REGULATION OF HEMODYNAMICS IN THE LEFT HEART FAILURE USING ADAPTIVE PREDICTIVE CONTROL BASED ON NEURAL NETWORKS

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Abstract: Hemodynamic variables are regulated by the infusion of several drugs in a clinical setting. To control the hemodynamics, multiple automated drug-delivery systems have been developed, and the robust controllers that can tolerate various responses to therapeutic agents have been desired. The purpose in the present study is to evaluate the control performance of a multiple adaptive predictive control based on neural networks ($MAPC_{NN}$) under the wide changes of patient's sensitivities to therapeutic agents, drug interactions and external disturbances. The NN components in the $MAPC_{NN}$ learned cardiac output and mean arterial pressure as the nonlinear model response made from hemodynamics of canine heart failure. The $MAPC_{NN}$ showed a robust control performance under the unknown conditions of sensitivities to drugs, drug interactions, and external disturbances.

Introduction

To regulate cardiac output (CO) and mean arterial pressure (MAP) simultaneously, the combined infusion of an inotoropic agent and a vasodilator has shown to benefit a patient with heart failure in a clinical setting [4]. The inotropic agent increases the force and velocity of contraction and results in directly augmenting CO. On the other hand, the vasodilator reduces the ventricular outflow resistance and results in the decrease of MAP [1]. Adaptive controllers have shown the feasibility of implementing a multivariable drug delivery system for the simultaneous control of CO and MAP using the combination of an inotropic agent and a vasodilator [6]. To perform a robust control, multiple model or adaptive predictive controllers have been developed, and they have adequately adjusted the hemodynamic parameters in the presence of the drug interaction [3], [7].

Because neural networks (NN) can express nonlinearities and interactions to system responses in the presence of the unstable response variability with exogenous perturbation, it is expected that the NN is simply designed and increase the robustness for the drug delivery system compared with the model- or rule-based controllers. An adaptive predictive control based on NN (APC_{NN}) was applied to the MAP control during acute hypotension, and resulted in the robust control against the large disturbance [2]. The application of the APC_{NN} to multivariable controls ($MAPC_{NN}$) might be effective in regulating CO and MAP using dobutamine (DBT) as an inotropic agent and sodium nitroprusside (SNP) as a vasodilator in heart failures. The purpose of this study, therefore, is to evaluate the performance of the $MAPC_{NN}$ to regulate CO and MAP using DBT and SNP with heart failures under the non-linear and non-stationary patient responses containing the wide changes

