Proceedings of the
47th IEEE Conference on Decision and Control
Cancun, Mexico, Dec. 9-11, 2008

Stability Analysis and Estimate of the Region of Attraction of a Human Respiratory Model

Raul Villafuerte, Sabine Mondié and Silviu-Iulian Niculescu

Abstract— **In this paper, we complete the stability analysis of the human respiratory nonlinear time delay model introduced by [9]. More precisely, we present a detailed mathematical analysis of the stability of the trivial equilibrium of the nonlinear model, an estimate of its region of attraction and exponential estimates of the solutions starting in this region for two distinct control strategies: linear and Hill controllers, respectively. The proposed approach is constructive and it is based on the use of Lyapunov-Krasovskii functionals of complete type for time-delay systems with a cross term in the derivative.**

I. Introduction

Roughly speaking, the respiratory system is characterized by the presence of two types of processes: distribution of O_2 to the cells and the elimination of the CO_2 in the tissues of the body. In this context, the breathing process in the physiological circuite controlling the carbon-dioxide level in the blood is a *transport* process, that is typically represented by a set of delay differential equations. A common irregularity in human respiration is characterized by cyclic fluctuations in ventilation accompanied by cyclic variations of the respiratory gas partial pressure in blood. This phenomenon is called periodic breathing or Cheyne-Stokes respiration. In [9], one of the models describing such breathing dynamics is discussed and the stability of a linear approximation is presented by using standard frequency-domain techniques: detection of the first crossing (if any?!) with respect to the imaginary axis as a function of the systems' parameters and the computation of the corresponding delay margin (see, e.g., [2], [1] for further discussions on these techniques). A geometric intuitive argument leading to similar conclusions was proposed in [7].

The aim of this paper is to propose a deeper analysis of the stability properties of the trivial solution of the nonlinear system proposed by Vielle and Chauvet in [9]. In this sense, we will exploit the particular structure of the system and the properties of the system's nonlinearities. Furthermore, the analysis is completed by providing an estimate of its region of attraction and an exponential estimate of the solutions whose initial conditions are in this region. These concept of control systems are important from a physiological point of view because they give some insight into questions such as: how far from the equilibrium the system can be perturbed and how fast will it go bach to the equilibrium?. Furthermore, the theoretical treatment allows further analysis of the effect of the physiological parameters on these system characteristics.

To the best of the authors' knowledge, there does not exist similar results for the analysis of the respiration system. In this paper, we address these problems by using Lyapunov-Krasovskii functionals of complete type with cross term in the time derivative. Such an approach is inspired by the ideas introduced in [5].

The remaining paper is organized as follows: In section 2 we introduce the respiratory system proposed by [9]. Section 3 is devoted to fundamental results on time delay systems and Lyapunov-Krasovskii functionals of complete type with cross term in the time derivative. In section 4, we give the main theoretical results on stability, region of attraction and exponential estimates. Finally, in section 5, we perform the detailed analysis of the stability properties of the corresponding respiratory system in the two controllers configurations. The paper ends with some concluding remarks.

II. Mathematical model of the respiratory system

The respiratory system can be viewed as an interconnection between some *plant* in which CO_2 exchanges take place and some *controller* which regulates the CO_2 partial pressures in the body by acting on the air flow in lungs using the arterial CO_2 partial pressure sensed by the peripheral chemoreceptors with a time lag h.

The plant has two state variables, P_L and P_T which denote the CO_2 partial pressures in lungs and tissues and $F(\cdot)$ is the controller function. The transport delay mentioned above appears in the equation by the controller action F, which is an appropriate nonlinear function of the CO_2 partial pressure P_L. The model of the respiratory system is

$$\begin{aligned} \dot{P}_T(t) &= -\frac{Q_a}{V_T}P_T(t) + \frac{Q_a}{V_T}P_L(t) + \frac{M}{\alpha V_T} \\ \dot{P}_L(t) &= \frac{\alpha Q_a B}{V_L}P_T(t) - \frac{\alpha Q_a B}{V_L}P_L(t) \\ &\quad - \tfrac{1}{V_L}(P_L(t) - P_I)F(P_L(t-h)). \end{aligned} \tag{1}$$

The parameters V_T: volume in tissues, V_L: volume in lungs, B: Barometric pressure minus water vapor pressure, Q_a: blood flow, α: CO_2 dissociation curve slope, M: CO_2 metabolic production rate and P_I: partial pressures for exterior, are all positive. It is necessary to consider the following constraints based on physiological properties: first, $P_L > P_I$ and second, $F(x)$ is a continuous positive function defined on

Department of Automatic Control CINVESTAV-IPN, A.P. 14-740, México D.F., MEXICO. {rvillafuerte,smondie}@ctrl.cinvestav.mx
Laboratoire des Signaux et Systèmes (L2S), CNRS-Supélec, rue Joliot Curie, 91192, Gif-sur-Yvette, France. Silviu.Niculescu@lss.supelec.fr

$\mathbb{R}^+$ which has a zero value for $x \leq x_o$ and a strictly positive derivative for $x > x_0$.

