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A Controller for Automatic Regulation of Induced Paralysis During Surgery

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Abstract—This paper presents a strategy for automatic control of induced paralysis using vecuronium bromide during surgery. The controller is self-tuning and adapts to inter-patient and intra-patient response variations while optimizing the output variance and infusion rate. In particular, the controller is capable of accommodating the variations of pure time delays in patient response. The performance of the controller is evaluated using an experimentally derived pharmacokinetic and nonlinear pharmacodynamic model of patient response. The results indicate that the controller provides robust regulation of the paralysis level with no output offset.

Keywords—Neuromuscular, Paralysis, Adaptive control, Vecuronium.

INTRODUCTION

Automatic control of paralysis offers significant clinical advantage in the operating rooms. Paralysis or muscle relaxation is an important component of most anesthetic procedures. It is especially of importance during surgical cases that require patient immobility. The frequent monitoring of the level of paralysis is vital for proper control and for assessing the reversal of paralysis at the end of surgery. The need for constant monitoring of the degree of paralysis adds to the work load of the anesthesiologists, who must also concentrate on other variables during surgery. Hence, a reliable automated method of inducing and maintaining paralysis can contribute significantly to the improvement of patient care.

One of the modern muscle relaxants presently in clinical use for initiation and maintenance of paralysis is the non-depolarizing agent, vecuronium bromide. Vecuronium has become popular because of its shorter duration of action and rapid metabolism, without causing cardiovascular side effects (1). Also, the shorter half-life of vecuronium allows efficient continuous infusion.

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At present, the anesthesiologist manually controls the degree of neuromuscular block. To monitor the paralysis level, the anesthesiologist applies four short duration (2 ms each) electrical pulses called train-of-four to the ulnar nerve and visually observes the resulting twitches in the fingers and the thumb (2). However, manual control is subjective, inaccurate and plagued by:

- Wide inter-patient response variability and sensitivity to drug;
- an unstable patient pharmacodynamic profile fluctuating between over-dosage and under-dosage (3);
- existence of a dead time between the administration of the drug and observed response (3);
- introduction of new shorter-acting drugs like vecuronium and atracurium compounding the existing problems, as boluses have to be frequently administered and recovery can be rapid and unpredictable at times.

Recognizing these problems, investigators have tried several different control techniques to explore the automation of inducing paralysis. The simplest closed loop control (4) was an on-off control, and the variation in relaxation was 15%. Ritchie *et al.* (5) reported an average overshoot of 9.9% using a fixed gain proportional, integral and derivative (PID) controller. Ausbury and Linkens (6) used proportional control with fair amount of success, but had a steady state offset of 7.1%. Clinical trials by Jaklitsch *et al.* (7) using a digital PID algorithm resulted in a 5.5% offset. Simulation studies by Jaklitsch *et al.* (8) using a heuristic adaptive controller reduced the steady state error to less than $\pm 1\%$, and improved on their earlier PID attempt (7). Another group of investigators conducted clinical trials (9,10) using a mathematical model; they reported a steady state offset of 2% using d-tubocuranine and 0.2% with atracurium. Using a self-tuning controller (3), the above group (9,10) were able to overcome wide individual response variations for atracurium. However, a mean offset of -4.7% was present. A recent clinical study by O'Hara *et al.* (11) reported a steady state error of 3%; however, their controller is not adaptive to changes in the patient parameters.

Despite significant refinements, the proposed control methods are still beset with sensitivity to individual patient response parameters, variations in the response time delay, lack of drug optimization, and offset in the induced level. Moreover, none addressed variations in pure time delay, a factor that can cause closed loop instability (12).

In this paper, we present the application of a pure-time-delay-accommodating controller for the automatic regulation of vecuronium during surgery. The development of the control algorithm was initiated by Behbehani *et al.* (13); Delapasse (14) applied it to the problem of regulating the mean arterial blood pressure (MABP) using sodium nitroprusside (SNP). Simulation trials have revealed that the controller is robust, adaptive for a wide range of changing patient gains and response delays, and at the same time optimizes the infused drug (14). Previously, this controller was applied to linear processes only. We have extended its application to the closed loop control of paralysis using vecuronium, which has nonlinear response characteristics.

CONTROL ALGORITHM

The developed controller (14) combines the integrating self-tuning (IST) control algorithm of Tuffs and Clarke (15) with the time-delay compensation technique developed by Vogel and Edgar (16) to accommodate varying time delays. A complete derivation of the control algorithm is provided in (14). We present the main results here to illustrate its implementation.

The derivation of the controller is based on the assumption that the plant to be controlled is linear and is represented by a modified Controlled Auto Regressive Integrated Moving Average (CARIMA) process given by

$$A(z^{-1})y(t) = z^{-k\min}B_E(z^{-1})u(t) + \frac{C(z^{-1})\zeta(t)}{\Delta}. \quad (1)$$

where $u(t)$ and $y(t)$ are the process input and output, respectively; $A(z^{-1})$ and $C(z^{-1})$ represent polynomials of order n in the backward shift operator z^{-1}; $\zeta(t)$ is an independent random variable with zero mean representing stochastic disturbances; k_{min} is the lower bound on the system pure time delay; $\Delta = 1 - z^{-1}$ is a differencing operator defined by (14); and B_E is defined as follows:

$$B_E = b_o' + b_1'z^{-1} + \ldots b_r'z^{-r}, \quad (2)$$

where

$$r = k_{max} - k_{min} + n.$$

The factor B_E (Eq. 2) is selected to allow inclusion of sufficient terms for expressing the time delay between the maximum and minimum expected delays, k_{max} and k_{min}, respectively. The CARIMA model after delay compensation is written as

$$A(z^{-1})y(t) = z^{-1}\Sigma B_E u(t) + \frac{C(z^{-1})\zeta(t)}{\Delta} \quad (3)$$

where

$$\Sigma B_E = \sum_{i=0}^{i=r} b_i'. \quad (4)$$

Note that the model (Eq. 3) allows the actual time delay to be unknown. However, it does require the knowledge of the lower and upper bound of the delay.

