Models and Their Uncertainty for BP Maintenance during Spinal Anesthesia Using Phenylephrine

Parry FUNG*, Mihai HUZMEZAN*, Roger DESJARDINS**, Ali KAMANI**

***Abstract*—Phenylephrine is used to treat maternal hypotension induced by spinal anesthesia. Studies show that phenylephrine is able to correct hypotension but an overdose could result in bradycardia and hypertension. The response of this drug has not been fully investigated and hence it creates significant workload for the anesthetists. They are required to adequately and continuously regulate the dose of phenylephrine.**

A model of blood pressure and associated uncertainty, during spinal anesthesia, is derived for use with an automatic drug delivery system. The model of input-output relationship is arranged into a 10-state multivariable model, using clinical data and the subspace identification and the prediction error method. The relationship among the output (patient's blood pressure), the primary input (phenylephrine) and measured disturbances (spinal anesthesia and heart rate) is considered. Uncertainties in the model parameters, reflecting a diverse patient population based on a 40 cases observational study, are arranged in a linear fractional structure.

***Index Terms*—Blood Pressure Control, Phenylephrine**

I. INTRODUCTION

Studies show that hypotension occurs in up to 85% of the patients undergoing spinal anaesthesia [1]. Recent studies have suggested that use of ephedrine to correct maternal hypotension, during spinal anesthesia for Cesarean section, is associated with higher incidence of fetal acidosis, when compared to phenylephrine [2]. There is an increasing support in the medical community for phenylephrine to treat hypotension with better fetal outcome. However, there are no studies available in the literature to demonstrate the lowest effective dose of phenylephrine to correct maternal hypotension without producing side effects (e.g. hypertension and reflex bradycardia) [3].

At present, the pregnant patient's response to phenylephrine is not fully described and determined. Therefore to enable better care there is a need to investigate how the patient reacts to phenylephrine. This can further lead to the development of an automatic/advisory drug delivery system that physicians can rely upon in controlling maternal hypotension. The computerized system will first calculate the dosage and duration of the phenylephrine effect, and then administer the drug according to the patient model through a electronic infusion pump. The precision achieved will allow the anesthetists to closely manipulate maternal hypotension.

Clinical data were collected from patients subjected to spinal anesthesia for Cesarean section. If hypotension orrcurred, patients were randomized to receive one of the following phenylephrine doses: 20, 40, 60 or 80 micrograms, to treat hypotension following spinal anesthesia. If the patient's Systolic Blood Pressure (SBP) was observed to be under 100mmHg or less than 80% of her baseline for roughly 70 seconds, phenylephrine was administered according to the approved clinical protocol. If the blood pressure did not rise above 100mmHg after the initial dose, double the dose, up to 100 micrograms was administered.

The scope of this paper was confined to data analysis and modelling. The clinical aspect of this project was addressed in another paper[4]. Data was collected from 40 cases, from which a nominal patient model was derived. Data analysis was conducted with the help of the Matlab System Identification Toolbox which implements subspace and structured ARMAX algorithms. In Section II of this paper, the data acquisition and signal conditioning for identification was disclosed, followed by the identification procedure presented in Section III. In Section IV the models and their uncertainty were shown. In Section V the results of model validation were displayed followed by conclusions in Section VI.

II. DATA ACQUISITION AND CONDITIONING

The patient's SBP fluctuates subject to heart rate [5] while the amount of phenylephrine and drugs associated with spinal anesthesia are injected. The patient was modelled as a discrete linear time invariant MISO model. The disturbance part of the model was characterized by influence of spinal anesthesia and heart rate upon SBP. The manipulated variable to process variable input-output model looks at the influence of phenylephrine upon SBP.

