Simulation Setup for a Closed-Loop Regulation of Neuro-Muscular Blockade

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Abstract. We describe a simulation infrastructure for a comprehensive testing of safety, security and performance in a specific medical device (Relaxometry Controller) being developed by RGB Medical. The apparatus is designed to monitor and regulate patient's blood pressure and muscle relaxation during surgery and anesthesia. The controller is at the laboratory testing level under ongoing development and before practical deployment it needs full accreditation by national healthcare agencies. By having a simulation infrastructure, we investigated the controller's übehaviour in various pre-defined clinical test scenarios.

Keywords: Simulation in closed loop feedback control system · Medical device · Anesthesia · Neuro-muscular transmission

1 Introduction

We developed the infrastructure for a simulation setup designed to support the development of an infusion pump controller based on the NMTcuff™ (RGB Medical Devices, Alfonso Gomez 42, 28037 Madrid, Spain) technology for the purpose of relaxometric measurement of pharmacologically induced neuro-muscular transmission. Its first version was the popular TOFcuff™ device, which recently has evolved into the more advanced VISION DUO and VISION AIR/NMT multiparameter monitors. They incorporate the ability for objective surveillance of neuro-muscular transmission (NMT) during the infusion of neuro-muscular blocking agents (NBA) such as rocuronium or cisatracurium. These drugs are administered during general anesthesia for various types of surgery with the intention to inhibit inadvertent movement of the patient. Various states of neuro-muscular blockade may be necessary for different stages of surgery and anesthesia.

Our mission described herein is to develop a safe, reliable, and efficient control algorithm for an automated intravenous infusion of NBA. The objective of the infusion algorithm is to administer the right amount of the NBA that ensures the required level of neuro-muscular blockade over time. The latter is measured

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in the traditional units of standard relaxometry: train of four ratio (TOFr), train of four count (TOFc), and post-tetanic count (PTC) [3]. The two corresponding goals are: 1) to maintain the necessary level of NMB during surgery, and 2) to enable the fastest possible recovery from NMB as soon as the surgery is finished, and the patient should emerge from anesthesia.

The algorithm takes into account the patient's response to drug doses (patient model) based on pharmacokinetic data from the literature that has been obtained in clinical practice [4,5]. The mentioned algorithm has at its core a 3-compartment pharmacokinetic model, which reflects reasonably well the dynamic changes of the drug concentration in the plasma. The calculated concentrations give an estimated pharmacodynamic effect on blocking the neuromuscular transmission on a simplified surrogate relaxometric scale encompassing 10 TOFr, 4 TOFc and 16 PTC levels. The validity of the patient model is essential for the overall performance of the algorithm. Due to lack of relevant clinical studies, we substituted the missing clinical data with experimental data.

2 Pharmacokinetic/Pharmacodynamic Model of Rocuronium

Pharmacokinetic (PK) and *Pharmacodynamic* (PD) models play a very important role in our simulation infrastructure. Based on clinical studies, these models describe the pharmacological effects caused by the drug on the human body (PD) as well as the metabolism and elimination of the drug (PK). In the herein reported case, we deal with rocuronium and its blocking effects on the neuromuscular transmission.

Pharmacokinetics describes the dynamic distribution of the intravenously administered drug within patient's body and the changes in its concentration over time. According to the employed model, the patient's body is divided into 3 compartments, which represent the blood volume (central compartment) and the perfused organs (a fast as well as a slow distribution compartment). Intercompartmental flows are described by differential Eqs. (1–3), with an input flow $I(t)$ modeling the intravenously administered drug. The state variable C_i defines an absolute current amount of the drug into the compartment i. Drug concentration C_{inp} in the central compartment represents the resulting effect on neuromuscular blockade (NMB).

$$\frac{dC_1}{dt} = I(t) - (k_{13} + k_{12})C_1 + k_{21}C_2 + k_{31}C_3 \tag{1}$$

$$\frac{dC_2}{dt} = k_{12}C_1 - k_{21}C_2 \tag{2}$$

$$\frac{dC_3}{dt} = k_{13}C_1 - k_{31}C_3 \tag{3}$$

Numerical simulation of Eqs. (1–3) is implemented using Euler integration method with $\Delta = 1\,\mathrm{s}$ time step. The intercompartmental rate constants were

obtained from a clinical study [1]. Their mean values for normal patients are $k_{12} = 0.259$, $k_{21} = 0.163$, $k_{13} = 0.060$, $k_{31} = 0.012$, $k_{10} = 0.119$ (min^{-1}).

