ORIGINAL RESEARCH ARTICLE

Formulation and Validation of an Extended Sigmoid Emax Model in Pharmacodynamics

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Abstract

Purpose or Objective Drug concentration–response curves (DRCs) are crucial in pharmacology for assessing the drug effects on biological systems. The widely used sigmoid Emax model, which accounts for response saturation, relies heavily on the effective drug concentration (ED_{50}). This reliance can lead to validation errors and inaccuracies in model fitting. The Emax model cannot generate multiple DRCs, raising concerns about whether the dataset is fully utilized.

Methods This study formulates an extended Emax (eEmax) model designed to overcome these limitations. The eEmax model generates multiple DRCs from a single dataset by using various estimated α's $\in [0,100]$, while keeping ED_α fixed, rather than estimating an ED_{50} value as in the Emax model.

Results This model effectively captures a broader range of concentration–response behavior, including non-sigmoidal patterns, thus providing greater flexibility and accuracy compared to the Emax model. Validation using various drug-response data and PKPD frameworks demonstrates the eEmax model's improved accuracy and versatility in handling concentration–response data.

Conclusions The eEmax model provides a robust and flexible method for drug concentration–response analysis, facilitating the generation of multiple DRCs from a single dataset and reducing the possibility of validation errors. This model is particularly valuable for its ease of use and its capability to fully utilize datasets, providing its potential in PKPD modeling and drug discovery.

Keywords drug concentration–response curve · mathematical modeling · drug effect · Emax model · pharmacokinetics-pharmacodynamics (PKPD)

Introduction

A concentration-response curve (DRC) represents an organism's response to a specific stimulus, typically a chemical, over a designated exposure time [1]. In pharmacology, the DRC illustrates the organism's response to a drug at various doses, indicating drug efficacy. The response rate corresponds to the drug dose, with drug concentration on the *x*-axis and response on the *y*-axis, commonly forming a sigmoid shape due to saturation effects at high concentrations [2–4].

The sigmoid Emax model, derived from receptor occupancy theory, is particularly effective in capturing these sigmoidal patterns [5]. This model is used to elucidate drug concentration–response relationships, with key parameters including ED_{50}, which represents the concentration causing 50% of the maximum response. ED_{50} contains EC_{50} for 50% of the maximum effect, and IC_{50} for 50% inhibition of the desired activity [6]. The Hill coefficient (n) determines the curve's steepness at ED_{50} [7]. This model accurately characterizes concentration–response relationships by exhibiting a sigmoidal shape, and the model is as follows [8]:

$$E(C) = \frac{E_{max}C^n}{ED_{50}^n + C^n},$$

where E_{max} denotes the maximum response (effect) of the drug concentration C. However, accurately determining ED_{50} can be an inefficient and expensive way due to the need for repeated experiments [9, 10]. Additionally, n depends on the drug-target binding ratio but is often used for model fitting purposes, particularly in the context of chemotherapies [11, 12]. Another limitation is that the Emax model generates only one DRC prediction per dataset, which may be unreliable for validation and does not fully utilize the available data.

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To address these challenges, we propose an extended Emax (eEmax) model. This model can generate multiple DRCs from a single dataset by utilizing the response data. Instead of estimating ED_{50} and n in the Emax model, the eEmax model estimates the response α and n while keeping ED_α unchanged, as obtained from dataset. Here, ED_α, $\alpha \in [0,100]$, represents the drug concentration that elicits a response of $\alpha\%$ of maximal effect E_{max}. The eEmax model can provide several benefits: (i) It generates multiple DRCs by utilizing data points; (ii) It eliminates the need to determine a specific concentration ED_{50}; (iii) While the equation appears more complex than the Emax model, the number of parameters to be estimated remains the same; (iv) It captures a broader range of shapes, including sigmoid shapes, making it broadly applicable to pharmacokinetics/pharmacodynamics (PKPD) areas [11, 13–21].

Our study is supported by several published and experimental data, including a PKPD study on antibiotic agents. The study is organized as follows: In the Materials and Methods section, we provide the development of the eEmax model. In the Results section, we demonstrate the process for estimating parameters and comparing them with the Emax model. Additionally, we present the method to generate multiple DRCs. We next examine a case where the Emax model fails to fit the data, but the eEmax model accurately captures the data. We also provide an ensemble mean and confidence interval utilizing these DRCs. We show that this model can be incorporated into PKPD modeling in place of the Emax model, demonstrating reliable data fit quality. In the Discussion section, we highlight the differences between the Emax and eEmax models for parameter estimation. We emphasize the improvement of our study and compare it with other studies, demonstrating how the eEmax model addresses the limitations of the Emax model.

