Observers for the Seidel–Herzel model of human autonomic-cardiorespiratory system ⋆

A. Othmane [*,**] **H. Mounier** [**]

[*] *Université Paris-Saclay, CNRS, CentraleSupélec, Laboratoire des signaux et systèmes, 91190, Gif-sur-Yvette, France (e-mail: {amine.othmane,hugues.mounier}@l2s.centralesupelec.fr)*
[**] *Chair of Systems Theory and Control Engineering, Saarland University, 66123 Saarbrücken, Germany (e-mail: a.othmane@lsr.uni-saarland.de)*

Abstract: The Seidel-Herzel model of the autonomic-cardiorespiratory system is used in this work to derive three observers for the estimation of the concentrations of the neurotransmitters and external excitations of the sympathetic and parasympathetic systems. The observers require noninvasive measurements of respiration and blood pressure which simplifies the development of patient-specific applications. The errors stemming from model approximations and uncertain parameters are analyzed. The applicability of the approach is discussed in a simulation study.

Keywords: Nonlinear observers, physiology, autonomic-cardiorespiratory system

The interactions between the autonomic nervous, the cardiovascular and the respiratory systems control the autonomic-cardiorespiratory regulation. A variety of models describing the autonomic-cardiac regulation have been developed. All these models can be grouped into ones yielding hybrid systems where switching phenomena appear (Olufsen et al. (2007, 2006); Ottesen and Olufsen (2011); Seidel (1997); Seidel and Herzel (1995)), and others containing solely Lipschitz continuous functions (Ataee et al. (2012); Cavalcanti and Belardinelli (1996); Fowler and McGuinness (2005); Olufsen and Ottesen (2012); Ottesen (1997a,b); Ottesen et al. (2014)). However, only a few works e.g. Ataee et al. (2012); Seidel (1997); Seidel and Herzel (1995) incorporate the effects of the respiratory system. The models developed in Seidel and Herzel (1995) and Seidel (1997), analyzed and refined further in Dudkowska and Makowiec (2007); Duggento et al. (2012); Kotani et al. (2005); Rabinovitch et al. (2015); Seidel and Herzel (1998) cover heart rate regulation, respiratory sinus arrhythmia and resonant interaction of respiration and blood pressure oscillations (Mayer waves). They are hybrid systems involving nonlinear delayed differential equations and different switching phenomena.

Different approaches for the estimation of the parameters of these models have already been developed in Marquis et al. (2018); Olufsen and Ottesen (2012); Ottesen et al. (2014); Seidel (1997), for example. The online estimation of unmeasured quantities using observers has, however, gained little attention. While blood pressure, heart rate, and respiration rate, and respiration flow can be accurately measured using noninvasive approaches, activities of the parasympathetic and sympathetic systems are, however, difficult to measure. Online estimation of these activities is crucial to design patient-specific applications or better understand the involved mechanisms.

In this work, the description of the baroreflex, the autonomic nervous system, the respiratory system, and the neurotransmitters developed in Seidel (1997) are briefly recalled. It is shown that the instantaneous blood pressure, the activity of the respiratory neurons, and the heart rate can be seen as exogenous signals, an input, and an output, respectively, of a dynamic system described by ordinary differential equations involving time delays and nonlinearities. A significant obstacle in the analysis of this model is its complex hybrid nature combined with the numerous nonlinearities and delays complicating the design of observers. To use standard tools for estimation and observation problems, a continuous but physiologically valid approximation is needed. This idea has already been used in Olufsen and Ottesen (2012); Ottesen et al. (2014); Seidel (1997) for parameter estimation. It is used here, perhaps for the first time, to design observers to estimate neurotransmitter concentrations and external inputs exciting the nervous system. The effects of this approximation and that of parameter uncertainties on the estimation error are analyzed in detail.

This work is structured as follows. Notation is introduced in Section 1. In Section 2, models for the baroreceptors, the respiratory and the autonomous nervous systems, and the concentrations of the neurotransmitters are presented. The estimation of the concentrations in the absence of external excitations of the nervous system is discussed in Section 3. Their simultaneous estimation with external excitations of the sympathetic and parasympathetic systems are discussed in Sections 4 and 5.

⋆ This work is supported by the "ADI 2018" project funded by the IDEX Paris-Saclay, ANR-11-IDEX-0003-0, and is part of ANR project MindMadeClear number ANR-17-CE40-0005

1. NOTATIONS

The Gamma function is denoted Γ. For a vector $a \in \mathbb{R}^n$, $\|a\|$ denotes any p-norm. A signal $x : t \mapsto x(t)$ delayed by $\theta \in \mathbb{R}_+$ is denoted $\delta^\theta x(t) \coloneqq x(t-\theta)$. The explicit time dependency is omitted when no confusion can occur.

Denote by g a saturation function satisfying the assumption 1 and by γ its Lipschitz-constant.

Assumption 1. Let $g : \mathbb{R} \to \mathbb{R}$ be a differentiable function vanishing at zero and satisfying

$$\lim_{x\to-\infty} g(x) = -1, \quad \lim_{x\to\infty} g(x) = 1 \quad \text{and} \quad \frac{\mathrm{d}}{\mathrm{d}x} g(x) > 0.$$

2. MODEL

The model introduced in Seidel (1997) is briefly recalled.

