Preprints of the 18th IFAC World Congress
Milano (Italy) August 28 - September 2, 2011

A computer control system for the regulation of blood volume, heart rate and blood pressure during kidney dialysis ⋆

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Abstract: In this paper, a computer controlled system has been developed and tested to maintain the hemodynamic stability of kidney failure patients undergoing dialysis. The system uses ultrafiltration rate (UFR) and dialysate sodium concentration (DSC) as the control inputs to regulate the changes in relative blood volume (RBV) and percentage change in heart rate (ΔHR) while maintaining systolic blood pressure (SBP) within constraints during the course of dialysis. First a linear parameter varying (LPV) system has been proposed to model the hemodynamic response of patients during dialysis. UFR and DSC are imposed as the inputs and the model computes the RBV, ΔHR and SBP during dialysis. Next, a controller is proposed based on model predictive control approach utilizing pre-defined constraints on the control inputs (UFR and DSC) as well as the output (SBP) and minimizing an objective function. The designed control system was experimentally verified on patients. The design and implementation of such a system is a positive step towards developing state-of-the-art technologies capable of preventing dialysis induced complications.

1. INTRODUCTION

Human kidneys regulate fluid and electrolyte balance to maintain the fluid volumes and ion compositions within tight limits. The failure of kidneys results in fluid retention and accumulation of several ions and solutes. The consequences may be life threatening. Dialysis serves as a life sustaining therapy for kidney failure patients in which the patient's blood is withdrawn from the body through arterial vein. It is then passed through an artificial kidney called dialyser and the cleaned blood is returned to the body through venous vein. The whole process takes around 4-5 hr and is repeated thrice weekly.

In conventional dialysis, the machine parameters are set to constant values at the start of dialysis. These parameters include the rate of fluid removal, termed as ultrafiltration rate (UFR), which is calculated based on the patient's ideal dry weight, dialysis duration, and fluid overload status, dialysate sodium concentration (DSC), dialysate temperature, dialysate flow rate and blood flow rates. The removal of around 2-5 L of fluid during a dialysis session results in relative hypovolemia and a decrease in venous return, which leads to a reduction in circulatory blood volume. This progressive reduction in blood volume leads to the activation of compensatory mechanisms to ensure the hemodynamic stability of the patient.

One of the most serious complications during dialysis is the sudden decrease in blood pressure. A major cause of such drop is the imbalance between rapid ultrafiltration and vascular refilling from the interstitial space to the blood stream Daugirdas [1991]. The reduction in plasma volume can lead to a drop in blood pressure which is normally compensated by peripheral vasoconstriction mediated by sympathetic nerve activity Palmer and Henrich [2008]. Avoiding a critical decline in blood volume as well as maintaining cardiovascular compensatory mechanisms can help to avoid dialysis-induced complications, resulting in better overall health of kidney failure patients.

With this motivation, this paper proposes a computer control system, designed to maintain the hemodynamic stability of kidney failure patients undergoing dialysis. First a linear parameter varying (LPV) system to model the hemodynamic response of patients during dialysis is proposed. UFR in L/hr and DSC in mmol/L are imposed as the inputs and the model computes the RBV, ΔHR and systolic blood pressure (SBP) during the course of dialysis. Based on this LPV model, a computer control system is presented. The aim of the system is to regulate RBV as well as HR during dialysis while maintaining SBP within stable range. The designed computer-controller is based on a model predictive control (MPC) approach utilizing pre-defined constraints on the control inputs (UFR and DSC) as well as the output (SBP). The block diagram of the developed system is shown in Fig. 1.

In comparison to the previously proposed biofeedback system, the proposed controller not only tracks RBV but also tracks the changes in HR, which is an important compensatory response to fluid loss during dialysis. The system also explicitly puts a constraint on the SBP which is the real target of such system. From control methodology point of view, previously

⋆ This work was supported in part by the Australian Research Council.

