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Approach to assess accuracy of syringe pumps in target-controlled infusion mode

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Abstract

Target-controlled infusion (TCI) requires that the syringe pump accurately follows a volumetric profile calculated by the TCI controller, leading to the concentration setpoint actually being reached. Until now, no method for quantifying dosing accuracy in TCI mode has been published. We propose an adaptation to the test procedure described in IEC standard 60601-2-24 for quantifying syringe pump accuracy to measure the performance characteristics of TCI by amending the flow rate measurement with calculation of the resulting effect site concentration. In the proposed procedure, infusion rates in TCI models are measured for a number of test patient parameters covering the applicable range of age, height and weight for the underlying patient models. The same pharmacokinetic-dynamic (PK/PD) models as implemented on the pumps are used to calculate the actual effect site concentration using the "PKPD Tools for Excel" by Minto and Schnider (2009) [1]. An exemplary test case evaluation with simulated data is given to illustrate feasibility.

I. Introduction

Target-controlled infusion (TCI) algorithms enable anesthesiologists to quantitatively set intravenous anesthetic drug concentrations in the patient. TCI algorithms are based on pharmacokinetic-dynamic (PK/PD) models (e.g., [2] and [3] for propofol and [4] for remifentanil). Multiple syringe pump manufacturers implement algorithms for TCI (e.g., [5]) that solve PK/PD models dependent on patient biometrics to derive drug flow profiles to reach a target plasma or effect site concentration (Ce_{target}).

Syringe pumps are constructed using step motors to deliver accurate infusions at a constant rate over a long time (> 30 min). Thus, a pump requires a non-negligible time interval until the realized flow rate reaches the rate setpoint; generally, this time interval is longer at lower rate setpoints [6]. IEC 60601-2-24 Subclause 201.12.1.102 [7] defines a measurement procedure for assessing the accuracy of syringe pumps at static infusion rates. In contrast, the infusion rate in TCI is varied in intervals on the order of 10 s. TCI algorithms constitute a pure *feed-forward* system. In daily practice, anesthesiologists titrate Ce_{target} to compensate remaining unknown errors or deviations, based on the observed effect.

Proper operation of the utilized syringe pumps is noted as a factor contributing to the safety of TCI [8]. Yet no standardized measurement procedure to quantify the dosing accuracy of syringe pumps in TCI mode could be identified from the literature. A measurement setup designed for micro-flow measurements is presented in [9]. However, this is optimized for the requirements encountered in the calibration of flowmeters and not for TCI pumps with changing rates.

In this paper, we present an approach to measure and quantify TCI system performance. Particularly, this

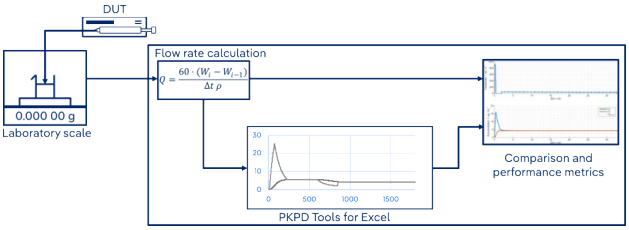

Figure 1: Schematic of the measurement system used, illustrating the physical setup and evaluation system.

is quantified in measuring the flow rate and calculating the resulting effect site concentration, then comparing it to the pump settings using standardized parameters (section II). In preliminary tests, this approach has been shown good results on a realistic setup; however due to confidentiality reasons, we cannot include these results in this publication. In section III, we present a simulated test case with realistic data, to demonstrate the fidelity of our proposed approach.

II. Methods

Test parameters are chosen to cover all parameters of the TCI method. This includes biometric covariates of the patient, target settings (drugs, pharmacological and target concentrations), and disposable syringe types and manufacturers. Test patients are selected using population-based data to achieve good coverage of biometric covariates realistically encountered when providing anesthesia. Covariates should not be selected outside of the permissive range of the PK model or the pump.

A standard syringe type, such as the B. Braun Original Perfusor Syringe (50 mL) should be used for all measurements. To further reduce variability from disposable syringes, these should be sourced from the same manufacturing lot. The drug concentration to be set and used in all calculations is $20\,\mathrm{mg\,mL^{-1}}$ for propofol and $50\,\mu\mathrm{g\,mL^{-1}}$ for remifentanil.

