An Adaptive Approach to Target Controlled Infusion

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Abstract—This paper proposes an adaptive approach to improve the performance of Target Controlled Infusion (TCI) based strategies. The method determines an adequate drug dose profile that drives the drug effect on the individual patient to a desired target in a pre-specified period of time. It combines an optimal variance constrained drug dose design with a hybrid identification of the individual patient dynamics. Simulation results based on a bank of one hundred neuromuscular blockade patient models are presented to demonstrate the feasibility of the proposed method.

I. INTRODUCTION
Automated technologies are becoming spread in Biomedicine, where there is an increasing demand for secure and robust strategies. Particular attention has being paid to the development of methods and devices that are capable of determining and applying an adequate drug dosage regimen to the individual patient. This is the case for instance in general anaesthesia.

The design of individualized drug dosage regimens depend on the characteristics of the clinical problem to be solved [1], [2]. Target Controlled Infusion (TCI) design strategies [3] are nowadays widely accepted due to its specific features. Alternatively to the feedback concept, where measurements of the control variable are made and the errors between the set point and the actual value are used to correct the control action, TCI is a feedforward control strategy that relies on the application of pharmacokinetic/pharmacodynamic (PK/PD) population models to design the dose profile.

Under the assumption that a reliable PK/PD population model is available to identify the individual patient dynamics, TCI devices calculate the drug dose to be administered such that a target value on the PD effect concentration is reached. Furthermore, these open-loop control devices do not compensate for a mismatch between the model and the patient dynamics. Therefore, they are not completely adequate for drug administration [4].

The major contribution of this study consists in the development of an optimal control strategy that copes with the need for adaptation in TCI. The proposed strategy designs the adequate drug dosage regimen that drives the drug effect to a desired target in a pre-specified period of time. The design includes clinical restrictions imposed on the class of allowable dosage regimens, such as its constancy, as well as hard or soft constraints on the infusion rate. Furthermore, the maintenance dose to sustain the desired effect concentration after the pre-specified period of time is calculated from the parameters of a model for the individual patient dynamics identified by a hybrid identification method [5]. The proposed methodology is illustrated in the case where the effect measured on the patient corresponds to the neuromuscular blockade (NMB) level and the drug to the muscle relaxant atracurium.

This remainder of this paper is organized as follows. Section II presents: a brief overview of the general TCI strategy, a description of the NMB model; the optimal transient dose design method under hard constraints; the identification methodology; and the developed adaptive approach to TCI, comprising a recursive and a non-recursive input variance constrained method. Section III shows the results obtained by the application of the proposed methodology to the NMB case study. Finally, section IV draws the conclusions.

II. ADAPTIVE TCI STRATEGY
The goal of the proposed adaptive approach is to improve the commonly accepted TCI strategy. To that end, a hybrid method for patient identification and steady-state drug dose calculation is combined with an optimization procedure to determine the loading dose to be administered during a predefined transient period.

A. Target Controlled Infusion
TCI allows for a controlled infusion in such a manner as to attempt to achieve a user-defined drug concentration in a body compartment or tissue of interest [6]. In order to accomplish that, the time course of infusion rates are predicted by validated PK population models. The PD behaviour of the drug in each patient is assessed by the anaesthetist from the patient’s overall external physiological state and is then used to set the desired target concentration. Throughout the surgery, the anaesthetist using a TCI system re-adjusts the target concentration as required on clinical grounds and based on his clinical experience and individual requirements of the patient. Hence, the feedforward TCI open-loop system is closed by the clinician.

B. NeuroMuscular Blockade Model
One of the anaesthetic agents usually administered to a patient undergoing general anaesthesia for surgery purposes is the muscle relaxant or neuromuscular blocker. The NMB level of a patient is typically quantified between 0% (full
paralysis) and 100% (full muscular activity). In the case of an intravenous administration of the muscle relaxant atracurium, the dynamic response of the NMB may be modeled as proposed in [7]. There, the drug infusion rate \( u(t) \) [\( \mu g kg^{-1} min^{-1} \)] is related with the so-called effect concentration \( C_e(t) \) [\( \mu g ml^{-1} \)] through a linear dynamic PK/PD model, given by