The digitization of these models was performed at a 10-second sampling rate. SBP and heart rate data were collected from the existing Datex/AS5 monitor at the BC Women's Hospital in Vancouver BC, Canada by connecting the monitor through the serial port to a Dell data acquisition laptop running the S5 Collect software provided by Datex Ohmeda. The injection of drugs (spinal anesthesia and phenylephrine) was marked manually by the built-in snapshot function of the monitor. SBP was measured using a non-invasive reading with the cuff inflated as frequently as possible. The time to inflate the SBP cuff was about 35 seconds hence data between the effective data samples were generated by the monitor via extrapolation. The data was often corrupted and hence such inaccurate or missing data are occasionally observed. The data was processed and interpolated based on clinical knowledge.

The data was divided into 3 partitions shown in Fig. 1 and filtered by a first order low pass filters selected according to measured signal-to-noise ratios. The filter cutoff

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frequency of 1Hz for partition 1 was the highest since the response in heart rate was acknowledged to be almost instantaneous. The cutoff frequency for partition 2 at 0.7Hz was the lowest because this was the noisiest data partition. Noise was caused by patient movement. The cutoff frequency of partition 3 was also selected to be 1Hz in order to capture the fast dynamics of phenylephrine. To achieve the aforementioned decisions the frequency response of the filtered data was examined to determine the best frequency range for each low pass filter. The SBP data was first-order-detrended for removal of its linear trend.

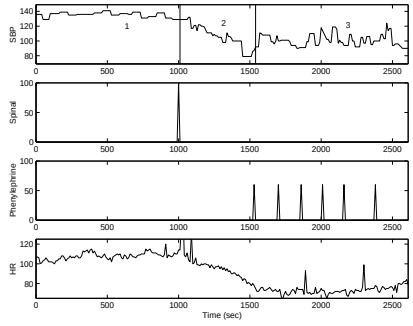


Fig. 1. The three Partitions of a Typical Case: 1-Normal, 2-After Administration of Spinal Anesthesia, 3-After Administration of Phenylephrine.

III. System Identification

Individual additive effects of phenylephrine, spinal anesthesia and heart rate response on the final output suggested that the hypothesis of a linear model was fairly realistic. Therefore individual responses were extracted by direct simple addition and subtraction. The first attempt was made to identify the system as three independent SISO systems. In partition 1, heart rate was the only input and SBP is the output, therefore the response of heart rate was identified by feeding the data into Matlab as if it was a SISO system. Then in partition 2, the same procedure was performed to discover the response of spinal anesthesia except that the effect of heart rate was subtracted from the SBP output. Lastly, spinal anesthesia and heart rate response were subtracted from SBP in partition 3 to identify the phenylephrine response.

The model however extracted did not agree very well with the clinical data. The main flaw was that partition 2 is so short that the complete spinal anesthesia response cannot be observed. This resulted in over-estimation of the spinal anesthesia gain. Since this exaggerated spinal anesthesia gain was subtracted from partition 3, the phenylephrine response became inaccurate.

It was concluded that the entire dataset in Fig.1 had to be identified simultaneously, as a MISO system. The subspace method was chosen for this system identification due to the nature of the problem. Since the subspace method, unlike other methods such as ARX and ARMAX, is non-iterative, a reasonable solution could be found even when input excitation was limited to only one excitation from the spinal anesthesia and a few from the phenylephrine administration[6]. Even though this method was superior to identifying three partitions independently, a number of cases were still discovered to have negative gain for phenylephrine and positive gain for spinal anesthesia. After investigation, it was concluded that the oscillations coupled with the complex components in the identified poles and zeros were the cause of the incorrect modelling.

In order to further refine the model, structured ARMAX was employed to parameterize the gains and the zeros but not the poles. The locations of the poles were first computed at the average location among cases solely with real poles after the results of the subspace method. Then only the gain and location of zeros were estimated once again using ARMAX. Gains and zeros were identified for each cases and their mean were derived for the nominal model. The structured ARMAX approach identified much fewer cases with complex zeros. The refinement technique successfully eliminated the number of outliers to three and ten in the phenylephrine channel and spinal anesthesia channel, respectively. Outliers were discarded in the mean model estimation because of their complex components. Due to the fact that the iterative search of structured ARMAX involves a certain degree of randomness, results were slightly different every time but variations were small compared to uncertainties analyzed and discussed in the next section.

