DOI: 10.2478/awutm-2025-0006

Annals of West University of Timisoara
Mathematics and Computer Science
61 (2025), 61–74

Multiple time scales method for a two dimensional system with distributed delays

Maria Roxana Matei

Abstract Building on the simplified mathematical model derived from the dynamics of the hypothalamic-pituitary-adrenal (HPA) axis, which describes the interactions between ACTH and cortisol through a system of differential equations with distributed delays, this paper focuses on the criticality analysis of the Hopf bifurcation. This analysis is conducted using the method of multiple time scales, which is applicable to systems with arbitrary distributed delays and indicates whether the Hopf bifurcation leads to a stable or unstable limit cycle. Furthermore, the approach presented in this paper can be applied to a broader class of systems that exhibit similar structural properties, extending its relevance beyond the specific biological context considered here.

AMS Subject Classification (2020) 34D23; 91B39; 91B55
Keywords multiple time scales; equilibrium point; Hopf bifurcations; distributed time delay

1 Introduction

The starting point of this article is the dynamics of the hypothalamic-pituitary-adrenal (HPA) axis using a simplified model that captures the interactions between ACTH and cortisol which was previously studied in [6].

The simplified HPA model comprises a system of two differential equations that incorporate general distributed delays

$$\begin{cases} \dot{A}(t) = f\left(\int_0^\infty h_c(s)C(t-s)ds\right) - \beta_a A(t) \\ \dot{C}(t) = g\left(\int_0^\infty h_a(s)A(t-s)ds\right) - \beta_c C(t) \end{cases} . \tag{1.1}$$

The system models the concentrations of ACTH denoted by $A(t)$ and cortisol denoted by $C(t)$ at time t with elimination constants β_a, β_c being positive.

Feedback functions $f, g : [0,\infty) \to (0,\infty)$ represent the negative feedback of cortisol on ACTH and the positive feedback of ACTH on cortisol, both being monotonous, smooth and bounded on $[0,\infty)$ where f is strictly decreasing and g is strictly increasing. They are represented by Hill functions, see [1,4,7]:

$$f(x) = \gamma\left(1 - \mu\frac{x^m}{u^m + x^m}\right), \quad g(x) = \eta\frac{x^n}{v^n + x^n},$$

with $m, n \geq 1, \gamma > 0, u, v > 0$ and $\mu, \eta \in (0,1]$.

The delay kernels $h_a, h_c : [0,\infty) \to [0,\infty)$ are probability density functions representing the delayed stimulation of cortisol by ACTH (h_a) and delayed inhibition of ACTH by cortisol (h_c) satisfying:

$$\int_0^\infty h_j(s)ds = 1, \qquad j \in \{a,c\},$$

where

$$\tau_j = \int_0^\infty s h_j(s)ds, \qquad j \in \{a,c\},$$

are the average time delays associated to the delay kernels h_j.

Previously, we analyzed the presence of a positive equilibrium point, being a solution of the following algebraic system:

$$\begin{cases} f(C) = \beta_a A \\ g(A) = \beta_c C \end{cases}$$

and obtained that the system has a unique equilibrium point $E = (A^\star, C^\star)$.

A sufficient condition for delay-independent asymptotic stability was established ensuring that the equilibrium is asymptotically stable when $b < \beta_a\beta_c$, where

$$b = -f'(C^\star)g'(A^\star) > 0.$$

In the absence of delays, the equilibrium was proven to be locally asymptotically stable.

Studying the stability using linearization techniques (see [12,13]), we have the corresponding characteristic equation:

$$(z + \beta_a)(z + \beta_c) + bH_a(z,\tau_a)H_c(z,\tau_c) = 0, \tag{1.2}$$

where $H_j(z,\tau_j) = \int_0^\infty e^{-zs}h_j(s)ds$, for $j \in \{a,c\}$, denote the Laplace transforms of the delay kernels h_j.

We investigated the occurrence of Hopf bifurcations and using the root locus method, we searched for pure imaginary roots $z = \pm i\omega$ (with $\omega > 0$) for the characteristic equation [11], [13]. This approach led us to a system of equations that describe the critical frequencies for the Hopf bifurcation.

This system provides implicit equations for the bifurcation curves in the (τ_a, τ_c)-plane. We showed that these bifurcation curves are determined by the intersection of two surfaces in the (τ_a, τ_c, ω)-space. When it is not possible to eliminate ω analytically, we can still identify the Hopf bifurcation curves by projecting the intersection of these surfaces onto the (τ_a, τ_c)-plane.

Furthermore, we proved that the pure imaginary complex conjugate roots corresponding to the bifurcation must have multiplicity 1, which is one of the necessary conditions required for the occurrence of a Hopf bifurcation. We also examined the transversality condition and determined the orientation of the normal vector to the bifurcation curve, governed by a specific sign condition. The main theoretical result that we obtained refers to the fact that Hopf bifurcations occur near the equilibrium point $(A^\star, C^\star)$ of system (1.1) along specific curves in the (τ_a, τ_c)-plane (described above).

An important detail in the analysis of the Hopf bifurcation is the criticality analysis that represents the focus of this paper, using the method of multiple time scales. The advantage of this method compared to central manifold reduction is that it can also be used in the case of arbitrary distributed delays as in [5] and [8]. The criticality of the bifurcation tells us whether a stable or unstable limit cycle results from the Hopf bifurcation.

This paper is structured into four main sections. In the first section we introduce the simplified HPA model, in Section 2 we study the criticality analysis by the multiple time scales method and Hopf bifurcation analysis for studying limit cycles. In Section 3 we compute some numerical simulations for the Dirac case which confirms a supercritical Hopf bifurcation leading to a stable limit cycle when the critical delay is exceeded, as shown in the phase portraits of Figure 1. Section 4 concludes with a summary of the findings and recommendations for future research.

