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Limit Cycles in the Model of Hypothalamic–Pituitary–Adrenal Axis Activity

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Abstract

Oscillatory behavior in a three-dimensional system of differential equations which represents a sub-network of the model of hypothalamic-pituirary-adrenal axes activity is analysed. We show that Hopf bifurcations and degenerate Hopf bifurcations (Bautin bifurcations) can occur in the system for chemically relevant values of parameters, so the system can have two limit cycles.

1 Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is a complex neuroendocrine system with the main purpose to regulate various bodily processes under basal physiological conditions and during stress. This is achieved by regulating the plasma levels of corticosteroids secreted from adrenal glands (see for details [12, 15, 18]). Understanding the mechanism of HPA axis is of great value since stress and many illnesses are associated with short- or long-term perturbations of the HPA dynamics. Examples of such illnesses are: primary (Addison's disease) and secondary adrenocortical insufficiency, Cushing's syndrome, visceral obesity, diabetes, hypertension, osteoporosis and major depression (more in [15,19]). A key feature of the HPA system is the oscillatory dynamics which is essential for its self-organization and self-regulation. Models capable to simulate interactions between the hormones which regulate functioning of HPA and at the same time capable to simulate an appropriate oscillatory dynamics can be very useful tools for understanding behavior of this system and the illnesses which are associated with malfunction of the system. In order to achieve these goals four-dimensional model of HPA system was proposed in [9].

The oscillatory dynamics is an essential feature of the HPA axis, therefore understanding which parts of the proposed model are essential for existence of oscillatory dynamics and ability to optimize its dynamics is of a great importance. In the previous study [14] a detailed analysis of the model of hypotalamic-pituitary-adrenal axes activity [9] was carried out with the aim to obtain detail understanding of its dynamical properties. The stability analysis using the stoichiometric network analysis (SNA) [4, 5] was carried out and functional sub-models responsible for existence of the oscillatory dynamics and saddle-node bifurcations were derived. In this paper a further analysis of one of sub-models is carried out in order to obtain detailed understanding of its dynamical properties. This sub-model is presented in Table 1.

$\xrightarrow{k_1} X$	(R1)
$X \xrightarrow{k_3} Y$	(R2)
$Y \xrightarrow{k_4} Z$	(R3)
$Y + 2Z \xrightarrow{k_6} 3Z$	(R4)
$Y \xrightarrow{k_8} P_1$	(R5)
$Z \xrightarrow{k_9} P_2$	(R6)

Table 1. The sub-model derived from the model of HPA axis capable to produce oscillatory dynamics in [14]

In this sub-model, species X, Y and Z represent CRH (corticotropin-releasing hormone), ACTH (adrenocorticotropic hormone) and CORT (cortisol), respectively. The qualitative analysis and numerical simulations of the model are done by solving the set of ordinary differential equations derived from the mass action kinetics:

$$\begin{aligned}\dot{x} =& k_1 - k_2x,\\ \dot{y} =& k_2x - k_3y - k_4y - k_5yz^2,\\ \dot{z} =& k_3y - k_6z + k_5yz^2.\end{aligned} \tag{1.1}$$

By solving equations (1.1) time dependent concentration profiles are obtained. Variables x, y and z correspond to the concentrations of CRH, ACTH and CORT, respectively, while $k_1 - k_6$ represent reaction rate constants which are positive parameters. As it can be seen from system (1.1) the considered model is an autonomous system and knowing initial conditions and laws which govern its dynamics allows us to predict possible dynamical states, which are of great importance for the model optimization.

Geometrically, for autonomous systems of ODEs it is convenient to study the trajectories (also called orbits), which are projections of the solutions on the phase space. Usually, after some time solutions of autonomous systems approach some attractors. The simplest attractors which can appear in 3-dimensional autonomous polynomial systems are singular points (steady states) and limit cycles. A limit cycle is a closed orbit with no other closed orbits in its neighborhood. If trajectories are approaching the attractor when time increases, the singular point or the limit cycle is stable and it is unstable when approaching happens when time decreases. It is very difficult to describe the global dynamics of nonlinear systems of ODEs, so usually a local analysis is performed. Efficient methods for the qualitative investigation of ODEs are presented, e.g. in [1, 7, 8, 10]. Our main interest in this work is the detection of limit cycles since the oscillatory dynamics is a defining feature of HPA systems. Therefore, in the present paper a detailed analysis of the considered model has been carried out with the aim to derive exact conditions under which Hopf bifurcations emerge and system can exhibit oscillatory dynamics. Additionally, the complex structure of degenerated Hopf bifurcations is also analyzed.