The developed controller minimizes the following cost function,

$$J = E\{[Py(t + k) - Rw(t)]^2 + [Q'u(t)]^2\}, \quad (5)$$

where $E\{.\}$ is the expected value, $P(z^{-1})$ is a user defined polynomial and represents the inverse of the desired closed loop response model, $y(t + k)$ is the predicted value of $y(k)$, $w(t)$ is the desired output, R is a weighting polynomial, and $Q'(z^{-1})$ is a user defined input weighting polynomial.

The control law can be derived as (14)

$$[Q + \Delta G(z^{-1})]u(t) + F'(z^{-1})y(t) - H(z^{-1})w(t) = 0, \quad (6)$$

where $G(z^{-1})$, $F'(z^{-1})$ and $H(z^{-1})$ represent polynomials in the backward shift operator z^{-1}, computed as part of the control calculations.

Fig. 1 shows a schematic of the delay accommodating controller. By simplifying the inner feedback loop shown in Fig. 1, the control signal for the delay-accommodating controller is obtained as

$$u(t) = \frac{A(w(t) - (1 + \Delta F))y(t)}{P\Sigma B_E + AQ - (1 + \Delta F)B_E z^{-k\min}}. \quad (7)$$

The closed loop output is given by

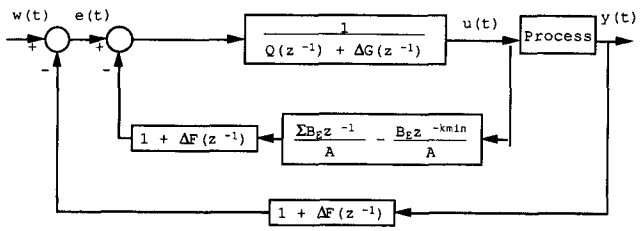

FIGURE 1. Block diagram of the delay accommodating controller.

$$y(t) = \frac{z^{-k}Bw(t)}{(P\Sigma B_E + AQ + z^{-k}B(1 + \Delta F) - B_E z^{-kmin}(1 + \Delta F)} + \frac{\{P\Sigma B_E + AQ - z^{-kmin}B_E(1 + \Delta F)\}\zeta(t)}{P\Sigma B_E + AQ + z^{-k}B(1 + \Delta F) - B_E z^{-kmin}(1 + \Delta F)}. \quad (8)$$

At steady state, $Q(z^{-1})$ is zero, $P(1)$ is unity and $B(z^{-1})$, $B_E(z^{-1})$ and ΣB_E are all equal.

Prior to control action, there is an initial estimation period during which a pseudo-random binary sequence (PRBS) is applied to the patient model for estimating the process parameters (a_i and b'_i of the plant, Eq. 1).

$Q(z^{-1})$ represents a first-order transfer function, and dictates the weighting on the control signal. We used the following $Q(z^{-1})$ based on a form suggested by Tuffs (15):

$$Q(z^{-1}) = \lambda'|\Sigma B_E|(1 - z^{-1}), \quad (9)$$

where λ' is a user defined coefficient, controlling the degree of weighting. The magnitude of $Q(z^{-1})$ approaches zero at steady state. This eliminates $u(t)$ from the cost function (Eq. 5) and lets the controller diminish the output offset.

As indicated, the derivation of the above controller is based on the assumption that the system under its control is a linear system. However, as will be described below, the patient response to vecuronium has a nonlinear pharmacodynamic component.

PATIENT RESPONSE MODEL

To investigate and evaluate the control strategy, we conducted computer simulations using the patient simulation model developed by Jaklitsch *et al.* (8). Jaklitsch *et al.* (8) found this model adequate for routine monitoring of neuromuscular blockade, predicting the patient response in the 0–100% range. Fig. 2 shows the proposed patient model. In this figure, the input $i(t)$ is the drug infusion rate (mg/kg), Td is the response pure delay (s), k_{12} is the rate constant (s^{-1}), α and β are pharmacokinetic parameters (s^{-1}) that reflect the drug elimination rates, and $c(t)$ is the amount of drug per body weight in the effect compartment (mg/kg).

The pharmacodynamics of vecuronium is modeled by the well known Hill equation proposed by Wagner (17). Eq. 10 describes the nonlinear pharmacodynamics of the patient response to vecuronium:

$$y(t) = \frac{100}{\left(1 + \left(\frac{c(t)}{\sigma^*ED50}\right)^{\gamma}\right)}, \quad (10)$$

where $y(t)$ is the twitch response due to the concentration of the drug in the main compartment, σ is a constant of proportionality, the term ED50 defined in (18) is the mean dose for 50% relaxation, and γ is a pharmacodynamic constant defined as follows:

$$\gamma = 2.94/\ln(ED95/ED50), \quad (11)$$

where ED95 is the mean dose required for 95% relaxation.

To overcome the nonlinearity of the patient response to vecuronium, an inverse block of the form shown in Eq. 12 was added to linearize the response of the system:

$$c(t) = \sigma^*ED50\left(\left(\frac{100}{y'(t)}\right) - 1\right)^{\frac{1}{\gamma}}, \quad (12)$$

where $y'(t)$ is the paralysis level, given by the difference between the maximum twitch (100%) and the observed twitch response,

$$y'(t) = 100 - y(t). \quad (13)$$

Table 1 shows the nominal patient model parameters (8).

SIMULATION METHOD

All computer simulations were performed using the software package MATRIX$_x$ (19) on a VAX/VMS 8800 computer (20). Fig. 3 depicts the simulated system consisting of the patient and controller model in the MATRIX$_x$ environment.