2.1 Baroreceptors

Baroreceptors, sometimes also called pressure receptors, are neural cells wound around blood vessels. They are located along the aorta with the most important ones in the aortic arch directly at the heart and at the sinus caroticus in the neck. The aortic nerve and the carotid sinus convey their signals to the brain. Experimental investigations have shown that the baroreceptors' activity depends on both the pressure and its time derivative. It has a sigmoidal shape, i.e. they start to fire only when the blood pressure reaches a threshold, and attains a saturation when it becomes high. These effects can be modelled by

$$\bar{\nu}_\mathrm{b} = (p_{\mathrm{b,c}} - p_{\mathrm{b},0}) \left(1 + g\left(\tfrac{p - p_{\mathrm{b,c}} + k_\mathrm{b}\dot{p}}{p_{\mathrm{b,c}} - p_{\mathrm{b},0}}\right)\right),$$

with $\bar{\nu}_\mathrm{b}$ the baroreceptors spike frequency, p the blood pressure, $p_{\mathrm{b},0}$ the pressure for which the static response $\dot{p}$ drops to zero, and k_b, $p_{\mathrm{b,c}}$ are positive scalar parameters.

Since the shape of the pressure wave changes along the aorta, the different baroreceptors have different pressure inputs. The conduction time of their signals to the brain depends also on their location. This is not taken into account in the latter equation but can be modelled using a convolution with a Green function $q(\cdot)$ such that their broadened activity is given as

$$\nu_\mathrm{b}(t) = \int_{-\infty}^{\infty} q(t-\tau)\, \bar{\nu}_\mathrm{b}(\tau)\mathrm{d}\tau, \tag{1a}$$

with

$$q(t) = \begin{cases} 0 & \text{for } t \leqslant 0, \\ \frac{1}{\sigma}\Xi_{2+\eta/\sigma}\left(\frac{t}{\sigma}\right) & \text{for } t > 0, \end{cases}$$

where

$$\Xi_l(x) = \tfrac{x^{l/2-1}\mathrm{e}^{-x/2}}{2^{l/2}\Gamma(l/2)}.$$

The parameter η is the delay to the maximum response and σ is a measure for the width of the kernel.

2.2 Medulla and autonomic nerves

The medullary circulation centers combine the impulses from the baroreceptors, the different cerebral regions, and the respiratory neurons. The sympathetic and parasympathetic nerves convey its output to the heart. The following characteristic are known from physiology:

- An increased activity of the aortic nerve and of the carotid nerve sinus reduces the sympathetic activity.
- An increased activity of the aortic nerve and of the carotid nerve sinus enhances the parasympathetic activity.
- The strength of these influences is determined by the phase of the respiratory cycle.

Thus, the sympathetic and parasympathetic activities denoted ν_s and ν_p, respectively, are modelled as

$$\nu_\mathrm{s} = \max\left\{0, k_{\mathrm{s,r}}\nu_\mathrm{r} - (1 + k_{\mathrm{s,br}}\nu_\mathrm{r})\,\nu_\mathrm{b} + \nu_{\mathrm{s},0}\right\}, \tag{1b}$$

$$\nu_\mathrm{p} = \max\left\{0, k_{\mathrm{p,r}}\nu_\mathrm{r} + (1 + k_{\mathrm{p,br}}\nu_\mathrm{r})\,\nu_\mathrm{b} + \nu_{\mathrm{p},0}\right\}, \tag{1c}$$

with the positive scalar parameters $k_{\mathrm{p,r}}$, $k_{\mathrm{p,br}}$, $\nu_{\mathrm{p},0}$, $k_{\mathrm{s,r}}$, $k_{\mathrm{s,br}}$ and $\nu_{\mathrm{s},0}$. The activity of respiratory neurons, denoted ν_r, is modelled as

$$\nu_\mathrm{r}(t) = \tfrac{1}{2} - \tfrac{1}{2}\sin\left(2\pi\tfrac{t - t_\mathrm{insp} + \theta_\mathrm{r}}{T_\mathrm{r}}\right), \tag{1d}$$

with $T_\mathrm{r} > 0$ the respiration period, $t_\mathrm{insp} \geqslant 0$ the time of last inspiration beginning, and $\theta_\mathrm{r} \geqslant 0$ is a phase shift.

2.3 Concentration of neural transmitters

The sympathetic and parasympathetic activities regulate the concentrations of neurotransmitters which in turn influence the heart rate. Noradrenaline is the sympathetic one and acetylcholine is the parasympathetic one. Experimental investigations have shown that the effect of the sympathetic activity is attenuated as the level of parasympathetic one increases. Due to the finite transport time of information in the nerves, time delays appear in the system and cannot be neglected. Denote by c_p and c_s the concentrations of acetylcholine and noradrenaline, respectively. Their dynamics can be described by

$$\tau_\mathrm{s}\dot{c}_\mathrm{s} = -c_\mathrm{s} + g\left(b_\mathrm{s}\delta^{\theta_\mathrm{s}}\nu_\mathrm{s}\right)\left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right) \tag{1e}$$

$$\tau_\mathrm{p}\dot{c}_\mathrm{p} = -c_\mathrm{p} + g\left(b_\mathrm{p}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right), \tag{1f}$$

where $\tau_\mathrm{s} > 0$ and $\tau_\mathrm{p} > 0$ are time constants, $\theta_\mathrm{s} \geqslant 0$ and $\theta_\mathrm{p} \geqslant 0$ are the transport delays of the sympathetic and parasympathetic activities, respectively, and b_s, a_s and b_p are positive scalar parameters. The initial conditions are $c_\mathrm{s}(t_0) = c_{\mathrm{s}0}$ and $c_\mathrm{p}(t_0) = c_{\mathrm{p}0}$.