2 Methods

It is well known that properties of solutions of systems of differential equations depend on parameters of the equations. Sometimes a small perturbation of parameter values causes significant changes in the behavior of the system. These changes in the topological structure are called bifurcations, see e.g. [7, 8, 10] for details.

Among bifurcations of periodic solutions the most important are Hopf bifurcations. A Hopf bifurcation can occur in a system with a singular point (steady state) which has two purely imaginary complex conjugated eigenvalues. In the case when the system has a two-dimensional center manifold passing through the singular point, if we perturb the initial parameters so that the eigenvalues are not purely imaginary anymore, two scenarios are possible. In the first scenario, the singular point is a stable focus on the local center manifold and after the perturbation it loses its stability. As the result of the perturbation, the trajectories from some small neighborhood of the equilibrium point converge towards the stable limit cycle. This case is known as a supercritical Hopf bifurcation. In the second case unperturbed fixed point is an unstable focus and after the perturbation it becomes a stable equilibrium, surrounded with an unstable limit cycle. This is known as a subcritical Hopf bifurcation; see e.g. [8, 10, 17] for more details.

In order to efficiently perform the stability analysis of the considered model and also the analysis of detected bifurcations, as well as emerging limit cycles, Lyapunov functions were used as follows. Consider the system

$$\begin{aligned} \dot{u} &= U(u,v) = au + bv + U_1(u,v), \\ \dot{v} &= V(u,v) = cu + dv + V_1(u,v), \end{aligned} \tag{2.1}$$

where U_1 and V_1 are polynomials without constant or linear terms and the matrix

$$M = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

has two purely imaginary eigenvalues. A Lyapunov function of system (2.1) is a function of the form

$$\Psi(u,v) = \sum_{i+j=2}^{\infty} a_{ij} u^i v^j, \tag{2.2}$$

where $a_{ij} \in \mathbb{R}$ and it is positive in some neighborhood of the origin. In the case when $\operatorname{Tr} M = 0$ it is possible to find function (2.2) such that

$$\mathfrak{X}(\Psi) := \frac{\partial \Psi(u,v)}{\partial u} U(u,v) + \frac{\partial \Psi(u,v)}{\partial v} V(u,v) = g_1(u^2+v^2)^2 + g_2(u^2+v^2)^3 + ... \tag{2.3}$$

The function g_n on the right hand side of this equation, which is expressed as a polynomial in the coefficients of system (2.1), is called the n-th *focus quantity* of system (2.1). If $g_n = 0$ for all n, then $\Psi(u,v)$ is the first integral of the system and the singular point at the origin is a center. When $\sum_{i+j=2} a_{ij} u^i v^j$ is a positive defined quadratic form and

$g_1 < 0$ ($g_1 > 0$), the singular point at the origin is a stable (unstable) focus (see e.g. [3]). With small perturbations of parameters of the initial system we can cause changes in the signs of the focus quantities and consequently in the behaviour of trajectories in the neighborhood of the singular point, which can change the stability and limit cycles can bifurcate from the origin. If the first k focus quantities of the system are equal to zero and $g_{k+1} < 0$ ($g_{k+1} > 0$), the singular point is a weak stable (unstable) focus of the order $k+1$, which can give rise to $k+1$ limit cycles after suitable perturbations. This is said to be a degenerated Hopf bifurcation (also called the Bautin bifurcation) (see e.g. [2, 11, 16] for more details).

3 Hopf bifurcations in the model

The basis for our investigation is the analysis of singular points of equations (1.1), that is, the points in the phase space where the right hand side of (1.1) vanishes. Simple computations show that system (1.1) has only one singular point with the real coordinates. Its coordinates are very complicated and to simplify the further calculations we set the z-coordinate to be $z = 1$, that is, we impose the condition

$$k_4 = \frac{(k_3 + k_5)(k_1 - k_6)}{k_6}. \tag{3.1}$$

The real singular point is now

$$A\Big(\frac{k_1}{k_2}, \frac{k_6}{k_3 + k_5}, 1\Big) \tag{3.2}$$

and we proceed with the further analysis for this point.