A brief description of the different blocks in Fig. 3 follows. The controller block represents the delay-accommodating controller described earlier. The controller was implemented with a sampling rate of 20 s. The size of the a_i and b'_i vectors was limited by assuming a max-

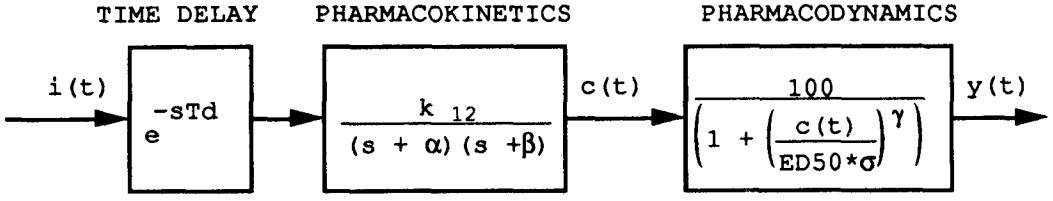

FIGURE 2. Patient model of vecuronium (7).

TABLE 1. Nominal patient model parameters (7).

Model parameters	Value with units
k_{12}	$2.833 * 10^{-3}\ s^{-1}$
	Range (0.833 to 6.833) $* 10^{-3}\ s^{-1}$
α	$5.376 * 10^{-3}\ s^{-1}$
β	$6.172 * 10^{-4}\ s^{-1}$
ED50	0.027 mg/kg
ED95	0.056 mg/kg
σ	0.315
γ	4.03
Td	78 s

imum expected (k_{max}) of five sample intervals, and the maximum plant order (n) of 5. The magnitude of $P(z^{-1})$, which is a user defined second order polynomial, was set to unity, a dead beat controller. To achieve zero offset at steady state, the magnitude of λ' (Eq. 9), as well as the polynomials $H(z^{-1})$, $R(z^{-1})$ and $Q'(z^{-1})$ (Eqs. 5 and 6), were selected to be unity.

In Fig. 3, limiter No. 1 prevents negative infusion and caps the maximum allowed infusion to the patient model at 0.0556 (μg/kg)/s, a clinically recommended value. The paralysis block represents the twitch response in terms of percent paralysis. Limiter No. 2 eliminates the singularity produced at 100% paralysis by limiting the maximum level to 99.99%. The inverse blocks are used for linearizing the patient response and the set point. The gain blocks scale the control input, output and the set point appropriately to avoid numerical computation problems with small numbers, since the output of the linearizing block is small. However, the gain blocks have no effect on the control strategy.

Since the patient response characteristics are unknown, initial estimates of these characteristics, based on the model assumed in (3), are needed before the closed control of the infusion can commence. We devised a fixed duration initial induction/estimation period that achieves this objective and also provides for a rapid induction of paralysis at the beginning of the surgery. Specifically, a bolus injection determined by the anesthesiologist is given at the start of this initial induction/estimation interval, followed by a sequence of small fixed amplitude pseudo-random binary infusions (PRBS). The bolus size, the PRBS injection values and the patient response to these inputs are used to obtain the initial estimates. During this time, the closed loop control remains disabled, while the combination of the bolus and PRBS injections accomplish a rapid induction of the paralysis. It is noted, however, that after the initial induction/estimation period, the controller is enabled and while it controls the infusion level, it also continues to update the patient parameter estimation. Hence, it adapts to the changes in the patient response and, in particular, changes in the pure time delay.

Simulations with initial induction/estimation periods ranging from 1 to 10 min were conducted to identify the time period adequate to obtain a good estimate of the patient model parameters. As indicated above, during the initial estimation period, the closed-loop controller was disabled and a pseudo-random binary sequence (PRBS) with a magnitude of 0.0157 (μg/kg)/s, a clinically safe value, was infused to the patient. An initial estimation period of 200 s was found to be satisfactory, as it covered the transient period of the response and provided the controller with necessary information for initial estimate of the patient response parameters.

For the simulation studies, we assumed that a predetermined bolus dose is used for all patients. The size of this initial bolus was selected with the objective of achieving paralysis of 90% or higher as quickly as possible. Simulations with a nominal patient parameter model revealed that a bolus size of 0.028 mg/kg was optimum to establish adequate paralysis for initiating intubation and surgical procedures. This bolus was given while the feedback loop remained open over the first 20 s of the initial 200 s estimation period.

CONTROLLER PERFORMANCE EVALUATION

To evaluate the controller performance, we conducted simulation experiments with different patient parameters and in the presence of external disturbances. We determined the maximum overshoot, settling time, mean offset at steady state, and the mean steady state infusion rate for a step reduction in muscle twitch (increase in paralysis).

Fig. 4 shows the response of a patient with nominal parameters following the delivery of the bolus; the nominal values for patient response model are summarized in Table 1. The desired level of 90% paralysis was achieved with minimum overshoot and the response settled in 8 min. The mean steady state offset and infusion were 0.07% and 1.03 (μg/kg)/min, respectively.

To evaluate the controller's ability to adapt to different patient drug sensitivity, simulation runs with different patient gains were performed. A less sensitive patient was simulated with a drug sensitivity gain half the nominal value, as shown in Fig. 5. This resulted in stable control; however, the settling time increased (16 min) due to the lower sensitivity of the patient to the drug. The steady state error was again negligible.