Materials and Methods

Model Derivation

Let $E = E(C)$ be the effect (or response) over a drug concentration C. Consider first a generalized logistic differential equation:

$$\frac{dE}{ds} = nE\left(1 - \left(\frac{E}{E_{max}}\right)^v\right), \tag{1}$$

where v is a shape parameter with a positive value, n is the Hill coefficient, and E_{max} is the maximum effect. s is a continuous latent variable implicitly depending on C, i.e., $s = f(C)$. We can find an analytic solution of Eq. (1), by defining F as $F = \left(E/E_{max}\right)^v$. Then, the rate of change in E is given by $E' = \frac{1}{v}F^{\frac{1}{v}-1}E_{max} \cdot F'$. Substituting E' into Eq. (1), we get $F' = nvF(1 - F)$. This differential equation can be easily calculated and the solution is of $F = e^{nvs+k}/(1 + e^{nvs+k})$. Notably, k is a constant value. Inclusion of E results in

$$E^v = \frac{e^{nvs}E_{max}^v}{e^{-k} + e^{nvs}}. \tag{2}$$

To formulate the eEmax model, let C be the drug concentration such that $s = ln(C)$ and ED_α be equal to $ED_\alpha = e^{-\frac{k}{nv}}$. Substitution of s and k into Eq. (2) gives

$$E^v = \frac{E_{max}^v C^{nv}}{ED_\alpha^{nv} + C^{nv}}. \tag{3}$$

The eEmax model is then presented as follows:

$$E = \frac{E_{max}C^n}{\left(ED_\alpha^{nv} + C^{nv}\right)^{\frac{1}{v}}}. \tag{4}$$

Particularly, v determines the curvature of the growth curve. If E is equal to $(1/2)^{\frac{1}{v}}E_{max}$, we have $(1/2)^{\frac{1}{v}}\left(ED_\alpha^{nv} + C^{nv}\right)^{\frac{1}{v}} = C^n$ from Eq. (4). Then we get $C = ED_\alpha$. This shows that ED_α can be understood as the drug concentration that gives a response of $(1/2)^{\frac{1}{v}} \cdot E_{max}$, and so α represents $(1/2)^{\frac{1}{v}} \cdot 100$, a positive real value. From Eq. (4), we can readily deduce the followings:

1) When the value of v is set to 1, the model is reduced to the Emax model.
2) If α is known, then v can be found as $1/log_2(100/\alpha)$ from $\alpha = (1/2)^{\frac{1}{v}} \cdot 100$ (eg., if $\alpha = 25$, then $v = 1/2$).
3) As v approaches zero and $n = o\left(\frac{1}{v}\right)$, we observe that the derivative of E with respect to s can be expressed as:

$$E'(s) = nE\left(1 - \left(\frac{E}{E_{max}}\right)^v\right) = vnE \cdot \frac{1 - e^{vln\left(\frac{E}{E_{max}}\right)}}{v} \rightarrow \mu E \cdot ln\left(\frac{E_{max}}{E}\right), \text{ where } \mu = vn.$$

This approximation leads to the Gompertz model, which is characterized by exponential growth in the initial phase, followed by decelerating growth.

4) When the condition C is much larger than the ED_α, i.e., $C \gg ED_\alpha$, E approximates E_{max}. Conversely, when $ED_\alpha \gg C$, E is approximately proportional to C^n.

The Process Using eEmax Model

A primary benefit of this approach is that it can generate multiple DRCs. The following steps outline how to predict the drug concentration–response relationship using the eEmax model:

(i)   Select drug concentrations ED_α's and corresponding response α's from the dataset and calculate v's using $\alpha = (1/2)^{1/v} \cdot 100$. If response is not given in the range $[0, 100]$, use a scale transformation to find α's.

(ii) Choose additional drug concentrations and determine the corresponding v's.

(iii) Estimate the parameters n's and v's values to fit data. The key difference here is the estimation of α's while keeping the concentration ED_α's fixed, instead of estimating ED_{50} as in the Emax model.

(iv) Using the equation $\alpha = (1/2)^{\frac{1}{v}} \cdot 100$, find the values α's.

(v)   Generate DRCs using the estimated values of n's and α's in the Eq. (4), while keeping ED_α's unchanged.

Results

Parameter estimation was performed using 'lsqnonlin', MATLAB 2022b, solving for nonlinear least-square data fit. Data fit quality was assessed by the relative error with L^2 norm, defined as $\|u_{approx} - Data\|_2 / \|Data\|_2$, where u_{approx} represents model predictions. Data was obtained from the published studies (see detailed below).

