Review Article

Response surface models in the field of anesthesia: A crash course

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ABSTRACT

Drug interaction is fundamental in performing anesthesia. A response surface model (RSM) is a very useful tool for investigating drug interactions. The methodology appeared many decades ago, but did not receive attention in the field of anesthesia until the 1990s. Drug investigations typically start with pharmacokinetics, but it is the effects on the body that clinical anesthesiologists really care about. Typically, drug interactions are divided into additive, synergistic, or infra-additive. Traditional isobolographic analysis or concentration-effect curve shifts are limited to a single endpoint. Response surface holds the complete package of isobolograms and concentration effect curves in one equation for a given endpoint, e.g., loss of response to laryngoscopy. As a pharmacodynamic tool, RSM helps anesthesiologists guide their drug therapy by navigating the surface. We reviewed the most commonly used models: (1) the Greco model; (2) Reduced Greco model; (3) Minto model; and (4) the Hierarchy models. Each one has its unique concept and strengths. These models served as groundwork for researchers to modify the formula to fit their drug of interest. RSM usually work with two drugs, but three-drug models can be constructed at the expense of greatly increasing the complexity. A wide range of clinical applications are made possible with the help of pharmacokinetic simulation. Pharmacokinetic-pharmacodynamic modeling using the RSMs gives anesthesiologists the versatility to work with precision and safe drug interactions. Currently, RSMs have been used for predicting patient responses, estimating wake up time, pinpointing the optimal drug concentration, guide therapy with respect to patient’s well-being, and aid in procedures that require rapid patient arousal such as awake craniotomy or Stagnara wake-up test. There is no other model that is universally better than the others. Researchers are encouraged to find the best fitting model for different occasions with an objective measure. Copyright © 2015, Taiwan Society of Anesthesiologists. Published by Elsevier Taiwan LLC. All rights reserved.

1. Introduction

The collective of anesthetic drugs share a common but unique property. Rapid onset and offset are required to ensure ease of titration to cope with surgical stimuli, provide good surgical condition, and prevent excessive and prolonged postoperative somnolence. Anesthesiologists practice rapid drug interactions every day. Since no single drug is capable of producing all the elements of a balanced anesthesia alone, we rely on the combined effects of multiple drugs. Many anesthesiologists build their regimens based on years of experience. The ultimate goal is to produce the desired effect: loss of response to various stimuli or suppression of the autonomic reflexes to noxious stimuli while avoiding excessive cardiovascular or respiratory depression, and the concentration range can sometimes be therapeutically narrow. Cutting back months or years of training is possible with an existing guide, such as a drug model. One good example is the advent of target controlled infusions.2

The search for drug interaction began since more than 100 years ago.1 Evolution of the pharmacodynamics analysis to response surface models (RSM) has been around for decades. Box and Wilson3 came up with the first idea of optimization using RSM. The introduction into the field of anesthesia occurred in the 1990s5,6 and later blossomed with a number of works. The study of RSMs only considers the pharmacodynamics, the type of interaction most relevant to anesthesia. Investigations primarily focused on effects such as loss of response to verbal command,7–11 reduced perception,12–15 or loss of response to noxious stimuli (pain surrogates,16–20 laryngoscopy,18–20 laryngoscopy,8–11,16,21–23), the appearance of unwanted side effects (cardiovascular depression,24–26

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respiratory depression\(^{19,25}\), predicting certain physiology-based monitor values\(^{22}\) (Bispectral Index\(^{1,3,16,24–28}\), entropy\(^{1,16,28}\), composite variability index\(^{28}\)) and even an index of well-being.\(^{29}\) RSMs can be extended to simulate patient’s recovery and arousal time.\(^{20,21,30}\) They have important clinical implications and many are already incorporated into real-time displays.

