

## Review

## Generalized synchronization of regulate seizures dynamics in partial epilepsy with fractional-order derivatives

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## ABSTRACT

The dynamical behavior and the synchronization of epileptic seizure dynamics, with fractional-order derivatives, is studied in this paper. Knowing that the dynamical properties of ictal electroencephalogram signal recordings during experiments displays complex nonlinear behaviors, we analyze the system from chaos theory point of view. Based on stability analysis, the system presents three equilibrium points with two of them unstable. Moreover, the system reveals attractor points from the phase portrait analysis. In addition, the largest Lyapunov exponent displays positive values after a given period of time. These observations characterize a chaotic behavior of epileptic seizure dynamics. Therefore, based on the Ge-Yao-Chen partial region stability theory, the synchronization of the system is achieved and simulations prove that the control technique is very efficient. Further studies based on phase synchronization show that we are able to force infected population of neurons by epilepsy into synchronization with uninfected one through a coupling constant. In addition, based on the phase locking value time evolution (phase synchronization) of the system, we realize that fractional-order derivative induces quick synchronization compared to integer order derivative. These results might be very interesting from the medical point of view, because by applying the proposed control method, one may be able to regulate (or reduce) seizure amplitude which, if kindly implemented in practice, will provide excellent therapeutic solution to drug resistant patients with epilepsy.

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## 1. Introduction

The central nervous system (CNS) is subdivided in two main parts which are the spinal cord and the brain, both mainly made of basic unit called neurons and communicating each other through synapses. Electrical stimulation, even weak as possible, can cause neurons to spike, and spikes spreading in a wrong way may cause complex disorders in the brain most often known as epilepsy. It was demonstrated that, epilepsy is one of the most common neurological disorders, with an estimated prevalence of 1% people worldwide and more than 2% in families with low income [1,2]. However, in about 66% of population with epilepsy, scientists proved that although seizures cannot be stopped definitively, they can be satisfactorily controlled via antiseptic epileptic drugs or variety of surgical options. Amongst them, one denotes the close loop

neuromodulation which is a promising tool based on an accurate prediction of seizure occurrence [2].

Researchers have detected that epilepsy is originated from fast electrical discharge on the electroencephalogram (EEG) of the patient [3]. Based on this, the common way for epileptic diagnosis is through the analysis of the EEG [4]. Within the last three decades, it was proved, via interictal recordings, that seizures are preceded by detectable and measurable changes in the brain dynamics. These changes were associated with the existence of a transitional interictal activities into the preictal state [5,6]. This discovery widely motivates intense researches on the origin of seizures in the brain including seizure dynamics [7–10]. Therefore, by exploiting the phenomenological model called epileptor [11,12], seizure dynamics might be modeled using a set of five first-order differential equations with five state variables, subdivided into three groups: the first subset ( $x_1, y_1$ ), representing the fast electrical discharge on the EEG of the patient, the second subset ( $x_2, y_2$ ), slower than the first one, representing the spike wave event and finally the third variable  $z$ , known as the slowest, representing the permit-

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tivity coupling associated to the homeostatic regulation of the cell [13–16]. The above discovery highly motivated scientists to further study the dynamics of seizures. Thus, an EEG signal algorithm was developed by Chris et al. [17] using the theory of nonlinear dynamics. Comparing the results provided by analyzing signals generated from non-epileptogenic hippocampus and neocortex to those provided by analyzing the dynamical properties of EEG signals generated from epileptogenic focus, they revealed the conclusion that, epileptic brains repeatedly (intermittently) make abrupt transition into and out of the ictal state. This particular behavior is most often observed in nonlinear dynamical systems exhibiting chaotic behavior. Further to this observation, other studies based on Lyapunov theory provided that, epileptic seizure dynamics exhibits chaotic behavior. This statement is also supported by three main points which are: the nonlinearity in the ictal EEG signal, the positive sign of the Lyapunov exponents obtained by computation and finally the existence of spatiotemporal transition from interictal EEG dynamics to seizure activities [5].

Although many research works focus on understanding seizures, it still requires deep studies regarding its origin, as well as its dynamics. Some authors assimilated epileptic seizures to hypersynchronous electrical discharges on the EEG of the patient which somewhat contradicts the idea for which recurrent seizures are due to complex interactions between neuronal networks characterized by heterogeneity of neuronal firing. Therefore, a fundamental question emerges: do seizures precede synchronous activities of neurons or synchronization precedes seizures? The motivation in providing an answer to this question led researchers on epilepsy to pay particular attention to synchronous activities occurring in the brain. According to Penfield and Jasper [18], hypersynchronization is the most plausible cause of seizures. In fact, epileptic patterns imply a complexity of the mechanism underlying pathological synchronization, which has been identified in the hippocampus [19]. In addition, one also observes mutual excitations of neurons via excitatory recurrent collateral and depolarizing synapses including gap junctions, field effects and ionic changes [19]. Moreover, deep studies have shown that combination of excitatory and inhibitory neurons in a network is required to induce synchronized firing patterns [20,21]. In contrast to many authors who claim that seizures induce synchronization, it is obtained from deeper experiments that, seizures come before synchronous activities of neurons. It therefore seems like seizures induce synchronization which induces itself termination. Although research works on the topic made significant conclusions concerning this problem, understanding seizures dynamics remains a big challenge. This includes how the problem might be overcome from the patient brain. Therefore, several acceptable pharmacantiepileptic drugs have been proposed, but many patients remain resistant to those drugs. This may be due to lack of deep understanding of seizure dynamics from the theoretical point of view.

Taking into consideration the fact that the epileptor model exhibits chaotic behavior as we mentioned in the previous paragraph, we propose in this work, to examine the problem from chaos synchronization point of view, with application to two identically coupled epileptors with fractional-order derivatives. It was demonstrated that fractional-order differentiation can more efficiently contribute to stimulus anticipation and assessments of frequency phase shift of neurons compared to integer-order differentiation [22–25]. For this reason, Dong et al. [26] proved that by modeling neurons activities with fractional-order derivatives, the firing frequency is greater than that with integer-order derivatives. Moreover, due to its complexity, fractional-order differentiation may then better describe the dynamics of seizures in the brain. Indeed, with the memory effects and history dependence that fractional-order brings, the control systems have the possibil-

ity to use all of the past information for control and decision [27]. In our previous works, we proved that fractional-order derivative induces quick synchronization compared to integer-order differentiation [22,23]. The main motivation behind this work includes, but not limited to, the problem of seizure control. Whereas, we expect that, by making coupled epileptor models behave in the same way (synchronization), one may be able, in practice, to regulate seizure amplitudes as well as control seizures which may provide excellent solution to epileptic problem in the therapeutic point of view. That is, the synchronization is approached in this work by the Ge-Yao-Chen (GYC) partial region stability theory [28], which has been proved to be more efficient compared to existing control techniques.

The paper is structured as follows: after presenting the origin, cause and propagation of seizures in Section 2, we model epilepsy with five state variables, taking into account the fractional-order differentiation. The same section analyzes also the chaos properties of epileptor and provide stability analysis of the system. Section 3 presents the synchronization of identically coupled epileptors with different initial conditions using, the GYC partial region stability theory. Finally, some concluding remarks are presented in Section 4.

