advantage in terms of implementing various models to reflect different magnitudes of interindividual and residual errors associated with estimating the baseline, which is limited in the individual analysis setting.

Ideally complete washout of the drug effect under homeostasis is confirmed by the return to baseline value being equal or close to the initial value. Thus not only the starting value but the departure from the baseline and the progression back to the baseline can provide information about the baseline. These components could be utilized to obtain reliable estimates of baseline parameters regardless of estimation or fixation. Our study showed Method E led to least bias and imprecision when the data sufficiently captures a full response profile compared to methods that involve fixing the baseline. In the case where the profile does not completely return to baseline (i.e., 7 time points), the two methods were comparable. If the baseline has to be fixed, bias and imprecision could be reduced by using average values of initial and late measurements instead of relying on a single observation. While Method E performed slightly better, overall relative performance between Methods E and F2 was similar and the difference became negligible when there were more sampling points in the return phase. Although not tested in this study, averaging two or more initial observations would serve a similar purpose.

In terms of individual parameters, bias in the estimation of SC_{50} was most sensitive to the variability in data and the fitting methods used, with Method E giving the least bias. For S_{max} Method F1 resulted in the least bias and its bias was similar regardless of residual variability or number of data points. Parameters k_{out} and k_{in} were the most robust parameters as they did not differ to a larger extent with different methods used. The effects on k_{in} were reflective of the effects on R_0 and k_{out} as it was resolved as a secondary parameter ($R_0 \cdot k_{out}$). The parameter most poorly estimated was SC_{50} which was the largest contributor to the overall bias and precision. This was expected as two or three dosages over a wide range may be required for its reliable estimation. Krzyzanski et al. [14] demonstrated that higher doses yield least biased estimates for all IDR parameters, especially for SC_{50} and S_{max} . We thus used a relatively high dose of 10,000 to optimize recovery of parameters. An even higher dose of 100,000 was also tested to ensure minimal dependence of parameter estimates on selected doses. These simulations had the advantage of use of appropriate models and initial estimates for the model parameters and residual variability as the same values were used to simulate the datasets. Real data would present added challenges of more complex pharmacokinetics, less optimal study design, possible need for extended IDR models, and other complications.

In summary, we illustrated some major concerns in use of IDR models with baseline-normalized data and provided modified PD equations for IDR models applicable to various types of baseline-normalized data while retaining original baseline information for characterization of pharmacodynamic responses. When handling the baselines in IDR models, estimation (Method E) resulted in less bias and better precision compared to fixation (F1). In case of a rich dataset with sufficient information on the return to baseline phase, Method F2 would be an option to consider. The findings suggest that Method E offers no significant advantage over Method F1 if there is insufficient information on the return to baseline phase; in general, however, it is thought that Method E will be more robust because it will not put undue weight on a single measured value that can be biased by unknown measurement error.

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Appendix 1: the impact of truncating negative values to a LLOQ in simulated datasets

Handling of observations below the LLOQ or negative values (in case of simulated data) in data analysis has been a matter of concern and investigation. A recent study which examined biexponential pharmacokinetic functions showed that truncation of normal distributions by simply ignoring or replacing them with the LLOQ led to model misspecification and biased parameter estimates [15]. The severity of such bias would be a function of various factors, including fraction of LLOQ adjustments, type and nature of model applied, and magnitude of random error. In analyses using simulated datasets, it would be best to prevent the occurrence of negative values in simulations either by re-parameterization (avoiding a negative values) or log-transformation. Otherwise, to avoid biased estimations, it was suggested to use originally simulated data even with negative values. However, in real life situations such as with measurement of most pharmacologic effects, negative values would likely not exist. In simulating IDR models with effects which fall below zero, common sense would seem to argue towards use of 0 or $\frac{1}{2}$ LLOQ values since the fitted models would predict 0 as an actual lowest possible value (Models I and IV).

The data sets that were used in the main article included noise-added response values below zero. This seemed to be due to having an additive portion of residual error model, and the analyses were performed in the presence of such negative values. The portion of negative values in each data set varied depending upon type of IDR model and amount of residual error. The percentages of negative values in simulations were higher with residual error of 30%, at most 2–3% for IDR Models II, III, and IV. For the datasets simulated using IDR Model I, however, due to the nature of the model yielding a downward curve and maximum responses reaching near zero, up to 20% was noticed at $RV = 30\%$. In order to assess the impact of truncation of negative values to a limit of detection, we performed additional analyses. The analyses were done for the same datasets, but we set those simulated negative values to 0.1 which was assumed to be the limit of detection.