The final input-output relationship was modelled as a discrete transfer function matrix, as in Fig. 2. Two zeros and three poles were observed to be sufficient to approximate dynamics of phenylephrine and heart rate dynamics. For spinal anesthesia, an external integrator and a delay of 18 samples were augmented to the 2-zero-3-pole system. The integrator compensates the first order trend of the data and the delay accounts for the 180 seconds dead time in the spinal anesthesia response when the sampling rate was set at 10 seconds. The 180 seconds dead time was an estimate drawn from observation and clinical knowledge.

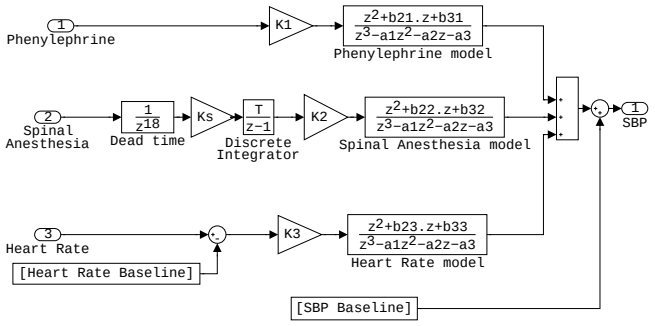


Fig. 2. The Patient Model.

Each input has its own zeros and gains but shares the same poles. The gain Ks exists only in the spinal anesthesia input corresponding to the integrator gain. The heart rate input and SBP output are measured above patient's baseline. If the delay in spinal anesthesia input is considered external to the system model, the three discrete transfer functions can be converted into a 10-state MISO system.

IV. Model and Model Uncertainty

The nominal discrete transfer function model can be rearranged into a canonical state space model for uncertainty analysis (Fig. 3). The relationship of parameters between the state space and transfer function model is demonstrated in the equations for the A, B and C matrices. For simplicity, the integrator augmented in the spinal anesthesia channel is not included in the uncertainty analysis. Nonetheless the variance for the integrator gain, Ks, is 1000 times less than the mean; therefore neglecting this uncertainty for Ks is acceptable.

$$A = \begin{bmatrix} a1 & 1 & 0 \\ a2 & 0 & 1 \\ a3 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 1.2456 & 1 & 0 \\ 0.0919 & 0 & 1 \\ -0.3523 & 0 & 0 \end{bmatrix} \quad (1)$$

$$B = \begin{bmatrix} K_1 & K_2 & K_3 \\ K_1 b_{21} & K_2 b_{22} & K_3 b_{23} \\ K_1 b_{31} & K_2 b_{32} & K_3 b_{33} \end{bmatrix} = \begin{bmatrix} 0.3893 & -0.6213 & 0.0091 \\ 0.2842 & -1.0247 & 0.0062 \\ -0.0436 & 0.0901 & -0.0016 \end{bmatrix} \quad (2)$$

$$C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \quad (3)$$

$$Ks = 0.0153 \quad (4)$$

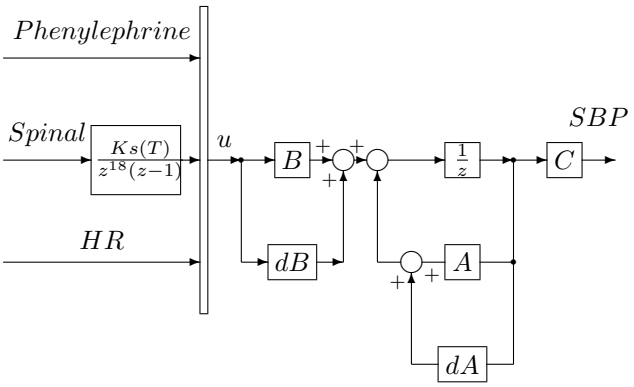


Fig. 3. Linear Fractional Uncertainty Model with the Delay and Integrator Separated.

