Toward An Advisory System For Cesarean Section Spinal Anesthesia [1]

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Abstract

Phenylephrine is a drug used at BC Women's Hospital, Vancouver BC to treat maternal hypotension induced by spinal anesthesia. Its dosage is mainly determined in a heuristic manner by the anesthetist's experience. Since an overdose of phenylephrine can result in bradycardia and hypertension, anesthesiologists are in need of a systematic method to calculate the correct dose. This problem is formulated in control engineering framework. An advisory system offers the optimal dosage of phenylephrine that ensures an appropriate blood pressure response, while rejecting disturbances created by the spinal anesthesia at the same time.

The solution involves identifying the patient model. The advisory system is designed such that the model predictive controller recommends the adequate phenylephrine infusion, which has to be approved by the anesthesiologist in charge. The safety aspects related to the human subjects are dealt by constraints implemented within the advisory system. Upcoming clinical trials of the advisory system should confirm the value of this project in the near future.

Keywords: Spinal Anesthesia, Phenylephrine, Cesarean Section, Hypotension, Advisory System.

1 Introduction

Before performing Cesarean Section surgery, patients are anesthetized by the administration of the spinal anesthesia solution (SAS). While the SAS promotes a pain-free environment during the surgery, it induces hypotension at a probability rate up to 85% [7]. Hypotension is a result of sympathetic blockade which causes peripheral vasodilatation. Each anesthesiologist has a preference for a number of different solutions and combination of solutions that have been used for spinal anesthesia; however the solution is standardized in this study.

From a clinical point of view, hypotension is undesirable, especially during a Cesarean Section. Lower blood pressure (BP) means reduced blood flow to the placenta and less oxygen delivery to the fetus which could suffer from significant hypoxia. Ephedrine or phenylephrine (PE) is used to treat maternal hypotension. Although PE is regarded as the better choice in some studies [4], the current pharmacological profile of PE is limited to a suggested dose from 20 to 100 μg and its approximate half life. We proposed that anesthesiologists need a more definitive guideline on the PE dosage to prevent overdose and its side effects (hypertension and bradycardia).

This motivates the development of an advisory drug delivery system, which is capable of determining the appropriate PE dosage and administer the corresponding dose through an electronic infusion device. The development of the advisory system can be summarized in four phases: data collection (Section 2), data conditioning (Section 3), modeling (Section 4)and advisory system design (Section 5).

2 Data Acquisition

Following informed consent, data was collected from 70 randomly selected patients undergoing Cesarean Section spinal anesthesia at the BC Women's Hospital. Patients with significant medical disease, pregnancy complications or extreme weight and height were excluded. The dataset of 70 cases is essentially the same set of data that was published in 2003 [3], supplemented by a few more cases that were collected following the same protocol. Fifty nine cases out of the 70 (84%) were hypotensive. All the patients were preloaded with normal saline, 30 ml/kg (pre-pregnant weight) within 30 minutes prior to the administration of spinal anesthesia. Administration of SAS was standardized for all patients for dose, position and intervertebral space. The standardized SAS consisted of hyperbaric bupivacaine 0.75%, preservative free morphine 200μg and fentanyl 15μg. Total volume of the solution was 2.0ml.

Each episode of hypotension (defined as systolic BP $<$ 100mmHg or 80% of the patient's baseline BP recorded prior to the surgery, which ever was lowest) was treated with PE during the time period between the injection of SAS and the birth of infant. The dosage of PE depended on a random grouping of the patients. There are 4 groups, 20-40-60-80 μg. However, if it was observed that the dose was not strong enough to treat hypotension, a doubled dose of up to 100μg was injected. The study follows a strict protocol approved by the ethical review board of the hospital.

Noninvasive BP measurements are recorded every 10 seconds from a Datex AS5 monitor (Datex, Finland), connected via a serial port to a Dell laptop running Datex S5 Collect software . The electrocardiogram (ECG) and photo-plethysmogram (PPG) are recorded by the same software but with a sampling rate of 300Hz. The administration of drug or special events were marked with the snapshot function of the monitor; hence are fully synchronized with the data. Despite the 10-second sampling rate, the minimum repeat inflation time for the cuff was roughly 35 seconds. Data points between cuff inflations come from an interpolation performed by the monitor. Such data is observed to be less reliable and poorly conditioned, as indicated in Fig. 1. Our previous work demonstrates that more frequent BP measurement is essential for modeling. For this, we developed a novel method based on pulse transit time (PTT).