Model Prediction and Improvement of the eEmax Model Compared to the Emax Model

DRC predictions using the eEmax model were performed with published data from the study [22]. EC_α was used in place of ED_α in the Eq. (4). The ratio $Effect/E_{max}$ over concentrations from data were obtained shown in Fig. 1(a). Among the various responses $Effect/E_{max}$, we selected three α values 19, 45, and 70. Corresponding drug concentrations were $EC_{19}(20nM)$, $EC_{45}(50nM)$, and $EC_{70}(70nM)$. Using $\alpha = (1/2)^{1/v} \cdot 100$, we obtained v as $0.4174, 0.8681$, and 1.9434, respectively. We then estimated n's as $3, 1.5$, and 1.3, respectively. Using these values, the DRCs are predicted, as shown in Fig. 1(a). All DRCs were within range of standard
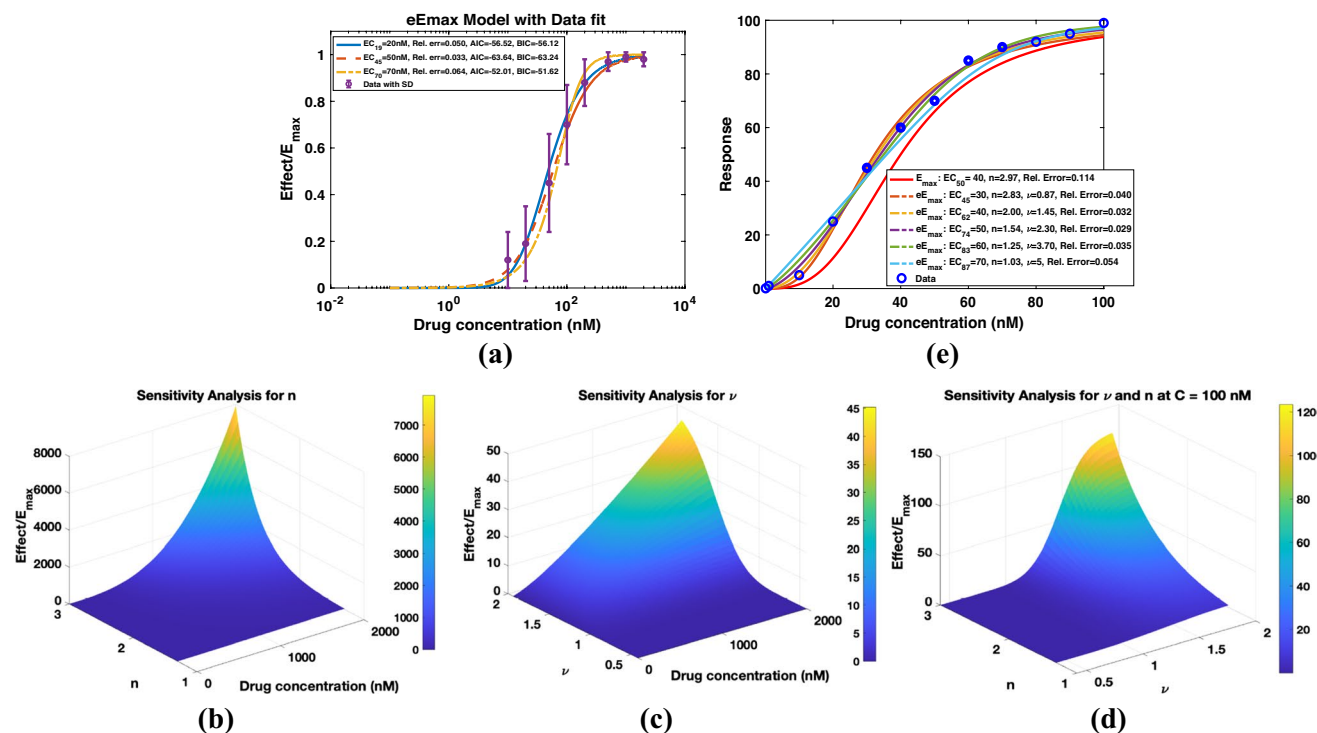

Fig. 1 (**a**) Model prediction without data estimation of v. The Hill coefficients n's are estimated by 3, 1.5, and 1.3, respectively. α's are calculated using $(1/2)^{1/v} \cdot 100$. (**b**) Sensitivity analysis for n. n's are variated from 1.3 to 3. Drug concentrations are variated from 0 to 2000 nM. (**c**) Sensitivity analysis for v. v's are variated from 0.4174 to 1.9434. (**d**) Sensitivity analysis for n and v. n and v values are simultaneously variated from 1.3 to 3 and from 0.4174 to 1.9434, respectively, showing positive correlation with $Effect/E_{max}$. (**e**) Model fit conducted by the Emax and eEmax model with various data points. Two parameters EC_{50} and n are estimated for the Emax model, while v and n are estimated for the eEmax model. Unlike the eEmax model, the Emax model shows poor to fit (relative error greater than 0.1).

