STABILITY, INSTABILITY IN DELAY EQUATIONS MODELING HUMAN RESPIRATION

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Stability, Instability in Delay Equations Modeling Human Respiration

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Abstract

A system of delay equations describing a simple model of the respiratory control mechanism in humans is considered and conditions guaranteeing stability, instability of steady-state equilibrium solutions of that system are presented.

1 Introduction

Understanding the mechanism producing unstable patterns of ventilation has potential significance for the prevention and treatment of various forms of irregularities in human respiration (i.e., periodic breathing, sleep apnea, SIDS, ... etc). Recent modeling studies have demonstrated that it may be beneficial to consider the above process as a manifestation of feedback induced instabilities in the respiratory system (see e.g. [9], [3], [2], [10], and the references therein). In [9] a general mathematical model to study the process leading to periodic breathing is outlined. This model can be described as a set of nonlinear parameter dependent delay differential equations with multiple circulatory transport delays. In view of the previous discussion it seems to be necessary to perform a nonlinear stability analysis, or at least a bifurcation analysis, on the proposed model equations in order to validate them for the intended purposes. (Note that in [9] the analysis is restricted to studying linearized

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system response for harmonic excitations.) On the other hand, due to the complexity of the delay systems, i.e., relatively large number of states and system parameters in it, and the presence of multiple (presumably noncommensurate) delays, the only feasible way to carry out such a study is by computational means. The development and justification of computational methods to investigate stability and instability of trajectories corresponding to complex systems, such as the one in [9], is greatly aided by the availability of analytical results obtained on similar models with simpler structure.

The aim of this paper is to present a stability analysis for a simplified model of the respiratory system. (Related computational issues will be discussed in a forthcoming publication.)

In Section 2 we study modeling issues and formulate our simplified model for the respiratory system. The stability results are contained in Section 3.

2 Model Equations

In this section we provide a brief discussion on respiratory models to motivate the type of equations we study in Section 3.

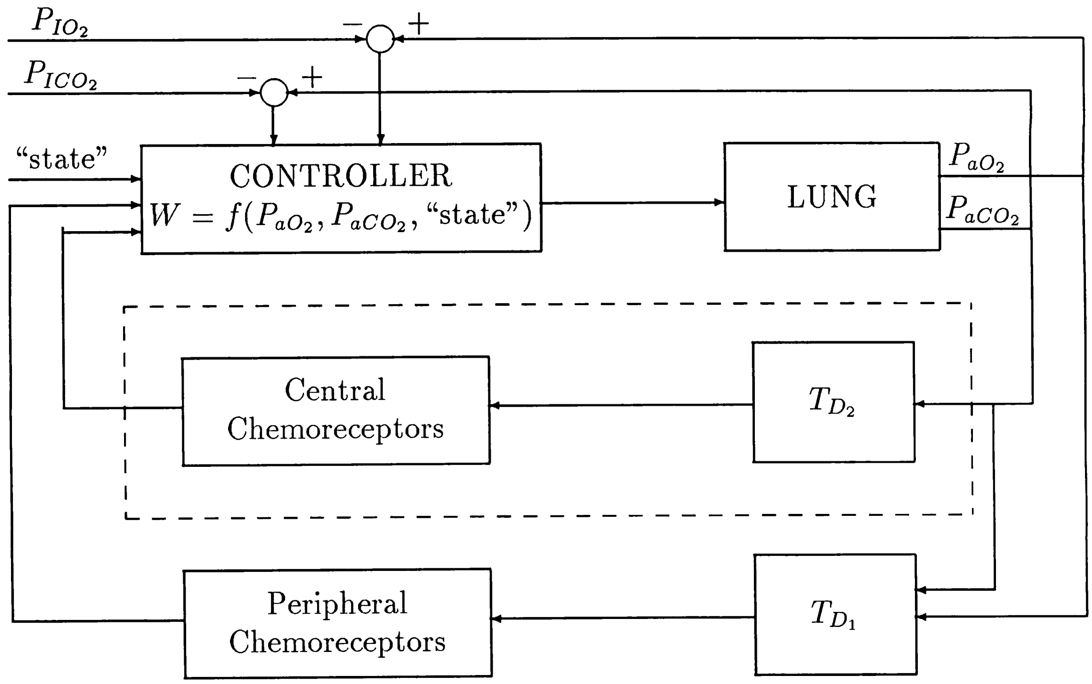

Figure 1: Block diagram of respiratory control system.