2. Drug interactions

2.1. Isobolograms

To begin with, a basic understanding of drug interactions is required. Several methods exist. Isobolographic analysis was very common but is still used today.\(^{31}\) It is not universally applicable since it illustrates only a single effect endpoint each time. However, by simply looking at the isobolograms, we can easily identify the type of drug interaction. Three types of drug interactions exist: (1) additive; (2) synergistic; or (3) infra-additive. A commonly used reference for additive drug effect is the Loewe additivity (simple form expressed in Eq. 1):

\[
\text{Interaction index} = \frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} \begin{cases} 
< 1 : \text{synergy} \\
= 1 : \text{additivity} \\
> 1 : \text{infra-additive} 
\end{cases}
\]  

\[\text{[1]}\]

\(C_A\) denotes the concentration of Drug A, and \(C_{50A}\) is the concentration required for Drug A to reach half maximal effect. The same applies for Drug B. Other references lines such as Bliss independence\(^2\) or the Median-effect method\(^2\) are available. Greco et al.\(^5\) advocated the use of Loewe additivity as the universal reference line for RSM and until now, RSMs in the field of anesthesiology still adopt it. Drug interactions are anticipated with drugs that hold different mechanisms of action. Most of the anesthetics bear more than one site of action and the magnitude of interaction becomes utterly important for anesthesiologists.

2.2. Concentration-effect curve

Second in line is the concentration-effect curve, or dose-response curve. Most anesthetic drugs can be described using the sigmoid \(E_{\text{max}}\) model, or the Hill model for a single drug (Eq. 2):

\[
E = E_0 + \left(\frac{E_{\text{max}} - E_0}{1 + U^g}\right)
\]

\[\text{[2]}\]

\(E\) is the effect, or the probability of the investigating endpoint. \(E_0\) is the effect while no drug is present, and \(E_{\text{max}}\) is the maximal effect attainable. When dealing with binomial data, e.g., response or no response, \(E_0\) would be 0 and \(E_{\text{max}}\) would be 1. This will reduce the equation to a simpler form (Eq. 3):

\[
E = \frac{U^g}{1 + U^g}
\]

\[\text{[3]}\]

\(U\) is the normalized ratio of the drug concentration with respect to \(C_{50}\). \(C_{50}\) is the concentration required to reach half maximal drug effect and \(g\) is the steepness of the curve. Eq. (3) delineates the basis of all the RSMs to come, with different modifications done to \(U\).

2.3. Response surface models

The reader must now aware of the limitations of the above analyses. Only a few effect endpoints can be analyzed each time and in order to characterize all the possible interactions, multiple separate studies are needed. The concept of the response surface is simple: to create a surface that encompass the complete set of isobolograms, concentration-effect curves and the shift of concentration-effect curve in the presence of another drug. As with isobolograms, the shape of the three-dimensional surface can give readers clues on how the drug combinations interact (Figure 1). We will look into some of the most commonly used models. The models can be generalized into two categories. First are the models that carry one interaction parameter, while the second group converts the interaction parameter into a mathematical function. The first group includes the Greco model\(^5,6\) in both full and reduced forms, Machado model\(^24\), Plummer model\(^23\) and Carter model.\(^26\) They assume the surface is smooth and interactions outside the scope of synergism, additivity, and infra-additivity are not adequately described. Those with an interaction function include Minto model,\(^7\) Fidler model,\(^3,17\) and Kong model.\(^3\) These models, albeit with increased complexity, can graph virtually any type of drug interaction. Drug interactions are often assumed to interact equally throughout the entire concentration range, as with the single interaction models. In reality, different levels of synergism, additivity, or even antagonism may actually be at play interspersed throughout the surface. Isoboles from such response surface would appear zigzagged and nonuniform. Another model, with a more physiological approach, is the Boullion Hierarchy model. We will take a closer look at some of the most commonly cited models: Greco model, Minto model, and the Hierarchy model.

