

Multiple Model Predictive Control of Hemodynamic Variables: An Experimental Study

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Abstract—A multiple model predictive controller is designed to regulate mean arterial pressure and cardiac output in critical care subjects using inotropic and vasoactive drugs. The algorithm uses a multiple model adaptive approach in a model predictive control framework to account for inter- and intra-patient variability and explicitly handle drug rate constraints. The controller is experimentally evaluated on canines that are pharmacologically altered to exhibit symptoms of hypertension and depressed cardiac output.

I. INTRODUCTION

Critical care patients such as those in intensive care or undergoing surgery require close monitoring of hemodynamic variables. Physicians maintain patient states within acceptable operating ranges by infusing several drugs and/or intravenous fluids. For example, sodium nitroprusside (SNP) and phenylephrine (PNP) are used in regulation of mean arterial pressure (MAP) and dopamine and intravenous fluids are used for increasing cardiac output (CO). In addition, they may be required to administer anesthetics and monitor the depth of anesthesia (DOA) during surgical procedures. It is desirable to have an automated system that closes the loop on primary variables, but monitors secondary variables and performs diagnostics. This allows the physician to spend more time monitoring the patient for conditions that are not easily measured, and assures that the physician is always “in the loop”.

The vast amount of research on blood pressure control was initiated by Slate et al. [1] who used a PID controller with empirical tuning rules to control MAP using SNP. Since then, more complex control schemes have been used in automation of hemodynamic regulation. Isaka and Sebald [2] provide a comprehensive review of the single-input single-output (SISO) system. Martin et al. [3] and Kwok et al. [4] have reported the use of adaptive control methodologies for blood pressure regulation during surgery. There has also been a significant research effort in the simultaneous regulation of MAP and CO. Serna et al. [5] reported on the simultaneous control of CO and MAP using DPM and SNP. As the CO measurements were available at a rate much slower than MAP, they essentially decoupled the DPM-CO loop from the MAP-SNP loop. One of the more advanced studies in the two-input two-output system was done by Voss et al. [6] on canines. They used the Control Advance Moving Average Controller (CAMAC) which is a class of extended horizon controllers, with a recursive least squares estimate of model parameters. The advantages to this controller are its robustness and ability to handle systems with varying and unknown dead times. Yu et al. [7] used a multiple model adaptive control approach (MMAC) for regulating MAP and CO in canine experiments. Held and Roy [8] developed an expert system that

used a fuzzy controller for controlling MAP and CO using SNP and DPM.

Model based predictive control, which can be implemented quite naturally on constrained multivariable systems, has also been considered for drug delivery (Gopinath et al. [9], Rao et al. [10]). An important issue in the design of drug infusion systems is the need to impose bounds on dosages and infusion rates to avoid overdosing or drug toxicity. For example, sodium nitroprusside (SNP) used in reducing hypertension should be infused less than $10 \mu\text{g kg}^{-1} \text{min}^{-1}$. Alternatively, the physician may want to specify an operating range of the mean arterial pressure instead of a specific setpoint. While most control strategies discussed thus far handle such constraints in an ad hoc manner, the primary advantage to MPC is its ability to handle constraints explicitly. Its optimization-based framework allows computation of the optimal infusion rates subject to input and output constraints.

While adaptive control strategies rely on using a nominal model with on-line adaptation, model predictive approaches depend on the accuracy and availability of a model capable of predicting the patient responses. In all the studies cited above, it is very important to note that the motivation to develop advanced strategies is due to the multi-variable, nonlinear behavior of physiological systems. The inherent difficulty arises in the choice of a model, its structure and the associated parameter identification for design and validation of the control system on real subjects.

In this work we present a novel approach combining the MPC and MMAC strategies for regulation of hemodynamic variables. A multiple model strategy is used to provide a prediction model for an MPC framework. This approach has the combined advantage of allowing model adaptation to handle inter- and intra-patient variability and the ability to handle explicit input and output constraint specifications often desired by the critical care physicians. The controller was demonstrated in experiments on three canines that were pharmacologically altered to exhibit hypertension and depressed cardiac states.

II. MODEL PREDICTIVE CONTROL

Model predictive control is an optimization-based approach that has been successfully applied to a wide variety of control problems. The basic mechanism is to select a sequence of future M control moves to minimize an objective function (usually sum of squares of predicted errors) over a prediction horizon of P sample times. Although a horizon of M control moves is calculated, only the first move is implemented, correction for plant-model mismatch is made, and the optimization is performed again.