2 Criticality analysis through the method of Multiple Time Scales (MTS)

Denoting the convolutions

$$(h_a * A)(t) = \int_0^\infty h_a(s)A(t-s)ds, \quad (h_c * C)(t) = \int_0^\infty h_c(s)C(t-s)ds,$$

from (1.1) we obtain:

$$\begin{cases} \dot{A}(t) = f\,(h_c * C)(t) - \beta_a A(t) \\ \dot{C}(t) = g\,(h_a * A)(t) - \beta_c C(t) \end{cases}.$$

If τ_a is the average time delay for the delay kernel h_a, and τ_c is the average time delay for h_c, denoting $\tau_a + \tau_c = \tau$, $\tau_a = p\tau$, $\tau_c = (1-p)\tau$, where $p \in (0,1]$, we obtain that $\frac{\tau}{\tau_c} = \frac{1}{1-p}$ and $\frac{\tau}{\tau_a} = \frac{1}{p}$, and therefore, we introduce the modified delay kernels:

$$\widehat{h}_c(t) = \tau_c h_c(\tau_c t) \quad \text{with} \quad h_c(\tau s) = h_c\left(\tau_c \frac{\tau}{\tau_c} s\right) = \frac{1}{\tau_c}\widehat{h}_c\left(\frac{\tau}{\tau_c}s\right) = \frac{1}{\tau_c}\widehat{h}_c\left(\frac{s}{1-p}\right),$$

$$\widehat{h}_a(t) = \tau_a h_a(\tau_a t) \quad \text{with} \quad h_a(\tau s) = h_a\left(\tau_a \frac{\tau}{\tau_a} s\right) = \frac{1}{\tau_a}\widehat{h}_a\left(\frac{\tau}{\tau_a}s\right) = \frac{1}{\tau_a}\widehat{h}_a\left(\frac{s}{p}\right).$$

It is easy to verify that $\widehat{h}_a$ and $\widehat{h}_c$ are probability density functions with the mean equal to 1. Introducing the nondimensional variables:

$$\begin{cases} a(t) = A(\tau t) \\ c(t) = C(\tau t) \end{cases}$$

we have:

$$\dot{a}(t) = \tau \dot{A}(\tau t) = \tau \left[f\left(h_c * C\right)(\tau t) - \beta_a A(\tau t)\right] = \tau \left[f\left(\int_0^\infty h_c(s) C(\tau t - s) ds \right) - \beta_a A(\tau t)\right].$$

Changing the variable $s = \tau s'$ we have that:

$$\begin{aligned} \dot{a}(t) &= \tau \left[f\left(\tau \int_0^\infty h_c(\tau s') C(\tau(t - s')) ds' \right) - \beta_a a(t)\right] \\ &= \tau f\left(\frac{\tau}{\tau_c} \int_0^\infty \widehat{h}_c\left(\frac{\tau s}{\tau_c}\right) c(t-s) ds \right) - \tau \beta_a a(t) \\ &= \tau f\left(\frac{1}{1-p} \int_0^\infty \widehat{h}_c\left(\frac{s}{1-p}\right) c(t-s) ds \right) - \tau \beta_a a(t) \\ &= \tau f\left(\widetilde{h}_c * c\right) - \tau \beta_a a(t), \end{aligned}$$

where $\widetilde{h}_c(s) = \frac{1}{1-p}\widehat{h}_c\left(\frac{s}{1-p}\right)$ is a probability density function, with the mean:

$$\int_0^\infty s\widetilde{h}_c(s) ds = \int_0^\infty \frac{s}{1-p}\widehat{h}_c\left(\frac{s}{1-p}\right) ds = (1-p)\int_0^\infty s\widehat{h}_c(s) ds = 1 - p.$$

In the same way, we deduce that $\widetilde{h}_a(s) = \frac{1}{p}\widehat{h}_a\left(\frac{s}{p}\right)$ is a probability density function with the mean p. Hence, the following nondimensional system is obtained:

$$\begin{cases} \dot{a}(t) = \tau f\left(\widetilde{h}_c * c\right) - \tau \beta_a a(t) \\ \dot{c}(t) = \tau g\left(\widetilde{h}_a * a\right) - \tau \beta_c c(t) \end{cases}.$$

We consider the Taylor expansions of the functions f and g as follows:

$$\begin{cases} f(C) = f(C^*) + f'(C^*)(C - C^*) + \frac{f''(C^*)}{2}(C - C^*)^2 + \frac{f'''(C^*)}{6}(C - C^*)^3 + h.o.t. \\ g(A) = g(A^*) + g'(A^*)(A - A^*) + \frac{g''(A^*)}{2}(A - A^*)^2 + \frac{g'''(A^*)}{6}(A - A^*)^3 + h.o.t. \end{cases}$$

where h.o.t. stands for higher order terms. Using the transformation $u(t) = a(t) - A^*$, $v(t) = c(t) - C^*$, we have:

$$\begin{cases} \dot{u}(t) = & \tau \Big[f(C^*) + f'(C^*)(\widetilde{h}_c * c - C^*) + \frac{f''(C^*)}{2}(\widetilde{h}_c * c - C^*)^2 + \frac{f'''(C^*)}{6}(\widetilde{h}_c * c - C^*)^3 \\ & \quad + \text{h.o.t.} - \beta_a a(t) \Big] \\ \dot{v}(t) = & \tau \Big[g(A^*) + g'(A^*)(\widetilde{h}_a * a - A^*) + \frac{g''(A^*)}{2}(\widetilde{h}_a * a - A^*)^2 + \frac{g'''(A^*)}{6}(\widetilde{h}_a * a - A^*)^3 \\ & \quad + \text{h.o.t.} - \beta_c c(t) \Big] \end{cases}$$

We also know that

$$(\widetilde{h}_c * c - C^*)(t) = \int_0^\infty \widetilde{h}_c(s)c(t-s)ds - C^* = \int_0^\infty \widetilde{h}_c(s)\left(c(t-s) - C^*\right)ds = \widetilde{h}_c * v,$$

$$(\widetilde{h}_a * a - A^*)(t) = \int_0^\infty \widetilde{h}_a(s)a(t-s)ds - A^* = \int_0^\infty \widetilde{h}_a(s)\left(a(t-s) - A^*\right)ds = \widetilde{h}_a * u,$$

and hence, we obtain:

$$\begin{cases} \dot{u}(t) = -\tau\beta_a u(t) + \tau f'(C^*)(\widetilde{h}_c * v)(t) + \tau\frac{f''(C^*)}{2}(\widetilde{h}_c * v)^2(t) + \tau\frac{f'''(C^*)}{6}(\widetilde{h}_c * v)^3(t) + h.o.t. \\ \dot{v}(t) = -\tau\beta_c v(t) + \tau g'(A^*)(\widetilde{h}_a * u)(t) + \tau\frac{g''(A^*)}{2}(\widetilde{h}_a * u)^2(t) + \tau\frac{g'''(A^*)}{6}(\widetilde{h}_a * u)^3(t) + h.o.t. \end{cases} \tag{2.1}$$