2.4 Heart rate

The heart rate, denoted h, depends on the concentration of the neurotransmitters acetylcholine and noradrenaline. While an increase in the first causes a reduction of the heart rate, an increase in the second induces a raise. It is defined as the time elapsed between two beats and thus is a piecewise constant function of time. Different pulsatile models for the dynamics of h have been discussed in the literature. See for instance Olufsen et al. (2007, 2006); Seidel (1997); Seidel and Herzel (1995, 1998). This approach yields a hybrid system. In order to use the well established methods from control theory developed for continuous-time systems, the heart rate h is approximated in this work by a continuous-time function f of the concentrations c_p and c_s, i.e.

$$h = f(c_\mathrm{p}, c_\mathrm{s}). \tag{1g}$$

For it to be physiologically valid, f has to satisfy for all concentrations c_s and c_p the conditions

$$\tfrac{\partial}{\partial c_\mathrm{p}} f(c_\mathrm{p}, c_\mathrm{s}) < 0, \quad \text{and} \quad \tfrac{\partial}{\partial c_\mathrm{s}} f(c_\mathrm{p}, c_\mathrm{s}) > 0, \tag{1h}$$

discussed above. These conditions describe the physiological observation that the heart rate is increased by an elevation of sympathetic transmitter and decreased by an elevation of vagal transmitter.

Two possible definitions for the function f satisfying this conditions have been proposed in the literature. First, a linear combination of the neurotransmitters, i.e.

$$h = f(c_\mathrm{s}, c_\mathrm{p}) \cong h_1(c_\mathrm{s}, c_\mathrm{p}) = h_0 + \alpha c_\mathrm{s} - \beta c_\mathrm{p}, \qquad \text{(1i)}$$

with $h_0, \alpha, \beta > 0$, was introduced in Olufsen and Ottesen (2012); Seidel and Herzel (1998). While it was proposed using a phenomenological description, it can be seen here as a linearization of the function f around the intrinsic heart rate h_0. Second, A combination of the neurotransmitters involving a coupling term, i.e.

$$h = f(c_\mathrm{s}, c_\mathrm{p}) \cong h_0 + \alpha c_\mathrm{s} - \beta c_\mathrm{p} - \gamma c_\mathrm{s} c_\mathrm{p}, \qquad \text{(1j)}$$

with $h_0, \alpha, \beta, \gamma > 0$, was proposed in Ottesen et al. (2014). Note that for the conditions in (1h) to be fulfilled, it is not sufficient that the parameters are strictly positive.

2.5 Discussion

The model in (1) involves different parameters, measured and unmeasured signals. Continuous-time measurements are necessary for the development of estimation algorithms. The heart rate can be measured using electrocardiography. The inspiration times can be computed from the output of a spirometer measuring the airflow. Noninvasive measurement of the arterial blood pressure can be obtained using the volume-clamp method Bogert and van Lieshout (2005). Hence, in the sequel, the pressure, the heart rate, and the inspiration times are assumed to be measured. In this setting, the activity ν_r of the respiration neurons is the only signal that a person can freely act on by varying the inspiration times. Hence, from a system theoretic viewpoint, the concentrations c_p and c_s are viewed as two-state components, the activity ν_r of the respiration neurons as an input, the blood pressure p and its time derivative $\dot{p}$ as exogenous signals and the heart rate as the output of the system. For lack of space, the problem of parameter identification is not addressed in this work. Only the estimation of unknown signals, i.e. the concentrations of the neurotransmitters and possible external excitations of the sympathetic and parasympathetic systems are considered.

3. ESTIMATION OF THE CONCENTRATIONS IN THE ABSENCE OF EXTERNAL EXCITATIONS

Let

$$u_1 = g\left(b_\mathrm{s}\delta^{\theta_\mathrm{s}}\nu_\mathrm{s}\right)\left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right),$$
$$u_2 = g\left(b_\mathrm{p}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right),$$

and note that $u_1, u_2 \in [0,\, 1]$. From physiological considerations it follows that for healthy patients the concentrations c_s and c_p can only be positive and that the dynamics of c_p are slower than those of c_s, i.e. $\tau_\mathrm{p} < \tau_\mathrm{s}$. The ansatz

$$\hat{\tau}_\mathrm{s}\dot{\hat{c}}_\mathrm{s} = -\hat{c}_\mathrm{s} + u_1 + l_1\hat{\tau}_\mathrm{s}(h - \hat{h}), \quad \hat{c}_\mathrm{s}(t_0) = \hat{c}_{\mathrm{s}0} \in \mathbb{R}_+$$
$$\hat{\tau}_\mathrm{p}\dot{\hat{c}}_\mathrm{p} = -\hat{c}_\mathrm{p} + u_2 + l_2\hat{\tau}_\mathrm{p}(h - \hat{h}), \quad \hat{c}_\mathrm{p}(t_0) = \hat{c}_{\mathrm{p}0} \in \mathbb{R}_+$$
$$\hat{h} = h_0 + \alpha\hat{c}_\mathrm{s} - \beta\hat{c}_\mathrm{p},$$

