# All Models Are Wrong

ANESTHESIOLOGISTS are master pharmacologists. In the course of our training, we learn that certain types of drugs, the hypnotics, suppress consciousness. We learn that other types of drugs, the analgesics, suppress nociception. Through training and experience, we learn to induce oblivion with judicious combinations of hypnotics and analgesics. We learn to leverage the synergistic interaction of hypnotics and analgesics to decrease total dose and reduce toxicity.

The synergy between hypnotics and analgesics is captured in "response surface" models.[1] The response surface is a three-dimensional relationship among two drugs and a single drug effect, as shown in figure 1. The X and Y axes are the concentrations of the hypnotic and the analgesic, in this case sevoflurane and remifentanil. The Z axis shows drug effect, in this case the probability of "nonresponse" to tracheal intubation. Isobole lines on the response surface show specific hypnotic-analgesic concentrations associated with 5%, 20%, 50%, 80%, and 95% probability of nonresponse.

There are many ways to mathematically characterize response surfaces for anesthetic drugs. During the past decade, response surface models of the interaction of hypnotics and analgesics have been proposed by Minto et al.,[2] Nieuwenhuijs et al.,[3] Mertens et al.,[4] Bouillon and colleagues,[5,6] Manyam et al.,[7] Kern et al.,[8] Fidler and Kern,[9] and Schumacher et al.[10] In this issue of ANESTHESIOLOGY, Heyse et al. compare several of these models to identify those most useful to clinicians.[11]

Figure 1 is the model they selected to describe the probability of response to intubation for any combination of sevoflurane and remifentanil. The gold line in figure 1 shows the concentration of sevoflurane associated with a 95% probability of not responding to intubation for any concentration of remifentanil. This represents the adequately anesthetized
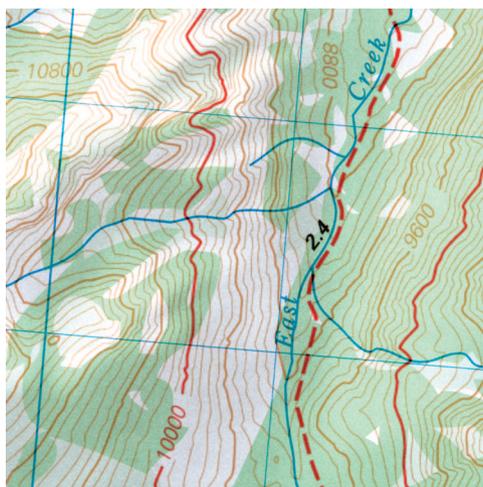
"Because the model is robust, it provides guidance for how the analgesic and hypnotic components interact and may inform our search for the mechanism of general anesthesia."

patient. The green line in figure 1 shows the concentration of sevoflurane associated with only a 5% probability of not responding for any concentration of remifentanil. This represents the awake patient. The steep surface in figure 1 shows the narrow range that separates the awake patient from the adequately anesthetized patient. We titrate hypnotics and opioids to navigate the patient's consciousness from wakefulness to oblivion and back.

Figure 2 views the response surface in figure 1 directly from the top. This is easier to visualize, and several commercially available anesthesia drug delivery systems incorporate this view to inform clinicians of the expected response to any combination of hypnotic and analgesic. These systems plot the patient's path during anesthesia. The trajectory shows where the patient has been, where the patient is now, and how long it will take for the patient to transition from more than 95% probability of nonresponse (an anesthetized patient) to less than 5% probability of nonresponse (an awake patient). The region of the surface with more than 95% probability of nonresponse varies from high concentrations of sevoflurane and very little remifentanil to modest concentrations of sevoflurane and large concentrations of remifentanil. Based on clinical considerations, the anesthesiologist chooses the dose of each drug to achieve more than 95% probability of nonresponse. Often this choice reflects the relative speed of offset of the hypnotic and opioid at the end of anesthesia. When using an opioid with ultrarapid metabolism, the most rapid offset will occur when anesthesia is maintained in the rightward portion of the more than 95% region that minimizes the dose of the slower-offset sevoflurane.