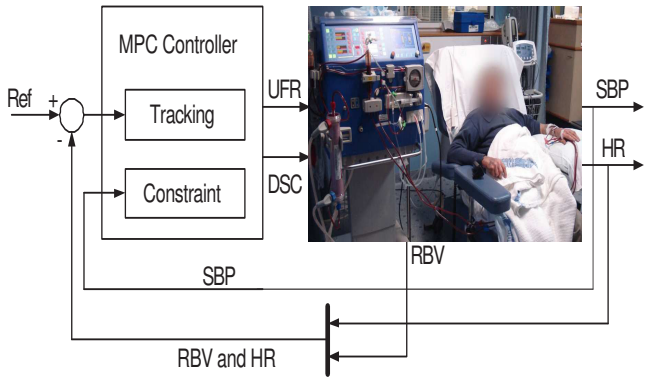

Fig. 1. Components of a computer control system.

developed BVT systems Santoro et al. [2008] have used PID controllers, whereas in this paper we have proposed an MPC-based control approach. This approach is advantageous to PID due to its robustness to changes in system parameters, ability to handle constraints and straight forward applicability to large multi-variable systems. MPC predicts the future behavior of the system for some finite interval and calculates an optimal control input over that future interval. As this control methodology depends on the model of the system, a multiple model approach has been utilized so as to account for the possible large variabilities between patients.

An initial idea of the proposed LPV model was presented in our previous paper Javed et al. [2010], however the previous model used UFR as input to predict RBV and HR and was identified only for conventional dialysis so was unable to model plasma refilling. Compared to the previous model, in this paper we have proposed a design that incorporates DSC as a second input. The initial idea of the controlled system was presented in our previous work Javed et al. [2010], but that system used only one control input (UFR) and was lagging an explicit constraint on the SBP. In addition only computer simulations were carried out. In this study, the designed computer control system is experimentally validated, and its performance is demonstrated in actual dialysis sessions involving human patients.

2. THE MODEL

We proposed a LPV multi-input multi-output (MIMO) system to model the hemodynamic response to dialysis. The model inputs are the UFR and the DSC and outputs are the RBV, ΔHR and SBP. It can be represented in a discrete-time state space model as:

$$\begin{aligned}\mathbf{x}_{k+1} &= \mathbf{A}_k\mathbf{x}_k + \mathbf{B}_k\mathbf{u}_k + \mathbf{F} + w_k \\ \mathbf{y}_k &= \mathbf{C}_k\mathbf{x}_k \end{aligned} \tag{1}$$

where

$$A_k = \begin{bmatrix} (1-\xi) & 0 & 0 \\ b_{1,k} & 1 & 0 \\ c_{1,k} & 0 & 1 \end{bmatrix},$$

$$B_k = \begin{bmatrix} \alpha a_{1,k} & -\beta a_{1,k} \\ 0 & 0 \\ 0 & c_2 \end{bmatrix},$$

$$F = \begin{bmatrix} a_2 \\ 0 \\ c_3 x_{3,0} - 0.5c_2 \end{bmatrix}, C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \tag{2}$$

where $\mathbf{x}(\mathbf{k}) = [x_{1,k} \quad x_{2,k} \quad x_{3,k}]^T$, $x_{1,k}$ is the RBV, $x_{2,k}$ is ΔHR, $x_{3,k}$ is SBP, $\mathbf{u}(\mathbf{k}) = [u_{1,k} \quad u_{2,k}]^T$, $u_{1,k}$ is the UFR in L/hr, $u_{2,k}$ is the DSC in mmol/L normalized to a range of 0 and 1 corresponding to 135 and 145 mmol/L respectively, w_k is the system noise, y_k is the system output, k is the sampling time, $x_{3,0}$ is the pre-dialysis SBP. $a_{1,k}$, $b_{1,k}$, and $c_{1,k}$ are the time-varying system parameters and ξ, a_2, c_2 and c_3 are time-invariant parameters.

