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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.

Keywords: Bifurcation; Optimization; Control; Serotonin; Dopamine; Norepinephrine

Background

Blier[1] studied the crosstalk between the norepinephrine and serotonin systems and its role in the antidepressant response. Monteiro, et al.[2] developed analytical results for a Wilson-Cowan neuronal network model. Brown, et al.[3], investigated the influence of spike rate and stimulus duration on noradrenergic neurons. Savic, et al.[4] developed a mathematical model of the hypothalamo-pituitary-adrenocortical system and its stability analysis. Best, et al.[5], studied homeostatic mechanisms in dopamine synthesis and release. Best, et al.[6] researched Serotonin synthesis, release and reuptake in terminals: a mathematical model. Bowen[7] studied the relationship between mood instability and depression. Hamon, et al.[8], investigated monoamine neurocircuitry in depression and strategies for new treatments. Akar, et al.[9] performed a nonlinear analysis of EEGs of patients with major depression during different emotional states. Bowen, et al.[10] showed that moods in clinical depression are more unstable than severe normal sadness. Bangsgaard, et al.[11] performed patient-specific modelling of the HPA axis related to the clinical diagnosis of depression. Bachmann, et al.[12] studied the various methods for classifying depression in single-channel EEG using linear and nonlinear signal analysis. Liu, et al.[13] investigated the emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. Perez-Caballero[14] researched the monoaminergic system and depression. Menke, et al.[15] investigated the role of the HPA axis as a target for depression. Loula, et al.[16] produced an individual-based model for predicting the prevalence of depression. Loula, et al.[17] developed a game theory-based model for predicting depression due to frustration in competitive environments. Shao, et al.[18] discovered the associations

among monoamine neurotransmitter pathways, personality traits and major depressive disorders. Xu, et al.[19] performed a mental health informatics study on the mediating effect of the regulatory emotional self-efficacy. Nemesure, et al.[20], developed a predictive model of depression and anxiety using electronic health records and a novel machine learning approach with artificial intelligence. Lu, et al.[21] 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.[22] 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 neurodynamic model involving Serotonin, Dopamine and Norepinephrine[22]. 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.

Model Equations[22]

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

$$\frac{d(sv)}{dt} = \alpha - a(sv) + b(dv)sv + c(nv)sv$$
$$\frac{d(dv)}{dt} = \beta - e(dv) - f(dv)sv$$
$$\frac{d(nv)}{dt} = -g(nv) + h(dv)$$

The base parameter value is

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[22].

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

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

$x \in R^n$ 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

$$Aw = 0$$

Where A is

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha]$$

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

$y \quad (y_1, y_2, y_3, y_4, ...y)$ must align with $\hat{w} = (w_1, w_2, w_3, w_4, ...w_n)$. Since

$$J\hat{w} = Aw = 0$$

the n+1 th 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

$$Az = 0$$
$$Aw = 0$$

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,

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

@ indicates the bialternate product while I_n is 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[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.

Multiobjective nonlinear model predictive control (MNLMPC)

The rigorous multiobjective nonlinear model predictive control (MNLMPC) method developed by Flores Tlacuahuaz, et al.[33] was used.

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

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

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

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

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

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[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[35] and confirmed as a global solution with BARON[36].

The steps of the algorithm are as follows

Optimize $\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i)$ and obtain q_j^*.

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.

Implement the first obtained control values

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.

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 Fig. 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)**.

