Analysis and Control of a Neurodynamic Model

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Abstract
The dynamic interaction between Serotonin, Dopamine and Norepinephrine is very complex and nonlinear, and it is important to understand the nonlinearity and develop strategies to control the interactions effectively. In this work, bifurcation analysis and multiobjective nonlinear model predictive control are performed on a neurondynamic model involving Serotonin, Dopamine, and Norepinephrine. Bifurcation analysis is a powerful mathematical tool used to deal with the nonlinear dynamics of any process. Several factors must be considered, and multiple objectives must be met simultaneously. The MATLAB program MATCONT was used to perform the bifurcation analysis. The MNLMPC calculations were performed using the optimization language PYOMO in conjunction with the state-of-the-art global optimization solvers IPOPT and BARON. The bifurcation analysis revealed the existence of a Hopf bifurcation point. The Hopf bifurcation point, which causes an unwanted limit cycle, is eliminated using an activation factor involving the tanh function.

1. Background

Blier studied the crosstalk between the norepinephrine and serotonin systems and its role in the antidepressant response. Monteiro et al, developed analytical results for a Wilson-Cowan neuronal network model. Brown et al, investigated the influence of spike rate and stimulus duration on noradrenergic neurons. Savic et al, developed a mathematical model of the hypothalamo-pituitary-adrenocortical system and its stability analysis. Best et al, studied homeostatic mechanisms in dopamine synthesis and release. Best et al, researched Serotonin synthesis, release, and reuptake in terminals: a mathematical model. Bowen studied the relationship between mood instability and depression [1-7]. Hamon et al, investigated monoamine neurocircuitry in depression and strategies for new treatments. Akar et al, performed a nonlinear analysis of EEGs of patients with major depression during different emotional states. Bowen et al, showed that moods in clinical depression are more unstable than severe normal sadness. Bangsgaard et al, performed patient-specific modeling of the HPA axis related to the clinical diagnosis of depression. Bachmann et al, studied the

various methods for classifying depression in single-channel EEG using linear and nonlinear signal analysis. Liu et al, investigated the emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. Perez-Caballero researched the monoaminergic system and depression. Menke et al, investigated the role of the HPA axis as a target for depression [8-15]. Loula et al, produced an individual-based model for predicting the prevalence of depression. Loula et al, developed a game theory-based model for predicting depression due to frustration in competitive environments [16,17]. Shao et al discovered the associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorders [18]. Xu et al, performed a mental health informatics study on the mediating effect of the regulatory emotional self-efficacy. Nemesure et al, developed a predictive model of depression and anxiety using electronic health records and a novel machine learning approach with artificial intelligence. Lu, et al developed a semi-supervised random forest regression model based on co-training and grouping with information entropy for evaluation of depression symptoms

severity. Loula et al used a dynamical systems approach to investigate the relationship between monoamine neurotransmitters and mood swings.

In this work, bifurcation analysis and multiobjective nonlinear model predictive control are performed on the neurondynamic model involving Serotonin, Dopamine, and Norepinephrine the paper is organized as follows. First, the model equations are presented, followed by a discussion of the numerical techniques involving bifurcation analysis and multiobjective nonlinear model predictive control (MNLMPC). The results and discussion are then presented, followed by the conclusions [19-22].

1.1 Model Equations
In this model, sv, dv, nv, represent the serotonin, dopamine, and norepinephrine in the blood plasma. The model equations are

$$\frac{d(sv)}{dt} = \alpha - a(sv) + b(dv)sv + c(nv)sv$$

$$\frac{d(dv)}{dt} = \beta - e(dv) - f(dv)sv \qquad (1)$$

$$\frac{d(nv)}{dt} = -g(nv) + h(dv)$$

The base parameter value are
a = 20; b = 0.001; c = 0.04; e = 3; f = 0.1; g = 2; h = 80; α = 50; β = 200;
More details are found in [22].

1.2. Bifurcation Analysis
The MATLAB software MATCONT is used to perform the bifurcation calculations. Bifurcation analysis deals with multiple steady-states and limit cycles. Multiple steady states occur because of the existence of branch and limit points. Hopf bifurcation points cause limit cycles . A commonly used MATLAB program that locates limit points, branch points, and Hopf bifurcation points is MATCONT [23,24]. This program detects Limit points(LP), branch points(BP), and Hopf bifurcation points(H) for an ODE system

$$\frac{dx}{dt} = f(x,\alpha) \qquad (2)$$

$x \in R^n$ Let the bifurcation parameter be α. Since the gradient is orthogonal to the tangent vector, The tangent plane at any point $w=[w_1,w_2,w_3,w_4,....w_{n+1}]$ must satisfy

$$Aw = 0 \qquad (3)$$

Where A is

$$A = [\partial f \,/\, \partial x \quad | \,\partial f \,/\, \partial \alpha \,] \qquad (4)$$

where $\partial f \,/\, \partial x$ is the Jacobian matrix. For both limit and branch points, the Jacobian matrix $J = [\partial f \,/\, \partial x]$ must be singular.