The intravenous infusion $I(t) = B(t) + F(t)$ represents the input to this PK/PD system. $B(t)$ denotes a discrete input (a bolus in (ml)) administered at the time t. Similarly, $F(t)$ denotes a continual flow defined in $(ml\,hour^{-1})$. Rocuronium is being administered in a diluted solution at $10\,\mathrm{mg\,ml}^{-1}$, while both eventual inputs need to be numerically transformed into appropriate weight (μg) and time units $(\mu g\,s^{-1})$.

The current amount $C_1(t)$ (μg) of rocuronium is distributed within so called volume of distribution V_d (ml), resulting in the current concentration $C_{inp}(t) = C_1(t)/V_d$ of rocuronium in the blood plasma. The volume of distribution is an uncertain attribute of PK/PD modeling and differs significantly among patients. For this reason, V_d is variable in our experiments with a default value $38\,\mathrm{ml\,kg}^{-1}$ of patient's total body weight [1,2].

2.1 Pharmacodynamic Effect of Rocuronium

The neuro-muscular blocking effect of rocuronium is determined from the current C_{inp} concentration and is mapped into the proprietary TOF and PTC scales. Pharmacologic literature refers widely to the so called Hill function (4) computing the effect from C_{inp}, EC_{50} and γ, where EC_{50} denotes the concentration leading to half effect and γ is a shape coefficient.

$$E_i(C_{inp}) = \frac{C_{inp}^{\gamma}}{EC_{50}^{\gamma} + C_{inp}^{\gamma}} \cdot 100 \tag{4}$$

We assume that E_i denotes the NMB effect in four twitches $i = 1, 2, 3, 4$ of TOF method. Then we obtain TOF amplitudes $TOF_i = 100 - E_i$ in the TOF defined range $\langle 0, 100 \rangle$. See Table 1 for particular coefficients. Finally, we have TOF ratio $TOFr = TOF_4/TOF_1$ and TOF count $TOFc$ as the number of twitches with nonzero amplitude $TOF_i > 0$.

Table 1. Coefficients of effect function for four TOF twitches.

TOF twitch	EC_{50} $(\mu g\,ml^{-1})$	γ
1	0.823	4.79
2	0.823/1.1	4.79/1.1
3	0.823/1.3	4.79/1.25
4	0.823/1.5	4.79/1.33

Post-tetanic count (PTC) is the other measurement method, giving NMT on a 16-step integer scale from 0 to 15. PTC measurement becomes essential for NMT monitoring when $TOFC = 0$. In this case the TOF measurement cannot sense any deeper relaxation. When $TOFc = 0$, PTC has already arrived at

approximately 8 counts. For this reason, we set the corresponding C_{inp} as the half effect concentration EC_{50} in the PTC's Hill function. This value can be obtained analytically from the inverse function $E_1^{-1}(100)$ in its maximum effect.

3 Architecture of the Simulation Infrastructure

Our simulation infrastructure consists of two separate tools *NMT-Simulator* and *Test Case Manager*. Both are interconnected using the REDIS database system. The whole distributed system is depicted in Fig. 1.

The internal NMT-Simulator is made of these four components:

- The medical device monitor incorporate the enhanced NMTCuff^{TM} monitoring functionality plus the controller (CNT) feature for the automated regulation of the patient's NMT. The controller implements various strategies of automated anesthesia.
- The infusion pump (PUMP) is a medical device that is remotely controlled by the monitor and provides the intravenous infusion of the drug. The infusion pump can administer discrete boluses (indicated in ml) or manage a continuous drug flow (indicated in $ml\,hour^{-1}$).
- The patient model (PM) is a mathematical model of patient's response to rocuronium. The model integrates PK/PD as they were described in Sect. 2. This component outputs the essential state variables such as C_{inp}, TOF and PTC effects, and the estimated time for total recovery.
- The NMT sensor (SENSOR) is measuring patient's NMT using TOF and PTC methods. Intervals between measurements samples are determined by the controller.