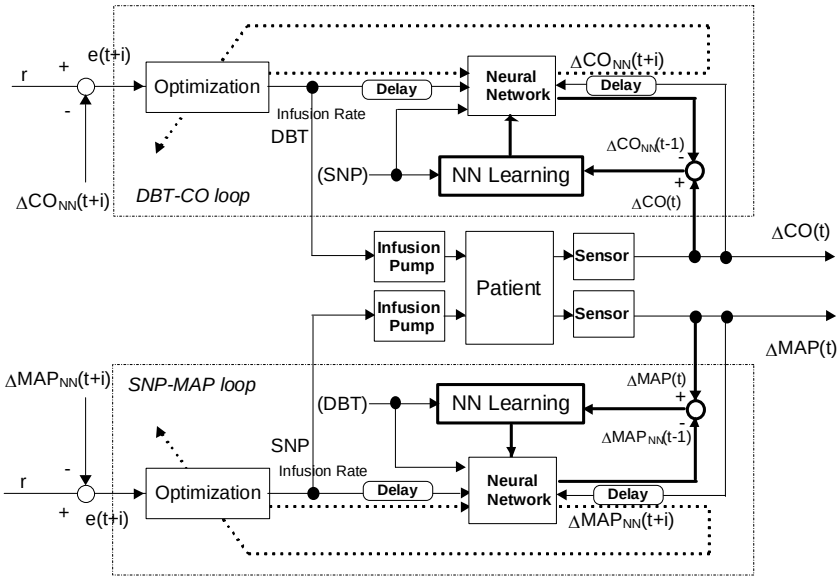

Figure 1. $MAPC_{NN}$ for the regulation of hemodynamics

ISSN: 1727-1983

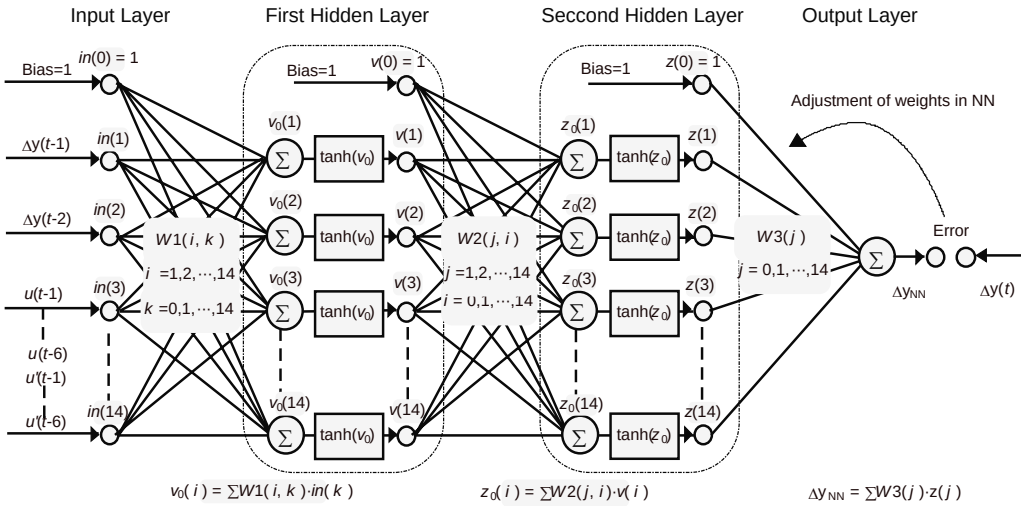

Figure 2. A multilayer feed-forward NN with two hidden layers

of the drug sensitivities, interactions, and acute disturbances.

Materials and Methods

Modeling. To make the response model to therapeutic agents, the animal study was performed. The animal study conformed to *the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health* (NIH Publication No. 85-23, revised 1996). The acute ischemic heart failure in anesthetized dogs (n = 5) was induced by microsphere embolization of the left main coronary artery. The dogs were ventilated artificially with oxygen-enriched room air. A double-lumen catheter was introduced into the right femoral vein for administration of pharmaceutical agents using a computer-controllable infusion pump (CFV-3200; Nihon Kohden, Tokyo, Japan). CO and MAP were recorded at 10-Hz sampling rate.

Models for the responses to therapeutic agents were made from the experimental data in canine left heart failure. The step responses of CO and MAP changed (ΔCO and ΔMAP) from baseline value immediately after the acute heart failure (baseline: 74.2, 78.9, and 62.6 ml·kg^{-1}·min^{-1} in CO; 94.4, 92.1, and 86.5 mmHg in MAP) were recorded for 10-min DBT infusion at 3, 6, and 9 μg·kg^{-1}·min^{-1}. The step responses of ΔCO and ΔMAP (baseline: 74.1, 59.3, and 55.9 ml·kg^{-1}·min^{-1} in CO; 104.3, 103.6, and 99.4 mmHg in MAP) were measured for 10-min SNP infusion at 1, 2, and 4 μg·kg^{-1}·min^{-1}. The step responses recorded at 10-Hz sampling rate were averaged every 30 s. The step response of ΔCO or ΔMAP during the infusion of DBT at 6 μg·kg^{-1}·min^{-1} or SNP at 2 μg·kg^{-1}·min^{-1} was approximated to the linear first-order delay system with lag time in the continuous-time domain:

$$\Delta Y'(t) = \begin{cases} K \cdot \left[1 - \exp\left(-\dfrac{t - L}{T}\right)\right] & (t \geq L) \\ 0 & (t < L) \end{cases} \qquad (1)$$

where $\Delta Y'(t)$ is the step response of $\Delta CO(t)$ or $\Delta MAP(t)$, K is a proportional gain, L is a lag time, and T is a time constant. The fitted parameters to the averaged step responses in DBT and SNP were acquired by least squares method.