\[
\begin{pmatrix}
    z_1(t) \\
    z_2(t)
\end{pmatrix}
= \frac{1}{\lambda}
\begin{pmatrix}
    -\lambda_1 & 0 & 0 \\
    0 & -\lambda_2 & 0 \\
    \lambda & \lambda & -\lambda
\end{pmatrix}
\begin{pmatrix}
    z_1(t) \\
    z_2(t) \\
    C_e(t)
\end{pmatrix}
+ \begin{pmatrix}
    a_1 \\
    a_2
\end{pmatrix} u(t),
\]

where \( z_1(t) \), \( z_2(t) \) are state variables, \( \Theta_{PK}=[a_i [kg ml^{-1}], \lambda_i [min^{-1}]]_{i=1,2,3} \) and \( \lambda \) are patient-dependent parameters. In turn, \( C_e(t) \) is related with the expected NMB level \( r(t) \) (%) by means of a nonlinear static Hill equation [8].

\[
r(t) = f_{NL}(\Theta_{PD}, C_e(t)) = \frac{100C_{50}^2}{C_{50}^2 + C_e(t)}
\]

where \( C_{50}, \gamma \in \Theta_{PD}=[\lambda [min^{-1}], C_{50} [\mu g ml^{-1}], \gamma (dimensionless)] \) are also patient-dependent. Remark that in practice the intermediate signal \( C_e(t) \) is not measured and its theoretical value is used.

At the beginning of a surgery, in the induction phase, it is usual to administer a bolus of atracurium (typically 500 [\( \mu g kg^{-1} \)], that may be described by \( u_b = 500\delta(t) [\mu g kg^{-1}] \) (where \( \delta \) is the continuous time Dirac delta function). Furthermore, for control purposes, during the period where the bolus is acting, the value of the reference is fixed at a low level, being gradually raised to the set-point \( r^* \) (typically 10%) in order to avoid sudden changes, stabilizing on it after minute 75 (steady-state) [7].

Taking into account this parameterization and in order to cover a wide range of behaviours, a bank of nonlinear dynamic models \( \mathcal{M} = \{ M_i, \Theta_{PK}, \Theta_{PD} \}_{i=1,...,100} \) was generated using the probabilistic model discussed in [9].

Fig. 1 shows the NMB response and effect concentration for each model in \( \mathcal{M} \) subject to the initial bolus.

For each of these patient models, it is possible to obtain from the corresponding parameterization \( \{ \Theta_{PK}, \Theta_{PD} \} \) the constant infusion dose \( u_{as} \) that should be given to drive the limiting value of NMB level to a prefixed reference \( r^* \):

\[
\lim_{t \to \infty} r(t) = r^* \Rightarrow u(t) = u_{as} H(t - t_0)
\]

\[
u_{as} = g_{NL}(\Theta_{PD}, \Theta_{PK}, r^*) = C_{50}^2 \left( \frac{(100/r^*-1)\gamma}{\lambda_1 + \lambda_2} \right)
\]

where \( H \) is the Heaviside step function and \( t_0 \) is the time beyond which \( u_{as} \) should be administered.

The practical implementation of this strategy is not straightforward since the time evolution of the measured response \( r(t) \) is highly dependent on the time instant \( t_0 \) that is chosen to start infusing \( u_{as} \). Depending on the choice of \( t_0 \), we may face different situations that can be health threatening if not avoided: a too large recovery time, a high overshoot in the transient period, or even the convergence of the NMB level to values far from the desired target and accepted range. If \( t_0 \) is too small (i.e. \( u_{as} \) is infussed right after the bolus administration), the recovery can only take place after a long period of time, resulting both on a too long transient phase with an undesired overdosing and a poor reference tracking. If \( t_0 \) is the time instant where \( r(t) \) is near some value in the recovery period, NMB may present a high overshoot, and probably in some clinical cases the continuous drug infusion may not be sufficient to maintain the patient in a proper level to perform surgical procedures. Overall, the choice of the time instant \( t_0 \) seems to be critical and has a great impact on the time evolution of the NMB level if no further action is taken. However, this problem can be overcome defining a time instant \( t_1 > t_0 \) such that in the time interval \( [t_0,t_1] \) the NMB is taken from its value \( r(t_0) \) at \( t_0 \) to a prespecified value \( r(t_1) = r^* \) at \( t_1 \).

