DOI: 10.48011/asba.v2i1.1624

Relating Lurie's problem, Hopfield's network and Alzheimer's disease.

R. F. Pinheiro [*,***,****] **D. Colón** [*] **L. L. R. Reinoso** [**]

[*] *Automation and Control Lab., Telecom and Control Department, University of São Paulo, São Paulo, Brazil (e-mail: rafael.pinheiro@usp.br; diego@lac.usp.br).*
[**] *Computer Engineering and Digital Systems Department, University of São Paulo, São Paulo, Brazil (e-mail: loubrysrojas@usp.br).*
[***] *Nove de Julho University, São Paulo, Brazil (e-mail: rafael.pinheiro@uni9.pro.br).*
[****] *Sant'anna University Center, São Paulo, Brazil (e-mail: rafael.pinheiro@unisantanna.br).*

Abstract: Alzheimer's disease is a degenerative brain disorder that affects millions of people around the world and still without cure. A very common application of Hopfield neural networks is to simulate a human memory as well as to evaluate problems of degeneration and memory loss. On the other hand, from the control area, one has Lurie's problem, which emerged in the 1940s and which still does not have a general solution. However many works and results came in an attempt to solve it. In this paper, the Hopfield's network is shown as a particular case of Lurie's problem, then one of the consequences of Alzheimer's disease, memory failure, is modeled using Hopfield's networks and finally a recent result of Lurie's problem is applied to the computationally modeled disease to correct the problem of memory loss. The correction is made using a controller via DK-iteration. Simulations are performed to validate the computational model of the disease and to demonstrate the effectiveness of the application of the recent Lurie's problem theorem. Therefore, in addition to the results presented, this work aims at encouraging the researches in the area, so that in the future, better diagnostic and treatment conditions will be achieved.

Resumo: A doença de Alzheimer é uma doença degenerativa do cérebro que afeta milhões de pessoas em todo o mundo e ainda sem cura. Uma aplicação muito comum das redes neurais de Hopfield é simular a memória humana, bem como avaliar problemas de degeneração e perda de memória. Por outro lado, da área de controle, tem-se o problema de Lurie, surgido na década de 40 que ainda não tem uma solução geral, porém muitos trabalhos e resultados surgiram na tentativa de resolvê-lo. Neste artigo, a rede de Hopfield é mostrada como um caso particular do problema de Lurie. Então, uma das consequências da doença de Alzheimer, a perda de memória, é modelada usando as redes de Hopfield. Um resultado recente do problema de Lurie é aplicado à doença modelada computacionalmente para corrigir o problema de perda de memória. A correção é feita usando um controlador via iteração DK. Simulações são realizadas para validar o modelo computacional da doença e demonstrar a eficácia da aplicação do recente teorema do problema de Lurie. Portanto, além dos resultados apresentados, este trabalho visa incentivar as pesquisas na área, para que, no futuro, sejam alcançadas melhores condições de diagnóstico e tratamento.

Keywords: Lurie's problem; Hopfield's Networks; Alzheimer's disease; $\mathcal{H}_\infty$ Control; μ-Analysis; DK-iteration.

Palavras-chaves: Problema de Lurie; Redes de Hopfield; Doença de Alzheimer; Controle $\mathcal{H}_\infty$; Análise μ; Iteração DK.

1. INTRODUCTION

In a woman of 51 years old, Alzheimer (1907) described clinical observations, whose anatomical features were unusual to any previously known disease. The first symptom, which the woman demonstrated, was the idea of being jealous of her husband, and in a short time, she developed a rapid memory loss. This terrible disease became known by name of its discoverer. It is a degenerative disease that leads to death, and one of its main consequences is the loss of memory due to synaptic losses (Terry, 2000). Although it has been documented more than a hundred years ago, the understanding of its final cause still represents a mystery to neuroscience.

Linked to neuroscience, the artificial neural networks (ANN) are computational methods inspired in the functioning of biological neurons, which has been widely used in several areas, including medicine (Gil et al., 2009; Al-Shayea, 2011). In particular, one has Hopfield neural network (HNN), proposed by Hopfield (1984). HNN has been applied considerably in several areas, like optimization problems (Kaskurewicz and Bhaya, 1995) and other applications such as presented in Braga et al. (2005): implementation of an identification systems of military target used in aircraft model B-52; user authentication systems; oil exploration; prediction in the financial market. Currently the network has awakened great interest by theoretical, biological (Monteiro, 2006), because they can simulate self-associative memory as cited by Iyerngar and Balagani (2004) and can be used in simulations of stages of Alzheimer's disease (AD).

On the other hand, we have Lurie's problem (LP), which has arisen due to a problem of automatic control of an aircraft. LP was conceived (Lurie and Postnikov, 1944), which is also known in the literature as absolute stability problem, and is part of the area of control engineering. This problem was studied for many researchers, as Krasovskii (1953), Popov (1961), and Kalman (1963). Research on the LP also went on to other areas, such as chaos synchronization (Liao and Yu, 2008); convex approach (Gapski and Geromel, 1994); neural networks (Pinheiro and Colón, 2019); linear parameter varying (LPV) system (Yu and Liao, 2019); and μ analysis (Abtahi and Yazdi, 2019). In works like Liao and Yu (2008) and Pinheiro and Colón (2019) is shown that HNN is a particular case of Lurie type system.