An overview of the respiratory system is shown in Figure 1. The controller responds to inputs from the central and peripheral chemoreceptors which respond to changes in CO_2

and O_2 concentrations. The input–output relationship of the controller is also influenced by changes in the state (i.e., sleep, wakefulness.) The controller gain is ventilation (W), and W together with the inspired CO_2 and O_2 concentrations (i.e., P_{ICO_2} and P_{IO_2}) influence the behavior of the controlled system (i.e., lung (plant)–controller closed loop, see Figure 1). The plant equations are balance equations for O_2 and CO_2 concentrations. T_{D_1} and T_{D_2} represent the transport delays between the lung and the peripheral and central chemoreceptors, respectively.

Khoo at al. [9] employed a model of the ventilatory system similar to the one outlined in Figure 1. The conclusion in [9] is that the ventilatory oscillations are predominantly mediated by the peripheral chemoreceptors. In this paper we concentrate on the effects due to the peripheral chemoreceptors (i.e., Figure 1 with the units inside the dotted area omitted) in the control system. Note that a similar study was carried out in [11] except that there the dependence on the O_2 concentration was not included.

We consider the system of nonlinear delay equations

$$\begin{aligned} \frac{d\tilde{x}}{dt} &= p - \alpha W\Big(\tilde{x}(t-\tau), \tilde{y}(t-\tau)\Big)(\tilde{x}(t) - x_I) \\ \frac{d\tilde{y}}{dt} &= -\sigma + \beta W\Big(\tilde{x}(t-\tau), \tilde{y}(t-\tau)\Big)(y_I - \tilde{y}(t)), \end{aligned} \tag{2.1}$$

where $\tilde{x}(\cdot)$ and $\tilde{y}(\cdot)$ denote arterial CO_2 and O_2 concentrations, respectively; $W(\cdot,\cdot)$ is the ventilation function; $\tau > 0$ is the transport delay (i.e., $\tau = T_{D_1}$ on Figure 1); x_I and y_I are inspired CO_2 and O_2 concentrations; p is the CO_2 production rate, σ is the O_2 consumption rate, and α, β are positive constants.

We now transform system (2.1) to a form more convenient for the stability analysis in the next section by introducing

$$x(t) = a(\tilde{x}(t) - x_I), \qquad y(t) = b(y_I - \tilde{y}(t)), \tag{2.2}$$

where a and b are constants to be determined. Simple calculations yield

$$\begin{aligned} \frac{dx}{dt} &= a\frac{d\tilde{x}(t)}{dt} &&= ap - a\alpha W\Big(x_I + \frac{1}{a}x(t-\tau), y_I - \frac{1}{b}y(t-\tau)\Big)\frac{x(t)}{a} \\ \frac{dy}{dt} &= -b\frac{d\tilde{y}(t)}{dt} &&= b\sigma - b\beta W\Big(x_I + \frac{1}{a}x(t-\tau), y_I - \frac{1}{b}y(t-\tau)\Big)\frac{y(t)}{b}. \end{aligned}$$

Choosing the constants a and b as

$$a = \frac{1}{p}, \qquad b = \frac{1}{\sigma},$$

we obtain the "scaled" equations

$$\begin{aligned} \frac{dx}{dt} &= 1 - \alpha V\Big(x(t-\tau), y(t-\tau)\Big)x(t) \\ \frac{dy}{dt} &= 1 - \beta V\Big(x(t-\tau), y(t-\tau)\Big)y(t) \end{aligned} \tag{2.3}$$

