SLOW MANIFOLD OF A NEURONAL BURSTING MODEL

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ABSTRACT

We consider a three-variables model of neuronal bursting elaborated by Hindmarsh and Rose which is one of the most used mathematical representation of the widespread phenomenon of oscillatory burst discharges that occur in real neuronal cells. Using a kinematics method developed in our previous works, we provide the slow manifold analytical equation of such model and discuss its attractivity, i.e., its stability.

1. Hindmarsh - Rose model of bursting neurons

The transmission of nervous impulse is secured in the brain by action potentials. Their generation and their rhythmic behaviour are linked to the opening and closing of selected classes of ionic channels. The membrane potential of neurons can be modified by acting on a combination of different ionic mechanisms. Starting from the seminal works of Hodgkin-Huxley [7-11] and FitzHugh-Nagumo [3, 12], the Hindmarsh-Rose [6, 13] model consists of three variables: x, the membrane potential, y, an intrinsic current and z, a *slow* adaptation current.

$$\begin{cases} \frac{dx}{dt} = y - f(x) - z + I \\ \frac{dy}{dt} = g(x) - y \\ \frac{dz}{dt} = \varepsilon \left(h(x) - z \right) \end{cases} \tag{1}$$

I represents the applied current, $f(x)$ and $g(x)$ are respectively cubic and quadratic functions which have been experimentally deduced [5].

$$\begin{aligned} f(x) &= ax^3 - bx^2 \\ g(x) &= c - dx^2 \end{aligned}$$

ε is the time scale of the slow adaptation current and $h(x)$ is the scale of the influence of the *slow* dynamics, which determines whether the neuron fires in a tonic or in a burst mode when it is exposed to a sustained current input. In the following two different functions $h(x)$ will be used:

$$h(x) = \begin{cases} x - x^* \\ K \frac{\mu^{(x+1+k)} - 1}{\mu^{(1+2k)} - 1} \end{cases} \tag{2}$$

where k, K and μ are constants.

It can be written as a system of differential equations defined in a compact E included in $\mathbb{R}$:

$$\frac{d\vec{X}}{dt} = \begin{pmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{pmatrix} = \overrightarrow{\Im} \begin{pmatrix} f(x,y,z) \\ g(x,y,z) \\ \varepsilon h(x,y,z) \end{pmatrix} \tag{3}$$

with

$$\overrightarrow{X} = {}^t \left[x_1, x_2, ..., x_n \right] \in E \subset \mathbb{R}$$

and

$$\overrightarrow{\Im}(\overrightarrow{X}) = {}^t \left[f_1(\overrightarrow{X}), f_2(\overrightarrow{X}), ..., f_n(\overrightarrow{X}) \right] \in E \subset \mathbb{R}$$

The vector $\overrightarrow{\Im}$ defines a velocity vector field in E whose components f_i which are supposed to be continuous and infinitely derivable with respect to all x_i and t, i.e., are C^∞ functions in E and with values included in $\mathbb{R}$, check the assumptions of the Cauchy-Lipschitz theorem. For more details, see for example [2].

A solution of this system is an integral curve $\vec{X}(t)$ tangent to $\overrightarrow{\Im}$ whose values define the *states* of the *dynamical system* described by the Eqs. (3). Since none of the components f_i of the velocity vector field depends here explicitly on time, the system is said to be *autonomous*. Moreover, the presence of the small multiplicative parameter ε in one of the components of the velocity vector field makes it possible to consider the system (3) as a *slow-fast* autonomous dynamical system (S-FADS). So, it possesses a slow manifold, the equation of which may be determined. Paradoxically, we will see below that this model is not *slow-fast* in that sense.

2. Analytical slow manifold equation

There are many methods of determination of the analytical equation of the slow manifold. The classical one based on the singular perturbations theory [1] is the so-called *singular approximation method*. But, in this specific case, one of the hypothesis of the Tihonov's theorem is not checked since the *fast dynamics* of the *singular approximation* has a periodic solution. Thus, another approach developed by Ginoux *et al.* [4] which consist in using the *Differential Geometry* formalism is proposed.