deviation with small relative errors (Rel.err) as 0.05 for EC_{19}, 0.033 for EC_{45} and 0.064 for EC_{70}. Corresponding Akaike and Bayesian Information Criterion (AIC and BIC, respectively) were calculated and showed a positive correlation with the relative errors (Fig. 1(a)). This process demonstrated how the eEmax model fits the data and generates DRCs by utilizing n and v. We obtained different DRCs using fixed EC_α's obtained from a single data set. Sensitivity analysis plot for the two parameters were also investigated: for n (Fig. 1(b)), for v (Fig. 1(c)) and for both n and v (Fig. 1(d)). The parameter ranges of n and v were from 1.3 to 3 and from 0.4174 to 1.9434, respectively. Both parameters were positively correlated with $Effect/E_{max}$.

We next considered an in-silico dataset to show that DRC from the eEmax model closely reflected the dataset better than those from the Emax model. We again used Eq. (4) and EC_α was used as follows. Drug concentrations were given by $EC_\alpha = [0.1, 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100]$ (nM) and corresponding responses were $\alpha = [0.1, 1, 5, 25, 45, 60, 70, 85, 90, 92, 95, 99]$, as shown in Fig. 1(e). The data shape is a steeper at the beginning phase and a skewed at the end phase (not sigmoid pattern). E_{max} is set 100 (fixed) and we choose EC_α's are 30, 40, 50, 60, and 70 nM for the test. Corresponding α values are chosen as 45, 60, 70, 85 and 90. v values were obtained using the above equation and set as initial guesses. In the model fit process, for the Emax model, we estimated n and EC_{50}, but for the eEmax model, n and v were estimated. Notably, because of the relation between α and v, α values are changed while the values of EC_α are

unchanged. This process revealed the difference between the Emax and eEmax model estimation. In the Emax model, we estimated n and drug concentration EC_{50}, but in the eEmax model, n and α (due to v) were estimated while drug concentrations, EC_α's, remained unchanged. Estimated values are shown in Fig. 1(e). We observed that drug concentrations remained unchanged, but α values changed comparing to the data after estimation. In Fig. 1(e), the eEmax model compared to the Emax model better captures data, but the Emax model exhibited poor DRC prediction, with Rel.err > 0.1. This is because EC_{50} should belong between the value 30 and 40 based on data, but the estimated EC_{50} was 40. In contrast, DRC's conducted by the eEmax model accurately predict the data, supported by the relative error less than 0.06. The failure of the Emax model to fit the data occurs because the data shape does not follow a sigmoid shape, indicating that the eEmax model applies to more general cases.

Application to EGFR Inhibitor-Resistant NSCLC Tumors: Which Data Points can be Used?

Using published data [23], we compared the Emax and eEmax models for four inhibitory drugs. The IC_{20} values for Gefitinib (0.007 µM), LY3009120 (0.25 µM), Trametinib (0.008 µM), and SCH772984 (0.25 µM) presented in Table I are known and were applied to the eEmax model, modified from the Emax model as follows:

Table I Dose–Response Data of Gefitinib, LY3009120, Trametinib and SCH772984

| Drug	Concentration, µM	Unit	Drug	Concentration, µM	Unit
Gefitinib	0.001499998	97.76	LY3009120	0.0499995	98.54
	0.002749993	95.63		0.077498803	97.23
	0.004749977	89.8		0.118747167	92.55
	0.008499927	75.74		0.183743231	81.62
	0.015249766	50.98		0.274984354	71.67
	0.027499246	22.22		0.449960459	60.37
	0.04999755	11.68		0.674908401	40.46
	0.089992117	4.23		1.049779951	21.37
	0.154975729	2.91		1.624474094	15.82
	0.279921622	2.85		2.498750625	11.22
Trametinib	0.001499996	98.85	SCH772984	0.0499995	95.16
	0.002749985	94.27		0.077498803	97.14
	0.004999951	85.99		0.118747167	92.86
	0.008999839	73.89		0.183743231	83.44
	0.016249471	48.09		0.274984354	74.78
	0.029998229	25.46		0.449960459	66.84
	0.052494377	10.89		0.674908401	46.63
	0.097481053	5.79		1.049779951	18.14
	0.177437419	3.71		1.624474094	5.28
	0.319795331	2.91		2.498750625	2.29
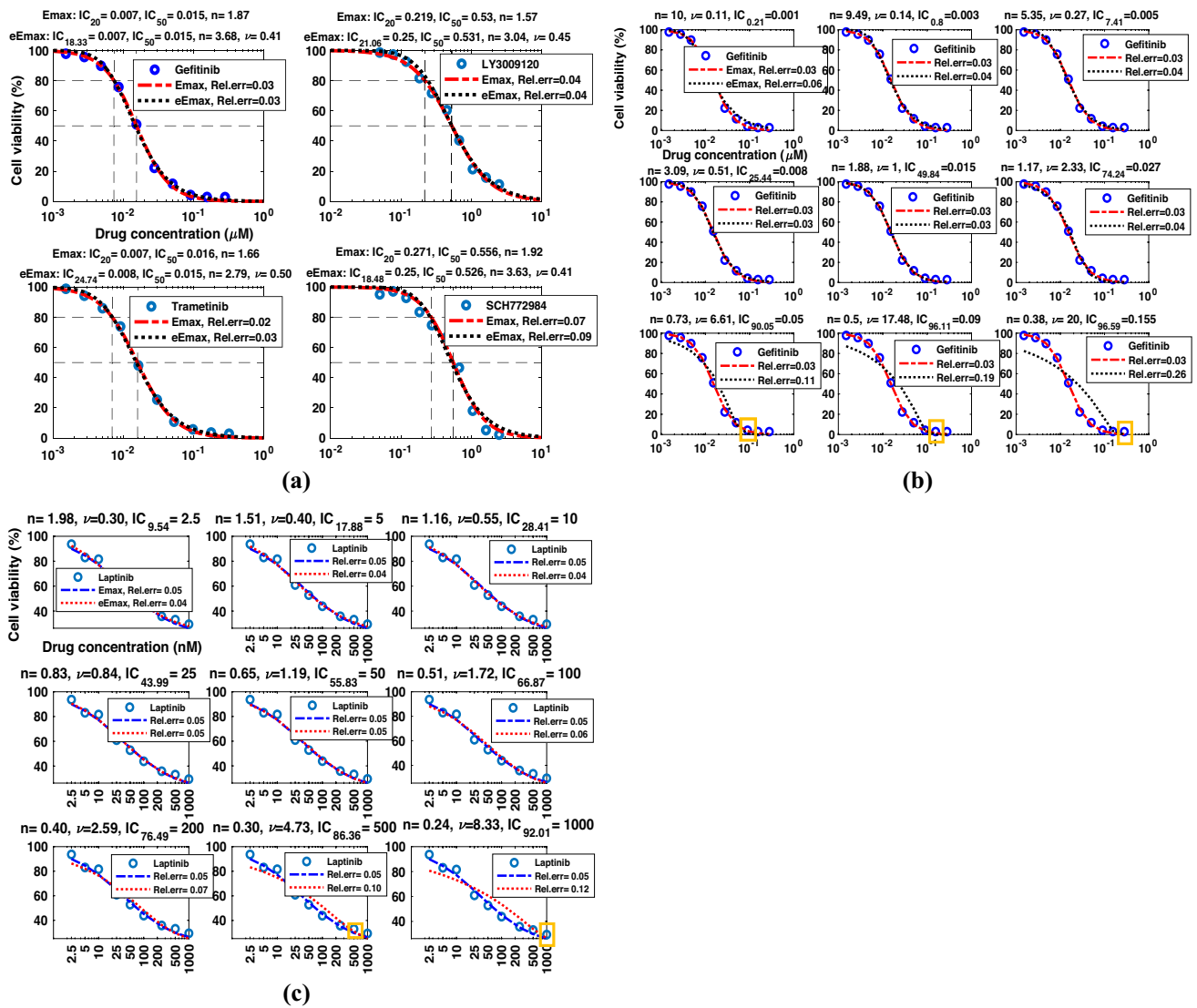
Fig. 2 (**a**) A comparison of dose–response curves (DRCs) of the Emax and eEmax models. (n, IC_{50}) and (n, v) are estimated for the Emax and eEmax models, respectively. Estimated parameters are shown in the subtitle. Corresponding α values are also given. From estimated values, IC_{20} for the Emax model and IC_{50} for the eEmax model are predicted. Four drugs are considered with the relative errors shown in legends. (**b**) Tests for selected IC_α's from all data in Gefitinib. Two parameters (n, v) are estimated, and DRC prediction is worse when $IC_\alpha \geq 0.05\mu M$. The relative error is greater than 0.1 when $\alpha \geq 90.05$ (last 3 data points). (**c**) Tests for Lapatinib. The DRC predictions of lapatinib are presented and a similar pattern is observed. Particularly, data fit is poor when the relative error is greater than or equal to 0.1 when $\alpha \geq 86.36$ (last 2 data points).

