Differential flatness and Liouvillian character of two HPA axis models

Florentina Nicolau, Hugues Mounier

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F. Nicolau *,** **H. Mounier** **

* *Quartz EA7393 Laboratory, ENSEA, 95014 Cergy-Pontoise, France.*
** *Université Paris-Saclay, CNRS, CentraleSupélec, Laboratoire des signaux et systèmes, 91190, Gif-sur-Yvette, France. (e-mail: {florentina.nicolau, hugues.mounier}@centralesupelec.fr)*

Abstract: In this paper, we study two existing quantitative models of the hypothalamic-pituitary-adrenal (HPA) axis from a control systems theory viewpoint, that is, we suppose that we can act on the dynamics of the HPA axis throughout some parameters, which are the system inputs. In particular, we will focus on flatness and Liouvillian properties of the considered control systems of the HPA axis. We first study the minimal three-dimensional model Bangsgaard and Ottesen [2017] which is shown to be flat, and then we consider the more involved and important model proposed in Rao and Androulakis [2019, 2020], with seven states, for which we prove that flatness no longer holds. The more involved model satisfies however a similar but weaker property than flatness: it is a Liouvillian system.

Keywords: HPA axis model, flat system, Liouvillian systems, nonlinear control systems.

1. INTRODUCTION

The Hypothalamic-Pituitary-Adrenal (HPA) axis describes the interactions between the hypothalamus, the pituitary gland and the adrenal glands. This HPA axis is a major neuroendocrine system which controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure, see, e.g., Carroll et al. [2007], Conrad et al. [2009], Hankins et al. [2008], Pariante and Lightman [2008]. Therefore, understanding the interplay between its various elements is an interesting and important problem and several mathematical models have been proposed in the literature as a useful tool for a better comprehension of the different phenomena as well as for pointing out different ways in which malfunctioning may occur; see, e.g., the survey by Androulakis [2021] and the references therein. Once appropriate models are developed, it is important to analyze their mathematical and structural properties. In this paper, we study two existing quantitative models of the HPA axis, in the form of ordinary differential equations, from control systems theory viewpoint, that is, we suppose that we can act on the dynamics of the state variables throughout some system parameters, which play the role of the inputs. We first consider the minimal three-dimensional model proposed in Bangsgaard and Ottesen [2017] with state variables the concentrations of corticotropin releasing hormone, adrenocorticotropic hormone and cortisol, and as control variable the parameter modeling the strength of the auto-up-regulation of corticotropin releasing hormone concentration. Then we study the more involved, very insightful and representative model proposed in Rao and Androulakis [2019, 2020], with seven states, incorporating the transcription and translation of the glucocorticoid receptor and the dynamics of the nuclear translocation of the activated complex inducing a negative feedback. We will see it as a three-input control system with inputs the parameters modeling the effects of chronic stress on the HPA axis (namely, k_{p3} feedforward adrenal sensitivity, K_{p1} hypothalamic negative feedback, and K_{p2} pituitary negative feedback). These parameters can indeed be considered as slowly varying inputs, through neural plasticity mechanism.

An important property of control systems is that of differential flatness (which we shall simply call flatness in the sequel). The notion of flatness was introduced in control theory in the 1990's, by Fliess et al. [1995, 1999], and has attracted a lot of attention because of its multiple applications for several important control problems (like constructive controllability or how to steer the system, trajectory generation and trajectory tracking, how to reconstruct non measured variables from the outputs, etc.). Flat systems form a control systems class whose set of trajectories can be parametrized by m functions (forming a flat output) and their time-derivatives, m being the number of controls. Therefore the time-evolution of all state and control variables can be determined from that of the flat output (and its derivatives) without integration yielding a parametrization of all the system's trajectories.

The literature on flatness properties of control systems in neuroscience is very limited. The only publications that we are aware of are Rigatos [2013], where two cases of lumped parameter oscillators were studied, and our recent work Nicolau and Mounier [2022], where flatness of networks of two synaptically coupled excitatory-inhibitory neural modules is analysed. In this paper, we study flatness of the considered HPA axis models and show that while the minimal model is flat, the involved model is not. The increased detail model however exhibits an interesting property that can be seen as an extension of flatness: it is a Liouvillian control system. Liouvillian and flat systems share a similar property: in order to derive the

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trajectories of a Liouvillian system, we use time-derivatives of an output (the Liouvillian output) but we also need integration of differential equations whose solutions are analytically known, see, e.g., Chelouah [1997].

The paper is organized as follows. In Section 2, we recall the definitions of flat and Liouvillian systems. In Section 3, we give our main results: we show that the single-input three-dimension model is flat, while the increased detail model is never flat, but is always Liouvillian. We provide proofs of our main results in Section 4.

2. DEFINITIONS

Consider the nonlinear control system

$$\Xi : \quad \dot{x} = F(x,u),$$

where x is the state defined on a open subset X of $\mathbb{R}^n$, u is the control, taking values in an open subset U of $\mathbb{R}^m$, and $\dot{x}$ denotes the time-derivative $\dot{x} = \frac{dx}{dt}$. The dynamics functions F_i, $1 \leqslant i \leqslant n$, are smooth (the word smooth will always mean $\mathcal{C}^\infty$-smooth, away from singularities) and $\mathrm{rk}\,\frac{\partial F}{\partial u} = m$. Fix an integer $l \geqslant -1$ and denote $U^l = U \times \mathbb{R}^{ml}$ and $\bar{u}^l = (u, \dot{u}, \ldots, u^{(l)})$. For $l = -1$, the set U^{-1} is empty and $\bar{u}^{-1}$ in an empty sequence.

