Robust control design for automatic regulation of blood pressure

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Abstract: The problem of automatic administration of vasoactive drugs to a patient can be treated as a regulation problem of a system, which is characterised by large parametric uncertainty, non-Gaussian disturbances and unmodelled dynamics, yet carries strict requirements in terms of robustness and performance. A number of approaches have been proposed in the past to tackle this problem, particularly for the postoperative management of blood pressure in cardiac surgery patients. We describe the design of a robust multiple-model adaptive control (RMMAC) architecture and investigate whether this can overcome some issues observed with earlier methods. Key features of RMMAC are robust optimal controller design using an iterative $\mu$ synthesis algorithm and improved system estimation. Simulation results indicate that RMMAC is capable of avoiding transient instability and delivering performance in the face of significant parameter changes over time and large disturbances including non-zero-mean signals. The findings support further research into RMMAC as a potentially viable approach to the design of safer automatic closed-loop drug administration technologies capable of operating under challenging clinical conditions such as may arise in an intraoperative setting.

1 Introduction

The cardiovascular system is essential to the life of the human body. It is a hydraulic system, which utilises blood as its working fluid and, as such, can be characterised in terms of pressure and flow. Mean arterial pressure (MAP) and cardiac output (CO) are two key variables used by clinicians to describe the system’s operating point. Only a relatively narrow range of operating points are compatible with life and, under normal (physiological) conditions, the human body is equipped with internal control systems to maintain a suitable and steady operating point in the face of external stimuli. In patients whose autonomic regulation is impaired or insufficient, medical intervention is required to ensure that the system does not drift away from the physiological range for MAP and CO. This is generally achieved by intravenous infusion of suitable drugs.

This paper focuses on the vasoactive drug sodium nitroprusside (SNP) and its use in the management of acute hypertension (a temporary state of dangerously elevated MAP) in peri-operative and intensive care settings [1]. SNP is a vasodilator, that is, a drug which causes the tension in the walls of arterioles to be reduced, thereby lowering blood pressure. It is fast-acting and is powerful enough to cause dangerous hypotension and/or cyanide toxicity if overdosed [2]. Significant variability (up to 30-fold [3]) in sensitivity to the drug exists among different patients and the sensitivity can even change for one patient over time. Close monitoring by nursing staff and regular ‘titration’ (adjustment) of the dose depending on the patient’s response are therefore required to achieve the clinical goals of lowering MAP and ensuring patient safety.

The tasks of regular MAP monitoring and SNP dose adjustment are time consuming and, when carried out by a human operator, can be imprecise. An automatic system to provide closed-loop regulation of MAP would appear to be, in this context, an attractive technology for its potential to both improve clinical outcomes and reduce healthcare costs [4]. The dose-response model for SNP, however, is characterised by time delays, modelling uncertainty, time-varying parameters and output disturbances [3], rendering the MAP regulation problem a challenging one from an engineering perspective. Clinically desirable control performance cannot be achieved with a single controller and this has been recognised by several authors, leading to a variety of adaptive control strategies being proposed over the last three decades, including self-tuning regulators [5–7], multiple-model adaptive control (MMAC) [2, 8], model-reference adaptive control [9] and model-predictive control [10], as well as fuzzy control [11] and rule-based non-linear control [12, 13]. For a comprehensive review, we refer the reader to [4, 14]. Only one device, the IVAC Titrator (IVAC Corporation, San Diego, CA, USA), was ever commercialised for the postoperative regulation of blood pressure. However, it enjoyed very little success and was soon withdrawn from the market [15]. It is remarkable that although clinical trials have shown that automatic control has the potential to
This third-order linear, open-loop stable, single-input–single-output (SISO) model consists of three compartments modelled as first-order linear systems representing the systemic circulation, the pulmonary circulation and the drug effect site. An internal loop exists to account for recirculation of the drug within the cardiovascular system. A pure time-delay effect is observed at the input. In accordance with [8], we assume the time constants to be known and time-invariant ($\tau_1 = 50s$, $\tau_2 = 10s$, $\tau_3 = 30s$) and consider a large range of variability for the patient’s gain factor $K \in [0.25, 9.5]$ mmHg/h/ml (sensitivity for an SNP concentration of $200\mu g/ml$) and the time-delay parameter $T \leq 50s$. In the interest of model generality, we also assume considerable variability in the recirculation constant $\alpha \in [0.25, 0.75]$ (Notation: $x \in [a, b] = a \leq x \leq b$). We note that although the time constants are assumed fixed, changes in $\alpha$ can shift the position of the system poles. The extent of intrapatient variability is not well documented in the literature, but, from clinical data published in [21], we extrapolated that up to a four-fold change in sensitivity over 1 h could be expected in patients undergoing cardiac surgery. As we were unable to locate information on time-variability of the other two variable parameters, we assume here the maximum expected rate of change for $T$ and $\alpha$ to be that achieving a change equal to the full range of variability over 1 h. To the authors’ knowledge, the above combination of parametric uncertainty and time-variability results in the most general description ever adopted for this system.

