IJCSI International Journal of Computer Science Issues, Vol. 7, Issue 5, September 2010
ISSN (Online): 1694-0814
www.IJCSI.org

Evaluation of Computer-aided Drug Delivery System with a Human Operator

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Abstract

To assist the judgment of human operators, a computer-aided drug delivery system with adaptive predictive control is suggested. The assisting system can predict future responses of a patient to drug infusions, calculate optimal inputs, and present those values on a monitor. Regardless of sudden disturbance such as bleeding, human operators of the computer-aided system were able to control arterial blood pressure. To improve the computer-aided system, future studies will be required to consider the method for emergency warning or correspondence to multiple drug infusions.

Keywords: *Adaptive Predictive Control, Computer-aided System, Neural Networks, Arterial Blood Pressure, System Evaluation*

1. Introduction

Shortage of anesthesiologists is a serious social problem especially in local areas of Japan [1]. Under such a condition, a constant effect of medical treatment is desired, regardless of degree of advancement in system operators. As a possible solution, the effects of automated therapy systems without human operations have been expected [2]. However, to make these practicable, further improvement is needed. To widely advance automated systems, many issues such as their approval as medical instruments and responsibility for medical accidents must be resolved. Accordingly, a computer-aided system to assist in decision-making by an operator rather than by automated systems may become effective.

As an effective method for automatic control of biological information, the application of intelligent control systems has been studied. For instance, automated drug infusion systems with neural networks (NN) and fuzzy theory for blood pressure control have been developed and evaluated [3]-[7]. In particular, the significant differences exist between the abilities of residents and those of accomplished physicians. For example, it is difficult for beginners to appropriately grasp the characteristics of drug responses reflecting the history of past inputs and outputs or to correspond to an acute emergency such as bleeding. Therefore, the effectiveness of intelligent control systems may be applied to the quick decision making of inexperienced beginners.

A computer-aided drug delivery system using adaptive predictive control with NN was suggested in this study; effectiveness was evaluated in human operators. 1) In blood pressure control using a single drug, the learning effect of the assistant system on beginners without pharmacological knowledge was investigated. 2) The accuracy of correspondence to an unknown and acute emergency was assessed using the assistant system.

2. Control System

2.1 Adaptive Predictive Control with NN

Figure 1A shows a block diagram of an adaptive predictive control with NN (APC-NN) and a human operator. Predicted future outputs to drug inputs were displayed (Fig. 1B), by using the APC-NN to emulate arterial blood pressure (BP) response. A system operator can determine the appropriate inputs, referencing the predicted values (green circles in Fig. 1B) calculated by a computer as well as personal experience in arterial pressure control.

The APC-NN is a control system where the NN recursively learns the characteristics of mean BP responses and determines predicted future outputs. In the closed loop controls, the NN initially learned about BP response every 10 s ("*Learning Loop*"). The learned BP_{NN} response was used for the prediction of future outputs by the NN

("*Prediction Loop*"). A human operator determined final infusion rates, referencing the predicted outputs.

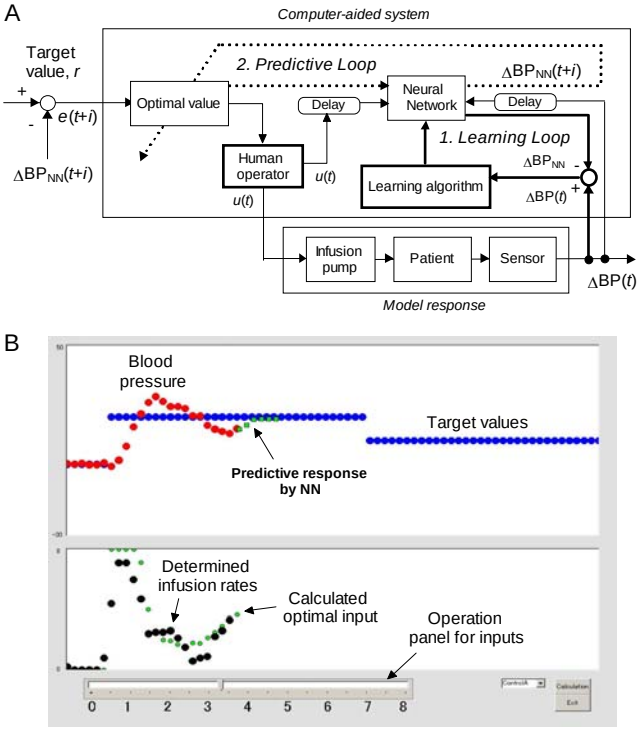

Fig. 1 Drug delivery system with APC-NN. A: Block diagram of a controller. B: Example of a control display.