In our bibliographic research, we found papers that relate in some way HNN to AD (Morrison et al., 2017; Sergio et al., 2009; Swietlik et al., 2019; Thuraisingham, 2015; Tabekoueng et al., 2020) and papers that connect LP with HNN (Aouiti et al., 2019; Kaskurewicz and Bhaya, 1995; Liao and Yu, 2008; Pinheiro and Colón, 2019). But, we did not find works that relate the LP, HNN and AD. In this sense, we believe that the originality of this work is to relate those three areas of research. Thus, using HNN we present a modeling of one of the consequences of AD, which is memory loss, as suggested in (Pinheiro and Colón, 2019, 2020). Although the use of HNN in AD modeling is not new (Sergio et al., 2009; Thuraisingham, 2015), here it is done in a different way. We do this in continuous-time based on external inputs (like in Zhou et al. (2016)), and in those it is done in a discrete time domain. Other differences are: in paper Sergio et al. (2009) the HNN is used to train the Venn's networks which models the AD; in Thuraisingham (2015) the HNN is used in conjunction with a mean field theory; in Zhou et al. (2016) the model is based on external inputs, but it does not use HNN. Therefore, the modeling of neuropathology in this paper can be considered as a contribution.

Another contribution of this work is in the application of the recent result presented by Pinheiro and Colón (2020), which is the design of a controller via DK-iteration to correct the effect of the memory loss in computationally modeled disease. In practical terms, there is still a certain difficulty in accessing the brain neurons. But with all technological development, as already seen in works such as Morrison et al. (2017), it is promising that in the near future, areas of electrical engineering, such as artificial neural networks and artificial intelligence will bring even more efficient solutions for the diagnosis, treatment and cure of AD.

This work is organized as follow: In section 2, one has the theoretical background. In section 3, a healthy memory and a impaired memory are modeled. In section 4, we have the application of Theorem 8 of Pinheiro and Colón (2020) in the modeled network. Throughout sections 3 and 4, simulations are carried out to validate the model and demonstrate the effectiveness of the application. Finally, in section 5, the overall results are summed up in the conclusion and followed by a prospect for future research.

2. THEORETICAL BACKGROUND

This section sets forth the necessary bases around the AD, HNN and LP to proceed with the modeling and application in the following sections.

2.1 Alzheimer's Disease

AD is a degenerative brain disease that deteriorates cognitive abilities and motor functions. It was first described in a 51-year-old woman by German psychiatrist and pathologist Alois Alzheimer (Alzheimer, 1907). Its causes are uncertain and unreliable, being its method of diagnosis made through the patient's medical history, neurological, psychiatric, clinical examinations, neuropsychological tests, and laboratory studies. For a definite diagnosis, it is necessary to deepen histopathology (Mckhann et al., 1984), that is, an analysis of all the composition of brain tissue, which is not possible with the patient in life. Its symptoms involve memory loss (Terry, 2000), progressive dementia, agitation, apathy, depression, loss of appetite, muscle contractions and others. There is no cure for AD, however there are medications to slow down and relieve the symptoms (Fillit and Cummings, 2000; Hake, 2002).

The classical neuropathological marks of AD involve characteristics of macroscopic and microscopic dimensions. These markers are useful for the diagnosis of the disease. In general, the macroscopic aspects are: 15% to 35% brain weight reduction, cortex atrophy, ventricular dilation, reduced hippocampus and decreased blood flow (Freitas, 2006). The microscopic aspects in general are: Synaptic loss, neuronal death, amyloid plaque findings and neurofibrillar entanglements (Selkoe, 2001; Freitas, 2006).

Neurons communicate with each other at contact points called synapses. In a synapse, a neuron sends a message to a target neuron. Synaptic loss is responsible for cognitive decline. It does not come only from the loss of neurons, so much so that it is possible in a specific region to have fewer synaptic connections than neurons. This fact indicates that synaptic loss precedes neuronal loss and, consequently, remaining neurons have low synaptic connections between their partners. For this reason, synaptic density is considered one of the main cognitive declines in AD (Scheff et al., 2007).

2.2 Lurie's Problem (LP)

Lurie and Postnikov (1944) proposed a problem and searched the necessary and sufficient conditions to the global asymptotic stability of the null solution of that system (that is, the equilibrium point), becoming known in the literature as LP or problem of absolute stability. The problem comes to studying a system with multiple-input-multiple-output (MIMO) as in the Fig. 1, with a nonlinear part (nonlinearities f) and a linear part (L).

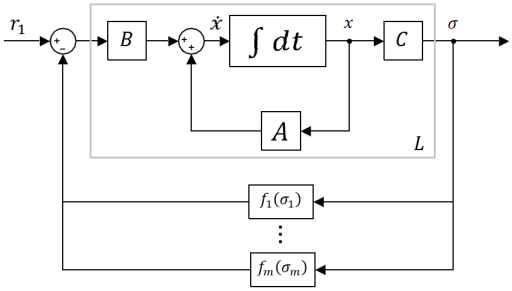

Figure 1. Block diagram of the MIMO Lurie type system.