Equations (1) and (2) form a discrete-time LPV system. The UFR and DSC are imposed as model inputs which influence the blood volume in the intravascular compartment measured as RBV. However at times when the UFR is stopped and/or DSC level is lowered, the plasma refilling from interstitial and intracellular compartments to the intravascular compartment dominates. This is modeled by the terms (1-ξ) and a_2. It is assumed that both UFR and DSC affect the RBV in opposite ways as increasing the UFR will result in more fluid being removed from intravascular compartment leading to a lower RBV whereas increasing the DSC enhances plasma refilling through an increase in osmolarity, which favors water shifts from the intracellular to the extracellular compartments favoring plasma volume preservation. The parameters α and β define the weights on the effect of UFR and DSC to RBV with $\alpha > \beta$ indicating a direct effect of UFR on RBV and an indirect effect due to DSC.

The overall reduction in circulating blood volume causes mild hypovolemia that perturbs the cardiovascular system. This leads to reflex sympathetic excitation and parasympathetic inhibition, thereby compensating for arterial and venous pressure reduction Cavalcanti et al. [2004]. A recent study has shown an increase in HR at the later phase of dialysis with a drop in RBV Javed et al. [2009]. So the change in HR is assumed to be linked with the RBV.

For the maintenance of BP, various factors superimpose themselves in complex nonlinear ways, and these include those that affect the vascular refilling rate from interstitial fluid evident by RBV and those that influence the action of short-term cardiovascular control mechanisms Ursino and Innocenti [1997]. The use of DSC also has an independently beneficial effect on BP behavior. Using a high DSC, the patient can often tolerate large BV losses with fewer hypotensive symptoms compared to traditional dialysis using a lower dialysate sodium de Vries et al. [1990]. A temporary increase in plasma sodium allows the autonomic nervous system to make better compensatory adjustments to counteract blood pressure reductions due to BV losses Maeda et al. [1988], Swartz et al. [1982], Santoro et al. [1994]. As the SBP response depends on the pre-dialysis SBP on a particular day during dialysis so an extra term has been incorporated. Also it has been assumed that the SBP response is mainly influenced by RBV when a DSC of 140 mmol/L is used as in conventional dialysis.

The time-varying parameters $a_{1,k}$, $b_{1,k}$ are defined as:

$$a_{1,k} = a_{01,k} + \gamma\, a_{11,k} \tag{3}$$

$$b_{1,k} = \zeta_1 b_{01,k} + \zeta_2 b_{11,k} \tag{4}$$

where $a_{01,k}$, $a_{11,k}$, $b_{01,k}$ and $b_{11,k}$, are time-varying parameters which are not profile dependent or in other words the same parameter tracks are used for one patient, whereas γ, ζ_1 and ζ_2, are time-invariant and are identified to model an individual patient's response for different profiled dialysis sessions.

2.1 Experimental Protocol for System Identification

The experimental work was carried out at the Hemodialysis Unit, Prince of Wales Hospital, Sydney, Australia. The study design and protocol was reviewed and approved by the Human Research Ethics Committee of the Prince of Wales Hospital, Sydney and informed consent was obtained from all subjects. A group of 12 renal failure patients were asked to participate in the study. All patients were routinely dialyzed three times weekly for 4-5.5 hr.

Four different protocols were designed based on changing the profiles of UFR and DSC. These include: (i) constant UFR and DSC, (ii) linearly decreasing UFR and DSC, (iii) step decrease in UFR and DSC and (iv) square change in UFR and DSC. Each patient underwent start-of-week dialysis with each of the four dialysis protocols for four consecutive weeks. During the other two sessions in the week, conventional dialysis was performed with constant UFR and DSC.

Throughout dialysis, a continuous ECG was recorded in lead II configuration using a bio-amplifier (ST4400, ADInstruments, Sydney, Australia) and was digitized at a sampling rate of 1 kHz. BP was monitored every 20-30 min during dialysis. RBV was also monitored at 2 min intervals using a blood volume sensor (BVS) embedded in the dialysis machine. The BVS uses an optical sensor for transmitting light through the cuvette in the BL200B bloodline (Gambro Dasco S.p.A., Medolla, Italy). At the start of the dialysis, the BVS performs a functional self test, calibration and then evaluates the RBV by measuring the blood density. The blood volume is expressed as a percentage of the starting blood volume by measuring the hematocrit at the start of dialysis and at any particular time during dialysis using the formula given by:

$$RBV_t(change\ in\ percentage) = \left(\frac{Ht_t}{Ht_0} - 1\right) \times 100 \qquad (5)$$

where Ht_0 is the hematocrit at the start of dialysis and Ht_t is the hematocrit level at time t during dialysis.