The simulation results of a patient with high drug sensitivity (an increased gain of $k_{12} = 6.50 * 10^{-3}\ s^{-1}$, more than 200% of the nominal K_{12} value) at a steady state level of 80% paralysis is illustrated in Fig. 6. The initial 0.028 mg/kg bolus, injected while the controller was disabled during the initial induction/estimation period, created an overshoot. When the closed-loop control was enabled after 200 s, it attempted to apply a series of infusion inputs in order to control the paralysis at the desired level. But the negative inputs cannot be physically applied to the

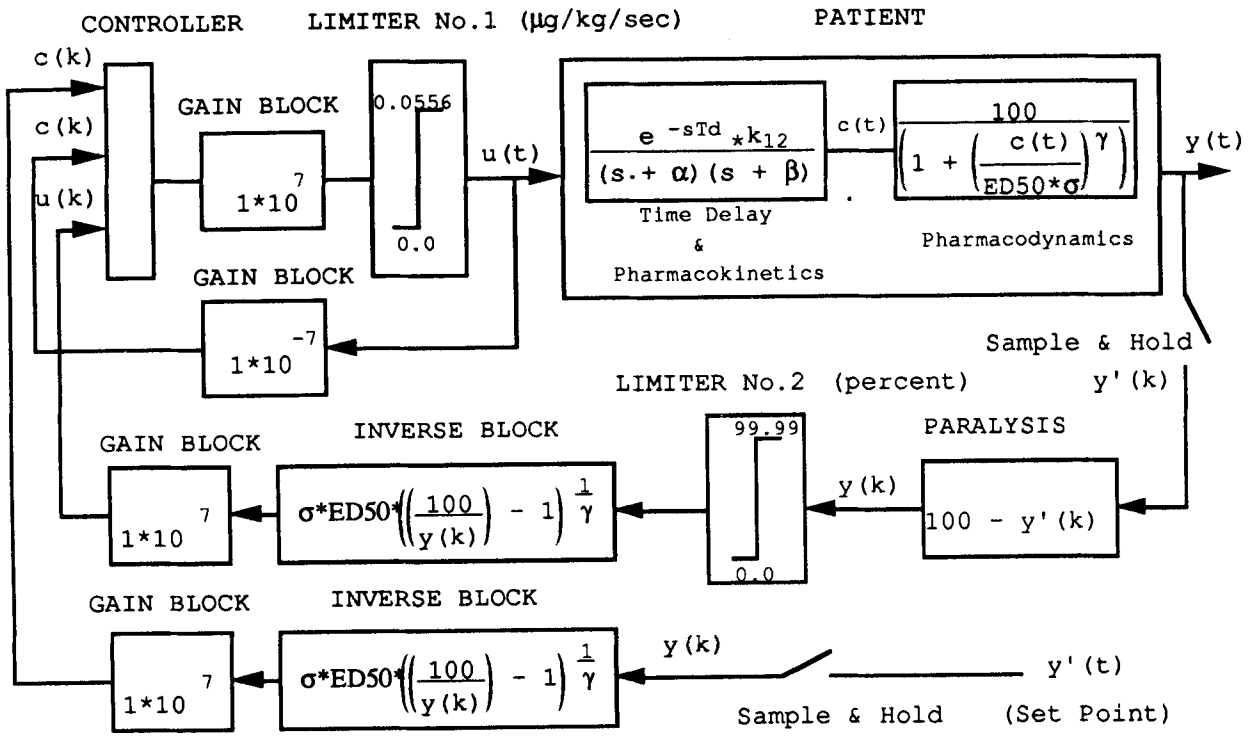

FIGURE 3. Schematic representation of the simulated system.

patient, as the infused drug can only be removed from the patient through metabolic elimination process and not by the controller. This unidirectional input limit is modeled in the simulation by the limiter No. 1 block shown in Fig. 3 which limits the infusion to be none negative and less than the maximum level of 3.5 (μg/kg)/min. Hence, the actual injections to the patient that are shown in Fig. 6b differ from what the controller has commanded. However, both the input and patient response information are used for control action calculations, and this affected the controller's estimate of the patient parameters adversely. Therefore, the controller did not cease the infusion until further input and output were obtained, about 7 min after the controller was activated. Therefore, the controller obtained a better estimate of the patient parameters, and achieved a smooth transition to the desired response level.

To illustrate that the initial overshoot is due to the manually injected bolus, we simulated the response of the same patient with a bolus of 0.00191 mg/kg, a dose substantially smaller than the original bolus (0.028 mg/kg). Figure 7 illustrates the response of the patient with this smaller bolus, and its impact on the initial maximum overshoot and the settling time. As seen in Fig. 7b, the lower bolus eliminated negative inputs by the controller.

Note that the initial overshoot following bolus infusion may indeed be desirable as it expedites the intubation. However, it can be eliminated by starting with a small manually injected bolus.

The impact of changes in the patient response delay on

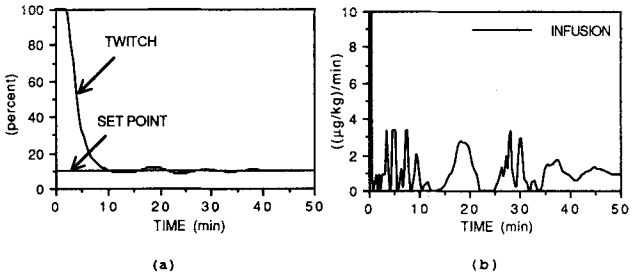

FIGURE 4. Computer simulation with a bolus of 0.028 mg/kg and $y'(t)$ = 90%. (a) Twitch response. (b) Infusion rate. Patient parameters were k_{12} = 2.833 * 10^{-3} s^{-1}, α = 5.37 * 10^{-3} s^{-1}, β = 6.12 * 10^{-4} s^{-1}, Td = 78s. Steady state infusion was 1.03 (μg/kg)/min.