The method to measure the dosing accuracy of syringe pumps is adapted from the standard IEC 60601-2-24 [7]. The setup is shown in Fig. 1. The volume delivered by the syringe pumps is continuously weighed using a laboratory scale (Sartorius CPA225D), reading out the weight values via the scale's serial port at a sampling frequency of $\sim 5\,\mathrm{Hz}$. Flow rate Q is calculated from

$$Q_i = \frac{60 \cdot (m_i - m_{i-1})}{\Delta t \cdot \rho}, \tag{1}$$

where m_i, m_{i-1} are the weights measured at the instant i and the previous instant $i-1$; Δt is the time interval between these instants and ρ is the density of the infusate liquid [7]. As determined in [7] and for safety reasons, distilled water is used as the infusate in all cases; density is corrected according to temperature using data from [10]. Measures have to be taken to control evaporation of the liquid. This can be achieved by layering a thin film of oil over the liquid and using an infusion cannula (18 Gauge) to infuse below this layer, also dampening the transient pulsation from a drop falling onto the liquid surface. Until this point, the proposed test procedure matches the standardized approach in [7]. The calculated flow rate $Q(t)$ is then introduced into the "PKPD Tools for Excel" [1] and the resulting plasma and effect compartment concentrations calculated by applying the same PK model as on the device under test. This model is indicated either in the instructions for use or in the pump's drug library. The resulting calculated concentration $Ce_{\mathrm{calculated}}$ is then compared to the set target concentration Ce_{target}. Performance is characterized with the method presented in [11], based on the difference between the setpoint and actual concentrations calculated from the infusion rate. The performance error (PE) is calculated with the formula

$$\mathrm{PE} = \frac{(Ce_{\mathrm{calculated}} - Ce_{\mathrm{target}})}{Ce_{\mathrm{target}}} \cdot 100\,\% \tag{2}$$

The inaccuracy (median absolute performance error, MDAPE) of the concentration trajectory is calculated as

$$\mathrm{MDAPE} = \mathrm{median}\,\{|\mathrm{PE}|_i, i = 1 \ldots N\}, \tag{3}$$

with N being the number of instants where PE is calculated. The average steady-state performance error (AVGSTATPE) is calculated over the last 10 minutes of the test time to ensure all pharmacokinetics have settled. The average and worst overshoot (AVGOVS and MAXOVS) are calculated by subtracting the target concentration from the calculated $Ce(t)$:

$$\mathrm{AVGOVS} = \mathrm{avg}(Ce(t) - Ce_{\mathrm{target}}) < 0 \tag{4}$$

$$\mathrm{MAXOVS} = \max(Ce(t) - Ce_{\mathrm{target}}) < 0 \tag{5}$$

If all error metrics are within ±5 %, the testcase is marked as passed.

All calculations are performed using MATLAB (R2025b, MathWorks Inc., Natick, MA), using the Component Object Model (COM) Integration to communicate with Excel spreadsheets (Microsoft, Redmond, WA).

Factors contributing to the uncertainty of the flow measurement are quantified according to the "Guide to the expression of uncertainty in measurement" (GUM) [12]. Combined uncertainty u_c is defined as the sum of the individual uncertainties of the variables y:

$$u_c = \sqrt{\sum_{i=1}^{N} u_i^2(y)}. \tag{6}$$

The laboratory scale itself is a source of uncertainty u_{scale}. This consists of uncertainty due to resolution (1×10^{-5} g), reproducibility (5×10^{-5} g), linearity (1×10^{-5} g), temperature dependence and calibration. The latter are negligible if the scale calibrated before each measurement campaign and environment temperature is kept constant.