of a linear observer with parameters $l_1, l_2 \in \mathbb{R}$ and state $[\hat{c}_\mathrm{s},\, \hat{c}_\mathrm{p}]^T$ is considered in the sequel. The quantities $\hat{\tau}_\mathrm{s}$ and $\hat{\tau}_\mathrm{p}$ represent identified values for the time constants and are defined as

$$\hat{\tau}_\mathrm{s} = \tau_\mathrm{s} - \Delta_\mathrm{s}, \quad \hat{\tau}_\mathrm{p} = \tau_\mathrm{p} - \Delta_\mathrm{p}, \quad \Delta_\mathrm{p}, \Delta_\mathrm{s} \in \mathbb{R},$$

such that $\tau_\mathrm{s} > \Delta_\mathrm{s}$ and $\tau_\mathrm{p} > \Delta_\mathrm{p}$. The quantities Δ_p and Δ_s are Parameter uncertainties. The convergence of the estimation error and the robustness of the observer with respect to parameter uncertainties are analyzed in the sequel. Furthermore, the error due to the approximation of the heart rate by a linear combination of the neurotransmitters is considered.

With $e = [e_\mathrm{s},\, e_\mathrm{p}]^T = [c_\mathrm{s} - \hat{c}_\mathrm{s},\, c_\mathrm{p} - \hat{c}_\mathrm{p}]^T$, the error dynamics read

$$\hat{\tau}\dot{e} = -\left(I + \hat{\tau}LC\right)e - \hat{\tau}Lw(c_\mathrm{s}, c_\mathrm{p}) + \Delta\tau[c_\mathrm{s},\, c_\mathrm{p}]^T, \qquad (2)$$

with

$$e(t_0) = [c_{\mathrm{s}0} - \hat{c}_{\mathrm{s}0},\, c_{\mathrm{p}0} - \hat{c}_{\mathrm{p}0}]^T = e_0,$$
$$C = [\alpha,\, -\beta], \quad L = [l_1,\, l_2]^T,$$
$$\hat{\tau} = \mathrm{diag}(\tau_\mathrm{s}, \tau_\mathrm{p}) + \mathrm{diag}(\Delta_\mathrm{s}, \Delta_\mathrm{p}) = \tau + \Delta,$$

and w the error between the approximated heart rate and the true one , i.e.

$$w(c_\mathrm{s}, c_\mathrm{p}) = f(c_\mathrm{s}, c_\mathrm{p}) - h_0 - C[c_\mathrm{s},\, c_\mathrm{p}]^T.$$

Proposition 2. (Robustness of the first observer). Let κ be a $\mathcal{KL}$ function and $k, \bar{w}, \bar{c} > 0$ some scalars. If $l_1 > 0$ and $l_2 < 0$, then for every initial error e_0, a $T \geqslant 0$ exists such that the solution of 2 satisfies

$$\|e(t)\| \leqslant \kappa\left(\|e_0\|, t - t_0\right), \quad t_0 \leqslant t \leqslant T \qquad \text{(3a)}$$
$$\|e(t)\| \leqslant \mu(l_1, l_2), \quad t \geqslant T, \qquad \text{(3b)}$$

with $\mu(l_1, l_2) = k\left(\|L\|\,\bar{w} + \bar{c}\right)/\left(l_1 - l_2\right)$.

The proof of the proposition is omitted here for lack of space. The inequalities (3a) and (3b) show that e is uniformly bounded for all $t \geqslant t_0$ and uniformly ultimately bounded with the ultimate bound μ. It can be verified that if $\hat{\tau}_\mathrm{s} \neq \hat{\tau}_\mathrm{p}$ there always exit l_1 and l_2 such that these inequalities are satisfied. This conditions corresponds to the observability condition of the system when the output is assumed to be (1i). It is not restrictive as experiments have shown that the dynamics of acetylcholine are faster than those of noradrenaline. The error bound is a function of l_1 and l_2 and it is straightforward to verify that it satisfies $\lim_{l_1 \to \infty} \mu(l_1, l_2) = \lim_{l_2 \to -\infty} \mu(l_1, l_2) = k\bar{w}$. When the gains approach zero, the bound increases as its denominator approaches zero. However, when the gains vanish, there is no output injection any more and the estimation error is only given by the error in the parameters. The effect of the initial conditions will vanish exponentially, since the origin of the uncontrolled system is exponentially stable. The following proposition analyses the effect of the parameters l_1 and l_2 on the error $e_h(t) = h(t) - \hat{h}(t)$. It can be shown that the error e_h can be made arbitrary small.