2.2 Model Response

The model parameters were estimated for all 12 patients using the four profiled dialysis sessions and the average mean square error (MSE) $\pm$ standard error of mean (SEM) between the measured and the simulated states for the 12 patients was 1.77 ± 0.50 for RBV, 6.28 ± 1.75 for ΔHR and 11.10 ± 1.16 for SBP.

3. CONTROLLER DESIGN

First the system defined in (1) was rearranged in the form of a general linear time-varying state-space system of the form:

$$\begin{aligned} \mathbf{x}_{k+1} &= \mathbf{A}_k\mathbf{x}_k + \mathbf{B}_k\mathbf{u}_k \\ \mathbf{y}_k &= \mathbf{C}_k\mathbf{x}_k \end{aligned} \qquad (6)$$

In order to incorporate the constant terms, an extra state was introduced so the state vector is given by:

$$\mathbf{x}(k) = [x_{1,k} \quad x_{2,k} \quad x_{3,k}\ 1]^T \qquad (7)$$

The system matrices are given by:

$$A_k = \begin{bmatrix} (1-\xi) & 0 & 0 & a_3 \\ b_{1,k} & 1 & 0 & 0 \\ c_{1,k} & 0 & 1 & c_3x_{3,0} - 0.5c_2 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$B_k = \begin{bmatrix} \alpha a_{1,k} & -\beta a_{1,k} \\ 0 & 0 \\ 0 & c_2 \\ 0 & 0 \end{bmatrix}$$

$$C = \begin{bmatrix} 0 & 0 & 1 & 0 \end{bmatrix}, \qquad (8)$$

The cost function given in Eq. (**??**) was rearranged in a way to penalize the deviation of the states $x_{1,k}$ and $x_{2,k}$ from the reference trajectories $R_{1,k}$ and $R_{2,k}$ respectively. Another objective was to keep both the control inputs as close as possible to each other so that when a higher UFR is applied, the DSC is increased to ensure stability of patient. The cost function takes the form:

$$\begin{aligned} \mathbf{V_N^0} = &\sum_{i=k+1}^{k+P} \left[(\hat{x}_{1,k} - \eta_1 R_{1,k})^2 + (\hat{x}_{2,k} - \eta_2 R_{2,k})^2\right] \\ &+ \sum_{i=k}^{k+M-1} (u_{1,k} - \eta_3 u_{2,k})^2 \end{aligned} \qquad (9)$$

where η_1, η_2, and η_3 are the weighting factors. The constraints were applied on the control inputs as well as the output. The constraint on UFR is given by:

$$0 \le u_{1,k} \le UFR_{max} - (m/T_d)k;\ k = 0, 1, \ldots, M-1 \qquad (10)$$

The constraint was based on the lower limit of 0 corresponding to no ultrafiltration and a time-varying upper limit starting with UFR_{max} and linearly decreasing with a patient specific slope m and the dialysis duration T_d where k is the current sampling time. The upper and lower limits on DSC are based on exponentially decreasing and increasing DSC levels from 145 and 135 mmol/L respectively, such that there is no sodium imbalance by the end of dialysis. The constraint on DSC is given by:

$$\begin{aligned} -(0.5 - 0.5e^{-0.01k}) \le u_{2,k} \le (0.5 + 0.5e^{-0.01k}); \qquad (11) \\ k = 0, 1, \ldots, M-1 \end{aligned}$$