In order to perform the stability analysis we linearize system (1.1) at the point A and obtain the following result.

Proposition 1. *The conjugated complex eigenvalues of system* (1.1) *linearized at A have zero real parts when the following conditions on the parameters k_1, k_3, k_5 and k_6 are fulfilled:*

$$k_1 = \frac{(k_5 - k_3)k_6^2}{(k_3 + k_5)^2}, \tag{3.3}$$

$$k_5 > k_3, \tag{3.4}$$

$$-\frac{(k_3 + k_5)^2}{k_3 - k_5} < k_6 < \frac{2k_5(k_3 + k_5)^2}{(k_3 - k_5)^2}. \tag{3.5}$$

Proof. We compute the Jacobian matrix of system (1.1) and evaluate it at the point A, defined by (3.2), obtaining

$$J(A) = \begin{pmatrix} -k_2 & 0 & 0 \\ k_2 & -\frac{k_1(k_3+k_5)}{k_6} & -\frac{2k_5k_6}{k_3+k_5} \\ 0 & k_3+k_5 & \frac{(-k_3+k_5)k_6}{k_3+k_5} \end{pmatrix}. \tag{3.6}$$

The eigenvalues of the matrix $J(A)$ are:

$$\lambda_1 = -k_2, \quad \lambda_{2,3} = \frac{1}{2(k_3+k_5)k_6}(R \pm \sqrt{R^2+s}), \tag{3.7}$$

where

$$R = -k_1k_3^2 - 2k_1k_3k_5 - k_1k_5^2 - k_3k_6^2 + k_5k_6^2, \quad s = \frac{4(k_3+k_5)^2k_6^2D}{k_2}.$$

Let

$$D = -\frac{k_2(k_1(k_3-k_5)(k_3+k_5)^2k_6 + 2k_5(k_3+k_5)^2k_6^2)}{(k_3+k_5)^2k_6}$$

be the determinant of the matrix $J(A)$.

The eigenvalues $\lambda_{2,3}$ are pure imaginary when $R = 0$ and $D < 0$. Solving the equation $R = 0$ we find

$$k_1 = \frac{(k_5-k_3)k_6^2}{(k_3+k_5)^2}.$$

Taking into account that $D < 0$ two additional conditions

$$k_5 > k_3, \quad -\frac{(k_3+k_5)^2}{k_3-k_5} < k_6 < \frac{2k_5(k_3+k_5)^2}{(k_3-k_5)^2},$$

are obtained by solving the semialgebraic system

$$D < 0 \wedge k_1 > 0 \wedge k_2 > 0 \wedge k_3 > 0 \wedge k_4 > 0 \wedge k_5 > 0 \wedge k_6 > 0$$

with the command `Reduce`[1] of the computer algebra system MATHEMATICA. ■

Without loss of generality in order to simplify calculations we move the origin of the coordinate system to the point A using the substitution

$$w = x - \frac{k_1}{k_2}, \quad u = y - \frac{k_6}{k_3-k_5}, \quad v = z - 1.$$

[1]`Reduce` solves given equations or inequalities for chosen variables, eliminates quantifiers and returns simplified expressions as the ones above. It uses cylindrical algebraic decomposition (CAD) introduced by Collins in [6] for real domains and Gröbner basis methods for complex domains.

Then from (1.1) we obtain the system

$$\begin{aligned} \dot{w} =& - k_2 w, \\ \dot{u} =& k_2 w + \frac{(k_3-k_5)k_6}{k_3+k_5}u - \frac{2k_5k_6}{k_3+k_5}v - 2k_5uv - \frac{k_5k_6}{k_3+k_5}v^2 - k_5uv^2, \\ \dot{v} =& (k_3+k_5)u + \frac{(k_5-k_3)k_6}{k_3+k_5}v + 2k_5uv + \frac{k_5k_6}{k_3+k_5}v^2 + k_5uv^2. \end{aligned} \tag{3.8}$$