2.1. Singular approximation method

The *singular approximation* of the *fast* dynamics constitutes a quite good approach since the third component of the velocity is very weak and so, z is nearly constant along the periodic solution.

On the one hand, since the system (3) can be considered as a (S-FADS), the *slow* dynamics of the *singular approximation* is given by:

$$\left(\sum\nolimits_{as}\right) \begin{cases} f(x,y,z) = 0 \\ g(x,y,z) = 0 \end{cases} \tag{4}$$

The resolution of this reduced system composed of the two first equations of the right hand side of (3) provides a one-dimensional *singular manifold*, called *singular curve*. This curve doesn't play any role in the construction of the periodic solution. But we'll see that there exists all the more a *slow dynamics*.

On the other hands, it presents a *fast* dynamics which can be given while posing the following change:

$$\tau = \varepsilon t \Leftrightarrow \frac{d}{dt} = \varepsilon \frac{d}{d\tau}$$

The system (3) may be re-written as:

$$\frac{d\vec{X}}{d\tau} = \begin{pmatrix} \frac{dx}{d\tau} \\ \frac{dy}{d\tau} \\ \frac{dz}{d\tau} \end{pmatrix} = \overrightarrow{\Im} \begin{pmatrix} \varepsilon^{-1} f(x,y,z) \\ \varepsilon^{-1} g(x,y,z) \\ h(x,y,z) \end{pmatrix} \tag{5}$$

So, the *fast* dynamics of the *singular approximation* is provided by the study of the reduced system composed of the two first equations of the right hand side of (5).

$$\left.\frac{d\vec{X}}{d\tau}\right|_{fast} = \begin{pmatrix} \frac{dx}{d\tau} \\ \frac{dy}{d\tau} \end{pmatrix} = \overrightarrow{\Im} \begin{pmatrix} \varepsilon^{-1} f(x,y,z^*) \\ \varepsilon^{-1} g(x,y,z^*) \end{pmatrix} \tag{6}$$

Each point of the *singular curve* is a singular point of the *singular approximation* of the *fast* dynamics.

For the z value for which there is a periodic solution, the *singular approximation* exhibits an unstable focus, attractive with respect to the *slow* eigendirection.

2.2. Kinematics methods

Now let us consider the three-dimensional system defined by (3). In this new approach it is first necessary to define the instantaneous acceleration vector of the *trajectory curve* $\vec{X}(t)$. Since the functions f_i are supposed to be C^∞ functions in a compact E included in $\mathbb{R}$, it is possible to calculate the total derivative of the vector field $\overrightarrow{\Im}$ defined by (3). As the instantaneous vector function $\overrightarrow{V}(t)$ of the scalar variable t represents the velocity vector of the mobile M at the instant t, the total derivative of $\overrightarrow{V}(t)$ is the vector function $\overrightarrow{\gamma}(t)$ of the scalar variable t which represents the instantaneous acceleration vector of the mobile M at the instant t. It is noted:

$$\overrightarrow{\gamma}(t) = \frac{d\overrightarrow{V}(t)}{dt} \tag{7}$$

A new approach of determining the *slow manifold* equation, called *osculating plane method* has been proposed in [4].

It states that the osculating plane equation to the *trajectory curve* $\vec{X}(t)$, integral of the *dynamical system* described by the Eqs. (3), constitutes the *slow manifold* equation of a (S-FADS) defined by Eq. (3).

Proposition 1.

