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Individualized closed-loop anesthesia through patient model partitioning

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***Abstract*— Closed-loop controlled drug dosing has the potential of revolutionizing clinical anesthesia. However, inter-patient variability in drug sensitivity poses a central challenge to the synthesis of safe controllers. Identifying a full individual pharmacokinetic–pharmacodynamic (PKPD) model for this synthesis is clinically infeasible due to limited excitation of PKPD dynamics and presence of unmodeled disturbances. This work presents a novel method to mitigate inter-patient variability. It is based on: 1) partitioning an *a priori* known model set into subsets; 2) synthesizing an optimal robust controller for each subset; 3) classifying patients into one of the subsets online based on demographic or induction phase data; 4) applying the associated closed-loop controller. The method is investigated in a simulation study, utilizing a set of 47 clinically obtained patient models. Results are presented and discussed.**

***Clinical relevance*— The proposed method is easy to implement in clinical practice, and has potential to reduce the impact from surgical stimulation disturbances, and to result in safer closed-loop anesthesia with less risk of under- and over dosing.**

I. INTRODUCTION

A. Closed-loop anesthesia

Closed-loop anesthesia means that anesthetic drugs are automatically dosed based on feedback from a clinical sensor, as shown in Fig. 1. The concept was introduced in the 1950s and has since developed into an interdisciplinary research area, as exemplified by [1], [2], [3].

In the considered setting, the WAV_{CNS} depth of hypnosis (DoH) index [4], reported by the NeuroSENSE NS-901 monitor (NeuroWave Systems Inc., Cleveland Heights, OH.), is used to control the intravenous infusion rate of the hypnotic agent propofol.

B. Inter-patient variability

The DoH response to propofol displays a large variation between patients. This variability comes from differences in the distribution and elimination of drug in the body, influenced by physiological parameters such as age, weight, liver function etc. [5].

To guarantee system safety across an intended demographic cohort, a closed-loop controller needs to robustly stabilize the anesthetic state of each individual within it. This can be achieved through robust control techniques [3], in which case a single controller parameter set is used across the cohort. In contrast, adaptive control provides individualized controllers, where the individualization is based on initial patient responses to the therapy.

The main disadvantage of the robust approach is that it becomes conservative if the variability within the cohort is large, manifested by slow responses to changes in DoH setpoint or disturbance attenuation. On the other hand, adaptive techniques require excitation of the controlled dynamics, in order to learn the dynamics to which the controller should adapt. Adjusting drug titration to excite the PKPD-dynamics is typically not justifiable unless such adjustments are directly motivated by the current state of the patient, severely limiting clinical applicability.

C. Approach

This work considers a controller design, which fuses the robust and adaptive approaches. It only relies on demographic parameters available *a priori*, or parameters which can be readily estimated from representative induction phase data. The induction phase is the temporal episode during which the patient transitions from fully aware to a setpoint DoH. This phase is relatively rich in excitation of the considered dynamics, and generally free from unmodeled responses caused by unmeasurable surgical stimulation.

However, induction phase data is typically not sufficiently describing for identification of a full PKPD model [6]. Rather than attempting identification of PKPD models, or falsification, as investigated in [7], the approach taken here is instead to design a small set of robust controllers *a priori* – each optimized for a subset of existing patient models – and select the most appropriate one of them, based on data available by the end of the induction phase.

Two problems are considered:

1) How can a clinically obtained PKPD model set (representing a patient cohort) be partitioned, in order to maximize robust performance within each partition, while keeping down the total number of partitions? This gives an upper bound on performance, but is practically infeasible, since it requires full model knowledge for each patient.
2) How can (the same) model set be partitioned, based on patient data, which is available by the end of the induction phase? This gives insight into the clinical potential of the proposed method.

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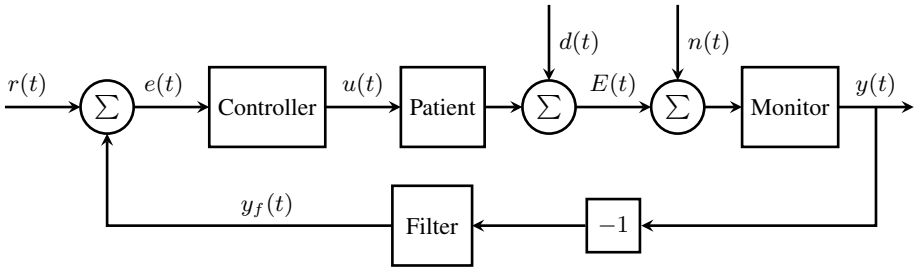

Fig. 1. Block diagram overview of the closed-loop control anesthesia system. Signals: r – DoH setpoint; e – control error; u – infusion rate (control signal); d – exogenous disturbance (surgical stimulation); n – measurement noise; E – DoH; y measured DoH; y_f – low-passed filter version of y.