Obviously, $w = 0$ is the invariant plane of system (3.8) and the trajectories approach the invariant plane exponentially. Thus, it is sufficient to study the dynamics of (3.8) reduced on the invariant plane, that is, the dynamics of the two-dimensional system

$$\begin{aligned} \dot{u} =& \frac{(k_3-k_5)k_6}{k_3+k_5}u - \frac{2k_5k_6}{k_3+k_5}v - 2k_5uv - \frac{k_5k_6}{k_3+k_5}v^2 - k_5uv^2 = \widetilde{U}(u,v), \\ \dot{v} =& (k_3+k_5)u + \frac{(k_5-k_3)k_6}{k_3+k_5}v + 2k_5uv + \frac{k_5k_6}{k_3+k_5}v^2 + k_5uv^2 = \widetilde{V}(u,v). \end{aligned} \tag{3.9}$$

The Jacobi matrix J_0 at the origin of system (3.9) is

$$J_0 = \begin{pmatrix} \frac{(k_3-k_5)k_6}{k_3+k_5} & -\frac{2k_5k_6}{k_3+k_5} \\ k_3+k_5 & \frac{-k_3k_6+k_5k_6}{k_3+k_5}. \end{pmatrix} \tag{3.10}$$

Computing its eigenvalues we obtain

$$\lambda_{1,2} = \pm\frac{1}{k_3+k_5}\sqrt{P}, \tag{3.11}$$

where

$$P = k_6(-2k_5(k_3+k_5)^2 + (k_3-k_5)^2k_6).$$

Proposition 1 gives the necessary conditions for the Hopf bifurcation in systems (1.1) and (3.9). To study limit cycle bifurcations in more details we compute the function (2.2) and the focus quantities g_1 and g_2 satisfying the identity (2.3) for system (3.9), that is,

$$\tfrac{\partial\Psi(u,v)}{\partial u}\widetilde{U}(u,v) + \tfrac{\partial\Psi(u,v)}{\partial v}\widetilde{V}(u,v) = g_1(u^2+v^2)^2 + g_2(u^2+v^2)^3 + \dots. \tag{3.12}$$

The calculations yield:

$g_1 = (2k_5k_6(4(k_3-k_5)k_5(k_3+k_5)^2 + (k_3+3k_5)(k_3^2-6k_3k_5+k_5^2)k_6 + 2k_3(-k_3+k_5)k_6^2))/(3(k_3+k_5)^5 + 4k_5(k_3+k_5)^3k_6 + 4(k_3+k_5)(k_3^2-2k_3k_5+4k_5^2)k_6^2)$,

and

$g_2 = (2k_5(480k_5^4(-k_3+k_5)(k_3+k_5)^{14} + 16k_5^3(k_3+k_5)^{12}(-75k_3^3+327k_3^2k_5-185k_3k_5^2+77k_5^3)k_6 - k_5^2(k_3+k_5)^{10}(195k_3^5+2313k_3^4k_5-14682k_3^3k_5^2+23674k_3^2k_5^3-9897k_3k_5^4+829k_5^5)k_6^2 -$

$k_5(k_3+k_5)^8(15k_3^7+561k_3^6k_5+1481k_3^5k_5^2-18505k_3^4k_5^3+34953k_3^3k_5^4-20473k_3^2k_5^5+7967k_3k_5^6+2961k_5^7)k_6^3-k_5(k_3+k_5)^6(-6k_3^8-1733k_3^7k_5+3783k_3^6k_5^2-20397k_3^5k_5^3+23659k_3^4k_5^4+3865k_3^3k_5^5+41181k_3^2k_5^6+8793k_3k_5^7+759k_5^8)k_6^4+2k_5(k_3+k_5)^4(54k_3^9+724k_3^8k_5-919k_3^7k_5^2+6693k_3^6k_5^3-2499k_3^5k_5^4-1443k_3^4k_5^5+19011k_3^3k_5^6-26921k_3^2k_5^7-6175k_3k_5^8+4819k_5^9)k_6^5-4(k_3-k_5)(k_3+k_5)^2(9k_3^{10}+36k_3^9k_5-637k_3^8k_5^2+782k_3^7k_5^3-4619k_3^6k_5^4-1004k_3^5k_5^5+6731k_3^4k_5^6-22194k_3^3k_5^7+15650k_3^2k_5^8+9388k_3k_5^9-2478k_5^{10})k_6^6+2(k_3-k_5)^3(36k_3^9+27k_3^8k_5-228k_3^7k_5^2-1508k_3^6k_5^3+3364k_3^5k_5^4-1506k_3^4k_5^5-3452k_3^3k_5^6+18436k_3^2k_5^7+10680k_3k_5^8-1977k_5^9)k_6^7-24(k_3-k_5)^5(2k_3^6+9k_3^5k_5+96k_3^3k_5^3-30k_3^2k_5^4+259k_3k_5^5-24k_5^6)k_6^8+24k_3(k_3-k_5)^7(4k_3^2-7k_3k_5+16k_5^2)k_6^9))/(3(k_3+k_5)^3(-2k_5(k_3+k_5)^2+(k_3-k_5)^2k_6)^2(3(k_3+k_5)^4+4k_5(k_3+k_5)^2k_6+4(k_3^2-2k_3k_5+4k_5^2)k_6^2)(5(k_3+k_5)^6+6k_5(k_3+k_5)^4k_6+12(k_3+k_5)^2(k_3^2-2k_3k_5+2k_5^2)k_6^2+8k_5(3k_3^2-6k_3k_5+8k_5^2)k_6^3))$.