The Test Case Manager (TCM) is a computer program designed to manage all simulation experiments and to perform statistical postprocessing.

This distributed infrastructure has a star topology with REDIS in its core. All involved components are connected solely to REDIS, which simplifies the necessary communication among the interfaces. Apart from data storage capability, REDIS also grants a message brokering feature. The simulation process is based on sequential passing of activity between the components in a pre-defined communication protocol. Since all components need to implement just one technical interface (to REDIS) and to apply a simple protocol, the overall concept is very flexible and robust. Moreover, this concept allows for abstractions above the components, so that the technical implementation of each component may differ depending on the employed experiment. Every component can be plugged in as a real hardware or as its simulation model.

We consider currently the patient model in the form of mathematical construct only, however, real humans might participate in case of approved clinical experiments.

Every experiment is assigned a unique string identifier denoted as $expID$ (for example "vm.tc.fwsim.1"). This $expID$ identifies a corresponding data record (hash type) and message channel within REDIS. Data hash keys are accessed via

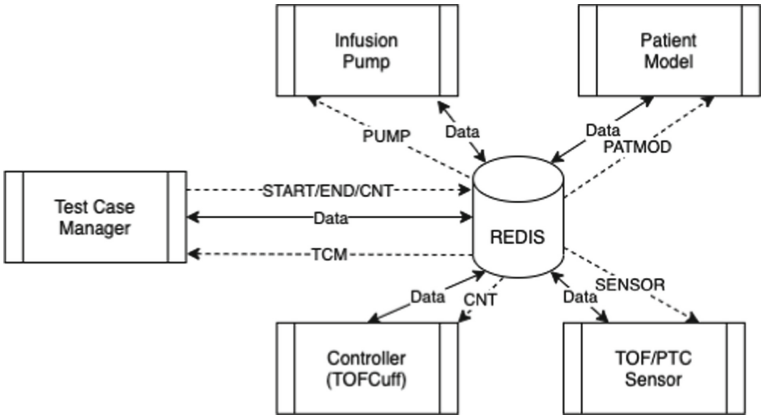

Fig. 1. Scheme of the simulation infrastructure. Dotted lines – control commands. Solid lines – data transfers.

`hset expID key` and `hget expID key` commands. The messaging follows the Publish/Subscribe paradigm, and therefore $expID$ defines a temporary channel for the $expID$ experiment, to which all components may send messages. All messages are broadcasted to all components. For more details, see the REDIS technical documentation [6].

4 The Simulation Protocol

All participants must subscribe for receiving messages at REDIS and implement correctly the following protocol. We may denote a REDIS message (sent or received) as tuple $(expID, msg)$ where $expID$ identifies the experiment, and msg holds the message body (with values START, END, CNT, PUMP, PM, SENSOR, TCM).

As it is stated above, TCM generates and executes simulation experiments under various conditions. For every experiment, TCM runs a procedure depicted in Algorithm 1. The procedure begins with generating a unique $expID$. Then TCM uploads a set of internal attributes describing the experiment into a corresponding REDIS data record that is shared among the distributed components. The simulation itself begins with $(expID, START)$ message. Upon this signal, all components download the experiment's data record, reset their internal state and get ready for a new experiment.

Finally, TCM repeats several simulation cycles with an increasing model time. The components are activated sequentially in the order TCM, CNT, PUMP, PM, SENSOR and then back to TCM. Every activated component executes its own procedure and then calls the successive component.

Algorithm 1. Managing a single experiment from TCM.

```
// experiment ID must match the vm.* pattern
expID := generate an unique experiment identifier
// start with initial model time
mtime := 0
// upload all experiment attributes to REDIS into expID data record
hset(expID, key, value) for all key
// initiate the experiment. All components get ready.
publish(expID, "START")
// run the simulation until the end of model time
while mtime <= MAXTIME {
    hset(expID, "mtime", mtime)
    // activate the first component in the loop
    publish(expID, "CNT")
    // wait until the loop ends when SENSOR calls TCM
    waitUntilMessage(expID, "TCM")
    // download the entire experiment data record and store it
    dict := hget(expID, key, value) for all keys
    save "dict" locally
    // shift the model time
    mtime := mtime + timeStep
}
// terminate the experiment
publish(expID, "END")
```