2.2 Signals and sampling rate

The system receives a control signal $u$ at the input, that is, the drug administration rate in ml/h, and exhibits an MAP drop $P_{\text{drop}}$ at the output. This differs from the output of the system $y$, which is given by the affine transformation $y = p_0 - P_{\text{drop}}$, where the offset term $p_0$ represents the patient’s ‘natural’ value of MAP when no drug is administered. It is important to note that in many past adaptive control approaches $p_0$ has been deemed measurable (at time $t=0$ s) and constant or, at most, affected by broadband random noise. This is a convenient description for control design purposes, however, it is not realistic from a clinical perspective. Indeed, breathing and renin–angiotensin activation have been recognised as potential disturbances in [3]. Perioperative events including surgical trauma and the concurrent administration of other drugs are also mentioned in [22]. In this work, $p_0$ is modelled as an arbitrary signal with a mainly low-frequency spectrum (as detailed in Section 3.1.1).

![Block description of the patient model (open-loop plant)](image-url)

**Fig. 1** Block description of the patient model (open-loop plant)

Notation: $u$ input signal (drug infusion rate); $T$ pure delay constant; $\tau_1, \tau_2, \tau_3$ time constants; $\alpha$ recirculation fraction; $K$ sensitivity (gain) parameter; $P_{\text{drop}}$ MAP drop owing to $u$; $p_0$ patient’s natural MAP in the absence of pharmacological intervention; $y$ output MAP; $w$ measurement noise; $y_{\text{meas}}$ actual measured MAP

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deliver superior outcomes to manual control [16–18], operator-based open-loop control of drug infusion still remains the current standard of care in the clinical setting.

We have considered whether there may be residual safety concerns associated with the models used, or particular features of the operation of proposed approaches, which would make clinical operators uncomfortable with reliance on automatic administration as it has been proposed thus far. In earlier work [19], we analysed the approach of [8] and advocated caution against possible instances of undesirable behaviour which we were able to simulate under particular operating conditions characterised by the presence of time-varying patient parameters and a range of disturbances including non-zero-mean signals.

This paper presents a new approach for automatic closed-loop SNP administration based on recent results in the area of robust multiple-model adaptive control (RMMAC) [20]. We show through computational modelling that RMMAC, which employs optimal techniques for robust controller design ($\mu$ synthesis) and system identification, can achieve improved stability and performance, under challenging operating conditions, over previous adaptive control approaches designed for this application. RMMAC can cater systematically and explicitly for modelling uncertainty (an inherent characteristic of all pharmacological models), as well as incorporate performance constraints on input and output signals, which we deem to be key advantages of this methodology in the context of drug delivery applications. We propose that RMMAC may provide a general platform for the development of safer and thus more clinically viable automatic drug delivery technology.

The structure of the paper is as follows. Section 2 provides an outline of the patient model and the control problem; Section 3 describes the proposed control architecture; Sections 4 and 5 describe and provide the results of two numerical simulations; Section 6 analyses the results and discusses directions for future research.

2 Problem description

2.1 Patient response model

An experimentally validated model of a patient’s response to SNP is given by the transfer function of (1) ([8], modified from the [3]). A block diagram representation is shown in Fig. 1.

$$\frac{P_{\text{drop}}(s)}{U(s)} = e^{-Ts} \frac{K(\tau_3 s + 1)}{(\tau_3 s + 1)(\tau_2 s + 1) - \alpha(\tau_1 s + 1)}$$

($1$)

\[\begin{array}{c}
\text{delay} \\
\text{systemic circ.} \\
\text{effect site} \\
\text{pulmonary circ.}
\end{array}\]

\[\begin{array}{c}
u \\
e^{-T} \\
\frac{1}{\tau_1 s + 1} \\
\frac{1}{\tau_2 s + 1} \\
\frac{1}{\tau_3 s + 1} \\
K \\
P_{\text{drop}} \\
p_0 \\
w \\
y \\
y_{\text{meas}}
\end{array}\]

Notation: $u$ input signal (drug infusion rate); $T$ pure delay constant; $\tau_1, \tau_2, \tau_3$ time constants; $\alpha$ recirculation fraction; $K$ sensitivity (gain) parameter; $P_{\text{drop}}$ MAP drop owing to $u$; $p_0$ patient’s natural MAP in the absence of pharmacological intervention; $y$ output MAP; $w$ measurement noise; $y_{\text{meas}}$ actual measured MAP
The actual measured output signal $y_{\text{meas}}$, as shown in Fig. 1, is given by the combination of signal $y$ and noise $w$, which describes both beat-by-beat fluctuations in MAP and the errors associated with the acquisition and processing of the signal from the patient. Upon analysis (not shown here) of a number of MAP traces from intensive care patients obtained from the MIMIC II database [23], we have deemed white Gaussian noise with a standard deviation of 2 mmHg to be a suitable model for $w$. This choice is consistent with the assumptions of other authors [2, 9, 24].