II. METHODS

A. Patient model set

The patient model set used in this study was originally published in [6]. It consists of $n = 47$ pediatric PKPD models (19 F, 26 M (2 unknown), age (median (range)) 12 years (6–16), weight 47 kg (21–82), height 155 cm (119–181)). Each model relates propofol infusion rate u to DoH (clinical effect) E. The dynamics to be controlled are the series connections of such a PKPD patient model, and the linear dynamics $M(s) = 1/(T_M s+1)^2$, with $T_M = 8$ s, of the considered NeuroSense EEG monitor. It provides the $\mathrm{WAV_{CNS}}$ index, being a DoH measure with values close to 100 representing the fully aware state, 0 corresponding to an iso-electric EEG and 50 being a common setpoint for many surgical procedures [8]. For this reason, the considered PKPD models have all been linearized around an operating point corresponding to 50 $\mathrm{WAV_{CNS}}$.

The combined PKPD and monitor model relates the infusion rate u (input) to the measured clinical effect y (output), as schematically illustrated in Fig. 1.

It is known that linearized propofol PKPD models display a large variation in phase lag between patients [6]. The lag can be represented as a delay in low-order models and corresponds to the time it takes for the DoH to be affected by the anesthetics. In the considered patient model set, the delay ranges $1-120$ s with a median delay of 45 s.

The clinical effect in absence of a drug is termed E_0. In the considered data set, E_0 is $91.4(87.1-94.6)$ (median(range)). Both delay and E_0 can be readily estimated from induction phase $\mathrm{WAV_{CNS}}$ data.

B. Partitioning

We propose a method of minimizing the effects of inter-patient variability through patient model partitioning, comprising the following steps:

1) Partition the patient model set into subsets through clustering;
2) Optimize a robust controller for each subset, which maximizes performance while ensuring robustness over the subset;
3) When a new patient is to be anesthetized, determine which subset the patient belongs to through either *a priori* demographic information or through the induction phase response obtained with a controller robust across the entire model set;
4) Perform a smooth (continuous control signal) switch to the optimal controller synthesized under point 2 for the subset determined under point 3.

Steps 1–3 can be performed offline *a priori*, while step 4 is to be performed online for each new treatment. (Steps 1–3 can subsequently be repeated as more data becomes available.)

The two extremes of $m = 1$ subset and $m = n$ subsets correspond to a single robust controller and a fully individualized (adaptive) design, respectively. The former does not provide any advantage, and the latter is practically infeasible since it relies on complete model knowledge for each patient. In-between, there exist a multitude of possible partitionings. For a set of n elements (models), it is possible to construct B_n unique partitions (including the two extremes above), where B_n is the n^{th} Bell number. It grows rapidly in n, with $B_{47} > 10^{43}$, rendering exhaustive evaluation infeasible. Predetermining to partition into $m \leq n$ subsets instead results in m^n partitionings, which already for $m = 2$ results in $> 10^{14}$ partitionings for $n = 47$.

As a practically viable alternative to exhaustive evaluation, partitioning through clustering heuristics is considered. Further below, three bases for partitioning the model set are considered. It is of particular interest to investigate:

1) How much can performance be increased, when going from $m = 1$ to $m > 1$ subsets?
2) How close to the performance limited indicated by point 1 is it possible to get by only using patient (model) properties that are available by the end of the induction phase.

1) Partitioning using full model knowledge: Assuming full knowledge of the PKPD dynamics on an individual level provides an upper bound on achievable performance. However, this is clearly an unrealistic assumption. (Were such knowledge available, one could simply design an optimal individualized controller, voiding the need for any of the methodology to be introduced.)

The ν-gap metric provides a measure of pairwise "distance" between transfer function models, subjected to negative feedback. A thorough and technical introduction is provided in [9].

In the application at hand, it is natural to create partitions such that models within each subset behave similarly under negative feedback so that a small ν-gap between any pair of models within a given subset is desirable.

