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Impact of control on agitation–sedation dynamics

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Abstract

Agitation in the critically ill damages patient health and increases length of stay and healthcare costs. The control model presented captures the essential dynamics of the agitation–sedation system, and is statistically validated using recorded infusion data for 37 patients. Derivative focused control is seen to provide an essentially bolus-driven management approach, which is shown to be an effective means of managing agitation, given consistent agitation measurement. Improved agitation management using feedback of patient agitation reduces the modelled mean and peak agitation levels 68.4% and 52.9% on average, respectively, illustrating the effectiveness of simple control in this non-linear system.

Keywords: Biomedical control; Physiological models; PD controllers; Non-linear dynamics; Patient agitation; Sedation administration

1. Introduction

Effective delivery of sedation in the intensive care unit (ICU) is fundamental to providing comfort and relief to the critically ill, yet common sedation practice often results in over-sedation. Insufficient sedation exacerbates anxiety and agitation, and increases the risk of self-extubation. Over-sedation is damaging to patient health and increases the length of stay and healthcare costs (Kress, Pohlman, O'Connor, & Hall, 2000). Several recent studies have highlighted the benefits of drug delivery protocols based upon sedation assessment scales (Brattebo et al., 2002; Smyrnios et al., 2002; Szokol & Vender, 2001; Barr & Donner, 1995). In particular, very simple protocols minimising over-sedation have reduced the length of stay by up to 35%, as well as reducing total drug requirements (Kress et al., 2000; Brattebo et al., 2002).

Agitation–sedation cycling describes the oscillation between states of agitation and over-sedation observed in sedated, critically ill patients. The underlying non-linear dynamics of the agitation–sedation cycle are not well understood, and many complex interactions contribute to observed patient behaviour. Traditional therapeutic treatment methods rely heavily upon the knowledge, experience and intuition of the medical staff, the 'art of medicine', introducing variability and inconsistency. Computerised sedative infusion protocols that enable consistency of care and minimise fluctuations in treatment can improve patient healthcare, simplify administration, and minimise drug consumption and staff duties, while reducing costs. In spite of these significant potential advantages, current computer-assisted infusion control systems in the ICU are still in their infancy (Shaw, Dove, Greenfield, Rudge, & Chase, 2003b; Smith & Reves, 1995).

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The primary limitations to the development of automated sedative infusion protocols include the lack of a consistently quantifiable objective agitation scale and a limited understanding of the underlying system dynamics. Protocols based upon subjective measures of agitation introduce variability between assessors and lack consistency over time. Recently developed quantitative agitation measures will enable better management of patient agitation (Lam, Starfinger, Chase, Shaw, & Agogue, 2003; Lam, 2003; Starfinger, Lam, Chase, Shaw, & Agogue, 2003; Starfinger, 2003; Shaw et al., 2003a; Chase, Starfinger, Lam, Agogue, & Shaw, 2004b). This research creates models that capture the essential dynamics required to enable agitation-based feedback control systems for automated sedation administration using these quantified agitation measurements.

While a multitude of pharmacokinetic models have been developed, no models of their interaction with patient agitation dynamics exist. This paper presents a simple quantitative model to capture the essential agitation–sedation dynamics in the critical care patient. Model validation is achieved through statistical comparison of simulated infusion profiles with recorded infusion data for 37 ICU patients. Finally, the potential of this model to develop improved agitation management methods using patient agitation feedback control is demonstrated through simulations using derivative focused control.

2. Model

The mathematical model builds upon a well-known two-compartment pharmacokinetic model (Wood & Wood, 1990), adding patient agitation as a third state variable:

$$\frac{dC_c}{dt} = -K_1 C_c + \frac{U}{V_d}, \tag{1}$$

$$\frac{dC_p}{dt} = -K_2 C_p + K_3 C_c, \tag{2}$$

$$\frac{dA}{dt} = w_1 S - w_2 \int_0^t C_p(\tau) e^{-K_4(t-\tau)}\, d\tau, \tag{3}$$

where C_c is the drug concentration in the central compartment in mg/L, C_p is the drug concentration in the peripheral compartment in mg/L, U is the intravenous infusion rate in mg/min, V_d is the volume of distribution in L, A is an agitation index, S is the stimulus invoking agitation, K_{1-4} are parameters related to drug elimination and transport with units min^{-1}, and w_1 and w_2 are relative weighting coefficients of the stimulus and drug effect, respectively. Time is represented by t, and τ is the variable of integration in the convolution integral of Eq. (3).

This model is intended to be the simplest necessary to capture the essential dynamics of the agitation–sedation system. Therefore, K_{1-4} are assumed constant over time, although they can be treated as slow moving functions of time to model more complicated, very long-term phenomena such as tachyphylaxis or fatty tissue distribution (Hughes, Glass, & Jacobs, 1992).

Eq. (1) represents the kinetics of drug infusion and distribution, while Eq. (2) represents the transport of sedative from the infusion site to the effect site, which for sedative and analgesic drugs is the central nervous system. An acceptable approximation for this effect site concentration is considered by some authors to be the drug concentration in the cerebrospinal fluid (Meineke et al., 2002; Cousins & Mather, 1984).

The non-linear Eq. (3) was developed based upon physiological observations of critical care patient behaviour. Specifically, it states that the rate of change of agitation depends upon the magnitude of the stimulus relative to the cumulative effect of the sedative agent. Stimulus in this context refers to the combined effect of inherent pain, distress, or loss of inhibition caused by the diseased/injured state of the patient, and the therapeutic and diagnostic procedures performed by medical staff.

Under constant stimulus levels, observed agitation typically falls or remains unchanged upon increased infusion of sedative agents. Similarly, patients become more agitated by increased stimulus, due to procedures or condition, if infusion rates are not increased. Patient agitation is primarily reduced by the cumulative effect of current and prior sedation administration, as modelled by the convolution term in Eq. (3).

Eqs. (1)–(3) represent a model of the interaction between sedative agents and patient agitation–sedation dynamics to evaluate the effectiveness of sedative infusion protocols and automated infusion systems. More complex pharmacokinetics and pharmacodynamics can be added to identify and develop the level of complexity required to capture the essential system dynamics.

3. Model verification

Sedative drug infusion data was recorded using an electronic drug infusion device (Greenfield, Dove, & Shaw, 2001; Shaw et al., 2003b; Rudge, Chase, Shaw, & Wake, 2003; Shaw et al., 2003a) for all ICU patients admitted to the Christchurch Hospital ICU during a nine month period and requiring more than 24 h of sedation. The device infuses a fixed sedative-analgesic solution, based on critical care nursing assessment of patient agitation using a modified version of the Riker Sedation Agitation Scale (Riker, Picard, & Fraser, 1999; Shaw et al., 2003b; Lam et al., 2003). These infusions are