A final remark concerns the use of continuous-time models and methods when MAP is a quantity that cannot be measured continuously and the determination of a meaningful sampling rate for the operation of the proposed control system. In order to operate with a realistic signal, we treat $y_{\text{meas}}$ as a discrete-time signal with a sampling time of 2 s. From a clinical implementation perspective this would mean obtaining MAP as a stepwise signal given by the average of arterial pressure (such as would be measured continuously by an intra-arterial catheter) over each heart beat, where a heart beat can be defined, for example, as the time between repeated features of an electrocardiogram recording or by another equivalent measure. Such a signal retains as much dynamic information about MAP as possible and is not monitoring equipment-specific. The time delay introduced by the required signal-processing operations (1 beat) is also negligible when compared with the system’s own large time delay. Since heart rate varies in patients, in order to work with a data stream with uniform step lengths we consider $y_{\text{meas}}$ as a downsampled version of the previously described signal according to a sampling rate $f_s = 0.5$Hz (thus implying that no loss of MAP information would occur as long as a patient exhibits a heart rate $\geq 30$ bpm). The dynamics of the patient response for frequencies in excess of $10^{-1}$Hz can be deemed negligible, therefore we consider $f_s$ to be fast enough to allow us to adopt continuous-time methods for controller synthesis.

3 Control architecture

In Fig. 2, we show the block diagram of the RMMAC architecture for this drug delivery application. In an MMAC system, it is assumed that the behaviour of the controlled plant (response of patient MAP to SNP) can be matched at any time by that of one of a series of candidate models included in a model bank. A suitable controller designed for the best-matching model is placed in the feedback loop, where it is expected to yield satisfactory performance. A common issue with multiple-model methods is the determination of the breadth of the uncertainty space which the models need to cover for and the number of models required to achieve this. An advantage of RMMAC is that the choice of the models to be included in the bank naturally follows from the controller design process. In RMMAC, controllers are designed for robust performance using $\mu$ synthesis; the operation of matching the real plant with the best candidate model involves the use Kalman filters and a probability estimator.

3.1 Controller design

3.1.1 Modelling for robust design: A comprehensive block diagram for the model is shown in Fig. 3. It includes a description of parametric uncertainty for the gain and toxicity imposes an upper limit for drug infusion rate at 3 ml/mg/min [2].

2.3 Control performance requirements

Closed-loop control of MAP should achieve:

- a settling time of 10 min or less;
- a maximum overshoot of 10 mmHg during transients, corresponding to approximately 10% of the signal range, as physiological MAP is normally between 70 and 110 mmHg;
- during steady-state operation, MAP should be contained within $\pm 5$ mmHg of the desired set-point value;
- under no circumstances should the system display resonant (persistent oscillatory) or unstable behaviour or cause MAP to drop below a pre-determined threshold level (danger threshold).

As the drug is administered intravenously, an infusion pump is in the loop. Actuator slew rate limitations therefore need to be considered in the design. Also, metabolic
Fig. 3 System model used for the robust controller design

Fig. 4 Upper bound (dashed) for the multiplicative modelling error (solid) introduced by treating delay as an unmodelled dynamic

recirculation parameters

\[ \alpha = 0.5 + 0.25\delta_1, \quad K_1 = K_{nom} + K_2\delta_2 \]
\[ \delta_1, \delta_2 \in \mathbb{R}, \quad |\delta_1| \leq 1, \quad |\delta_2| \leq 1 \]

following the assumptions that \( \alpha = (0.5 \pm 0.25) \) and \( K_1 = (K_{nom} \pm K_2) \) where \( K_{nom} \) is the nominal sensitivity value and \( K_2 \) is half the width of the uncertainty range.