If $I(x_0, y_0, z_0)$ is one of the equilibrium points of a dynamical system defined by Eqs. (3) and represented by the instantaneous velocity vector $\overrightarrow{V}(t)$ from which the instantaneous acceleration vector $\overrightarrow{\gamma}(t)$ is deduced, then, the plane (P) going through the fixed point $I(x_0, y_0, z_0)$ and having for direction vectors the instantaneous vectors $\overrightarrow{V}(t)$ and $\overrightarrow{\gamma}(t)$ is defined by the coplanarity condition between $\overrightarrow{V}(t)$, $\overrightarrow{\gamma}(t)$ and $\overrightarrow{IM}$ formed starting from any fixed point I and from any point $M(x,y,z)$ belonging to (P). So,

$$\forall\, M \in (P) \Leftrightarrow \exists\, (\mu, \eta) \in / \, \overrightarrow{IM} = \mu\overrightarrow{V} + \eta\overrightarrow{\gamma}$$

This coplanarity condition may be written:

$$\overrightarrow{IM} \, . \left(\overrightarrow{V} \wedge \overrightarrow{\gamma}\right) = 0 \tag{8}$$

Thus, this equation represents the *slow manifold* of the slow-fast autonomous dynamical system (S-FADS) defined by Eq. (3).

Moreover, this model (3) exhibits some striking features. Due to the presence of the small multiplicative parameter ε in the third components of its velocity vector field, instantaneous velocity vector $\overrightarrow{V}(t)$ and instantaneous acceleration vector $\overrightarrow{\gamma}(t)$ of the model (3) may be written:

$$\overrightarrow{V} \begin{pmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{pmatrix} = \overrightarrow{\Im} \begin{pmatrix} O(\varepsilon^0) \\ O(\varepsilon^0) \\ O(\varepsilon^1) \end{pmatrix} \tag{9}$$

and

$$\vec{\gamma}\begin{pmatrix}\ddot{x}\\ \ddot{y}\\ \ddot{z}\end{pmatrix} = \frac{d\overrightarrow{\Im}}{dt}\begin{pmatrix}O\left(\varepsilon^1\right)\\ O\left(\varepsilon^1\right)\\ O\left(\varepsilon^2\right)\end{pmatrix} \tag{10}$$

where $O\left(\varepsilon^n\right)$ is a polynomial of n degree in ε

Then, it is possible to express the vector product $\overrightarrow{V} \wedge \overrightarrow{\gamma}$ as:

$$\overrightarrow{V} \wedge \overrightarrow{\gamma} = \begin{pmatrix}\dot{y}\ddot{z} - \ddot{y}\dot{z}\\ \ddot{x}\dot{z} - \dot{x}\ddot{z}\\ \dot{x}\ddot{y} - \ddot{x}\dot{y}\end{pmatrix} \tag{11}$$

Taking into account what precedes Eqs. (9-10), it follows that:

$$\overrightarrow{V} \wedge \overrightarrow{\gamma} = \begin{pmatrix}O\left(\varepsilon^2\right)\\ O\left(\varepsilon^2\right)\\ O\left(\varepsilon^1\right)\end{pmatrix} \tag{12}$$

So, it is obvious that since ε is a small parameter, this vector product may be written:

$$\overrightarrow{V} \wedge \overrightarrow{\gamma} \approx \begin{pmatrix}0\\ 0\\ O\left(\varepsilon^1\right)\end{pmatrix} \tag{13}$$

Then, it appears that if the third component of this vector product vanishes then both instantaneous velocity vector $\overrightarrow{V}(t)$ and instantaneous acceleration vector $\overrightarrow{\gamma}(t)$ are collinear. This result is particular to this kind of model which presents a small multiplicative parameter in one of the right-hand-side component of the velocity vector field and makes it possible to provide their *slow manifold* equation.

Proposition 2.

If a (S-FADS) has its small parameter ε in one of the right-hand-side component of its instantaneous velocity vector $\overrightarrow{V}(t)$, then the *slow manifold* equation associated to this dynamical system is provided by the collinearity condition between its instantaneous velocity vector $\overrightarrow{V}(t)$ and instantaneous acceleration vector $\overrightarrow{\gamma}(t)$.

$$\dot{x}\ddot{y} - \ddot{x}\dot{y} = 0 \tag{14}$$

Another method of determining the *slow manifold* equation proposed by Rossetto *et al.* [14] consists in considering the so-called *tangent linear system approximation*. Then, a coplanarity condition between the instantaneous velocity vector $\overrightarrow{V}(t)$ and the *slow* eigenvectors of the *tangent linear system* gives the *slow manifold* equation.

$$\overrightarrow{V}.\left(\overrightarrow{Y_{\lambda_2}} \wedge \overrightarrow{Y_{\lambda_3}}\right) = 0 \tag{15}$$

where $\overrightarrow{Y_{\lambda_i}}$ represent the *slow* eigenvectors of the *tangent linear system*. But, if these eigenvectors are complex the *slow manifold* plot may be interrupted.