As shown by Vielle and Chauvet [9], the equilibrium point of system (1) $(\overline{P}_T, \overline{P}_L)$ satisfies:

$$\overline{P}_T = \overline{P}_L + \frac{M}{\alpha Q_a}, \quad (2)$$

$$F(\overline{P}_L) = \frac{BM}{\overline{P}_L - P_I}. \quad (3)$$

Under the above assumptions the equation (3) admits a unique solution $\overline{P}_L$ hence, it follows from (2) that system (1) admits the unique equilibrium point

$$(\overline{P}_T, \overline{P}_L) = (\overline{P}_L + M/\alpha Q_a, \overline{P}_L). \quad (4)$$

By introducing the new variable $y_1(t) = P_T(t) - \overline{P}_T$, $y_2(t) = P_L(t) = \overline{P}_L$ and considering a first order Taylor series approximation $F(x) \approx F(\overline{P}_L) + F'(\overline{P}_L)(x - \overline{P}_L)$, the system (1) can be rewritten as:

$$\frac{d}{dt}\begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix} = A_0 \begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix} + A_1 \begin{pmatrix} y_1(t-h) \\ y_2(t-h) \end{pmatrix} + f(y_1(t), y_2(t), y_1(t-h), y_2(t-h)). \quad (5)$$

Here, $F'(\overline{P}_L) = \frac{\partial F(x)}{\partial x}\mid_{x=\overline{P}_L}$. The linear part of (5) is known as the nominal system:

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} = A_0 \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} + A_1 \begin{pmatrix} x_1(t-h) \\ x_2(t-h) \end{pmatrix}. \quad (6)$$

Here

$$A_0 = \begin{pmatrix} -a & a \\ b & -(b+c) \end{pmatrix}, \quad \text{and} \quad A_1 = \begin{pmatrix} 0 & 0 \\ 0 & -d \end{pmatrix},$$

$a = \frac{Q_a}{V_T}$, $b = \frac{\alpha Q_a B}{V_L}$, $c = \frac{F(\overline{P}_L)}{V_L}$, $d = \frac{F'(\overline{P}_L)(\overline{P}_L - P_I)}{V_L}$, $k = \frac{F'(\overline{P}_L)}{V_L}$ are positive constants and the nonlinear part of system (5) is

$$f(y_1(t), y_2(t), y_1(t-h), y_2(t-h)) = (0, k y_2(t) y_2(t-h))^T. \quad (7)$$

In the sequel, we focus our analysis on two classical controller schemes F:

Linear controller:

$$F(x) = \delta(x - \rho), \quad \text{for } x \geq \rho, \quad F(x) = 0 \text{ for } 0 \leq x \leq \rho, \quad (8)$$

where $\delta > 0$ and $\rho > 0$ are the gain and the apneic threshold (value under which air flow is zero), respectively. The function has a zero value for $x \leq x_0 = \rho$.

Hill controller:

$$F(x) = V_m \frac{x^n}{\theta^n + x^n}, \quad x \geq 0, \quad (9)$$

where $V_m > 0$, $n > 0$ and $\theta > 0$ are the maximum air flow, the Hill coefficient and Hill parameter, respectively. The function has a zero value for $x \leq x_0 = 0$.

According to the stability analysis of system (6) in the frequency domain presented in [9], the characteristic quasipolynomial of this system is

$$q(s,h) = |sI - A_1 - A_2 e^{-sh}| = q_1(s) + q_2(s) e^{-sh}. \quad (10)$$

where $q_1(s) = s^2 + (a+b+c)s + ac$, $q_2(s) = sd + ad$.

The analysis of the roots of $q(s,0)$ and $q(s,h)$ on the imaginary axis, $h > 0$, leads to the following stability results:

Theorem 1: [9] [Delay-independent stability] If a, b, c, d are strictly positive coefficients and $c \geq d$, then the trivial solution of the nominal system (6) is asymptotically stable for all $h \geq 0$.

Theorem 2: [9] [Delay-dependent stability] If a, b, c, d are strictly positive coefficients and $c < d$, then the trivial solution of the nominal system (6) is asymptotically stable for $h \in [0, h_o)$ and unstable for $h \geq h_0$, where

$$h_o = \frac{arg\left(-\frac{q_2(i\omega_o)}{q_1(i\omega_o)}\right)}{w_o}, \quad \text{and} \quad 0 < h_0 < 2\pi/\omega_o, \quad (11)$$

$$\omega_o = \sqrt{(-r_1 + \sqrt{r_1^2 - 4r_2})/2} \neq 0. \quad (12)$$

Here, $r_1 = (a+b)^2 + 2bc + c^2 - d^2$ and $r_2 = a^2(c^2 - d^2)$.