Delay is treated as an unmodelled dynamic of the system. The worst-case delay is \( T = 50 \text{ s} \) and neglecting it would introduce a multiplicative modelling error of \( e^{-sT} - 1 \). This error can be bounded by the high-pass transfer function \( W_{um}(\omega) \) as shown in Fig. 4. The block surrounded by the dotted box in Fig. 3 has transfer function

\[ 1 + \Delta_{um} \cdot W_{um}, \quad \Delta_{um} \in \mathcal{H}_{\infty}, \quad \|\Delta_{um}\|_{\infty} \leq 1 \]

and is an effective representative of all possible patient delay dynamics for \( T \leq 50 \text{ s} \).

The structure of Fig. 3 represents the system description used for controller design. A signal called set-point disturbance (SPD) is added to the output of the plant and represents the possible variations in \( p_0 \) as discussed in Section 2. SPD is assumed to be a predominantly low-frequency signal and is generated using an arbitrary signal \( (w_{fi} : \|w_{fi}(\omega)\|_{\infty} \leq 1) \) filtered by a low-pass system with transfer function \( W_{spd}(\omega) \) (Table 1). This corresponds to admitting MAP fluctuations occurring at a maximum rate of approximately 10 mmHg/min, which we deemed a suitably large rate of change in the interest of model generality. The same filter is also used as a command prefilter for the reference signal \( (w_{2} : \|w_{2}(\omega)\|_{\infty} \leq 1) \), which is set by the clinician (we presume this will be a step-wise signal) and specifies the required MAP drop. While a prefilter may not be strictly necessary for this application in which reference changes are likely to be few and infrequent, we must define a frequency-domain bound for exogenous signals for the purpose of using \( \mu \) synthesis for controller design. The enforcement of such bound through a prefilter will ensure that the design assumptions are not violated in practice. The transfer function \( W_{spd}(\omega) \) is a suitable bound/prefilter for the reference since it has a steady-state gain of 32 dB and a range of \( \pm 40 \text{ mmHg} \) from baseline can be deemed sufficient to cover all possible setpoint requirements. Its pole location also corresponds to a settling time of less than 10 min, which complies with the performance requirements of Section 2.3 in terms of command following. We remark that there is no specific reason other than computational convenience behind our decision to use \( W_{spd} \) as both a disturbance colouring filter and a command prefilter. Measurement noise is modelled as a random Gaussian signal \( w_2 \) filtered by the high-pass filter \( W_{um} \) (Table 1).

Two weighting transfer functions are also included to reflect the performance requirements for the system. These are essential for controller synthesis as will be discussed in the next subsection. Weighting function \( W_p \) is the performance weight placed on the error signal \( (W_p : \|W_pY(\omega)\|_{\infty} \leq 1) \); it imposes a maximum error of 6 dB \( (\pm 2 \text{ mmHg}) \) at steady state and 22 dB \( (\pm 12.5 \text{ mmHg}) \) at higher frequencies. Weighting function \( W_u \) places constraints on the control signal \( (W_u : \|W_uU(\omega)\|_{\infty} \leq 1) \) in terms of maximum amplitude at low frequency \( (200 \text{ ml/h}, \text{ roughly equivalent to the toxicity threshold for a 65 kg patient}) \) and penalises high-frequency control dynamics.

<table>
<thead>
<tr>
<th>Table 1 Transfer function reference table</th>
<th>Block name</th>
<th>Transfer function</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( W_{spd} )</td>
<td>( \frac{40}{(12s^2 + 11s + 1)} )</td>
<td>SPD and reference filtering</td>
<td></td>
</tr>
<tr>
<td>( W_{um} )</td>
<td>( \frac{0.025s + 0.075}{(700s + 1)^2} )</td>
<td>measurement noise filter</td>
<td></td>
</tr>
<tr>
<td>( W_p )</td>
<td>( \frac{(2500s + 1.4)^2}{s} )</td>
<td>weighting TF (output signal)</td>
<td></td>
</tr>
<tr>
<td>( W_u )</td>
<td>( \frac{20s + 200}{800s + 1} )</td>
<td>weighting TF (control signal)</td>
<td></td>
</tr>
</tbody>
</table>
3.1.2 Controller design via $\mu$ synthesis: The new controllers were obtained using the technique of mixed-$\mu$ synthesis. Due to space limitations, $\mu$ synthesis will not be described in detail here and interested readers can refer to specialised texts such as [25]. For the scope of this paper it will be sufficient to explain that the structured singular value $\mu$—a commonly used tool in $\mathcal{H}_\infty$ optimal control—is defined as

$$\mu(M(j\omega)) = \sup_{\omega \in \mathbb{R}^+} \inf_{\delta(\omega)} \{ \| \delta(I - M\delta) \|_\infty : \det(I - M\delta) = 0 \}$$  \hspace{1cm} (2)$$

where $\delta$ indicates the maximum singular value and the $M$–$\Delta$ structure is a particular form of the interconnected system as shown in Fig. 5. In our particular setting

$$\Delta = \begin{bmatrix} \delta_1 & 0 & 0 & 0 \\ 0 & \delta_2 & 0 & 0 \\ 0 & 0 & \Delta_m & 0 \\ 0 & 0 & 0 & \Delta_p \end{bmatrix}, \quad \text{where} \quad \{ \Delta_p, \Delta_m \} \subseteq \mathbb{C}^{3 \times 2} \quad \| \Delta_p \|_\infty \leq 1, \| \Delta_m \|_\infty \leq 1$$