Finally a constraint has been applied on the SBP, introduced as the output constraint of the form:

$$SBP_{min} \le y_k \le SBP_{max};\ k = 0, 1, \ldots, P-1 \qquad (12)$$

These constraints were incorporated in the controller design to solve a constrained optimal control problem of the form:

$$\mathbf{U^0} = arg\ \min_U(\mathbf{V_N^0}(x, r, u)) \qquad (13)$$

subject to the constraints expressed in the form

$$\mathbf{LU} \le \mathbf{K} \qquad (14)$$

The matrices in Eq. (14) are defined as:

$$L = [I \;\; -I \;\; D \;\; -D]^T \tag{15}$$

$$K = [\overline{c}_{1\ max} \;\; \overline{c}_{2\ max} \;\; \overline{c}_{1\ min} \;\; \overline{c}_{2\ min} \;\; \overline{c}_{3\ max} \;\; \overline{c}_{3\ min}]^T \tag{16}$$

and

$$U = [u_{1,k} \;\; \dots \;\; u_{1,k+M-1} \;\; u_{2,k} \;\; \dots \;\; u_{2,k+m-1} \;\;]^T \tag{17}$$

where I is $(2M\text{x}2M)$ identity matrix and D is following $(P-1\text{x}2M)$ matrix

$$D = \begin{bmatrix} CB & 0_{1x2} & \dots & 0_{1x2} \\ CAB & CB & \dots & 0_{1x2} \\ \vdots & \vdots & \ddots & \vdots \\ CA^M B & CA^{M-1}B & \dots & CAB \end{bmatrix}, \tag{18}$$

and

$$\overline{c}_{1\ max} = [\overline{c}_{1,k\ max} \;\; \dots \;\; \overline{c}_{1,k+M-1\ max}]^T \tag{19}$$

$$\overline{c}_{2\ max} = [\overline{c}_{2,k\ max} \;\; \dots \;\; \overline{c}_{2,k+M-1\ max}]^T \tag{20}$$

$$\overline{c}_{1\ min} = [\overline{c}_{1,k\ min} \;\; \dots \;\; \overline{c}_{1,k+M-1\ min}]^T \tag{21}$$

$$\overline{c}_{2\ min} = [\overline{c}_{2,k\ min} \;\; \dots \;\; \overline{c}_{2,k+M-1\ min}]^T \tag{22}$$

$$\overline{c}_{3\ max} = [\overline{y}_{max} - CAx_0 \;\; \dots \;\; \overline{y}_{max} - CA^{P-1}x_0]^T \tag{23}$$

$$\overline{c}_{3\ min} = [\overline{y}_{min} - CAx_0 \;\; \dots \;\; \overline{y}_{min} - CA^{P-1}x_0]^T \tag{24}$$

Considering the high variability between patients as well as the variability within the same patient on different days, it is inadequate to use a fixed model for predicting the hemodynamic variables. So a multiple model approach was utilized. At each sampling time k the model parameters were updated based on minimizing the mean square error between the actual states and the estimated states from different models. In mathematical terms, the following cost functions were solved:

$$\min_{\xi, a_{1,k}, a_2, b_{1,k}} \left(\sum_{i=1}^{k} (X_1(i) - \hat{X}_1(i))^2 + (X_2(i) - \hat{X}_2(i))^2 \right) \tag{25}$$

and

$$\min_{c_{1,k}, c_2, c_3} \left(\sum_{i=1}^{k} (X_3(i) - \hat{X}_3(i))^2 \right) \tag{26}$$

The updated system parameters were then input to the MPC in order to find the optimal control inputs that were used to predict the future states. Our proposed control system is an adaptive MPC system and it is well known that stability issues may arise in such controllers (e.g., Goodwin et al. [2001]). However our system has time-varying coefficients therefore it cannot be naturally extended over an infinite time interval hence the issue of stability over infinite time is not relevant to our approach.

4. COMPUTER CONTROLLED SYSTEM

By using the control design presented in the previous section, a computer control system was implemented for the regulation of RBV and HR while maintaining SBP within a stable range. Its configuration is as shown in Fig. 1.