The stability of the linear part of the nonlinear time delay system gives indeed a rough idea of the stability properties of the trivial solution of the system, however it is highly desirable to have a deeper understanding of the stability properties of the nonlinear model. In the following two sections we recall the theoretical results needed for this analysis.

III. LYAPUNOV-KRASOVSKII FUNCTIONALS OF COMPLETE TYPE

We summarize the result presented in [6] on functionals with prescribed time derivative with cross terms.

If a time delay system of the form

$$\dot{x}(t) = A_0 x(t) + A_1 x(t-h), \quad (13)$$

where A_0 and $A_1 \in \mathbb{R}^{n \times n}$, is exponentially stable, then for any given positive definite matrices $W_i \in \mathbb{R}^{n \times n}$, $i = 0,1,2$ and a symmetric real matrix $Z \in \mathbb{R}^{n \times n}$ such that

$$\begin{pmatrix} W_0 & ZA_1 \\ A_1 Z & W_1 \end{pmatrix} > 0,$$

the functional

$$\begin{aligned} v(x_t) &= -x^T(t) Z x(t) + x^T(t) U(0,W) x(t) \\ &+ 2x^T(t) \int_{-h}^{0} U(-h-\theta, W) A_1 x(t+\theta) d\theta \\ &+ \int_{-h}^{0}\int_{-h}^{0} x^T(t+\theta_1) A_1^T U(\theta_1 - \theta_2, W) A_1 x(t+\theta_2) d\theta_1 d\theta_2 \\ &+ \int_{-h}^{0} x^T(t+\theta)\left[W_1 + (h+\theta) W_2\right] x(t+\theta) d\theta, \end{aligned} \quad (14)$$

satisfies the following conditions:

$$\frac{dv(x_t)}{dt} = -w(x_t), \quad \forall\, t \geq 0, \quad (15)$$

$$\alpha_1 \|x(t)\|^2 \leq v(x_t) \leq \alpha_2 \|x_t\|_h^2, \quad \forall\, t \geq 0. \quad (16)$$

Here,

$$\begin{aligned} w(x_t) =& x^T(t)W_0x(t)+x^T(t-h)W_1x(t-h) \\ &+2x^T(t)ZA_1x(t-h) \\ &+\int_{-h}^{0} x^T(t+\theta)W_2x(t+\theta)d\theta, \end{aligned} \quad (17)$$

$\alpha_1 \in (0,\alpha^*]$, with α^* such that

$$\begin{pmatrix} W_0 & ZA_1 \\ A_1^TZ & W_1 \end{pmatrix} + \alpha^* \begin{pmatrix} A_0+A_0^T & A_1 \\ A_1^T & 0 \end{pmatrix} > 0, \quad (18)$$

and $\alpha_2 > 0$ satisfies

$$\alpha_2 \geq \kappa(1+h). \quad (19)$$

where, $\kappa \geq \{u_{zo}+hu_1a_1, u_1a_1+w_1+hw_2+hu_1a_1^2\}$, $u_{oz} = \|U(0,W)-Z\|$, $u_1 = \max_{\tau\in[0,h]}\{\|U(\tau,W)\|\}$, $a_1 = \|A_1\|$ and $w_i = \|W_i\|$, $i=1,2$.

The matrix $U(\tau,W)$ is called the Lyapunov matrix associated to $W = W_0+W_1+hW_2-A_0^TZ-ZA_0 \in \mathbb{R}^{n\times n}$ [8]. It is the unique solution of the analogue of the Lyapunov Equation for time delay systems with is:

$$U'(\tau) = U(\tau)A_0 + U(\tau-h)A_1, \quad \tau \geq 0, \quad (20)$$

$$U(-\tau) = U^T(\tau), \quad \tau \geq 0, \quad (21)$$

$$-W = U'(+0)-U'(-0). \quad (22)$$

IV. Stability analysis of the trivial solution

In what follows we introduce results on the stability properties of the solutions of nonlinear systems achieved in the framework of Lyapunov-Krasovskii functionals of complete type.

We analyze nonlinear systems of the form

$$\begin{aligned} \dot{y}(t) &= A_0y(t)+A_1y(t-h)+f(y(t),y(t-h)), \\ y(\theta) &= \psi(\theta), \quad \theta\in[-h,0], \end{aligned} \quad (23)$$

where $A_0, A_1 \in \mathbb{R}^{n\times n}$ are given matrices, h is the delay and $\psi \in \mathfrak{C}$ is the initial function. The set of all continuous function segment is given by $\mathfrak{C} := C([-h,0],\mathbb{R}^n)$. This system satisfy the following assumptions:

(A1) The linear part of system (23),

$$\dot{x}(t) = A_0x(t)+A_1x(t-h),$$

is exponentially stable.