2.2 NN Output

To assess the BP response, a multilayer feed-forward NN with two hidden layers was used. The NN structure was a nonlinear autoregressive moving average model [8] as follows: $\Delta BP_{NN}(t)$ is the BP change estimated by the NN.

$$\Delta BP_{NN}(t) = f(\Delta BP(t\text{-}1), u(t\text{-}1), \ldots, u(t\text{-}6)) \quad (1)$$

The input layer in the NN is composed of past input and output. $\Delta BP(t\text{-}1)$ is the actual BP change induced by norepinephrine (NE) infusion before one sampling interval. The duration of past infusion rates determined by a human operator (u) was set to 1 min. The input values were sent through the first and second hidden layers and the output layer. When the NN calculated output, the hyperbolic tangent function was applied 14 times (seven times in each hidden layer).

2.3 Backpropagation Algorithm

To identify the BP response and determine the initial weights, NN was trained using the output of the model response to random inputs. The backpropagation algorithm was used in the online mode. All connection weights were adjusted to decrease the error function by the backpropagation learning rule based on the gradient descent method.

The BP_{NN} predicted by NN was compared with the observed BP; its error was calculated by the following function.

$$E = \frac{1}{2} \cdot \varepsilon^2 = \frac{1}{2} \cdot [\Delta BP - \Delta BP_{NN}]^2 \quad (2)$$

ε shows the difference between actual BP as a supervised signal and BP_{NN} predicted by the NN before update of the connection weights. The error is back propagated through the network. The connection weight is updated by the gradient descent of E as a function of the weights.

$$w^* = w + Kn \cdot \Delta w \quad (3)$$

where

$$\Delta w = \frac{\partial E}{\partial w} = -\varepsilon \cdot \frac{\partial BP_{NN}}{\partial w}$$

w and w^* are the weights of each connection before and after update, respectively. Δw is the modified weight and Kn is the learning rate. The backpropagation algorithm was performed in the following order: output, second hidden, and first hidden layers. The total number of weights was 120.

2.4 Initial Weights in NN

To determine the initial weights, the NN learned the BP model response. The weights before learning were randomly assigned between -1 and 1. The infusion rate of NE (-4 to 6 μg/kg/min) was randomly assigned; learning calls were replicated 300,000 times. Normalization was performed by dividing all outputs by 50. The learning rate, Kn, was 0.01.

NN learning resulted in an absolute error of approximately 0.9 mmHg compared with the model response. The trained NN was used in the system evaluation with the learning rate set to $Kn = 0.1$ to quickly converge target values.

2.5 Cost Function

The APC-NN calculated the optimal infusion rate that minimized the cost function:

$$Q(t) = \sum_{i=1}^{N_p} [r(t+i) - \Delta BP_{NN}(t+i)]^2 \quad (4)$$

Np is a prediction horizon, $r(t+i)$ is a prescribed target value of BP control at time point $t+i$, and $BP_{NN}(t+i)$ is the

BP predicted by NN. Future output can be estimated by $BP_{NN}(t)$ derived from the backpropagation algorithm. Q contained the predicted output after Np steps to suppress sudden changes in infusion rate. Np was set to 5 in this study. The cost function was minimized by a downhill Simplex method for a quadratic function [7].

3. System Evaluation

3.1 Participants

Participants were fourteen healthy volunteers. They were divided into two groups: computer-aided group using APC-NN (assist group; n = 7, 27.4 ± 5.0 years) and non-assist group (n = 7, 26.6 ± 3.4 years). All participants had no experience with drug delivery or specific pharmacological knowledge. The condition of the participants was verified before the experiment. Informed consent was obtained from all participants after a complete description of the experiment.

3.2 Simulation Task

(A) Modeling of blood pressure response
To make a model for BP response to a drug infusion, the average step response changed from baseline during a 5-min NE infusion (3 μg/kg/min) in anesthetized rabbits (n = 3) was used (Fig. 2) [5]. NE is generally used for the increase in blood pressure. The BP response (10-Hz sampling rate) was averaged every 10 s. The step response of BP was approximated by the first-order delay system with a pure time delay:

$$\Delta \mathrm{BP}(t) = K \cdot \left[1 - \exp\left(-\frac{t-L}{T}\right)\right] \quad (t \geq L) \qquad (5)$$

K is a proportional gain [mmHg/(μg/kg/min)], T is a time constant (s), and L is a pure time delay (s). If $t < L$, then $\Delta\mathrm{BP}(t) = 0$. K = 20, T = 49, and L = 10 were derived from approximation of the averaged step response.

