

A model for the interaction of two chemicals

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Abstract

We describe a method for studying the interaction of two anesthetic agents, Morphine and Midazolam, acting simultaneously in the same individual. Representing the levels of the two chemicals by diffusion processes, we assume their interaction is governed by a linear combination of the separate components. Pharmacological data is used to estimate the model parameters and, in particular, to determine the coefficient in the linear combination. This leads to the conclusion that the two chemicals have a counteractive effect. © 2005 Elsevier Ltd. All rights reserved.

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1. Introduction

It is well-known that the flow of a chemical in the human body and its concentration at various times can be described by a differential equation. After an initial dose of the chemical is injected into the system, some of it will escape through excretion and the amount of chemical remaining in the system will decay over time. Observation of this phenomenon suggests that the concentration $x(t)$ of the chemical in the system at time t can be modeled by a linear differential equation of the form

$$\frac{dx}{dt} = -\alpha x + f. \quad (1)$$

Here α is a positive constant that denotes the relative rate of elimination of the chemical from the body and f is a generally decreasing function. Kinetic models of this type have been extensively studied (see e.g. the book of Jacquez (1985), papers of Sen and Mohr (1990), Krewski et al. (1991), and many other works).

As pointed out by Ferrante et al. (2003), the function f may be subject to random fluctuations from a variety of physical and physiological sources. This has led to the

introduction of stochastic versions of the model (1), where the function f is assumed to contain a white noise component. In this case, Eq. (1) is more properly interpreted as a stochastic differential equation

$$dx = (-\alpha x + g) dt + h dw, \quad (2)$$

where w is a Wiener process and g and h are deterministic functions. Models of this type have been studied by Matis and Hartley (1971), Matis et al. (1983), Matis (1988), Sen et al. (1992), Ferrante et al. (2003) and others. An important feature of these works is the calculation of the internal variability of the system as defined by the variance of the process x .

The objective of this paper is to develop a stochastic model to study the nature of the interaction of two chemicals, Morphine and Midazolam, acting in combination in a single individual. We assume that the combined effect is an a priori *unknown* linear combination of the two chemicals. The main objective of the paper is to determine this linear combination.

The underlying methodology is as follows. The amounts of Morphine and Midazolam in the system at any given time are assumed to follow diffusion processes x_1 and x_2 of the form (2), driven by the same Wiener process w . We further assume that the combined effect x of the chemicals is given by the linear combination $x \equiv$

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$x_1 + cx_2$ of the two processes, for a value of c in the range $[-1, 1]$. In Section 2, we give formulae for the mean and variance of the process x and identify the distribution of x as Gaussian. In Section 3, we use pharmacological data to estimate the parameter c , together with the other unknown parameters in the model. These estimates are obtained using a weighted least-squares method based on the mean and variance formulae in Section 2. Section 4 is a discussion and summary of the paper. We conclude with an appendix in which the mathematical results stated in Section 2 are derived.

2. Distribution theorems

We specialize model (2). Assume that the level of concentration x of the drug in the system follows a linear stochastic differential equation of the form

$$dx = (-\alpha x + ve^{-\beta t}) dt + \kappa dw. \tag{3}$$

Here v is the initial amount of chemical, β is its rate of absorption, κ is a diffusion constant, and w is a standard Wiener process. The rates α , β , and the diffusion coefficient κ are considered to be constants. We assume that the initial concentration $x(0)$ is zero. The following results, whose proofs are given in the appendix, will be needed in Section 3.

Theorem 1. *For each $t > 0$, the random variable $x(t)$ has a Gaussian distribution with mean*

$$\frac{v}{\alpha - \beta} (e^{-\beta t} - e^{-\alpha t}) \tag{4}$$

and variance

$$\frac{\kappa^2}{2\alpha} (1 - e^{-2\alpha t}). \tag{5}$$

We now describe the distribution of a linear combination of two processes satisfying equations of form (3). To this end, consider the linear stochastic differential equations

$$dx_i = (-\alpha_i x_i + ve^{-\beta_i t}) dt + \kappa_i dw$$

with $x_i(0) = 0$ for $i = 1, 2$. Since the chemicals are acting simultaneously, we assume the equations for x_1 and x_2 are driven by the same noise process w . Set

$$\mu_i(t) = \frac{v_i}{\alpha_i - \beta_i} (e^{-\beta_i t} - e^{-\alpha_i t})$$

and

$$\sigma_i^2(t) = \frac{\kappa_i^2}{2\alpha_i} (1 - e^{-2\alpha_i t}).$$

In the sequel, let x denote the process

$$x(t) = x_1(t) + cx_2(t).$$

Theorem 2. *The process x is Gaussian. Furthermore $x(t)$ has mean $\mu_1(t) + c\mu_2(t)$ and variance*

$$\sigma_1^2(t) + c^2\sigma_2^2(t) + \frac{2c\kappa_1\kappa_2}{\alpha_1 + \alpha_2} (1 - e^{-(\alpha_1 + \alpha_2)t}).$$