In plain language, $\mu$ represents the inverse of the minimum increase in plant uncertainty which would result in the system being unable to meet the required specifications with a particular controller $C$ in the loop. A result derived from the small gain theorem states that the system is capable of providing robust performance if $\mu \leq 1$ [26].

The $\mu$ synthesis approach to controller design involves an iterative search, among the set of stabilising controllers $C$, to identify the controller which achieves the largest robustness margin, that is, the smallest value of $\mu$.

$$\inf_{C \in \mathcal{L}^\circ} \sup_{\omega \in \mathbb{R}^+} \mu(M(j\omega))$$  \hspace{1cm} (3)$$

Software tools for $\mu$ synthesis are available as part of the Matlab Robust Control Toolbox. Mixed-$\mu$ synthesis, which we use, is an extension of the $\mu$ synthesis algorithm, which can account for the fact that the uncertainty space of some of the parameters is real and not complex. This reduces, to some extent, the conservativeness of the resulting controller design.

3.1.3 Controller design results: The $\mu$ synthesis method can be used in an iterative fashion in order to establish how many robust controllers are actually required in order to meet the specifications of the control problem. Following the approach of [20], we programmed an iterative Matlab algorithm to determine the maximum achievable performance of the system as a function of the range of plant uncertainty considered. Achievable performance is rated according to a scalar parameter $A_p$, which multiplies the performance weight, that is, $W_p = A_p \cdot W_e$. The algorithm operates as follows:

1. Set $A_p = 1$;
2. Set up the interconnected system of Fig. 3, include the required range of uncertainty and use $W_p$ as the performance weight on the error signal;
3. Run the mixed-$\mu$ synthesis tool on the system generated at step 2;
4. If the value of $\mu$ is just below unity ($0.985 \leq \mu \leq 1$), $A_p$ is deemed to represent the maximum achievable performance and the controller synthesised at step 3 can ensure that performance level is met, otherwise, $A_p$ is increased or decreased as required and another iteration (starting at step 2) takes place.

As the performance weights $W_p$ and $W_e$ represent the required minimum performance for the system, a final value of $A_p \geq 1$ means that a controller exists such that the system can exceed the requirements, whereas $A_p < 1$ indicates that $\mu$ synthesis cannot produce a suitable controller to meet the required performance over the considered uncertainty set.

All runs of the algorithm included the full complex uncertainty introduced by delay and the full range of real parametric uncertainty associated with the recirculation constant $\alpha$, while a variety of subsets of the uncertainty set of $K$ were considered. This was done to obtain comparable results with multiple-model approaches in the literature such as [2, 8], where $K$ is considered to be the only varying parameter.

Fig. 6 shows the three fundamental design cases that we used to evaluate a trade-off between the number of controllers and the maximum achievable $A_p$, as a function of the breadth of the uncertainty subset of $K$ considered:

- A global non-adaptive robust controller (GNARC), that is, a controller able to provide robust performance over the full uncertainty range of $K$. The maximum $A_p$ achieved was 0.026, indicating that a single-controller architecture would not meet the requirements of this problem.
- Fixed non-adaptive robust controllers (FNARCs), that is, multiple controllers (ideally, infinitely many), each designed to maximise performance for a point value of $K$ (no uncertainty on $K$). The results of this design case are representative of the maximum achievable performance with a multiple-controller system. It is clear from the graph in Fig. 6 that such an ideal system would be able to meet and even significantly exceed the required level of performance, more notably so in the high-$K$ region of the uncertainty range.
- Local non-adaptive robust controllers (LNARCs), that is, controllers capable of providing satisfactory performance over non-infinite subsets of the uncertainty space of $K$. This design case represents the “middle ground” between the GNARC and the FNARCs. A controller design covering a larger uncertainty subset will result in a system with inferior performance. It is up to the designer, therefore, to strike a suitable compromise between controller bank complexity (number of controllers) and system performance (maximum $A_p$). In the results shown, we defined suitable
performance as either $A_p = 1$ (the minimum required) or 60% of the minimum FNARC over the corresponding uncertainty subset, whichever the greatest. Five controllers were required to cover the whole uncertainty range of $K$.