## 2. Mathematical model of epileptor

### 2.1. Description, cause and propagation of epileptic seizures in the brain

Seizure is a symptom referring to episodic excessive, recurrently and disorderly neuronal activity in the brain. Generally, seizures have been subdivided into two main groups which includes partial and generalized seizures [29,30]. By partial seizure, we mean abnormal neural activity, localized in a particular area of cerebral hemisphere and presenting a discernible focal or localized onset, while generalized seizure refers to simultaneous abnormal neural activity of the whole brain. However, this work deals with abnormal neural activity in the hippocampus, like the fast and recurrent electrical discharges on the EEG. That is the reason why partial seizure is our main concern in this paper noticing that, when a partial seizure becomes generalized, it is referred to as a partial seizure with secondary generalization. Partial seizure is also known as focal onset aware seizure. In addition, in patients with epilepsy, simple partial seizures are the most common type of seizures. However, complex partial epilepsy seizures occur more often than the simple one, although most of them start as simple partial seizure. It may be difficult to make difference between complex partial seizure and simple partial seizure in infants and patients with cognitive or speech difficulties as impairment in consciousness can be difficult to access in these patients.

Based on clinical signs, symptoms and EEG localization, simple partial seizure can be further subdivided into four types including: (i) focal motor seizures, (ii) focal sensory seizures, (iii) automatic seizures and (iv) psychological seizures [29]. Moreover, epilepsy is associated to a central nervous disorder in which brain activities become abnormal inducing seizures or periodic unusual sensations, behavior or consciousness. It has no identifiable cause in more than 50% of patients, while for some of them the condition may be due to various factors including, and no limited to, genetic influence. Researches on epilepsy linked some types to specific genes [29,30]. However, for most of the patients genes are only part of the cause. Here, we mean some genes can make some people more sensitive to environmental conditions that trigger seizures like head trauma, which may be a result of an accident or some traumatic injury. Furthermore, head conditions that cause damage to the brain such as tumors or strokes can trigger seizures. In some cases, infectious diseases such as meningitis,

AIDS and viral encephalitis may also induce seizures. Epilepsy may therefore be understood as developmental disorders like autism and neurofibromatosis. Even though several research works have been developed to understand epilepsy, no one is able to the best of our knowledge, to clearly explain its development, but some basic mechanism related to basic principles of normal neurophysiology have been proposed. Amongst them, one denotes the electrical signal in neurons that takes two forms which are the action potential, propagating down the axon of the neuron from the soma to the axon terminal, translocating information within a neuron and transmission of information between neurons accomplished by chemical synapses.

The process by which a partial seizure spreads within the brain occurs, when there is sufficient activation to recruit surrounding neurons leading to a loss of surround inhibition and spread of seizure activity into contiguous areas through cortical connections or via the corpus callosum. Indeed, the propagation of bursting activities is prevented by intact hyperpolarization and a region of surrounding inhibition induced by inhibitory neurons. Then, there is a recruitment of surrounding neurons through many mechanisms with sufficient neural activation. In fact, an increase in extracellular  $K^+$  which blunts the extent of hyperpolarizing outward  $K^+$  current depolarizing nearest neighboring neurons, an accumulation of  $Ca^{2+}$  in pre-synaptic terminals enhancing neurotransmitter release, a depolarization-induced activation of the *N-methyl-D-aspartate* (NMDA) subtype of the amino acid receptor causing more  $Ca^{2+}$  influx and activation, may provide deep explanation to the cause and propagation of partial seizure. Although significant works have been investigated in predicting and stopping seizures, it remains a big challenge as mentioned earlier. That is, we provide in this paper theoretical analysis of seizure dynamics expecting that it might enhance its understanding and we therefore suggest that one may instead of trying to stop, but control epileptic seizures in order to regulate its amplitude.

## 2.2. Epileptor as a dynamic multiscale model of seizures with five state variables with fractional-order derivatives

As already mentioned, the epileptor is a phenomenological model of partial seizures namely seizure-like-event (SLE). This model is related to neural discharges within a time-scale from 10 milliseconds to seconds and is related to some ionic current mechanisms producing negative feedback. The epileptor takes into consideration a slow permittivity variable for extracellular effects related to energy consumption and tissue oxygenation, a fast subsystem  $(x_1, y_1)$  describing the fast electrical discharges on the EEG during partial seizures, with the very shortest time scale, a slower subsystem  $(x_2, y_2)$  introducing the spike-wave events (SWE) within a shorter time scale. However, within a time scale quite greater than the previous ones, the evolution of the very slow variable  $z$  leads the neural population through seizures.

The first ensemble  $(x_1, y_1)$  is linearly inhibited by the second in order to have fast discharge only during the wave part of the SWE via a nonlinear function  $f_1(x_1, x_2)$ , while the second ensemble  $(x_2, y_2)$  is excited by the first one through a low-pass-filter coupling to generate simultaneously the SWE and the interictal spike via a function  $f_2(x_2)$ . Both systems are therefore, mutually coupled through the slow permittivity, via a function  $h(x_1)$  which only depends on  $x_1$  due to the fact that the first ensemble acts directly through the permittivity variable.

The fast subsystem is adapted to the usual Hindmarsh-Rose model and is given by Jirsa et al. [14]:

$$(S_1) : \begin{cases} \dot{x}_1 = \frac{1}{\tau_1} [y_1 - f_1(x_1, x_2) - z + I_{rest_1}], \\ \dot{y}_1 = y_0 - d_1 x_1^2 - y_1, \\ \dot{z} = \frac{1}{\tau_0} [r(s(x_1 - x_0) - z)], \end{cases} \quad (2.1)$$

and the slow subsystem, describing the spike-wave event, is modeled as follows [13]:

$$(S_2) : \begin{cases} \dot{x}_2 = -y_2 + x_2 - x_2^3 - e(z - f) + 2u(x_1) + I_{rest_2}, \\ \dot{y}_2 = \frac{1}{\tau_2} [-y_2 + f_2(x_2)], \end{cases} \quad (2.2)$$

where,

$$u(x_1) = k \int_{t_0}^t e^{-\gamma(\tau-t)} x_1(\tau) d\tau, \quad f_1(x_1, x_2) = \begin{cases} -ax_1^2 + bx_1^3, & \text{if } x_1 < 0, \\ (x_2 - c(z-d)^2)x_1, & \text{if } x_1 \geq 0, \end{cases} \quad \text{and } f_2(x_2) = \begin{cases} 0, & \text{if } x_2 < -\alpha, \\ \beta(x_2 + \alpha), & \text{if } x_2 \geq -\alpha. \end{cases} \quad (2.3)$$

Combining systems  $(S_1)$  and  $(S_2)$ , and taking into consideration Eq. (2.3), leads to the so-called epileptor:

$$\begin{cases} \dot{x}_1 = \frac{1}{\tau_1} [y_1 - f_1(x_1, x_2) - z + I_{rest_1}], \\ \dot{y}_1 = y_0 - d_1 x_1^2 - y_1, \\ \dot{x}_2 = -y_2 + x_2 - x_2^3 - e(z - f) + 2u(x_1) + I_{rest_2}, \\ \dot{y}_2 = \frac{1}{\tau_2} [-y_2 + f_2(x_2)], \\ \dot{z} = \frac{1}{\tau_0} [r(s(x_1 - x_0) - z)], \end{cases} \quad (2.4)$$

which is a system of five first order differential equations describing seizure dynamics in the brain. However, as previously mentioned, the system with fractional-order derivatives is more suitable for describing neuronal activities of the brain during seizure-like-events. Given that the system is dimensionless, taking the fractional-order differentiation on the left hand side does not affect the right hand side of Eq. (2.4). One obtains in fact, the generalization of Eq. (2.4) since it also contains integer-order derivative depending on the volume of the fractional-derivative parameter. This leads to the set of equations:

$$\begin{cases} D_t^\alpha x_1 = \frac{1}{\tau_1} [y_1 - f_1(x_1, x_2) - z + I_{rest_1}], \\ D_t^\alpha y_1 = y_0 - d_1 x_1^2 - y_1, \\ D_t^\alpha x_2 = -y_2 + x_2 - x_2^3 - e(z - f) + 2u(x_1) + I_{rest_2}, \\ D_t^\alpha y_2 = \frac{1}{\tau_2} [-y_2 + f_2(x_2)], \\ D_t^\alpha z = \frac{1}{\tau_0} [r(s(x_1 - x_0) - z)], \end{cases} \quad (2.5)$$

where the operator  $D_t^\alpha(\cdot)$  defines the fractional-order derivatives in the sense of Caputo [31,32], which, applied to a differentiable function  $f$  is written as:

$$D_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_{t_0}^t (t-\tau)^{n-\alpha-1} f^{(n)}(\tau) d\tau, \quad (2.6)$$

where  $0 < \alpha < 1$ ,  $n$  the next nearest integer to  $\alpha$ . In Eq. (2.4),  $x_1$  describes the membrane potential during the fast discharges,  $\tau_1$  the time constant determining the time interval where discharges occur in the brain, while  $x_2$  introduces the neuronal activity during SWE within the time interval  $\tau_2$ . The variables  $y_1$  and  $y_2$  introduce the recovery for the fast and slower subsystems respectively.  $z$  represents the activity dependent changes caused by homeostatic mechanisms of regulation of neuronal excitability. The time constants  $\tau_0$ ,  $\tau_1$  and  $\tau_2$  are such that,  $\tau_1 < \tau_2 < \tau_0$ . The parameter  $x_0$  is the resting membrane potential introducing the degree of epileptogenicity,  $I_{rest_1}$  and  $I_{rest_2}$  are, respectively, the resting current of the fast and slow subsystems. The parameters of Eq. (2.4) are chosen as follows:  $a = 3$ ,  $b = 1$ ,  $c = 0.6$ ,  $d = 5$ ,  $d_1 = 4$ ,  $e = 0.3$ ,  $f = 3.5$ ,  $r = 1$ ,  $s = 4$ ,  $\alpha = 0.25$ ,  $\beta = 1$ ,  $\gamma = 0.01$ ,  $k = 0.1$ ,  $x_0 = -1.6$ ,  $y_0 = 1$ ,  $I_{rest_1} = 3.1$ ,  $I_{rest_2} = 0.45$ ,  $\tau_0 = 2857$ ,  $\tau_1 = 1$ ,  $\tau_2 = 10$ , with the initial conditions  $x_{10}, y_{10}, x_{20}, y_{20}, z_0 = (0, -5, 0, 0, 3)$ . The time evolution of the state functions for the fast and slow subsystems including the slowest variable have been simulated and their behaviors are shown on Fig. 1(a), while Fig. 1(b) depicts the time evolution of the overall neuronal activity (or the local field potential) given by  $\psi(t) = x_1(t) + x_2(t)$ , where we can clearly observe seizure events.

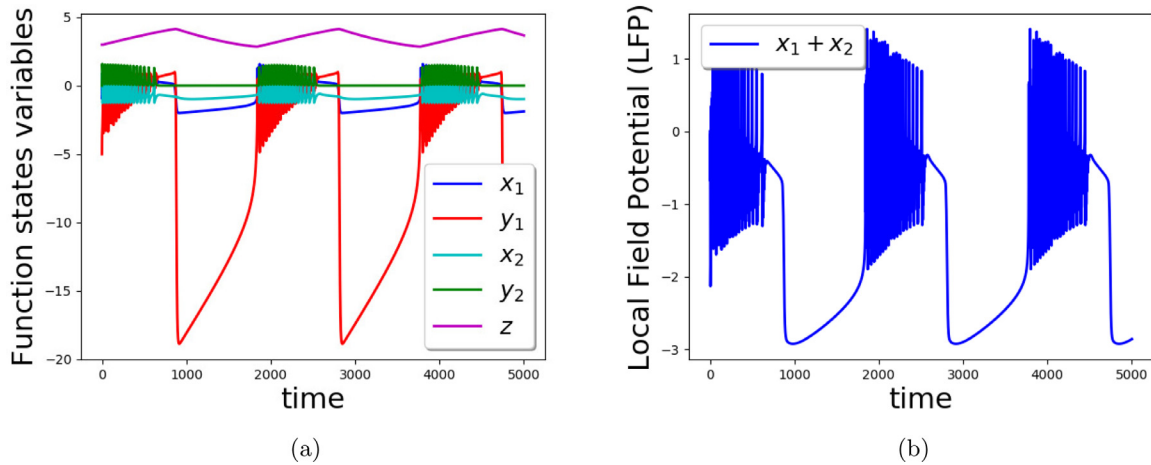


**Fig. 1.** Time evolution of the variable state functions of the epileptor with fractional-order derivatives (panel (a)) and the local field potential or the overall activity of the brain during seizures event (panel (b)), obtained for  $\alpha = 0.98$ , with initial conditions  $x_{10}, y_{10}, x_{20}, y_{20}, z_0 = (0, -5, 0, 0, 3)$ .

### 2.3. Stability analysis of the epileptor

Here, possible fixed points and their stability are studied in the epileptor model with fractional-order derivatives. For this reason, let us reconsider our system given by Eq. (2.5) and let  $E(x_1^e, x_2^e, y_1^e, y_2^e, z^e)$  be the equilibrium point of the considered system. Therefore, as well as integer-order derivatives, the fractional-order derivatives of the system state variables at this point is zero. This leads to:

$$\begin{cases} 0 = \frac{1}{\tau_1} [y_1^e - f_1(x_1^e, x_2^e) - z^e + I_{rest1}], \\ 0 = y_0 - d_1(x_1^e)^2 - y_1^e, \\ 0 = -y_2^e + x_2^e - (x_2^e)^2 - e(z^e - f) + 2u(x_1^e) + I_{rest2}, \\ 0 = \frac{1}{\tau_2} [-y_2^e + f_2(x_2^e)], \\ 0 = \frac{1}{\tau_0} [r(s(x_1^e - x_0) - z^e)], \end{cases} \quad (2.7)$$

where  $f_1(x_1^e, x_2^e)$  and  $f_2(x_2^e)$  are defined by Eq. (2.3). Further calculations on Eq. (2.7) lead to the following:

$$\begin{cases} \begin{cases} b(x_1^e)^3 + (d_1 - a)(x_1^e)^2 + sx_1^e - (sx_0 + y_0 + I_{rest1}) = 0, \\ (x_1^e)^3 - \frac{(2cd_1s - d_1 + 2cs^2x_0^2)}{cs^2}(x_1^e)^2 + \frac{(2csd + cd^2 + cs^2x_0^2 + s)}{cs^2}x_1^e - \frac{sx_0 + y_0 + I_{rest1} - x_2^e}{cs^2} = 0, \end{cases} & \forall x_1 \leq 0, \\ \begin{cases} (x_1^e)^3 - x_2^e - 2kx_1^e + es(x_1^e - x_0) - ef - I_{rest2} = 0, \\ (x_2^e)^3 + (\beta - 1)x_2^e + \beta\alpha - es(x_1^e - x_0) + ef - 2kx_1^e - I_{rest2} = 0, \end{cases} & \forall x_1 > 0, \end{cases} \quad (2.8)$$

The resolution of this equation provides that, the system does not have a fixed point  $\forall x_1 > 0$ , while for  $x_1 \leq 0$ , the system has two saddle points and one equilibrium point  $E_1$  given  $x_2 > -\alpha$ , with coordinates

$E_1(-0.751, 0.433, -1.820, 0.683, 3.396)$ . While it presents two equilibrium points for  $x_1 \leq 0$  and  $x_2 \leq -\alpha$ , which are  $E_2(-0.751, -0.747, -1.820, 0.000, 3.396)$  and  $E_3(-0.751, -0.389, -1.820, 0.000, 3.396)$ .