The BP response as a model was calculated by the convolution integral in the discrete-time domain:

$$\Delta \mathrm{BP}_{\mathrm{model}}(t) = \sum_{\tau=0}^{N_m} g(\tau) \cdot \Delta T \cdot u(t-\tau) \qquad (6)$$

where

$$g(t) = \frac{K}{T} \cdot \exp\left(-\frac{t-L}{T}\right)$$

u is the infusion rate (μg/kg/min) and g is the unit impulse response (mmHg) calculated from the derivative values of the step response of Eq. (5). ΔT is a sampling rate; Nm is the finite number of terms in the model for the unit impulse response. K, T, and L are the same as in Eq. (5). Parameters were set to ΔT = 10, Nm = 30, K = 20/3, T = 49, and L = 10. Randomized noises (±1 mmHg) were added to outputs.

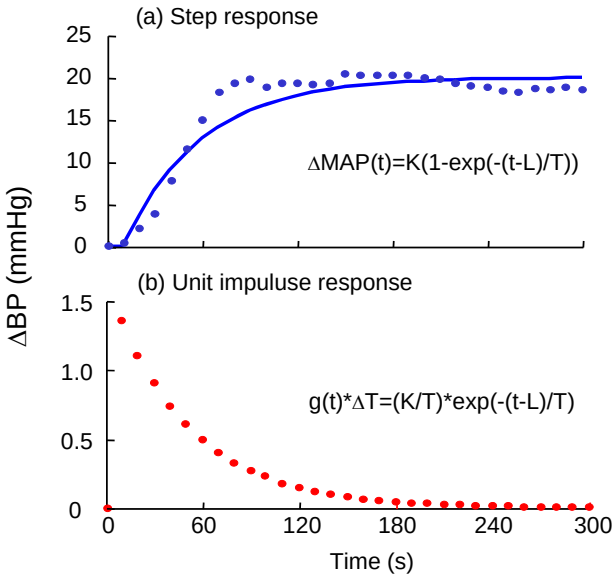

Fig. 2 The average step response changed from baseline during a 5-min NE infusion (a) and the unit impulse response (b).

(B) BP control
Using the model response and the suggested control system, the BP control tasks were performed. The objectives of the first and second tasks were to study the effect of initial learning of beginners on BP control. Target values were set to two steps: +20 mmHg (60-400 s) and +10 mmHg (410-720 s). Although the actual control time was 720 s, the single trial in this study was performed in an abridged form: 288 s (4 s × 72 times) meaning total thinking time for selection of drug infusion rates.

The purpose of the third task was to study the accuracy of correspondence to an unexpected emergency (e.g., the sudden change induced by bleeding). Target values were the same as those in the first and second tasks. A large disturbance of -30 mmHg was added to the BP response in the last half of the task (360-720 s).

3.3 Procedures

Immediately before the control tests, all participants were instructed to regulate BP responses to the target values, controlling drug infusion rates as correctly as possible.

Although the experimenter also instructed that the drug infusion rate correlated with the BP increase, other instructions for properties of the drug response were not given. The participants were required to carefully maintain BP values within the limited values (-30 to +50 mmHg). When the time reached 4 s, the time limit for considering drug infusion rate, the BP response after 10 s to the determined input value was automatically output. Input values could be easily controlled by operation of two cursor keys: "←" and "→" indicating decrease and increase of drug infusion rate. The participants experienced the moving speed of input values using the cursor keys before the experiment.

Each participant performed the following control tasks.

1) *First trial*. For all participants of both groups, the ability to regulate BP as beginners was evaluated, using the model response.

2) *Second trial*. In the non-assist group, the same task as the first was performed with no instructions; the learning effect of the experience of first trial was evaluated. In the assist group, computed optimal inputs and future BP responses were newly displayed. Before this trial, the experimenter instructed that the green circles on a screen meant predicted values and optimal inputs calculated by the computer. No other concrete instructions or practice was given.

3) *Third trial*. In both groups, the ability of correspondence to a sudden emergency (disturbance of -30 mmHg) was evaluated. For all participants, the existence of the large disturbance was never instructed. Predictive responses and optimal inputs were continuously displayed in the assist group.