The input-output representation of MPC is based on finite step response (FSR) or the finite impulse response (FIR) convolution

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model. This is a non-parametric representation of the process and is simply the open-loop response to a unit step or unit impulse input. The output prediction based on the impulse convolution model and the history of manipulated variable values u at the k^{th} sampling instant is given by

$$\hat{y}_k = \sum_{i=1}^N H_i u_{k-i} \quad (1)$$

where H_i is the i^{th} impulse response coefficient matrix. N is the number of terms in the model, usually chosen to correspond to the settling time of the model.

A general form of the optimization problem at time step k is

$$\min_{u(k) \dots u(k+M-1)} \sum_{i=k}^{k+P} e_i^T Q e_i + \sum_{i=k}^{k+M} \Delta u_i^T R \Delta u_i$$

subject to:

$$\begin{aligned} u_{\min} &\leq u_i \leq u_{\max} \\ u_{i-1} - \Delta u_{\max} &= u_i = u_{i-1} + \Delta u_{\max} \\ u_i &= u_{k+M-1} \text{ for all } i > k + M - 1 \end{aligned} \quad (2)$$

where at step i , e_i is a vector of model predicted errors ($e_i = r_i - \hat{y}_i^c$) r_i is the setpoint, \hat{y}_i^c is the vector of corrected model predictions that accounts for model mismatch, u_i is the vector of manipulated variables and Q and R are the output and input weighting matrices. Absolute and velocity constraints on the manipulated variable are included. We use the standard constant additive disturbance assumption to correct for model error for all future time steps.

III. MULTIPLE MODEL PREDICTIVE CONTROL

Conventional MMAC approach [11], uses a bank of models to capture the possible input-output behavior of patient responses to drug dosages. The control parallel is to use a bank of controllers, to achieve a desired closed-loop performance from a wide variety of possible patients; controller k is designed and tuned based on model k from the model bank. Using a Bayesian approach, the probability of each model representing the patient response is computed and the resultant control action is the probability-weighted average of control moves of each controller. The model probabilities get altered as the drug sensitivities change in inter/intra patient variations. The primary advantage to this approach is that no *a priori* model identification is necessary during initial stages of drug administration.

Although the approach is sub-optimal it allows flexibility to handle a system with large variability such as drug infusion where designing a single nonlinear model is not practical or possible. The emphasis is more on robustness than on performance. However explicit handling of constraints using MPC for each model is computationally unwieldy for a large model bank. To preserve a multiple model approach that explicitly handles constraints, we use a single constrained MPC controller with a weighted model bank for response predictions, as shown in fig.1. A probability-weighted average of output predictions from a bank of models is used in a MPC framework to calculate drug infusion rates for regulation of mean arterial pressure and cardiac output. This approach has the combined advantage of model adaptation according to patient variations and the ability to handle explicit input and output constraint specifications often desired by critical care physicians.

The advantage to multiple-model predictive control (MMPC) is that a large number of models can be used and constraints explicitly handled. The issues for MMPC are similar to standard MMAC - determining the choice and number of models to encompass the plant behavior. This may require detuning of MMPC so that it is sufficiently robust in the possible range of prediction models stemming from the model bank.

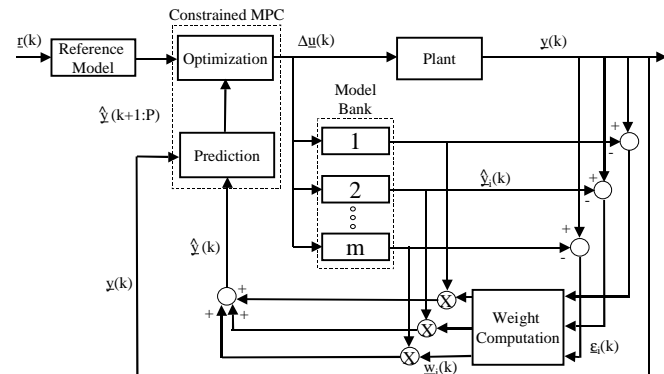


Fig.1. Schematic of the MMPC strategy.