3. Application of the model to pharmacological data and parameter estimation

Researchers in pharmacology are interested in the effects of two chemicals, Morphine, and Midazolam, when administered simultaneously. Morphine, an anesthetic agent, is used widely but may have undesirable side effects at high dosages. Midazolam, a milder agent in a similar chemical group, has been shown to have minimal side effects, even when administered in high dosages. It also has been shown to either increase or decrease anesthetic activity depending on the relative combined concentration of Morphine and Midazolam (Niv et al., 1988; Tejwani et al., 1990). Experimental data has been obtained concerning the effect of Morphine when applied with varying levels of Midazolam. Of particular interest is the question of whether a combination of the two chemicals can produce the desired anesthetic effect, which should peak to maximum strength within an hour and gradually leave the system in 5–6 h.

Experimenters have collected data from a group of five laboratory rats. They administered Morphine at two levels, low (10 μg .) and high (30 μg .) and Midazolam at high (30 μg .) level to make cross combination levels of the drugs. The combined effects of these two chemicals were then observed on the group of rats. Measurements were recorded of the average percentages of the animals exhibiting tail flickering when placed on a hot plate, at 12 time points between 0 and 360 min. A measurement of 100% indicates the strongest analgesic effect in a scale of 0% to 100% (details of the experiment are reported in Rattan et al. (1991) with descriptive statistics).

We use this data to study the nature of the interaction of the two chemicals, as indicated in Section 1. The sets of measurements are labeled in the paper as data set 1 (referred to as set 1) corresponding to the high initial levels of both Morphine and Midazolam, and data set 2 (referred to as set 2) corresponding to the low initial level of Morphine and high initial level of Midazolam.

Even though the distribution of $x(t)$ is Gaussian, the maximum likelihood estimates of the parameters in the model are difficult to compute analytically. Instead, we numerically estimate the parameters by the weighted least-squares method using the formulae for the mean and variance given in Section 2. A nonlinear regression fit of the model to the data is obtained using the iterative process in SAS. We minimize the weighted sum of squares (WSS) in the

Table 1
Estimated parameter values for the model $x(t)$

Data	α_1	β_1	α_2	β_2	c	R^2
Set 1	.1654 ± .0535	.0204 ± .0047	.0892 ± .0345	.1276 ± .0297	−1.000 ± .0540	99.27%
Set 2	.0118 ± .0021	.2200 ± .0532	.0142 ± .0043	1.0629 ± .0867	−0.9357 ± .0270	99.8%

±, Indicates asymptotic standard errors.

following expression:

$$WSS = \sum_{t=1}^{12} \frac{(x(t) - [mean(x(t))])^2}{var(x(t))},$$

where the mean and variance of $x(t)$ are computed from the formulae given in Theorem 2, with subscript 1 corresponding to Morphine and subscript 2 corresponding to Midazolam.

Because we are limited to small data sets and we lack information on the variability of the measurements at each time point, we are forced to assign values to κ_1 and κ_2 . Since we have no a priori reason to believe that these differ, we assign the value 1 to both parameters. In the parameter estimation in data set 1 we take both v_1 and v_2 to be 30. For the second data set we take v_1 to be 10 and v_2 to be 30. These values represent the initial levels of the two drugs. The estimates for the five remaining parameters, together with their standard errors are given in Table 1. This table also shows the corresponding coefficients of determination, R^2 , for the model fits (see Tanner, 1996).

We note that for data set 1, the estimated coefficient c in the linear combination $x \equiv x_1 + cx_2$ is equal to -1 , whereas for the second data set it is close to -1 . Furthermore, the coefficients of determination with these values of c are *very close* to 1 for both data sets, showing that the models fit the data extremely well. An examination of Figs. 1 and 2, which show the fitted curves for the mean of x together with the data points, confirms this quantitative result.

This provides strong evidence that the linear combination $x = x_1 - x_2$ is a plausible model of the interaction of the two chemicals. We conclude that Morphine and Midazolam have a *subtractive effect* when acting in combination, a somewhat surprising result.

Figs. 3 and 4 show 95% confidence bands, together with the means of the model for the two sets of data. These bands are based on the coefficients from Table 1. The confidence bands are quite tight in both cases.