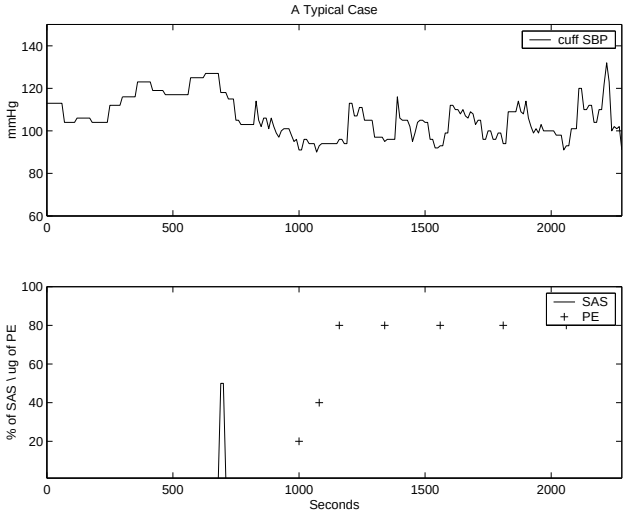

Figure 1: A typical case with a dose of SAS and several doses of PE injected.

3 Inferring BP from PTT

In order to improve the quality of the data and reduce model uncertainty, a continuous BP algorithm has been developed using the PTT and the principle of energy conservation. The algorithm was not developed at the time of data collection hence throughout all cases the administration of PE was based on BP measured by the cuff only. The PTT is detected from the ECG and the PPG. As we had not intended to use the PTT at the time of data collection, only 22 cases out of the 59 hypotensive cases had the ECG and PPG adequately recorded. Therefore the modeling in this paper is based on 22 cases.

The PTT-to-BP algorithm relies on a simplified model of the vessel from the patient's heart to finger, assuming cross sectional area remains constant and its length is known. A previous study suggests a noninvasive BP measurement can be obtained by employing PTT because blood pressure is correlated to the speed of the pulse wave, which is inversely proportional to PTT [2]. A modified version of the Bramwell and Hill equation relating PTT and BP [1] based on energy conservation was employed.

The PTT calculated in this study is the time a pulse takes to travel from the heart to the finger, where the PPG is measured. Fig. 2 displays a case comparing the continuous BP measurement with the BP cuff measurement. While they both contain noise, the continuous BP contains less discontinuities (sharp edges) and flat plateaus.

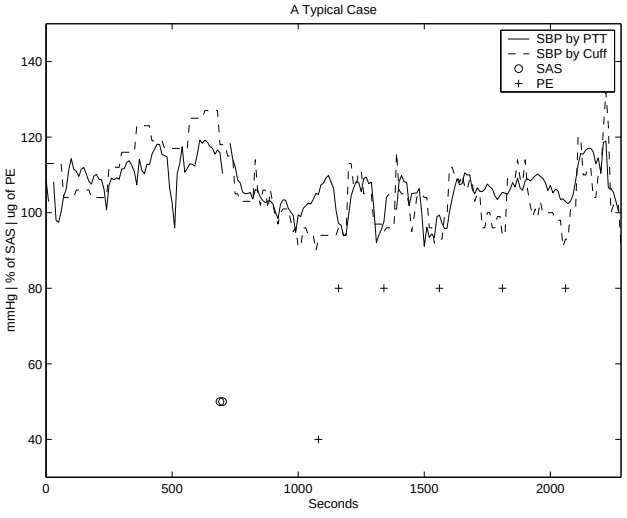

Figure 2: A comparison (same case as in Fig. 1) between the measurement from the BP cuff and the one from PTT.

Illustrated in Fig. 3, the PTT is estimated as the time

between the R peak of the ECG and its corresponding maximum slope of the PPG. Since both waveforms are collected at a high sampling rate of 300Hz, the PTT has a fine resolution of 1/300 seconds. The detection of R peak in ECG and maximum slope in PPG are programmed by decomposing the ECG and the differentiated PPG by stationary wavelet transform (SWT) [9], which is able to extract special features and denoise the signal. The SWT components at different frequency levels are then analyzed by a rule based system.

Note that the R peak marks the electrical excitation of the contraction of the heart not the exact contraction time. Therefore, the lag time between the electrical signal and the actual mechanical motion, known as the pre-ejection period (PEP), is also included in the PTT calculation. Previous research has suggested that PEP is correlated with the administration of vasoconstrictive drug such as PE [6]. Therefore, it is contemplated that the rise in blood pressure caused by PE is reflected through PEP.