Denoting

$$w = \begin{pmatrix} u \\ v \end{pmatrix}, \; \widetilde{h} * w = \begin{pmatrix} \widetilde{h}_a * u \\ \widetilde{h}_c * v \end{pmatrix} = \begin{pmatrix} \widetilde{h}_a & 0 \\ 0 & \widetilde{h}_c \end{pmatrix} * \begin{pmatrix} u \\ v \end{pmatrix}$$

we observe that system (2.1) can be written in the form below:

$$\dot{w}(t) = -\tau \begin{pmatrix} \beta_a & 0 \\ 0 & \beta_c \end{pmatrix} w(t) + \tau \begin{pmatrix} 0 & f'(C^*) \\ g'(A^*) & 0 \end{pmatrix} (\widetilde{h} * w)(t) + \tau F\left((\widetilde{h} * w)(t)\right).$$

We will use the following notations:

$$f_1 = f'(C^*), \; g_1 = g'(A^*), \; f_2 = \frac{f''(C^*)}{2}, \; g_2 = \frac{g''(A^*)}{2}, \; f_3 = \frac{f'''(C^*)}{6}, \; g_3 = \frac{g'''(A^*)}{6},$$

$$L = \begin{pmatrix} \beta_a & 0 \\ 0 & \beta_c \end{pmatrix}, \quad M_k = \begin{pmatrix} 0 & f_k \\ g_k & 0 \end{pmatrix}, \quad F(w) = M_2 w^2 + M_3 w^3,$$

where $w^2 = w \odot w$ and $w^3 = w \odot w \odot w$, with $\odot$ representing the Hadamard product, i.e. the element-wise application of the power function. With these notations, system (2.1) becomes

$$\dot{w}(t) = -\tau L w(t) + \tau M_1(\widetilde{h} * w)(t) + \tau F\left((\widetilde{h} * w)(t)\right) \tag{2.2}$$

At the critical value $\tau = \tau^*$ of the time delay, the corresponding linearized system is:

$$\dot{w}(t) = L_{\tau^*} w(t) \tag{2.3}$$

where the linear operator is given below:

$$L_{\tau^*} w = -\tau^* L w + \tau^* M_1(\widetilde{h} * w).$$

We assume that for the critical value τ^* of the average delay, the linear operator L_{τ^*} has complex conjugated eigenvalues $\pm i\omega$. Let q be an eigenvector of L_{τ^*} corresponding to the eigenvalue $i\omega$. Hence $w(t) = e^{i\omega t}q$ is a solution to the linear system, which gives:

$$i\omega q = -\tau^* L q + \tau^* M_1 \widetilde{H}(i\omega) q,$$

or equivalently:

$$\Gamma(i\omega) q = 0,$$

where $\Gamma(z) = zI_2 + \tau^* L - \tau^* M_1 \widetilde{H}(z)$, and we will further denote $\gamma(z) = \det \Gamma(z)$. Obviously, from the characteristic equation, we have $\gamma(i\omega) = \det \Gamma(i\omega) = 0$. We apply the method of multiple time scales in the system (2.2). Using this technique, we expand a solution of system (2.2) in terms of ϵ as follows:

$$w(t, \epsilon) = \sum_{k=1}^{\infty} \epsilon^k w_k \left(T_0, T_2\right), \tag{2.4}$$

where $T_j = \epsilon^j t$ for $j \in \{0, 2\}$ represent multiple time scales and $\epsilon > 0$ is a nondimensional book-keeping parameter. Using the notations:

$$\frac{d}{dt} = D_0 + \epsilon^2 D_2, \quad \text{where} \quad D_0 = \frac{\partial}{\partial T_0},\ D_2 = \frac{\partial}{\partial T_2},$$

by computing the derivative of $w(t, \epsilon)$ with respect to t, we obtain:

$$\frac{d}{dt} w(t, \epsilon) = \sum_{k=1}^{\infty} \epsilon^k \left(D_0 w_k + \epsilon^2 D_2 w_k\right) = \epsilon D_o w_1 + \epsilon^2 D_0 w_2 + \epsilon^3 \left(D_2 w_1 + D_0 w_3\right) + O\left(\epsilon^4\right) \tag{2.5}$$

The state variable with time delay can be expressed as:

$$w(t - s; \epsilon) = \sum_{k=1}^{\infty} \epsilon^k w_k \left(T_0 - s, T_2 - \epsilon^2 s\right). \tag{2.6}$$

Denoting $W_k(\epsilon) := w_k \left(T_0 - s, T_2 - \epsilon^2 s\right)$ in equation (2.6) and using Taylor expansion, we obtain:

$$\begin{aligned} W_k(\epsilon) &= w_k \left(T_0 - s, T_2 - \epsilon^2 s\right) = W_k(0) + W_k'(0)\epsilon + \frac{W_k''(0)}{2}\epsilon^2 + \frac{W_k'''(0)}{6}\epsilon^3 + O\left(\epsilon^4\right) \\ &= w_k \left(T_0 - s, T_2\right) - s D_2 x_k \left(T_0 - s, T_2\right) \epsilon^2 + O\left(\epsilon^3\right), \end{aligned} \tag{2.7}$$

where

$$\begin{aligned} W_k{}'(\epsilon) &= D_2 w_k \left(T_0 - s, T_2 - \epsilon^2 s\right) (-2\epsilon s) \implies W_k{}'(0) = 0, \\ W_k{}''(\epsilon) &= D_2^2 w_k \left(T_0 - s, T_2 - \epsilon^2 s\right) \left(4\epsilon^4 s^2\right) - 2s D_2 w_k \left(T_0 - s, T_2 - \epsilon^2 s\right) \\ &\implies W_k{}''(0) = -2s D_2 w_k \left(T_0 - s, T_2 - s\right). \end{aligned}$$