The function $f(z_0,z_1)$ satisfies

(A2) $f(0,0) = 0$,

(A3) $f(z_0,z_1)$ satisfies a Lipschitz condition in a neighborhood of the origin,

(A4) for any $\gamma > 0$ there exits $\varepsilon = \varepsilon(\gamma) > 0$ such that if $\|(z_0,z_1)\| < \varepsilon$ then $\|f(z_0,z_1)\| < \gamma\|(z_0,z_1)\|_Q$, where

$$\|(z_0,z_1)\|_Q^2 = \begin{pmatrix} z_0 \\ z_1 \end{pmatrix}^T \underbrace{\begin{pmatrix} Q_{11} & Q_{12} \\ Q_{12} & Q_{22} \end{pmatrix}}_{Q\in\mathbb{R}^{2n\times 2n}} \begin{pmatrix} z_0 \\ z_1 \end{pmatrix}.$$

Next, we derive new proofs for the asymptotic stability conditions of the trivial solution of the nonlinear system (23), for the estimate of the region of attraction of the trivial solution, and we give exponential estimates for the solutions starting in the region of attraction.

A. Stability of the trivial solution of nonlinear systems

We obtain asymptotic stability conditions for the trivial solution that follows from the condition that the time derivative of the functional (14) along the trajectories of system (23) is negative.

Lemma 3: Consider a nonlinear system of the form (23). Given positive definite matrices $W_i \in \mathbb{R}^{n\times n}$, $i=0,1,2$ and a symmetric real matrix $Z \in \mathbb{R}^{n\times n}$ such that

$$\begin{pmatrix} W_0 & ZA_1 & 0 \\ A_1^TZ & W_1 & 0 \end{pmatrix} > 0,$$

then the time derivative of the functional (14) along the trajectories of the system remains negative for γ such that

$$\gamma\mathscr{M} < \mathscr{N}, \quad (24)$$

where

$$\mathscr{M} = \begin{pmatrix} \frac{\Gamma+u_{oz}}{h}(Q_{11}+I_n) & \frac{\Gamma}{h}Q_{12} & 0 \\ \frac{\Gamma}{h}Q_{12} & \frac{\Gamma}{h}Q_{22} & 0 \\ 0 & 0 & a_1u_1I_n \end{pmatrix}, \quad (25)$$

$$\mathscr{N} = \begin{pmatrix} \frac{W_0}{h} & \frac{ZA_1}{h} & 0 \\ \frac{A_1^TZ}{h} & \frac{W_1}{h} & 0 \\ 0 & 0 & W_2 \end{pmatrix}. \quad (26)$$

Here, $\Gamma = (u_{oz}+a_1u_1h)$.

Furthermore, the trivial solution of the nonlinear system (23) is asymptotically stable.

Proof: As system (23) is exponentially stable, the Lyapunov-Krasovskii functional (14) whose time derivative along of the trajectories of (23) is $-w(x_t)$ where $w(x_t)$ is given in (17). The time derivative of $v(y_t)$ along the trajectories of system (23) is

$$\begin{aligned} \frac{dv(y_t)}{dt} =& -w(y_t) \\ &+2f^T(y(t),y(t-h))\Big[\,\big(\,U(0)-Z\,\big)y(t) \\ &+\int_{-h}^{0} U(-h-\theta)A_1y(t+\theta)d\theta\Big]. \end{aligned} \quad (27)$$

From Assumption $A4$, for every $\gamma > 0$ the function $f(z_0,z_1)$ satisfies $\|f(z_0,z_1)\| < \gamma\|(z_0,z_1)\|_Q$. Substituting this inequality into (27), we get

$$\begin{aligned} \frac{dv(y_t)}{dt} <& -w(y_t)+2\gamma u_{oz}\ \|y(t)\|\ \|(y(t),y(t-h))\|_Q \\ &+2\gamma a_1u_1\int_{-h}^{0}\ \|y(t+\theta)\|\ \|(y(t),y(t-h))\|_Q d\theta \\ \leq& \int_{-h}^{0} \begin{pmatrix} y(t) \\ y(t-h) \\ y(t+\theta) \end{pmatrix}^T [\gamma\mathscr{M}-\mathscr{N}] \begin{pmatrix} y(t) \\ y(t-h) \\ y(t+\theta) \end{pmatrix} d\theta \end{aligned} \quad (28)$$

where $\mathscr{M}$ and $\mathscr{N}$ are given by (25) and (26), respectibility. Therefore, we have that

$$\frac{dv(y_t)}{dt} < 0$$

for $\gamma > 0$ such that

$$\gamma\mathscr{M} < \mathscr{N}$$

and it follows that there exists $\zeta > 0$ such that the time derivative of the functional (14) along the trajectories of system (23) satisfies

$$\frac{dv(y_t)}{dt} < -\zeta\|(y(t), y(t-h))\|^2.$$

Furthermore, as the linear part is assumed to be exponentially stable we have that

$$\alpha_1\|y(t)\|^2 \le v(y_t) \le \alpha_2\|y_t\|_h^2, \quad \forall\, t \ge 0.$$

where α_1 and α_2 are obtained from (18) and (19), respectability. Clearly, the functional $v(y_t)$ satisfies the conditions of the Krasovskii asymptotic stability theorem [3] and we conclude that the trivial solution of system (23) is asymptotically stable. ■