### C. Optimal transient dose design

Assuming linear time-invariant dynamics, the PK/PD system drug response may be modeled by the following discrete-time state-space system

\[
\begin{align*}
x(t+1) &= \Phi x(t) + \Gamma u(t) \\
y(t+1) &= C x(t+1)
\end{align*}
\]

where \( u(t) \in \mathbb{R} \) is the input (piecewise constant drug dose infusion), \( x(t) \in \mathbb{R}^{n \times 1} \) the state-vector, \( y(t) \in \mathbb{R} \) is the output (effect concentration of the drug), \( C \in \mathbb{R}^{1 \times n} \), \( \Phi \in \mathbb{R}^{n \times n} \) and \( \Gamma \in \mathbb{R}^{n \times 1} \) (with \( n \) equal to the system order). It should be stressed that \( \Phi \) and \( \Gamma \) are dependent on the values of \( \Theta_{PK} \) and \( \Theta_{PD} \). This dependence on the parameters is omitted only for the sake of simplicity in representation.

Given an initial time \( t_0 \), an initial state \( x(t_0) = X_0 \), and an input signal \( u(t) \) defined for all \( t \), a solution of (3) for \( t > t_0 \) is given by [10]

\[
y(t) = C \phi(t,t_0) X_0 + \sum_{\tau=t_0}^{t-1} C \phi(k,\tau+1) \Gamma u(\tau)
\]

where \( \phi(i,j) = \Phi^{i-j} \) for \( i \geq j + 1 \).

Consider the schematic representation of Fig. 2. The evolution of the system \( P \) from \( t_0 \) (the beginning of drug
infusion) to \( t_1 = t_0 + p \) (the time to steady-state) can then be represented by

\[
Y = \Sigma X_0 + SU
\]

where

\[
Y = \begin{pmatrix}
y(t_0 + 1) \\ y(t_0 + 2) \\ \vdots \\ y(t_0 + p - 1) \\ y(t_1)
\end{pmatrix},
\]

\[
\Sigma = \begin{pmatrix}
C \Phi \\ C \Phi^2 \\ \cdots \\ C \Phi^{p-1} \\ C \Phi^p
\end{pmatrix},
\]

\[
U = \begin{pmatrix}
u(t_0) \\ u(t_0 + 1) \\ \vdots \\ u(t_0 + p - 2) \\ u(t_1 - 1)
\end{pmatrix},
\]

\[
S = \begin{pmatrix}
C \Gamma \\
C \Phi \Gamma \\
\vdots \\
\cdots \\
C \Phi^{p-1} \Gamma \\
C \Phi^p-2 \Gamma \\
\cdots \\
C \Phi \\
C \Gamma
\end{pmatrix}
\]

The reference profile in the effect concentration is obtained from the pre-fixed \( C_e^* = f_{NL}^*(\Theta_{PD}, r^*) \) and \( C_e^*(t_0) = f_{NL}^*(\Theta(t_0)) \) (block \( B \) of Fig. 2):

\[
C_e^* = \begin{pmatrix}
C_e^*(t_0) \\
C_e^*(t_0 + 1) \\
\vdots \\
\cdots \\
C_e^*(t_1)
\end{pmatrix}
\]

Making \( Y = C_e^* \) in (5), the drug dosage \( u(t) \) for \( t \in [t_0, t_1] \) is found by minimizing \( J(U) \) over a class of admissible regimens \( U \) (block \( Z \) of Fig. 2):

\[
\min_{U \in \mathcal{U}} J(U) = \min_{U \in \mathcal{U}} \| SU - \mathcal{G} \|^2
\]

Here \( SU \) represents the system’s forced response and \( \mathcal{G} = Y - \Sigma X_0 \).

A first attempt was performed in order to solve (7) considering \( U = \{ U : [t_0, t_1] \to \{ u_{ss}, P_{max} \} \} \). Here, \( P_{max} \) should be interpreted as the maximum drug rate, defined as a function of the patient weight, the maximum speed of the syringe pump and possibly other clinical constraints.