Substituting the equation (2.7) in equation (2.6) we have that:

$$\begin{aligned} w(t - s; \epsilon) =& \epsilon w_1(T_0 - s, T_2) + \epsilon^2 w_2(T_0 - s, T_2) + \\ &+ \epsilon^3 \left[-s D_2 w_1(T_0 - s, T_2) + w_3(T_0 - s, T_2)\right] + O\left(\epsilon^4\right) \end{aligned}$$

and therefore, the convolution can be expressed as:

$$\begin{aligned} (\widetilde{h} * w)(t; \epsilon) = \epsilon & \int_0^\infty \widetilde{h}(s) w_1(T_0 - s, T_2) ds + \epsilon^2 \int_0^\infty \widetilde{h}(s) w_2(T_0 - s, T_2) ds \\ &+ \epsilon^3 \left[- \int_0^\infty s \widetilde{h}(s) D_2 w_1(T_0 - s, T_2) ds + \int_0^\infty \widetilde{h}(s) w_3(T_0 - s, T_2) ds \right] \\ &+ O\left(\epsilon^4\right) \end{aligned} \tag{2.8}$$

From now on, we introduce the following notations:

$$W_k(T_0,T_2)=\int_0^\infty \widetilde{h}(s)w_k(T_0-s,T_2)ds,\quad J(T_0,T_2)=\int_0^\infty s\widetilde{h}(s)D_2w_1(T_0-s,T_2)ds.$$

Dropping the arguments, we obtain:

$$(\widetilde{h}*w)=\epsilon W_1+\epsilon^2W_2+\epsilon^3(W_3-J)+O\left(\epsilon^4\right),$$

which implies that:

$$(\widetilde{h}*w)^2=(\widetilde{h}*w)\odot(\widetilde{h}*w)=\epsilon^2W_1^2+2\epsilon^3W_1\odot W_2+O\left(\epsilon^4\right),$$
$$(\widetilde{h}*w)^3=\epsilon^3W_1^3+O\left(\epsilon^4\right).$$

Substituting all we have obtained so far in equation (2.2) we have that :

$$\begin{aligned}&\epsilon D_ow_1+\epsilon^2D_0w_2+\epsilon^3\left(D_2w_1+D_0w_3\right)=\\&\qquad=-\tau L(\epsilon w_1+\epsilon^2w_2+\epsilon^3w_3)+\tau M_1[\epsilon W_1+\epsilon^2W_2+\epsilon^3(W_3-J)]\\&\qquad\quad+\tau M_2(\epsilon^2W_1^2+2\epsilon^3W_1\odot W_2)+\tau\epsilon^3M_3W_1^3+O\left(\epsilon^4\right)\end{aligned}$$

Next, we introduce the detuning parameter δ to describe the nearness of τ to its critical value τ^* by $\tau=\tau^*+\epsilon^2\delta$, which leads to the following equations written up to ϵ^3 order:

$$\begin{aligned}&\epsilon: D_0w_1+\tau^*Lw_1-\tau^*M_1(\widetilde{h}*w_1)=0\\&\epsilon^2: D_0w_2+\tau^*Lw_2-\tau^*M_1(\widetilde{h}*w_2)=\tau^*M_2W_1^2\\&\epsilon^3: D_0w_3+\tau^*Lw_3-\tau^*M_1(\widetilde{h}*w_3)=-D_2w_1-\delta Lw_1+\delta M_1(\widetilde{h}*w_1)\\&\quad-\tau^*M_1J+2\tau^*M_2(W_1\odot W_2)+\tau^*M_3W_1^3\end{aligned}\tag{2.9}$$

Noticing that the first equation of (2.9) is similar to the linear homogeneous equation (2.3) if we regard w_1 as depending on time T_0, the solution is given by

$$w_1(T_0,T_2)=B(T_2)e^{i\omega T_0}q+\overline{B}(T_2)e^{-i\omega T_0}\overline{q}\tag{2.10}$$

where q is the eigenvector of the operator L_{τ^*} corresponding to the eigenvalue $i\omega$ and $B(T_2)$ is a scalar function. Next, we calculate:

$$\begin{aligned}W_1(T_0,T_2)&=\int_0^\infty\widetilde{h}(s)w_1(T_0-s,T_2)ds=\int_0^\infty\widetilde{h}(s)B(T_2)e^{i\omega(T_0-s)}q\,ds+c.c.\\&=B(T_2)e^{i\omega T_0}\widetilde{H}(i\omega)q+c.c.\end{aligned}$$

where c.c. stands for the complex conjugate terms. Therefore, taking into account that $\widetilde{H}(i\omega)$ is a diagonal matrix, we get:

$$\begin{aligned}W_1^2&=W_1\odot W_1=B(T_2)^2e^{2i\omega T_0}\widetilde{H}(i\omega)^2q\odot q+|B(T_2)|^2|\widetilde{H}(i\omega)|^2q\odot\overline{q}+c.c.\\&=B(T_2)^2e^{2i\omega T_0}\widetilde{H}(i\omega)^2q^2+|B(T_2)|^2|\widetilde{H}(i\omega)|^2|q|^2+c.c.\end{aligned}$$

where $|q|^2 = q \odot \overline{q}$. Substituting in the second equation of (2.9) it follows that:

$$D_0 w_2 + \tau^* L w_2 - \tau^* M_1(\widetilde{h} * w_2) = \tau^* B(T_2)^2 e^{2i\omega T_0} M_2 \widetilde{H}(i\omega)^2 q^2 + \tau^* |B(T_2)|^2 M_2 |\widetilde{H}(i\omega)|^2 |q|^2 + c.c. \tag{2.11}$$

Based on the superposition principle, we search for a particular solution of (2.11) for the first non-homogeneous term, of the following form: $e^{2i\omega T_0} K_1(T_2)$, which gives (by simple replacement):

$$\Gamma(2i\omega) K_1(T_2) = \tau^* B(T_2)^2 M_2 \widetilde{H}(i\omega)^2 q^2,$$

and hence:

$$K_1(T_2) = \tau^* B(T_2)^2 \Gamma(2i\omega)^{-1} M_2 \widetilde{H}(i\omega)^2 q^2.$$