B. Estimate of the region of attraction

The set of initial conditions of the system (23) that generates trajectories that converge to zero as t approaches infinity is called the region of attraction. Finding the exact region of attraction analytically might be difficult or even impossible. In [10] the Lyapunov-Krasovskii functional associated to the nominal linear system is used to provide an *estimate of the region of attraction*. The formal definitions is the following:

Definition 4: Let the trivial solution of system (23) be asymptotically stable. The set

$$R_A = \{\psi \in \mathfrak{C} \,:\, y(t;\psi) \text{ is defined } \forall\, t \ge 0 \text{ and } y(t;\psi) \underset{t\to\infty}{\longrightarrow} 0\},$$

is the **region of attraction** of the trivial solution of system (23).

Definition 5: Let the trivial solution of system (23) be asymptotically stable. A set, $\Omega \in \mathfrak{C}$ of initial functions is said to be an **estimate the region of attraction** of the trivial solution of system (23) if

i. $0_h \in \Omega$,
ii. $\Omega \subset R_A$.

The result stated below provides an estimate of the region of attraction of the trivial solution of system (23):

Theorem 6: Consider a system of the form (23) and let γ^* be the maximum positive constant such that (24) holds. Then, the set

$$\Omega = \{\psi \in \mathfrak{C} \mid \|\psi\|_h < \sqrt{\frac{\alpha_1}{\alpha_2}}\varepsilon/2\}, \tag{29}$$

is an estimate of the region of attraction of the trivial solution of the system. Here, the constants $\varepsilon = \varepsilon(\gamma^*)$ is obtained from condition $A4$ and the constants α_1 and α_2 are given in (18) and (19).

Proof: We demonstrate that the set (29) satisfies the Conditions of Definition 5.

First, we observe that the set (29) contains the trivial solution, i.e., $\psi = 0_h \in \Omega$.

Now, we demonstrate that for any initial condition in the set (29) the solution of system (5) converge to zero as t approaches infinity.

By Lemma 3 and assumption **(A4)** we get that for $\gamma > 0$ such that (24) holds, there exists $\varepsilon = \varepsilon(\gamma) > 0$ such that

$$\|(y(t), y(t-h))\| < \varepsilon \;\Rightarrow\; \dot{v}(y_t) < 0, \quad \forall\, t \ge 0.$$

This implies that the functional $v(y_t)$ is decreasing for all $t \ge 0$, hence

$$v(y_t) \le v(\psi), \quad \forall\, t \ge 0.$$

So, it follows from (16) that

$$\alpha_1\|y(t)\|^2 \le v(y_t) \le v(\psi) \le \alpha_2\|\psi\|_h^2, \quad \forall\, t \ge 0,$$

therefore, for any $\psi \in \Omega$ we have that

$$\|y(t)\| \le \frac{\varepsilon}{2}, \quad \forall\, t \ge 0.$$

Moreover,

$$\|y(t)\| \le \frac{\varepsilon}{2}, \quad \Rightarrow \quad \dot{v}(y_t) < 0, \quad \forall\, t \ge 0.$$

Thus,

$$\lim_{t\to\infty} y(t,\psi) = 0, \quad \forall\; \psi \in \Omega. \tag{30}$$

We conclude that the set described by (29) is an estimate of the region of attraction of the trivial solution of system (5). ■

C. Exponential estimates of the system response

In this section, we obtain an exponential estimate of the solution of system (23) with given initial condition ψ in the estimate of the region of attraction.

Corollary 7: Consider a system of the form (5). Then, for any $\psi \in \Omega$ the solution $y(t,\psi)$ of system (5) satisfies the following exponential estimate

$$\|y(t,\psi)\| \le \sqrt{\frac{\alpha_2}{\alpha_1}}\|\psi\|_h e^{-\beta t}, \quad t \ge 0, \tag{31}$$

where $2\beta = \min\{\lambda_{\min}(R_1)/\eta_1, \lambda_{\min}(R_2)/\eta_2\}$, $\eta_1 = u_{zo} + hu_1a_1$, $\eta_2 = u_1a_1 + w_1 + hw_2 + hu_1a_1^2$, $R_2 = W_2 - \gamma\; a_1u_1I_n$ and $R_1 = \begin{pmatrix} W_0 - \gamma[\Gamma + u_{oz}][Q_{11} + I_n] & ZA_1 - \gamma\Gamma Q_{12} \\ A_1^T Z - \gamma\Gamma Q_{12} & W_1 - \gamma\Gamma Q_{22} \end{pmatrix}$.