where the function $V(\cdot,\cdot)$ is defined as

$$V(x,y) = W(x_I + px, y_I - \sigma y). \tag{2.4}$$

3 Stability Analysis

We now consider the system in scaled coordinates, (i.e. (2.3)) and investigate the questions of existence, uniqueness, and stability of equilibria. It appears to be biologically realistic (see e.g. [9]) to assume that $W(u,v)$ is increasing as a function of u and decreasing as a function of v, for $u > x_I$ and $v < y_I$. We therefore make the following assumption (see also the defining equation (2.4)):

$$\text{(H)} \qquad \begin{array}{l} V(x,y) \text{ is a differentiable function, } V(0,0) = 0, \text{ and} \\ \dfrac{\partial V(x,y)}{\partial x} > 0, \ \dfrac{\partial V(x,y)}{\partial y} > 0, \ x > 0, \ y > 0 \end{array}$$

Remark 3.1 *The region $x > 0$, $y > 0$ corresponds to $\tilde{x} > x_I$, $\tilde{y} < y_I$ in the original variables.*

Theorem 3.2 *Assume hypothesis (H). Then there is a unique positive equilibrium of system (2.3).*

Proof: If there is an equlibirium $\bar{x}$, $\bar{y}$, we see from (2.3) that $\bar{x} \neq 0$, $\bar{y} \neq 0$, and $\bar{x} = \beta\bar{y}/\alpha$. Therefore

$$\beta V\left(\frac{\beta\bar{y}}{\alpha}, \bar{y}\right) = \frac{1}{\bar{y}} \tag{3.1}$$

Since $V(0,0) = 0$ and $V\left(\frac{\beta\bar{y}}{\alpha}, \bar{y}\right)$ is increasing in $\bar{y}$, there is a unique positive solution $\bar{y}$ of (3.1). With this $\bar{y}$, define $\bar{x} = \beta\bar{y}/\alpha$, and we have

$$\alpha V(\bar{x},\bar{y}) = \alpha V\left(\frac{\beta\bar{y}}{\alpha}, \bar{y}\right) = \frac{\alpha}{\beta\bar{y}} = \frac{1}{\bar{x}}$$

Hence $\alpha\bar{x}V(\bar{x},\bar{y}) = 1 = \beta\bar{y}V(\bar{x},\bar{y})$ so $(\bar{x},\bar{y})$ is an equilibrium.

Example 3.3 In the paper of Mackey and Glass [11], the function $V(x)$ was taken, as example, to be of the form $V(x) = V_m x^n/(\Theta^n + x^n)$, where V_m and Θ are positive constants and n is a positive integer. Analogously, we may consider the radially symmetric function

$$V(r) \equiv V(x,y) = \frac{V_m r^n}{\Theta^n + r^n}, \qquad r = \sqrt{x^2 + y^2} \tag{3.2}$$

which satisfies $\partial V/\partial x > 0$, $\partial V/\partial y > 0$ when $x > 0$, $y > 0$. In the case $n = 1$, we can explicitly compute the equilibrium $\bar{r} = \sqrt{\bar{x}^2 + \bar{y}^2}$. Since $\bar{x} = \beta\bar{y}/\alpha$,

$$\bar{r}^2 = \left(\frac{\beta\bar{y}}{\alpha}\right)^2 + \bar{y}^2 = k^2\bar{y}^2, \qquad k^2 = \frac{\beta^2 + \alpha^2}{\alpha^2}.$$

Equation (3.1) becomes

$$\frac{\beta V_m \bar{r}}{\Theta + \bar{r}} = \frac{k}{\bar{r}},$$

and therefore

$$\beta V_m \bar{r}^2 - k\bar{r} - k\Theta = 0. \tag{3.3}$$

Solving (3.3) we obtain

$$\bar{r} = \frac{1}{2}\delta\left\{1 + \sqrt{1 + \frac{4\Theta}{\delta}}\right\},$$

where $\delta = \dfrac{k}{\beta V_m}$.