Proposition 3. Let $t_i \geqslant T$ and $t_{i+1} > t_i$, with T from proposition 2, be two consecutive times where the heart beats. For any $l_1 > 0$ and $l_2 < 0$ there exists positive functions $\gamma_1, \gamma_2 > 0$ such that the error $e_h(t) = h(t) - \hat{h}(t)$ satisfies for all $t \in [t_i,\, t_{i+1}[$

$$\|e_h(t)\| \leqslant \gamma_1\left(l_1, l_2\right)\mathrm{e}^{-CLt} - \gamma_2\left(l_1, l_2\right),$$

with

$$\lim_{l_1 \to \infty} \gamma_2\left(l_1, l_2\right) = \lim_{l_2 \to -\infty} \gamma_2\left(l_1, l_2\right) = 0.$$

Proof. Knowing that the true output in (1g) is a piecewise constant function with respect to time it holds that $\dot{h}(t) = 0$, for all $t \in [t_i,\, t_{i+1}[$, and it follows that

$$\begin{aligned}\dot{e}_h(t) &= \dot{h}(t) - \dot{\hat{h}}(t)\\ &= -CLe_h(t) + C\hat{\tau}^{-1}\hat{c}(t) + Cu(t),\end{aligned}$$

with $u(t) = [u_1(t),\, u_2(t)]^T$, $\hat{c}(t) = [\hat{c}_\mathrm{s}(t),\, \hat{c}_\mathrm{p}(t)]^T$ and the initial condition $e_h(t_i) = h(t_i) - \hat{h}(t_i) = e_{hi}$ for all $t \in [t_i,\, t_{i+1}[$. The explicit solution of this differential equation in this interval reads

$$\begin{aligned}e_h(t) = {}& \mathrm{e}^{-CL(t-t_i)}e_{hi}\\ &+ \int_{t_i}^{t} \mathrm{e}^{-CL(t-\tau)}C\hat{\tau}^{-1}\hat{c}(\tau) + Cu(\tau)\mathrm{d}\tau.\end{aligned}$$

Proposition 2 gives a bound μ for the norm of the estimation error of the concentrations of the neurotransmitters. Since the real concentrations are also bounded, It follows that the estimated ones are as well, i.e. $\|\hat{c}(t)\| \leqslant \mu(l_1, l_2) + \bar{c}$, with $\bar{c}$ the bound of the true concentrations, with μ from Proposition 2,. From the definition of u, it follows that $\|u(t)\| \leqslant 2$. Thus, the later solution satisfies for all $t \in [t_i,\, t_{i+1}[$

$$\begin{aligned}\|e_h(t)\| &\leqslant \mathrm{e}^{-CL(t-t_i)}\,\|e_{hi}\|\\ &\quad + \left(\left\|C\hat{\tau}^{-1}\right\|(\mu + \bar{c}) + 2\,\|C\|\right)\int_{t_0}^{t} \mathrm{e}^{-CL(t-\tau)}\mathrm{d}\tau\\ &\leqslant \mathrm{e}^{-CL(t-t_i)}\,\|e_{hi}\|\\ &\quad + \left(\left\|C\hat{\tau}^{-1}\right\|(\mu(l_1,l_2) + \bar{c}) + \|C\|\,\bar{u}\right)\tfrac{\mathrm{e}^{-CLt}-1}{LC}\\ &= \gamma_1(l_1,l_2)\,\mathrm{e}^{-CLt} - \gamma_2(l_1,l_2),\end{aligned}$$

with

$$\begin{aligned}\gamma_1(l_1,l_2) &= \mathrm{e}^{CLt_i}\,\|e_{hi}\| + \gamma_2(l_1,l_2),\\ \gamma_2(l_1,l_2) &= \tfrac{\left\|C\hat{\tau}^{-1}\right\|(\mu(l_1,l_2)+\bar{c}) + \|C\|\bar{u}}{LC}.\end{aligned}$$

The constant γ_2 requires some further analyses with regard to its dependency on l_1 and l_2. While $\left\|C\hat{\tau}^{-1}\right\|\bar{c} + \|C\|\,\bar{u}$ is independent of l_1 and l_2, the bound $\left\|C\hat{\tau}^{-1}\right\|\mu(l_1,l_2)$ is not. However,

$$\tfrac{\mu(l_1,l_2)}{LC} = k\tfrac{\bar{w}\sqrt{l_1^2+l_1^2}+\bar{c}}{\theta(l_1-l_2)(\alpha l_1 - \beta l_2)}$$

approaches zero when l_1 and/or l_2 approach infinity. Thus,

$$\lim_{l_1\to\infty}\gamma_2(l_1,l_2) = \lim_{l_2\to-\infty}\gamma_2(l_1,l_2) = 0.$$

This proposition states that the estimation error is bounded by two components: The first one represents an exponentially decreasing part. The second one is a bound depending solely on the gains l_1 and l_2. It decreases with increasing absolute value of the gains. Due to the discrete nature of the measured heart rate, this observer can be seen as a predictor-corrector: Each time the heart beats, the estimations are corrected.

4. ESTIMATION OF THE CONCENTRATIONS AND AN EXCITATION OF THE SYMPATHETIC SYSTEM

For a piecewise constant external excitation x_s of the sympathetic system, the model can be summarized as

$$\begin{aligned}\tau_\mathrm{s}\dot{c}_\mathrm{s} &= -c_\mathrm{s} + g\left(b_\mathrm{s}\left(\delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + x_\mathrm{s}\right)\right)\left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right)\\ \tau_\mathrm{p}\dot{c}_\mathrm{p} &= -c_\mathrm{p} + g\left(b_\mathrm{p}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\\ \dot{x}_\mathrm{s} &= 0,\\ h &= f(c_\mathrm{s}, c_\mathrm{p}),\end{aligned}$$

with the initial conditions $c_\mathrm{s}(t_0) = c_{\mathrm{s}0}$, $c_\mathrm{p}(t_0) = c_{\mathrm{p}0}$ and $x_\mathrm{s}(t_0) = x_{\mathrm{s}0}$.