We make the following observations concerning the other estimated parameters in the model. The rate α_1 in Table 1 is large, indicating a rapid elimination of Morphine when combined with Midazolam. This confirms the expected result that Morphine, in combination with Midazolam, has a high elimination rate

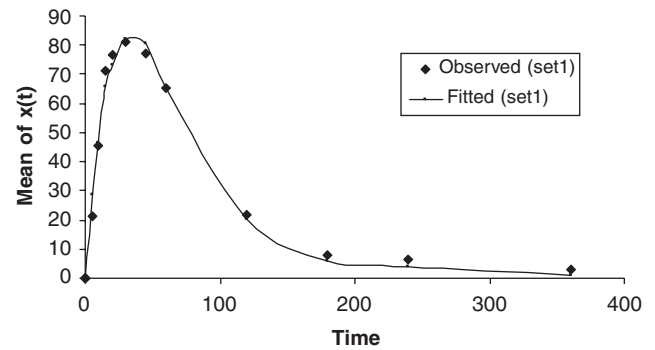


Fig. 1. The mean of $x(t)$ is shown here with the observed values for data set 1 using the weighted equation for the model.

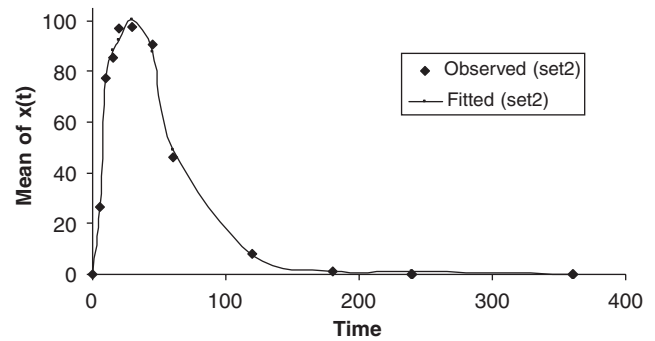


Fig. 2. The mean of $x(t)$ is shown here with the observed values for data set 2 using the weighted equation for the model.

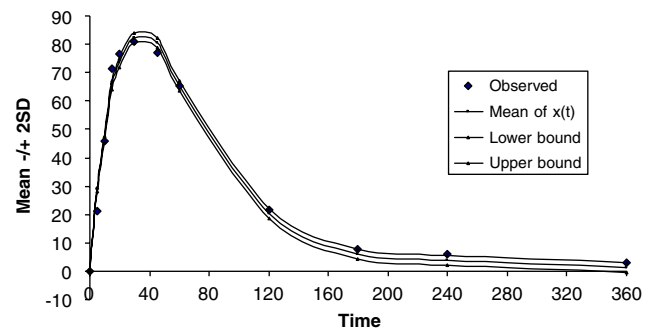


Fig. 3. Ninety-five percent confidence intervals for mean of $x(t)$ for data set 1.

(whereas Morphine acting alone is known to have a low elimination rate as is evident from the first row of Table 2). Furthermore, the absorption rate of Midazolam, β_2 , is high in Table 1, which may indicate that, at these

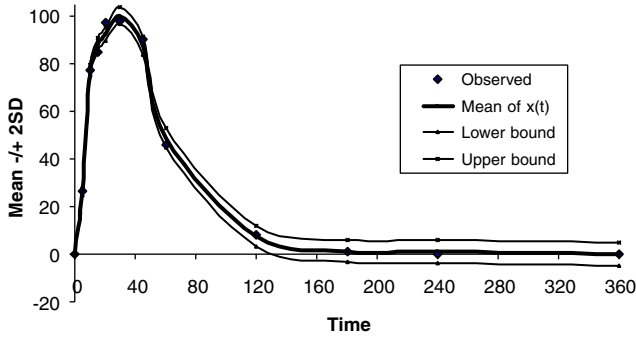


Fig. 4. Ninety-five percent confidence intervals for mean of $x(t)$ for data set 2.

Table 2
Estimated parameter values for two levels of Morphine acting alone

Initial level	α	β
30 μg	.097 \pm .0039	.000239 \pm .000129
10 μg	.3549 \pm .0317	.0599 \pm .00826

\pm , Indicates asymptotic standard errors.

levels, the second chemical is inhibiting the first chemical.

For the second data set the rates of elimination α_1 and α_2 are small and the rates of absorption β_1 and β_2 are higher. Furthermore the rate β_1 is much higher than β_2 , indicating that the second chemical may be dominating the combined effect. Comparing with second row in Table 2, we note that β_1 is higher than the absorption rate of Morphine when acting alone. This suggests that Midazolam enhances the effect of a low level of Morphine.

As is apparent from both the data sets and the fitted curves, the anesthetic effects peak within 50–60 min of administering the drugs and leave the system after 360 min.