We used the recursive Bayes theorem for the weighting scheme. The theorem calculates the conditional probability of the i^{th} model in the bank being the true model of the plant given this population of models. The probabilities are assumed to be stochastic in nature and Gaussian and thus take a form of the exponential of the negative square of the residuals. The recursive Bayes theorem for the k^{th} step and i^{th} model is

$$P_{i,k} = \frac{\exp\left(-\frac{1}{2} \varepsilon_{i,k}^T K \varepsilon_{i,k}\right) P_{i,k-1}}{\sum_{j=1}^N \exp\left(-\frac{1}{2} \varepsilon_{j,k}^T K \varepsilon_{j,k}\right) P_{j,k-1}} \quad (3)$$

where ε is the model residual at the current step. The algorithm is computationally inexpensive and insures that probabilities are bounded between 0 and 1. Large values in the convergence matrix, K , will magnify the residuals and cause a speed-up of model reduction to a single model. Unfortunately Bayesian weighting is not conducive to blending with the only steady state probabilities being either 0 or 1. To keep models alive in the bank an artificial cutoff, δ , is used. For $p < \delta$, the probability is reset to $p = \delta$ and not allowed to go to 0. These models are then excluded from being weighted such that

$$\begin{aligned} W_{i,k} &= \frac{P_{i,k}}{\sum_{j=1}^N P_{j,k}} \quad \text{for } P_{i,k} > \delta \\ W_{i,k} &= 0 \quad \text{for } P_{i,k} = \delta \end{aligned} \quad (4)$$

To design the bank of models we used a combinatorial approach where we designed SISO banks and then combined them to make a MIMO bank. The reason for this was simply due to the difficulty in designing appropriate MIMO models for the drug infusion problem. The key assumption is that given bounded SISO models for both static gains and dynamics then the MIMO interactions will be

bounded as well. By MIMO interactions, we mean that the SISO input-output relations are modified due to the effects of other drugs/inputs as the case is in multivariable systems. As long as the bank of SISO models bounds the entire possible range of input-output behavior, the combined MIMO model bank will be able to adequately describe the process behavior. The drawback to this approach is that the number of model combinations increases geometrically. The objective is to form a moving average which becomes our prediction model. This differs from most uses of standard MMAC where the general assumption is that a model in the bank actually matches the plant at some phase of the process. The winner takes all strategy prevails and Bayes recursive algorithm is used more for switching purposes than for blending. MMPC can still be used in this manner. However, based on our experience during the canine experiments, it is unlikely that our model bank will have any one model that is actually equivalent to the drug infusion process. In fact all our best controlled runs were when no model dominated and the worst runs were when an outlying model was locked onto since the bank of models did not bound the plant properly.

For a highly variable system where model design is very difficult we chose basic models of first and second order plus time delay for our SISO banks. Global features of the plant such as static gains, time constants and time delays can be readily evaluated from step responses for each drug. The difficulty in creating the SISO banks is the sparsity of data available in the literature not only for static gains but also for the pharmacodynamics of the drugs. Therefore estimating time delays and time constants for the possible range of canine responses is difficult. Creating model banks is still a work in progress requiring more experimentation with canines.

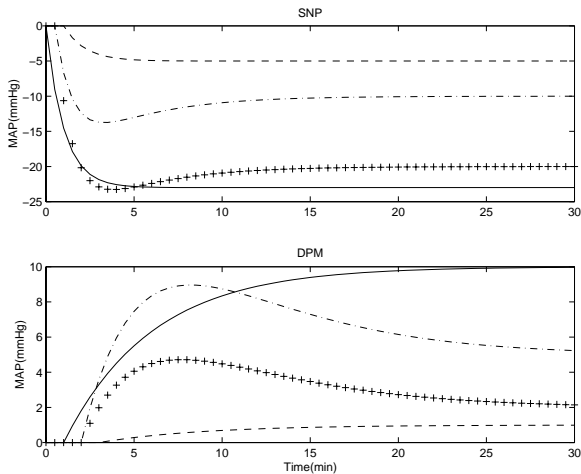


Fig.2. Step response plots for unit inputs of SNP and DPM vs. MAP to indicate the bounds on the SISO model banks.