2.1 Flatness and feedback linearization The fundamental property of flat systems is that all their solutions can be parametrized by a finite number of functions and their time-derivatives. Although flatness is a relatively recent notion, introduced in control theory in the 1990's, Fliess et al. [1995, 1999], it actually has a long history and a similar notion, of systems of undetermined differential equations integrable without integration, goes back to Hilbert [1912] and Cartan [1914]. Indeed, the control system $\Xi : \dot{x} = F(x,u)$ can be seen as an underdetermined differential system consisting of n equations $\dot{x}_i = F_i(x,u)$, for $1 \leqslant i \leqslant n$, and $n+m$ variables (n states and m controls). The difference between the number of variables and the number of equations gives the number of degrees of freedom of the system. It follows that m functions can be chosen freely. In the context of control systems, one usually chooses freely the input $(u_1(t), \ldots, u_m(t))$, then integrates in order to compute the state $x(t)$. But is it the only way to do it? In order to answer this question, consider the following simple single-input system:

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= u. \end{aligned} \tag{1}$$

We can choose freely $u(t)$, then integrate it once to compute $x_2(t)$, and then integrate it a second time to compute $x_1(t)$. Let us now choose freely $x_1(t)$, differentiate it once to get $x_2(t)$, and then differentiate $x_2(t)$ to obtain $u(t)$. It follows that system (1) admits two parametrizations: one via the input, for which we have to integrate twice (which is, in the general case of $\dot{x} = F(x,u)$, difficult, and sometimes, even impossible analytically), and one via the state x_1 for which we have to differentiate twice (which is always possible in a simple way). Hence there are underdetermined differential systems (aka control systems) which are solvable without integration (namely flat control systems).

Definition 1. The system $\Xi : \dot{x} = F(x,u)$ is *flat* at $(x^*, \bar{u}^{*l}) \in X \times U^l$, for $l \geqslant -1$, if there exists a neighborhood $\mathcal{O}^l$ of $(x^*, \bar{u}^{*l})$ and m smooth functions $\varphi_i = \varphi_i(x, u, \dot{u}, \ldots, u^{(l)})$, $1 \leqslant i \leqslant m$, defined in $\mathcal{O}^l$, having the following property: there exist an integer r and smooth functions γ_i, $1 \leqslant i \leqslant n$, and δ_j, $1 \leqslant j \leqslant m$, such that

$$x_i = \gamma_i(\varphi, \dot{\varphi}, \ldots, \varphi^{(r-1)}) \text{ and } u_j = \delta_j(\varphi, \dot{\varphi}, \ldots, \varphi^{(r)}) \tag{2}$$

for any C^{l+r}-control $u(t)$ and corresponding trajectory $x(t)$ that satisfy $(x(t), u(t), \ldots, u^{(l)}(t)) \in \mathcal{O}^l$, where $\varphi = (\varphi_1, \ldots, \varphi_m)$ and is called a *flat output*.

It is commonly accepted, see Fliess et al. [1999], Lévine [2009], that flatness is a local and generic property, that is, the desired description (2) is local and holds out of singular states and singular values of controls. In our study, all functions φ_i depend on x only, i.e., we have $\varphi_i = \varphi_i(x)$, for all $1 \leqslant i \leqslant m$, and ensure flatness around any nominal point x^* of the state space (that is, there are no singularities for flatness).

Not all control systems are flat (and the first who gave a counter-example was Hilbert [1912]), but a class of systems that are well known to be flat is the static feedback linearizable one. The control system $\Xi : \dot{x} = F(x,u)$ is said to be locally static feedback linearizable if it can be transformed via a local diffeomorphism $z = \phi(x)$ and an invertible feedback transformation $u = \psi(x,v)$ to a linear controllable system $\Lambda : \dot{z} = Az + Bv$. The diffeomorphism $\phi(x)$ is simply a change of coordinates, while the feedback $\psi(x,v)$ plays the role of a change of coordinates in the control space depending on the state. The problem of static feedback linearization was solved by Jakubczyk and Respondek [1980] and, independently, by In general, a flat system is not linearizable by static feedback, with the exception of the single-input case for which flatness is equivalent to static feedback linearization (thus the conditions of Theorem 3, stated in Appendix A, are also necessary and sufficient for flatness), see Charlet et al. [1991], Pomet [1995]. Flat systems can be seen as a generalization of static feedback linearizable systems. Namely they are linearizable via dynamic, invertible and endogenous feedback, see Fliess et al. [1995], Pomet [1995] for definitions of those notions. We will see that in our analysis, flatness of the considered systems always reduces to the study of flatness for a single-input system or subsystem, so to static feedback linearization.