The linear ΔCO or ΔMAP response as a model was calculated by the convolution integral in the discrete-time domain:

$$\Delta Y^*(t) = \sum_{\tau=0}^{N_m} g(\tau) \cdot \Delta T \cdot u(t - \tau) \qquad (2)$$

$u(t)$ is the infusion rate of DBT or SNP. $g(t)$ is the unit impulse response of ΔCO or ΔMAP, and it is calculated from the derivative values of the step response in (1). ΔT is sampling interval (s) and Nm is the finite number of terms in the model for the unit impulse response. ΔT and Nm were set to 30 s and 20 for simulation study. Table 1 shows the parameters of K, T, and L used for simulation study.

Table 1. Model parameters in linear- and nonlinear-fitting functions

	Linear			**Nonlinear**	
	K	***T***	***L***	P_1	P_2
DBT CO	15.8	164.3	30	105.3	0.028
DBT MAP	4.4	65.2	30	22.8	0.145
SNP CO	3.0	40.6	60	37.7	0.051
SNP MAP	-12.5	209.4	60	-26.2	-0.085

The proportional gain, K, the time constant, T, the lag time, L, the response range, p_1, and the coefficient of gain, p_2.

To express the nonlinearity of ΔCO or ΔMAP response, $\Delta Y^*(t)$ as the linear response was modified through the following sigmoidal function:

ISSN: 1727-1983

$$\Delta Y(t) = p_1 \cdot \tanh\left(\frac{p_2 \cdot \Delta Y^*(t)}{2}\right) \quad (3)$$

where p_1 is the response range which shows the difference between the maximum and minimum values of ΔY, and p_2 is a coefficient of gain. The parameters (p_1 and p_2) were determined by least squares method (see Table 1).

The model responses containing the patient sensitivity to therapeutic agents and the drug interaction are expressed as

$$\begin{cases} \Delta CO_m(t) = a1 \cdot \Delta Y_{11}(t) + a2 \cdot \Delta Y_{12}(t) \\ \Delta MAP_m(t) = b1 \cdot \Delta Y_{21}(t) + b2 \cdot \Delta Y_{22}(t) \end{cases} \quad (4)$$

where $\Delta Y_{11}(t)$ or $\Delta Y_{12}(t)$ is ΔCO response in DBT or SNP infusion. $\Delta Y_{21}(t)$ or $\Delta Y_{22}(t)$ is ΔMAP response in SNP or DBT infusion. The a_1, a_2, b_1, or b_2 is the proportional gain of the patient sensitivity to the drug.

Control Design. Figure 1 shows a block diagram of a $MAPC_{NN}$ system for the regulation of the hemodynamics. The $MAPC_{NN}$ is a control system where the NN recursively learns the characteristics of a patient using their observed response to drug infusions, and then determines the predicted output after *Np* steps. First, in the closed loop controls, the NN learned about ΔCO_m or ΔMAP_m response once every 30 s. Second, the learned ΔCO_{NN} or ΔMAP_{NN} was used for the prediction of future ΔCO_{NN} or ΔMAP_{NN} responses. Two components of the NN were prepared for the drug delivery controls of the DBT-CO loop and the SNP-MAP loop.

A multilayer feed-forward NN with two hidden layers (Fig. 2) was used to emulate ΔCO_m or ΔMAP_m response. In a single NN component, the number of units in first hidden layer of a NN was set to 14 being the same number as the input units. Nonlinear changes in ΔCO_m or ΔMAP_m are predicted through NN. The input layer contained the past DBT and SNP infusion rate for 3 min.