So, in order to avoid such inconvenience, this equation has been multiplied by two conjugate equations obtained by circular permutations.

$$\left[\overrightarrow{V}\cdot\left(\overrightarrow{Y_{\lambda_2}} \wedge \overrightarrow{Y_{\lambda_3}}\right)\right]\cdot\left[\overrightarrow{V}\cdot\left(\overrightarrow{Y_{\lambda_1}} \wedge \overrightarrow{Y_{\lambda_2}}\right)\right]\cdot\left[\overrightarrow{V}\cdot\left(\overrightarrow{Y_{\lambda_1}} \wedge \overrightarrow{Y_{\lambda_3}}\right)\right] = 0$$

Then it has been transformed into a real analytical *slow manifold* equation which can be written:

$$\sum_{i,j,k}^{3} \alpha_{ijk}\dot{x}^i\dot{y}^j\dot{z}^k = 0 \tag{16}$$

where α_{ijk} are coefficients only depending on the functional jacobian matrix elements of the *tangent linear system*. These coefficients are available at the address: http://ginoux.univ-tln.fr

Proposition 3.

The coplanarity condition (15) transformed into the equation (16) provides the *slow manifold* equation of system (3).

3. Application to neuronal bursting models

3.1. Hindmarsh-Rose 84'model

In the beginning we will be interested in analyzing the first three-dimensional model conceived by Hindmarsh and Rose in 1984 [6]. This model is exactly the same as the one described in the first section but for which $h(x)$, is defined as a linear function (2):

$$h(x) = s\left(x - x^*\right)$$

where (x^*, y^*) are the co-ordinates of the leftmost equilibrium point of the model (1) without adaptation, i.e., $I = 0$. The Hindmarsh-Rose 84' model is defined by:

$$\begin{cases}\frac{dx}{dt} = y - ax^3 + bx^2 - z + I\\ \frac{dy}{dt} = c - dx^2 - y\\ \frac{dz}{dt} = \varepsilon\left(s\left(x - x^*\right) - z\right)\end{cases} \tag{17}$$

Parameters used for numerical simulations are:

$a = 1$, $b = 3$, $c = 1$, $d = 5$, $\varepsilon = 0.005$, $s = 4$, $x^* = \frac{-1-\sqrt{5}}{2}$ and $I = 3.25$.

Then, using the new approach presented in the above section, i.e., the *kinematics method*, it is possible to provide the *slow manifold* of the Hindmarsh-Rose 84'model.

In Fig. 1 is presented the *slow manifold* of the Hindmarsh-Rose 84'model determined with the *osculating plane method*.

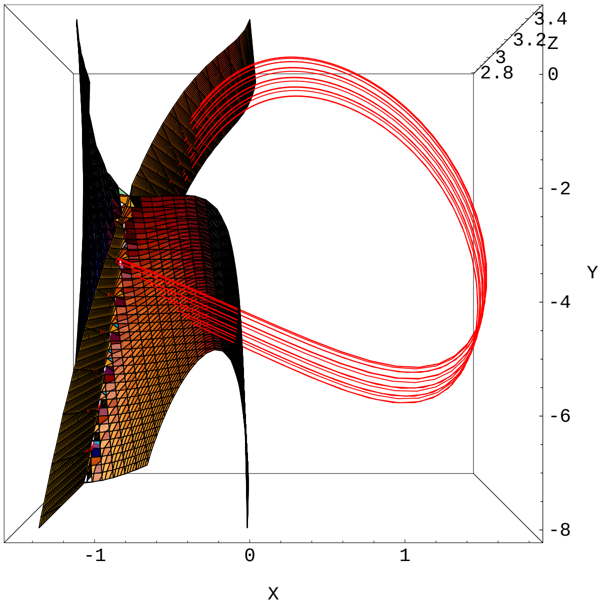

Figure 1. *Slow manifold* with the *osculating plane method* (proposition 1).