Repeating the same process for the second non-homogeneous term, we seek a particular solution of the form $K_2(T_2)$, and once again, a simple replacement leads to:

$$\Gamma(0) K_2(T_2) = \tau^* |B(T_2)|^2 M_2 |\widetilde{H}(i\omega)|^2 |q|^2,$$

finally providing:

$$K_2(T_2) = \tau^* |B(T_2)|^2 \Gamma(0)^{-1} M_2 |\widetilde{H}(i\omega)|^2 |q|^2.$$

Hence, the solution of equation (2.11) is:

$$w_2(T_0, T_2) = e^{2i\omega T_0} K_1(T_2) + K_2(T_2) + c.c. \tag{2.12}$$

As the next step, we calculate:

$$W_2(T_0, T_2) = \int_0^\infty \widetilde{h}(s) w_2(T_0 - s, T_2) ds = e^{2i\omega T_0} \widetilde{H}(2i\omega) K_1(T_2) + K_2(T_2) + c.c.$$

$$\begin{aligned}
W_1 \odot W_2 = W_2 \odot W_1 &= \left[e^{2i\omega T_0} \widetilde{H}(2i\omega) K_1(T_2) + K_2(T_2) + c.c.\right] \odot \left[e^{i\omega T_0} B(T_2) \widetilde{H}(i\omega) q + c.c.\right] \\
&= e^{i\omega T_0} \left[2B(T_2) K_2(T_2) \odot \left(\widetilde{H}(i\omega) q\right) + \overline{B(T_2)} \widetilde{H}(2i\omega) K_1(T_2) \odot \left(\overline{\widetilde{H}(i\omega) q}\right)\right] \\
&\quad + c.c. + N.S.T. \\
&= e^{i\omega T_0} \left[2B(T_2) \widetilde{H}(i\omega)(K_2(T_2) \odot q) + \overline{B(T_2)} \widetilde{H}(2i\omega) \overline{\widetilde{H}(i\omega)} (K_1(T_2) \odot \overline{q})\right] \\
&\quad + c.c. + N.S.T. \\
&= e^{i\omega T_0} \tau^* B(T_2) |B(T_2)|^2 2\widetilde{H}(i\omega) \left(\left(\Gamma(0)^{-1} M_2 |\widetilde{H}(i\omega)|^2 |q|^2\right) \odot q\right) \\
&\quad + e^{i\omega T_0} \tau^* B(T_2) |B(T_2)|^2 \widetilde{H}(2i\omega) \overline{\widetilde{H}(i\omega)} \left(\left(\Gamma(2i\omega)^{-1} M_2 \widetilde{H}(i\omega)^2 q^2\right) \odot \overline{q}\right) \\
&= e^{i\omega T_0} \tau^* B(T_2) |B(T_2)|^2 \Phi(i\omega, q)
\end{aligned}$$

where

$$\begin{aligned}
\Phi(i\omega, q) = &2\widetilde{H}(i\omega) \left(\left(\Gamma(0)^{-1} M_2 |\widetilde{H}(i\omega)|^2 |q|^2\right) \odot q\right) \\
&+ \widetilde{H}(2i\omega) \overline{\widetilde{H}(i\omega)} \left(\left(\Gamma(2i\omega)^{-1} M_2 \widetilde{H}(i\omega)^2 q^2\right) \odot \overline{q}\right),
\end{aligned}$$

followed by

$$\begin{aligned}W_1^3 &= (W_1 \odot W_1) \odot W_1\\ &= \Big[B(T_2)^2 e^{2i\omega T_0}\widetilde{H}(i\omega)^2 q^2 + |B(T_2)|^2|\widetilde{H}(i\omega)|^2|q|^2 + c.c.\Big] \odot \Big[B(T_2)e^{i\omega T_0}\widetilde{H}(i\omega)q + c.c.\Big]\\ &= 3e^{i\omega T_0}B(T_2)|B(T_2)|^2|\widetilde{H}(i\omega)|^2\widetilde{H}(i\omega)(q^2\odot\overline{q}) + c.c. + \text{N.S.T.},\end{aligned}$$

$$\begin{aligned}J(T_0,T_2) &= \int_0^\infty s\widetilde{h}_a(s)D_2 w_1(T_0-s,T_2)\,ds = B'(T_2)e^{i\omega T_0}\int_0^\infty s\widetilde{h}_a(s)e^{-i\omega s}\,ds\,q + c.c.\\ &= -e^{i\omega T_0}B'(T_2)\widetilde{H}'(i\omega)q + c.c.\end{aligned}$$

where c.c. stands for the complex conjugate terms and N.S.T. stands for terms that do not produce secular terms. We continue with the last equation of (2.9):

$$\begin{aligned}D_0w_3 + \tau^* Lw_3 - \tau^* M_1(\widetilde{h} * w_3) = &- D_2 w_1 - \delta L w_1 + \delta M_1(\widetilde{h} * w_1) - \tau^* M_1 J\\ &+ 2\tau^* M_2(W_1 \odot W_2) + \tau^* M_3 W_1^3.\end{aligned} \tag{2.13}$$

From the first equation of (2.9) we note that:

$$-\delta L w_1 + \delta M_1(\widetilde{h} * w_1) = \frac{\delta}{\tau^*}D_0 w_1,$$

and knowing from (2.10) that $w_1(T_0,T_2) = B(T_2)e^{i\omega T_0}q + c.c.$, we obtain that the right hand side of (2.13) is

$$\begin{aligned}R(T_0,T_2) &= -B'(T_2)e^{i\omega T_0}q + \frac{\delta}{\tau^*}B(T_2)i\omega e^{i\omega T_0}q\\ &\quad + \tau^* B'(T_2)e^{i\omega T_0}M_1\widetilde{H}'(i\omega)q + \tau^* e^{i\omega T_0}B(T_2)|B(T_2)|^2\Psi(q^2\odot\overline{q}) + \text{c.c.} + \text{N.S.T.}\\ &= -B'(T_2)e^{i\omega T_0}\Big[I_2 - \tau^* M_1\widetilde{H}'(i\omega)\Big]q + \frac{\delta}{\tau^*}B(T_2)i\omega e^{i\omega T_0}q\\ &\quad + \tau^* e^{i\omega T_0}B(T_2)|B(T_2)|^2\Psi(i\omega,q) + \text{c.c.} + \text{N.S.T.}\end{aligned}$$

where

$$\Psi(i\omega,q) = 2\tau^* M_2\Phi(i\omega,q) + 3M_3|\widetilde{H}(i\omega)|^2\widetilde{H}(i\omega)(q^2\odot\overline{q}).$$