As we gathered more data during the experiments we refined our model banks. The model banks presented here are the final form. Each SISO bank had 8 first order plus dead time (FOPDT) models and 2 second order plus dead time (SOPDT) models. The first order models were split into two groups, one with a nominal time constant and time delay and another set with longer time constants and time delay. Each set of FOPDT models has 4 different gains. The upper and lower bounds of dynamics that the model bank spanned is shown as step response plots in figures 2 and 3. The FOPDT bounds are made up of the shortest time constant/delay with largest gain and the longest time constant/delay with smallest gain. Only SNP vs. CO is significantly different than the FOPDT descriptions. The

combined SISO banks form the MIMO bank that is then weighted via the recursive Bayes theorem to form the prediction model for the constrained MPC.

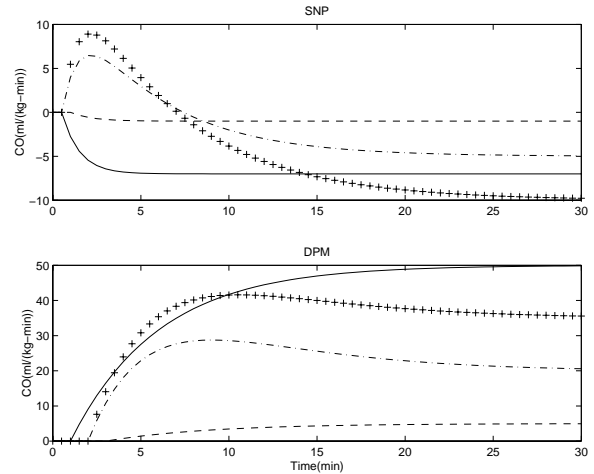


Fig.3. Step response plots for unit inputs of SNP and DPM vs. CO to indicate the bounds on the SISO model banks.

The overall control objective is to maintain two hemodynamic variables, mean arterial pressure (MAP) and cardiac output (CO), at desired setpoints by automated infusion of inotropic and vasoactive drugs. SNP is administered for arterial vasodilation. Dopamine (DPM) is used as an inotrope to enhance cardiac performance; Phenylephrine (PNP) is used for arterial vaso-constriction. The controller was initially evaluated and tuned in closed-loop simulations using an elaborate non-linear canine circulatory model [12] as the “patient” before moving to the experimental phase.

III. EXPERIMENTAL SETUP

The controller was evaluated on three mongrel dogs under IACUC approved protocol. The experiments were performed on six experimental days with 3 to 5 runs each day. Following induction of a surgical plane of anesthesia, the animal was intubated and mechanically ventilated (Siemens-Elena 900C Servo-Ventilator) with isoflurane or halothane anesthesia. An arterial line was placed in the femoral artery to provide continuous arterial pressure tracings on a Mennen Horizon monitor. A Swan-Ganz catheter (Baxter Edwards Swan Ganz Intellicath CCO/VIP Thermodilition), connected to a Baxter Vigilance monitor, was introduced in the pulmonary arterial tree to provide continuous cardiac output measurement. Control calculations were performed on a Dell Pentium II PC running a custom built Windows-based GUI. The pressure and flow measurements were received from the monitors through RS-232 ports. The control loop was closed with rotary infusion pumps (Critikon Simplicity 2100A) modified to accept digital inputs via a digital output card. The sampling time for the controller was set at 30 seconds. The closed-loop control results for two experimental runs are presented in the next section.

IV. RESULTS

The responses to the drugs administered varied greatly depending on the anesthetic used as well as the canine that received the drugs. Isoflurane lowers systemic vascular resistance yet the contractility of the heart and the baroreceptor reflex remain relatively strong. With isoflurane, the MAP setpoint chosen will determine the baroreceptor

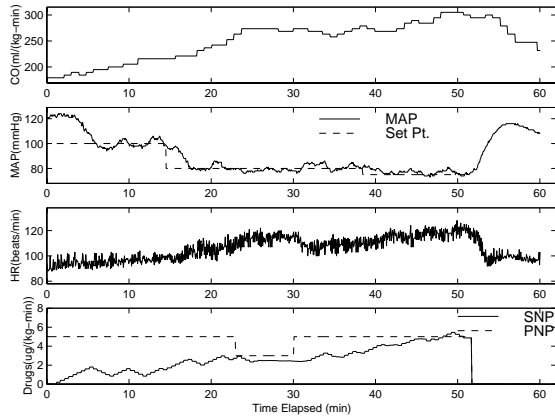


Fig. 4. Case 1: MAP control of hypertensive canine under isoflurane using sodium nitroprusside (SNP). Phenylephrine (PNP) used to induce hypertension.