$$E = E_0 - I_{max} \cdot \frac{C^n}{\left(IC_\alpha^{n \cdot v} + C^{n \cdot v}\right)^{\frac{1}{v}}}, \tag{5}$$

with $E_0 = 100$ and $I_{max} = 100$. To generate DRC's, (n, IC_{50}) and (n, v) were estimated using the Emax and eEmax models (Eq. (5)), respectively. After estimation, we obtained α's from estimated v's so that we get $IC_{18.33} = 0.007$(Gefitinib), $IC_{21.06} = 0.25$(LY3009120), $IC_{24.74} = 0.008$(Trametinib), and $IC_{18.48} = 0.25$(SCH772984). We predicted IC_{50} values using Eq. (5): 0.015(Gefitinib), 0531(LY3009120), 0.015(Trametinib) and 0.526(SCH772984), compared to the IC_{20} and IC_{50} values with the Emax model (Fig. 2(a)). While

a specific data point was used, the eEmax model accurately captured the data with the small relative errors.

To determine whether accurate DRCs can be generated from all data points, we investigated the Gefitinib dataset (10 points). We again estimated n's and v's (Fig. 2(b)). DRC dynamics obtained from the first nine data points were plotted, with the relative error to assess the model fit quality. The eEmax model is valid with the relative error less than 0.1 when $IC_\alpha < 0.05nM$, suggesting that DRCs obtained from the first six data points provide accurate prediction, but not the others. This indicates that a condition to apply the eEmax model is to choose data points which reflect the shape of curves.

Table II Lapatinib Dose–Response Data. LPT Concentration and Mean Response with Standard Deviation. Four Trials were Conducted and Standard Deviations were Measured

LPT concentration(nM)	Response (mean)	SD
0	100.00	5.33
1	85.97	3.68
2.5	93.66	8.30
5	83.02	4.23
10	81.63	2.38
25	60.93	1.13
50	52.82	3.76
100	43.86	2.92
250	35.81	1.04
500	33.10	0.62
1000	29.44	0.68

Similarly, we tested the eEmax model using lapatinib (LPT) data from the previous study [24], excluding the first two concentrations (0 nM and 1 nM). The dose–response relationship was presented in Table II. With $E_0 = 100$ and $I_{max} = 80$, parameter estimation presented: $[n, IC_{50}] = [0.7364, 34.8953]$ for the Emax model, and for the eEmax model, we obtain various $[n, v]$, with the relative errors in Fig. 2(c). The eEmax model's predictions were consistent with previous findings, remaining valid for concentrations up to $IC_{76.49} = 200$. This again supports the necessity of choosing proper data points. Thus, once suitable m data points are chosen, we may generate m DRCs.

Ensemble Generation from the eEmax Model: Response Transformation

A published study [25] investigated an inhibition response using the inhibition model presented as follows:

$$log_{10}E = log_{10}E_0 + \frac{E_{max}T^n}{EC_{50}^n + T^n}, \tag{6}$$

where, $log_{10} E_0(cfu/mL) = 1.6, E_{max} = -6.3, EC_{50} = 48.9$, and $n = 4.953$ are provided. The minimum response was -4.8. The concentration–response data is presented in Table III. We estimate EC_{50} using the Eq. (6) and find $EC_{50} = 48$, which is close to the given value $EC_{50} = 48.9$. Next, the eEmax model can be defined as:

$$log_{10}E = log_{10}E_0 + \frac{E_{max}T^n}{\left(EC_{\alpha}^{nv} + T^{nv}\right)^{1/v}}.$$

Using the relationship between E_{max} and initial response ($log_{10}E_0$), a simple equation, $\alpha = -\frac{100}{6.3}(x - 1.6)$, $x \in [-4.8, 1.6]$, representing x as true response (given by log_{10}), can be utilized to get scaled response α's. That is, response can be transformed into α from 0 to 100. Thus, for example, $\alpha = 0$ and 50 can be represented as 0% and 50%, from 100% response, respectively. Using the linear equation, we can find true response -1.55 when $\alpha = 50$, which approximately agrees with $EC_{50} = 48$. We now choose four data set (red circles in Fig. 3) to estimate n and v. That is, we find $\alpha = 18.10, 42.54, 69.52$ and 83.97 and then corresponding concentrations are $EC_{18.10} = 34.83$, $EC_{42.54} = 44.89, EC_{69.52} = 59.76$ and $EC_{83.97} = 69.96$.

After estimation, n and α values are shown in Fig. 3. The DRC's from the eEmax model predict data well, with a small relative error (less than 0.1), similar to the Emax model. Compared to the Emax model, the eEmax model generates multiple DRCs and can provide confidence interval and ensemble mean curve. This extension to the Emax model highlights the usefulness of the eEmax model. In addition, from various DRCs, we may conduct statistical analysis and reflects variations in DRCs.