2.4. Full Greco model

The full Greco model:

\[
E_{\text{max}} = \frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} + \alpha \times \left(\frac{C_A}{C_{50A}} \times \frac{C_B}{C_{50B}}\right)^\gamma + 1
\]

\[\text{[4]}\]

\(E\) is the model calculated effect. For binomial data, it is often referred to as the probability of reaching \(E_{\text{max}}\) from 0 to 1. \(E_{\text{max}}\) is the maximal achievable effect, often set to 1 (100% chance of loss of response to certain stimuli) and thus is often omitted during parameter estimation. \(C_A\) and \(C_B\) are the drug concentrations for Drug A and Drug B. \(C_{50A}\) and \(C_{50B}\) are the concentrations of either Drug A or Drug B alone that will reach 50% maximal effect. The interaction parameter is \(\alpha\). Interaction is synergistic when \(\alpha > 0\), infra-additive when \(\alpha < 0\), and additive when \(\alpha = 0\). As mentioned previously, RSMs are extensions with modification to \(U\) in the sigmoid \(E_{\text{max}}\) model (Eq. 3). In the Greco model, \(U = \frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} + \alpha \times \left(\frac{C_A}{C_{50A}} \times \frac{C_B}{C_{50B}}\right)^\gamma + 1\) is the steepness of the surface. Bol et al.\(^39\) also proposed a model that is very similar to the original Greco model but adjusted for categorical data, and looks identical to the Greco model presented here. The Greco model assumes that both Drug A and Drug B can exert a targeted effect alone. One downside to this is when applying opioids to a hypnosis model, it would infer that opioids can produce hypnosis alone. This would not be true since opioids are known to produce hypnosis unreliably.\(^40\) The results the Greco model give when an opioid and a hypnotic agent are combined to attain hypnosis does give us some hints. Opioid \(C_{50}\) are often magnitudes higher than clinically used concentrations. As such, the reduced Greco model can be derived to solve the opioid \(C_{50}\) parameter problem.

2.5. Reduced Greco model

A \(C_{50}\) orders higher than \(C\) will end up with a very small and negligible ratio \(C/C_{50}\). The effect of opioids (assume Drug B) alone can be dropped out. We then rewrite the full Greco model as:
Figure 1. Response surface models for different types of drug interactions. Response surface models showing (A) synergistic, (B) additive, and (C) infra-additive interactions. Each panel contains a response surface (left) and an isobologram showing the 50% probability isobole (right). Synergistic (Panel A), additive (Panel B), and infra-additive interactions (Panel C) are shown here. Synergism is demonstrated by bowing of the isobole toward the origin, and infra-additivity appears to concave oppositely. Additivity isobole is equivalent to the Loewe Additivity.
There are two ways to reduce the model. Firstly combining $\alpha$ and $C_{50B}$ into $\alpha'$ and rearrange Eq. (5):

$$E = \left[ \frac{C_A}{C_{50A}} + \alpha' \left( \frac{C_A}{C_{50A}} \times \frac{C_B}{C_{50B}} \right) \right]^{\gamma} + 1 (5)$$

Secondly, we can go from Eq. (5) and assume $\alpha$ to be 1. This will give:

$$E = \left[ \frac{C_A}{C_{50A}} \times (1 + \alpha' \times C_B) \right]^{\gamma} + 1 (6)$$

$$E = \left[ \frac{C_A}{C_{50A}} \times (1 + C_B/C_{50B}) \right]^{\gamma} + 1 (7)$$

$C_{50B}$ now carry a different definition. It is the concentration needed to reduce $C_{50A}$ by a factor of two, or double the effect of $C_A$. In Eq. (6) is $(C_A/C_{50B} \times (1 + \alpha' \times C_B))$, and $(C_A/C_{50A} \times (1 + C_B/C_{50B}))$ in Eq. (7). Both Eqs. (6) and (7) are the final forms of a reduced Greco model. They produce identical results. Reducing the model uses the same concept mentioned by Mertens et al.21

2.6. Minto model

This model is powerful in that it can capture all the drug interactions on the surface, even if they are nonuniform. Minto first proposed this model and converted the midazolam-propofol-alfentanil triple drug pharmacodynamic results35 into RSM analysis. Let us take a look at the formula:

$$E = \left\{ \frac{(U_A + U_B)}{(U_A + U_B U_B)} \right\}^{\gamma(\theta)} + 1 (8)$$