Therefore, the term which appears next to $e^{i\omega T_0}$ in the right side of equation (2.13) is:

$$E(T_2) = -B'(T_2)\Big[I_2 - \tau^* M_1\widetilde{H}'(i\omega)\Big]q + \frac{\delta}{\tau^*}B(T_2)i\omega q + \tau^* B(T_2)|B(T_2)|^2\Psi(i\omega,q).$$

Substituting into equation (2.13) we have that:

$$D_0 w_3 + \tau^* L w_3 - \tau^* M_1(\widetilde{h} * w_3) = E(T_2)e^{i\omega T_0} + c.c + N.S.T. \tag{2.14}$$

Looking for a solution of the form:

$$w_3(T_0,T_2) = e^{i\omega T_0}P(T_2) + c.c.$$

we obtain

$$i\omega e^{i\omega T_0}P(T_2) + \tau^* L e^{i\omega T_0}P(T_2) - \tau^* M_1\widetilde{H}(i\omega)e^{i\omega T_0}P(T_2) = e^{i\omega T_0}E(T_2),$$

and hence:

$$\Gamma(i\omega)P(T_2) = E(T_2). \tag{2.15}$$

Taking into account that $\det \Gamma(i\omega) = 0$, by the Fredholm alternative, it follows that the linear system (2.15) has a solution if and only if $E(T_2) \in \ker\left(\overline{\Gamma(i\omega)}^T\right)^{\perp}$. Hence, for any solution y of the adjoint system

$$\overline{\Gamma(i\omega)}^T y = 0$$

we must have:

$$\langle y, E(T_2)\rangle = \bar{y}^T E(T_2) = 0.$$

Moreover, for convenience, we will choose a particular solution of the adjoint system, which satisfies:

$$\bar{y}^T\left[I_2 - \tau^* M_1 \widetilde{H}'(i\omega)\right] q = 1 \quad \Leftrightarrow \quad \bar{y}^T \Gamma'(i\omega) q = 1.$$

Summarizing, our aim is to choose the vectors q and $\bar{y}$ such that:

$$\begin{cases} \Gamma(i\omega)q = 0 \\ \bar{y}^T\Gamma(i\omega) = 0 \\ \bar{y}^T\Gamma'(i\omega)q = 1 \end{cases}. \tag{2.16}$$

We consider the following vectors which satisfy system (2.16):

$$\mathrm{q} = \begin{pmatrix} 1 \\ \frac{\beta_a\tau + i\omega}{f_1\tau\widetilde{H}_c(i\omega)} \end{pmatrix} \quad \text{and} \quad \mathrm{y} = \begin{pmatrix} \frac{f_1 g_1 \tau^2 \widetilde{H}_a(i\omega)\widetilde{H}_c(i\omega)}{(\beta_a\tau + i\omega)\Gamma'(i\omega)} \\ \frac{y_1(\beta_a\tau + i\omega)}{g_1\tau\widetilde{H}_a(i\omega)} \end{pmatrix}.$$

The orthogonality condition $\bar{y}^T E(T_2) = 0$ is equivalent to:

$$B'(T_2) = \bar{y}^T\left[\frac{\delta}{\tau^*}B(T_2)i\omega q + \tau^* B(T_2)|B(T_2)|^2\Psi(i\omega, q)\right],$$

which gives the equation in normal form:

$$B'(T_2) = \frac{i\omega\delta}{\tau^*}\left(\bar{y}^T q\right) B(T_2) + \tau^*\left[\bar{y}^T\Psi(i\omega, q)\right] B(T_2)|B(T_2)|^2. \tag{2.17}$$

Therefore, with the above calculations and using [9, 10] we conclude:

Theorem 2.1. *If the real parts of the coefficients appearing in normal form (2.17), or equivalently, if*

$$-\Im\left(\bar{y}^T q\right) \quad \textit{and} \quad \Re\left(\bar{y}^T\Psi(i\omega, q)\right)$$

have opposite / identical sign, then the Hopf bifurcation occurring along the curve (γ) in a neighborhood of the equilibrium state $x^\star$ is supercritical / subcritical, and the resulting limit cycle is stable / unstable.

Remark 2.1. We can further express the terms that appear in the coefficients of the normal form (2.17) using the following formulas, which result from extensive calculations:

$$\overline{y}\ q = \frac{\overline{\widetilde{H}_c(i\omega)}(\beta_a\tau + i\omega) + \widetilde{H}_c(i\omega)(\beta_c\tau - i\omega)}{\overline{\gamma'(i\omega)}}.$$

We write $\Psi(i\omega, q)$ as a sum of $\psi_1 + \psi_2 + \psi_3$ and obtain

$$\overline{y}\cdot\psi_1 = \frac{3f_1\overline{\widetilde{H}_c(i\omega)\widetilde{H}_a(i\omega)}\left(f_3g_1(\beta_a\tau + i\omega)^2 + g_3\tau^2\widetilde{H}_a^2(i\omega)\right)}{\tau\overline{\gamma'(i\omega)}},$$

$$\begin{aligned}\overline{y}\cdot\psi_2 = &\frac{4\overline{\widetilde{H}_a(i\omega)\widetilde{H}_c(i\omega)}\left|\widetilde{H}_a(i\omega)\right|^2 f_1^3g_2\tau^2\left(g_2(\beta_a\tau - i\omega)\widetilde{H}_a^2(i\omega) + \beta_af_1f_2g_1(\beta_a\tau + i\omega)\right)}{f_1(\beta_a\tau - i\omega)(\beta_a\beta_c - f_1g_1)\tau\ \overline{\gamma'(i\omega)}}\\ &+\frac{4\overline{\widetilde{H}_c(i\omega)}f_2\left|\beta_a\tau + i\omega\right|^2\left(f_1^2f_2g_1^2(\beta_a\tau + i\omega)\overline{\widetilde{H}_a(i\omega)} + \beta_cg_2(\beta_a\tau - i\omega)\widetilde{H}_a(i\omega)\right)}{f_1(\beta_a\tau - i\omega)(\beta_a\beta_c - f_1g_1)\tau\ \overline{\gamma'(i\omega)}},\end{aligned}$$