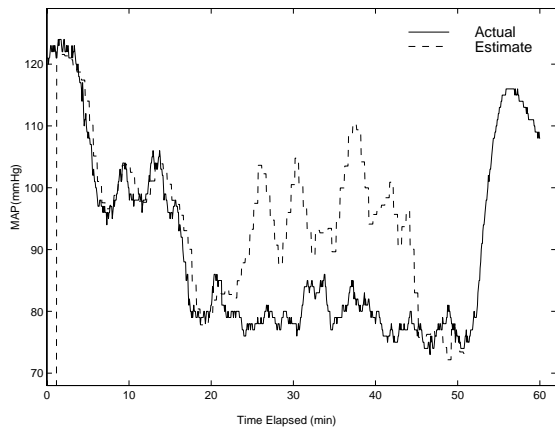


Fig 5. Case 1: Model bank estimation versus the actual MAP output. Although PNP disturbance at $t=23.6$ min causes poor estimation to occur for next 20 min. control remains very good.

response either towards the setpoint or against it strongly perturbing the drug effects on the canine. For halothane with 50% nitrous oxide, systemic vascular resistance, baroreceptor reflex and the heart's contractility are all compromised. Because halothane depresses CO values the pharmacodynamics are very slow, having time delays and time constants in some experiments more than double the values on the same canine under isoflurane.

Case 1: SISO SNP vs. MAP

For MAP control, the experimental results were very good with typical setpoint tracking of ± 10 mm Hg and settling times of under 10 to 15 minutes. Figures 4 and 5 are for a 19 kg female canine under isoflurane. It was the first experimental day using the MMPC approach. The SISO bank for SNP vs. MAP was an ad hoc selection of 22 first order and second order models without time delays based for the most part on our work with the nonlinear model simulations [10]. Fig. 4 illustrates the fairly tight control of MAP. Again our experience has been that as long as the model banks bound the plant there will be decent control performance. Phenylephrine is infused to mimic a hypertensive patient. Sodium nitroprusside is the controlled input to lower MAP. MAP setpoints are maintained within ± 5 mm Hg with settling times of less than 7

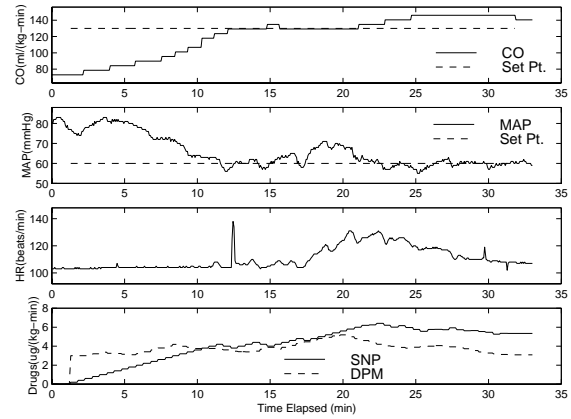


Fig. 6. Case 2: MAP and CO control of depressed CO canine under halothane. Dopamine (DPM) and sodium nitroprusside (SNP) are controlled inputs.

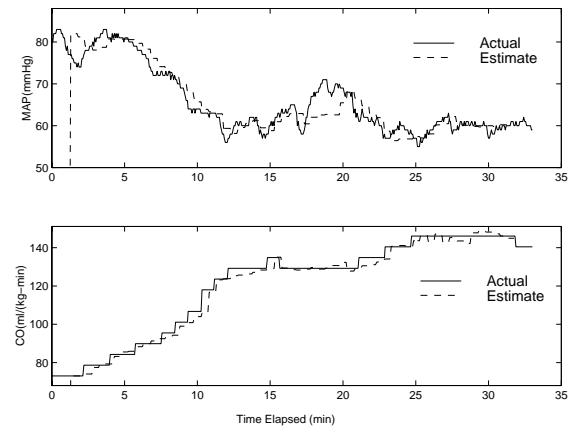


Fig. 7. Case 2: Model bank estimation of MAP and CO versus actual outputs.