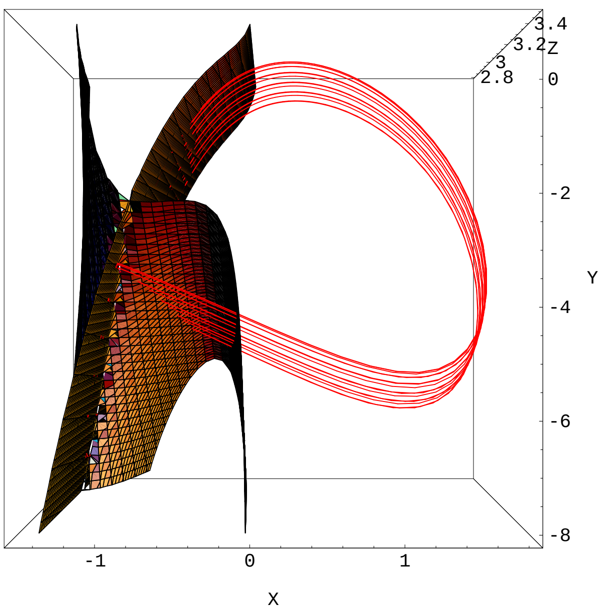

Figure 2. *Slow manifold* with the *collinearity condition* (proposition 2).

With the proposition 2 the *slow manifold* is provided with the use of the *collinearity condition* between both instantaneous velocity vector $\overrightarrow{V}(t)$ and instantaneous acceleration vector $\overrightarrow{\gamma}(t)$.

The smallness of the parameter ε is responsible for the great similarity between the Fig. 1 and Fig. 2.

The Fig. 3 presents the *slow manifold* of the Hindmarsh-Rose 84'model obtained with the *tangent linear system approximation*.

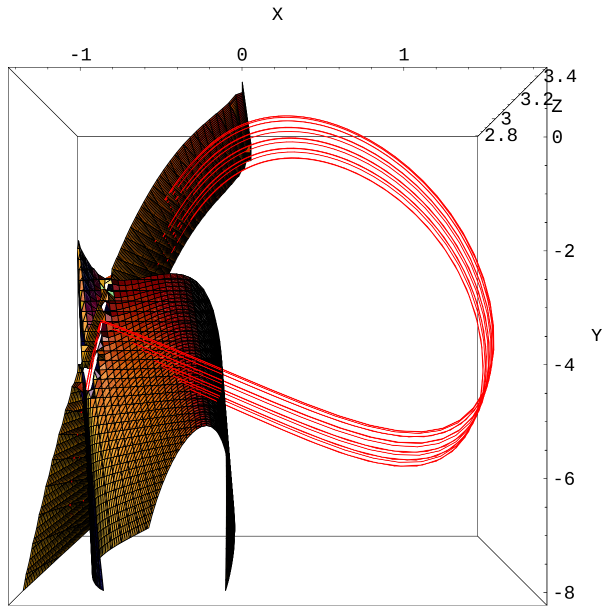

Figure 3. *Slow manifold* with the *tangent linear system approximation* (proposition 3).

Thus, an explicit analytical equation of the *slow manifold* of model (17) has been provided in three different manners increasing each time the quality of the approximation till obtaining the whole this *slow manifold.*

Moreover, while using a new criterion of attractivity of manifolds proposed in our previous works [4] and which consists in considering the sign of the total derivative of the *slow manifold* equation, it is possible to show that the *slow manifold* is attractive for the *trajectory curve* $\vec{X}(t)$, integral of the *dynamical system*. So, it delimits *stability* domains of the phase space for these *trajectories*.