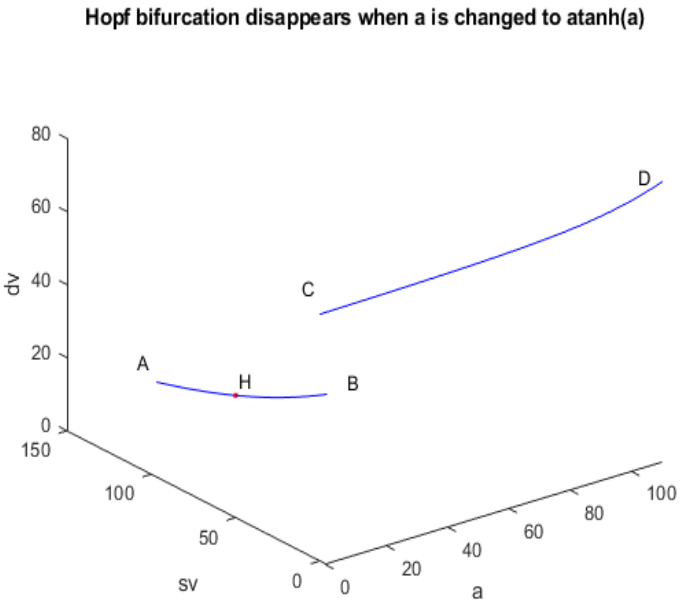

Figure 1a: Hopf on AB disappears when a is modified to atanh(a)(CD).

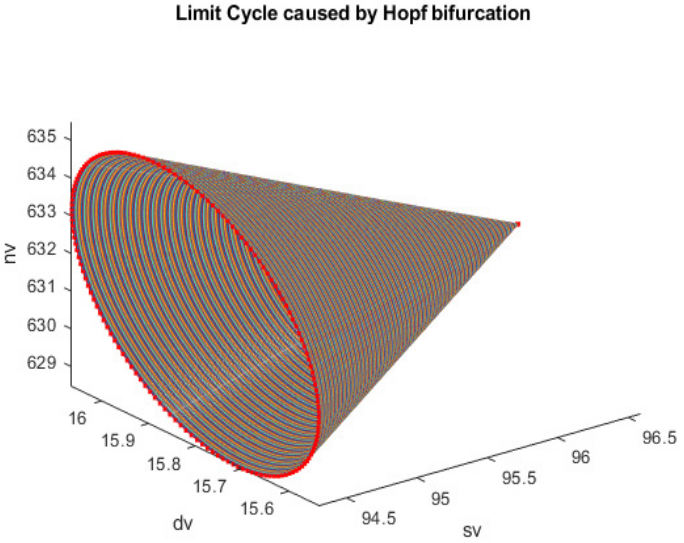

Figure 1b: limit cycle caused by Hopf bifurcation point.

The tanh activation factor causes the Hopf bifurcation to disappear, validating the analysis of Sridhar[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.

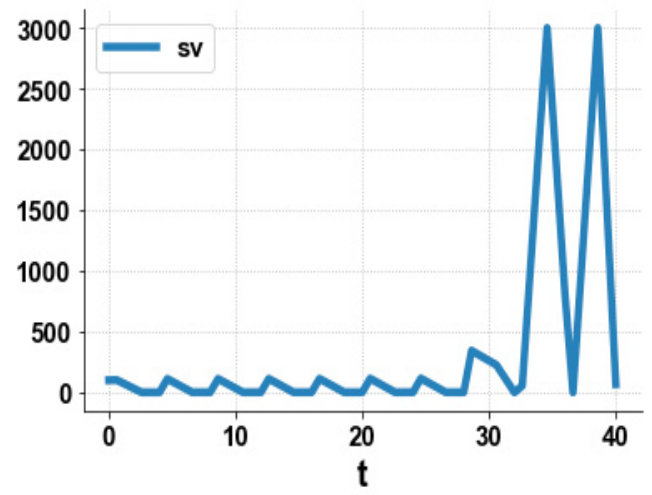

Figure 2a: MNLMPC (sv vs t)