The diagram in Fig. 1 is expressed by the following system of differential equations:

$$\begin{cases} \dot{x} = Ax - Bf(\sigma) + Br_1, \\ \sigma = Cx, \end{cases} \tag{1}$$

where $x \in \mathbb{R}^n$ is the state vector, $f = [f_1, f_2, \cdots, f_m] \in \mathbb{R}^m$ is a vector of unknown but fixed functions and $\sigma \in \mathbb{R}^m$. Also the matrices $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{m\times n}$ are known and fixed and $A \in \mathbb{R}^{n\times n}$ is Hurwitz, know and fixed. In general, the nonlinear functions $f_j(\sigma_j)$ are continuous and restricted to the first and third quadrants of the plane. Here we will deal with nonlinearities of the type $f_j \in F_{(0,k_j)}$, where:

$$F_{(0,k_j]} := \{f_j | f_j(0) = 0, 0 < \sigma_j f_j(\sigma_j) \leq k\sigma_j^2, \sigma_j \neq 0\}, \tag{2}$$

It can be assumed, without loss of generality, that the set of line vectors $c_i = (c_{i1}, ..., c_{in})$, $i = 1, 2, ..., m$ of matrix C, are linearly independent, and with the purpose of separating the variables, by a transformation (Liao and Yu, 2008) the system (1) can be transformed in the following:

$$\dot{y} = \tilde{A}y + \sum_{j=n-m+1}^{n} \tilde{b}_j \tilde{f}_j(y_j), \tag{3}$$

or:

$$\dot{y}_i = \sum_{j=1}^{n} \tilde{a}_{ij} y_j + \sum_{j=n-m+1}^{n} \tilde{b}_{ij} \tilde{f}_j(y_j). \tag{4}$$

2.3 HNN and its Relationship with LP

HNN was proposed by Hopfield (1984) and is part of an area known as neurodynamics. It can be represented by the following system of nonlinear differential equations:

$$C_i \frac{du_i}{dt} = -\frac{u_i}{R_i} + \sum_{j=1}^{n} T_{ij} V_j + I_i, \qquad i = 1, 2, ..., n, \tag{5}$$

where $C \in \mathbb{R}^n$, $u \in \mathbb{R}^n$, $R \in \mathbb{R}^n$, $T \in \mathbb{R}^{nxn}$, $I \in \mathbb{R}^n$, and $V_j = g(u_i)$. The functions g can be defined as $g : \mathbb{R} \to [0, 1]$ and is continuously differentiable and monotonically increasing, or $g_i'(u_i) > 0$. This functions are called activation functions and usually are sigmoidal functions. The continuous model of HNN can be thought as an electric circuit (for more details Pinheiro (2015)).

The problem of stability of HNN was initially discussed by Hopfield (1984). He first defined a function which he called as computational power function:

$$E(V) = -\frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} T_{ij} V_i V_j - \sum_{i=1}^{n} V_i I_i + \sum_{i=1}^{n} \frac{1}{R_i} \int_0^{V_i} g_i^{-1}(s) ds. \tag{6}$$

Then, he showed that $\frac{dE}{dt} < 0$ if the weight matrix T is symmetric and if no neuron feeds itself back, thus concluding the stability of the network (see Fig. 2).

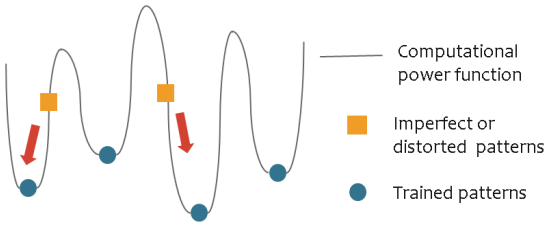

Figure 2. Hopfield's stability.

In Liao and Yu (2008) and Pinheiro and Colón (2019) is shown that HNN can be considered a special case of MIMO Lurie type system. Thus, considering the equation (5) after some changes of variables, it can take the following form:

$$\frac{dx_i}{dt} = -d_i x_i + \sum_{j=1}^{n} b_{ij} f_j(x_j). \tag{7}$$

In relation to the function f, we have $f \in F_{(0,k]}$. Comparing the equations in (7) with the equations in (4):

$$\dot{y}_i = \sum_{j=1}^{n} \tilde{a}_{ij} y_j + \sum_{j=n-m+1}^{n} \tilde{b}_{ij} \tilde{f}_j(y_j),$$

one has that the HNN is a special case of a MIMO Lurie type, where $\tilde{a}_{ij} = 0$, $i \neq j$, $\tilde{a}_{ii} = -d_i < 0$, e $m = n$.

3. MODELING MEMORY LOSS DUE TO ALZHEIMER'S DISEASE VIA HOPFIELD NETWORKS

In this work, we model one of the consequences of Alzheimer's disease: memory loss. In order to do this, it

is computationally modeled via a HNN the decrease of synapse strength between the neurons, because this is one of the causes of memory loss in Alzheimer's disease, as seen in the section 2.1.

From (5), in the equation (8) we have established a neural network conceiving a system of ordinary differential equations of 12th order, that is, 12 Hopfield's neurons with architecture according to Fig. 3, which is represented visually by a $3x4$ digital sign. A equação 8 gera as figuras 7, 9 e 11.

$$\dot{u}_i = -d_i u_i + T_{i,n-(i-1)} \tanh(u_{n-(i-1)}) + I_i. \quad (8)$$

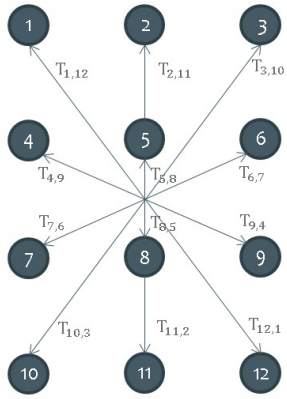

Figure 3. Network architecture to simulate a $3x4$ digital sign.