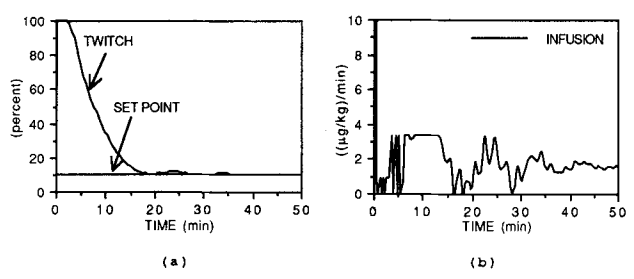

FIGURE 5. Computer simulation with a bolus of 0.028 mg/kg and $y'(t)$ = 90%. (a) Twitch response. (b) Infusion rate. Patient parameters were: k_{12} = 1.833 * 10^{-3} s^{-1}, α = 5.37 * 10^{-3} s^{-1}, β = 6.12 * 10^{-4} s^{-1}, Td = 78s. Steady state infusion was 2.66 (μg/kg)/min.

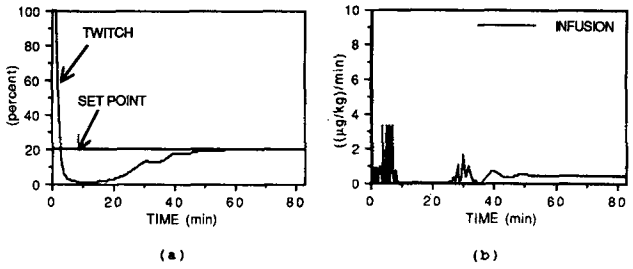

FIGURE 6. Computer simulation with a bolus of 0.028 mg/kg and $y'(t)$ = 80%. (a) Twitch response. (b) Infusion rate. Patient parameters were $k_{12} = 6.50 * 10^{-3}\ s^{-1}$, $\alpha = 5.33 * 10^{-3}\ s^{-1}$, $\beta = 7.50 * 10^{-4}\ s^{-1}$, Td = 60s. Steady state infusion was 0.44 (μg/kg)/min.

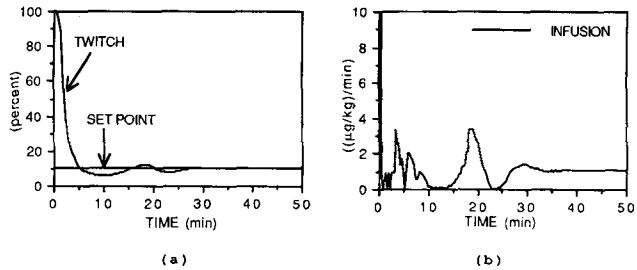

FIGURE 8. Computer simulation with a bolus of 0.028 mg/kg and $y'(t)$ = 90%. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 3.67 * 10^{-3}\ s^{-1}$, $\alpha = 5.67 * 10^{-3}\ s^{-1}$, $\beta = 7.85 * 10^{-4}\ s^{-1}$, Td = 12s. Steady state infusion was 1.08 (μg/kg)/min.

the control performance was evaluated by conducting simulations with different delays (8). The simulation result of a patient with a reduced delay of 12 s (compared with a nominal value of 78 s) is illustrated in Fig. 8. It can be seen that decreasing the transport delay did not deteriorate control performance.

Figure 9 shows the response of a nominal gain patient with an increased delay of 114 s. When compared with the response of a nominal delay patient (Fig. 4), a small initial overshoot of 5.93% was observed, and the mean steady state offset was negligible (0.32%).

The ability of the controller to reject external disturbances in the form of noise was evaluated at different paralysis levels. External noise with signal-to-noise ratios (SNR) ranging from −3 dB to 18 dB (comparable to that expected in the operating rooms) was added to the patient response (8). The contaminated patient response was then filtered by a first-order low pass filter, with a corner frequency of 0.002 Hz, before it was fed back to the controller. A description of the added noise follows.

The SNR is defined as the logarithm of the ratio of the expected power, E, of the twitch, $y(t)$, to that of the noise, $y(n)$:

$$\text{SNR} = 10 \log \left(\frac{Ey(t)^2}{Ey(n)^2} \right). \qquad (14)$$

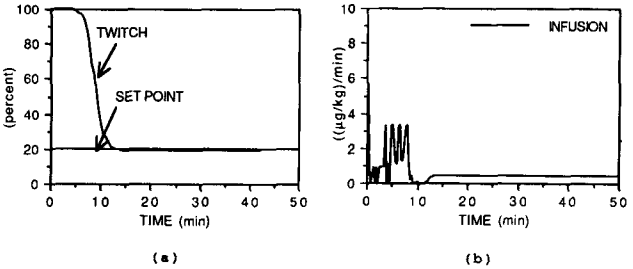

FIGURE 7. Computer simulation with a bolus of 0.00191 mg/kg, $y'(t)$ = 80%. (a) Twitch response. (b) Infusion rate. Patient parameters were $k_{12} = 6.50 * 10^{-3}\ s^{-1}$, $\alpha = 5.33 * 10^{-3}\ s^{-1}$, $\beta = 7.50 * 10^{-4}\ s^{-1}$, Td = 60s. Steady state infusion was 0.44 (μg/kg)/min.

The noise, $y(n)$, was modeled by superimposing a zero mean random noise sequence with a non-zero mean random noise sequence. The amplitude of the non-zero mean noise was chosen to be greater than that of the zero mean noise (8); its mean was selected to obtain the desired SNR. The combined noise, $y(n)$, was then added to the patient twitch response. To clarify the procedure for generating the simulated noise, the following simple example is given. If the zero mean PRBS has a standard deviation of 0.6 and the mean of the non-zero mean PRBS is 28.46% with a standard deviation of 0.8, then the combined noise will have a mean of 28.46% and the standard deviation of unity. Hence, for a paralysis level of 90%, the signal-to-noise ratio will be 10 dB.