2.2 Triangular Liouvillian systems Liouvillian systems can be seen as an extension of flat systems Chelouah [1997, 2010], Crespo et al. [2021], see also Kiss et al. [2002] for an application to motion planning for robotic manipulation. We have seen in Section 2.1 that the main property of flat systems is that all state and control variables of the system can be directly expressed, without any integration of differential equations, in terms of the flat output and a finite number of its time-derivatives. So called Liouvillian systems share a similar property, but in order to derive the trajectories of a Liouvillian system, we also need integrations of differential equations whose solutions are known analytically. Before giving a formal definition, let us illustrate this remark through the following example, see Chelouah [1997]:

$$\begin{aligned} \dot{x}_1 &= x_2 + a(x) \\ \dot{x}_2 &= x_3 \\ \dot{x}_3 &= u, \end{aligned} \tag{3}$$

where the smooth function a is given either by $a(x) = x_1^2$ or by $a(x) = x_2^2$ or by $a(x) = x_3^2$. It is easy to see that in the first two cases, the above system is flat with $\varphi = x_1$ being a flat output, but if $a(x) = x_3^2$, then (3) is not flat (it does not satisfy the necessary and sufficient conditions of Theorem 3, see Appendix A). However, in the latter case, system (3) contains the flat subsystem $\dot{x}_2 = x_3$, $\dot{x}_3 = u$, for which $\varphi = x_2$ is a flat output, and the trajectory of x_1 can be obtained by integrating the differential equation $\dot{x}_1 = \varphi(t) + \dot{\varphi}(t)^2$ (which is linear in the x_1-variable), i.e., we have $x_1(t) = \int \varphi(t) + \dot{\varphi}(t)^2 \mathrm{d}t$. It follows that a differential parametrization of all the system variables is no longer possible, but, instead, an integral-differential parametrization could be established. The Liouvillian property is thus slightly weaker than flatness: a system is Liouvillian if there exists an output (that we call Liouvillian output), of the same dimension as the input, and some functions for which we have to solve some (linear) differential equations, such that all the system variables can be expressed in terms of the Liouvillian output and those fuctions and a finite number of their time-derivatives (see Definition 2 for a formal definition). It follows that flatness based control approaches can be extended up to solving a finite number of (linear) differential equations (which is, in general, simpler than integrating the system differential equations).

The notion of Liouvillian systems is defined in Chelouah [1997], Crespo et al. [2021], Srinivasan [2020] using differential algebra. We adopt here a slightly different formulation (see also Kiss et al. [2002] for a related definition). In what follows, the Liouvillian output (which is the analogous of a flat output) is denoted by $\varphi = (\varphi_1, \ldots, \varphi_m)$ and the functions for which we have to solve some differential equations are denoted by ξ_k; there are p of them, with $p \geqslant 1$, i.e., $\xi = (\xi_1, \ldots, \xi_p)$. For $0 \leqslant k \leqslant p$ and integers $\nu \geqslant 0$ and $\eta \geqslant 0$, denote

$$(\bar{\bar{\xi}}_k^{\,\nu}, \overline{\varphi}^{\,\eta}) = (\xi_1, \ldots, \xi_1^{(\nu)}, \ldots, \xi_k, \ldots, \xi_k^{(\nu)}, \varphi_1, \ldots, \varphi_1^{(\eta)}, \ldots, \varphi_m, \ldots, \varphi_m^{(\eta)}),$$

where there are no ξ-functions if $k = 0$. The above notation is used in relation (4) of Definition 2 below. Notice the double bar associated to the ξ-functions: the first bar indicates that among $(\xi_1, \ldots, \xi_p)$ we consider $(\xi_1, \ldots, \xi_k)$ only, while the second bar is related to the order of the time-derivatives. When we write $\overline{\varphi}^{\,\eta}$, all components of the output $\varphi = (\varphi_1, \ldots, \varphi_m)$ are taken into account (notice that there is no lower-index associated to φ) and the bar is related to the order of the time-derivatives.

Definition 2. A strongly accessible[1] system $\Xi : \dot{x} = F(x, u)$ is *triangular Liouvillian* at $(x^*, \bar{u}^{*l}) \in X \times U^l$, for $l \geqslant -1$, if there exists a neighborhood $\mathcal{O}^l$ of $(x^*, \bar{u}^{*l})$, m smooth functions $\varphi_i = \varphi_i(x, u, \dot{u}, \ldots, u^{(l)})$, $1 \leqslant i \leqslant m$, and a finite number $p \geqslant 1$ of smooth functions $\xi_k = \xi_k(x, u, \dot{u}, \ldots, u^{(l)})$, $1 \leqslant k \leqslant p$, given by the differential equations

$$\begin{aligned} \xi_k^{(\mu_k)} &+ a_k^{\mu_k - 1}(\bar{\bar{\xi}}_{k-1}^{\,\nu}, \overline{\varphi}^{\,\eta}) \cdot \xi_k^{(\mu_k - 1)} + \cdots \\ &+ a_k^0(\bar{\bar{\xi}}_{k-1}^{\,\nu}, \overline{\varphi}^{\,\eta}) \cdot \xi_k = b_k(\bar{\bar{\xi}}_{k-1}^{\,\nu}, \overline{\varphi}^{\,\eta}),\ 1 \leqslant k \leqslant p, \end{aligned} \tag{4}$$