In Zhou et al. (2016) is suggested how to treat the components I and u of the equation (8). The entries I (bias) is the pattern to be memorized, given by the vector $I = [I_1, I_2, I_3, I_4, I_5, I_6, I_7, I_8, I_9, I_{10}, I_{11}, I_{12}]$. For example, for the network to memorize the letter L, the following vector must be provided (note that 1 represents black and -1 represents white):

$$I = [1, -1, -1, 1, -1, -1, 1, -1, -1, 1, 1, 1] = \begin{bmatrix} 1 & -1 & -1 \\ 1 & -1 & -1 \\ 1 & -1 & -1 \\ 1 & 1 & 1 \end{bmatrix}. \quad (9)$$

The initial conditions of the u states are patterns to be recovered, given by the vector $u^0 = [u_1^0, u_2^0, u_3^0, u_4^0, u_5^0, u_6^0, u_7^0, u_8^0, u_9^0, u_{10}^0, u_{11}^0, u_{12}^0]$. The vector d is composed of fixed positive constants, because it is a condition to be Hopfield network. We chose $d = 1$ for simplicity. In order to have a stable network the T matrix must be symmetrical. We use a matrix of $T_{12\times12}$ symmetrical with main diagonal zero. We can not say how a real biological neural network is connected. We chose T_0 like in equation (10) for simplicity. We will see that values around $0.005T_0$ represents healthy neurons, and values around $0.6T_0$ represents irreversible memory loss. The stability condition of the network and the correct adjustment of the weights ensure healthy memory. The network being stable, i.e., the matrix of weights being symmetric and without feedback of a neuron itself, ensures that, given an initial condition, the network finds an equilibrium point. This is a characteristic of the HNN, it is a locator of equilibrium points, as can be seen in the Fig. 2.

Given an initial condition, for the network to find the correct equilibrium point (the memorized pattern given by the vector I), it is necessary to adjust the weights. In the section 2.1, it is seen that cognitive impairment in patients with Alzheimer's disease is associated with loss of synapses. We have related these synaptic losses (see Fig. 4) to the disturbances in the weights of the Hopfield's network (see Fig. 5). In this case, the values T_{ij} can be considered the synaptic connection strength.

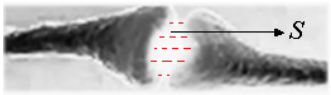

Figure 4. Synapse between neurons. S is strength of the connection.

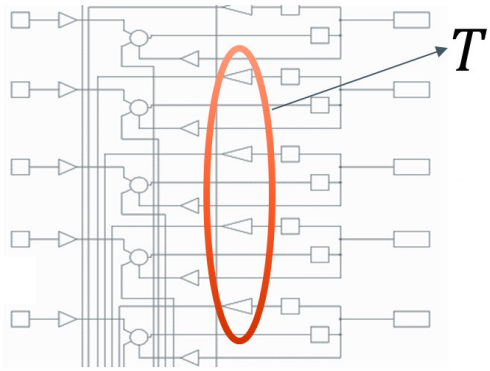

Figure 5. Hopfield's network via Simulink®.

Therefore, in our model, the lower the value of T_{ij} the greater the connection strength (S) between the neurons. In this situation we have a healthy memory. And the higher the value of T_{ij} the lower is the connection strength (S) between the neurons, which starts to remit in synaptic losses, leading to memory loss, characterizing Alzheimer's disease. The box in Fig. 6 summarizes the process of modeling memory loss.

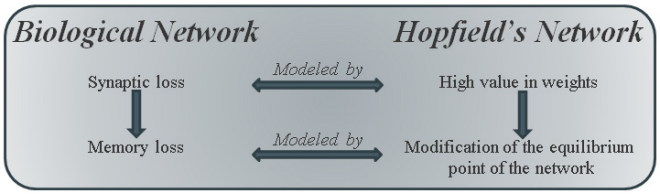

Figure 6. Memory loss modeling process.

3.1 Simulation

The purpose of the simulation is to show the functioning of the Hopfield's network as a healthy memory and then as a pathology (Alzheimer's disease). The selected input must be the letter L as (9), and we use the initial condition $u^0 = [0, 0.5, 0, -1, 0, 0.5, 0, 1, 1, -1, 1, 1]$.

Healthy Network: In order to have a healthy network, we insert the matrix of weights $T = 0.005T_0$, where T_0 is as in (10). Note that the weight matrix T is symmetrical and no neuron feeds itself back, and this guarantees stability for the network. Now observing the 0.005 value, this constant

makes the weights small which leads the network to take as equilibrium points the I input as we observed in the temporal response of Fig. 7.

$$T_0 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1.5 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1.5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1.5 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1.5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1.5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1.5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1.5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}. \quad (10)$$

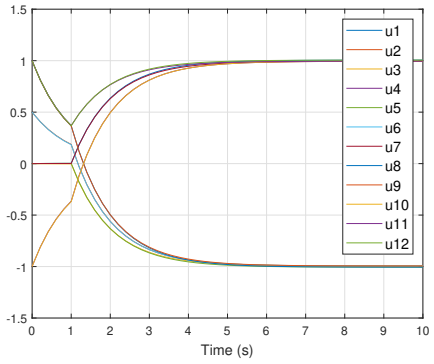

Figure 7. Healthy network temporal response.

Therefore, we have a healthy memory, that is, given any starting point for a memory (initial condition u^0) the network is able to remember the letter L. The Fig. 8 shows via a digital sign the evolution of the network in the process of remembering the letter L.