Proof: We obtain from (17) that

$$\begin{aligned}\dot{v}(y_t) \le &- \Big(y^T(t)\; y^T(t-h)\Big) R_1 \begin{pmatrix} y(t) \\ y(t-h) \end{pmatrix} \\ &- \int_{-h}^{0} y^T(t+\tau) R_2 y(t+\tau) d\tau \\ &\le - \lambda_{\min}(R_1)\|y(t)\|^2 - \lambda_{\min}(R_2)\int_{-h}^{0}\|y(t+\tau)\|^2 d\tau.\end{aligned} \tag{32}$$

It follows from (14) that

$$v(y_t) \le \eta_1\|y(t)\|^2 + \eta_2\int_{-h}^{0}\|y(t+\tau)\|^2 d\tau, \quad t \ge 0. \tag{33}$$

Now, using (32) and (33) we have that

$$\frac{dv(y_t)}{dt} + 2\beta v(y_t) \le 0, \quad t \ge 0, \tag{34}$$

where $2\beta = \min\{\lambda_{\min}(R_1)/\eta_1, \lambda_{\min}(R_2)/\eta_2\}$. Multiplying by $e^{-2\beta t}$ both sides of (34) we get

$$\frac{d}{dt}(e^{2\beta t}v(y_t)) < 0, \quad t \geq 0.$$

Integrating this inequality from 0 to t and using the fact that the solution goes to zero as t tends to infinity we get

$$v(y_t) \leq e^{-2\beta t}v(\psi), \quad t \geq 0,$$

thus (18) and (19) imply that

$$\alpha_1\|y(t)\|^2 \leq v(y_t) \leq e^{-2\beta t}v(\psi) \leq \alpha_2 e^{-2\beta t}\|\psi\|, \quad t \geq 0$$

and finally, recalling that $y(t)$ depends on ψ, i.e. $y(t) = y(t,\psi)$, we conclude that

$$\|y(t,\psi)\| \leq \sqrt{\frac{\alpha_2}{\alpha_1}}\|\psi\|_h e^{-\beta t}, \quad t \geq 0.$$

■

V. Analysis of the human respiratory system

We now use the results of the previous section to provide a detailed analysis of the stability properties of the respiratory system described in section 2.

It is straightforward to see that the nonlinear part (7) satisfies the assumptions A2 and A3. Next, we prove that assumption A4 also holds:

$$\begin{aligned}\|f(z_0,z_1,z_2,z_3)\|^2 &= (kz_1z_3)^2 \\ &\leq \frac{k^2}{4}(z_1^2+z_3^2)^2 \\ &\leq \frac{k^2}{4}\|(z_0,z_1,z_2,z_3)\|_Q^4 \\ &< \frac{k^2\varepsilon^2}{4}\|(z_0,z_1,z_2,z_3)\|_Q^2,\end{aligned}$$

where $Q = I_4$ is the identity matriz in $\mathbb{R}^{4\times 4}$. Therefore, for any $\gamma > 0$ there exits $\varepsilon = \varepsilon(\gamma)$ solution of the equation

$$\varepsilon = \frac{2\gamma}{k} \tag{35}$$

such that $\|f(z_0,z_1,z_2,z_3)\| < \gamma\|(z_0,z_1,z_2,z_3)\|_Q$ if $\|(z_0,z_1,z_2,z_3)\| < \varepsilon$.

A. Linear controller

We consider the system and the control parameters given in [9]:

$B = 713mmHg$, $M = 4.75mlCO_2s^{-1}$,
$Q_a = 100mls^{-1}$, $V_L = 3200ml$,
$\alpha = 0.0065mlCO_2ml^{-1}mmHg^{-1}$, $\sigma = 27.4$,
$P_I = 0.3mmHg$, $V_T = 15000ml$,
$\rho = 36.9$

The expressions (2) and (3) give the equilibrium $\overline{P}_L = 40mmHg$, $\overline{P}_T = 47.3mmHg$ and it follows from (8) that $F(\overline{P}_L) = 85.28mls^{-1}$ and $F'(\overline{P}_L) = 27.4$. Then, the parameters of system (5) are $a = 0.0067$, $b = 0.1448$, $c = 0.0267$, $d = 0.34$ and $k = 0.0086$.

We obtain from Theorem 2 that $\omega_o = 0.290355$ and that the critical delay is $h_o = 7.229$ hence the nominal system (6) is asymptotically stable for all $h \in [\,0,7.229)$ and unstable for all $h \geq 7.229$.

We are now ready to estimate the region of attraction of system (5) with the help of Theorem 6.