Illustrated in Fig. 3, dA contains uncertainty on the poles of the system and dB contains uncertainty on zeros and gains of the system. Since all three inputs share the same poles, only the first column of dA is nonzero. The distribution histograms for the twelve variables inside the A and B matrices are plotted in Fig. 4 and 5. It is worthwhile to mention that the A matrix was not refined by the structured ARMAX and it is an average of results from the subspace identification. Therefore, variables within the B matrix seem to be more normally distributed and more accurate than the ones in the A matrix. Experiment was carried out to refine the A matrix with structured ARMAX while variables in the B matrix were fixed, but the poor results in model validation suggested that refining the A matrix degrades the model.

According to common clinical practice, physicians often rely on the 95% confidence interval. If parameters are assumed to be normally distributed, the 95% confidence interval is between the mean plus or minus twice

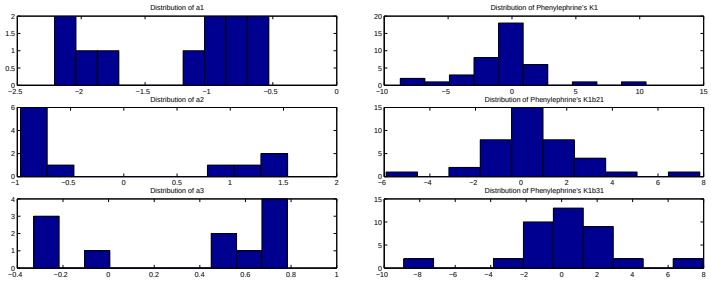


Fig. 4. Distribution of First Column of A and First Column of B.

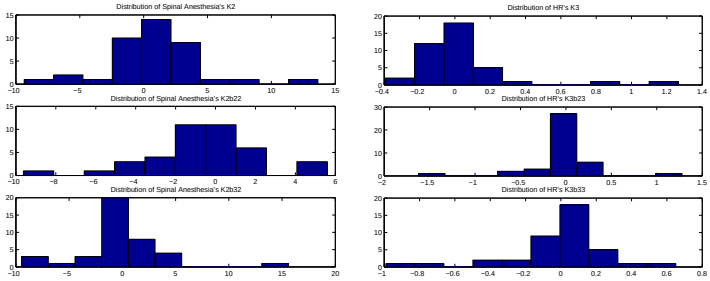


Fig. 5. Distribution of Second Column of B and Third Column of B

the standard deviation. dA and dB are determined from their corresponding variances and they are related to the linear fractional uncertainty model in Fig. 3.

$$dA = \pm \begin{bmatrix} da_1 & 0 & 0 \\ da_2 & 0 & 0 \\ da_3 & 0 & 0 \end{bmatrix} = \pm \begin{bmatrix} 1.288 & 0 & 0 \\ 2.173 & 0 & 0 \\ 0.935 & 0 & 0 \end{bmatrix} \quad (5)$$

$$dB = \pm \begin{bmatrix} db_{11} & db_{12} & db_{13} \\ db_{21} & db_{22} & db_{23} \\ db_{31} & db_{32} & db_{33} \end{bmatrix} = \pm \begin{bmatrix} 6.485 & 4.129 & 5.923 \\ 7.299 & 5.510 & 8.270 \\ 0.554 & 0.766 & 0.555 \end{bmatrix} \quad (6)$$

Physicians often investigate the 95% confidence level of the maximum correction in SBP by phenylephrine, which is the peak gain of an impulse response. Table I shows the mean, standard deviation and 95% confidence range (normal distribution assumed) of the SBP correction by using different dose of phenylephrine.