Figure 8. Temporal evolution of the memory of the letter L via digital sign.

Network with Alzheimer's Disease: First, we simulate the weakening of the synaptic connection between the neurons. We increase the value of the weight by 100 times, i.e., instead of multiplying the T_0 matrix, in (10) by 0.005, we multiply by 0.5, i.e., $T = 0.5T_0$. In the network, an equilibrium points change, according to the temporal response of Fig. 9, models memory loss in Alzheimer's disease. Note that the network remains stable, but now with other equilibrium points. In the representation by the digital sign in Fig. 10, we see that the network loses the ability to remember the letter L correctly.

Finally, we take $T = 200T_0$. Note in Fig. 11 that the network assumes new equilibrium points, and by the digital sign of Fig. 12, it completely looses its memory, not being able to remember the letter L.

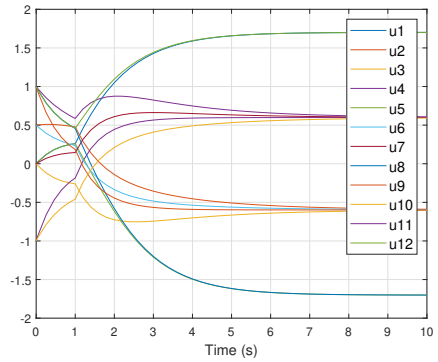

Figure 9. Temporal response for network with partial memory loss.

Figure 10. Temporal evolution of the letter L for network with partial loss of memory via digital sign.

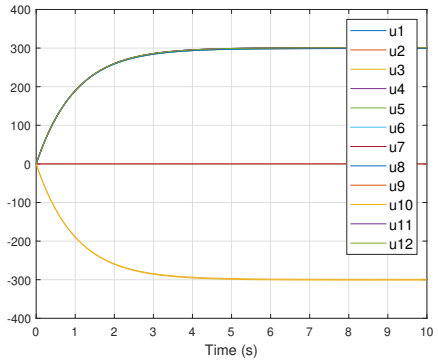

Figure 11. Temporal response of the worst case of memory loss.

Figure 12. Complete loss of memory via digital sign.

4. APPLICATION OF A RESULT OF LURIE'S PROBLEM IN HOPFIELD'S NETWORK

In this section, we make an application of the theorem 8 of Pinheiro and Colón (2020). This theorem together with μ-synthesis (via DK-iteration), provide mechanisms for the design of a controller that ensures robustness of stability and performance for the network in (8). The goal is to correct the memory failure in the network, thus simulating a kind of cure in the computationally modeled disease. The notation μ means the singular structured value of a function and was developed by Doyle (1982). The DK-iteration, proposed by Doyle (1985), is a synthesis method of robust controllers that combines $\mathcal{H}_\infty$ design with μ-analysis.

Theorem 1. Given a controller $K(s)$ and $[0, k_j]$ the sectors that include $f_j \in F_{(0,k_j]}$ for $j = 1, ..., m$, then the system (1) with the controller $K(s)$ in feedback loop is robustly stable and have robustness of performance, if and only if:

$$\mu_{\tilde{\Delta}}[F_U(P, K)] < 1, \quad \forall\omega, \tag{11}$$

where:

$$P(s) = \begin{bmatrix} -C(sI - A_0)^{-1}B & -I & -C(sI - A_0)^{-1}E \\ C(sI - A_0)^{-1}B & I & C(sI - A_0)^{-1}E \\ C(sI - A_0)^{-1}B & 0 & C(sI - A_0)^{-1}E \end{bmatrix}, \tag{12}$$

$$F_U(P, K) = M(s) = \begin{bmatrix} M_{11}(s) & M_{12}(s) \\ M_{21}(s) & M_{22}(s) \end{bmatrix}, \tag{13}$$

$$\begin{gathered} M_{11} = I + C(sI - A_0)^{-1}BK(s)(-I)[I \\ +C(sI - A_0)^{-1}BK(s)]^{-1}, \\ M_{12} = C(sI - A_0)^{-1}E + C(sI - A_0)^{-1}BK(s)(-C)(sI \\ -A_0)^{-1}E[I + C(sI - A_0)^{-1}BK(s)]^{-1}, \\ M_{21} = C(sI - A_0)^{-1}E + C(sI - A_0)^{-1}BK(s)(-I)[I \\ +C(sI - A_0)^{-1}BK(s)]^{-1}, \\ M_{22} = C(sI - A_0)^{-1}E + C(sI - A_0)^{-1}BK(s) - C(sI \\ -A_0)^{-1}E[I + C(sI - A_0)^{-1}BK(s)]^{-1}, \end{gathered}$$

with:

$$A_0 = \begin{bmatrix} a_{11} - \sum_{j=1}^{m} b_{1j}\frac{k_j}{2}c_{j1} & \dots & a_{1n} - \sum_{j=1}^{m} b_{1j}\frac{k_j}{2}c_{jn} \\ \vdots & \ddots & \vdots \\ a_{n1} - \sum_{j=1}^{m} b_{nj}\frac{k_j}{2}c_{j1} & \dots & a_{nn} - \sum_{j=1}^{m} b_{nj}\frac{k_j}{2}c_{jn} \end{bmatrix},$$

and:

$$E = \begin{bmatrix} -\frac{k_1}{2}b_{11} & \dots & -\frac{k_m}{2}b_{1m} \\ \vdots & \ddots & \vdots \\ -\frac{k_1}{2}b_{n1} & \dots & -\frac{k_m}{2}b_{nm} \end{bmatrix}.$$

Proof 1. It can be found in Pinheiro and Colón (2020), Theorem 8.