In order to study the stability of each equilibrium point, let us reconsider system (2.5) in the form  $D^\alpha X = JX$ , where  $J$  is the Jacobian matrix of the system at the equilibrium point  $X$ , a vector space defined so that  $X = [x_1, x_2, y_1, y_2, z]^T$ . For the equilibrium point  $E_1$ , the eigenvalues of the associated Jacobian matrix are given by:  $\lambda_1 = -3.598 + 0.869i$ ,  $\lambda_2 = -3.598 - 0.869i$ ,  $\lambda_3 = 0.168 + 0.167i$ ,  $\lambda_4 = 0.168 - 0.167i$  and  $\lambda_5 = -0.1$ . For the equilibrium point  $E_2$  one has:  $\lambda_1 = -3.598 + 0.869i$ ,  $\lambda_2 = -3.598 - 0.869i$ ,  $\lambda_3 = -0.492$ ,  $\lambda_4 = -0.355$  and  $\lambda_5 = -0.1$ . Finally for the equilibrium point  $E_3$ ,  $\lambda_1 = -3.598 + 0.869i$ ,  $\lambda_2 = -3.598 - 0.869i$ ,  $\lambda_3 = 0.289$ ,  $\lambda_4 = 0.157$  and  $\lambda_5 = -0.1$ .

By definition of fractional-order derivative systems [33], the epileptor model given by Eq. (2.5) is locally stable if and only

if there exist a critical real  $\alpha_c$  so that  $|\arg(\lambda)| \geq \frac{\pi}{2}\alpha_c$ , where  $\alpha_c$  denotes the order of the derivative,  $\lambda$  the eigenvalue of the associated Jacobian matrix. Therefore, considering the equilibrium point  $E_1$ , one has  $|\arg(\lambda_{1,2})| = 0.237$  corresponding to  $\alpha_c = 0.15$ , and  $|\arg(\lambda_{3,4})| = 0.37$  corresponding to  $\alpha_c = 0.498$ . For  $E_2$  and  $E_3$ , one has  $|\arg(\lambda_{1,2})| = 0.237$  corresponding to  $\alpha_c = 0.15$ . As a whole, having that the real part of  $\lambda_{3,4}$  are positive,  $E_1$  is a local unstable equilibrium point for all  $\alpha > \alpha_c = 0.498$ . This is similar for  $E_3$  since  $\lambda_{3,4,5}$  are positive. However, the equilibrium point  $E_2$  is found to be asymptotically stable for  $0 < \alpha < 1$ , due to the fact that  $\lambda_{3,4,5}$  and the real part of  $\lambda_{1,2}$  are negative. Further studies provide that, when the external current  $I_{rest1} > 1.2$  and  $|x_0| \leq 2.91$ , one get epileptic neurons exhibiting chaotic firing modes.

### 2.4. Chaos-based Lyapunov theory and phase portrait analysis of the system

Bifurcation diagrams and phase portraits are most often used to characterize the behavior (stable or unstable) of dynamical systems. However, the phase portrait shows how regions are occupied in the phase space. They are also used to detect any trace of chaos in a system. Fig. 2 depicts the phase portrait of the epileptor model with fractional-order derivatives. It reveals the presence of attractors with nonlinear characteristics as well as in the case of epileptor model with integer-order derivatives [17]. However, it is well known that Lyapunov Exponents (LEs) are very important tools to distinguish different kinds of behaviors occurring in dynamical systems. This subsection is therefore, devoted to its study regarding system (2.5) in order to characterize the degree of chaoticity of the system. LEs are often known as the generalization of eigenvalues of the Jacobian matrix of a flow. They indicate how two nearby trajectories diverge at global scale, via exponential growth rate norms of the fundamental matrix columns and via the singular values of the fundamental matrix. In addition, LEs display the evolution

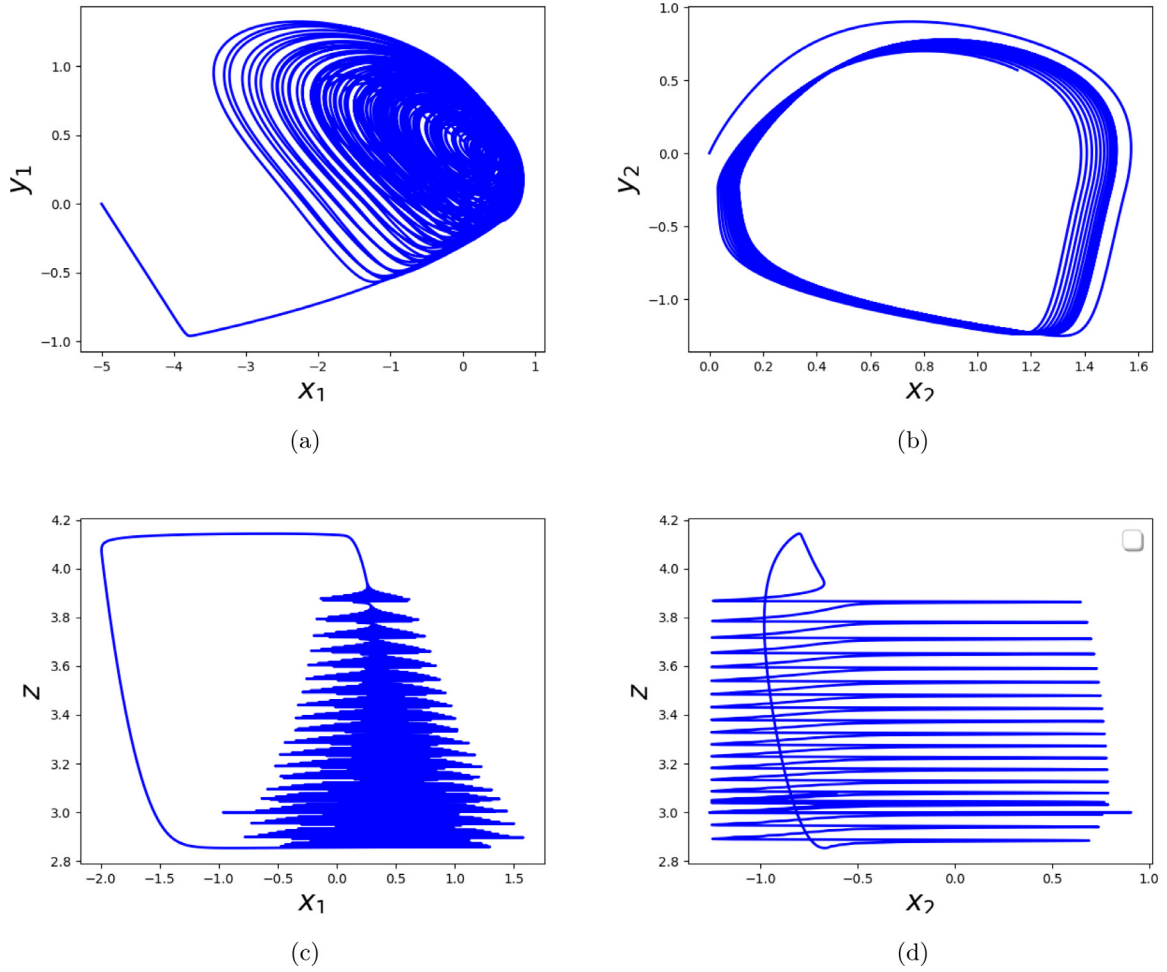


**Fig. 2.** Phase portraits of the epileptor with fractional-order derivatives obtained for  $\alpha = 0.98$ , with initial conditions  $x_{10}, y_{10}, x_{20}, y_{20}, z_0 = (0, -5, 0, 0, 3)$ .