The proposed method for solving problem (7) under hard constraints was applied in simulation to each patient in \( \mathcal{M} \) assuming the knowledge of the corresponding parameterization. In this study, \( t_0 \) was defined as the first instant during recovery where \( r(t) \) crosses the level of 5% and \( t_1 \) as minute 75 after bolus administration. As illustrated in Fig. 3, the results revealed the need to apply too large control signals (saturated at \( u(t) = P_{max} \)) to the patient in the transient period in order to guarantee the tracking of the predefined reference in the effect concentration. These drug dose regimens are not in accordance with the ones commonly used in clinical practice for continuous drug infusion, since it is desirable to maintain the administered drug dose as constant as possible.

D. Identification methodologies

In real practice, the parameterization of the model for the dynamics of each patient needs to be estimated \( (\hat{\Theta}_{PK}, \hat{\Theta}_{PD}) \). In this study, a hybrid strategy [5] is proposed in order to carry out such estimation. The hybrid method consists of a combination between a learning paradigm, like an artificial neural network, and an optimization algorithm for curve fitting, like Nelder-Mead or Levenberg-Marquardt. Given a new estimation case, the learning paradigm acts as an estimator and provides an initial guess of the sought parameterization using data collected from the patient. This paradigm learns how to provide a close initial guess from a priori available data concerning similar estimation cases. The optimization algorithm refines then, whenever necessary, the guess provided by the learning paradigm.

For comparison purposes two other identification strategies are also considered, namely the mean model and the nearest model. In the mean model approach usually considered in TCI, the parameter identification is carried out considering the mean parameterization of all known models \( (\Theta_{PK}, \Theta_{PD}) \). In the nearest model approach usually used for closed-loop control of NMB [11], each model is assumed to be parameterized with the model in \( \mathcal{M} \) whose response is closer to the measured patient response in the sense of the Mahalanobis distance [12].

E. Input variance constraint

In order to avoid too large control signals and syringe pump saturation, a variance constrained input strategy was developed based on [13]. Bolus administration followed by a piecewise constant drug administration (a model for the
intravenous infusion) are considered for PK/PD systems of order \( n \). The adaptive control problem can then be formulated as follows.

**Problem 1.** Given \( \alpha \geq 0 \) the problem is to minimize (7) subject to the inequality constraint

\[
\|U\|^2 \leq \alpha^2
\]  

(8)

Having already calculated the steady-state drug dose guess \( u_{ss} \) from (2), instead of aiming to determine the total amount of drug to give to the patient, we may want to determine which amount of drug must have to be added or decreased to that value for the effect concentration \( C_e(t) \) to follow the imposed reference profile \( C_e^* \). The PK/PD system description can then be seen as incremental, and \( u(t) \) may be decomposed in \( U = U_{ss} + \Delta U \). Hence, (5) is transformed into

\[
Y = \Sigma X_0 + SU_{ss} + S\Delta U
\]  

(9)

where

\[
U_{ss}^T = (u_{ss} \quad u_{ss} \quad \ldots \quad u_{ss})
\]

\[
\Delta U^T = (\Delta u(t_0) \quad \Delta u(t_0 + 1) \quad \ldots \quad \Delta u(t_0 + p - 1))
\]

and Problem 1 can be reformulated as

**Problem 2.** Given \( c \geq 0 \), find an \( \Delta U \) solving the Lagrangean function

\[
\mathcal{L}(f, \rho) = \|S\Delta U - B\|^2 + \rho\{\|\Delta U\|^2 - c^2\}
\]  

(10)

where \( \rho \) is as a Lagrange multiplier satisfying \( \rho\{\|\Delta U\|^2 - c^2\} = 0 \) and \( B = Y - \Sigma X_0 - SU_{ss} \).

The solution of the variance constrained input problem (10) is found here by two different approaches: non-recursively and recursively.

In the non-recursive approach, \( \Delta U \) is calculated at minute \( t_0 \) and \( U \) is then applied to the patient. However, this initial guess can be recursively corrected if we have access to the real effect that the drug dose is having on the patient.

Assuming a parameterization for each simulated patient, it is possible to evaluate each patient response \( r(t) \) after applying some drug amount. Inverting the Hill equation (1), the corresponding effect concentration is calculated and a new target profile \( C_e^* = Y \) can be defined. The hypothesis is that, by recursively updating the target effect concentration profile, the system errors that may come from identification inaccuracies can be on line reduced and reference tracking becomes more accurate.