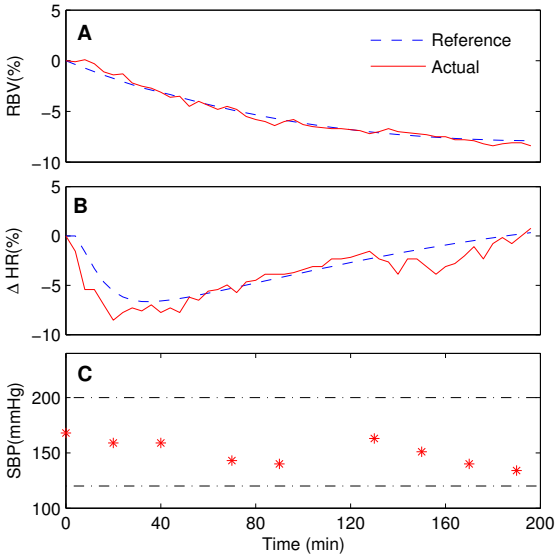

Fig. 2. Reference profiles and measured states of patient 1 during computer-controlled haemodialysis session

4.1 Experimental Protocol

The HR and RBV were recorded every 4 min whereas the SBP was recorded every 20 min in order to minimize the discomfort to patient due to cuff inflation. However in the presence of any symptoms of hypotension, the BP measurement was carried out immediately. The computer controller was implemented in MATLAB and the control inputs computed by the controller were manually applied to the dialysis machine every 4 min. As shown in Fig. 1, the controller has two main tasks: tracking RBV and HR and keeping SBP within constraints. When only HR and RBV (every 4 min) measurements are available, the controller only performs the tracking job, and when the SBP is also measured (every 20 min) along with RBV and HR, the controller incorporates the constraint on output along with tracking.

4.2 Experimental results

To validate the designed computer control system, it was tested on four subjects. Each patient initially underwent three consecutive dialysis sessions with constant UFR (based on the amount of fluid to be removed on that particular day) and constant DSC (140 mmol/L) in order to determine the reference profiles for RBV and HR. These reference profiles were chosen based on these three dialysis sessions along with the suggestions of our clinical collaborators. The goal of the controller was to regulate the patient's RBV and HR according to these profiles while maintaining the SBP within a stable range which was individualized due to each patient's medications and cause of kidney failure. The constraints on control inputs were based on the recommendations of nursing staff where the UFR was constrained to linearly decreasing profile and DSC was maintained to 140 mmol/L by the end of dialysis.

Patient 1 The reference profiles and actual states of Patient 1 during computer controlled dialysis session are shown in Fig. 2 and the control inputs computed by the controller and manually input to the machine are shown in Fig. 3. The patient

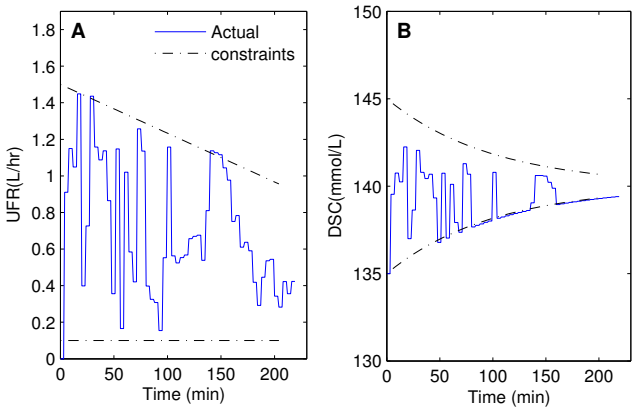

Fig. 3. Control inputs computed by the controller for patient 1 during computer-controled haemodialysis session

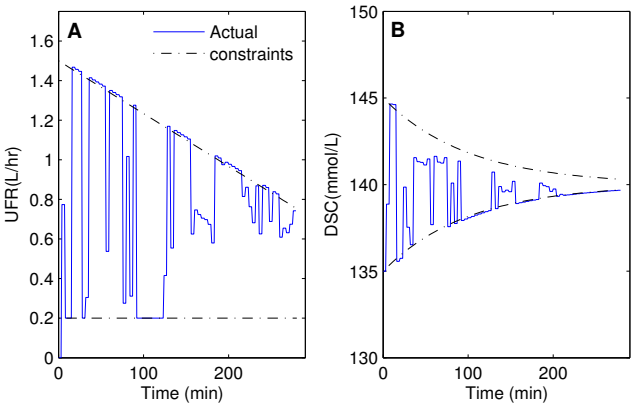

Fig. 5. Control inputs computed by the controller for patient 2 undergoing computer-controlled haemodialysis session

