Pulse-modulated feedback control in dosing applications*

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Abstract— **Dosing generally refers to feeding chemicals to a process until a desired level of effect is reached. The latter assumes that the effect of the chemicals on the process can be measured. Here, only discrete dosing is considered when calculated quantities of a chemical are introduced to the process at certain time instances. Applications of dosing are common in process and food industry, medicine, and biotechnology. The intermittent mode of discrete dosing calls for a hybrid (continuous-discrete) modeling of the closed-loop system, where the plant dynamics are captured by differential equations whereas the control law is described by difference equations. It is suggested that pulse-modulated feedback to be utilized for calculating the discrete doses and their timing from the continuously measured plant output in order to keep the process output within a pre-defined interval of values. Controller design methods are considered and illustrated by a simple control system of dosing a neuromuscular blockade agent in anesthesia.**

I. BACKGROUND

An everyday life example of a dosing application is following doctor's orders on medication regimen, for instance, "take one tablet twice a day". This is an open-loop dosing strategy that does not consider the medication effect in the patient. Further, increasing or decreasing each single dose corresponds to the mechanism of amplitude modulation in pulse-modulated control, whereas manipulating the dosing interval constitutes the principle of frequency modulation.

Besides pharmacotherapies, where drugs are administered in tablet or injection form, similar dosing problems characterized by (relatively rare) impulsive control action and continuous measurement of the effect are commonly found in space technology, water treatment, food, chemical and biochemical industries, agriculture, steel and mining industries, to name a few. An industrial dosing control system operates typically open-loop and is implemented by means of discrete logic or automata.

Relieving the burden of manual drug administration over lengthy periods of time requires automation. Surgery with operative time over two hours is common and has to be reliably supported by general anesthesia that allows patients to be unconscious and free of pain throughout the procedure.

General anesthesia is nowadays predominantly achieved by intravenous administration of sedatives (hypnotics), analgesics, and muscle relaxants, i.e. neuromuscular blockade (NMB) agents. In most cases, NMB agents are administered via continuous infusion. However, controlled boluses are recommended in some cases because intermittent doses allow serial evaluation and reduce the risk of developing myopathies due to prolonged paralysis [1]. The effect of NMB agents is routinely measured by neuromuscular monitors, devices that electrically stimulate a peripheral nerve while also quantifying the evoked responses. Compared to the administration of fixed doses (open-loop control), using the monitors for dose titration during the course of treatment significantly reduces the exposure to NMB drugs without affecting the observed clinical outcome [2].

The present contribution investigates the dynamical properties of a drug dosing system in a feedback framework. The NMB is selected as application due to the availability of reliable effect quantification that enables feedback control.

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II. MATHEMATICAL MODELS

Continuous part: Consider a time-invariant Wiener system whose measured output is a nonlinear function of the linear block output. The linear block is given by the state-space representation

$$\dot{x}(t) = Ax(t), \quad \bar{y}(t) = Cx(t), \tag{1}$$

where the matrices are

$$A = \begin{bmatrix} -a_1 & 0 & 0 \\ g_1 & -a_2 & 0 \\ 0 & g_2 & -a_3 \end{bmatrix}, C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}, \tag{2}$$

$a_1, a_2, a_3 > 0$ are distinct constants, and $g_1, g_2 > 0$ are positive gains. The measured output is then

$$y(t) = \varphi(\bar{y}), \tag{3}$$

where $\varphi(\cdot)$ is a smooth function.

Discrete part: Continuous-time system (1) is controlled by a pulse-modulated feedback that gives rise to instantaneous jumps in the state vector $x(t)$

$$x(t_n^+) = x(t_n^-) + \lambda_n B, \quad t_{n+1} = t_n + T_n, \tag{4}$$
$$B = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}^\top, \quad n = 0, 1, \ldots,$$

where

$$T_n = \bar{\Phi}(y(t_n)),\ \lambda_n = \bar{F}(y(t_n)).$$

In pulse-modulated control, $\bar{\Phi}(\cdot)$ is referred to as the frequency modulation function and $\bar{F}(\cdot)$ as the amplitude modulation function. The minus and plus in a superscript in (4) denote the left-sided and right-sided limits, respectively. The described by (4) control mechanism corresponds to plant (1) being subject to an impulsive action $\lambda_n B\delta(t_n)$ applied directly to the state vector, where $\delta(\cdot)$ is Dirac delta function.

With $\circ$ denoting composition, introduce the functions

$$\Phi(\cdot) \triangleq (\bar{\Phi} \circ \varphi)(\cdot), \quad F(z) \triangleq (\bar{F} \circ \varphi)(\cdot).$$

Then closed-loop system (1), (4) constitutes a hybrid (continuous-discrete) system that is able to exhibit a wide range of nonlinear dynamics phenomena but can also be designed to produce a desired behavior through the choice of the modulation functions $\bar{F}(\cdot)$, $\bar{\Phi}(\cdot)$.