This adaptive approach to TCI is schematically represented in Fig. 4 and the subjacent general algorithm consists of the following steps:

**Step 1.** Determination of \( t_0 \). The time instant \( t_0 \) is obtained from the impulse response (patient response to bolus \( u_{ad} \) administration) and corresponds to the point where \( r(t) \) crosses a predefined level.

**Step 2.** Patient identification. Using the data (NMB level) collected from the patient until \( t_0 \), identify the PK/PD parameters of the patient \( (\Theta_{PK}, \Theta_{PD}) \) (block \( i \) of Fig. 4).

Compute \( u_{ss} \) (2) (block \( i \) of Fig. 4) and determine the corresponding steady state effect concentration \( C_{e}(t_1) \) at time \( t_1 \) pre-fixed by the user (clinician) (block \( B \) of Fig. 4). Using \( r(t_0) \), calculate \( C_{e}(t_0) \) from the Hill equation inversion (1), and define the desired target effect concentration from \( t_0 \) to \( t_1 \) \( (C_{e}^* = Y \) in (9)) (block \( B \) of Fig. 4).

**Step 3.** Drug dose calculation. Determine \( \Delta U \) in (9) that minimizes the Lagrangean function (10). The Lagrange multiplier is updated via the following recurrent scheme

\[
\rho(j + 1) = \rho(j) + \rho\{\|\Delta U\|^2 - c^2\}
\]  

(11)

where \( \mu \) is a small real number.

**Step 4.** Measurement of the system response. Apply \( u(t) = u_{ss} + \Delta U(1) \) to the patient and measure the response \( r(t) \) of that dose administration. By inversion of the Hill equation (1) the corresponding level of effect concentration is obtained and used to define the new reference profile \( C_{e}^* \) for the next iteration. Repeat Step 3 and Step 4 until time \( t \) equals \( t_1 \).

**Step 5.** Steady state. From minute \( t_1 \) until the end of the process \( \Delta u \) is considered as zero and the patient receives as input the value of \( u_{ss} \).

If the non-recursive approach for drug dose calculation is considered, \( \Delta U \) is obtained in Step 3. The algorithm skips Step 4 and continues on Step 5.

**III. RESULTS**

For each of the referred approaches, a simulation study was carried out in model bank \( M \).

A. Non-recursive vs recursive approaches

Fig. 5 and 6 illustrate the responses for patient number 62 in \( M \) after application of the non-recursive (solid line) and recursive (dashed line) approaches. The proposed non-recursive adaptive approach to TCI tends to overdose the patient and NMB does not reach \( r^n \) at minute 75 (defined as \( t_1 \)), presenting a prolonged transient phase. In this strategy, the real level of response \( r(t) \) and consequently \( C_e(t) \) is not used to update the target concentration profile \( C_e^* \) in the transient phase \([t_0, t_1]\).

Fig. 7 shows the effect concentration for the recursive approach after applying the drug dose profile shown in Fig.
6 for patient 62. For questions of simplicity $C^*_e$ had been defined as linear from $C^*_e(1)$ to $C^*_e(t_1)$. Other approaches were tested considering more complex effect concentration target profiles with no improvement on the final result for reference tracking in $r(t)$ (results not shown). The bottom plot in Fig. 7 shows a zoom in the upper plot of effect concentration in order to better illustrate the consequence of updating the reference profile $C^*_e$ over time $[t_0, t_1]$. As shown in Fig. 7 the recursively updated $C^*_e$ present decreasing slope over time, becoming all of its values closer to $C_e(t_1)$. It is then expectable that the loading doses ($\Delta U$) converge to zero, avoiding, as consequence, to overdose the patient.

Fig. 5. NMB response for patient number 62 in $\mathcal{M}$ after application of the non-recursive (solid line) and recursive (dashed line) approaches. The 'dot' in the $xx$-axis indicates time instant $t_1$.

Fig. 6. Drug dose regimens obtained for patient number 62 in $\mathcal{M}$ after application of the non-recursive (solid line) and recursive (dashed line) approaches. The 'dot' in the $xx$-axis indicates minute 75 ($t_1$) where steady-state is supposed to be reached.