To simplify the analysis, the parameters of the system are assumed to be known. In Marquis et al. (2018); Olufsen and Ottesen (2012); Ottesen et al. (2014); Seidel (1997) different approaches for the estimation of these parameters have been developed for similar models and can be applied here as well. It is also assumed that the function f is linear in the concentrations, i.e. it is defined as in (1i). The ansatz

$$\begin{aligned}\tau_\mathrm{s}\dot{\hat{c}}_\mathrm{s} &= -\hat{c}_\mathrm{s} + g\left(b_\mathrm{s}\left(\delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + \hat{x}_\mathrm{s}\right)\right)\left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right)\\ &\quad + l_1(h - \hat{h})\\ \tau_\mathrm{p}\dot{\hat{c}}_\mathrm{s} &= -\hat{c}_\mathrm{p} + g\left(b_\mathrm{p}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right) + l_2(h - \hat{h})\\ \dot{\hat{x}}_\mathrm{s} &= l_3(h - \hat{h})\\ \hat{h} &= h_0 + \alpha\hat{c}_\mathrm{s} - \beta\hat{c}_\mathrm{p},\end{aligned}$$

of an nonlinear observer with parameters $l_1, l_2, l_3 \in \mathbb{R}$ is considered. The state and initial condition are denoted $\hat{c} = [\hat{c}_\mathrm{s},\, \hat{c}_\mathrm{p},\, \hat{x}_\mathrm{s}]^T$ and $\hat{c}(t_0) = [\hat{c}_{\mathrm{s}0},\, \hat{c}_{\mathrm{p}0},\, \hat{x}_{\mathrm{s}0}]^T$.

Let $e = [c_\mathrm{s} - \hat{c}_\mathrm{s},\, c_\mathrm{p} - \hat{c}_\mathrm{p},\, x_\mathrm{s} - \hat{x}_\mathrm{s}]^T = [e_\mathrm{s},\, e_\mathrm{p},\, e_{x_\mathrm{s}}]^T$. The error dynamics read

$$\begin{aligned}\tau_\mathrm{s}\dot{e}_\mathrm{s} = {}& -(1 + l_1\alpha)e_\mathrm{s} - l_1\beta e_\mathrm{p}\\ &+ \left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right)\left(g\left(b_\mathrm{s}\left(\delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + x_\mathrm{s}\right)\right)\right.\\ &\left. - g\left(b_\mathrm{s}\left(\delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + \hat{x}_\mathrm{s}\right)\right)\right)\\ \tau_\mathrm{p}\dot{e}_\mathrm{p} = {}& -l_2\alpha e_\mathrm{s} - (1 + l_2\beta)e_\mathrm{p}\\ \dot{e}_{x_\mathrm{s}} = {}& -l_3\alpha e_\mathrm{s} + l_3\beta e_\mathrm{p},\end{aligned} \tag{4}$$

with $e(t_0) = [c_{\mathrm{s}0} - \hat{c}_{\mathrm{s}0},\, c_{\mathrm{p}0} - \hat{c}_{\mathrm{p}0},\, x_{\mathrm{s}0} - \hat{x}_{\mathrm{s}0}]^T$. The next proposition characterizes the exponential stability of the origin of the error dynamics.

Proposition 4. (Stability of the second observer). Assume the saturation function g satisfies Assumption 1 and denote by γ its Lipschitz-constant. Let

$$A = \mathrm{diag}(1/\tau_\mathrm{s}, 1/\tau_\mathrm{p}, 0) - \mathrm{diag}(1/\tau_\mathrm{s}, 1/\tau_\mathrm{p}, 1)LC$$

with $L = [l_1,\, l_2,\, l_3]^T$ and $C = [\alpha,\, -\beta,\, 0]$, and P be the solution of the Lyapunov equation

$$PA + A^TP = -Q, \quad Q^T = Q.$$

The origin of (4) is globally exponentially stable if and only if

$$\gamma + \tfrac{b_\mathrm{s}}{2} + \tfrac{1}{2} < \tfrac{\lambda_{\min}(Q)}{2\lambda_{\max}(P)}.$$

Proof. For the stability analysis of the estimation error, the dynamics of e_s, i.e.

$$\begin{aligned}\tau_\mathrm{s}\dot{e}_\mathrm{s} = {}& -(1 + l_1\alpha)e_\mathrm{s} - l_1e_\mathrm{p}\\ &+ \left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right)\left(g\left(b_\mathrm{s}\left(\delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + x_\mathrm{s}\right)\right)\right.\\ &\left. - g\left(b_\mathrm{s}\left(\delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + x_\mathrm{s} - e_{x_\mathrm{s}}\right)\right)\right),\end{aligned}$$

are considered first. For the proof of stability, the system is rewritten such that it becomes the linear combination of an exponentially stable linear part and a nonlinear one vanishing at zero which will be seen as a perturbation. Let

$$\begin{aligned}z &= \delta^{\theta_\mathrm{s}}\nu_\mathrm{s} + x_\mathrm{s}\\ \kappa(z, e_{x_\mathrm{s}}) &= \left(1 - g\left(a_\mathrm{s}\delta^{\theta_\mathrm{p}}\nu_\mathrm{p}\right)\right)\Big(g\left(b_\mathrm{s}z\right) - g\left(b_\mathrm{s}(z - e_{x_\mathrm{s}})\right)\Big).\end{aligned}$$