By calculating pairwise distances between each pair of

models in the set using the ν-gap metric, a similarity matrix is obtained. Subsequent application of a clustering technique to this similarity matrix results in the desired partitioning, Three different such clustering methods have been considered.

The first considered clustering method is hierarchical clustering [10]. It can be graphically represented through a dendrogram, illustrating how the elements (models) are connected and successively merged to aggregate clusters. These connections are based on the average linkage, further explained in [11].

The second and third considered clustering methods are both spectral methods, relying on the Laplacian matrix of the similarity matrix on which eigenvalue decomposition is performed. A "standard" clustering method, such as k-means, can then be applied on eigenvectors corresponding to certain eigenvalues to create the clusters.

Spectral clustering has been performed according to the methods described in [12], and [13], respectively.

2) Partitioning using demographic parameters: Demographic parameters (e.g. age, gender, height and weight) constitute a clinically viable alternative, upon which to base partitioning of the model set. Patient models can then be placed in different subsets depending on if the demographic entity is larger or smaller than the median value of all patients in the model set.

3) Partitioning using induction phase data: Induction phase data can be used to readily estimate some parameters of the PD model, such as the delay and E_0. As for partitioning using demographic parameters, the patient models can be placed in different subsets depending on if the estimated value is larger or smaller than the median value of all models in the data set.

C. Controller optimization

A feedback controller is used to titrate propofol based on measured DoH. It needs to be tuned to match (physiological) variability within the patient population, here represented by a set of PKPD models.

Controller performance was defined as the ability to attenuate unmodeled (surgical) disturbances. More specifically, a disturbance model comprising an additive output step $d(t)$ with Laplace transform $D(s)$ (see Fig. 1) was considered, and attenuation performance was quantified in terms of the $\mathcal{L}_2$ norm of the resulting clinical effect $E(t)$, as motivated in [14]. Optimal robust control was considered with the same objective for each subset of the partitioning. The performance of a subset of the partitioning was defined as the worst case performance of all models within the subset.

The considered controller structure is the filtered PID controller, used in the clinical study [6], comprising an ideal parallel form PID controller with transfer function

$$C(s) = \left(k_p + \frac{k_i}{s} + k_d s\right), \tag{1}$$

in series with a low-pass filter to attenuate high frequency measurement noise, forming the filtered controller $K = FC$ with $F(s) = 1/(T_f s + 1)^2$, shown in Fig 1.

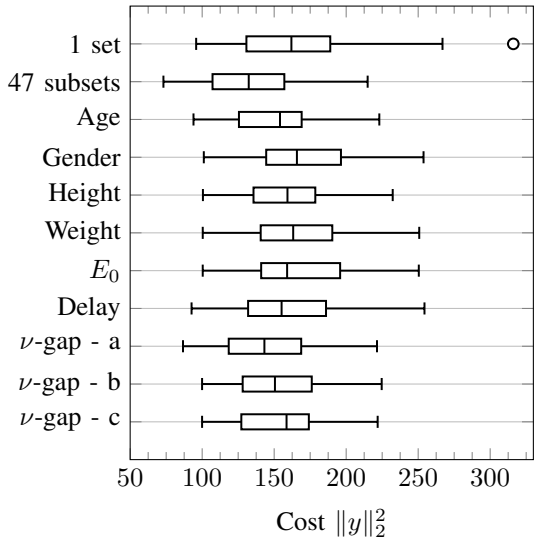

Fig. 2. Distribution of optimization cost $\|y\|_2^2$ across the patient model set for calculated controllers, where y is the clinical effect when the input is a step, for different partitioning methods. Nominal controller ($m = 1$ subset) and optimized individual controllers ($m = n = 47$ subsets) are used for comparison. All other partitions comprise $m = 2$ subsets. For partitioning on ν-gap, a is hierarchical clustering, b and c is spectral clustering with methods described in [12] and [13], respectively.