### 3.2 Patient-model matching and controller selection

The actual behaviour of the system is matched to that of one of a number of candidate models using a bank of Kalman filters and a posterior probability estimator (Fig. 2). Each Kalman filter uses information from the input signal $u(t)$ and measured output $y(t)$ to generate a one-step-ahead estimate of the state $\hat{x}(t+1)$ and corresponding output $\hat{y}(t+1)$ on the basis of the $i$th candidate model ($i \in \{1, 2, \ldots, N\}$) through a predict-update cycle as shown below:

**Predict cycle**

\[
\begin{align*}
\hat{x}_i(t+1|t) &= A_i\hat{x}_i(t) + B_iu(t) \\
\hat{y}_i(t+1|t) &= C_i\hat{x}_i(t+1|t) 
\end{align*}
\]

**Update cycle**

\[
\begin{align*}
r_i(t+1) &= y(t+1) - \hat{y}(t+1|t) \\
\hat{x}(t+1|t+1) &= \hat{x}_i(t+1|t) + Kr_i(t+1)
\end{align*}
\]

where the notation $\hat{a}(t+1|t)$ indicates the estimate of signal $a$ at time $t+1$ using information available up until time $t$; $r_i$ is the residual signal given by the difference between the estimate and the actual observed output; $A_i$, $B_i$, and $C_i$ are the state-space matrices describing the $i$th candidate model; $K$ is the Kalman filter innovation gain. In order to reproduce the approach of [20], a steady-state formulation for the Kalman filter was used for the purposes of the work described here. This means that $K$ was determined a priori on the basis of knowledge of the variance of the Gaussian components of SPD and measurement noise ($w_1$ and $w_2$, respectively, in Fig. 3).

The Kalman filtering approach requires that the system be linear-Gaussian. The description provided in Section 2 shows that this assumption is violated here. For now, we assume that non-Gaussian signal components can be taken to be either zero-mean signals of lower magnitude than the Gaussian components (which can, therefore, be dealt with reasonably by increasing the anticipated value for noise variance for the purpose of filter design) or non-zero-mean signals slower than the system’s dynamics (which can, therefore, be dealt with through the Kalman filter’s inherent adaptive capability). Simulations provided in [27] show that RMMAC can deal with some degree of non-Gaussianity under these conditions. Clearly, these assumptions could have implications in terms of the method’s clinical applicability and will be discussed further in section 6. A further issue lies with the presence of an unknown, yet potentially large delay term $T$, which Kalman filtering cannot take into account. A workaround for this problem...
was developed by adding redundancy to the estimation bank. The Kalman filter design was carried out on the basis of the linear part of the system alone to generate five filters (one for each robust controller range). The bank was then duplicated five times, with different amounts of delay (10, 20, 30, 40 and 50 s) being applied to the drug infusion signal $u$ entering each of the duplicate banks (see Fig. 7).

The 25 residual signals are then used in the following recursive posterior probability estimation

$$P_j(t + 1) = \frac{1}{N} \left( e^{-\frac{1}{2} r_j(t + 1) S_j^{-1} r_j(t + 1)} \right) P_j(t)$$

where $N = 25$ is the total number of Kalman filters; $r_j(t)$ is the difference (residual) between the measured output $y$ and the $j$th filter estimate $\hat{y}_j$; $S_j$ is the steady state residual covariance matrix of $r_j(t)$; $\beta_j = (1/(2\pi)^n/\sqrt{det S_j})$ is a constant scaling factor, and $P_j(t)$ is the probability that model $j$ is the model which best represents the patient behaviour at time $t$. This formulation is the same as adopted in [20].

On the basis of $P_j$, a switching signal $\sigma(t)$ for controller selection is generated

$$\sigma(t) = \sum_{k=1}^{N_C} a_k \sigma_k(t)$$

where $N_f = 5$ is the number of delay cases considered, $N_C$ is the number of controllers and $k = 1, \ldots, N_C$. Finally, the control signal $u(t)$ is given by

$$u(t) = \sum_{k=1}^{N_C} a_k \sigma_k(t) u_k(t)$$

where $u_k(t)$ is the control signal generated by controller $k$ in the controller bank.