Theorem 1. *a) If for system* (1.1) *conditions* (3.1), (3.3)-(3.5) *are satisfied and* $g_1 < 0$, *then the system admits a supercritical Hopf bifurcation.*

b) If for system (1.1) *conditions* (3.1), (3.3)-(3.5) *are satisfied and* $g_1 > 0$, *then the system admits a subcritical Hopf bifurcation.*

Proof. If the conditions of statement a) are satisfied by Proposition 1 the eigenvalues (3.11) are pure imaginary. For system (3.9) computing the function $\Psi(u,v)$ defined by (2.2) and (3.12) we find that the quadratic part of Ψ is

$$Q(u,v) = u^2 + \frac{2(k_5-k_3)k_6}{(k_3+k_5)^2}uv + \frac{2k_5k_6}{(k_3+k_5)^2}v^2. \tag{3.13}$$

The determinant of the quadratic form Q is

$$\widehat{D} = \frac{k_6\left(2{k_3}^2k_5 - {k_3}^2k_6 + 4k_3{k_5}^2 + 2k_3k_5k_6 + 2{k_5}^3 - {k_5}^2k_6\right)}{(k_3+k_5)^4}$$

Calculations show that under the conditions of the theorem $\widehat{D}$ is always positive, hence, by the Sylvester criterion Q is a positive defined quadratic form. Then, by (2.3) in a small neighborhood of the origin of (3.9) $\dot{\Psi}$ is negative defined. Thus, by the Lyapunov stability theorem the origin is a stable focus. From (3.3) it is obvious that it is possible to perturb parameters k_3 and k_5 in such way that the eigenvalues (3.11) have positive real parts. It means, a stable limit cycle appears at the invariant plane $x = \frac{k_1}{k_2}$ in the supercritical Hopf bifurcation.

Case b) is similar, however since $g_1 > 0$ the Hopf bifurcation is subcritical. ∎

4 Degenerate Hopf bifurcations

In this section we study the degenerate Hopf bifurcations and show that there are systems in family (1.1) with two small-amplitude limit cycles in a neighborhood of the point A.

Theorem 2. *System* (1.1) *has a weak focus of order 2 on the invariant plane* $x = \frac{k_1}{k_2}$ *if conditions* (3.1), (3.3)-(3.5) *are satisfied,*

$$k_6 = \frac{k_3^3 - 3k_3^2 k_5 - 17k_3 k_5^2 + 3k_5^3}{4k_3(k_3 - k_5)} + \frac{1}{4}\sqrt{\frac{k_3^6 + 26k_3^5 k_5 - 25k_3^4 k_5^2 + 44k_3^3 k_5^3 + 271k_3^2 k_5^4 - 70k_3 k_5^5 + 9k_5^6}{k_3^2(k_3 - k_5)^2}} \tag{4.1}$$

and

$$k_3 < k_5 < 3k_3 \quad or \quad k_5 > (3 + 2\sqrt{2})k_3.$$

The weak focus is stable when $g_2 < 0$ *and unstable when* $g_2 > 0$.