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Capillary forces on the cannula and buoyancy due to displacement of air by liquid are also negligible. An uncertainty in time $u_{\Delta t}$ is introduced by the serial readout of the laboratory scale. The variance in the sampling interval of the data packets was measured to be within 2×10^{-2} s. In preliminary investigations, mineral oil for vacuum pumps (Pfeiffer P3) was found adequate to reduce evaporation to $u_{\text{evap}} \leq 6 \times 10^{-5}\,\text{g}\,\text{h}^{-1}$ at 20°C. $u_{\Delta \text{m}}$ comes out to [9]

$$u_{\Delta m} = \sqrt{u_{\text{scale}}^2 + u_{\text{evap}}^2} \tag{7}$$

In determining flow rate Q (1), scale uncertainties u_{scale} have an impact on the mass increment Δm measured. The density ρ of the infusate has to be taken into account, which is why this uncertainty u_ρ is considered. The total relative uncertainty of Q according to GUM [12], [9] is

$$\frac{u_Q}{Q} = \sqrt{\left(\frac{u_{\Delta m}}{\Delta m}\right)^2 + \left(\frac{u_{\Delta t}}{\Delta t}\right)^2 + \left(\frac{u_\rho}{\rho}\right)^2} \tag{8}$$

With the available devices, flow uncertainty in the typical range of rates during the TCI maintenance phase (20 mL h^{-1} to 100 mL h^{-1}, c. Fig. 2a) is between 2.1 % to 2.8 %. Averaging over longer time intervals decreases uncertainty, at the cost of resolution.

III. Results

We present an example of our measurement algorithm by applying it to simulated data. A reference example for a male test patient (40 years, 170 cm, 75 kg) using the Eleveld model for propofol [3] and dosing for $Ce_{\text{target}} = 4\,\mu\text{g}\,\text{mL}^{-1}$ is presented in Fig. 2. The first test case is simulated based on an infusion regime calculated by a TCI algorithm [1]. Ce_{target} is met exactly, as expected (Fig. 2b). In the second case, the same infusion regime is modified to simulate expected syringe pump behavior: first, a median filter over 5 s is applied to $Q(t)$ to reflect the compliance of the system. Second, the start of the initial bolus is shifted by 15 s and the bolus rate reduced by 5 %, simulating an error in the high $Q(t)$ at the start of the case. Third, measurement noise is simulated by adding white noise of mean 0 and variance 1 (Fig. 2a). This results in an MDAPE of 1.28 % and AVGSTATPE/MAXSTATPE of −0.77 %/−0.97 %. The time to reach within 10 % of Ce_{target} is 35 s longer than in the reference case. Surprisingly, static error is almost completely eliminated within the test runtime; this is due to drug concentration in the plasma compartment equalizing with the effect site within $Ce_{\text{target}} \pm 1$ %, thus eliminating the influence of initial bolus inaccuracy.

IV. Discussion

An approach for verifying dosing performance of syringe pumps in TCI mode was presented. While using the established physical setup to measure the flow rate of the syringe pump [7], this approach amends the evaluation of TCI performance of the pump by applying widely accepted pharmacokinetic models [8]. The novelty of this approach lies in the standardization of test parameters, including a selection of patients biometrics to cover a wide range of possible covariates without leaving allowed operative conditions. Ce is calculated by using an established tool [1], accepted in the community and validated internally against reference implementations. Furthermore, the setup is precisely described to avoid influences from the specific implementation. Finally, the remaining deviation of the ideal behaviour results from the TCI algorithm and syringe pump implementation.

Nevertheless, the current test setup has several limitations. The accuracy may be increased by using a scale with a stronger real-time capable data output and lower drift. Furthermore, environmental conditions have to be controlled to keep additional uncertainties small. To check for a systematic error in the implementation of a TCI algorithm by a manufacturer, the same algorithm has to be evaluated on multiple pumps of the same model. If only one type of syringe is used, characteristics between disposables are not captured in the test results. Especially the proprietary siliconisation of the syringe body and plunger lead to different friction coefficients and differing dosing accuracy [13]. Reliable results of the pump's TCI performance can only be achieved if all syringes approved by the manufacturer are tested. Also, different performance is to be expected when using the actual pharmaceutical formulation of the drug. Manual manipulation of the pump has a measurable effect on the flow rate. In consequence, the test setup only allows for measuring one Ce_{target} setting. A common remote interface to the syringe pump, which permits changing the Ce_{target} setting may allow more sophisticated testing.