$$\begin{aligned}\overline{y}\cdot\psi_3 = &\frac{2\tau(\beta_a\tau - i\omega)\overline{\widetilde{H}_a(i\omega)\widetilde{H}_c(i\omega)}\left[f_1^2f_2g_1\tau\left(f_1^2g_2\tau(\beta_a\tau + 2i\omega)\widetilde{H}_a(i\omega)^2\right)\right]\widetilde{H}_c(2i\omega)}{f_1(\beta_a\tau - i\omega)\overline{\gamma'(i\omega)} + \tau\gamma(2i\omega)}\\ &+\frac{2\tau(\beta_a\tau - i\omega)\overline{\widetilde{H}_a(i\omega)\widetilde{H}_c(i\omega)}\left[f_2g_1\tau\left(f_2g_1(\beta_a\tau + i\omega)^2\widetilde{H}_a(2i\omega)\right)\right]\widetilde{H}_c(2i\omega)}{f_1(\beta_a\tau - i\omega)\overline{\gamma'(i\omega)} + \tau\gamma(2i\omega)}\\ &+\frac{g_2\widetilde{H}_a(2i\omega)\left[f_2(\beta_a\tau + i\omega)^2(\beta_c\tau + 2i\omega) + f_1^3g_2\tau^3\widetilde{H}_a(i\omega)^2\widetilde{H}_c(2i\omega)\right]}{f_1(\beta_a\tau - i\omega)\overline{\gamma'(i\omega)} + \tau\gamma(2i\omega)},\end{aligned}$$

where

$$\overline{\gamma'(i\omega)} = \tau(\beta_a + \beta_c) - 2i\omega + f_1g_1\tau^2\left(\overline{\widetilde{H}_a(i\omega)\widetilde{H}_c'(i\omega)} + \overline{\widetilde{H}_a'(i\omega)\widetilde{H}_c(i\omega)}\right)$$

and

$$\gamma(2i\omega) = (2i\omega + \tau\beta_a)(2i\omega + \tau\beta_c) - f_1g_1\tau^2\widetilde{H}_a(2i\omega)\widetilde{H}_c(2i\omega).$$

Example 2.1 (Dirac kernels)**.** In the case of Dirac kernels, the Laplace transforms H_a and H_c have the following form

$$\widetilde{H}_a(i\omega) = e^{i\omega\tau_a}, \widetilde{H}_c(i\omega) = e^{i\omega\tau_c}.$$

Substituting in the Remark (2.1) we obtain

$$\overline{y}\ q = \frac{e^{i\omega\tau_c}(\beta_a\tau + i\omega) + e^{-i\omega\tau_c}(\beta_c\tau - i\omega)}{\tau(\beta_a + \beta_c) - 2i\omega + f_1g_1\tau^2(\tau_a + \tau_c)e^{i\omega(\tau_a+\tau_c)}}$$

and writing $\Psi(i\omega, q)$ as a sum of $\psi_1 + \psi_2 + \psi_3$ we have the following values for ψ_1, ψ_2, ψ_3

$$\overline{y}\cdot\psi_1 = \frac{3f_1e^{i\omega(\tau_a+\tau_c)}f_3g_1(\beta_a\tau + i\omega)^2 + g_3\tau^2e^{i\omega(\tau_a+\tau_c)}}{\tau^2(\beta_a + \beta_c) - 2i\omega\tau + f_1g_1\tau^3(\tau_a + \tau_c)e^{i\omega(\tau_a+\tau_c)}},$$

$$\overline{y}\cdot\psi_2 = \frac{4e^{i\omega(\tau_a+\tau_c)} f_1^3 g_2 \tau^2 \left(g_2(\beta_a\tau - i\omega)e^{-2i\omega\tau_a} + \beta_a f_1 f_2 g_1(\beta_a\tau + i\omega)\right)}{f_1(\beta_a\tau - i\omega)(\beta_a\beta_c - f_1g_1)\left(\tau^2(\beta_a+\beta_c) - 2i\omega\tau + f_1g_1\tau^3(\tau_a+\tau_c)e^{i\omega(\tau_a+\tau_c)}\right)} + \frac{4e^{i\omega\tau_c} f_2 \left|\beta_a\tau + i\omega\right|^2 \left(f_1^2 f_2 g_1^2(\beta_a\tau + i\omega)e^{i\omega\tau_a} + \beta_c g_2(\beta_a\tau - i\omega)e^{-i\omega\tau_a}\right)}{f_1(\beta_a\tau - i\omega)(\beta_a\beta_c - f_1g_1)\left(\tau^2(\beta_a+\beta_c) - 2i\omega\tau + f_1g_1\tau^3(\tau_a+\tau_c)e^{i\omega(\tau_a+\tau_c)}\right)},$$

$$\overline{y}\cdot\psi_3 = \frac{2\tau(\beta_a\tau - i\omega)e^{-i\omega(\tau_a+\tau_c)}\left(f_1^2 f_2 g_1\tau\left(f_1^2 g_2\tau(\beta_a\tau + 2i\omega) + f_2g_1(\beta_a\tau + i\omega)^2\right)\right)}{f_1(\beta_a\tau - i\omega)\ \overline{\gamma'(i\omega)} + \tau\gamma(2i\omega)} + \frac{f_2g_2e^{-2i\omega\tau_a}(\beta_a\tau + i\omega)^2(\beta_c\tau + 2i\omega) + f_1^3 g_2^2\tau^3 e^{-2i\omega(2\tau_a+\tau_c)}}{f_1(\beta_a\tau - i\omega)\ \overline{\gamma'(i\omega)} + \tau\gamma(2i\omega)},$$

where

$$\overline{\gamma'(i\omega)} = \tau(\beta_a+\beta_c) - 2i\omega + f_1g_1\tau^2\left(\overline{\widetilde{H}_a(i\omega)\widetilde{H}_c'(i\omega)} + \overline{\widetilde{H}_a'(i\omega)\widetilde{H}_c(i\omega)}\right)$$

and

$$\gamma(2i\omega) = (2i\omega + \tau\beta_a)(2i\omega + \tau\beta_c) - f_1g_1\tau^2\widetilde{H}_a(2i\omega)\widetilde{H}_c(2i\omega).$$

3 Numerical simulations

For the numerical analysis, the elimination rates β_i, $i \in \{a, c\}$, are determined from the half-life values T_i of the ACTH and CORT hormones [2]. These rates are calculated using the formula $\beta_i = \frac{\ln(2)}{T_i}$. Given that the half-life of ACTH (T_a) is approximately 19.9 min and the half-life of CORT is approximately 76.4 min, the corresponding elimination rates are $\beta_a = 0.034831$ and $\beta_c = 0.00907$ (min^{-1}).