Proof. Solving with the command `Reduce` of MATHEMATICA the semi-algebraic system

$$g_1 = 0 \wedge k_3 > 0 \wedge k_5 > k_3 \wedge k_6 > 0 \wedge -\frac{(k_3 + k_5)^2}{k_3 - k_5} < k_6 < \frac{2k_5(k_3 + k_5)^2}{(k_3 - k_5)^2}$$

we obtain the conditions given in the statement of the theorem.

Since under these conditions the quadratic form (3.13) is positive defined from (3.12) by the Lyapunov theorem the weak focus of system (3.9) is stable if $g_2 < 0$ and unstable if $g_2 > 0$. ■

Theorem 3. *Two limit cycles can bifurcate from each weak focus of order 2 of system* (1.1) *under small perturbations. If the focus is stable, then the inner limit cycle is unstable and the outer one is stable. If the focus is unstable, then the inner limit cycle is stable and the outer one is unstable.*

Proof. Assume for determinacy that the weak focus of order 2 is stable. Since k_6 defined by (4.1) is a root of the polynomial g_1 we can slightly perturb the parameter k_3 in such way that g_1 becomes positive. As the result a stable limit cycle appears from the origin. Since (3.3) is still satisfied, using k_1 as the bifurcation parameter we obtain an unstable limit cycle bifurcating from the origin in the Hopf bifurcation. Since the perturbation of k_1 is small, the stable limit cycle is preserved.

If the weak focus of the order 2 is unstable, the reasoning is similar. ■

We now provide an example of system (1.1) with two limit cycles.

We move the origin to the singular point $A\left(\frac{k_1}{k_2}, \frac{k_6}{k_3+k_5}, 1\right)$ with the substitution $u = y - \frac{k_6}{k_3-k_5}, v = z - 1$ and reduce the consideration to the dynamics in the invariant plane $x = \frac{k_1}{k_2}$. Considering the imposed condition $k_4 = \frac{(k_3+k_5)(k_1-k_6)}{k_6}$ the system is now of the form

$$\begin{aligned}\dot{u} =& -\frac{k_1(k_3+k_5)}{k_6}u - \frac{2k_5k_6}{k_3+k_5}v - 2k_5uv - \frac{k_5k_6}{k_3+k_5}v^2 - k_5uv^2,\\ \dot{v} =&(k_3+k_5)u + \frac{(k_5-k_3)k_6}{k_3+k_5}v + 2k_5uv + \frac{k_5k_6}{k_3+k_5}v^2 + k_5uv^2.\end{aligned} \tag{4.2}$$

Taking into account the results obtained above we chose to set $k_5 = 0.7$ and $k_3 = 0.4$ and then calculate the other parameters: $k_6 = 11.1103, k_1 = 30.6049$.

For these parameter values the eigenvalues of the Jacobian of system (4.2) calculated at the origin are pure imaginary, $\lambda_{1,2} = \pm 2.52448i$, and $g_1 = 0, g_2 < 0$, $g_2 = -0.0132006$, which shows that the singular point at the origin of system (4.2) is a stable focus.

After the perturbation of the parameter k_6 to $k_6 = 11.4$, the focus quantity g_1 is positive ($g_1 = 0.013915$). Together with still negative g_2 we created a ring which has the vector field on the boundaries of opposite sign. According to the Poincaré-Bendixon theorem there is a limit cycle inside the ring and the origin becomes an unstable focus and a limit cycle bifurcates from the origin.

After the first perturbation the eigenvalues are still pure imaginary ($\lambda_{1,2} = \pm 2.5087i$) and now the first nonzero Lyapunov quantity is $g_1 > 0$ which are the conditions for subcritical Hopf bifurcation.

We perturb $k_1 = 32.2215$ to $k_1 = 32.25$ and real parts of eigenvalues of the Jacobian of system (4.2) become negative, $\lambda_{1,2} = -0.0013756 \pm 2.50699i$. The origin is now a stable focus and another limit cycle appears (Figures 1 and 2).