Robustness has been ensured by imposing constraints on the norms of the sensitivity S and complementary sensitivity $T = 1 - S$, as well as on the noise sensitivity KS transfer functions. Furthermore, a time domain constraint was imposed to limit the maximal WAV_{CNS} undershoot by M_y. Numerical values for the constraint levels M_s, M_t and M_{ks} were chosen to match the robustness of the clinically evaluated controller presented in [6], and the undershoot was limited to 20 % of the applied disturbance step magnitude. The constraints were enforced for all models within a given subset. The corresponding synthesis problem can be formulated as a constrained optimization problem (2).

$$\begin{aligned} \min_{K} \quad & \max_{\text{subset}} \|S_k(s)D(s)\|_2^2 \\ \text{subject to} \quad & \|S_k\|_\infty \le M_s \\ & \|T_k\|_\infty \le M_t \\ & \|KS_k\|_2 \le M_{ks} \\ & \mathcal{L}^{-1}\left(S_k(s)D(s)\right) \ge M_y. \end{aligned} \tag{2}$$

This problem was solved for each subset to yield parameters k_p, k_i, k_d of the PID controller (1), and T_f of the low-pass filter F.

Solving the problem involves consecutive simulations of the closed-loop response to the disturbance d, and the resulting minimum of (2) is quantifies the cost (reciprocal to performance) of the minimizing controller K.

III. RESULTS

Fig. 2 shows the distribution of optimization cost across the patient model set for the considered partitioning methods. The optimization cost (reciprocal to performance) obtained

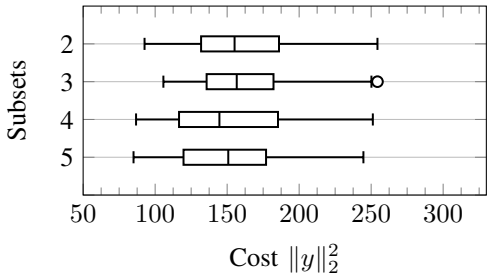

Fig. 3. Distribution of optimization cost $\|y\|_2^2$ across the patient model set, where y is the measured DoH resulting from a disturbance step d, for partitioning into $2, 3, 4, 5$ subsets based on the model delay.

with several partitions into $m = 2$ subsets is compared with that obtained when using a robust controller for the entire set ($m = 1$ subsets), as well as when utilizing fully individualized controllers ($m = 47$ subsets).

The performance improvement can be characterized by the relative decrease in optimization cost, distributed across the model set. Moving from $m = 1$ to $m = 47$ subsets, there is for instance a 32 % decrease of the worst-case cost, and a 19 % decrease of the median cost. As expected, one of the ν-gap-based methods (the one marked with a in Fig. 2) results in the highest improvement, 30 % worst case and 11 % median, when moving from $m = 1$ to $m = 2$ subsets. The clinically relevant clustering method yielding the largest improvement for the same scenario is based on patient age (marked *Age* in Fig. 2), resulting in a 29 % worst-case and a 5 % median cost decrease.

Fig. 3 shows the resulting cost for partitioning into $m = 2, 3 \ldots, 5$ subsets, based on induction phase response delay [6]. The outcome is representative for the considered clustering methods in that there is a notable improvement in going from $m = 1$ to $m = 2$ subsets, but only minor improvements associated with further increase of the number of subsets, beyond $m = 2$.

IV. DISCUSSION

Inter-patient PKPD variability is arguably the limiting factor for closed-loop control performance in automated anesthesia. This paper introduces a methodology to mitigate the effect of this variability, by classifying each patient using available demographic parameters or induction phase data. Robust controllers are optimized *a priori* based on a partition of a patient PKPD model set. The clustering procedure can be readily repeated if patient models are added to the set, or if another model set is being considered.

A simulation study based on 47 published pediatric PKPD models has shown that the approach is feasible, and that substantial performance improvement, in terms of disturbance attenuation and DoH setpoint tracking, is obtainable using a partition into two subsets. Optimizing individual controllers, as well as controllers for a partitioning based on the ν-gap between models were used to investigate an upper bound on achievable performance. The main result is that by partitioning into only two partitions based on age (readily available parameter), it is possible to obtain performance comparable to that of fully individualized controllers. The fact that age was found to be the most relevant of the considered parameter for the patient group at hand, motivates its previous use as a gain scheduling parameter [15], [3].

While the paper serves to demonstrate feasibility of a novel and clinically relevant method, the exact outcome (in terms of number of subsets and performance distribution) is expected to vary depending on the patient model set used for the *a priori* synthesis, as well as the exact formulation of the performance objective and robustness constraints.

A similar study where partitioning was made on age for adults into four subsets is [15], where it was found that partitioning of the model set by age improves performance. In this paper, more methods were evaluated and it was stated that two groups are enough for children and we found out that the result was almost as good as the performance limit for two subsets.

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