The models that performed best statistically in the analysis by Heyse et al. confirmed our clinical understanding of anesthetic drug interactions. For example, we know that sevoflurane can render a patient nonresponsive in the absence of remifentanil. This is captured in the sigmoidal sevo-

◆ This Editorial View accompanies the following article: Heyse B, Proost JH, Schumacher PM, Bouillon TW, Vereecke HEM, Eleveld DJ, Luginbühl M, Struys MMRF: Sevoflurane remifentanil interaction: Comparison of different response surface models. ANESTHESIOLOGY 2012; 116:311–23.
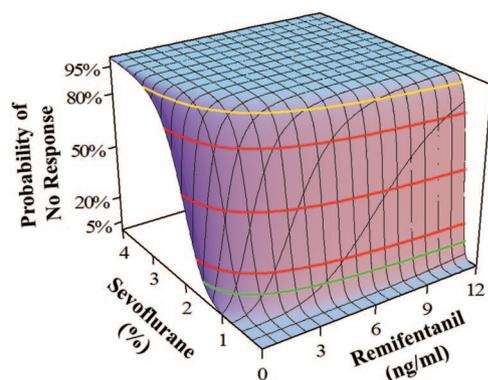
Fig. 1. Interaction of sevoflurane and remifentanil on the probability of response to intubation.

flurane concentration *versus* response curve on the left edge of figure 1, where the remifentanil concentration is 0. We also know that an opioid alone cannot reliably render the patient nonresponsive. This is reflected by the lack of a remifentanil concentration *versus* response relationship on the rightward edge of figure 1, where the sevoflurane concentration is 0.

Each model tested by Heyse *et al.* makes a slightly different assumption about the underlying biology. The most robust models incorporated a very specific assumption: opioids attenuate the noxious stimulus that activates the neural response circuitry, whereas hypnotics directly suppress the neural response circuitry. Glass suggested this mental model of the anesthetic state in 1998.[12] The model for the interaction of sevoflurane and remifentanil shown in figure 1 is a mathematical representation of Glass's suggestion. It accurately describes the observed responsiveness to a wide range of opioid and hypnotic concentrations. Because the model is robust, it provides guidance for how the analgesic and hypnotic components interact and may inform our search for the mechanism of general anesthesia.
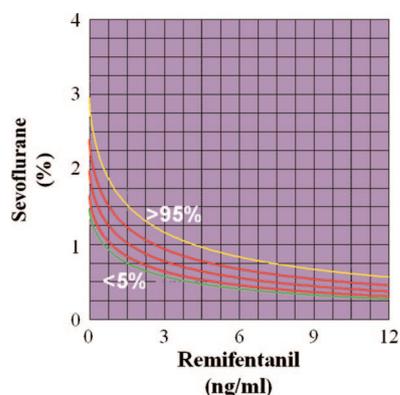
Fig. 2. The same interaction as seen in Figure 1, viewed from directly above.

As George Box said, "all models are wrong, but some are useful."[13] Response surface models are wrong. They reduce our complex physiology to a few mathematical elements. However, they are useful in guiding drug dosing and may provide guidance in our search for the fundamental mechanisms of general anesthesia.

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References

1. Box GEP, Wilson KB: On the experimental attainment of optimum conditions. J R Stat Soc Series B Stat Methodol 1951; 13:1–45

2. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. ANESTHESIOLOGY 2000; 92:1603–16

3. Nieuwenhuijs DJ, Olofsen E, Romberg RR, Sarton E, Ward D, Engbers F, Vuyk J, Mooren R, Teppema LJ, Dahan A: Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. ANESTHESIOLOGY 2003; 98: 312–22

4. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J: Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanil-propofol interactions. ANESTHESIOLOGY 2003; 99:347–59

5. Bouillon TW: Hypnotic and opioid anesthetic drug interactions on the CNS, focus on response surface modelling, modern anesthetics, Handbook of Experimental Pharmacology 182. Edited by Schuttler J, Schwilden H. Berlin Heidelberg, Springer-Verlag, 2008, pp 471–87

6. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. ANESTHESIOLOGY 2004; 100: 1353–72

7. Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD: Opioid-volatile anesthetic synergy: A response surface model with remifentanil and sevoflurane as prototypes. ANESTHESIOLOGY 2006; 105:267–78

8. Kern SE, Xie G, White JL, Egan TD: A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. ANESTHESIOLOGY 2004; 100:1373–81

9. Fidler M, Kern SE: Flexible interaction model for complex interactions of multiple anesthetics. ANESTHESIOLOGY 2006; 105:286–96

10. Schumacher PM, Dossche J, Mortier EP, Luginbuehl M, Bouillon TW, Struys MM: Response surface modeling of the interaction between propofol and sevoflurane. ANESTHESIOLOGY 2009; 111:790–804

11. Heyse B, Proost JH, Schumacher PM, Bouillon TW, Vereecke HEM, Eleveld DJ, Luginbühl M, Struys MMRF: Sevoflurane remifentanil interaction: Comparison of different response surface models. ANESTHESIOLOGY 2012; 116:311–23

12. Glass PS: Anesthetic drug interactions: An insight into general anesthesia: Its mechanism and dosing strategies. ANESTHESIOLOGY 1998; 88:5–6

13. Box GEP: Robustness in the strategy of scientific model building, Robustness in Statistics. Edited by Launer RL, Wilkinson GN. Waltham, Massachusetts, Academic Press, 1979, p 202