minutes after each setpoint change. The controller also rejects well the disturbance of lowering phenylephrine from 5 to $3 \mu\text{g kg}^{-1} \text{min}^{-1}$. CO and heart rate (HR) both increase throughout as the baroreceptor reflex fights to increase MAP above the setpoints chosen of 80 mm Hg and 75 mm Hg. This is clearly seen as well by the large up shoot in MAP after control ceases at $t=51$ min. The controller settings were $M=3$, $P=35$, $N=40$, $ywt=2$, and $uw=0$. SNP was constrained from 0 to $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ with the rate of infusion constrained to a maximum of $0.2 \mu\text{g kg}^{-1} \text{min}^{-1}$ per control move. Bayesian settings were a convergence factor of 0.05 and $\delta = 0.01$. Fig. 5 presents a comparison of actual MAP vs. the estimate from the weighted model bank. The estimate does well until the PNP disturbance is introduced. Although it takes 20 min. for the estimates to be worthwhile again the control response and performance is still very good. The model mismatch is accounted by the additive disturbance term in the MPC formulation. A similar formulation for obtaining weighted model is likely to reduce the estimate error more quickly.

Case 2: MIMO SNP & DPM vs. MAP & CO

Controlling MAP and CO is a much more difficult problem. The two hemodynamic variables are highly correlated and interdependent. Choosing a realizable setpoint for CO such that

dopamine can be kept in its inotropic infusion range of 2 to 7 $\mu\text{g kg}^{-1} \text{min}^{-1}$ is not trivial. CO response to dopamine can be roughly modeled as a first order system plus time delay. After Infusing halothane at levels to mimic congestive heart failure, canine responses to dopamine had time delays of 2-3 minutes and a time constant of 6-8 minutes. Therefore any overshoot in CO due to dopamine takes a long time to settle down. It is critical that not only gains, but also time constants and delays be well estimated, since any model mismatch in dopamine will result in poor CO control. In Figure 6, MAP and CO are controlled on a male 17.8 kg canine under halothane with the infusion of dopamine and sodium nitroprusside. Both reach setpoint in 12 minutes. MAP stays within +/- 10 mm Hg throughout the run. CO stays on or near the setpoint for 10 minutes until the canine responded to the slight overshoot in dopamine. It takes over 5 minutes for the overshoot in CO to start returning towards the setpoint. The overshoot in CO is directly related to the increase in HR (noise spike at 13 min. not withstanding). As HR begins to regress to a baseline value of 103 beats/min CO starts to return to setpoint. The controller settings were $M=3$, $P=35$, $N=60$, with weights of MAP-2, CO-1 and both inputs of 0. Constraints are SNP from 0 to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$ and DPM from 2 to 7 $\mu\text{g kg}^{-1} \text{min}^{-1}$ with a rate of infusion constraint of 0.2 per control move for each. Bayesian settings were a convergence factor of 0.05 for MAP and 0.5 for CO with $\delta = 0.00001$. The moving average of the weighted model bank provides very good estimates for both MAP and CO over the entire run. The highest probability obtained by any model during this run was 0.354. Blending of models was more the norm for the best control runs.

V. DISCUSSION & CONCLUSIONS

This control design has demonstrated its efficacy in canine experiments for both hypertensive and depressed cardiac output cases for two different maintenance anesthetics. Interpatient and inpatient variability are the most significant problems to any controller for drug infusion. This variability is compounded by the different anesthetics used in practice and their greatly varying effects on baseline heart contractility, systemic vascular resistance and the strength of the baroreceptor reflex. The success of drug delivery control system depends on its ability to accommodate such variations. We have presented a multiple-model predictive control approach that does not require *a priori* specification of model structure and parameters and explicitly handles constraint specifications. The Bayesian weighting scheme used is computationally inexpensive and effective in "building" a higher order prediction model from basic building blocks of first and second order models. Unlike typical adaptive schemes, the order of the weighted model is not fixed and gets altered dynamically to closely mimic plant behavior. The weighted model bank can account for the variability in the drug infusion system, providing a flexible and bounded prediction model for the online constrained optimization problem. However, it is critical to have the bank of models bound the possible plant behavior. Issues such as the determination of the number of models spanning a given range of system gains and dynamics need to be addressed.

We have specified exact setpoints on the output variables during the experiments while the clinical objective may to maintain the outputs within a range of values. The use of output constraints in the controller can easily lead to infeasible solutions in the optimization problems or unstable closed-loop behavior. Studies on handling such infeasibilities are in progress.

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