4 Numerical simulations

The RMMAC system described in Section 3 has been implemented in MATLAB and Simulink and tested in a number of computational simulations. Some results have been presented in a previous publication [28]. We present here two illustrative situations. The first case is one in which the pressure of a hypertensive but otherwise steady patient (fixed parameters and small-magnitude random fluctuations in $p_0$) is to be regulated over a period of several hours according to a step-wise reference signal. This is representative of a typical postoperative situation where successful automatic closed-loop administration of SNP has been achieved in the past. The second simulation represents a much more challenging case. The proposed system is set to follow the same step-wise regulation as in the first case in the presence of larger random baseline pressure variations combined with an upward DC change in $p_0$ (e.g. representing a very unstable patient with a worsening hypertensive state), and substantial changes in the delay and sensitivity parameters over time. While $K$ and $T$ are set to vary in a sinusoidal pattern in this example (for computational convenience), it should be clarified that the nature of the $\mu$ synthesis design is such that robust performance should be expected regardless of the shape of parameter variation as long as the correct controller for the region being traversed by the changing parameter is placed in the loop. In this regard, the challenge to the system lies in whether the probability estimator of Section 3.2 can successfully track $K$ – the key parameter for model selection – as it quadruples its value over 1 h, thus achieving the maximum expected rate of change as mentioned in Section 2.1. For the time-varying case, we ease the performance specifications and require an acceptable MAP error range of ±10 mmHg instead of ±5 mmHg as the system can be deemed to be in a transient throughout the experiment. The simulation conditions for the two cases are summarised in Fig. 8, together with the relevant results.

As well as RMMAC, two other control architectures taken from the literature were simulated under the same conditions. These were:

- A combined PD controller and self-tuning regulator which uses least-squares to estimate the response to SNP as an ARMAX model and implements a minimum variance control law (as in [6]) with infusion constraints (as in [7]) and an additional on-line dead time detection method (as in [5]) to cater for variable system delays. Although a detailed description of the IVAC Titrator device is not available in the literature, this architecture was deemed similar--notwithstanding any supervisory algorithms--to that used in the Titrator approach on the basis of available publications [16, 29].
- The MMAC architecture of [8], which employs seven candidate models selected with a prediction error method, seven PI controllers, and a bank of Smith’s predictors for delay compensation. This was chosen as an example of an earlier multiple-model method in the literature.

5 Results

The results of the first set of simulations (Fig. 8 – left) show that under steady conditions all three systems are capable of maintaining the patient stable and achieve the desired pressure drop while meeting the tracking performance requirements. These results are very similar to simulation results published by other authors [2, 7, 8], and indeed to the traces exhibited by postoperative patients during in vivo experiments [22].

However, a noticeable difference in performance between the systems can be seen in the second case (Fig. 8 – right), with the Titrator and MMAC approaches bursting into undesirable oscillations. The three bottom sets of graphs in Fig. 8 provide more information on the reasons underpinning failure of the non-RMMAC comparison systems. In the case of the MMAC system, while in the steady experiment convergence to the correct model (model 4 in this case) is good, an increased level of noise does force some occasional unnecessary controller switchings. The main issue for this approach is that output predictions on the basis of which the candidate models (and controllers) are compared relies on the value of $p_0$ measured at time $t = 0$ and assumed fixed. As a result, when $p_0$ is raised further the apparent sensitivity of the patient becomes
lower (increased infusion for an apparently unchanged required drop) and the accidental – albeit short-lived – switching of an incorrect, more aggressive controller (controller 2 in this case) is enough to cause undesirable hypotensive peaks. The self-tuning regulator faces a similar problem as can be seen by the result of the recursive parameter estimation (we extrapolated the DC gain for the estimated system, and show a comparison with the true value of $K$). While in the steady case the parameter estimate converges to the correct value, in the more disturbed experiment the sensitivity is underestimated, once again causing the system to burst into oscillations. Both non-RMMAC systems are able to resume effective control following these transient effects. However, the hypotensive peaks are a clear example of potentially dangerous dynamics which a safe system should ensure are avoided.

Fig. 8 Results of simulations
From the top: baseline MAP $p_0$ and required setpoint; controlled MAP for the MMAC, Titrator and RMMAC approaches; parameters $K$ and $T$ over time; probability results for matching models in MMAC; estimate of patient gain against real gain in the Titrator approach; probability results for matching models in RMMAC. The dotted lines in the controlled MAP traces indicate the allowed error range. The numbers in the model probability graphs indicate the model with the highest likelihood. (left) Settled patient, allowed tracking error $\pm 5 \text{mmHg}$. (right) Patient with time-varying parameters, allowed tracking error $\pm 10 \text{mmHg}$; the black arrows highlight instances of undesirable transient oscillations or issues with online estimation as discussed in the text.
In contrast, RMMAC remains within the prescribed $\pm \, 10\, \text{mmHg}$ error range, and the model probability graphs show that our approach retains the ability to correctly track the variations of $\kappa$ even under challenging circumstances.

6 Discussion and future work

This work presents a detailed description of the control design methodology for a new, RMMAC-based architecture for automated control of SNP infusion in acute hypertensive patients, together with two sets of results illustrative of the potential of the new approach in overcoming the limitations of past adaptive control solutions.