in time of the initial conditions containing in an  $n$ -dimensional sphere centered at  $x_0$  with radius  $\delta_0$ . In the asymptotic limit, LEs can be evaluated in general using the formula:

$$\lambda_i = \lim_{t \rightarrow \infty} \frac{1}{t} \log \left( \frac{l_i(t)}{l_i(0)} \right) \quad \text{for } i = 1, \dots, n, \quad (2.9)$$

where  $l$  denotes the length of a principal axis of ellipsoid corresponding to the  $i$ th LE. It is noticed that, if one of the LEs is positive, then nearby trajectories diverge, inducing sensitivity of the system to initial conditions, which may be seen as chaotic ( $\lambda_i > 0$ ). It therefore, turns out that, to obtain LEs, one must average the local exponential growth over a long time (infinite time in theory). It was shown that the behavior of the ellipsoid is related to the sum of LEs, then the almost stability of the trivial response of system (2.5) can be obtained by the largest Lyapunov exponent (LLE)  $\lambda_i = \lambda_{\max}$ , i.e., when  $\lambda_{\max} < 0$ , the trivial solution is almost certainly stable and unstable otherwise [34–37].

However, in industry or in practice, the notion of infinite time sounds unreal and this leads researchers to develop new practical methods allowing the evaluation of LEs at finite time interval (i.e. local LEs). This must depend on initial conditions, as well as the time interval of integration [34–37]. This last notion was recently studied by Kuznetsov et al. [38,39] when studying the Rabinovich system describing the process of interaction between waves in plasma. They found that the existence of a characteristic time-scale might imply that finite time LEs determine chaotic transport. Furthermore, finite time LEs differ from infinite time ones and may be equal only in some systems such as the Arnold's map [40].

Therefore, given the importance of LEs, we are interested, in this work, to those of the epileptor model with fractional-order derivatives. Upon this, the evaluation of LEs of fractional systems differs from that with integer-order and is given by:

$$\lambda_\alpha(f) = \lim_{t \rightarrow \infty} \sup \left\{ \frac{1}{t^\alpha} \log_\alpha \|f(t)\| \right\}. \quad (2.10)$$

This was recently implemented in matlab by Denca and Kuznetsov [41] using the predictor-corrector-Adam-Bashforth-Moulton algorithm. Fig. 3 represents the largest Lyapunov exponent associated to system (2.5) which shows the route of the system from stable to unstable behavior which, exhibits chaos. In addition, Chris et al. [17] reported that by evaluating the LLE of the EEG signal recorded from the electrode site that participate to the ictal EEG discharge, one finds positive LE. They also provided that the estimated values of the LLE during seizures (ictal state) are most often lower than that before the onset of the ictal discharge (preictal state). These results confirm our hypothesis for which the epileptor model with fractional-order derivatives exhibits, as well as the model with integer-order derivatives, a chaotic behavior, since the LLE remains positive after some given intervals of time.

Up to now, we have been dealing with asymptotic (infinite time) LEs which are often used when the time interval is large enough. However, for small time intervals, the notion of asymptotic LE becomes obsolete and in this case, it is called local LEs or transient LEs. In practice, these exponents must be computed over finite time intervals and must depend on initial conditions, as well as the time of integration, and this is known as finite time LE

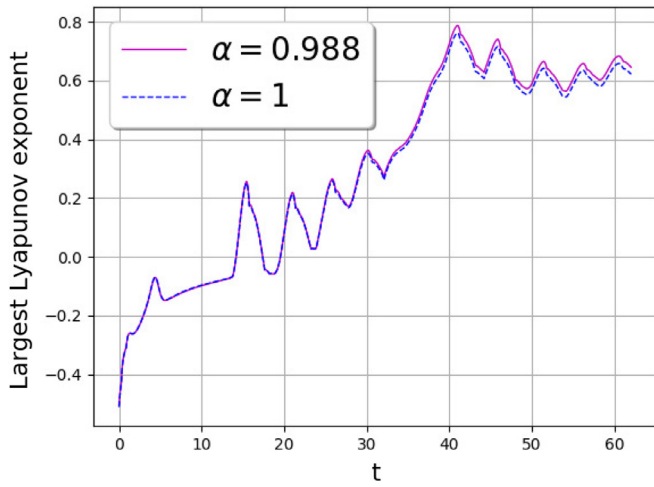


Fig. 3. Largest Lyapunov exponent of epileptor respectively for fractional- ( $\alpha = 0.98$ ) and integer- ( $\alpha = 1$ ) order derivatives.

[34–37]. That is why we have numerically computed in this work the LLE within a very short time interval. The next section of this paper is therefore devoted to the investigation of the synchronization of the system using the GYC partial region stability theory and explain how this can be useful or contribute in controlling seizure events or in reducing the amplitude of seizures occurring in patients with epilepsy.

### 3. Synchronization of regulate seizure dynamics with fractional-order derivatives

#### 3.1. Theory

Here, we study the synchronization of partial regulate seizures in the hippocampus, modeling its dynamics as a system of five differential equations with fractional-order derivatives. We expect that it may be helpful in controlling and regulating seizure amplitude. That is, the GYC partial region stability theory is of great interest for the purpose. Indeed, this theory consists in making the error dynamics always happen in the first quadrant, so that  $e_i \geq 0 \forall i = 1, \dots, n$ , with  $e_i$  the error dynamics. It was demonstrated that this control technique is more efficient compared to adaptive synchronization, lag synchronization, etc., as it induces less simulation error. It is easily implementable, and the Lyapunov function may be chosen as a simple linear function of error [28].

Let us reconsider the epileptor model with fractional-order derivatives given by Eq. (2.5), which is considered as the master (or drive) system, while the corresponding slave (or response) system is written as:

$$\begin{cases} D_t^\alpha x_{11} = \frac{1}{\tau_1} [y_{11} - f_1(x_{11}, x_{21}) - z_1 + I_{rest1}] + U_1(t), \\ D_t^\alpha y_{11} = y_0 - d_1 x_{11}^2 - y_{11} + U_2(t), \\ D_t^\alpha x_{21} = -y_{21} + x_{21} - x_{21}^3 - e(e_5) + 2u(x_{11}) + I_2 + U_3(t), \\ D_t^\alpha y_{21} = \frac{1}{\tau_2} [-y_{21} + f_2(x_{21})] + U_4(t), \\ D_t^\alpha z_1 = \frac{1}{\tau_0} [r(s(x_{11} - x_0) - z_1)], \end{cases} \quad (3.1)$$

where  $U_1(t)$ ,  $U_2(t)$ ,  $U_3(t)$ ,  $U_4(t)$  are the control inputs, implicitly time-dependent, to be kindly designed. The error dynamics between the driver and response systems is derived as follows:

$$\begin{cases} D_t^\alpha e_1 = \frac{1}{\tau_1} [e_2 - e_5 - (f_1(x_1, x_2) - f_1(x_{11}, x_{21}))] - U_1(t), \\ D_t^\alpha e_2 = -e_2 - d_1(x_1^2 - x_{11}^2) - U_2(t), \\ D_t^\alpha e_3 = -e_4 + e_3 - (x_2^3 - x_{21}^3) - e(e_5) + 2(u(x_1) - u(x_{11})) - U_3(t), \\ D_t^\alpha e_4 = \frac{1}{\tau_2} [-e_4 + (f_2(x_2) - f_2(x_{21}))] - U_4(t), \\ D_t^\alpha e_5 = \frac{1}{\tau_0} [rse_1 - re_5], \end{cases} \quad (3.2)$$

with  $e_1(t) = x_1(t) - x_{11}(t) + 100$ ,  $e_2(t) = y_1(t) - y_{11}(t) + 100$ ,  $e_3(t) = x_2(t) - x_{21}(t) + 100$ ,  $e_4(t) = y_2(t) - y_{21}(t) + 100$ ,  $e_5(t) = z(t) - z_1(t) + 100$ . The number 100 added is to make the error always happen in the first quadrant as to satisfy the GYC partial region stability condition. The control input  $U_1(t)$ ,  $U_2(t)$ ,  $U_3(t)$ ,  $U_4(t)$  are designed so that the nonlinear parts in the error dynamics cancel. In addition, the more the controller is nonlinear, the more it is robust. In the control theory, nonlinearity in the controller is helpful to avoid chattering phenomenon. By the GYC partial region stability theory, let the Lyapunov function be a simple linear function of error given by:

$$V(t) = e_1(t) + e_2(t) + e_3(t) + e_4(t) + e_5(t), \quad (3.3)$$

which is positively semi-defined given that  $e_i(t) > 0 \forall i = 1, \dots, 5$ . Thus, its fractional derivative is defined as:

$$\begin{aligned} D_t^\alpha V(t) &= \frac{1}{\tau_1} [e_2 - e_5 - (f_1(x_1, x_2) - f_1(x_{11}, x_{21}))] \\ &\quad - U_1(t) - e_2 - d_1(x_1^2 - x_{11}^2) - U_2(t) - e_4 \\ &\quad + e_3 - (x_2^3 - x_{21}^3) - e(e_5) + 2(u(x_1) - u(x_{11})) - U_3(t) \\ &\quad + \frac{1}{\tau_2} [-e_4 + (f_2(x_2) - f_2(x_{21}))] - U_4(t) \\ &\quad + \frac{1}{\tau_0} [rse_1 - re_5]. \end{aligned} \quad (3.4)$$

By kindly designing the control inputs as,

$$\begin{aligned} U_1(t) &= e_1 - \frac{1}{\tau_1} [(1 - \theta(x_1))(bx_1^3 - ax_{11}^2) \\ &\quad + \theta(x_1)(x_2x_1 - cx_1(z - d)^2)] \\ &\quad - \frac{1}{\tau_1} [(1 - \theta(x_{11}))(bx_{11}^3 - ax_{11}^2) \\ &\quad + \theta(x_{11})(x_{21}x_{11} - cx_{11}(z_1 - d)^2)], \end{aligned} \quad (3.5)$$

$$U_2(t) = e_2 - d_1(x_1^2 - x_{11}^2), \quad (3.6)$$

$$U_3(t) = 2e_3 - (x_2^3 - x_{21}^3) + 2(u(x_1) - u(x_{11})), \quad (3.7)$$

$$U_4(t) = e_4 + \frac{1}{\tau_2} [\theta(x_2)(\beta(x_2 - \alpha)) - \theta(x_{21})(\beta(x_{21} - \alpha))], \quad (3.8)$$

the fractional derivative of the Lyapunov function given by Eq. (3.4) becomes:

$$\begin{aligned} D_t^\alpha V(t) &= -(1 - \frac{rs}{\tau_0})e_1 - e_2 - e_3 - (2 + \frac{1}{\tau_2})e_4 \\ &\quad - (e + \frac{1}{\tau_1} + \frac{r}{\tau_0})e_5 \leq 0, \end{aligned} \quad (3.9)$$

since  $e_i \geq 0 \forall i = 1, 2, \dots, n$  (by the GYC partial region stability theory criteria) and  $\frac{rs}{\tau_0} < 1$ . The function  $\theta(x)$  stands for the usual Heaviside step function. Under the above conditions, we are sure that if well implemented in practice, one will be able to control the epileptor of Eq. (2.5). However, the synchronization scheme of this section is applied to two coupled identical epileptors with different initial conditions, which may be slightly limited due to the fact that in reality neurons are always in permanent interaction each other.

#### 3.2. Synchronization of N-coupled epileptors with fractional-order derivatives

To get further insight in the synchronization of seizure dynamics, we reconsider instead of Eq. (2.5) describing a single neuronal dynamics, the most realistic case consisting of N-coupled

epileptors with fractional-order derivatives. In other words, it is known from experiments that distant discharges at remote location are transmitted via axons to target region  $i$  perturbing their homeostatic equilibrium [15,42]. According to Timothee et al. [15], this disturbance of ions homeostasis will depend on adjacent and distant neuronal discharges as a coupling term influencing the rate of change of the permittivity variable  $z_i$  of population  $i$ . This is due to the fact that, the fast discharge acts directly on the permittivity variable which ensures the connectivity between cells in the brain. Considering these effects, a rich N-coupled epileptors system with fractional-order derivatives can be written as follows:

$$\begin{cases} D_t^\alpha x_{1,i} = \frac{1}{\tau_1} [y_{1,i} - f_1(x_{1,i}, x_{2,i}) - z_i + I_{rest1,i}], \\ D_t^\alpha y_{1,i} = y_0 - d_1 x_{1,i}^2 - y_{1,i}, \\ D_t^\alpha x_{2,i} = -y_{2,i} + x_{2,i} - x_{2,i}^3 - e(z_i - f) + 2u(x_{1,i}) + I_{rest2,i}, \quad \forall i = 1, \dots, N, \\ D_t^\alpha y_{2,i} = \frac{1}{\tau_2} [-y_{2,i} + f_2(x_{2,i})], \\ D_t^\alpha z_i = \frac{1}{\tau_0} [r(s(x_{1,i} + \sum_{j=i+1}^{N-1} K_{ij}(x_{1,i} - x_{1,j}) - x_{0,i}) - z_i)], \end{cases} \quad (3.10)$$

with  $f_1(x_{1,i}, x_{2,i})$  and  $f_2(x_{2,i})$  given by Eq. (2.2). The delay of transmission is not taken into consideration because, the dynamics of seizures is already slow enough to render these delays negligible. For the reason of simplicity, we assume each population of neurons to be receiving signals only from its nearest neighbors, and we assume that, backward propagation of seizures is neglected. We also consider the time-scales of each population of neurons to be equal to those of individual epileptor.