Dose:	$20ug$	$40ug$	$60ug$	$80ug$
Mean	4.25	21.43	20.73	24.09
Std Dev	4.20	13.23	11.90	14.81
Range low	-4.15	-5.03	-3.07	-5.53
Range up	12.7	47.89	44.5	53.71

TABLE I: Mean, Std Deviation and 95% Ranges of SBP Correction(units in mmHg)

V. Model Validation

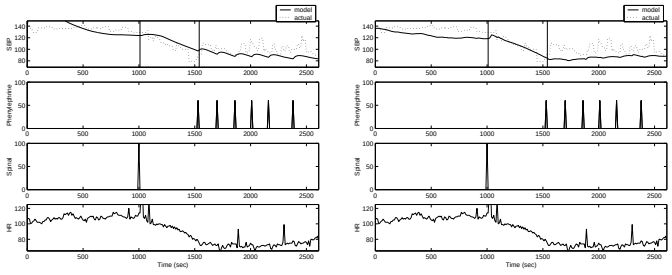
Simulations were run to validate the patient model. All forty cases were validated. Most clinical data matches the model, as in the left figure of Fig. 6. The solid line is the simulated SBP and the dash line is the clinical data.

In isolated cases, the model failed to reflect:

1. a constant offset;
2. an integrating factor in the phenylephrine;
3. estimate of the spinal anesthesia gain (K_2).

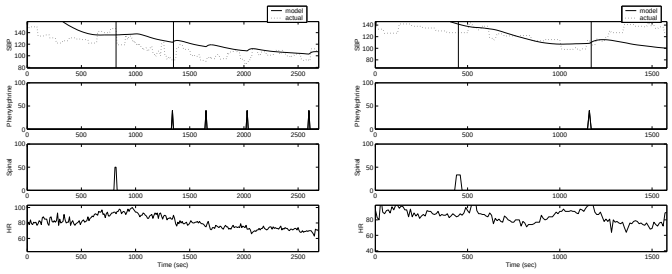
Some of these characteristics mentioned can be observed from model validations results presented in Fig. 7 and 8. This is the direction of future work.

An individual model was derived for the case displayed in the left figure of Fig. 6 and its model validation was shown on the right. The nominal model was comparable to the individual in terms of capturing features of the response. Although the fit was higher for the individual model, 44.71% compared to 53.78%, main features such as the peak gain of phenylephrine and the drop in SBP due to the spinal anesthesia were simulated gracefully in both models. The low fit percentage for the case-specific model was believed to be the contribution of errors in data due to the quality of the measurement.



Fit=44.71%. Fit=53.78%.

Fig. 6. Nominal Model Validation and Individual Model Validation



Fit=39.41%. Fit=2.273%.

Fig. 7. Offset Mismatch Model Validation and Integrating Action Mismatch in phenylephrine Model Validation

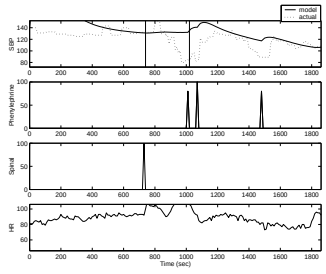


Fig. 8. Underestimate of K2 Model Validation, fit=-0.02563%.

VI. Conclusion

A nominal patient model of SBP response to phenylephrine when common disturbances such as, variations of the HR and administration of spinal anesthesia, are occurring was derived. Although the order of model was believed to be capable of representing the complexity of a patient, validations showed that the model matches clinical data by roughly 30-40% in most cases. Judging by the fact that the model derived from one particular case did not replicate the data better than the nominal model, it was concluded that data collected for this study contained significant noise. By averaging the model, errors and noises, the nominal model performs well when used to predict the relationship between HR, spinal anesthesia, phenylephrine and SBP. Improvements in the correctness of the model were expected if noise can be reduced by taking continuous SBP.

The response of phenylephrine had been analyzed formally and systematically. The results clearly benefited physicians and patients in terms of preventing the overuse of phenylephrine, which is recognized to cause hypertension with reflex bradycardia. Furthermore, the model will become starting point for an automatic/advisory drug delivery system, aimed at stabilizing SBP of patients by means of phenylephrine controlled administration.

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