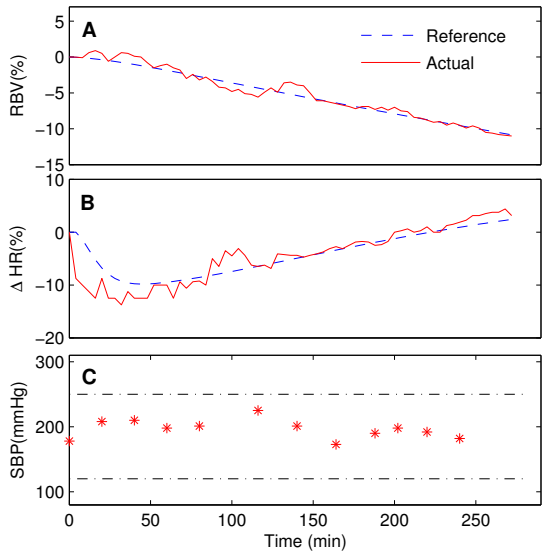

Fig. 4. Reference profiles and measured states of patient 2 during computer-controlled haemodialysis session

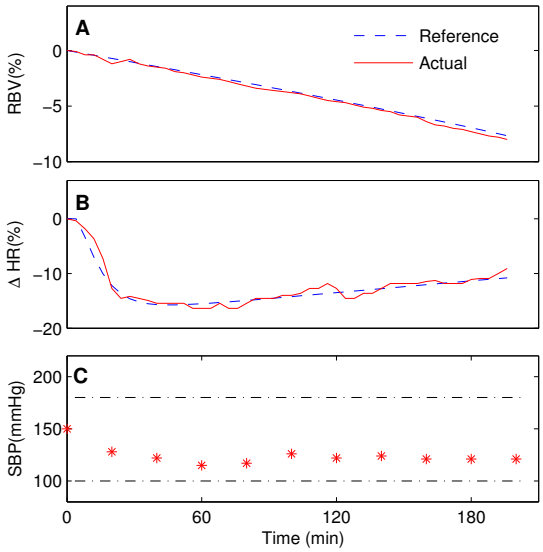

Fig. 6. Reference profiles and measured states of patient 3 during computer-controlled haemodialysis session

was haemodynamically stable and had no hypotensive episode during HD. It can be seen that the controller was able to track the RBV throughout dialysis, however there was an initial error between the reference and measured HR which was possibly due to the pre-dialysis HR selection on that particular day. However despite an initial error, the controller was able to track the HR after 30 min into dialysis.

Patient 2 Fig. 4 shows the reference profiles and actual states of Patient 2 and Fig. 5 shows the control inputs computed by the controller and manually input to the machine. The SBP of the patient remained within the stable range throughout dialysis. From Fig. 4 it can be noted that at the start of dialysis RBV did not dropped according to the profile and stayed close to 0 for which the controller computed a high UFR and DSC. However after 40-50 min into dialysis the RBV showed a decreasing trend. The HR response also deviated in the start of dialysis but converged to reference profile by 1 hr into dialysis. Overall the controller was able to track the RBV and HR according to the profile.

Patient 3 For patient 3, the reference profiles and actually measured states are shown in Fig. 6 and the control inputs calculated by the controller are given in Fig. 7. The overall response of this patient was quite good and resulted in a very small MSE between actual measured states and the reference profiles. The controller generated a higher UFR at the start of dialysis which is feasible in real dialysis patients as the patients are hypervolaemic at pre-dialysis and can tolerate high UFR at the start. Overall the controller did worked well and the SBP stayed within the defined safe limits.