For a limit point, there is only one tangent at the point of singularity. At this singular point, there is a single non-zero vector, y, where Jy = 0. This vector is of dimension n. Since there is only one tangent the vector $y = (y_1, y_2, y_3, y_4, \ldots y_n)$ must align with $\hat{w} = (w_1, w_2, w_3, w_4, \ldots w_n)$. Since

$$J\hat{w} = Aw = 0 \qquad (5)$$

the n+1th component of the tangent vector $w_{n+1} = 0$ at a limit point (LP).

For a branch point, there must exist two tangents at the singularity. Let the two tangents be z and w. This implies that

$$Az = 0$$
$$\qquad \qquad (6)$$
$$Aw = 0$$

Consider a vector v that is orthogonal to one of the tangents (say w). v can be expressed as a linear combination of z and w ($v = \alpha z + \beta w$). Since $Az = Aw = 0$; $Av = 0$ and since w and v are orthogonal, $w^T v = 0$. Hence $Bv = \begin{bmatrix} A \\ w^T \end{bmatrix} v = 0$ which implies that B is singular.

Hence, for a branch point (BP) the matrix $B = \begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular. At a Hopf bifurcation point,

$$\det(2f_x(x,\alpha)@I_n) = 0 \qquad (7)$$

@ indicates the bialternate product whileis I_n the n-square identity matrix. Hopf bifurcations cause limit cycles and should be eliminated because limit cycles make optimization and control tasks very difficult. More details can be found in Kuznetsov [25-27].

Hopf bifurcations cause limit cycles. The tanh activation function (where a control value u is replaced by) ($u \tanh u/\varepsilon$) is used to eliminate spikes in the optimal control profiles [28-31]. Sridhar (2024)[32] explained with several examples how the activation factor involving the tanh function also eliminates the Hopf bifurcation points. This was because the tanh function increases the oscillation time period in the limit cycle.

1.3. Multiobjective Nonlinear Model Predictive Control (MNLMPC)
The rigorous multiobjective nonlinear model predictive control (MNLMPC) method developed by Flores Tlacuahuaz et al (2012) [33] was used.

Consider a problem where the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ (j =1, 2..n) have to be optimized simultaneously for a dynamic problem

$$\frac{dx}{dt} = F(x,u) \qquad (8)$$

t_f being the final time value, and n the total number of objective variables and u the control parameter. The single objective optimal control problem is solved individually optimizing each of the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ The optimization of $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ will lead to the values q_j^*. Then, the multiobjective optimal control (MOOC) problem that will be solved is

$$\min(\sum_{j=1}^{n}(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*))^2 \tag{9}$$

$$subject\ to\ \frac{dx}{dt} = F(x,u);$$

This will provide the values of u at various times. The first obtained control value of u is implemented and the rest are discarded. This procedure is repeated until the implemented and the first obtained control values are the same or if the Utopia point where ($\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^*$ for all j) is obtained.

Pyomo (Hart et al, 2017)[34] is used for these calculations. Here, the differential equations are converted to a Nonlinear Program (NLP) using the orthogonal collocation method The NLP is solved using IPOPT (Wächter And Biegler, 2006)[35]and confirmed as a global solution with BARON (Tawarmalani, M. and N. V. Sahinidis 2005)[36].

The steps of the algorithm are as follows

1. Optimize $\sum q_j(t_i)$ and obtain q_j^*.
2. Minimize $(\sum_{j=1}^{n}(\sum_{t_i=0}^{t_i=t_f} q_j(t_i)-q_j^*))^2$ and get the control values at various times.

3. Implement the first obtained control values
4. Repeat steps 1 to 3 until there is an insignificant difference between the implemented and the first obtained value of the control variables or if the Utopia point is achieved. The Utopia point is when $\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^*$ for all j.