For the choice $h = 6.2$ and matrices

$$W_0 = \begin{pmatrix} 1.7692 & -1.4240 \\ -1.4240 & 3.9439 \end{pmatrix}, \quad W_1 = \begin{pmatrix} 0.7204 & -0.7394 \\ -0.7394 & 1.8496 \end{pmatrix},$$
$$W_2 = \begin{pmatrix} 0.1331 & -0.2107 \\ -0.2107 & 0.4520 \end{pmatrix}, \quad Z = \begin{pmatrix} -124.6269 & -0.0420 \\ -0.0420 & 0.0943 \end{pmatrix},$$

the function $U(\tau,W)$ associated to $W = W_0 + W_1 + hW_2 - ZA - A^TZ$ is computed by using the method exposed in [8]. In this case $u_{oz} = 231.0605$ and $u_1 = 106.5191$ and it follows from (24) that $\gamma \in (0,0.000776)$. For $\gamma = 0.000775$, it follows from (35) that $\varepsilon = 0.182$. On the other hand, we obtain from (18) and (19) that $\alpha_1 \in (0,4.578]$ and $\alpha_2 \geq 3280.521$.

Collecting the above information, we conclude from Theorem 6 that for $\alpha_1 = 4.577$ and $\alpha_2 = 3280.521$ the set

$$\Omega = \{\psi \in \mathfrak{C} \mid \|\psi\|_{6.5} \leq 0.003381\}.$$

is an estimate of the region of attraction of the trivial solution of system (5).
Furthermore, it follows from (31) in Corollary 7 that for any initial condition $\psi \in \Omega$ the solution $y(t,\psi)$ of system (5) satisfies

$$\|y(t,\psi)\| \leq 26.772\|\psi\|_{0.5}e^{-2.23\times 10^{-7}t}, \quad t \geq 0. \tag{36}$$

Now, we compute an estimate of the region of attraction of system (5) for $h = 0.5$. For matrices

$$W_0 = \begin{pmatrix} 1.2950 & -2.2286 \\ -2.2286 & 6.9090 \end{pmatrix}, \quad W_1 = \begin{pmatrix} 0.4801 & -0.9547 \\ -0.9547 & 2.8226 \end{pmatrix},$$
$$W_2 = \begin{pmatrix} 0.7401 & -1.9607 \\ -1.9607 & 5.5382 \end{pmatrix}, \quad Z = \begin{pmatrix} 0.4540 & -0.1972 \\ -0.1972 & 0.5658 \end{pmatrix},$$

we have that $u_{oz} = 84.3682$ and $u_1 = 84.8428$. It follows from (24) that given $\gamma \in (0,0.001414)$, the substitution of $\gamma = 0.001413$ in (35) yields $\varepsilon = 0.3301$ and we have from (18) and (19) that $\alpha_1 \in (0,5.207]$ and $\alpha_2 \geq 148.1897$.
We conclude from Theorem 6 that for $\alpha_1 = 5.206$ and $\alpha_2 = 148.1897$ the set

$$\Omega = \{\psi \in \mathfrak{C} \mid \|\psi\|_{0.5} \leq 0.03094\}$$

is an estimate of the region of attraction of the trivial solution of system (5).
Finally, the following exponential bound is obtained from (31): for any solution $y(t,\psi)$ of system (5) such that $\psi \in \Omega$ we have that

$$\|y(t,\psi)\| \leq 5.3353\|\psi\|_{0.5}e^{-2.554\times 10^{-7}t}, \quad t \geq 0. \tag{37}$$

B. Hill controller

Consider the following parameters of the Hill controller

$$\theta = 48.6mmHg, \quad Vm = 1330mls^{-1}, \quad n = 13.7.$$

It follows from (2) and (3) that the equilibrium is $\overline{P}_L$ =39.97mmHg, $\overline{P}_T$ =47.27mmHg. Substituting into (9) implies that $F(\overline{P}_L)$ =85.38mls^{-1} and $F'(\overline{P}_L)$ =27.39. The parameters of system (5) are now a =0.0067, b =0.1448, c =0.0267, d =0.3395 and k =0.0086.

We obtain from Theorem 2 that ω_o =0.2897 and h_o =7.249, hence the nominal system (6) is asymptotically stable for all $h \in [0, 7.249)$ and unstable for all $h \geq 7.249$.

For the choice h =6.2 and matrices

$$W_0 = \begin{pmatrix} 1.1229 & -0.9179 \\ -0.9179 & 2.9003 \end{pmatrix}, \quad W_1 = \begin{pmatrix} 0.4761 & -0.5304 \\ -0.5304 & 1.4970 \end{pmatrix},$$
$$W_2 = \begin{pmatrix} 0.0645 & -0.1005 \\ -0.1005 & 0.2564 \end{pmatrix}, \quad Z = \begin{pmatrix} -68.9521 & -0.0384 \\ -0.0384 & 0.0986 \end{pmatrix},$$

we obtain that u_{oz} =148.9777 and u_1 =80.0261. It follows from (24) that $\gamma \in$(0,0.000787). For γ =0.000786, it follows from (35) that ε =0.1837. We have from (18) and (19) that $\alpha_1 \in$(0,3.6366] and $\alpha_2 \geq$2285.4645.
Collecting the above information, we conclude from Theorem 6 that for α_1 =3.6365 and α_2 =2285.4645 the set

$$\Omega = \{\psi \in \mathfrak{C} \mid \|\psi\|_{6.5} \leq 0.003663\}.$$

is an estimate of the region of attraction of the trivial solution of system (5).
It follows from Corollary 7 that for any initial condition $\psi \in \Omega$ the solution $y(t,\psi)$ of system (5) satisfies

$$\|y(t,\psi)\| \leq 25.067\|\psi\|_{0.5} e^{-6.354\times 10^{-7} t}, \quad t \geq 0. \qquad (38)$$