The input values are sent through the first hidden layer, second hidden layer, and output layer [5]. The number of units in second hidden layer on a NN was set to 14 being the same number as the first hidden layer units. ΔY_{NN} in the output layer shows ΔCO or ΔMAP response mimicked by NN (ΔCO_{NN} or ΔMAP_{NN}). NN was trained by the output of ΔCO_m or ΔMAP_m to the random inputs. The error signal is propagated back through the network modifying the weights before the presentation of the next input. All connection weights are adjusted to decrease the error function by the backpropagation learning rule based on the gradient decent method. NN recursively learns the characteristics of the controlled system from ΔCO_m or ΔMAP_m response to DBT and SNP infusions. ΔCO_{NN} and ΔMAP_{NN} indicate the physiological parameters predicted by the NN. The initial connection weights of NN were determined from the learning results using the ΔCO_m and ΔMAP_m.

The prediction loop in the $MAPC_{NN}$ had to determine the optimal DBT or SNP infusion rate that minimized the cost function [$J(t)$].

$$J(t) = W \cdot [u(t) - u(t-1)]^2 + \sum_{i=1}^{N_p} [r(t+i) - \Delta Y_{NN}(t+i)]^2 \quad (5)$$

where W is the weight of input change, *Np* represents a prediction range, and $r(t+i)$ is the setpoint of ΔCO_m (J_1, W_1, Np_1, and r_1) or ΔMAP_m (J_2, W_2, Np_2, and r_2) control. $J(t)$ contained the predicted output after *Np* steps to suppress the sudden changes in DBT or SNP infusion rate [5]. The infusion rate of DBT was determined under the DBT-CO loop, and then that in the SNP was determined under the SNP-MAP loop.

Results

Determination of Control Parameters. To decide the initial weights in the NN for the $MAPC_{NN}$, the NN learned ΔCO_m or ΔMAP_m response. The learning of NN was repeated 100,000 times. The starting weights in the NN before the learning of ΔCO_m or ΔMAP_m response were given at random between -1 and 1. The infusion rate of DBT or SNP, then, was given at random between -4 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The ΔCO_m was divided by 200, and ΔMAP_m was divided by 100 for the normalization. Learning results of the NN respectively showed errors of 2.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in the DBT-CO loop and 1.5 mmHg in the SNP-MAP loop compared with the ΔY_m data. The trained NN was used for the following simulation study, and the learning rates of the NN were set to $K_{n1} = 0.2$ in the DBT-CO loop and $K_{n2} = 0.2$ in the SNP-MAP loop.

Evaluation of Controller. The control objective was to increase the low CO at the setpoint (+35 $ml \cdot kg^{-1} \cdot min^{-1}$) and to maintain the normal MAP at the setpoint (±0 mmHg). The control duration was 120 min. The pure time delays of patient responses were changed during 30–120 s. The parameters in Eq. (4), a_1, a_2, b_1, and b_2, were changed randomly from 1/3 to 3. The infusion rates were bounded as follows: $0 \le DBT \le 10$ $\mu g \cdot kg^{-1} \cdot min^{-1}$ and $0 \le SNP \le 6$ $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Figure 3 shows of the $MAPC_{NN}$ ($N_{p1} = N_{p2} = 12$, $W_1 = W_2 = 0.01$, $K_{n1} = K_{n2} = 0.2$, $r_1 = +35$ $ml \cdot kg^{-1} \cdot min^{-1}$, and $r_2 = \pm 0$ mmHg) under the unknown time-variant responses with acute disturbances. A(a) in the graph shows changes of the parameters of the time delays (L) in the unit impulse response of Eq. (2). A(b) indicates changes of the parameters (a_1, a_2, b_1, b_2) in Eq. (4). B(a) and C(a) show changes of acute disturbances and random noise added to ΔCO_m and ΔMAP_m responses. B(b) and C(b) show setpoints, ΔCO_m and ΔMAP_m (solid lines), and predicted outputs by NN (dashed lines). B(c) and C(c) are the weight changes in NN for controllers in DBT-CO and SNP-MAP loops: weights between input and first hidden layers (top), first and second hidden layers (middle), and second hidden and output layers