2. Results and Discussion

When bifurcation analysis is performed with a as the bifurcation parameter, a Hopf bifurcation point appears at (sv, dv, nv, a) values of (96.593811, 15.79856, 631.942427, 25.811127). This is seen on curve AB in Figure 1a. When a is modified to a(tanh(a)), the Hopf bifurcation point disappears as seen in curve CD in Figure 1a. The limit cycle caused by this Hopf bifurcation is shown in Figure 1b. The tanh activation factor causes the Hopf bifurcation to disappear, validating the analysis of [32].

For the MNLMPC sv (0) =100, dv(0)=50, nv(0)=50, a is the control parameters, and $\sum_{t_i=0}^{t_i=t_f} sv(t_i), \sum_{t_i=0}^{t_i=t_f} dv(t_i), \sum_{t_i=0}^{t_i=t_f} nv(t_i)$ were maximized individually, and each of them led to a value of 100, 50.5116, and 50. The overall optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} sv(t_i) - 100)^2 + (\sum_{t_i=0}^{t_i=t_f} dv(t_i) - 50.51168)^2 + (\sum_{t_i=0}^{t_i=t_f} nv(t_i) - 50)^2$ was minimized subject to the equations governing the model. This led to a value of 5473.68. The MNLMPC values of the control variable, a was 16.17225. The MNLMPC profiles are shown in Figures 2a-2d. The control profiles of a exhibits noise and this was remedied using the Savitzky-Golay filter to produce the smooth profile asg.
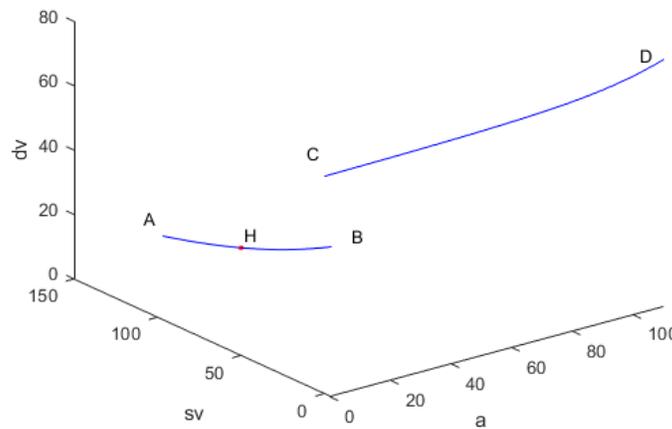

Figure: 1a Hopf on AB disappears when a is modified to atanh(a)(CD)

Limit Cycle caused by Hopf bifurcation
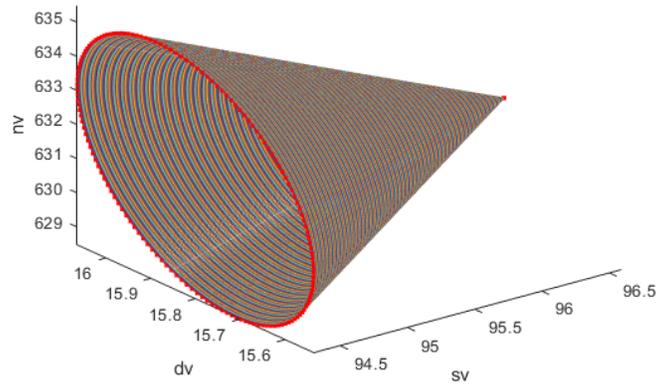

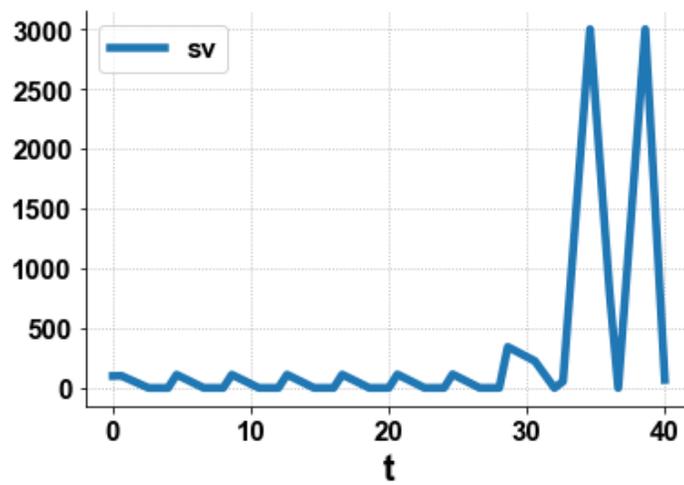**Figure:** 1b limit cycle caused by Hopf bifurcation point