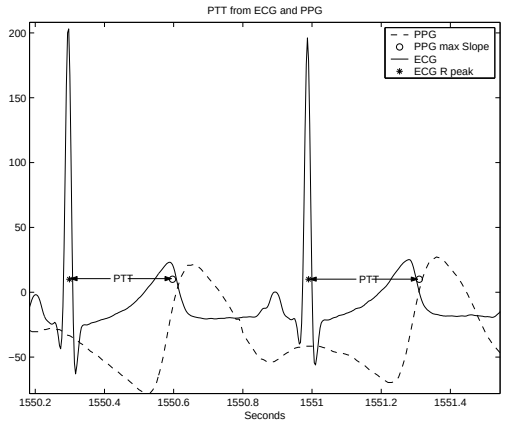

Figure 3: The definition of PTT.

4 System Identification

The main challenge for identification of this system is the lack of excitations. The measured disturbance, SAS, is only injected once in each case. Since PE is used to reject the SAS disturbance, the patient is always in non-steady state when PE administration begins. Therefore no direct method can be used to separate the response of SAS and PE. As a result, the response of SAS was estimated from the data of a non-hypotensive case, where no PE was administrated but the drop in BP was significant. The main assumption is that each patient reacts the same way except for a different gain and time delay. The time delay for each case is estimated by expert knowledge.

To reduce patient uncertainty, all data are treated as the fraction above or below the patient's baseline. Fig. 2 displays a typical case where one dose of SAS and several of PE are administered. Without subtracting the full response of SAS from the data, the response of PE will be under-estimated if raw data is used for system identification. The first and most challenging step is to estimate the SAS response. The full SAS response can only be observed in non-hypotensive cases, where the gain is usually small and hence the low signal to noise ratio. However there is one case presented in Fig. 4 where the patient's BP baseline is high enough that even with a BP drop of roughly 30mmHg, she did not require any PE treatment. Using the data from that particular case and the Matlab System Identification Toolbox, a discrete first order ARX model, augmented with an integrator and time delay is estimated for the SAS. The assumption made is that the SAS model for all patients shares the same pole but uses a different gain and time delay. With this assumption, the time delay is estimated manually and the gain is estimated by a least-squares fit between the impulse response of the SAS model and the data, as illustrated in Fig. 5.

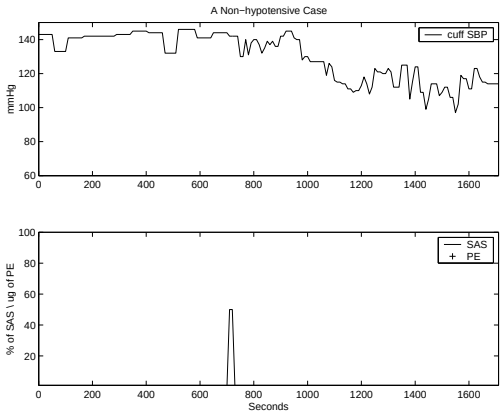

Figure 4: A non-hypotensive case with no administration of PE, even though there is significant decrease in BP.

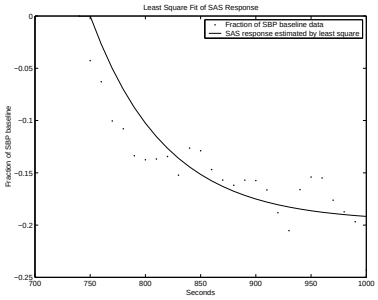

Figure 5: The least square fit of the SAS response.

The PE response can then be extracted from data by

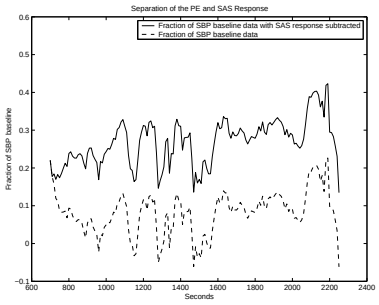

Figure 6: Subtraction of the SAS response from the raw data (same case as in Fig. 1).

subtracting the individual SAS response. Fig. 6 displays the difference between raw data and data being used for PE system identification. The simplest model to capture essential properties of the PE response has two poles and a gain. All 22 cases are processed with the 22 ARX PE model as results. As shown in the pole map in Fig. 7, the conjugated poles are localized around $0.97 \pm i0.15$ and most of them are stable. This justifies the assumption that all patients share the same pole in the SAS model estimation. Although it may also indicate too fast a sampling rate.