Application to PKPD Framework

Utilizing published data from studies [26, 27], we investigated the antibacterial effect of two drugs on two types of strains using the eEmax model integrated into the PKPD framework. The schematic diagram of the model is shown in Supplementary Information (S1 Fig), and the mathematical model is provided in (S2 text). Model analysis and simulation were performed with SimBiology. The parameters were presented in Table IV. The data fit from PK data is shown in Fig. 4(a). The obtained PK drug concentrations were applied to the eEmax model. The parameter values are also provided in Table IV. The eEmax model is applied to the tumor model in place of the Emax model.

The eEmax model accurately predicts bacteria inhibition data (Fig. 4(b)). We also tested other IC_α values, with similar results (not shown in the figures). The eEmax model

Table III Dose–Response Data Set in the Study [25]

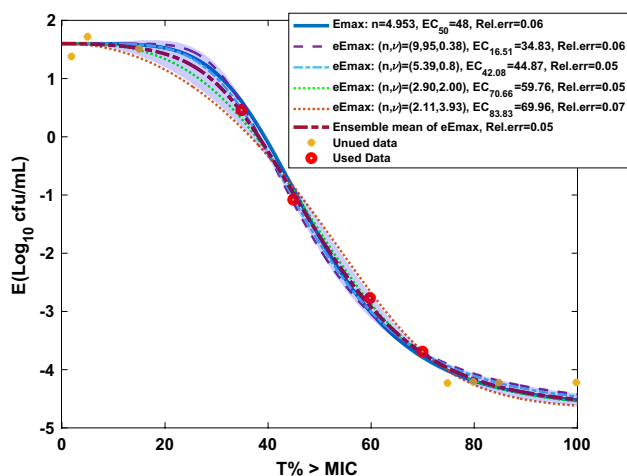| Drug Conc	1.84	4.96	14.96	34.83	44.89	59.76	69.96	74.8	79.8	84.8	99.8
Response	1.38	1.72	1.51	0.46	-1.08	-2.78	-3.69	-4.23	-4.21	-4.22	-4.22

Fig. 3 The minimal inhibitory concentration (MIC) and the percentage of drug concentration above the MIC (T% ˃ MIC) are presented. The EC_{50} is provided by the study, and DRC using the Emax model is represented by a blue solid curve. The four data points, given by red colors, are chosen to generate DRCs for applying to the eEmax model from the antimycoplasmal effect (E) over T% ˃ MIC. Estimated values (n, v) are presented in the legend. The ensemble mean, and confidence interval (shaded blue) over T% ˃ MIC are plotted.

supports effectiveness for PKPD modeling, providing accurate predictions.

Discussion

The drug concentration–response relationship is crucial because it helps determine the optimal dosage of a drug that maximizes therapeutic effects while minimizing adverse effects. The sigmoid Emax model is commonly utilized to determine this. The Emax model uses ED_{50}, which should be estimated unless found through accurate experiments. Studies utilize this step to predict a concentration–response curve for providing an optimal strategy for treatment [28, 29]. One of

the limitations of the Emax model is that it does not use all data information. Specifically, from a dataset, data to find the drug concentration ED_{50} is only used. Other drug concentrations can be predicted after estimating ED_{50}. To address this, we have formulated the extended Emax model (eEmax). At first glance, the eEmax model seems complex because it has an additional parameter v compared to the Emax model. However, we utilize data points to reduce the number of parameters that need to be estimated, resulted in the same number of parameters as the Emax model. A unique characteristic of the eEmax model is that ED_α values remain unchanged, but v is estimated, unlike ED_{50} in the Emax model. This model uses scaled responses α's (0 to 100%) from dataset, instead of finding ED_{50}. After choosing these values, the shape parameter v is estimated for data fit. Then, we can find estimated α's using the equation $\alpha = (1/2)^{1/v} \cdot 100$, while ED_α values remain unchanged.

The eEmax model addresses the limitations of the Emax model by offering a more flexible representation of dose–response relationships. The inclusion of a new parameter, v, provides a comprehensive measure of drug potency, allowing the model to capture diverse concentration–response data, including sigmoidal datasets. This model can generate multiple DRCs because it utilizes all data points. The eEmax model is particularly useful when one wants to verify the robustness of the model fit and to provide statistics such as mean, variances, and confidence intervals.