3.2. Hindmarsh-Rose 85'model

Now we are focussing our attention on the second three-dimensional model elaborated by Hindmarsh and Rose in 1985 [13]. This model is still the same as the one described in the first section but for which $h(x)$, is defined as an exponential function (2):

$$h(x) = K\frac{\mu^{(x+1+k)} - 1}{\mu^{(1+2k)} - 1}$$

where K and μ are constants. This function was chosen by the authors so that its gradient could be altered by altering μ without moving the equilibrium point , and so that:

$$h(-1-k) = 0$$

The Hindmarsh-Rose 85' model is defined by:

$$\begin{cases} \frac{dx}{dt} = y - ax^3 + bx^2 - z + I \\ \frac{dy}{dt} = c - dx^2 - y \\ \frac{dz}{dt} = \varepsilon\left(K\frac{\mu^{(x+1+k)}-1}{\mu^{(1+2k)}-1} - z\right) \end{cases} \tag{18}$$

Parameters used for numerical simulations are:

$a = 1$, $b = 3$, $c = 1$, $d = 1.077$, $\varepsilon = 0.005$, $\mu = 4.3$, $K = 2$, $k = \frac{-1+\sqrt{5}}{2}$ and $I = 4.5$

Then the *slow manifold* equation of this model is provided with the *kinematics method*, i.e., each proposition.

In Fig. 4 is presented the *slow manifold* of the Hindmarsh-Rose 85'model determined with the *osculating plane method*.

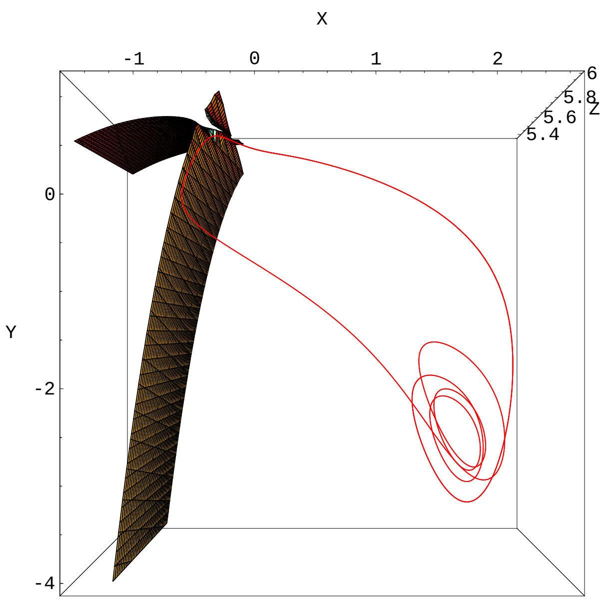

Figure 4. *Slow manifold* with the *osculating plane method* (proposition 1).

With the proposition 2 the *slow manifold* is provided with the use of the *collinearity condition* between both instantaneous velocity vector $\overrightarrow{V}(t)$ and instantaneous acceleration vector $\overrightarrow{\gamma}(t)$.

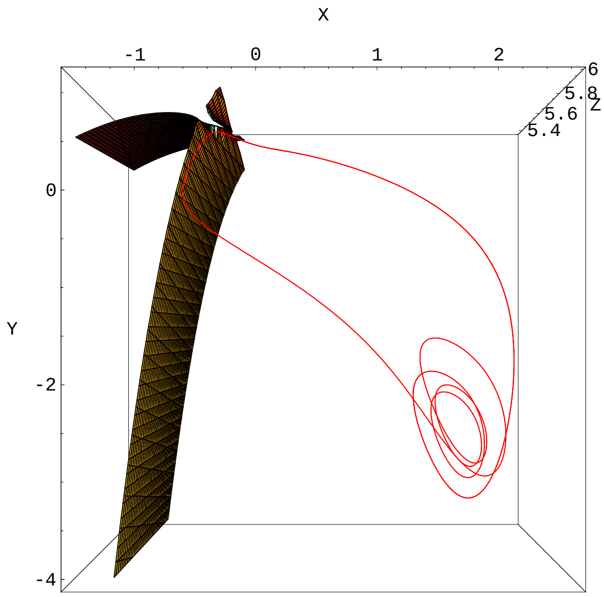

Figure 5. *Slow manifold* with the *collinearity condition* (proposition 2).