for some integers $\mu_k \geqslant 1$, $\nu \geqslant 0$ and $\eta \geqslant 0$, and smooth functions $a_k^0, \ldots, a_k^{\mu_k - 1}, b_k$, such that all functions φ_i and ξ_k are differentially independent, defined in $\mathcal{O}^l$, and have the following property: there exist integers q and r and smooth functions γ_i, $1 \leqslant i \leqslant n$, and δ_j, $1 \leqslant j \leqslant m$, such that

$$\begin{aligned} x_i &= \gamma_i(\varphi, \ldots, \varphi^{(r)}, \xi, \ldots, \xi^{(q)}) \\ u_j &= \delta_j(\varphi, \ldots, \varphi^{(r)}, \xi, \ldots, \xi^{(q)}) \end{aligned} \tag{5}$$

for any sufficiently smooth control $u(t)$ and corresponding trajectory $x(t)$ that satisfy $(x(t), u(t), \ldots, u^{(l)}(t)) \in \mathcal{O}^l$. The m-tuple $\varphi = (\varphi_1, \ldots, \varphi_m)$ is called a *Liouvillian output*.

The denomination "triangular Liouvillian" comes from the fact that the (linear) differential equations (4), to be solved in order to compute the functions ξ_k, have a triangular structure. Indeed, notice first, that for fixed k, equation (4) is linear with respect to ξ_k and its time-derivatives and, second, that its functional coefficients $a_k^0, \ldots, a_k^{\mu_k - 1}$ and b_k depend on $\bar{\xi}_{k-1} = (\xi_1, \ldots, \xi_{k-1})$ and their successive time-derivatives and they never involve $(\xi_k, \ldots, \xi_p)$ (but can depend on all φ_i, $1 \leqslant i \leqslant m$, and on a finite number of their successive time-derivatives).

[1] See Sussmann and Jurdjevic [1972] for that notion (implying, in particular, that for each k, equation (4) cannot involve $\xi_k^{(j)}$ only and that at least one a_k^j or b_k explicitly depends on some $\bar{\bar{\xi}}_{k-1}^{\,\nu}$ or $\overline{\varphi}^{\,\eta}$.

3. MAIN RESULTS

Our main results are given by Theorems 1 and 2 below, analyzing flatness of two different models of the HPA axis. We start our study by considering a minimal three-dimensional model with one input (Theorem 1), and then a representative more involved model with seven states and three inputs (Theorem 2).

3.1 Minimal three-dimensional model Consider first the following minimal model of the HPA axis containing the basic components of a mathematical structure capturing the macroscopic elements of the HPA axis (see Bangsgaard and Ottesen [2017]):

$$\begin{aligned} \frac{\mathrm{d}CRH}{\mathrm{d}t} &= a_0 + C(t)\frac{a_1}{1 + a_2(CORT)^2} \cdot \frac{CRH}{\mu + CRH} - \omega_1 CRH \\ \frac{\mathrm{d}ACHT}{\mathrm{d}t} &= \frac{a_3 CRH}{1 + a_4 CORT} - \omega_2 ACHT \\ \frac{\mathrm{d}CORT}{\mathrm{d}t} &= a_5(ACHT)^2 - \omega_3 CORT. \end{aligned} \tag{6}$$

The state variables are given by the concentrations of corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol (CORT), respectively, each of them evolving on $\mathbb{R}_+^*$. Hence the above dynamical model expresses the sequential activation "CRH $\to$ ACTH $\to$ Cortisol". The parameter a_1 represents the strength of the auto-up-regulation of CRH, and following Bangsgaard and Ottesen [2017], can be considered as an input of the (control) system. All remaining parameters are supposed to be nonzero and constant (we refer the reader to Bangsgaard and Ottesen [2017] for their interpretation and possible values), while $C(t)$ is a periodically extended bell-like function describing the circadian rhythm. In order to simplify notations, we will denote the states by x_{cr}, x_{ac} and x_{co}, the control by u, and use the notation $\dot{x}$ for the time-derivative of x, that is, the above system becomes:

$$\begin{aligned} \dot{x}_{cr} &= a_0 + \frac{C(t)}{1 + a_2 x_{co}^2}\frac{x_{cr}}{\mu + x_{cr}} u - \omega_1 x_{cr} \\ \dot{x}_{ac} &= \frac{a_3 x_{cr}}{1 + a_4 x_{co}} - \omega_2 x_{ac} \\ \dot{x}_{co} &= a_5 x_{ac}^2 - \omega_3 x_{co}. \end{aligned} \tag{7}$$

As explained in Section 2, we work locally, around a given $x^* = (x_{cr}^*, x_{ac}^*, x_{co}^*) \in (\mathbb{R}_+^*)^3$. According to the next theorem, the minimal HPA axis model is always flat around any $x^* \in (\mathbb{R}_+^*)^3$.

Theorem 1. The following equivalent conditions hold:

(F1) System (6), and equivalently, (7), is locally static feedback linearizable, around any $x^* \in (\mathbb{R}_+^*)^3$ and can be transformed into

$$\begin{aligned} \dot{z}_1 &= z_2 \\ \dot{z}_2 &= z_3 \\ \dot{z}_3 &= v. \end{aligned} \tag{8}$$

(F2) System (6), and equivalently, (7), is flat around any $x \in (\mathbb{R}_+^*)^3$ and $\varphi = x_{co} = CORT$ is a flat output.