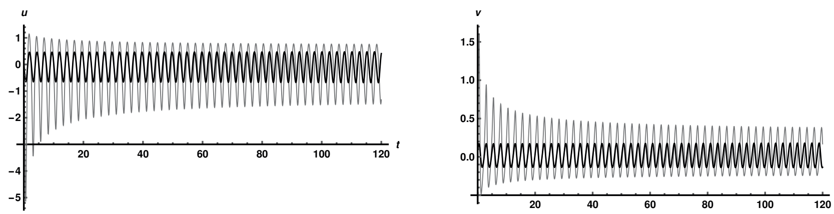

Figure 1. The solutions of system (4.2) with the initial conditions $u = 0$, $v = 0.3$ (in gray) and $v = 0.083$ (in black) after the second perturbation with parameter values $k_1 = 32.25$, $k_3 = 0.4$, $k_5 = 0.7$, $k_6 = 11.4$ are moving asimptotically towards the limit cycle with increasing time.

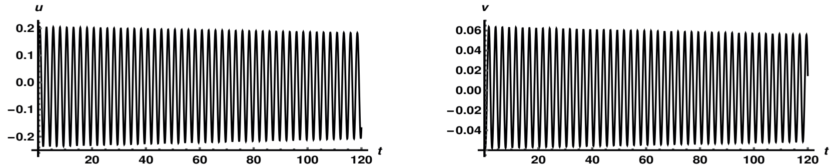

Figure 2. The solution of system (4.2) with the initial conditions $u = 0$ and $v = -0.04$ after the second perturbation with parameter values $k_1 = 32.25$, $k_3 = 0.4$, $k_5 = 0.7$, $k_6 = 11.4$ is moving asymptotically towards the singular point at the origin with increasing time.

For the value of parameters mentioned above, chosen $k_2 = 0.3$ and calculated $k_4 = 2.01184$ by (3.1), our initial differential system (1.1) now becomes

$$\begin{aligned} \dot{x} =& 32.25 - 0.3x, \\ \dot{y} =& 0.3x - 2.41184y - 0.7yz^2, \\ \dot{z} =& 0.4y - 11.4z + 0.7yz^2. \end{aligned} \tag{4.3}$$

Numerical simulations obtained for three initial problems are presented in Figure 3. Two limit cycles, one stable and one unstable, are evident. The trajectories converge to the singular point $A(107.5, 10.3636, 1)$, the invariant plane is $x = \frac{k_1}{k_2} = 107.5$.

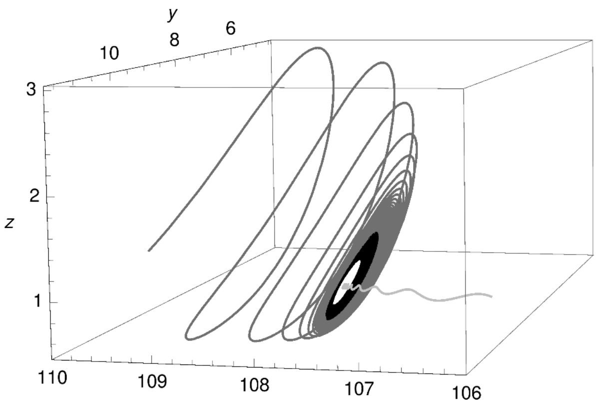

Figure 3. Solutions of the initial problems $x = 109.5$, $y = 10.3636$, $z = 1.3$ (in dark gray), $x = 107.5$, $y = 10.3636$, $z = 1.1$ (in black) and $x = 105$, $y = 10.3636$, $z = 0.95$ with parameter values $k_1 = 32.25$, $k_2 = 0.3$, $k_3 = 0.4$, $k_4 = 2.01184$, $k_5 = 0.7$, $k_6 = 11.4$ of system (4.3).

5 Conclusion

In this paper a sub-network of the model of hypothalamic-pituitary-adrenal axes activity, responsible for existence of Hopf bifurcations, was analyzed with the aim to determine its properties. In order to achieve this goal, expressions for the steady state solutions were obtained and the stability analysis was carried out. Conditions under which the considered model undergoes Hopf bifurcations were derived. A further analysis, based on the examination of the eigenvalues and focus quantities, found that the degenerated Hopf bifurcations occur. By applying the parameter perturbation techniques, branches of supercritical and subcritical Hopf bifurcations were found, the parameter conditions for the degenerated Hopf bifurcations were derived and two limit cycles were detected.

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