3.4 Data Analysis

Selected drug infusion rates and BP responses were recorded for later analysis. The average absolute value between actual BP and target values and the maximum negative response were calculated for each participant. The ground averages among all participants were then calculated. All data were presented as mean ± SD. Unpaired *t* tests were applied for comparison of intergroup differences. Statistical significance was assigned to differences with $p < 0.05$.

4. Results

The results for automatic control based on APC-NN are shown in Fig. 3. An overshoot was observed in an initial adjustment of BP to the target value of +20 mmHg; however, BP outputs totally converged on the target values, determining optimal drug inputs based on the predicted response by the NN. In correspondence to a sudden emergency, the automatic control was able to perform the appropriate BP regulation while neatly avoiding undershoot because of the online-learning of the NN.

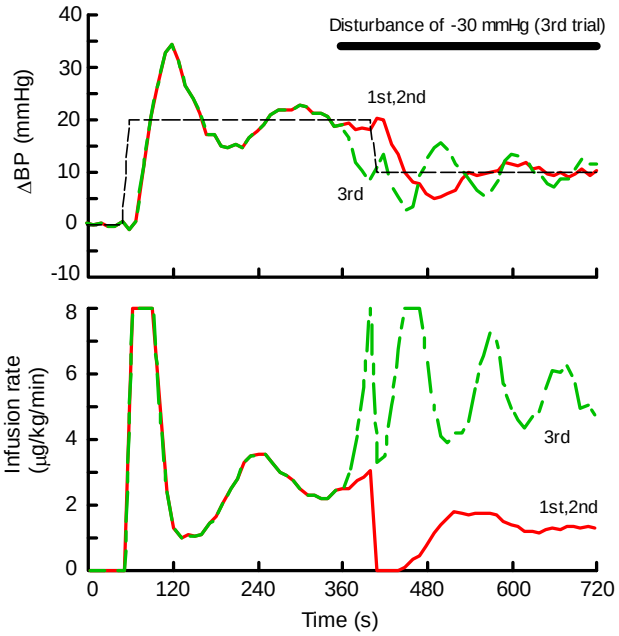

Fig. 3 BP control based on APC-NN. The third trial had an acute and unknown disturbance of -30 mmHg.

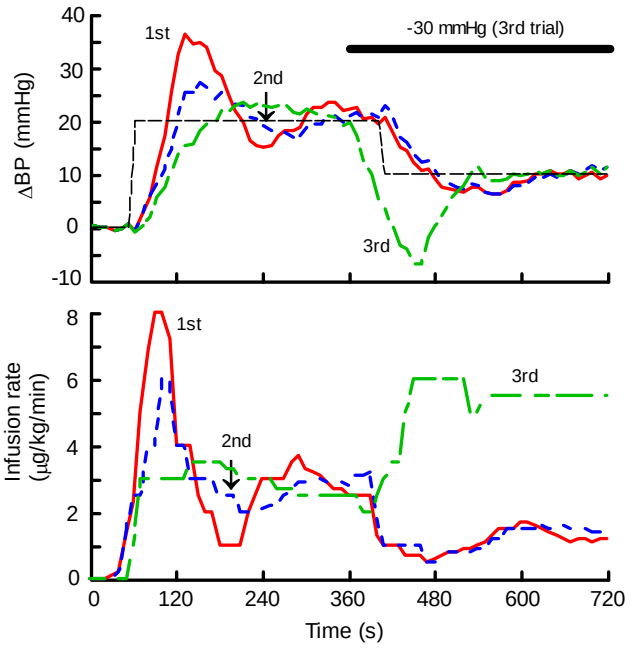

Fig. 4 Typical example of BP control in the non-assist group.

An example of BP control in the non-assist group is shown in Figure 4. Because of the same task as the first one, the second trial showed sufficient learning effects; however, in the third trial, correspondence to an unexpected and sudden disturbance was delayed, resulting in induction of a great undershoot.

An example of BP control in the assist group is shown in Figure 5. The second trial incorporated predicted outputs and optimal inputs as new information. A learning effect of the assistant system as well as experience from the first trial was indicated. In the assist group, the undershoot during the acute disturbance was inhibited, compared with the non-assist group.