The response of a patient with a nominal steady state gain (Table 1) and a delay of 24 s is illustrated in Fig. 10. External noise of SNR = 18 dB (Eq. 14) was added at the output. The introduction of noise created oscillations around the desired response; however, the magnitude of these oscillations were small (±5%). The overshoot during the transient period was only 4.68% and the mean steady state offset was 1.16%.

Figure 11 shows that the simulation results of a patient with an increased delay of 114 s was simulated in the presence of SNR = 18 dB. The peak overshoot was 4.07% following bolus delivery. The mean offset and in-

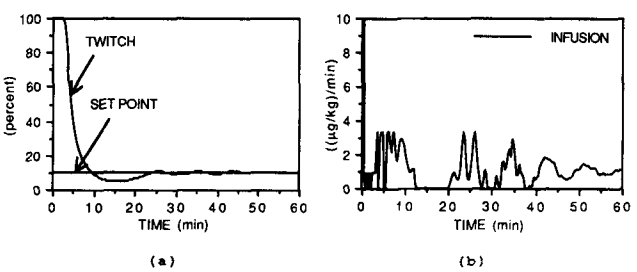

FIGURE 9. Computer simulation with a bolus of 0.028 mg/kg and $y'(t)$ = 90%. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 2.833 * 10^{-3}\ s^{-1}$, $\alpha = 5.37 * 10^{-3}\ s^{-1}$, $\beta = 6.12 * 10^{-4}\ s^{-1}$, Td = 114s. Steady state infusion was 1.02 (μg/kg)/min.

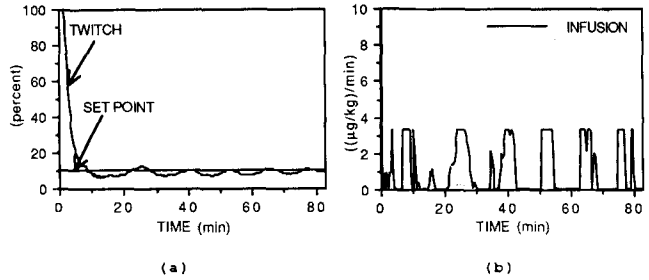

FIGURE 10. Computer simulation with a bolus of 0.028 mg/kg, $y'(t)$ = 90% and SNR = 18 dB. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 2.67 * 10^{-3}\ s^{-1}$, $\alpha = 4.33 * 10^{-3}\ s^{-1}$, $\beta = 7.16 * 10^{-4}\ s^{-1}$, Td = 24s. Steady state infusion was 0.88 (μg/kg)/min.

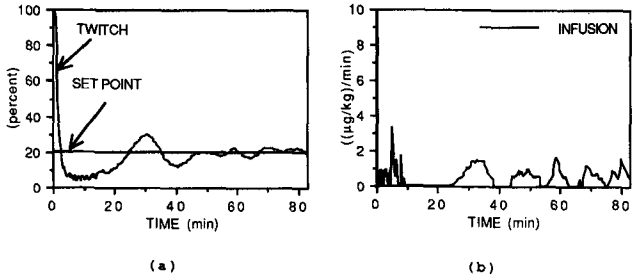

FIGURE 12. Computer simulation with a bolus of 0.028 mg/kg, $y'(t)$ = 80% and SNR = 18 dB. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 6.33 * 10^{-3}\ s^{-1}$, $\alpha = 7.50 * 10^{-3}\ s^{-1}$, $\beta = 6.17 * 10^{-4}\ s^{-1}$, Td = 18s. Steady state infusion was 0.90 (μg/kg)/min.

fusion at steady state were 1.68% and 0.93 (μg/kg)/min, respectively.

The results shown in Fig. 12 illustrate the effect of external noise SNR = 18 dB at a relaxation level of 80%. The presence of noise deteriorated the controller performance; the overshoot in the undesired direction (lower paralysis) was 10.23%. The mean offset and infusion at steady state were 0.09% and 0.57 (μg/kg)/min, respectively.

As in the case shown in Fig. 7, selecting a smaller bolus reduced the maximum overshoot seen in Fig. 12 to 5.92%. Figure 13 illustrates the response of the patient with a reduced bolus of 0.011 mg/kg.

The simulation results of Fig. 14 represent a high sensitivity patient with a delay of 30 s and a large noise level of SNR = 13 dB.

The high noise level and sensitivity (almost four times more sensitive than a nominal patient) created low amplitude and bounded oscillations in the response. However, the response deviation was always in the acceptable direction and stability of control maintained at all times. The mean offset at steady state was 4.33%.

To investigate the effect of changes in the parameters of the nonlinear block, the pharmacodynamic constant, σ, was increased by 50% from its nominal value. The increased value of σ slowed the transient response of a patient with nominal parameters (Fig. 15). A marginal increase in the infusion rate was present, and the steady state offset was virtually absent. Fig. 15 shows the response curves for this simulation and can be compared with those of Fig. 4.

DISCUSSION

The results of this study show that following the initiation of paralysis, the controller achieved the desired paralysis level and maintained a stable response with minimal steady state errors. The initiation of the paralysis is accomplished by using a single bolus together with a sequence of pseudo-random binary sequence (PRBS) of fixed amplitude and short duration injections, referred to as the initial induction/estimation period. This strategy achieves a rapid induction of paralysis which is frequently necessary for a quick start of the surgery.