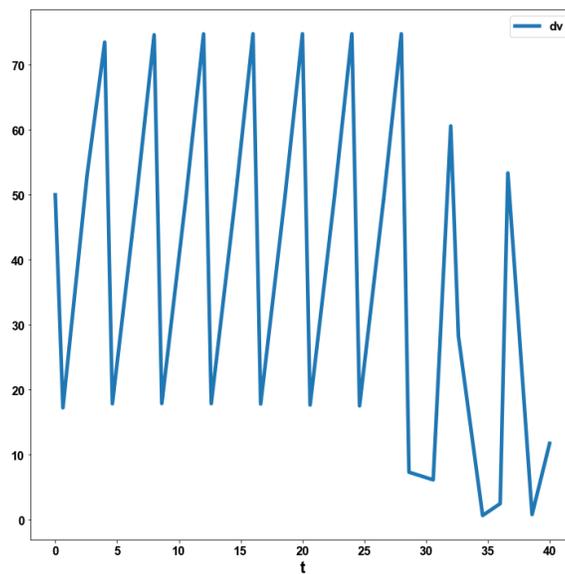**Figure:** 2a MNLMPC (sv vs t)
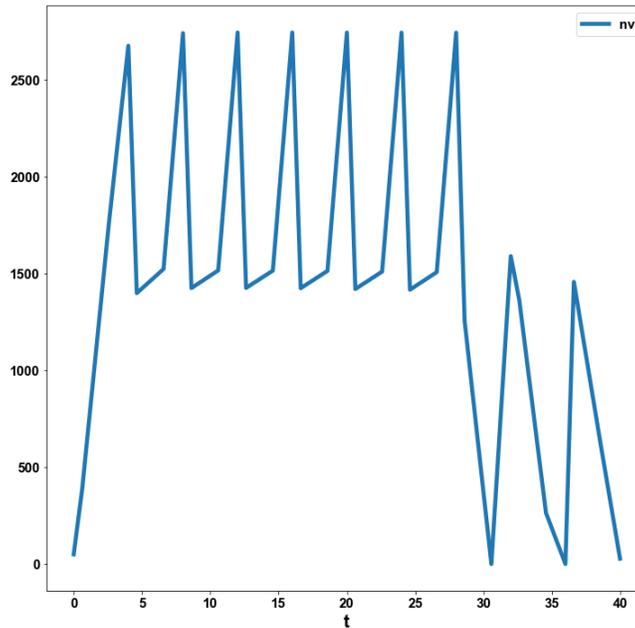

Figure: 2b MNLMPC (dv vs t)
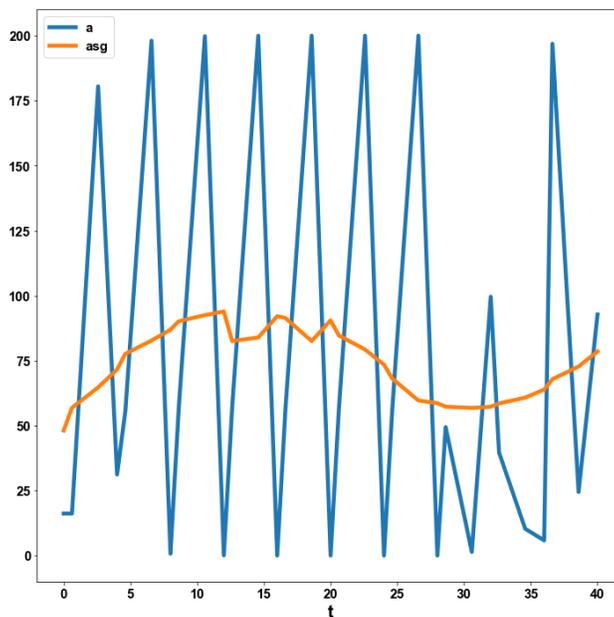
Figure: 2c MNLMPC (nv vs t)

Figure: 2d a,asg vs t.

3. Conclusions

Bifurcation analysis and multiobjective nonlinear control (MN-LMPC) studies on a Neurodynamic model involving Serotonin, Dopamine and Norepinephrine. The bifurcation analysis revealed the existence of a Hopf bifurcation point The Hopf bifurcation point, which causes an unwanted limit cycle, is eliminated using an activation factor involving the tanh function. A combination of bifurcation analysis and Multiobjective Nonlinear Model Predictive Control(MNLMPC) for a Neurodynamic model involving Serotonin, Dopamine, and Norepinephrine is the main contribution of this paper.

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