A. Pharmacokinetic-pharmacodynamic model

A minimally parametrized pharmacokinetic-pharmacodynamic (PKPD) model of the NMB agent *atracurium* is introduced in [3]. The output $y(t)$ [%] represents the effect of the NMB agent and is measured by a train-of-four neuromuscular monitor [4]. The maximal level of $y(t) = 100\%$ is achieved when the NMB is initiated and there is no drug in the bloodstream of the patient. The elements of the matrix A in (2) are parametrized in terms of a common factor $\alpha > 0$

$$a_1 = v_1\alpha, a_2 = v_2\alpha, a_3 = v_3\alpha, g_1 = v_1\alpha, g_2 = v_2v_3\alpha^2, \quad (5)$$

where $v_1 = 1$, $v_2 = 4$, $v_3 = 10$ are fixed coefficients calculated from clinical data. The PD part is modeled by a Hill function of order γ

$$y = \varphi(\bar{y}) = \frac{100C_{50}^{\gamma}}{C_{50}^{\gamma} + \bar{y}^{\gamma}(t)}, \quad \gamma > 0. \quad (6)$$

Here $C_{50} = 3.2425\ \mu\text{g ml}^{-1}$ is the drug concentration that produces 50% of the maximum effect.

III. Design

A controller design algorithm yields the parameters of the modulation functions in (4) for a given by the constants (α, γ) PKPD model and the parameters of a desired 1-cycle. The design procedure is covered in more detail in [5].

Select the parametrization of the modulation functions of controller (4) as piecewise affine, i.e.

$$\Phi(\xi) = \begin{cases} \Phi_2 & \Phi_2 < k_2\xi + k_1, \\ k_2\xi + k_1 & \Phi_1 \le k_2\xi + k_1 \le \Phi_2, \\ \Phi_1 & k_2\xi + k_1 < \Phi_1, \end{cases} \quad (7)$$

$$F(\xi) = \begin{cases} F_1 & k_4\xi + k_3 < F_1, \\ k_4\xi + k_3 & F_1 \le k_4\xi + k_3 \le F_2, \\ F_2 & F_2 < k_4\xi + k_3. \end{cases} \quad (8)$$

The parameter set k_1, k_2, k_3, k_4 and F_1, F_2, Φ_1, Φ_2 completely describes pulse-modulated controller (8), (7). The modulation functions limits, as well as the parameters of the desired (stationary) periodic solution, are derived from clinical practice and selected as $F_1 = 150\ \mu\text{g/kg}$, $F_2 = 400\ \mu\text{g/kg}$, $\Phi_1 = 11$ min, $\Phi_2 = 50$ min. Therefore, control law (4) cannot produce a dose higher than F_2 or lower than F_1. Further, there is at least one dose administered in Φ_2 minutes but not closer than Φ_1 minutes to the previous one.

The design aim is to render an orbitally stable 1-cycle with the parameters $\lambda = 300\mu\text{g/kg}$, $T = 20$ min in the closed-loop system comprising (1), (6), (4). The design procedure is composed of three steps.

Step 1: The fixed point corresponding to the desired periodic solution is calculated for model (1) as

$$X = \lambda(\mathrm{e}^{-TA} - I)^{-1}B, \quad \bar{y}_0 \triangleq CX.$$

Step 2: The coefficients k_2, k_4 are selected such that the Jacobian $Q'(X)$ is Hurwitz-stable

$$Q'(X) = A_\Phi + WKC, \ A_\Phi = \mathrm{e}^{A\Phi(\bar{y}_0)},$$

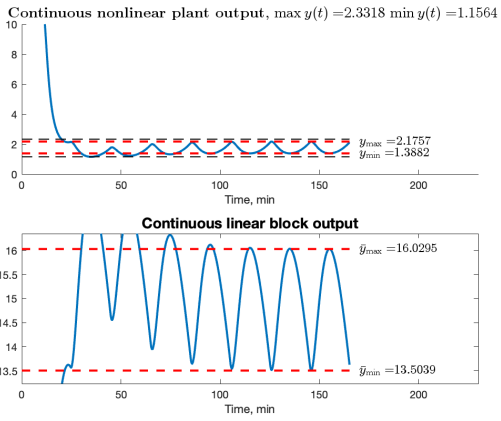

Fig. 1. Convergence to the 1-cycle from $x(0) = 0$ in the NMB model stabilized by the modulation function slopes $F'(y_0) = -0.15$, $\Phi'(y_0) = 0.29$. Top plot: the nonlinear output $y(t)$. The horizontal black dashed lines mark $\inf_t y(t)$ and $\sup_{t\in[T,5T]} y(t)$. The stationary output corridor values for the 1-cycle are marked in red. Bottom plot: the linear output $\bar{y}(t)$.

$$W = \begin{bmatrix} J & D \end{bmatrix}, K^{\top} = \begin{bmatrix} F'(\bar{y}_0) & \Phi'(\bar{y}_0) \end{bmatrix}.$$

Step 3: The rest of the coefficients of the modulation functions are obtained from

$$F(\bar{y}_0) = (\bar{F} \circ \varphi)(\bar{y}_0) = k_4\varphi(\bar{y}_0) + k_3 = \lambda,$$
$$\Phi(\bar{y}_0) = (\bar{\Phi} \circ \varphi)(\bar{y}_0) = k_2\varphi(\bar{y}_0) + k_1 = T.$$

A simulation of the designed controller in the closed-loop for the nominal parameters $(\bar{\alpha}, \bar{\gamma})$, starting induction of NMB $(x(0) = 0, y(0) = 100\%)$, is depicted in Fig. 1. The corridor of the output values under stationary conditions is calculated according to [6]. The output signal converges promptly to the stationary solution with a minimal overshoot.

References

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