The selection of duration of the initial induction/estimation period demands a compromise between two requirements. On one hand, it is desirable to minimize this period and allow the closed-loop control to start as quickly as possible. On the other, a short induction/estimation period may result in an inadequately identified patient response and, consequently, a poor closed-loop perfor-

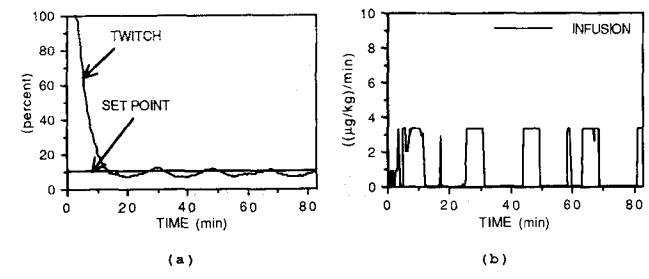

FIGURE 11. Computer simulation with a bolus of 0.028 mg/kg, $y'(t)$ = 90% and SNR = 18 dB. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 1.833 * 10^{-3}\ s^{-1}$, $\alpha = 4.33 * 10^{-3}\ s^{-1}$, $\beta = 4.67 * 10^{-4}\ s^{-1}$, Td = 114s. Steady state infusion was 0.93 (μg/kg)/min.

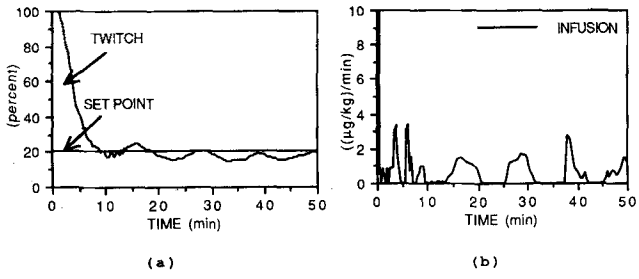

FIGURE 13. Computer simulation with a bolus of 0.011 mg/kg, $y'(t)$ = 80% and SNR = 18 dB. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 6.33 * 10^{-3}\ s^{-1}$, $\alpha = 7.50 * 10^{-3}\ s^{-1}$, $\beta = 6.17 * 10^{-4}\ s^{-1}$, Td = 18s. Steady state infusion was 0.57 (μg/kg)/min.

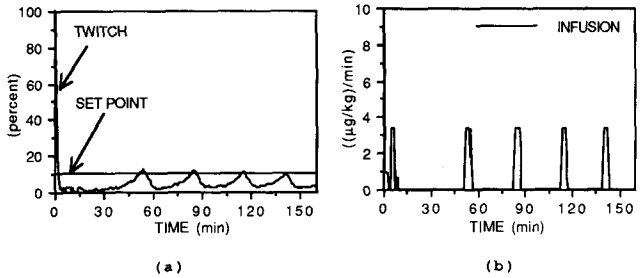

FIGURE 14. Computer simulation with a bolus of 0.028 mg/kg, $y'(t)$ = 90% and SNR = 13 dB. (a) Twitch response. (b) Infusion rate. Patient parameters were: $k_{12} = 5.83 * 10^{-3}\ s^{-1}$, $\alpha = 2.83 * 10^{-3}\ s^{-1}$, $\beta = 6.67 * 10^{-4}\ s^{-1}$, Td = 30s. Steady state infusion was 0.26 (μg/kg)/min.

mance. To strike a balance, we searched for an induction/estimation period that was satisfactory for a broad range of patient responses. The 200 s interval proved to be satisfactory for the cases considered. The need for estimation of the patient parameter during the initiation period has also been observed by Jaklitsch *et al.* (8). These investigators proposed a separate controller for this transient period. Using an *a priori* model of the patient response, they computed a "test" dose and adjusted it for injection into the patient. The resulting transient control had a variable induction/estimation period ranging from a mean value of 234 s (with 72 s standard deviation) to 696 s (with 252 s standard deviation) with a sample interval of 120 s. While the length of the initial induction/estimation period proposed in this paper is smaller (200 s) than that proposed in (8), the sample rate is six times faster; hence, more patient response information is obtained. The 200 s interval proved to be satisfactory for all cases studied.

The proposed initial induction/estimation scheme eliminates the need for the *a priori* model of the patient and makes the duration of the induction/estimation period constant and predictable. Further, it reduces the complexity of the control structure, since the same controller is used for both the transient and the steady state control. Since it is currently not possible to determine *a priori* a patient's response to the drug infusion, the patient response during the induction/estimation period is not predictable. Hence, selecting the initial bolus based on the anesthesiologist determination as is currently the clinical practice in inducing paralysis may be more desirable. That is, the anesthesiologist initially commands the computer to deliver the bolus that he or she considers appropriate for the initial manual induction as he or she would have selected normally when the automated system was not used. This will produce the desired rapid induction, while the patient response data is also collected for the controller to achieve and maintain the desired level from then on. In fact, we envision that in actual clinical practice the main application of an automated induced paralysis control system is in maintaining the paralysis level during the surgery rather than the initial transient phase; speed of induction is more critical during the initial induction phase.

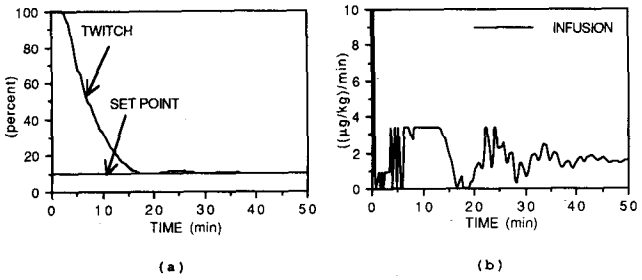

FIGURE 15. Computer simulation with a bolus of 0.028 mg/kg and $y'(t)$ = 90%. (a) Twitch response. (b) Infusion rate. Patient parameters were $k_{12} = 2.833 * 10^{-3}\ s^{-1}$, $\alpha = 5.37 * 10^{-3}\ s^{-1}$, $\beta = 6.12 * 10^{-4}\ s^{-1}$, Td = 78s. Steady state infusion was 1.89 (μg/kg)/min.