Remark 1. The notation $F_U(P, K)$ means upper linear fractional transformations that can be studied in detail for LP in Pinheiro and Colón (2020). The $\tilde{\Delta}$ matrix contains the parametric uncertainties δ of the robust control theory (see Skogestad and Postlethwaite (2007)).

The Algorithm 1, extracted from Pinheiro and Colón (2020), brings the procedures and Matlab® function suggested to perform the DK-iteration, whose theoretical bases can be found in Skogestad and Postlethwaite (2007). Note that the algorithm provides a matrix of controllers $K = diag[K_1(s), ..., K_{12}(s)]$, which must be placed in the network according to Fig. 13. In comparison with the network in Fig. 5, a feedback loop (in red) is created.

4.1 Simulation

In this simulation, the problem of memory failure in the network presented by Fig. 9 and Fig. 10 is corrected by means of controllers designed according to the Theorem 1 and Algorithm 1. The input and initial condition remain as in the simulation of the Section 3.1. The nonlinearities for Lurie type system in the design of the controllers are of the kind $f_i \in F_{(0,2]}$, $i = 1, ..., 12$, where 2 is the parameter for the variation of the parametric uncertainties. Note that the Theorem 1 refers to the system (1), so we should insert the parameters A, B and C obtained from the Hopfield's network of the computational model of the disease according to the equation (8). In this case one must assume:

$$A = diag[-1, ..., -1]_{(12\times12)}, \quad B = T,$$

$$\tilde{\Delta} = \begin{bmatrix} \delta_1 & & & & \\ & \ddots & & 0 & \\ & & \delta_{12} & & \\ & 0 & & \delta_{13} & \delta_{14} \\ & & & \delta_{15} & \delta_{16} \end{bmatrix}, \quad C = \begin{bmatrix} 0 & & 1 \\ & \iddots & \\ 1 & & 0 \end{bmatrix}_{(12\times12)}.$$

Remark 2. In the $\tilde{\Delta}$ matrix one has the nonlinearities f of the Lurie type system replaced by the uncertainties $\delta_1, ..., \delta_{12}$, and the uncertainties δ_{13}, δ_{14}, δ_{15} and δ_{16} are used to ensure robustness of performance (see Skogestad and Postlethwaite (2007) for more information).

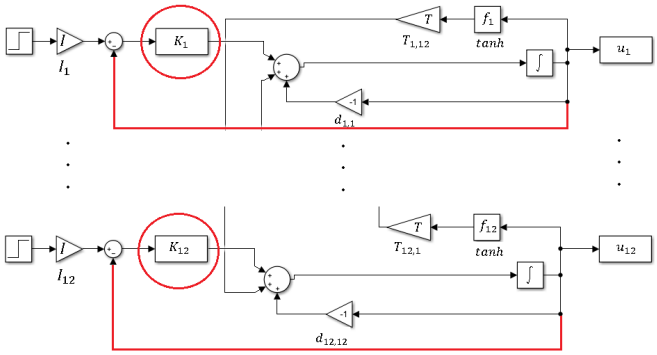

Figure 13. Hopfield's network with controllers.

Algorithm 1: DK-iteration

Result: A stabilizing controller $K(s)$ that guarantees robustness of performance.

Find the generalized nominal $P(s)$ as in (12) and the matrix $\tilde{\Delta}$;

Start with an initial guess for D, usually set $D = I$.

While ($\mu_{max} \geq 1$) or a prespecified maximum iteration number is not reached

Step K: Synthesize a $\mathcal{H}_\infty$-controller $K(s)$, that is, solve $min_K ||DF_U(P, K)D^{-1}||_\infty$ with fixed $D(s)$. Use Matlab® function $[K, \gamma, Info] = hinfsyn(DPD^{-1})$

Calculate $M(s)$, as in (13)

Step D: Find $D(j\omega)$ that minimizes $\bar{\sigma}(DMD^{-1}(j\omega))$ in each frequency, with fixed M. Use Matlab® function $mussvunwrap(Info)$

Adjust the magnitude of each element of $D(j\omega)$ to a stable and minimum phase transfer function $D(s)$. Use Matlab® function $fitfrd$

Calculate μ_{max}, where μ_{max} is equal to upper bound of μ. Use Matlab® function $mussv(frdModel, BlockStructure)$

endWhile

Remark 3. After the design of the controllers, the simulation is performed in the Simulink® (via ode45 Dormand-Prince method with variable-step) using the nonlinearities of the network (8), that is, the hyperbolic tangent. The weight matrix is $T = 0.5T_0$.

In the first iteration, $\mu_{max} = 1.000$ was found. Figure 14 shows the upper bound of μ reaching 1. This value of μ does not satisfy the condition (11).

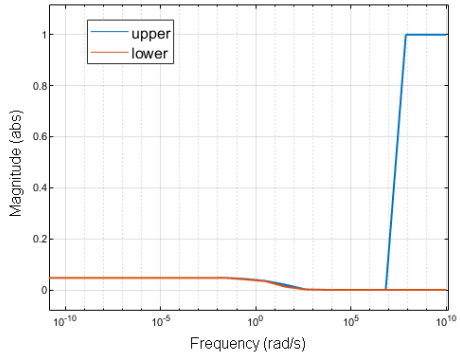

Figure 14. Condition (11) not satisfied.