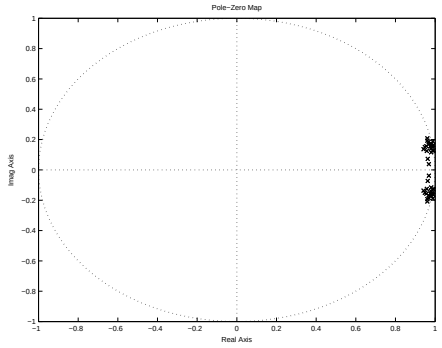

Figure 7: Distribution of the two poles of PE.

Although the inter-patient variability is small at the poles, for gain it is not. The DC gain varies between -0.0049 and 1.962, see Fig. 8. The uncertainty in gain is significant even though it can be assumed that the gain for PE can never be negative. No clear correlation is observed between the PE gain and the physical properties of the patient, such as actual weight, pre-pregnant weight, height, weight/height ratio and age. It is concluded that a gain adaptation is necessary in the advisory system.

Figure 9 summarizes the modeling of PE and SAS. A nominal model of PE can be derived from the average poles and the gain:

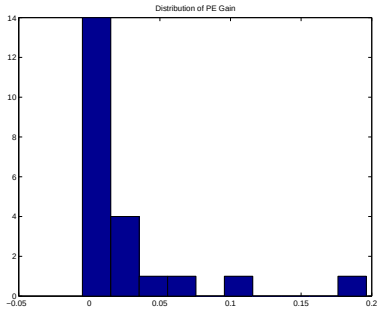

Figure 8: Distribution of the DC gain of PE.

$$\frac{KPE \cdot z}{(z-p)(z-\widetilde{p})} \tag{1}$$

$$\begin{array}{rcl} \overline{KPE} & = & 2.795e^{-4}, \\ 0 & \leq KPE \leq & 1.6917e^{-3} \end{array} \tag{2}$$

$$\begin{array}{rcl} \overline{p} & = & 0.9726 + i0.1478, \\ 0.9414 & \leq Re(p) \leq & 0.9923, \\ 0.0381 & \leq Im(p) \leq & 0.2083 \end{array} \tag{3}$$

The SAS ARX model is:

$$\frac{KSAS \cdot z}{z^k(z-1)(z-pSAS)} \tag{4}$$

Each patient has an individual gain and time delay,

$$pSAS = 0.863 \tag{5}$$

$$\begin{array}{rcl} \overline{KSAS} & = & -2.4195e^{-4}, \\ -7.2951e^{-4} & \leq KSAS \leq & -2.7158e^{-5} \end{array} \tag{6}$$

$$\begin{array}{rcl} \overline{k} & = & 20.56, \\ 4 & \leq k \leq & 56 \end{array} \tag{7}$$

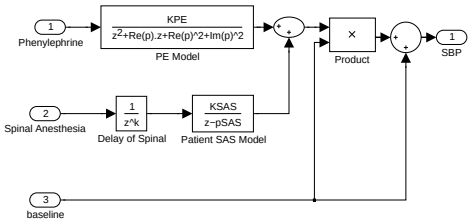

Figure 9: Patient Model in Matlab Simulink representation.

The model is validated by comparing an open loop simulation with the actual data of a case, shown in Fig. 10. The model mismatch lies primarily in the SAS model. From a control perspective, the disturbance model is less important and the mismatch can be compensated by a Kalman estimator [8]. The PE model fits the data well, given that its gain is customized for each particular case. It further confirms that a gain adaptation in the advisory system is the key for performing BP control.

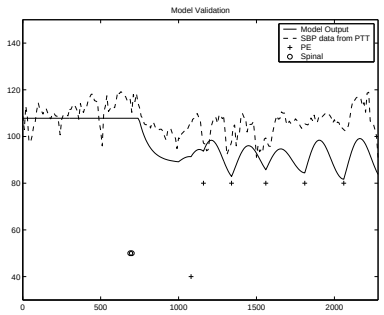

Figure 10: Model validation for the case in Fig. 1.

5 Proposed Advisory System

The goal of the advisory system is to promote accuracy and consistency of the drug delivery, without modifying the surgical procedures or introducing new monitor equipment. The setup time has to be relatively short and the user interface has to be user friendly. With this concept in mind, the group decided to employ the plugin feature of the Datex S5 Collect data collection software (Datex, Finland), which allows real-time data access from the existing Datex monitors. As a result, with an electronic infusion device and a laptop, the advisory system can be implemented without additional costs. The predictive controller of the system is designed such that the inter-patient variability, constraints, controllability and the frequency response of the system are carefully considered.