Selection of bolus size for the initial induction/estimation period impacts the level of overshoot, defined as the amount that the paralysis level exceeds the desired level. Such overshoots, however, may not be of any concern, since they do not hinder intubation or start of the surgery. Response oscillations that cause the actual paralysis level to fall short of the desired level (*i.e.*, overshoots in the direction below the desired response), must be limited, as they may impact the surgery. With the present scheme, only one case (Fig. 12) produced a limited (10.23%) overshoot in that direction. This is comparable to the overall overshoot average of 11.5% reported by Jaklitsch *et al.* (8) for similar set point and signal-to-noise ratio.

After the initial induction/estimation period, the closed-loop control of paralysis starts. However, the controller continues to utilize the input (infusion) and output (paralysis level) information to update the estimates of the patient response characteristics and, at the same time, adapt to the changes in these parameters.

Based on the results, the controller adapted to a wide range of patient gains, as evidenced by results shown in Figs. 4 through 7. The results in Figs. 8 and 9 illustrate the efficacy of the controller in handling patients with small and large transport delays, respectively. The control strategy performed well in the presence of noise levels expected in a clinical environment (Figs. 10–14). The overshoot and the steady state offset, when handling high sensitivity patients, were more pronounced, as evidenced in Fig. 14. However, the overshoot was always in the clinically acceptable direction (90% paralysis and above) with a magnitude of less than 10%. Fig. 15 reveals that increasing the pharmacodynamic constant, σ, decreases the patient sensitivity, and as a result, delays the onset of paralysis due to mismatch between the actual patient response and the inverse block. However, the controller maintained stability and showed a robust performance.

The performance of the control strategy was comparable with the other strategies that have been applied for closed-loop control of paralysis. Previously reported controllers (3–7, 9–11) have had overshoots ranging from 0.9 (3) to 10.1% (11) following bolus administration, whereas in our case, the average overshoot was 5.25% in most of our simulation tests. With respect to the steady state offset, the controller had a mean steady state error of 0.78%. The smallest offset, reported by Bradlow *et al.* (10) was 0.2%; the largest by DeVries *et al.* (4) was 15%. The mean drug infusion rate for vecuronium to maintain 90% relaxation reported in the literature is 1.1 (μg/kg)/min by DeVries *et al.* (4) and 1.5 (μg/kg)/min by Jaklitsch *et al.* (7). Our drug requirements were moderate and averaged 1.22 (μg/kg)/min at the 90% steady state level (its range was 0.26–2.96 (μg/kg)/min).

Our controller performance was comparable with that of a model-based self-adjusting two-phase (MST) controller developed by Jaklitsch *et al.* (8) to handle patients with the same set of parameters (Figs. 6–8 and 10–14). For these cases, the mean steady state offset was around 1%, except for that shown in Fig. 14 (4.33%). Further, the mean steady state infusion to maintain relaxation at 90% and 80% were 0.7875 (μg/kg)/min and 0.505 (μg/kg)/min., respectively. These comparison with 0.9425 (μg/kg)/min and 0.48 (μg/kg)/min required by the MST controller. The average overshoot following bolus administration was 7.42% (range, 0.33 to 11.08%), compared with the mean values of 3.4% to 11.5% reported by Jaklitsch *et al.* (8). None of the previous studies reported any investigation of time delay variations or changes in the pharmacodynamic parameter, σ.

Overall, the results of our simulation studies demonstrate that the controller is robust and adapts to a wide range of expected patient sensitivities, response delays and changes in the pharmacodynamic constant. The controller also tolerates external disturbances without becoming unstable.

CONCLUSIONS

In general, the results of this study reveal the adaptability, robustness and stability of the proposed control strategy. The controller incorporates the ability to withstand variations in time delay without needing an explicit estimate of the delay, and provides a virtually offset-free performance in the face of changing load disturbances. Additionally, it can tolerate a large change in the parameters of both the linear and nonlinear components of the patient response model. Since this control strategy does not rely on the patient response model, it can potentially be applied to control of other physiological parameters where significant pure time delay variations are present.

In summary, the controller appears to be suited for automatic control of paralysis. Undoubtedly, it must be tested and validated *in vivo* prior to its clinical application: this indeed is the next step in our investigation.

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NOMENCLATURE

$A(z^{-1}),B_E(z^{-1}),C(z^{-1})$ = polynomials in the backward shift operator z^{-1}, defining process dynamics
z^{-1} = backward shift operator
$y(t)$ = process model output (patient twitch response)
$u(t)$ = process model input (control signal)
$\zeta(t)$ = stochastic disturbance term
Δ = differencing operator
r = degree of B_E polynomial
n = process order
k_{max} = maximum expected delay
k_{min} = minimum expected delay
k = delay time expressed as sample intervals
J = cost function
$E\{\}$ = expected value
$P(z^{-1})$ = polynomial defining the inverse of the desired closed loop response model
$y(t + k)$ = predicted value of $y(t)$ at k sample intervals
$R(z^{-1}),Q'(z^{-1})$ = user defined weighting polynomials in z^{-1} used in the cost function
$w(t)$ = set point
$Q(z^{-1})$ = polynomial in z^{-1} which is a user defined weighting polynomial on the control signal
$F'(z^{-1}),G(z^{-1})$ = polynomials used in the control law
$H(z^{-1})$ = user defined set point modifying polynomial to ensure zero steady state offset
λ' = user defined weighting coefficient
$i(t)$ = drug infusion rate
Td = patient response time delay
k_{12} = patient sensitivity from the patient response model
α = pharmacokinetic parameter
β = pharmacokinetic parameter
$c(t)$ = amount of drug per body weight
ED50 = mean dose to suppress the twitch response by 50 percent
σ = pharmacodynamic constant
ED95 = mean dose to suppress the twitch response by 95 percent
γ = pharmacodynamic constant
$y'(t)$ = patient paralysis level
$Ey(t)$ = expected twitch response
$Ey(n)$ = expected noise level
$F(s)$ = filter transfer function