In the second iteration, as shown in Fig. 15, $\mu_{max} = 0.0067$ was obtained. This value satisfies the condition (11) of Theorem 1. Therefore, we have a matrix of controllers, $K = diag[K_1(s), ..., K_{12}(s)]$, that guarantee robustness of stability and performance for the network (8).

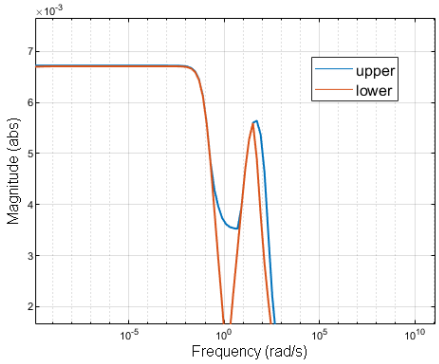

Figure 15. Value of μ that satisfies the condition (11) of Theorem 1.

Applying the controllers designed in the network, one has in Fig. 16 the temporal response following the input. One can observe that the response is very fast in this case and the transient is not observable. Finally, according to Fig. 17, it is observed that the network memory has been restored.

For networks with serious memory problems, as in Fig. 12, it was not possible to synthesize a controller to correct the problem of memory loss.

5. CONCLUSION

In this paper, one of the consequences of Alzheimer's disease, memory failure, is modeled through the Hopfield's network. In this modeling we could verify that the synaptic connection strength between neurons in a biological network is inverse in the modeled artificial neuronal network.

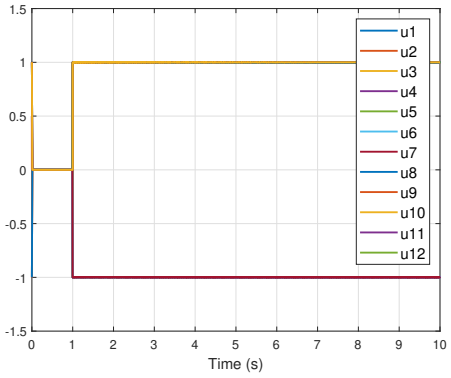

Figure 16. Temporal response of the network with controllers.

Figure 17. Temporal evolution of the letter L in digital sign for network controlled.

That is, a high weight in the artificial network models low synaptic interactions between biological neurons, causing memory loss.

In order to correct the problem of memory loss in the artificial network, a controller via $\mathcal{H}_\infty$ control techniques was designed using a recent theorem from the literature on Lurie's problem. Simulations showed the effectiveness of the model and controller. In the process of healing the artificial network using the controller, we found that for a high degree of memory loss, the controller cannot restore memory. This makes sense when observing a biological network, because it can mean the complete loss of synapses or the death of the neuron. Thus, for practical purposes for Alzheimer's disease, it is supposed that energy inputs in neurons not completely impaired may lead to attenuation in memory loss. This idea is in agreement with the discovery in Thuraisingham (2015). In this paper, the model suggests that the external stimuli in the brain will slow down this memory loss. Nevertheless, if the neuronal connections are already poor, then the enhancements will not be noticeable.

For future research, it is planned to model Alzheimer's disease using other types of networks, which include delay, other nonlinearities, and the application of other techniques such as adaptive control using only state feedback, which would represent new synapses. In addition, other control techniques can be explored, such as, the use of the linear parameter-varying (LPV) framework with the discrete-time domain and integral quadratic constraints IQC's. Finally, we wish to have a neuroscientist on the team, as we could bring the computational model even closer to the real one in order to provide better conditions for diagnosis and treatment for Alzheimer's disease.

REFERENCES

Abtahi, S. F., and Yazdi, A. (2019). Robust control synthesis using coefficient diagram method and μ-analysis: an