System (7) is a single-input control system, thus as expected, we recover the results of Charlet et al. [1991] according to which, a single-input control system is flat if and only if it is static feedback linearizable. Moreover, the linearizing output (that is, z_1 the top variable of the z-chain of (8)) and the flat output coincide (i.e., the diffeomorphism transforming (7) into (8) is such that $z_1 = x_{co} = CORT$).

From Theorem 1 it follows that the original system (7) is equivalent to the dynamics of the flat output x_{co}, obtained by differentiating two times the last equation of (7). More precisely, we get a relation of the form $x_{co}^{(3)} = \alpha(x_{co}, \dot{x}_{co}, \ddot{x}_{co}) + \beta(x_{co}, \dot{x}_{co}, \ddot{x}_{co})u$, where, in order to obtain the functions α and β we have to replace x_{ac} and x_{cr} by their expressions in terms of the flat output x_{co} and its successive time-derivatives (see flatness description (2) of Definition 1, and relations (11) and (12) in the proof of Theorem 1). After applying the invertible feedback transformation $\alpha + \beta u = v$, we get the trivial linear dynamics $x_{co}^{(3)} = v$, which, for instance, may be used for stabilized tracking of a given reference trajectory $x_{co,r}(t)$, see, e.g., Martin et al. [1996, 2002].

3.2 Increased detail seven-dimensional model We consider now the following HPA axis model of increased detail incorporating the transcription and translation of the glucocorticoid receptor (GR) and the dynamics of the nuclear translocation of the activated complex inducing the negative feedback (see Androulakis [2021], Rao and Androulakis [2020]):

$$\begin{aligned} \frac{\mathrm{d}CRH}{\mathrm{d}t} &= \frac{k_{p1}K_{p1}}{K_{p1} + DR(N)} - V_{d1}\frac{CRH}{K_{d1} + CRH} \cdot \left(1 + \frac{L}{1+L}\right) \\ \frac{\mathrm{d}ACHT}{\mathrm{d}t} &= \frac{k_{p2}K_{p2}CRH}{K_{p2} + DR(N)} - V_{d2}\frac{ACTH}{K_{d2} + ACTH} \\ \frac{\mathrm{d}CORT}{\mathrm{d}t} &= k_{p3}ACTH - V_{d3}\frac{CORT}{K_{d3} + CORT} \\ \frac{\mathrm{d}GR_{mRNA}}{\mathrm{d}t} &= k_{syn,GRm}\left(1 - \frac{DR(N)}{IC50_{GRm} + DR(N)}\right) - k_{deg}GR_{mRNA} \\ \frac{\mathrm{d}GR}{\mathrm{d}t} &= k_{syn,GR}GR_{mRNA} + r_f k_{re}DR(N) - k_{on}CORT \cdot GR \\ &\quad - k_{deg,GR}GR \\ \frac{\mathrm{d}DR}{\mathrm{d}t} &= k_{on}CORT \cdot GR - k_T DR \\ \frac{\mathrm{d}DR(N)}{\mathrm{d}t} &= k_T DR - r_f k_{re}DR(N). \end{aligned} \tag{9}$$

The binding of released $CORT$ to cytosolic GR leads to the formation of the receptor-glucocorticoid complex (DR). $DR(N)$ represents the nuclear activated receptor glucocorticoid complex, while GR_{mRNA} is the $DR(N)$ own transcription. The lumped effects of light on the HPA axis are captured by the term L. We send the reader to Rao and Androulakis [2019] for a detailed presentation and discussion of the model and its parameters. The above system can be considered as a three-input control system with inputs the hypothalamic negative feedback K_{p1}, the pituitary negative feedback K_{p2}, and the feedforward adrenal sensitivity k_{p3}. The parameters that are not modeled as inputs of the control system are supposed to be non zero and constant. Each state variable is assumed to evolve on $\mathbb{R}_+^*$. As for the minimal model, we denote the state of the above system by $x = (x_{cr}, x_{ac}, x_{co}, x_{grm}, x_{gr}, x_{dr}, x_{drn}) = (CRH, \ldots, DR(N)) \in (\mathbb{R}_+^*)^7$ and the nominal point around which we work by $x^* = (x_{cr}^*, \ldots, x_{drn}^*) \in (\mathbb{R}_+^*)^7$.

Theorem 2. Consider system (9) controlled by K_{p1}, K_{p2}, and k_{p3}, around any $x^* \in (\mathbb{R}_+^*)^7$. The following conditions hold:

(C1) System (9) is not locally static feedback linearizable around x^*.
(C2) System (9) is not flat at x^*.
(C3) System (9) is triangular Liouvillian at x^*, with $\varphi = (x_{cr}, x_{ac}, x_{drn})$ as a Liouvillian output.

Moreover, (C1) and (C2) are equivalent around x^*.