Fig. 7. Effect concentration for patient 62 in $\mathcal{M}$ (dashed line) for the recursive approach after applying the drug dose profile shown in Fig. 6. The 'dot' in the $xx$-axis indicates time instant $t_1$. In the bottom plot the solid line represents the first $C^*_e$ target profile calculated on time instant $t_0$. Dotted lines represent the recursively updated $C^*_e$ target profiles at two different time instants.

These preliminary results indicate a superior performance of the recursive approach which has been chosen to perform further simulation studies. In Fig. 8 NMB responses and corresponding drug doses obtained after recursively applying the adaptive TCI method to each model in $\mathcal{M}$ are shown. Until now, model behaviours were obtained considering $\Theta_{PK}$ and $\Theta_{PD}$ completely known. Nevertheless, in clinical practice the real patient parameterization is actually unknown and an identification strategy must be implemented to overcome this problem.

Fig. 8. NMB values (upper plot) and drug dose regimens (bottom plot) after applying the adaptive recursive approach to TCI strategy considering the patient parameterization completely known. The 'dot' in the $xx$-axis indicates time instant $t_1$.

B. Adaptive TCI to patients assuming unknown dynamics

In a first approach, each patient from $\mathcal{M}$ was assumed to be described by $\mathcal{M} = (\Theta_{PK}, \Theta_{PD})$ corresponding to the mean model. This is the first usual clinical guess for designing dose regimens. Fig. 9 shows drug doses and the corresponding NMB responses obtained after applying the adaptive TCI method to each model in $\mathcal{M}$. Note that since all patients in $\mathcal{M}$ are represented by the mean model $\bar{M}$, the constant drug dose $u_{ss}$, which is calculated from $\bar{M}$, is the same for all patients (bottom plot in Fig. 9). This explains the large variability in the transient period for the drug dose profile $u(t)=u_{ss} + \Delta u(t)$. Furthermore, remark that $r(t)$ exhibits a high variability both in the transient phase ($t \in [t_0, t_1]$) and at steady-state period ($t \geq t_1$). This behaviour is a consequence of the use of the mean model to describe the patients that exhibit a high degree of variability.

In a second approach, each patient from $\mathcal{M}$ was assumed to be described by its nearest model in the bank. Although this approach seemed to give origin to better fitted responses, results shown in Fig. 10 were not significantly different from the ones where the mean model had been considered. This has to due with the fact that there is parameter redundancy in NMB model, meaning that we can have a good initial description of the measured data with a bad individual parameter fitting [14].

Apart from the model with higher overshoot in $r(t)$ at the transient period (upper plot Fig. 10), the responses $r(t)$ present lower variability both in the transient phase and in the steady-state when compared with results where the patient is identified by the mean model.
Finally, in the proposed approach each patient from $\mathcal{M}$ was assumed to be described by the parameterization calculated by the hybrid method. Fig. 11 shows that $r(t)$ is maintained near the target value of 10% both in transient period and in steady-state phase with the mean overshoot between $t_0$ and $t_1$ always less than 20%, which is acceptable in clinical practice. With this adaptive strategy to TCI approach every model response $r(t)$ is taken to a value near 10% during time interval $[t_0, t_1]$. This strategy is a clear improvement to the commonly used TCI method that considers the mean model to identify the patients. Note that NMB responses variability is the lowest of the three identification approaches results.

IV. CONCLUDING REMARKS

This paper presents an adaptive approach to TCI that combines a hybrid identification method with an optimal control algorithm. The hybrid method builds a model of the individual patient dynamics and has already shown to be robust under the presence of noise and perturbations [14]. In turn, the control algorithm uses the information about the parameterization of this model to compute in an adaptive fashion the adequate drug dose profile that drives the drug effect on the individual patient to a desired target in a pre-specified period of time. This strategy uses the measurement of the actual response of the patient to continuously redefine the target profile to be followed. Hence, this is a feedback approach with improvements over the usual feedforward TCI.

Simulation tests were performed on a bank of one hundred neuromuscular blockade simulated patient models and the good results achieved encourage to extend the proposed adaptive TCI approach to real clinical data.

REFERENCES