Table 6 summarizes values of bias of individual parameter estimates of Models I, II, III, and IV using the three estimation methods. For IDR Models II and III, the percentage of bias did not differ from those values obtained from the original datasets. There were noticeable differences in IDR Model I, especially in residual error of 30% as 20% of data was affected by the LLOQ. The data truncation in IDR Model I led to the overall bias being rather lower with 30% residual error than with 20% residual error, and Methods F1 and F2 having less bias than Method E, which was different from the typical trends that we observed from the other three models. However, even for the case of IDR Model I, when the baseline R_0 is estimated, there was no difference. These changes occurred only in bias but not in precision (data not shown). For IDR Model IV, overall, the magnitudes of bias were downsized compared to those from data without the LLOQ, but the rank order of fitting methods was not changed and the trends remained the same, i.e., least bias in Method E followed by Method F2.

In summary, IDR Model I appeared to most affected by the data truncation in calculations of bias towards a higher residual error, which could lead to a different conclusion from the other cases. For the other IDR models, the magnitudes of bias and precision also changed in some scenarios. Nevertheless, the overall conclusions drawn from the current study regarding use of different baseline fitting methods remain the same in spite of this removal of negative values.

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Fig. 1.

Indirect response profiles that were originally simulated (**A** and **B**) and baseline-normalized as a ratio (**A1** and **B1**), change from baseline (**A2** and **B2**), and relative change from baseline (**A3** and **B3**) using IDR Model III. The values of model parameters were assumed to have differences in either k_{in} (Case A) or k_{out} (Case B) between two response curves

Fig. 2. Indirect response curves normalized for its baseline (ratio) after simulations using IDR Model I, II, and IV. The values of model parameters were assumed to have differences in either k_{in} (Case A) or k_{out} (Case B) between two response curves. Insets present the response profiles before baseline normalization

Fig. 3.

Simulated data sets using IDR Model III. The top panel shows response profiles with 13 time points at doses of 10,000 and 100,000 with various residual errors (RV = 10, 20, and 30%). The middle and bottom panels show simulated data sets with 8 and 7 observations at a dose of 10,000 and RV = 10, 20, and 30%. Each symbol represents mean and standard deviation from 1,000 hypothetical subjects

Fig. 4. Comparisons of overall bias between different fitting Methods E, F1, and F2. Each value was obtained by fitting IDR Model III to simulated data sets with 13, 8, and 7 time points

Fig. 5. Comparisons of overall precision between different fitting Methods E, F1, and F2. Each value was obtained by fitting IDR Model III to simulated data sets with 13, 8, and 7 time points

Fig. 6. Comparisons of overall bias and precision between different fitting Methods E, F1, and F2 for IDR Models I, II, and IV applied to datasets with 13 observations

Table 1

Comparison of model parameters estimated using original IDR models from baseline-normalized pharmacodynamic data (R/R_0) relative to their baseline value, $R_0 = 50$ (Grp I) or 80 (Grp II)

		Case A: Difference in k_{in}			Case B: Difference in k_{out}		
		True value	Grp I	Grp II	True value	Grp I	Grp II
Model I	I_{max}	0.8	0.8	0.8	0.8	0.8	0.8
	IC_{50}	4	4	4	4	4	4
	k_{out} (h^{-1})	0.4	0.4	0.4	0.4 or 0.25	0.4	0.25
	k_{in} (%/h)	20 or 32 ^a	0.4	0.4	20	0.4	0.25
	R_0	50 or 80	1	1	50 or 80	1	1
Model II	I_{max}	0.8	0.8	0.8	0.8	0.8	0.8
	IC_{50}	4	4	4	4	4	4
	k_{out} (h^{-1})	0.4	0.4	0.4	0.4 or 0.25	0.4	0.25
	k_{in} (%/h)	20 or 32 ^a	0.4	0.4	20	0.4	0.25
	R_0	50 or 80	1	1	50 or 80	1	1
Model III	S_{max}	5	5	5	5	5	5
	SC_{50}	4	4	4	4	4	4
	k_{out} (h^{-1})	0.4	0.4	0.4	0.4 or 0.25	0.4	0.25
	k_{in} (%/h)	20 or 32 ^a	0.4	0.4	20	0.4	0.25
	R_0	50 or 80	1	1	50 or 80	1	1
Model IV	S_{max}	5	5	5	5	5	5
	SC_{50}	4	4	4	4	4	4
	k_{out} (h^{-1})	0.4	0.4	0.4	0.4 or 0.25	0.4	0.25
	k_{in} (%/h)	20 or 32 ^a	0.4	0.4	20	0.4	0.25
	R_0	50 or 80	1	1	50 or 80	1	1