For a better understanding, we simplify the notation for the indices associated to the model parameters (compare relations (9) and (10)) and apply the invertible feedback transformation:

$$\begin{aligned} u_1 &= \frac{k_{p1}K_{p1}}{K_{p1} + x_{drn}} - V_{d1}\frac{x_{cr}}{K_{d1} + x_{cr}} \cdot \left(1 + \frac{L}{1+L}\right), \\ u_2 &= \frac{k_{p2}K_{p2}x_{cr}}{K_{p2} + x_{drn}} - V_{d2}\frac{x_{ac}}{K_{d2} + x_{ac}}, \\ u_3 &= k_{p3}x_{ac} - V_{d3}\frac{x_{co}}{K_{d3} + x_{co}}, \end{aligned}$$

to bring (9) into

$$\begin{aligned} \dot{x}_{cr} &= u_1 & \dot{x}_{grm} &= k_{s4}\left(1 - \frac{x_{drn}}{IC + x_{drn}}\right) - k_d x_{grm} \\ \dot{x}_{ac} &= u_2 & \dot{x}_{gr} &= k_{s5}x_{grm} + r_f k_{re}x_{drn} - k_{on}x_{co} \cdot x_{gr} \\ & & &\quad - k_{d5}x_{gr} \\ \dot{x}_{co} &= u_3 & \dot{x}_{dr} &= k_{on}x_{co} \cdot x_{gr} - k_T x_{dr} \\ & & \dot{x}_{drn} &= k_T x_{dr} - r_f k_{re}x_{drn}. \end{aligned} \tag{10}$$

The structural properties that we are studying are invariant with respect to feedback transformations, so flatness and Liouvillian characters of system (9) are equivalent to those of (10). Moreover, using the above form, it is easy to see that conditions (C1) and (C2) are equivalent. Indeed, notice that system (10) actually consists of two decoupled subsystems: a first linear subsystem whose state and control variables are (x_{cr}, x_{ac}) and (u_1, u_2), respectively, and a second nonlinear subsystem with state $(x_{co}, \ldots, x_{drn})$ and control u_3. Therefore system (10) is static feedback linearizable if and only if the single-input nonlinear subsystem is static feedback linearizable, if and only if it is flat. When proving Theorem 2, we show that the single-input nonlinear subsystem does not satisfy the necessary and sufficient conditions of Theorem 3, thus we deduce that system (10) is never flat. According to (C3), it is however triangular Liouvillian, with $(x_{cr}, x_{ac}, x_{drn})$ a Liouvillian output. We will see when proving condition (C3) that $\xi = (x_{grm}, x_{gr})$ is a pair of functions for which we have so solve two (linear) differential equations that respect the triangular structure (4) of Definition 2. Indeed, in order to compute x_{grm} we have to solve a linear differential equation depending on φ_3 only. The differential equation associated to x_{gr} is also linear, it involves φ_3, $\dot\varphi_3$ and $\ddot\varphi_3$, but also x_{grm} (so it has to be solved after computing x_{grm} by integrating its corresponding differential equation). All remaining state and control variables can be expressed in terms of φ and ξ and a finite number of their successive time-derivatives.

4. PROOFS

4.1 Proof of Theorem 1. Proof of (F1). In order to show that system (7) is locally, around x^*, static feedback linearizable, one can, for instance, check the necessary and sufficient conditions of Theorem 3, stated in the appendix, for the drift $f(x)$ and control vector field $g(x)$ of (7) (i.e., in compact form, we rewrite (7) as $\dot x = f(x)+g(x)u$). The system being in small dimension, it is actually immediate that the following change of coordinates [2] $z_1 = h(x) = x_{co}$, $z_2 = L_f h(x)$ and $z_3 = L_f^2 h(x)$ is valid around any $x^* \in (\mathbb{R}_+^*)^3$, and that, followed by the invertible static feedback transformation $v = L_f^3 h(x)+(L_g L_f^2 h(x))u$, brings system (7) into form (8).

Proof of (F2). It is easy to see that $\varphi = x_{co}$ is a flat output of system (7) around any $x^* \in (\mathbb{R}_+^*)^3$. Indeed, we have $\dot\varphi = a_5 x_{ac}^2 - \omega_3\varphi$ which locally yields

$$x_{ac} = \sqrt{\frac{\dot\varphi + \omega_3\varphi}{a_5}} = \gamma_2(\varphi,\dot\varphi), \tag{11}$$

(we use the lower index 2 to denote γ_2 because x_{ac} is the second component of the state vector x). From the equation of $\dot x_{ac}$, we deduce that

$$x_{cr} = (\dot\gamma_2(\varphi,\dot\varphi) + \omega_2\gamma_2(\varphi,\dot\varphi)) \cdot \frac{1+a_4\varphi}{a_3} = \gamma_1(\varphi,\dot\varphi,\ddot\varphi), \tag{12}$$

and finally, $\dot x_{cr}$ gives

$$u = (\dot\gamma_1(\varphi,\dot\varphi,\ddot\varphi) + \omega_1\gamma_1(\varphi,\dot\varphi,\ddot\varphi) - a_0) \cdot \frac{1+a_2\varphi^2}{C(t)} \cdot \frac{\mu + \gamma_1(\varphi,\dot\varphi,\ddot\varphi)}{\gamma_1(\varphi,\dot\varphi,\ddot\varphi)}$$
$$= \delta(\varphi,\dot\varphi,\ddot\varphi,\varphi^{(3)}).$$

We have just expressed all state and control variables with the help of $\varphi = x_{co}$ and its time-derivatives. Hence representation (2) of Definition 1 holds and the system is thus flat with $\varphi = x_{co}$ being a flat output at x^*.