ISSN: 1727-1983

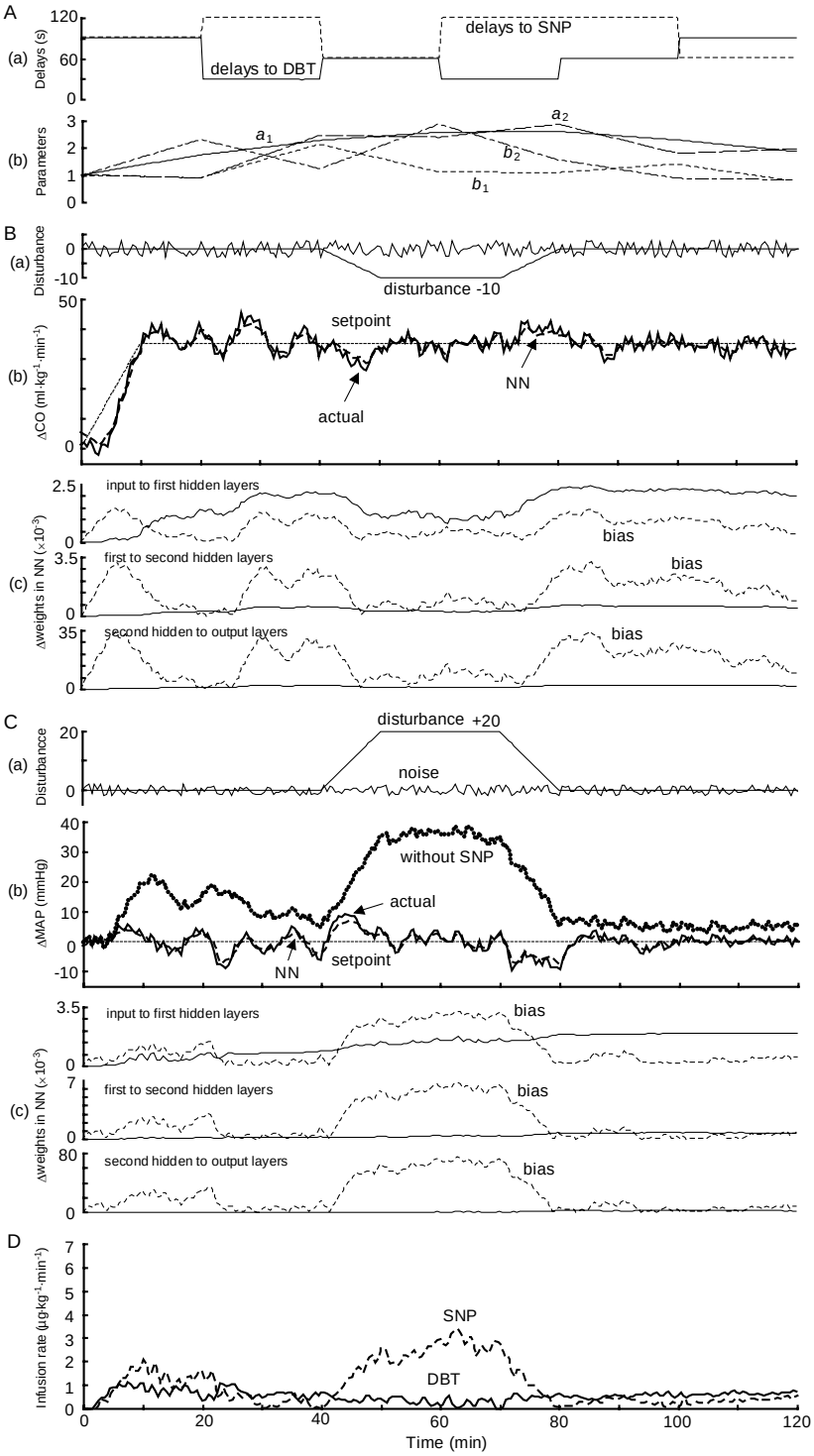

Figure 3. Simulation results of $MAPC_{NN}$ under unknown time-variant responses with disturbances

(bottom). D is the infusion rates of DBT (solid line) and SNP (dashed line).