4. Discussion

In this paper we have developed a stochastic model for the combined effect x of two chemicals, Morphine and Midazolam. It was assumed that x is expressible as a linear combination $x_1 + cx_2$ of two diffusion processes x_1 and x_2 representing the flow of the two chemicals. Experimental data was used to estimate the parameters in the stochastic differential equations describing the processes and, in particular, to determine the constant c in the linear combination. These estimates were obtained using the weighted least-squares method based upon formulae for the mean and variance of x given earlier in the paper.

The result of this analysis was presented in Table 1, and in Figs. 1, 2, 3 and 4. These figures show that the model fits the data extremely well, thus confirming its validity as a plausible description of the interaction of the two chemicals.

The main result of the paper is the determination of the constant c as being very close to -1 . This leads to the interesting conclusion that Morphine and Midazolam have a mutually counteracting effect when acting simultaneously.

Perhaps the most important aspect of the paper is the introduction of a methodology for studying the interaction of two chemicals in a pharmacological setting. The statistical results of the paper are based on small data sets. However, as more experimental data becomes available, this methodology can be used to refine the statistical results presented here.

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Appendix

The proofs of theorems 1 and 2 follow easily from the following theorem. This result is well known (see, e.g. Friedman (1975, Theorem 2.5, p.63) for a more general version of the theorem). We give an elementary proof here in order to make the paper self-contained.

Theorem A. Let $h : [s, t] \times \mathbf{R} \rightarrow \mathbf{R}$ be a continuous deterministic function, not identically zero. Then, for $s < t$, the stochastic integral

$$X \equiv \int_s^t h(u) \, dw(u)$$

has a Gaussian distribution with mean zero and variance σ^2 where

$$\sigma^2 = \int_s^t h^2(u) \, du. \tag{A.1}$$

Furthermore,

$$\text{Cov} \left(\int_0^s h(u) \, dw(u), \int_0^t h(u) \, dw(u) \right) = \int_0^s h^2(u) \, du. \tag{A.2}$$

Proof. Let $\Pi_n \equiv \{s = t_0 < t_1 < \dots < t_n = t\}$ denote a sequence of partitions of $[s, t]$ with mesh tending to

zero. Then the stochastic integral X is the limit in L^2 of the sequence

$$X_n = \sum_{i=1}^n h(t_i)[w(t_{i+1}) - w(t_i)]. \quad (\text{A.3})$$

(see e.g. Gard, 1988). The independent increment property of the Wiener process implies that each X_n is a sum of independent Gaussian random variables. Hence X_n is itself Gaussian and has mean zero and variance

$$\sigma_n^2 = \sum_{i=1}^n h^2(t_i)(t_{i+1} - t_i).$$

Note that $\sigma_n \rightarrow \sigma$ as $n \rightarrow \infty$. Let Φ denote a test function on \mathbf{R} . The dominated convergence formula yields

$$\begin{aligned} E[\Phi(X)] &= \lim_{n \rightarrow \infty} E[\Phi(X_n)] \\ &= \lim_{n \rightarrow \infty} \frac{1}{\sqrt{2\pi\sigma_n}} \int_{-\infty}^{\infty} \Phi(x) e^{-x^2/2\sigma_n^2} dx \\ &= \frac{1}{\sqrt{2\pi\sigma}} \int_{-\infty}^{\infty} \Phi(x) e^{-x^2/2\sigma^2} dx. \end{aligned}$$

Thus X has a Gaussian distribution with mean zero and variance σ^2 , as claimed.

Finally, (A.2) follows from (A.1) and the fact that, since the Wiener process has independent increments, the same is true for the process $\int_0^t h(u) dw(u)$. \square

Proof of Theorem 1. Solving Eq. (3) yields

$$x(t) = \frac{v}{\alpha - \beta} (e^{-\beta t} - e^{-\alpha t}) + \kappa \int_0^t e^{\alpha(s-t)} dw(s).$$

The Gaussian nature of $x(t)$ and (4) follow immediately from Theorem A. To obtain Eq. (5), we note that the variance of $x(t)$ is equal to the variance of the stochastic integral in Eq. (A.3). From Theorem 1, this is

$$\kappa^2 \int_0^t e^{2\alpha(s-t)} ds = \frac{\kappa^2}{2\alpha} (1 - e^{-2\alpha t}). \quad \square$$

Proof of Theorem 2. Following Eq. (A.3), we have

$$\begin{aligned} (x_1 - x_2)(t) &= \mu_1(t) - \mu_2(t) \\ &+ \int_0^t [\kappa_1 e^{\alpha_1(s-t)} - \kappa_2 e^{\alpha_2(s-t)}] dw(s). \end{aligned}$$

The proof of the theorem now follows the same lines as that of Theorem 1. We omit the details. \square

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