As previously, the synchronization is achieved by the GYC partial region stability theory. We assume system (3.10) (population (i)) to be the master (or driver) system and define the corresponding response system (population (j)) as:

$$\begin{cases} D_t^\alpha x_{1,j} = \frac{1}{\tau_1} [y_{1,j} - f_1(x_{1,j}, x_{2,j}) - z_{1,j} + I_{rest1,j}] \\ \quad + U_{1,j}(t), \\ D_t^\alpha y_{1,j} = y_0 - d_1 x_{1,j}^2 - y_{1,j} + U_{2,j}(t), \\ D_t^\alpha x_{2,j} = -y_{2,j} + x_{2,j} - x_{2,j}^3 - e(z_j - f) \\ \quad + 2u(x_{1,j}) + I_{rest2,j} + U_{3,j}(t), \\ D_t^\alpha y_{2,j} = \frac{1}{\tau_2} [-y_{2,j} + f_2(x_{2,j})] + U_{4,j}(t), \\ D_t^\alpha z_j = \frac{1}{\tau_0} [r(s(x_{1,j} + \sum_{i=j-1}^N K_{ji}(x_{1,j} - x_{1,i}) - x_{0,j}) - z_j)] \\ \quad + U_{5,j}(t). \end{cases} \quad \forall j = 2, \dots, N, \quad (3.11)$$

Through the similar procedure as in the case of single epileptor, we derive the error dynamics as:

$$\begin{cases} D_t^\alpha e_{1,ij} = \frac{1}{\tau_1} [e_{2,ij} - e_{5,ij} - (f_1(x_{1,i}, x_{2,i}) - f_1(x_{1,j}, x_{2,j}))] \\ \quad - U_{1,j}(t), \\ D_t^\alpha e_{2,ij} = -e_{2,ij} - d_1(x_{1,i}^2 - x_{1,j}^2) - U_{2,j}(t), \\ D_t^\alpha e_{3,ij} = -e_{4,ij} + e_{3,ij} - (x_{2,i}^3 - x_{2,j}^3) - e(e_{5,ij}) \\ \quad + 2(u(x_{1,i}) - u(x_{1,j})) - U_{3,j}(t), \\ D_t^\alpha e_{4,ij} = \frac{1}{\tau_2} [-e_{4,ij} + (f_2(x_{2,i}) - f_2(x_{2,j}))] - U_{4,j}(t), \\ D_t^\alpha e_{5,ij} = \frac{1}{\tau_0} [-s(x_{0,i} - x_{0,j}) + rse_{1,ij} \\ \quad + rs \sum_{l=j-1}^N K_{jl}e_{1,li} + rs \sum_{l=i+1}^{N-1} K_{jl}e_{1,li}] - U_{5,j}(t), \end{cases} \quad \forall i = 1, \dots, N, \quad (3.12)$$

with  $e_{1,ij} = x_{1,i} - x_{1,j} + 100$ ,  $e_{2,ij} = y_{1,i} - y_{1,j} + 100$ ,  $e_{3,ij} = x_{2,i} - x_{2,j} + 100$ ,  $e_{4,ij} = y_{2,i} - y_{2,j} + 100$ ,  $e_{5,ij} = z_i - z_j + 100$ ,  $i \neq j$ . Considering these equations, the Lyapunov function associated to these

N-coupled epileptors might be chosen as:

$$V(t) = \sum_{(i \neq j)=(1,2)}^{(N-1,N)} (e_{1,ij} + e_{2,ij} + e_{3,ij} + e_{4,ij} + e_{5,ij}), \quad (3.13)$$

which is assumed to be positively semi-defined since  $e_{l,ij} \geq 0 \forall l = 1, \dots, 5$ . With this assumption, we have:

$$\begin{aligned} D_t^\alpha V(t) = & \sum_{(i \neq j)=(1,2)}^{(N-1,N)} \left\{ \frac{1}{\tau_1} [e_{2,ij} - e_{5,ij} - (f_1(x_{1,i}, x_{2,i}) - f_1(x_{1,j}, x_{2,j}))] \right. \\ & - U_{1,j}(t) - e_{2,ij} - d_1(x_{1,i}^2 - x_{1,j}^2) - U_{2,j}(t) \\ & - e_{4,ij} + e_{3,ij} - (x_{2,i}^3 - x_{2,j}^3) - e(e_{5,ij}) + 2(u(x_{1,i}) \\ & - u(x_{1,j})) - U_{3,j}(t) + \frac{1}{\tau_2} [-e_{4,ij} + (f_2(x_{2,i}) - f_2(x_{2,j}))] \\ & - U_{4,j}(t) + \frac{1}{\tau_0} [-s(x_{0,i} - x_{0,j}) + rse_{1,ij} \\ & \left. + rs \sum_{l=j-1}^N K_{jl}e_{1,li} + rs \sum_{l=i+1}^{N-1} K_{jl}e_{1,li}] - U_{5,j}(t) \right\}, \end{aligned} \quad (3.14)$$

By kindly selecting the controller analogically as in the case of single epileptors, we write  $\forall i = 1, \dots, N-1, i \neq j$ ,

$$\begin{aligned} U_{1,j}(t) = & e_{1,ij} - \frac{1}{\tau_1} [(\theta(x_{1,i}) - 1)(bx_{1,i}^3 - ax_{1,i}^2) \\ & + \theta(x_{1,i})(x_{2,i}x_{1,i} - c(z_i - d)^2)] \\ & - \frac{1}{\tau_1} [(\theta(x_{1,j}) - 1)(bx_{1,j}^3 - ax_{1,j}^2) \\ & + \theta(x_{1,j})(x_{2,j}x_{1,j} - c(z_j - d)^2)], \end{aligned} \quad (3.15)$$

$$U_{2,j}(t) = e_{2,ij} - d_1(x_{1,i}^2 - x_{1,j}^2), \quad (3.16)$$

$$U_{3,j}(t) = 2e_{3,ij} - (x_{2,i}^3 - x_{2,j}^3) + 2(u(x_{1,i}) - u(x_{1,j})), \quad (3.17)$$

$$U_{4,j}(t) = e_{4,ij} + \frac{1}{\tau_2} [\theta(x_{2,i})(\beta(x_{2,i} - \alpha)) - \theta(x_{2,j})(\beta(x_{2,j} - \alpha))], \quad (3.18)$$

$$U_{5,j}(t) = \frac{1}{\tau_0} [-s(x_{0,i} - x_{0,j}) + rs \sum_{l=j-1}^N K_{jl}e_{1,li} + rs \sum_{l=i+1}^{N-1} K_{jl}e_{1,li}], \quad (3.19)$$

and we get,

$$D_t^\alpha V(t) = \sum_{(i \neq j)=(1,2)}^{(N-1,N)} \left[ -\left(1 - \frac{rs}{\tau_0}\right)e_{1,ij} - e_{2,ij} - e_{3,ij} - \left(2 + \frac{1}{\tau_2}\right)e_{4,ij} - \left(1 + e + \frac{r}{\tau_0}\right)e_{5,ij} \right] \leq 0, \quad (3.20)$$

which is negatively semi-defined since  $e_{li} \geq 0 \forall l = 1, \dots, 5, i = 1, \dots, N$ ,  $e, r$  and  $s$  are all positive,  $\tau_0, \tau_1$  and  $\tau_2$  are the time constants so, positive too.