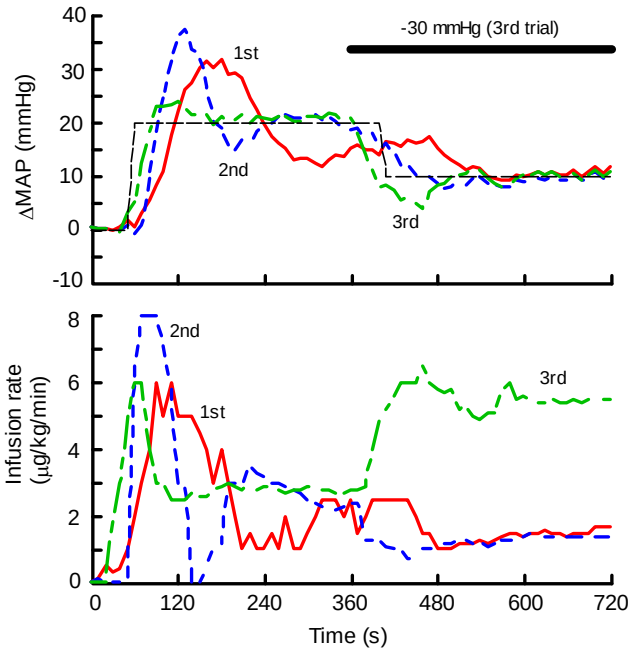

Fig. 5 Typical example of BP control in the computer-aided group.

Table 1 shows the average of absolute values between actual BP responses and targets in each control task. Especially, the third control trial in the assist group had the effectiveness of the assistant system: In the change of absolute values from the second trial to the third, the unpaired *t* test showed a significant difference between the non-assist and assist groups: 1.01 ± 0.77 versus -0.25 ± 0.64 mmHg; $p < 0.01$ in the one-tailed test. In addition, the maximum negative responses from the target value in both groups were assessed. In the change of maximum negative response between the second and third trials, the unpaired *t* test showed a significant difference: -9.11 ± 2.63 versus -5.50 ± 4.13 mmHg in the non-assist and assist groups; $p < 0.05$ in the one-tailed test.

Table 1: Average of the absolute value between actual BP responses and targets in each subject (mmHg).

Subjects No.	***Non-assist group***			***Assist group***		
	1st	*2nd*	*3rd*	*1st*	*2nd*	*3rd*
1	3.53	2.99	4.93	3.93	3.65	2.98
2	3.88	2.34	4.02	4.47	2.39	3.38
3	3.06	1.39	2.18	4.62	3.03	1.97
4	4.79	4.09	3.71	2.15	2.69	2.60
5	3.94	3.18	4.33	2.98	2.75	2.43
6	2.32	2.45	3.10	2.06	3.30	2.83
7	2.16	2.42	3.68	5.38	4.34	4.24
Average (SD)	3.38 (0.94)	2.70 (0.84)	3.71 (0.88)	3.66 (1.29)	3.17 (0.67)	2.92 (0.73)

5. Discussion

The computer-aided drug delivery system in this study made it possible for beginners to work on blood pressure control. In particular, the effect of the assist system on unexpected or acute emergency is expected. During a long constant state, humans regulating drug infusion rates may take a long time to recognize the emergency and respond with the correct treatment. Such delayed therapy may induce serious problems. In contrast, computers can quickly detect acute response changes and correctly regulate drug infusion rates, referencing the history of inputs and responses. Accordingly, an assistant system that can quickly communicate with the operator will be required under such emergencies. Furthermore, by predicting the conditions that humans make mistakes, presentation of some answers and a warning may become effective.

On the other hand, drug treatment based on a computer may induce a hunting phenomenon during acute and great changes in BP response; however, the system operator has a possibility of modifying the response changes well. For example, in the third trial of the assist group (Fig. 5), the operator was able to sufficiently converge to target values, avoiding the hunting phenomenon. Furthermore, compared with automated control (Fig. 3), system operators inhibited the initial overshoot. Accordingly, effective fusion in higher cognitive ability in humans as well as the merits of a computer will produce a better assistant system.

Because of the repeated tasks (first and second trials), the non-assist group gained sufficient learning about BP control, based on their experience in the first trial. Regardless of the unfamiliar assist system and easy

instructions immediately before the second trial, the assist group also had effective results. Accordingly, it is expected that the suggested system can be used as an assistant tool for beginners to easily make decisions about drug therapy.

6. Conclusion

The effectiveness of a computer-aided drug delivery system based on APC-NN was assessed from the viewpoint of the cognitive and learning abilities of beginners. A positive effect of the computer-aided system was observed in the case of an acute disturbance. In future studies, the assistant system will need effective fusion of the ability of quick searching for optimal inputs in computers with careful and delicate control in humans.

Acknowledgment

This study was funded by a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (KAKENHI, 22700466).

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