We now investigate asymptotic stability of the equlibrium of system (2.3), under hypothesis (H). By letting $\xi(t) = x(t) - \bar{x}$, $\eta(t) = y(t) - \bar{y}$ in (2.3), and then removing the nonlinear terms, we obtain the linear variational system

$$\begin{aligned} \frac{d\xi}{dt} &= -\alpha\bar{V}\xi(t) - \alpha\bar{x}\bar{V}_x\xi(t-\tau) - \alpha\bar{x}\bar{V}_y\eta(t-\tau) \\ \frac{d\eta}{dt} &= -\beta\bar{V}\eta(t) - \beta\bar{y}\bar{V}_x\xi(t-\tau) - \beta\bar{y}\bar{V}_y\eta(t-\tau) \end{aligned} \tag{3.4}$$

where $\bar{V} = V(\bar{x},\bar{y})$, $\bar{V}_x = V_x(\bar{x},\bar{y})$, and $\bar{V}_y = V_y(\bar{x},\bar{y})$. This may also be written in the form

$$\frac{d}{dt}\begin{pmatrix} \xi(t) \\ \eta(t) \end{pmatrix} + A\begin{pmatrix} \xi(t) \\ \eta(t) \end{pmatrix} + B\begin{pmatrix} \xi(t-\tau) \\ \eta(t-\tau) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix},$$

where

$$A = \begin{pmatrix} \alpha\bar{V} & 0 \\ 0 & \beta\bar{V} \end{pmatrix}, \quad B = \begin{pmatrix} \alpha\bar{x}\bar{V}_x & \alpha\bar{x}\bar{V}_y \\ \beta\bar{y}\bar{V}_x & \beta\bar{y}\bar{V}_y \end{pmatrix}.$$

The associated characteristic equation (see [1]) is

$$\det(\lambda I + A + Be^{-\tau\lambda}) = 0. \tag{3.5}$$

Let us first consider the case $\tau = 0$, for which (3.5) reduces to

$$\lambda^2 + (\alpha\bar{V} + \alpha\bar{x}\bar{V}_x + \beta\bar{V} + \beta\bar{y}\bar{V}_y)\lambda + \alpha\beta(\bar{V}^2 + \bar{x}\bar{V}\bar{V}_x + \bar{y}\bar{V}\bar{V}_y) = 0.$$

Because of the hypothesis (H), the coefficients in this equation are positive, and therefore the roots have negative real parts. Consequently, we have proved the following result.

Theorem 3.4 *If (H) holds and $\tau = 0$, the positive equilibrium $(\bar{x},\bar{y})$ is asymptotically stable.*

Now suppose that $\tau > 0$. Equation (3.5) then has the form

$$P(\lambda) + Q(\lambda)e^{-\tau\lambda} = 0, \tag{3.6}$$

where

$$P(\lambda) = \lambda^2 + (\alpha + \beta)\bar{V}\lambda + \alpha\beta\bar{V}^2 \tag{3.7}$$

and

$$Q(\lambda) = (\alpha\bar{x}\bar{V}_x + \beta\bar{y}\bar{V}_y)\lambda + \alpha\beta\bar{V}(\bar{x}\bar{V}_x + \bar{y}\bar{V}_y). \tag{3.8}$$

It is well-known that a necessary and sufficient condition for asymptotic stability of the equilibrium is that all roots of the charasteristic equation have negative real parts. Therefore, much effort has been devoted to searching for conditions on the polynomials P and Q that will imply that all roots have negative real parts. References to some of this literature may be found for example in [1], [8], [12], [4], [5]. Since $P + Qe^{-\tau\lambda}$ is an exponential polynomial, these conditions are somewhat difficult to express in a way that is useful in applications, and this is even more so for exponential polynomials coming from equations with more than one delay.