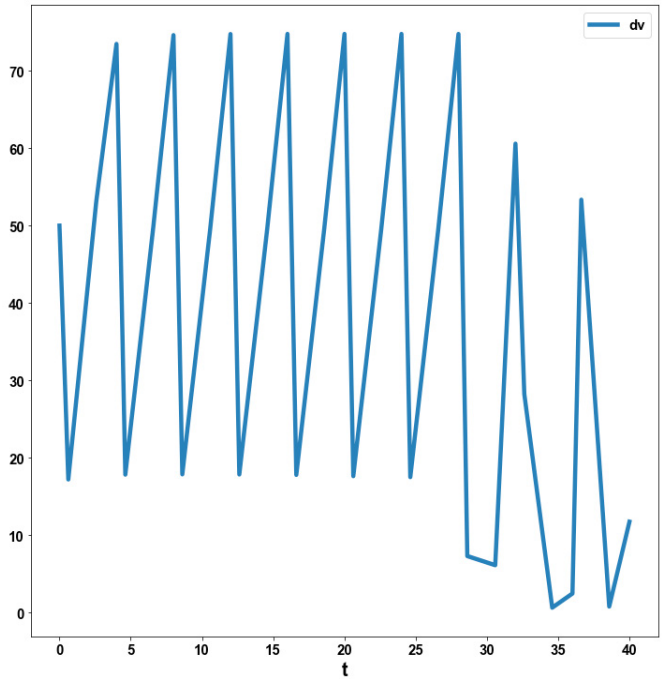

Figure 2b: MNLMPC (dv vs t).

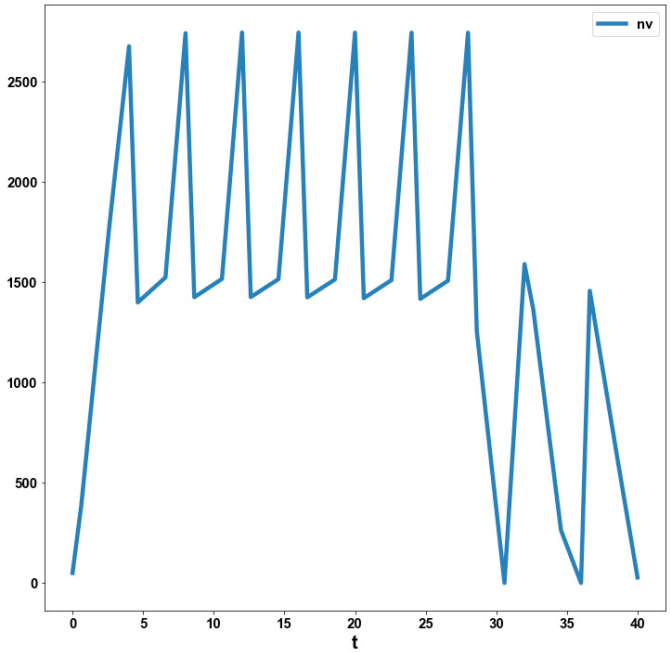

Figure 2c: MNLMPC (nv vs t).

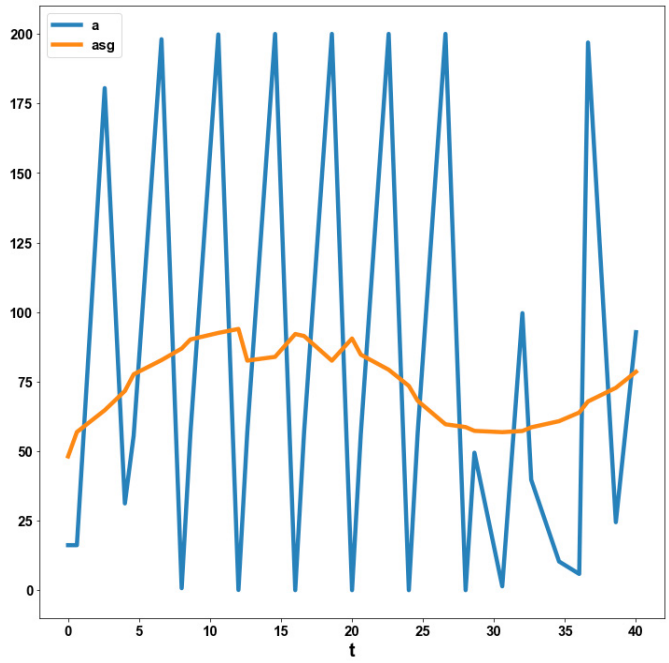

Figure 2d: a,asg vs t.

Conclusions

Bifurcation analysis and multiobjective nonlinear control (MNLMPC) 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.

Data Availability Statement

All data used is presented in the paper.

Conflict of Interest

The author, Dr. Lakshmi N Sridhar has no conflict of interest.

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