Mathematical models have positively impacted PKPD research by enabling precise predictions of drug behavior and effects in the body, thereby optimizing dosing regimens and improving therapeutic outcomes [30–33]. The sigmoid dose–response curve is widely used in PKPD and other studies [34–38], highlighting the importance of dose–response relationship in accurately assessing optimal treatments. The eEmax model provides significant advantages over the Emax model, such as the use of arbitrary drug concentrations and the generation of multiple

Table IV The Values of Parameters. v and n are Estimated Values, While the Others are Fixed Values. kgrowth: Growth Rate of Growing Cell. kdeath: Death Rate of Tumors. ICalpha: IC_α, Imax: Maximal Inhibition, ka: Elimination Rate of Drug, MIC: Minimum Inhibitory Concentration, Bmax: Maximum Tumor Number

| Name	Parameters				Units
	Drug1/Strain1	Drug1/Strain2	Drug2/Strain1	Drug2/Strain2	
kgrowth	1.46	1.46	2.01	2.01	1/hour
kdeath	0.187	0.187	0.234	0.234	1/hour
IC_α (ICalpha)	0.0455	0.0184	0.0949	0.1023	milligram/liter
Imax	3.9529	4.6113	2.083	3.3962	1/hour
CL (clearance)	2.37	2.37	0.346	0.346	liter/hour
Central (volume)	1.29	1.29	0.129	0.129	liter
ka	0.5	0.5	0.266	0.266	1/hour
MIC	0.012	0.0509	0.15	0.1116	milligram/liter
v (estimated)	2	1.0168	0.872	2	dimensionless
n (estimated)	0.0483	0.8365	1.21E-06	0.0069	dimensionless
Bmax	500000000	500000000	467000000	467000000	number
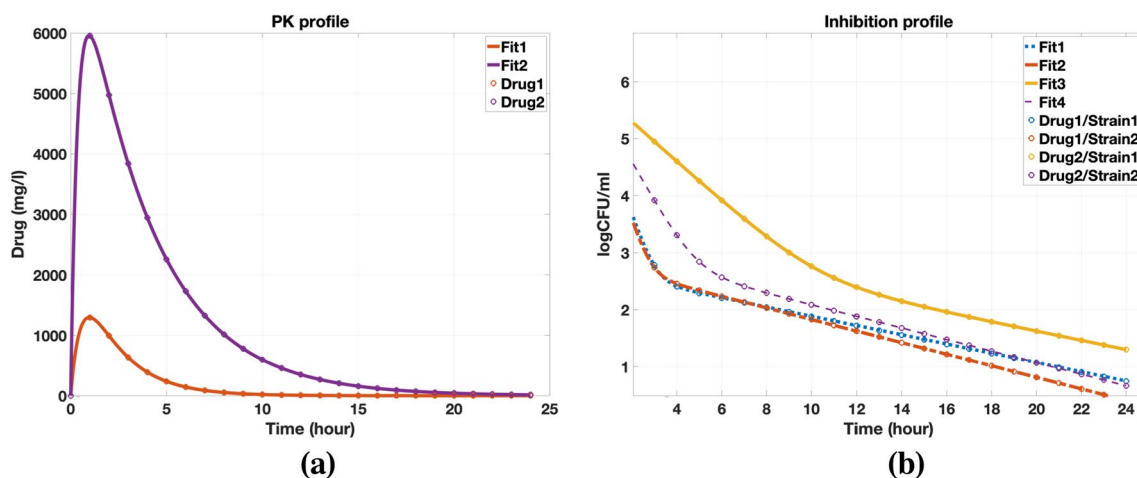
Fig. 4 Application to PKPD model. (**a**) The PK profile of two drugs administered is shown. (**b**) We estimate the parameters (n, v) in the eEmax model, which is incorporated into the bacteria model. Simulation result accurately captures all the data.

DRCs from a single dataset, evaluated through statistical analyses. This model is applicable to PKPD models requiring concentration–response relationships, such as tumor dynamics after drug administration, and can be used in direct link and indirect response models [28, 29, 39–41]. Also, the Emax model is applied to cooperative binding to understand molecular interactions in biological system, influencing drug design, enzyme regulation, and gene expression [42].

Despite its advantages, the eEmax model has a limitation in that suitable data points should be chosen to avoid wrong predictions. Not all drug concentrations are used as ED_α values. Some concentrations with very small or large α values could lead to poor fit. Response transformation to find α is easy but requires additional work. While these limitations exist, the eEmax model provides various benefits over the Emax model. The eEmax model provides a reliable method for analyzing dose–response data and generating multiple DRCs from a dataset. Additionally, this model can handle diverse data types rather than the Emax model, making it a valuable tool in PKPD modeling.

Author Contributions Conceived and designed the study: J.H.B. collected and analyzed the data and wrote the paper.

Data Availability All data generated or analyzed during this study are included in published articles.

Declarations

Competing Interests The author declares no conflicts of interest.

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