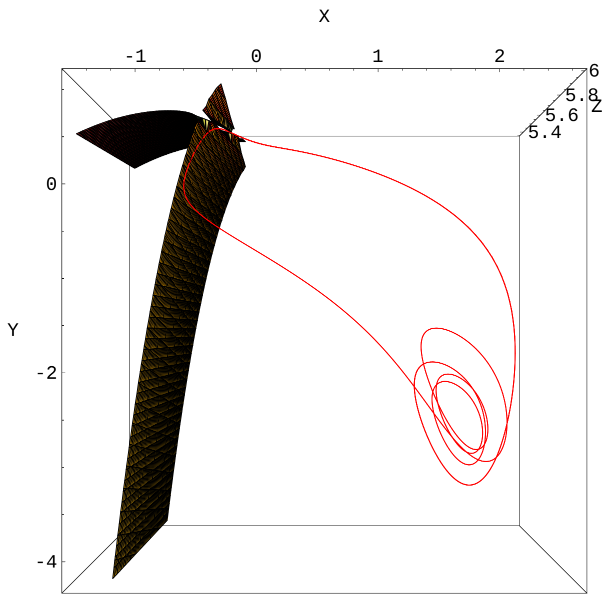

Figure 6. *Slow manifold* with the *tangent linear system approximation* (proposition 3).

The smallness of the parameter ε is still responsible for the great similarity between the Fig. 4 and Fig. 5. But in this case the presence of the exponential function $h(x)$ does not allow neglecting totally the first and the second components of the vector product (11).

The Fig. 6 presents the *slow manifold* of the Hindmarsh-Rose 85'model obtained with the *tangent linear system approximation*.

Nevertheless, an explicit analytical equation of the *slow manifold* of model (18) has been provided in three different manners increasing each time the quality of the approximation till obtaining the whole this *slow manifold.*

Here again, the new criterion of attractivity of manifolds which consists in considering the sign of the total derivative of the *slow manifold* equation, makes it possible to show that the *slow manifold* is attractive for the *trajectory curve* $\vec{X}(t)$, integral of the *dynamical system*. So, it delimits *stability* domains of the phase space for these *trajectories*.

4. Discussion

In this work the use of the *Mechanics* formalism and of the instantaneous acceleration vector provided new alternative methods of determination of the *slow manifold* equation of (S-FADS) with a small parameter ε in one of the right-hand-side component of its instantaneous velocity vector field:

- the *osculating plane method*, i.e., the coplanarity between the instantaneous velocity vector $\overrightarrow{V}$, the instantaneous acceleration vector $\overrightarrow{\gamma}$ and the vector $\overrightarrow{IM}$ formed starting from a fixed point of such dynamical systems and any point M,
- the *collinearity condition* between the instantaneous velocity vector $\overrightarrow{V}$, the instantaneous acceleration vector $\overrightarrow{\gamma}$.
- the *tangent linear system approximation*, i.e., the coplanarity condition between the instantaneous velocity vector $\overrightarrow{V}(t)$ and the *slow* eigenvectors transformed into a real analytical equation. This method need not calculating eigenvectors.

The attractivity criterion made it possible to establish the attractive feature of the *slow manifold* and so defined *stability* domains of the phase space for the *trajectories curves*, integral of such *dynamical system*.

The study of both Hindmarsh-Rose models in a kind of "comparative manner" allowed to show that the presence of an exponential function $h(x)$, more realistic than the linear one, doesn't prevent from determine the analytical equation of the *slow manifold*.

5. References

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