At the end of this section, we comment further on equations (3.6)- (3.8), but first we construct a special case wich is more easily handled. The special case is when $\alpha = \beta$. Equation (3.6) then reduces to

$$(\lambda + \alpha\bar{V})\left[\lambda + \alpha\bar{V} + \alpha(\bar{x}\bar{V}_x + \bar{y}\bar{V}_y)e^{-\tau\lambda}\right] = 0,$$

and consequently we only need to discuss the location of roots of the equation

$$\lambda + a + be^{-\tau\lambda} = 0, \qquad a = \alpha\bar{V}, \qquad b = \alpha(\bar{x}\bar{V}_x + \bar{y}\bar{V}_y). \tag{3.9}$$

The exact region of stability for (3.9) is the region in the (a, b)-plane bounded on the left by the line $a + b = 0$, $a\tau \geq -1$, and with upper boundary given by the equation

$$\tau(b^2 - a^2)^{1/2} = \arccos(-a/b), \qquad a\tau \geq -1.$$

([7], page 149). In the present case since we have $a > 0$, $b > 0$, the lower boundary is simply the positive a-axis. Moreover, the region of stability for all delays τ is simply $b < a$. The following result is therefore true.

Theorem 3.5 *If (H) holds and $\alpha = \beta$, the equilibrium $(\bar{x}, \bar{y})$ is asymptotically stable if, and only if, the parameter pair (a, b) lies in the region in the first quadrant with $a > 0$, $b > 0$, and upper boundary $\tau(b^2 - a^2)^{1/2} = \arccos(-a/b)$, where $a = \alpha\bar{V}$, $b = \alpha(\bar{x}\bar{V}_x + \bar{y}\bar{V}_y)$. The equilibrium is stable for all $\tau \geq 0$ if and only if $b < a$.*

If the parameter pair moves across the upper boundary, there is generally a Hopf bifurcation with emergence of a nontrivial periodic solution.

Example 3.6 For the situation described in Example 3.3, we have

$$a = \frac{\alpha V_m \bar{r}^n}{\Theta^n + \bar{r}^n}, \qquad b = \frac{\alpha n V_m \theta^n \bar{r}^n}{(\Theta^n + \bar{r}^n)^2}.$$

The condition for stability for all delays is $b < a$, which is $\bar{r}^n > (n-1)\Theta^n$. For $n = 1$, this is clearly true. For $n > 1$, since $k = \sqrt{2}$ we have $g\bar{r}^{n+1} = \bar{r}^n + \theta^n$ where $g = \alpha V_m/\sqrt{2}$, hence $\bar{r} \to 0$ as $g \to \infty$. Therefore the condition $\bar{r} > (n-1)\theta^n$ fails if αV_m is large, which corresponds to overly strong gain in the regulation.

We now return to a discussion of the general case, when $\alpha \neq \beta$, and to the equation (3.6). For equations with quadratic function P and linear function Q, a survey of what is known about stability in various cases is given in [4]. The recent book [12] provides a method for determining stability for more general problems, including problems with several delays, and is based on determining roots of certain real functions. Papers [6] and [5] show that if τ is regarded as a parameter, then as τ increases there may be a sequence of switches between stability and instability. For our purposes here, we construct the function

$$\begin{aligned} F(\omega) &= |P(i\omega)|^2 - |Q(i\omega)|^2 \\ &= \omega^4 + \left[(\alpha^2+\beta^2)\bar{V}^2 - (\alpha\bar{x}\bar{V}_x + \beta\bar{y}\bar{V}_y)^2\right]\omega^2 + \alpha^2\beta^2\bar{V}^2\left[\bar{V} - (\bar{x}\bar{V}_x + \bar{y}\bar{V}_y)^2\right]. \end{aligned}$$

Since we have stability for $\tau = 0$, by Theorem 3.4, the following result follows from [5], Theorem 1.

Theorem 3.7 *Assume hypothesis (H). Then:*

(i) *If $F(\omega) = 0$ has no positive roots, then the equilibrium $(\bar{x}, \bar{y})$ is asymptotically stable for all $\tau \geq 0$.*

(ii) *If $F(\omega) = 0$ has at least one positive root ω, and each positive root is simple, then as τ increases, stability switches may occur and there is a positive τ^* such that the equilibrium is unstable for all $\tau > \tau^*$.*

We observe that if $\bar{V} < \bar{x}\bar{V}_x + \bar{y}\bar{V}_y$, then $F(0)$ is negative and there is a positive root of $F(\omega) = 0$, and destabilization will occur for large τ. More precise conditions for the existence of a positive root of $F(\omega) = 0$ may be obtained similarly as in ([6], Section 5).

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