It can be shown that g satisfies $g(x) = \frac{1}{2}x + \epsilon(x)$, with ϵ being a Lipschitz continuous function with Lipschitz constant $\gamma + 1$, where γ is the Lipschitz constant of g. Then, the function κ can be rewritten as

$$\begin{aligned}\kappa(z, e_{x_s}) &= \left(1 - g\left(a_s \delta^{\theta_p} \nu_p\right)\right)\left(\tfrac{b_s}{2} e_{x_s}\right. \\ &\quad \left. + \epsilon\left(b_s z\right) - \epsilon\left(b_s\left(z - e_{x_s}\right)\right)\right) \\ &= \tfrac{b_s}{2} e_{x_s} - g\left(a_s \delta^{\theta_p} \nu_p\right) \tfrac{b_s}{2} e_{x_s} \quad = \tfrac{b_s}{2} e_{x_s} + \kappa_1(z, e_{x_s}).\end{aligned}$$

Since for all x and e_{x_s}, $\left|g(x)\right| \leqslant 1$, the function κ_1 can be upper bounded by

$$\begin{aligned}\left|\kappa_1(z, e_{x_s})\right| &\leqslant \tfrac{b_s}{2}\left|e_{x_s}\right| + \left|\epsilon\left(b_s\left(z\right)\right) - \epsilon\left(b_s\left(z - e_{x_s}\right)\right)\right| \\ &\leqslant \left(\gamma + \tfrac{b_s}{2} + 1\right)\left|e_{x_s}\right|.\end{aligned}$$

In this light, the error dynamics in (4) are rewritten as

$$\begin{aligned}\dot{e} &= (-\tau_1 - \tau_2 LC)e + \tau_1 b \kappa_1(z, e_{x_s}) \\ &= Ae + \kappa_2(z, e)\end{aligned} \tag{5}$$

with

$$\tau_1 = \begin{bmatrix} \frac{1}{\tau_s} & 0 & \frac{b_s}{2} \\ 0 & \frac{1}{\tau_p} & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad \tau_2 = \operatorname{diag}(\tfrac{1}{\tau_s}, \tfrac{1}{\tau_p}, 1),$$

$L = [l_1, l_2, l_3]$ and $b = [1, 0, 0]^T$. Thus, the error dynamics are written in the form of a perturbed linear differential equation with a perturbation term satisfying $\|\kappa_2(z, e)\| \leqslant (\gamma + b_s/2 + 1/2)\, \tau_s \|e\|$, with an upper-bound depending only on the Lipschitz-constant of g and b_s.

For all distinct non-zero τ_p and τ_s, the pair $(-\tau_1, C)$ is observable, i.e. the spectrum of $-\tau_1 - \tau_2 LC$ can be made arbitrary by an appropriate choice of the observer gains l_1, l_2 and l_3. In particular, it can be made Hurwitz, so that the origin of the system $\dot{e} = Ae$ is globally exponentially stable. Let $P = P^T > 0$ be the solution of the Lyapunov equation $PA + A^T P = -Q$, with $Q = Q^T > 0$, and $V(e) = e^T P e$ a Lyapunov function candidate. Its derivative along the solutions of (5) satisfy

$$\begin{aligned}\dot{V}(e) &= -e^T Q e + 2 e^T P g(z, e) \\ &\leqslant -\lambda_{\min}(Q) \|e\|^2 + 2\bar{\gamma} \lambda_{\max}(P) \|e\|^2,\end{aligned}$$

with $\bar{\gamma} = \gamma + b_s/2 + 1/2$. Hence, the origin of the error dynamics is globally exponentially stable if $\bar{\gamma} < \lambda_{\min}(Q)/(2\lambda_{\max}(P))$.

The strength of the foregoing proposition are the very general assumptions on the function g that are always met in practice. Hence, no specific form is required for the global exponential stability of the origin of (4). The ratio $\lambda_{\min}(Q)/(2\lambda_{\max}(P))$ is maximized when Q is the identity matrix. See for instance Khalil (2002). The maximum eigenvalue of P can be upper bounded using the results in Mori et al. (1986). The ideas developed in the proofs of the last section can be generalized to show that the error will be bounded in the presence of parameter uncertainties and errors stemming from the approximation the heart rate.