It still follows the basic form in Eq. (3) where $U = (U_A + U_B)/U_{50(\theta)}$. In the equation, $U_A = (C_A/C_{50A})$ and $U_B = C_B/C_{50B}$ Minto model introduced a new concept. They view the combination of Drug A and Drug B as a new drug, $\theta$.

$$\theta = \frac{U_B}{U_A + U_B} (9)$$

The model uses functions to represent the interaction and steepness. $U_{50}(\theta)$ and $\gamma(\theta)$ are as follows:

$$U_{50}(\theta) = 1 - \beta_2 U_A \theta + \beta_2 U_B \theta^2 (10)$$

$$\gamma(\theta) = C_B \times \gamma_A \times (1 - \theta) - \beta_4 \times \theta \times (1 - \theta) (11)$$

The actual interaction parameter is $\beta_{2,USO}$, when the value is 0, it denotes an additive effect. It is synergistic or antagonistic when $>0$ or $<0$, respectively. The ground in the model is for the new drug ratio, $\theta$, to have its own concentration-effect curve. Apparently, this model appeared far more complex. This form is actually reduced from the original Minto model, which he proposed a fourth polynomial function for each $U_{SO}(\theta)$ and $\gamma(\theta)$. The Minto model described here requires six parameters to be estimated, while in the most complex form 10 are needed. The model’s flexibility to embrace a variety of different degrees of drug interactions could become its weakness. Overfitting and overparameterization is discouraged by certain model comparison indices, for example the Akaike Information Criterion, by placing penalties on extra parameters.

2.7. Hierarchy model

This model was developed by Bouillon et al.8 based on concepts proposed by Kissin42 and Glass.43 Physiological sequences are delineated along with the development of the model formula. The backbone reasoning of the model states that one drug acts to reduce the intensity of a given stimulus, and the second drug produces the effect under the influence of reduced stimulus intensity. A great example would be to infer the relationship between an opioid (Drug B) and a hypnotic agent (Drug A). Assume a noxious stimulus is given to the patient (preopioid intensity, or $PreOI$). Opioids act on the spinal cord to reduce the pain intensity (postopioid intensity, or $PostOI$). The hypnotic agent then produces cortical suppression under the impact of $PostOI$ projected from the spinal cord. The formula still adopts the basic concept of the Hill model:

$$E = \frac{C_J}{(C_{50A} \times PostOI)^{\gamma} + C_A} (12)$$

$$PostOI = PreOI \times \left[ 1 - \frac{C_B^{\gamma_x}}{(C_{50B} \times PreOI)^{\gamma_x} + C_B^{\gamma_x}} \right] (13)$$

Assuming:

PreOI = 1

We can substitute $PostOI$ into in Eq. (12) and after slogging through the math, we end up with the final form of the hierarchy model:

$$E = \frac{\left( \frac{C_A}{C_{50A}} \times (1 + \left( \frac{C_B}{C_{50B}} \right)^{\gamma_x} \right)^{\gamma}}{1 + \left( \frac{C_A}{C_{50A}} \times (1 + \left( \frac{C_B}{C_{50B}} \right)^{\gamma_x} \right)^{\gamma}} (14)$$

It is important to keep the notion of a sequential drug action in mind. For Eq. 13, you can say that Drug B acts to reduce the concentration needed for Drug A to achieve E. To reduce the number of parameters, we can fix $\gamma_x$ to 1. The result becomes identical to the reduced Greco model in Eq. (7). When dealing with multiple stimuli, the numbers of parameters increase. Bouillon44 proposed a modification to solve for overparameterization: the scaled $C_{SO}$ and fixed $C_{SO}$ hierarchy model. Both are basically placing constraints over $C_{50A}$ and $C_{50B}$. The constraints for scaled $C_{SO}$ hierarchy model are:

$$C_{SOA} = C_{50A} \times PreOI_m$$

$$C_{SOB} = C_{50B} \times PreOI_m$$

This constraint is characterized by the simultaneous change in $PreOI$ for multiple stimuli ($PreOI_m$). $C_{SOB}$ then proportionally increase by the same fold from the initial $C_{SO}$ ($C_{SOA1}$ and $C_{SOB1}$).