The equilibrium state is associated with the 24-hour mean hormone concentrations, given by $a = 7.659$ pg/ml, representing the average ACTH level, and $c = 21$ pg/ml, reflecting the average free cortisol concentration.

The system incorporates feedback functions for ACTH and cortisol regulation, where $m = n = 5$, $\mu = 1$, $\gamma = 1.46$, $\eta = 55.43$ and $u = 3055pg/ml$, $v = 21pg/ml$ which correspond to the concentration levels of free cortisol and ACTH in a healthy individual.

For the Dirac case, the computed values are $-\Im\left(\overline{y}^T q\right) = -47.58$ and $\Re\left(\overline{y}^T\Psi(i\omega, q)\right) = 0.0002$, and since they have opposite signs, according to Theorem 2.1 the Hopf bifurcation is supercritical resulting in a stable limit cycle.

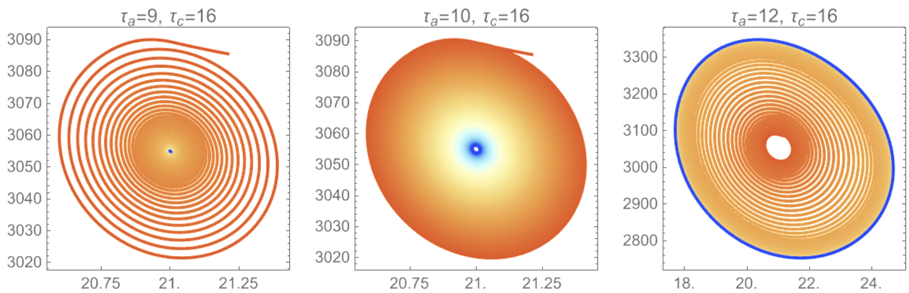

Figure 1: Phase portraits for system (1.1) in a neighborhood of the Hopf bifurcation

In Figure 1 we show that if we exceed the critical delay value of τ_a, fixing it at $\tau_c = 16$, we obtain an asymptotically stable limit cycle.

4 Conclusions

This paper focuses on the criticality analysis of the Hopf bifurcation curves in the pituitary-adrenal model with distributed time delays. In the presented analysis even if we used the mutiple time scales method for the pituitary-adrenal model, the method is applicable to other systems and mathematical models with similar structures [3].

References

[1] M. Andersen, F. Vinther, J. T. Ottesen, *Mathematical modeling of the hypothalamic-pituitary-adrenal gland (HPA) axis, including hippocampal mechanisms*, Math. Biosci. **246 (1)** (2013), 122-138.

[2] B. J. Carroll, F. Cassidy, D. Naftolowitz, N. E. Tatham, W. H. Wilson, A. Iranmanesh, P. Y. Liu, J. D. Veldhuis, *Pathophysiology of hypercortisolism in depression*, Acta Psychiatr. Scand. **115 (s433)** (2007), 90-103.

[3] S. L. Das, A. Chatterjee, *Multiple scales without center manifold reductions for delay differential equations near Hopf bifurcations*, Nonlinear Dyn. **30** (2002), 323-335.

[4] S. Gupta, E. Aslakson, B. M. Gurbaxani, S. D. Vernon, *Inclusion of the glucocorticoid receptor in a hypothalamic pituitary adrenal axis model reveals bistability*, Theor. Biol. Med. Model. **4 (1)** (2007), 8.

[5] E. Kaslik, E. - A. Kokovics, *Stability and bifurcations in scalar differential equations with a general distributed delay*, Appl. Math. Comput. **454** (2023), 128100.

[6] E. Kaslik, M. R. Matei, M. Neamţu, *Dynamics of a pituitary–adrenal model with distributed time delays*, Commun. Nonlinear Sci. Numer. Simul. **140** (2025), 108363.

[7] E. Kaslik, M. Neamţu, *Stability and Hopf bifurcation analysis for the hypothalamic-pituitary-adrenal axis model with memory*, Math. Med. Biol. **35 (1)** (2018), 49-78.

[8] A. H. Nayfeh, *Order reduction of retarded nonlinear systems - the method of multiple scales versus center-manifold reduction*, Nonlinear Dyn. **51 (4)** (2008), 483-500.

[9] A. H. Nayfeh, *The method of normal forms*, John Wiley & Sons, 2011.

[10] B. Niu, Y. Guo, W. Jiang, *An approach to normal forms of Kuramoto model with distributed delays and the effect of minimal delay*, Phys. Lett. A **379 (36)** (2015), 2018-2024.

[11] Y. Song, Y. Han, Y. Peng, *Stability and Hopf bifurcation in a unidirectional ring of n neurons with distributed delays*, Neurocomputing **121** (2013), 442-452.

[12] J. Yu, M. Peng, *Stability and bifurcation analysis for the Kaldor-Kalecki model with a discrete delay and a distributed delay*, Physica A **460** (2016), 66-75.

[13] Y. Yuan, J. Bélair, *Stability and Hopf bifurcation analysis for functional differential equation with distributed delay*, SIAM J. Appl. Dyn. Syst. **10 (2)** (2011), 551-581.

Maria Roxana Matei

Department of Mathematics, West University of Timişoara
Bd. V. Pârvan No. 4, 300223, Timişoara, Romania

E-mail: maria.matei@e-uvt.ro

Received: 1.04.2025

Accepted: 16.06.2025