5. ESTIMATION OF THE CONCENTRATIONS AND AN EXCITATION OF THE PARASYMPATHETIC SYSTEM

5.1 Observer

For a piecewise constant external excitation x_p of the parasympathetic system the model can be summarized as

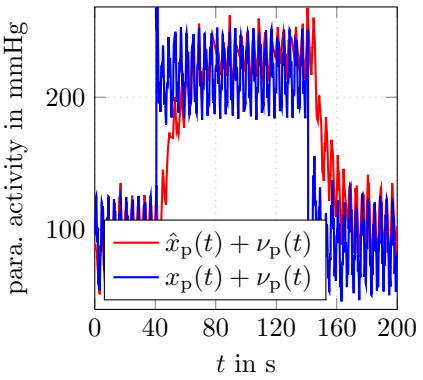

Fig. 1. Activity of the parasympathetic system with external excitation

$$\begin{aligned}\tau_s \dot{c}_s &= -c_s + g\left(b_s \delta^{\theta_s} \nu_s\right)\left(1 - g\left(a_s\left(\delta^{\theta_p} \nu_p + x_p\right)\right)\right) \\ \tau_p \dot{c}_p &= -c_p + g\left(b_p\left(\delta^{\theta_p} \nu_p + x_p\right)\right) \\ \dot{x}_p &= 0, \\ h &= f(c_s, c_p),\end{aligned}$$

with the initial conditions $c_s(t_0) = c_{s0}$, $c_p(t_0) = c_{p0}$ and $x_p(t_0) = x_{p0}$.

To simplify the analysis, the parameters of the system are assumed to be perfectly known. It is also assumed that the function f is linear in the concentrations, i.e. it is defined as in (1i). The ansatz

$$\begin{aligned}\tau_s \dot{\hat{c}}_s &= -\hat{c}_s + g\left(b_s \delta^{\theta_s} \nu_s\right)\left(1 - g\left(a_s\left(\delta^{\theta_p} \nu_p + \hat{x}_p\right)\right)\right) \\ &\quad + l_1(h - \hat{h}) \\ \tau_p \dot{\hat{c}}_s &= -\hat{c}_p + g\left(b_p\left(\delta^{\theta_p} \nu_p + \hat{x}_p\right)\right) + l_2(h - \hat{h}) \\ \dot{\hat{x}}_p &= l_3(h - \hat{h}) \\ \hat{h} &= f(\hat{c}_s, \hat{c}_p),\end{aligned} \tag{6}$$

of a nonlinear observer with parameters $l_1, l_2, l_3 \in \mathbb{R}$ and state $[\hat{c}_s, \hat{c}_p, \hat{x}_p]$ is considered. The state and initial conditions are $\hat{c} = [\hat{c}_s, \hat{c}_p, \hat{x}_p]^T$, and $\hat{c}(t_0) = [\hat{c}_{s0}, \hat{c}_{p0}, \hat{x}_{p0}]^T$, respectively. Proving the exponential convergence of the estimated quantities towards the true ones can be done using the same approach as in the sympathetic excitation case.

5.2 Simulations

The complete model of the autonomic-cardiorespiratory system developed in Seidel (1997) is simulated with an external excitation of the parasympathetic system. The observer in (6) is implemented such that all physical parameters including those in (1a)-(1c) have 10% variation from the nominal ones given in Seidel (1997). The parameters of the heart rate approximation are $h_0 = 1.11\,\mathrm{s}^{-1}$, $\alpha = 2.01\,\mathrm{s}^{-1}$ and $\beta = 20.45\,\mathrm{s}^{-1}$. The initial condition observer state is zero. The time derivative of the pressure is computed numerically using an algebraic derivative estimator. The gains of the observer are $l_1 = 2\,\mathrm{s}$, $l_2 = -5\,\mathrm{s}$ and $l_3 = -200\,\mathrm{mmHg}$. The saturation function is chosen to be the tanh function. The parameters in (1) where identified in Seidel (1997) such that the concentrations c_s and c_p are unitless.

Table 1. Mean relative errors for the interval [60 s, 120 s]

	symp.	para.	h	excitation
true param.	16%	5%	≈ 0%	5%
app. param.	20%	8%	≈ 0%	9%

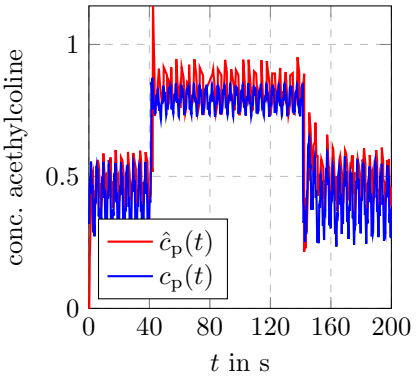

Fig. 2. Concentration of the neurotransmitter of the parasympathetic system

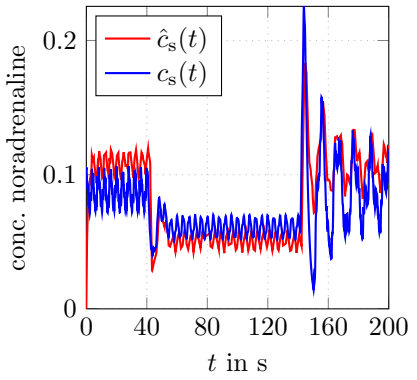

Fig. 3. Concentration of the neurotransmitter of the sympathetic system

The comparison of the estimated quantities and the true ones are given in Fig. 1,3, and 2. This simulation shows that despite the very coarse approximation of the heart rate by a linear combination of the concentrations of the neurotransmitters, the estimation of the external excitation yields acceptable results. However, the error in the estimation of c_s and c_p motivates the use of a more complex approximation.

Table 1 summarizes the mean relative estimation errors for the neurotransmitter concentrations and the excitation for the time interval [60 s, 120 s]. The values for an observer using the true parameters are given as a reference. These errors are stemming solely from the approximation of the heart rate.

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