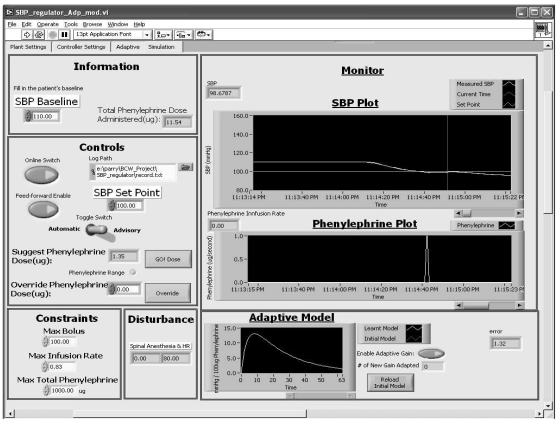

Figure 11: A screen shot of the advisory system.

The advisory system was coded in Labview 6.1 as this is the programming language supported by the S5 Collect software. The user interface (Fig. 11) presents the amount of PE administered and the current systolic BP trend, using both the cuff and PTT measurement. For initialization, the system requires the systolic BP baseline of the patient, the target set-point of BP (which can be changed any time) and the input constraints (e.g. maximum infusion rate, bolus and total PE administered). A state space model predictive controller pubilished by Macisjowski[5] is implemented, following the confirmation that the system is controllable. The internal states are estimated by a Kalman filter and the control input is computed by minimizing the receding horizon cost function:

$$J_k = \sum_{j=1}^{Hp} \hat{x}_{k+j}^T Q \hat{x}_{k+j} + \sum_{i=1}^{Hu} u_{k+i}^T R u_{k+i} \qquad (8)$$

The $\hat{x}$ is the estimated states and u is the input. The controller can be tuned by the square cost function matrices Q and R as well as the predicting horizon Hp. Better performance can be achieved by increasing the weight in the Q matrix, at a cost of robustness. Increasing the weight in R can detune the controller, and increasing Hp can enhance stability and robustness while sacrificing computational complexity. The tuning strategy is discussed extensively in Maciejowski's book. The tuning is based on the frequency response (Fig. 12) of the nominal model. With the open loop cut off frequency at about $3e^{-2}$ rad/s, the closed loop settling time is designed to be about one minute. The Kalman filter can also be tuned by its disturbance and noise covariance matrices.

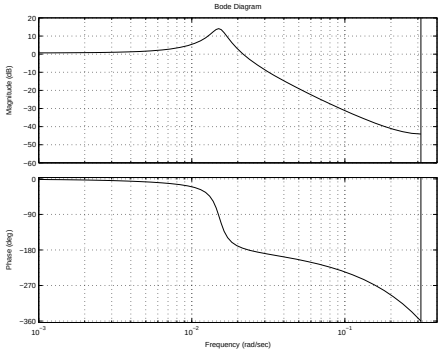

Figure 12: Frequency response of the nominal PE model.

Since this is an advisory system, the control input has to be filtered by the anesthesiologist's clinical knowledge. However, the anesthesiologist cannot examine each dose at every sampling interval. Therefore, at all times the system displays an accumulated dose of a number of current control inputs, as a guideline. The anesthesiologist can either follow the suggested dosage, or administer a selected dosage through the advisory system. To avoid an impulse response, the system delivers that accumulated PE bolus by spreading the dose over a certain period of time. All PE administration is logged for the anesthesiologist's record. To help justifying the decision, the system predicts the future systolic BP output for two scenarios: 1) when

the suggested dose is injected; 2) when nothing is injected. The system updates its prediction whenever a new BP measurement arrives. The gain of the internal PE model is recursively updated.

There are two safety issues for this system: the overdose of PE and hypotension. Overdosing of PE is avoided by the input constraints and anesthesiologist's judgment. When the system predicts hypotension, a continuous flashing of the drug injection button on the user interface serves as a silent alarm to the anesthesiologist.

6 Conclusions

An advisory system for hypotension treatment in Cesarean Section was developed. The modeling of the system is the most difficult phase as excitations are highly limited. The strict clinical protocol prohibits any artificial input for purpose of research.

In addition, the poor quality of the noninvasive BP measurement using the noninvasive BP cuff introduces a signaling problem. This was solved gracefully by the data conditioning using PTT.

The continuous BP reading makes the locations of the pole of the patient model obvious, concluding that the gain is the main source of inter-patient variability.

The advisory system is expected to be an elegant solution for hypotension treatment. As the advisory system has knowledge of the drug's transient response, it is able to at all times calculate the necessary PE dosage for different circumstances. Furthermore, the gain adaptation can ensure that the dose is tailored to each individual patient. When the drug delivery is handled by reliable electronics, consistency and gradual change in dosage are enforced. The advisory system should reduce the workload of the anesthesiologist by introducing a guideline for PE administration.

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