Finally, the equivalence of (F1) and (F2) follows from Charlet et al. [1991].

4.2 Proof of Theorem 2 The structural properties claimed by conditions (C1)-(C3) of Theorem 2 are feedback invariant (that is, do not depend on invertible static feedback transformations [3] of the form $u = \alpha(x)+\beta(x)v$), it follows that if they hold for system (10), then they are also satisfied for the original one (9). We thus show Theorem 2 for system (10).

Proof of (C1). In order to check whether system (10) is locally, around x^*, static feedback linearizable, we have to verify the necessary and sufficient conditions of Theorem 3, see Appendix A, for the drift $f(x)$ and control vector field $g(x)$ of (10) (i.e., in compact form, we rewrite (10) as $\dot x = f(x) + g(x)u$). By a straighforward computation, we have $\mathcal{D}^0 = \operatorname{span}\{\frac{\partial}{\partial x_{cr}}, \frac{\partial}{\partial x_{ac}}, \frac{\partial}{\partial x_{co}}\}$, $\mathcal{D}^1 = \mathcal{D}^0 + \operatorname{span}\{-\frac{\partial}{\partial x_{gr}} + \frac{\partial}{\partial x_{dr}}\}$, and $\mathcal{D}^2 = \mathcal{D}^1 + \operatorname{span}\{\frac{\partial}{\partial x_{gr}} - \frac{k_T}{k_{d5}}\frac{\partial}{\partial x_{dr}} + \frac{k_T}{k_{d5}}\frac{\partial}{\partial x_{drn}}\} = \mathcal{D}^1 + \operatorname{span}\{\zeta_1\}$, for which we denote the new direction of $\mathcal{D}^2$ (added with respect to $\mathcal{D}^1$) by ζ_1. The above distributions are clearly of constant rank (3, 4 and 5, respectively) and involutive (all generating vector fields being constant). From $\mathcal{D}^2$, we calculate

$$\begin{aligned}\mathcal{D}^3 = \mathcal{D}^2 &+ \operatorname{span}\{(-\frac{k_T}{k_{d5}}\frac{k_{s4}IC}{(IC+x_{drn})^2})\frac{\partial}{\partial x_{grm}} + (-k_{d5} \\ &+ \frac{k_T}{k_{d5}} r_f k_{re})\frac{\partial}{\partial x_{gr}} + \frac{k_T^2}{k_{d5}}\frac{\partial}{\partial x_{dr}} - \frac{k_T}{k_{d5}}(k_T + r_f k_{re})\frac{\partial}{\partial x_{drn}}\}, \\ &= \mathcal{D}^2 + \operatorname{span}\{\zeta_2\},\end{aligned}$$

where, similarly to ζ_1, now ζ_2 denotes the new direction of $\mathcal{D}^3$ not belonging to $\mathcal{D}^2$. We have

$$[\zeta_1,\zeta_2] = -2\left(\frac{k_T}{k_{d5}}\right)^2 \frac{k_{s4}IC}{(IC+x_{drn})^3}\frac{\partial}{\partial x_{grm}} \notin \mathcal{D}^3,$$

hence the distribution $\mathcal{D}^3$ is not involutive. It follows that the system is not static feedback linearizable.

Proof of (C2). In order to show that system (10) is not flat, notice that the dynamics associated to x_{grm}, x_{gr}, x_{dr} and x_{drn} are completely independent on x_{cr}, x_{ac} and u_i, $1 \leqslant i \leqslant 3$, see the hand-right side of (10). So system (10) actually consists of two decoupled subsystems whose states and controls are (x_{cr}, x_{ac}) and (u_1, u_2), and $(x_{co}, \dots, x_{drn})$ and u_3, respectively. The first subsystem is clearly flat and, the two subsystems being decoupled, it follows that flatness of (10) is actually equivalent to that of the second subsystem, which is a single-input control system and is flat if and only if it is static feedback linearizable. By repeating the proof of condition (C1) with $\mathcal{D}^0$ being replaced by $\mathcal{D}^0 = \operatorname{span}\{\frac{\partial}{\partial x_{co}}\}$, we conclude that the second subsystem is not static feedback linearizable and thus not flat. It follows that (10) is not flat either.

Proof of (C3). We show next that $\varphi = (x_{cr}, x_{ac}, x_{drn})$ is a Liouvillian output for system (10). The first two equations of (10) give $u_1 = \dot\varphi_1$ and $u_2 = \dot\varphi_2$, respectively. From $\dot x_{drn} = \dot\varphi_3$, we express x_{dr} as $x_{dr} = \frac{\dot\varphi_3 + r_f k_{re}\varphi_3}{k_T} = \gamma_6(\varphi_3,\dot\varphi_3)$. Then $\dot x_{dr} = \dot\gamma_6(\varphi_3,\dot\varphi_3)$ allows us to calculate $x_{co}\cdot x_{gr} = \frac{\dot\gamma_6 - k_T\gamma_6}{k_{on}} = \lambda(\varphi_3,\dot\varphi_3,\ddot\varphi_3)$. The dynamics of x_{grm} reads