4.1 Controller Component (CNT)

On receiving $(expID, CNT)$, the controller decides about the next configuration of the infusion pump at *mtime* in the context of the current $expID$ experiment. CNT outputs *bolus* and $infusion$ attributes to the experiment's data record in REDIS. The course of anesthesia in the sense of NMT regulation has basically two phases. In the first one, the so called *initial bolus* is administered in order to achieve a NMB to the level suitable for tracheal intubation. In the second phase, the system is supposed to keep the NMT at a predefined target level on the surrogate TOF/PTC scale. This automated regulation is implemented in various strategies that are parts of our experimenting.

The controller outputs the initial bolus $iBolus$ at $mtime = 0$. The amount is set to 0.7 $\mathrm{mg\,kg^{-1}}$ of patient's body weight (this dosage may differ according to particular patient's muscle-to-fat ratio or particular goals of the surgical procedure). In the further simulation cycles ($mtime > 0$), the controller may execute the following simulation strategies.

Basic Strategy. CNT adminsters repeatedly *repeBolus* (ml) boluses in regular time intervals *repeStep* (s). This methods implements a trivial approach in anesthesia when the controller is not supplied with NMT measurements feedback.

Forward Simulation Strategy. This strategy is based on CNT's ability to predict future evolution of PK/PD aspects in patient's body. Technically, CNT contains an integrated patient model that follows the steps of infusion and can simulate the future evolution of patient's NMT. This method computes a minimal bolus dosage that ensures patient's target NMT from *mtime* till $mtime + fwRange$. This method is incorporated for experimental purposes only. Its numerical complexity disqualifies that from practical deployment in the medical device.

Analytic Strategy. This strategy comes from clinical experience. In a simplified version, we assume regular PTC measurements every three minutes. With each fresh sample *current* (PTC) of NMT measurement, if $current \leq target$ then NMB is higher than required, this cycle ends with no further dose administered. Otherwise, CNT instructs the pump to deliver another bolus (5) based on the amount of $iBolus$.

$$nBolus = (current - target) \cdot 0.04 \cdot iBolus \tag{5}$$

4.2 Patient Model Component (PM)

The patient model resets its internal state on every $(expID, START)$ command and loads experiment's attributes from REDIS, such as patient's weight (V_d) and sensitivity to rocuronium (EC_{50}, γ).

In every simulation cycle, on receiving $(expID, PM)$ message, PM computes its internal PK/PD numerical simulation from the previous *mtime* to the current *mtime* in Δ time steps. PM exports C_{inp}, TOF amplitudes, TOFr, TOFc, PTC value and cumulative consumption of rocuronium. Moreover, PM invokes a nested simulation that steps further in model time until $TOFr \geq 0.95$ appears, and presents it as the so called *total recovery*.

5 Experimenting

The goal of this testing is to investigate the robustness of the implemented anestesiological strategies across a wide range of configurations of patients and their metabolic capacities. The experimenting is managed by TCM that randomly samples all configurations and submits the results through the simulation infrastructure. The space of all configurations is given by a Cartesian product of range of weight, patient's sensitivity to rocuronium, and of V_d, which represents various anestesiological scenarios, which in turn are tailored according to specific surgical procedures

The Test Case Manager statistically evaluates the time series of state variables outcoming from the patient model. Special care is taken for scenarios when NMB is permitted to be less intense. Inadvertant moves by the patients may cause harm and must therefore be suppressed by providing an adequate level of

NMB. A secondary goal is to minimize the total drug consumption of rocuronium, which beyond its economical relevance, also may shorten the time needed for total recovery. The desired level of total recovery from NMB is generally viewed as $TOFr \geq 0.95$, that in our practice has to be confirmed three times in a row. Before that level is achieved, anesthesia must be maintained.

6 Conclusion

We presented our simulation infrastructure that allows to extensively test various anestesiological strategies with an automated regulation of neuro-muscular blockade. Since in this area of medical research, real clinical data is scarce, simulation based on models is a feasible way to obtain experience with control algorithms and in order to optimize the underlying algorithm. Moreover, the presented architecture can inspire also other drug dosing/clinical effect projects.

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