Our analysis of past approaches suggests that they can be deemed reasonably safe in patients whose underlying MAP can be considered as almost stationary, such as may be expected in recovering postoperative patients. However, we advocate caution about undesirable behaviour which may occur under more challenging conditions as shown in our simulations. The presence of potentially non-zero-mean output disturbances is a particularly critical issue in this system. A control approach which (incorrectly) assumes the mean of $p_0$ to be constant may fail to distinguish between a change in patient sensitivity and a change in the DC component of $p_0$ and, as a result enact inappropriate control action thus rendering the closed-loop system unsafe. While it can be argued that the presence of transient oscillations would provide additional system excitation and facilitate the correct identification of the sensitivity parameter, because of the long dead times involved in this application transient instability may be dangerous. In light of these findings, we suggest that this lack of generality, although previously unreported in the literature, may have impacted on considerations about costs and perceived benefits of automated drug delivery technology and ultimately affected its uptake in the clinical setting to date.

The new RMMAC-based approach has delivered promising results, which support the feasibility of automatic SNP administration even in time-varying, highly disturbed conditions (e.g. as may be encountered in an intraoperative setting). As well as achieving stability and performance in simulations, we have shown that the RMMAC methodology offers a systematic process to incorporate knowledge of the model uncertainty into the design process. This a favourable characteristic in this field of application as pharmacological models are derived from population studies and therefore are inherently characterised by parametric uncertainty.

The use of an iterative $\mu$-synthesis approach to controller design, in particular, has allowed us to mathematically demonstrate that the required performance could not be attained over the expected range of parametric uncertainty using a single linear controller, thus conclusively recognising the necessity to employ adaptive control. In a multi-controller architecture, we defined a trade-off between the number of controllers and maximum achievable performance and we were able to cater for a broader range of modelling uncertainty than considered by previous authors using a lower number of controllers (5 against 7 used in [8] and 8 used in [2]).

With $\mu$-synthesis giving mathematical certainty of robust stability (and performance) of the interconnected system between each possible set of patient parameters and its matching controller, we have clearly exposed that the overall stability (and therefore ultimate safety) of the closed-loop system rests on reliable system identification, that is, in the ability of the system to track the patient’s parameters so that the correct controller can be placed in the loop at all times. This is a general issue in adaptive control and we have shown a simulation example of how a combination of time-varying parameters and non-zero mean disturbances may lead to incorrect system identification and consequently to inappropriate control action. Without resorting to additional layers of supervisory algorithms, RMMAC has displayed good performance and avoided periods of transient instability. This is largely because of the use of the redundant bank of Kalman filters of Fig. 7, which is able to because of deliver more accurate system estimation results than previous approaches. As we have already acknowledged, however, Kalman filtering is not the estimation tool of choice in the presence of time delays and non-Gaussian signals. Indeed, convergence of (6) to the correct model can only be mathematically guaranteed in an ideal environment with Gaussian-only input signals [27], which is clearly not the case here. Owing to the violation of this assumption, the RMMAC system presented cannot be deemed ‘robust’ in a strict control engineering sense. Improved performance and avoidance of transient instability over previous approaches can only be evaluated – and have been shown – heuristically through the results of simulations. While the main focus of this paper has been to set out the methodology for this approach, future work will report on the results of a broad simulation campaign which will consider a wide variety of cases and parameter variations. We also intend to investigate whether the approach may be further refined by utilising alternative system estimation techniques which are more suited to a non-Gaussian and possibly non-linear problems (e.g. particle filtering [30]).

Since this work deals with the control of patient haemodynamics, a further point for discussion is that in standard mechanistic models of circulation [31] MAP is controlled by both CO and vascular resistance and that while SNP acts on vascular resistance, it does not directly affect CO. A key question, therefore, concerns whether regulation of MAP alone is a sufficient condition to ensure patient safety. Indeed, joint control of MAP and CO has been recently proposed in [32]. Further discussions with clinicians will be required to evaluate whether there are clinical risks associated with MAP-only control (also using a single vasoactive drug) and whether multivariable control may be preferable. It should be noted, however, that in current clinical practice continuous monitoring of CO is characterised by calibration issues and low measurement accuracy [33]. As a result, the haemodynamic stability of patients is first and foremost managed by targeting MAP [1], particularly in the case of hypertension. In light of this, our work has focussed on MAP alone. Nonetheless, provided that pharmacological models for drug action and drug interactions are available, the same approach presented here could be extended, with minor complications, to handle a multi-drug, multi-signal (multiple-input, multiple-output) case.

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8 References

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