$$\dot x_{grm} + k_d x_{grm} = k_{s4}\frac{IC}{IC+\varphi_3},$$

which is a linear differential equation in x_{grm} depending on φ_3. It follows that $\xi_1 = x_{grm}$ has to be computed by solving this differential equation. Once $\xi_1 = x_{grm}$ has been computed, the linear (with respect to x_{gr}) differential equation

$$\dot x_{gr} + k_{d5}x_{gr} = k_{s5}\xi_1 + r_f k_{re}\varphi_3 - k_{on}\lambda(\varphi_3,\dot\varphi_3,\ddot\varphi_3)$$

gives $\xi_2 = x_{gr}$. From $x_{co}\cdot x_{gr} = \lambda(\varphi_3,\dot\varphi_3,\ddot\varphi_3)$, we can calculate $x_{co} = \gamma_3(\varphi_3,\dot\varphi_3,\ddot\varphi_3,\xi_2)$ and finally, from $\dot x_{co}$, we get $u_3 = \delta_3(\varphi_3,\dots,\varphi_3^{(3)},\xi_2,\dot\xi_2)$. The system is thus proven to be triangular Liouvillian with $\varphi = (x_{cr}, x_{ac}, x_{drn})$ a Liouvillian output and $\xi = (x_{grm}, x_{gr})$ the variables for which we need to solve two linear differential equations with a triangular structure.

[2] Where the Lie derivative $L_f h$, expressed in a coordinate system $(x_1,\dots,x_n)$ by $L_f h = \sum_{i=1}^n \frac{\partial h}{\partial x_i} f_i(x)$, evaluates the change of the scalar smooth function $h(x)$ along the vector field $f(x)$, and $L_f^{k+1}h = L_f(L_f^k h)$, for $k \geqslant 1$.

[3] We consider control-affine feedback transformations because the studied system is a control-affine one.

5. CONCLUSIONS AND FUTURE WORK

In this paper, we studied flatness and Liouvillian properties of two existing quantitative models of the HPA axis. We showed that the minimal three-dimensional model controlled by the strength of the auto-up-regulation of CRH is always flat, while the more involved model with seven states and three inputs is never flat. We proved that although not flat, the involved model however exhibits an interesting property: it is a triangular Liouvillian control system. Based on the Liouvillian character of the involved model, our future work will include trajectory tracking (more precisely, maintenance of the homeostatic glucocorticoid rhythms) of CRH, CORT and ACTH, robust to stress and light perturbations. In addition to the dynamics described by (9), we could also consider a slow actuator dynamics accounting for the neural plasticity behind the time-evolution of the parameters K_{p1}, K_{p2} and k_{p3}.

A. STATIC FEEDBACK LINEARIZATION

The problem of static feedback linearization was solved by Jakubczyk and Respondek [1980] and, independently, by Hunt and Su [1981], who gave geometric necessary and sufficient conditions that we recall in Theorem 3 below. Consider the following control-affine system [4]:

$$\Sigma : \dot{x} = f(x) + \sum_{i=1}^{m} u_i g_i(x), \quad x \in X \subset \mathbb{R}^n, u \in U \subset \mathbb{R}^m.$$

Define the following sequence of distributions $\mathcal{D}^0 = \operatorname{span}\{g_1, \ldots, g_m\}$ and $\mathcal{D}^{j+1} = \mathcal{D}^j + [f, \mathcal{D}^j] = \operatorname{span}\{g_i, ad_f g_i, \ldots, ad_f^{j+1} g_i, 1 \leqslant i \leqslant m\}$, where $j \geqslant 0$, $ad_f g_i$ denotes $ad_f g_i = [f, g_i]$, where the bracket represents the Lie bracket [5], and $ad_f^{j+1} g_i = [f, ad_f^j g_i]$.

Theorem 3. The following conditions are equivalent:

(FL1) Σ is locally static feedback linearizable, around $x^* \in X$;

(FL2) Σ is locally static feedback equivalent, around $x^* \in X$, to the Brunovský canonical form

$$(Br) : \begin{cases} \dot{z}_i^j &= z_i^{j+1} \\ \dot{z}_i^{\rho_i} &= v_i, \end{cases}$$

where $1 \leqslant i \leqslant m$, $1 \leqslant j \leqslant \rho_i - 1$, and $\sum_{i=1}^{m} \rho_i = n$;

(FL3) For any $j \geqslant 0$, the distributions $\mathcal{D}^j$ do not depend on u, are of constant rank, around $x^* \in X$, *involutive,* and $\mathcal{D}^{n-1} = TX$.

The Brunovský canonical form (Br), see Brunovsky [1970], consists of m independent chains of integrators $z_i = (z_i^1, \ldots, z_i^{\rho_i})$, for $1 \leqslant i \leqslant m$, of lengths, respectively, $\rho_1, \rho_2, \ldots, \rho_m$, and is clearly flat with $(\varphi_1, \ldots, \varphi_m) = (z_1^1, \ldots, z_m^1)$ a flat output.

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[4] Observe that all control systems considered in the paper are affine with respect to the control, but, in general, nonlinear with respect to the state variables.

[5] In a coordinate system $(x_1, \ldots, x_n)$, we have $[f, g] = Dg \cdot f - Df \cdot g$, where Df and Dg are the Jacobian matrices of f and g, respectively.

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