Now, we compute an estimate of the region of attraction of system (5) for $h = 0.5$. For matrices

$$W_0 = \begin{pmatrix} 1.1519 & -1.8149 \\ -1.8149 & 6.0994 \end{pmatrix}, \quad W_1 = \begin{pmatrix} 0.4742 & -0.9478 \\ -0.9478 & 2.9394 \end{pmatrix},$$
$$W_2 = \begin{pmatrix} 0.7106 & -1.9484 \\ -1.9484 & 5.7401 \end{pmatrix}, \quad Z = \begin{pmatrix} 0.7307 & -0.2806 \\ -0.2806 & 0.8604 \end{pmatrix},$$

we have that u_{oz} =87.3229 and u_1 =88.0762. It follows from (24) that $\gamma \in$(0,0.00147). Substituting γ =0.001469 into (35) yields ε =0.3433. We also have from (18) and (19) that α_1 <5.2729 and $\alpha_2 \geq$153.4108.

We conclude from Theorem 6 that for α_1 =5.2728 and α_2 =153.4108 the set

$$\Omega = \{\psi \in \mathfrak{C} \mid \|\psi\|_{0.5} \leq 0.03182\}.$$

is an estimate of the region of attraction of the trivial solution of system (5).

It follows from Corollary 7 that the solution $y(t,\psi)$ of system (5) such that $\psi \in \Omega$ satisfies

$$\|y(t,\psi)\| \leq 5.394\|\psi\|_{0.5} e^{-2.593\times 10^{-7} t}, \quad t \geq 0. \qquad (39)$$

Remark 8: The estimates of the regions of attractions presented here are simple but conservative. However these estimate improve those proposed in [4] and [5] (see, [10]). The matrices W_i, $i = 0, 1, 2$ and Z can be used as free parameters for further improvements. In view of the above, there is no major difference in using one controller scheme or the other.

VI. Concluding remarks

In this paper, we derive conditions under which the trivial solution of the nonlinear respiratory system proposed in [9] is asymptotically stable, and we propose an estimate of the region of attraction. Furthermore, explicit exponential bounds for the solutions starting in the estimate of this region are presented. Our analysis is performed for two control strategies: linear and Hill controllers. The approach considered in the paper is based on the use of Lyapunov-Krasovskii functionals of complete type with a cross term in the time derivative. Our current research on the problem includes the analysis of the effect of the physiological parameter of the respiratory system on the estimate of the region of attraction.

References

[1] Kenneth L. Cooke and Pauline van den Driessche. On zeroes of some transcendental equations. *Funkcialaj Ekvacioj*, 29:77-90, 1986.

[2] L.E. El'sgol'ts. *Introduction to the theory of differential equations with deviating arguments*. Holden-Day, Inc. San Francisco, USA, 1966.

[3] N.N. Krasovskii. On the application of the second method of Lyapunov for equations with time delays. *Prikl. Mat. Meh.*, 20:315-327, 1956.

[4] D. Melchor and S. Niculescu. On computing estimates of the attraction region a class of nonlinear time-delay systems. In Proceeding of IFAC Symposium on System Structure and Control, Oaxaca, México, 2004.

[5] D. Melchor and S. Niculescu. Estimates of the attraction region for a class of nonlinear time-delay systems. *IMA Journal on Mathematical Control and Information*, 2007.

[6] S. Mondié, V. Kharitonov, and O. Santos. Complete type Lyapunov-Krasovskii functionals with a given cross term in the time derivative. Proceeding of the European Control Conference, Seville, Spain, 2005.

[7] S.-I. Niculescu, C.I. Morărescu, W. Michiels, and K. Gu. Geometric ideas in the stability analysis of delay models in biosciences. In I. Queinnec *et al.*, editor, *Biology and control theory: Current challenges*, volume 317 of *Lecture Notes in Control and Information Sciences*, pages 217–259. Springer Verlag, 2007.

[8] G. Ochoa and V.L. Kharitonov. Lyapunov matrices for neutral type time delay systems. *2nd ICEEE*, 347-350, 2005.

[9] B. Vielle and G. Chaveta. Delay equation analysis of human respiratory stability. *Mathematical Biosciences*, 105-122, 1998.

[10] R. Villafuerte and S. Mondie. On improving estimate of the region of attraction of a class of nonlinear time delay system. Sixth IFAC workshop on time-delay systems, Nantes, France, 2007.