Patient 4 The computer-controlled haemodialysis system was also tested on one patient who usually had asymptomatic hypotensive episodes during regular HD. The reference profiles and the actually measured states for that patient during a controller based dialysis session are shown in Fig. 8 and the inputs computed by controller and manually input to the machine are shown in Fig. 9. It can be observed that at the 210^{th} min the SBP dropped to the lower constraint (marked by circle in Fig. 8) which was overcome by an increase in DSC and a drop in UFR

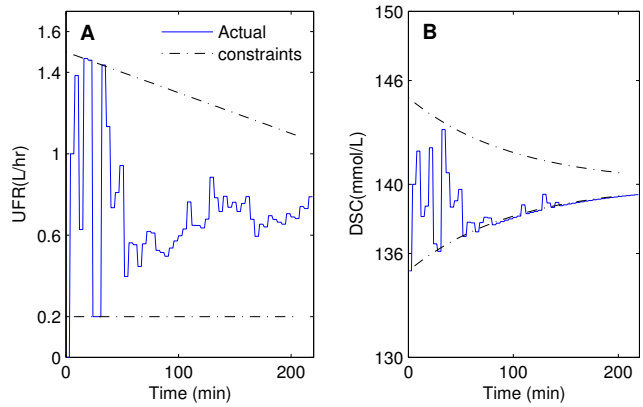

Fig. 7. Control inputs computed by the controller for patient 3 undergoing-computer controlled haemodialysis session

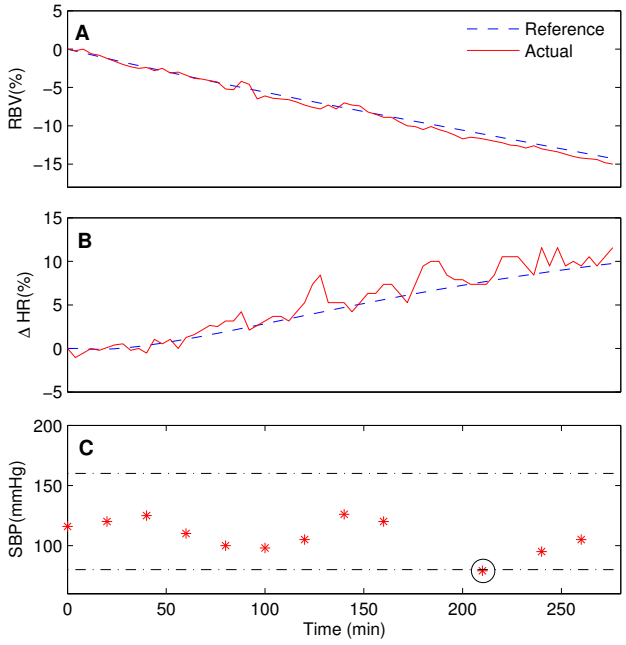

Fig. 8. Reference profiles and measured states of patient 4 during computer-controlled haemodialysis session

(marked by circle in Fig. 9) at that time. Overall the controller tracked the RBV and HR to reference trajectories well.

5. CONCLUSIONS

In this paper, an LPV state-space system has been proposed to model the hemodynamic response of patient during dialysis. The model parameters were estimated based on profiled dialysis sessions. Based on this model, an MPC-based controller was designed to track the changes in RBV and HR during dialysis while maintaining SBP within bounds to avoid hypotensive or hypertensive episodes. The designed computer controlled system has been successfully applied on actual dialysis sessions for the regulation of RBV and HR while maintaining SBP as well as control inputs (UFR and DSC) within constraints.

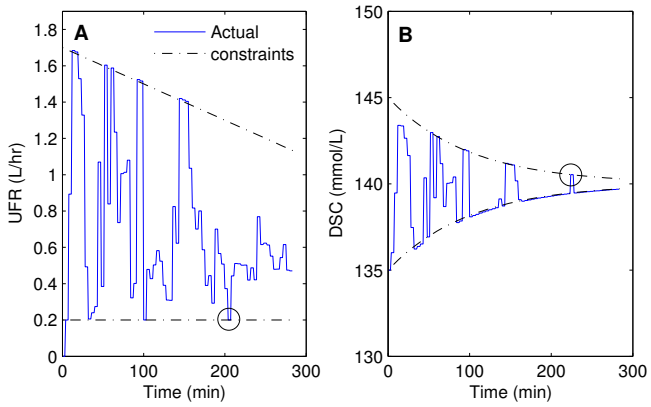

Fig. 9. Control inputs computed by the controller for patient 4 during computer-controlled haemodialysis session

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