^aUnit for the true value of k_{in} is Response/h

Table 2

Percent bias for PD parameters for various study designs using IDR Model III

Time points	Dose	Fitting methods	$S_{\max}$			SC_{50}			k_{out}			k_{in}^a			R_0		
			10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%
13	10,000	E	5.27	9.73	12.5	6.37	14.5	25.6	2.42	3.72	2.87	4.19	7.45	10.5	2.48	4.68	7.61
		FI	3.02	2.05	2.46	14.6	36.3	57.2	3.61	6.53	8.84	0.04	2.13	2.92	b	–	–
		F2	2.64	3.13	2.01	9.07	21	29.9	2.79	4.64	3.53	2.17	1.85	0.32	–	–	–
8	100,000	E	3.14	10.7	16.1	10.7	33.8	33.8	1.33	2.97	3.95	3.42	8.37	10.4	1.72	4.61	7.64
		FI	2.01	4.67	4.79	15.2	52.4	87.3	2.05	6.24	11.4	1.47	3.74	0.95	–	–	–
		F2	0.98	3.75	2.51	12.2	37.0	35.8	1.73	3.17	4.13	1.61	3.89	1.51	–	–	–
7	10,000	E	6.17	13.2	18.0	13.5	29.8	38.0	4.15	6.96	10.1	5.69	11	15.8	3.67	7.33	10.5
		FI	0.7	0.01	0.47	23	48.2	66.8	6.45	12.9	16.4	0.74	1.6	4.34	–	–	–
		F2	1.30	2.72	2.25	21.2	37.5	41.5	5.48	9.46	12.5	1.46	4.42	3.88	–	–	–
7	10,000	E	9.41	18	26.9	12.3	25.8	36.1	4.16	6.73	9.4	8.09	15.0	20.1	4.47	9.63	14.0
		FI	1.09	0.95	0.16	19.8	38.6	43.6	6.17	10	12.4	1.18	1.64	5.06	–	–	–

^aSecondary parameter, calculated as $k_{out} \cdot R_0$

^bNot estimated

Table 3

Percent precision for PD parameters for various study designs using IDR Model III

Time points	Dose	Fitting methods	$S_{\max}$			SC_{50}			k_{out}			k_{in}^a			R_0		
			10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%
13	10,000	E	31.6	50.3	66.4	167	297	418	40.6	63.7	80.4	41	61.1	76.1	11.8	18.8	25.2
		FI	48.1	81.4	119	196	442	734	40.0	62.7	75.5	46	68.3	91.0	b	—	—
	F2	31.4	48.5	66.6	174	294	384	40.4	60.3	74.2	39.8	59.3	75.4	—	—	—	
100,000	E		23.0	43.2	62.7	132	334	582	32.8	56.0	72.9	33.9	53.7	67.6	13.72	20.53	27.8
		FI	38.0	67.4	94.6	156	504	911	34.0	56.2	72.7	36.4	59.6	78.8	—	—	—
	F2	24.5	40.2	57.7	138	319	530	33.1	54.4	69.9	33.1	52.1	65.5	—	—	—	
8	10,000	E	41.4	70.5	96.2	220	394	546	57.1	78.8	90.3	58.8	82.9	92.7	15.9	23.4	30.7
		FI	50.7	85.1	118	241	546	826	54.5	70.2	75.1	56.6	82.7	95.7	—	—	—
	F2	41	60.5	83.4	222	364	491	54.7	73.1	82.0	54.9	76.9	89.4	—	—	—	
7	10,000	E	45.7	78.3	115	220	395	532	58.3	81.6	91.4	57.5	81	89.1	19.2	28.4	37.6
		FI	51.1	84.5	113	238	435	584	55.8	73.9	80.2	56	80.3	94.3	—	—	—

^aSecondary parameter, calculated as $k_{out} \cdot R_0$ ^bNot estimated

Table 4

Percent bias of PD parameter estimates obtained from IDR Models I, II, and IV applied to simulated data sets with 13 observations at a dose of 10,000