Followed are the constraints for fixed $C_{SO}$ hierarchy model:

$$C_{SOA} = C_{SOA} \times PreOI_m$$

$$C_{SOB} = C_{SOB}$$
C_{50B} is fixed and remains the same for all stimuli. Both modified hierarchy models are feasible and nicely fitted into volunteer data. Although the models we went through were dealing with binomial responses, the model can be generalized to fit continuous data. In cases like BIS, E_{max}, E_0 must be taken into account and follow the concept of Eq. (2).

### 3. Clinical application

It is somewhat vague on how the models actually work if we only look at the math and technical part. First of all, we can substitute the drug with their equipotency ratio and the models can be generalized to cover most of the anesthetics. The potency ratios for fentanyl, sufentanil, alfentanil, and remifentanil, based on minimum alveolar concentration reduction studies in humans, are: $-1:12:0.0625:12^{26,45}$. By multiplying by 1.2, we can convert the model from remifentanil to fentanyl. Alternatively, another potency ratio between opioids for fentanyl, sufentanil, alfentanil, and remifentanil [1:9:(1/70):(1/2.3)], based upon infusion pharmacokinetic studies (58,49) can be selected. A similar minimum alveolar concentration-based transformation can be done with the volatile inhalation agents. Table 1 lists the current RSM literature in the field of anesthesia. It is obvious most studies were conducted with drugs that have short equilibration time, allowing very rapid steady state equilibration between plasma and effect-site concentrations. Two studies not listed here were the atypical designs that did not encompass an opioid and a hypnotic, but rather chose sevoflurane and propofol as their study drugs (10,27). Table 1 was meant to review RSM literature only. There are certainly many other pharmacodynamic studies using a different, but very similar basic concept. Hendrickx et al. (56) did a thorough review on the anesthetic drug–drug interactions beyond RSMs.

The RSMs are usually built on volunteer models using the crisscross design developed by Short et al. (57). The method was design and proven to be efficient and required as little as 20 volunteers to craft a robust model. How the models fare outside of a carefully controlled environment is a challenge and many authors have been digging into it (2,10,20,30,58). A great benefit that extends from the model responses are the simulation of wake up time. Anesthesiologists are often challenged with the question by both colleagues in the operation room and patient’s family in the post-operative recovery unit or ward. By selecting and applying an existing model, it is possible to give a specific time range, often within minutes, regarding time to arousal.

We now take a look at the analyses carried out by Ting et al. (30) on the prediction of wake-up time during scoliosis correction surgery to perform the Stagnara wake-up test. This is a good example of generalization from the original sevoflurane-remifentanil model to a clinically used desflurane-fentanyl regimen. Loss or response were assessed using OAA/S (Observer’s assessment of alertness/sedation) scale (59). Three models with loss of response as endpoints (OAA/S < 2, OAA/S < 3 and OAA/S < 4) were built. Each patient’s temporal course of drug concentration and effect was calculated retrospectively. The model’s wake up target was the 50% probability isobole. Of the three models, the OAA/S < 2 model most accurately predicted the time patients would respond and follow the wake-up test (Figure 2). The average difference between true patient arousal and the model’s prediction was −2.6 ± 3.6 minutes. Simulations like this not only give an estimated range of time, but also are capable of dredging up the optimal concentration combination for the quickest recovery.

### 4. Conclusion

Response surface modeling took a leap forward in the past two decades, partly owing to the advancements in computing technology that made the complex optimization process possible. Powerful as it is, users may need to select or modify the model to suit the hypothesis of interest. Clinically we often give more than two drugs to a patient. Should more complex models be built, e.g., when a patient receives premedication with a benzodiazepine or an antihistamine? There are still numerous drug combinations beyond the hypnotic-opioid boundary. We have only exploited a few of them.
One must keep in mind that all the models are just approximations to the true one, that can never be precisely sketched out. Models have been carefully built and are now used clinically. Results were proven to agree with clinical observations. The versatility of the RSMs is limited. Dearth of research still calls for more works to be completed.

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