The ΔCO converged on the setpoint within 10 min. The SNP suppressed the hypertension (+6.1 vs. +22.8 mmHg with or without SNP) induced by DBT. At 40 min, acute disturbances were added to the responses. The ΔCO and ΔMAP quickly converged on the setpoint within 10 min, whereas the transient hypertension was induced (+9.4 vs. +38.9 mmHg with or without SNP). The average errors between setpoints and observed responses were 4.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in CO and 2.7 mmHg (15.3 mmHg without SNP) in MAP during the control.

Discussion

Application of $MAPC_{NN}$ to a multiple hemodynamic control accomplished the robust regulation of CO and MAP under various changes of the patient's responses to drugs and disturbances. The $MAPC_{NN}$ suppressed those disturbances quickly and performed stabilized

ISSN: 1727-1983

control under unexpected acute disturbances. Under time-variant patient responses with time delays, which are a crucial obstacle to stable control, the $MAPC_{NN}$ provided sufficient control performance.

The two-NN models of average responses with heart failure were considered in the calculation of the appropriate multiple drug infusion rates of DBT and SNP to mitigate the enormous number of trials associated with the control design. The controllers described herein are an effective means of adjusting to various patients' idiosyncratic sensitivities to drugs and describing nonlinear responses to drugs. A controller based on NN solves those problems because it markedly decreases the number of models required for the control design of the various changes of hemodynamics compared with model predictive controllers or fuzzy controllers.

Irrespective of the wide range of actual physiological responses, CO and MAP in the $MAPC_{NN}$ approached the setpoints promptly because of the guided setpoint of CO during the initial 10-min control considering the optimization of both the stability and speed for the $MAPC_{NN}$. The designed $MAPC_{NN}$, therefore, will be feasible for application to automatic drug therapy in heart failures. However, when rapid treatment using drugs against more acute and large disturbances is required during hemodynamic controls, another supplemental system might be required. Diagnoses of characteristics of patients' responses to drugs or tuning weights of NN during closed-loop controls may also be effective for hemodynamic controls to accelerate the NN learning speed.

The primary control target was the increase of low CO in acute heart failure. Therefore, the control for CO induced hypertension. The $MAPC_{NN}$ suppressed hypertension using optimal infusion of SNP as well as increasing CO using DBT to an optimal target value. The SNP suppresses the increase in preload through the decrease of SVR because of increasing venous compliance for retaining the blood in the veins and lowering the venous return to the heart.

Because the fluid infusion, blood transfusion, anesthesia, and muscular blockade as well as the therapeutic agents controlled in this study are common in clinical practice, robust controllers that can adjust physiological responses to further multiple drugs should be designed. The $MAPC_{NN}$ tested herein can be extended simply to multivariate control systems under such clinical conditions for drug therapy with heart failure. The acute left heart failure of dogs induced in this study resulted in the low CO and normal MAP. The $MAPC_{NN}$ showed the identical control performance in changes over the pathology of hemodynamics in heart failure of simulation study. The $MAPC_{NN}$, also, was adequately able to tolerate hemodinamic responses in actual heart failures of dogs, linking to apply the controller to clinical situations.

Conclusions

$MAPC_{NN}$ was designed and evaluated in simulation studies to regulate the CO and MAP in acute heart failure using the DBT and SNP under the nonlinear and wide changes of the patient sensitivity to drugs and the drug interaction. $MAPC_{NN}$ showed a robust control performance under the wide ranges of drug responses. To apply the $MAPC_{NN}$ to clinical situations, the further studies will be required.

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ISSN: 1727-1983