Model	Fitting methods	$S_{\max}$			SC_{50}			k_{out}			k_{in}^a			R_0		
		10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%
IDR I	E	4.24	7.86	8.42	1.43	18.0	17.7	0.72	6.46	7.42	0.73	9.87	10.1	1.35	1.96	2.06
	FI	1.29	2.52	2.30	11.6	21.3	23.9	1.15	8.77	11.1	6.27	3.50	11.1	b	-	-
	F2	2.70	3.06	2.53	3.28	17.2	14.8	1.76	3.98	4.09	2.54	3.35	3.42	-	-	-
IDR II	E	1.79	2.53	0.82	3.05	23.7	24.6	0.19	17.7	23.1	1.57	16.7	17.1	2.46	4.12	5.85
	FI	6.71	8.78	12.0	18.9	36.6	35.9	1.03	13.2	12.1	11.5	29	36.6	-	-	-
	F2	3.64	7.64	9.52	4.26	24.4	32.3	1.15	11.8	13.7	4.65	17.7	23.8	-	-	-
IDR IV	E	5.65	13.8	19.2	0	14.5	25	1.52	1.30	0.57	0.95	2.04	1.57	1.62	2.03	2.28
	FI	0.63	3.58	6.88	22.4	36.3	58.8	0.44	2.27	4.89	9.83	12.1	15.1	-	-	-
	F2	1.23	6.85	12.3	3.69	21	29.5	0.52	0.93	3.26	2.98	5.63	4.84	-	-	-

^aSecondary parameter, calculated as $k_{out} \cdot R_0$

^bNot estimated

Table 5

Percent precision of PD parameter estimates obtained from IDR Models I, II, and IV applied to simulated data sets with 13 observations at a dose of 10,000

Model	Fitting methods	$S_{\max}$			SC_{50}			k_{out}			k_{in}^a			R_0		
		10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%
IDR I	E	32.9	33.6	34.1	198	197	206	74.3	93.9	108	76.2	105	124	11.2	15.7	19.5
	FI	28.9	35.5	45.7	211	221	241	78.9	122	143	97.8	168	215	^b	–	–
	F2	34.6	36.8	38.3	217	210	226	75.3	97.5	114	84.3	116	142	–	–	–
IDR II	E	37.7	42.1	42.4	172	184	189	80.3	106	136	77.5	96.1	123	11	15.3	20
	FI	26.8	29.3	38.4	150	168	196	109	172	236	91.1	125	145	–	–	–
	F2	33.8	34	35.2	150	173	196	87.1	98.5	147	78.2	88.5	126	–	–	–
IDR IV	E	77.5	96.3	112	293	404	475	114	149	203	112	146	195	13.7	20.0	26.0
	FI	87.7	104	132	480	650	820	111	145	173	115	151	195	–	–	–
	F2	73	88.6	101	294	412	493	111	147	200	111	148	190	–	–	–

^aSecondary parameter, calculated as $k_{out} \cdot R_0$

^bNot estimated

Table 6

Percent bias for PD parameters estimated from IDR Models I–IV using the sets of data which were first simulated for 13 data points at a dose of 10,000 and then those values less than zero were set to LLOQ

Model	Fitting methods	$S_{\max}$			SC_{50}			k_{out}			k_{in}^a			R_0		
		10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%	10%	20%	30%
IDR I	E	4.24	7.49	8.43	1.43	17.8	17.3	0.72	6.28	7.33	0.73	9.8	9.68	1.35	1.93	2.03
	FI	1.29	2.51	7.03	11.6	20.2	4.57	1.78	8.97	9.1	6.27	3.5	3.12	b	–	–
	F2	2.7	3	1.45	3.28	17.2	8.23	1.76	4.57	2.38	2.54	3.52	3.33	–	–	–
IDR II	E	1.79	2.53	0.82	3.05	23.7	25	0.19	17.7	23.6	1.57	16.7	17.1	2.46	4.12	5.85
	FI	6.71	8.78	11.9	18.9	36.6	36.7	1.03	13.2	13.4	11.5	29	37.5	–	–	–
	F2	3.64	7.64	9.52	4.26	24.4	31.8	1.15	11.8	13.4	4.65	17.7	23.6	–	–	–
IDR III	E	5.27	9.73	12.4	6.37	14.5	25	2.42	3.72	2.72	4.19	7.45	10.4	2.48	4.68	7.62
	FI	3.02	2.05	2.46	14.6	36.3	58.8	3.61	6.53	8.84	0.04	2.13	2.92	–	–	–
	F2	2.64	3.13	2.01	9.07	21	29.5	2.79	4.64	3.57	2.17	1.85	0.32	–	–	–
IDR IV	E	3.98	11.5	19.0	2.25	4.41	3.36	0.47	1.79	1.38	1.50	1.68	2.19	0.88	0.80	0.75
	FI	0.17	2.02	4.67	17.7	26.2	35.0	1.50	2.90	6.75	0.45	0.68	0.90	–	–	–
	F2	0.11	4.51	10.9	1.62	1.50	2.32	2.48	4.47	3.85	0.00	0.02	0.03	–	–	–

^aSecondary parameter, calculated as $k_{out} \cdot R_0$

^bNot estimated