The drug concentrations selected for the tests (Propofol 20 mg mL^{-1}, Remifentanil 50 µg mL^{-1}) are the highest commercially available for these drugs. Any TCI algorithm has to take this concentration into account when calculating the flow profile. Generally, syringe pumps are more accurate at higher flow rates; with the given concentrations, the flow rates encountered in the study are the lowest a TCI pump will have to realize. This establishes unfavorable conditions, meaning that results for dosing accuracy measured with our proposed approach will improve at lower drug concentrations.

Overall, the goal of the approach is to quantify the performance of syringe pumps applying TCI targets. Performance errors of PK/PD models in patients generally are around 21 % to 34 % depending on the study population [2], [3]. A syringe pump might introduce, through its mechanical properties or implementation errors in the TCI algorithm, additional errors which might lead to the target not being met. As TCI does not rely on a feedback mechanism, the pump cannot verify that the drug actually delivered to the patient matches the target.

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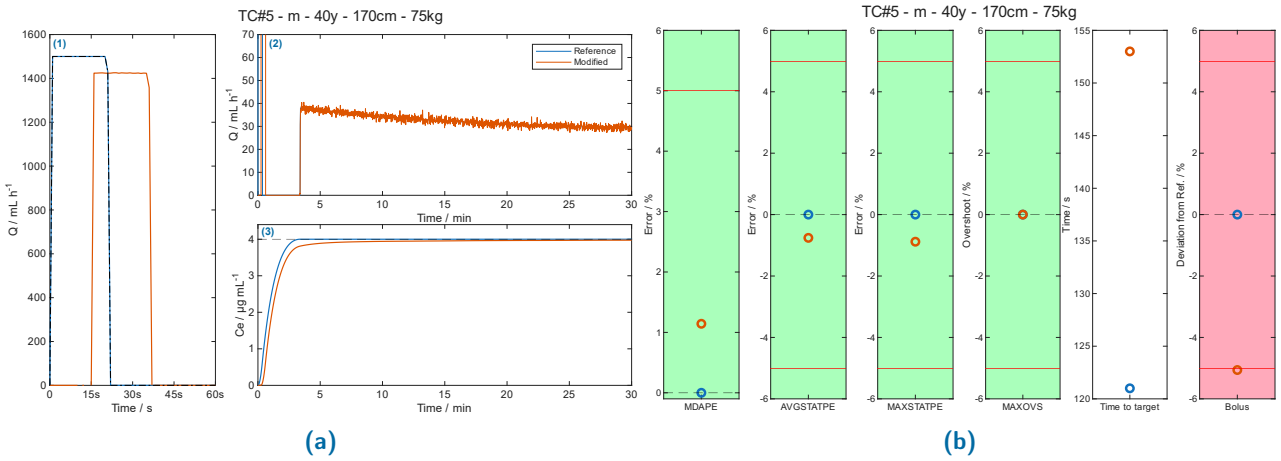

Figure 2: (2a): Simulated reference test case (male, 40 years, 170 cm, 75 kg, Eleveld model [3] with Opioid). Flow rate during the initial bolus (a)(1) and over the duration of the test case (a)(2) result in Ce (a)(3). The unmodified case is plotted in blue, the case modified to represent realistic behavior in orange. (2b): performance metrics for the test case calculated according to [11]. The unmodified flow rate produces no error in Ce; while the error metrics evaluating static performance in the modified case are within tolerance (indicated by red lines), the inaccuracy of the initial bolus exceeds 5 %, leading to this performance criterion being marked "failed".

Thus, the proposed approach may be used to prove that no relevant additional errors are added by a pump.

V. Conclusion

TCI is a tool in daily clinical use, yet lacks a well-defined method of assessing correct implementation and measurement of the expected performance [8]. As we found no test procedure, we propose a common framework for testing the performance of syringe pumps in both standard volumetric and TCI modes. Since the physical setup does not differ from the standardized setup for the assessment of volumetric modes [7], the effort required for implementation is reasonable.

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Author's statement

Conflict of interest: CB and WK are employees of Drägerwerk AG & Co. KGaA.

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