aerospace example. *Int. J. Dynam. Control,* 7, 595–606.
Al-Shayea, Q. K. (2011). Artificial neural networks in medical diagnosis. *Intern. J. Comp. Sci.,* 8(2), 150-154.
Alzheimer, A. (1907). Uber Eine Eigenartige Erkrankung der Hirnrinde (in German). *Allg. Zeitschrift Psychiatrie und phychish-Gerichtliche Medizin,* 64, 146-148.
Aouiti, C., Li, X., Miaadi, F. (2019). Finite-time stabilization of uncertain delayed-Hopfield neural networks with a time-varying leakage delay via non-chattering control. *Sci. China Technol. Sci.,* 62, 1111–1122.
Braga, A.P., Carvalho, A.C.P.L., Ludemir, T.B. (2005). *Redes Neurais Artificiais: Teoria e Aplicacões,* LTC, RJ.
Doyle, J. (1982). Analysis of feedback systems with structured uncertainty, in *IEE Proceedings D - Control Theory and Applications*, 129(6), 242-250
Doyle, J. (1985). Structured uncertainty in control system design, in *24th IEEE CDC*, pp. 260-265
Fillit, H. Cummings, J. (2000). Practice guidelines for the diagnosis and treatment of Alzheimer's disease in a managed care setting: Part II–Pharmacologic therapy. Alzheimer's Disease (AD) Managed Care Advisory Council. *Manag Care Interface,* pp. 51-56.
Freitas, E.V., (2006). *Tratado de Geriatra e Gerontologia,* Guanabara Koogan 2nd edn., Rio de Janeiro.
Gapski, P.B. and Geromel, J.C. (1994). A convex approach to the absolute stability problem. *IEEE Trans. Automat. Contr.,* 25, 613-617.
Gil, D., Johnsson, M., Chamizo, J.M.G., et al. (2009). Application of artificial neural networks in the diagnosis of urological dysfunctions. *Expert Syst. Applic.,* 36(3), 5754-5760,
Hake, A.M, (2002). The Treatment of Alzheimer's Disease: The Approach from a Clinical Specialist in the Trenches. *Seminars In Neurology,* 22(1), 071-074.
Hopfield, J.J. (1984). Neurons with graded response have collective computational properties like those of two-state neurons. In *Proceedings of the National Academy of Sciences of the USA,* 81(10), 3088-3092.
Iyerngar, V. and Balagani, K. (2004). The Use of Artifical Neural Networks to Study and Improve Neural Synaptic Promoters and Connectivity in Alzheimer's Disease States. In *IEEE 4th Intern. Conference on Intelligent Syst. Design and Application,* pp. 525-530.
Kalman, R.E. (1963). Liapunov functions for the problem of Lurie in automatic control. *Proc. Natl. Acad. Sci.,* 49(8), 201-205.
Kaszkurewicz, E. and Bhaya, A. (1995). Comments on Necessary and Sufficient Condition for Absolute Stability of Neural Network. *IEEE Trans. Circ. Syst.,* 42, 497-499.
Krasovskii, N.N. (1953). On the stability of the solutions of a system of two differential equations (in Russian). *Prikl. Mat. i Mekh,* 17, 651-672.
Liao, X. and Yu, P. (2008). *Absolute Stability of Nonlinear Control Systems*, 2nd edn. Netherlands: Springer.
Lin, H., Wang, C., Tan, Y. (2020). Hidden extreme multistability with hyperchaos and transient chaos in a Hopfield neural network affected by electromagnetic radiation. *Nonlinear Dyn.,* 99, 2369-2386.
Lurie, A.I. and Postnikov, V.N. (1944) On the theory of stability of control systems (in Russian). *Prikl. Mat. i Mekh.,* 8(3), 246-248.
Mckhann, G., Drachman D., Folstein M., et al. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology,* 34(7), 939-944.
Monteiro, L.H.A. (2006). *Sistemas Dinâmicos.* Livraria da Física 2nd edn., São Paulo.
Morrison, M., Maia, P.D., Kutz, J.N. (2017). Preventing Neurodegenerative Memory Loss in Hopfield Neuronal Networks Using Cerebral Organoids or External Microelectronics. *Computational and Mathematical Methods in Medicine,* Article ID 6102494, 13 pages.
Pinheiro, R.F. (2015). The Lurie problem and applications to neural networks (in Portuguese). Master's thesis, USP, São Paulo.
Pinheiro, R.F. and Colón, D. (2019). An Application of the Lurie problem in Hopfield neural networks. In: Fleury A., Rade D., Kurka P. (eds) Proceedings of DINAME 2017. DINAME 2017, *Lecture Notes in Mechanical Engineering*, pp. 371-382. Springer, Cham.
Pinheiro, R.F., Colón, D. (2020). On the μ-Analysis and Synthesis of MIMO Lurie Type Systems with Application in Complex Networks *Circuits Syst Signal Process.* https://doi.org/10.1007/s00034-020-01464-0
Popov, V.M. (1961). Absolute stability of nonlinear systems of automatic control. *Rem. Control,* 22(8), 857-875.
Scheff, S.W., Price, D.A., Schmitt, F.A., et al. (2007). Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology* 68(18), 1501-1508.
Selkoe, D.J. (2001). Alzheimer's Disease: Genes, Proteins, and Therapy. *Physiological Reviews,* 81(2), 741-766.
Sergio, A.T., Braga, D.S., Buarque, L.N.F. (2009). Computational Modeling of Alzheimer's Disease Symptoms Using Venn's Network. In: CBRN 2009, *Anais do IX Congresso Brasileiro de Redes Neurais,* 8 pages. ABRICOM/SBIC, Ouro Preto.
Skogestad, S. and Postlethwaite, I. (2007). *Multivariable Feedback Control: Analysis and Design*, 2nd-edn. John Wiley and Sons. New York.
Swietlik, D. Bialowas, J., Morys, J., Kusiak, A. (2019). Computer Model of Synapse Loss During an Alzheimer's Disease-Like Pathology in Hippocampal Subregions DG, CA3 and CA1—The Way to Chaos and Information Transfer. *Entropy,* 21, 408.
Tabekoueng, N. Z., Kengne, J., Fotsin, H.B. (2020). Coexistence of Multiple Stable States and Bursting Oscillations in a 4D Hopfield Neural Network. *Circuits Syst Signal Process,* 39, 3424–3444.
Terry, R.D., (2000). Cell Death or Synaptic Loss in Alzheimer Disease. *Journal Of Neuropathology and Experimental Neurology,* 59(12), 1118-1119.
Thuraisingham, R.A. (2015). Dementia and Hopfield model. *J. Neural Transm.,* 122, 773–777.
Yu, X. and Liao, F. (2019). Preview tracking control for discrete-time nonlinear Lur'e systems with sector-bounded nonlinearities. *Transactions of the Institute of Measurement and Control,* 41(10), 2726-2737.
Zhou, C., Zeng, X. Yu, J., et al. (2016). A unified associative memory model based on external inputs of continuous recurrent neural networks. *Neurocomputing,* 186, pp. 44-53.