### 3.3. Controlling seizures dynamics: measure of synchronization via phase locking value (PLV)

We focus on the synchronization of coupled epileptor models with fractional-order derivatives. We have shown in Section 3.1 using the usual GYC partial region stability theory, that under the controller inputs  $U_1(t)$ ,  $U_2(t)$ ,  $U_3(t)$  and  $U_4(t)$ , we were able to

achieve the synchronization of two identical uncoupled epileptors. Although the technique used is very suitable, we cannot exactly determine how strong both signals are closer one to another. Since, we are interested on the propagation and control of seizure dynamics, two types of populations of neurons are considered: the first population supposed infected by epilepsy and the second population healthy. We propose to analyze the propagation and control of seizure dynamics from population (i) to population (j) based on phase synchronization. To achieve this, we consider neuron (1) of population (i) and neuron (2) of population (j), i.e.,  $i = 1$  for Eq. (3.10) and  $j = 2$  for Eq. (3.11), respectively. Additionally, we also consider for the reason of simplicity,  $K_{12} = 0$  and  $K_{21} = K$ . Indeed, phase synchronization is a technique essentially based on making the phases of two chaotic systems, with different initial conditions behave similarly. This implies that two populations of neurons, showing activities of different oscillators, might present related properties (phase) [43–46]. There exist several measures of phase synchronization. Among them, one denotes the mainly used, which is Phase Locking Value (PLV) evaluation, also known as mean phase coherence [47]. In fact, the PLV is an important measure of synchronization of neural activities. It was shown that the phase locking between the activity of primary and secondary motor areas can be related to the coordinated antagonistic muscles [48]. It measures the instantaneous phase difference of two signals that may be connected or which instantaneous phase evolves together. In this case, both signals are said to be locked and their difference is constant. This implies that, if we consider two signals  $\Psi_1(t)$  and  $\Psi_2(t)$  with their corresponding phases  $\Phi_1(t)$  and  $\Phi_2(t)$ , one has,  $|\Phi_2(t) - \Phi_1(t)| \leq \text{constant}$ . Below is presented a brief description of mathematical evaluation of PLV of two coupled epileptors. Let us then, reconsider Eqs. (3.10) and (3.11) and limit ourselves to two neurons, one from infected population (i) (i.e.  $|x_{0,1}| < 2.91$ ) and the other from healthy population (j) (i.e.  $|x_{0,2}| > 2.91$ ) both connected through a coupling constant  $K$ , with  $x_0$  the neuron excitability parameter which is well defined in Section 2. Let us therefore, define the local field potential (or overall activity) of neurons (1) and (2) as  $\Psi_1(t) = x_{1,1}(t) + x_{2,1}(t)$  and  $\Psi_2(t) = x_{1,2}(t) + x_{2,2}(t)$ , respectively. The main goal is to evaluate how strong should be the coupling  $K$  for both populations to behave similarly (or synchronize) under the controller inputs  $U_{1,2}(t)$ ,  $U_{2,2}(t)$ ,  $U_{3,2}(t)$ ,  $U_{4,2}(t)$ ,  $U_{5,2}(t)$  as defined by Eqs. (3.15)–(3.19), and further study the effects of the order of the derivative on the speed of synchronization. The approach is to evaluate the PLV associated to the phase difference between neurons (1) and (2). Let  $\Phi_1(t)$  and  $\Phi_2(t)$  be the phase associated to the activities  $\Psi_1(t)$  of neuron (1) and  $\Psi_2(t)$  of neuron (2), respectively. From each signal, the instantaneous phase should be extracted. This is done by means of a narrow-band pass filtering or equivalently the convolution with narrow band complex Wavelet such as that of Morlet [49]. Considering this transformation for each signal, one obtain:

$$BP\{\Psi_1(t)\} = \text{Ibrace}\Psi_1(t)\}_{BP,H} = \{\Psi_1(t)\}_{BP} + \{\Psi_1(t)\}_H = A_1(t) \exp(-j\Phi_1(t)),$$

and

$$BP\{\Psi_2(t)\} = \{\Psi_2(t)\}_{BP,H} = \{\Psi_2(t)\}_{BP} + \{\Psi_2(t)\}_H = A_2(t) \exp(-j\Phi_2(t)),$$

where  $BP$  stands for band-pass,  $H$  for Hilbert, with  $\{\Psi_1(t)\}_H = j\tilde{\Psi}_1(t)$  and  $\{\Psi_2(t)\}_H = j\tilde{\Psi}_2(t)$ , representing the Hilbert transforms of  $\Psi_1(t)$  and  $\Psi_2(t)$ , respectively.  $A_1(t)$  and  $A_2(t)$  stand for the amplitudes of the signals. The instantaneous phase corresponds therefore to the angle between the real and the imaginary parts of the Hilbert analytical signal or alternatively the angle between the original signal and its Hilbert transform, i.e.,

$$\Phi_1(t) = \arctan\left\{\frac{\tilde{\Psi}_1(t)}{\Psi_1(t)}\right\}, \quad (3.21)$$

$$\Phi_2(t) = \arctan\left\{\frac{\tilde{\Psi}_2(t)}{\Psi_2(t)}\right\}, \quad (3.22)$$

where  $\tilde{\Psi}_1(t)$  and  $\tilde{\Psi}_2(t)$  are defined by:

$$\tilde{\Psi}_1(t) = \frac{1}{\pi} p.v \int_{-\infty}^{+\infty} \frac{\Psi_1(\tau)}{t - \tau} d\tau, \quad (3.23)$$

and

$$\tilde{\Psi}_2(t) = \frac{1}{\pi} p.v \int_{-\infty}^{+\infty} \frac{\Psi_2(\tau)}{t - \tau} d\tau. \quad (3.24)$$

with  $p.v$  standing for Cauchy principal values. Considering Eqs. (3.21) and (3.22), the instantaneous phase locking value corresponding to activities of neurons (1) and (2) is given by:

$$PLV(t) = \frac{1}{N} \left| \sum_{k=0}^{N-1} \exp\{-j(\Phi_2(t, k) - \Phi_1(t, k))\} \right| \\ = \frac{1}{N} \sqrt{\left[ \sum_{k=0}^{N-1} \cos(\Phi_2(t, k) - \Phi_1(t, k)) \right]^2 + \left[ \sum_{k=0}^{N-1} \sin(\Phi_2(t, k) - \Phi_1(t, k)) \right]^2}. \quad (3.25)$$

From this expression, it is obvious that  $PLV(t) \in [0,1]$ . Complete synchronization corresponds to  $PLV(t) \rightarrow 1$ , while desynchronization corresponds to  $PLV(t) \rightarrow 0$  as the time increase. Therefore, populations (i) and (j) behaviors are similar during their evolution in time, when  $PLV(t) \rightarrow 1$ . That means, one may be able to control seizure dynamics in patients with epilepsy if the above condition is satisfied.

### 3.4. Numerical results and discussion

All the numerical simulations have been carried out using the Adam-Basforth-Moulton method, with the integration time step of 0.01.

Fig. 4 depicts the phase portraits of the error dynamics for two coupled epileptors with fractional-order derivatives as given by Eqs. (3.10) (master system or neuron (1)) and (3.11) (slave system or neuron (2)) showing how the error system occupies the phase space. It is observed from this figure that, all errors always happen in the first quadrant, then positive, which is the necessary and sufficient condition for the GYC partial region stability theory. In addition, regarding Fig. 5 representing the time evolution of the errors state functions, it is observed that under controller inputs  $U_{1,j}(t)$ ,  $U_{2,j}(t)$ ,  $U_{3,j}(t)$ ,  $U_{4,j}(t)$  and  $U_{5,j}(t)$ , as given by Eqs. (3.15)–(3.19), each error goes to zero when the time increases, implying that by kindly implementing these controller inputs, we are able to control or synchronize two uncoupled epileptors with fractional-order derivatives as well as those with integer-order derivative. This result may be very important in practice as it might provide very good therapeutic solutions to drug resistant patients with epilepsy, by building an electronic model which may be forced into synchronization with the nonlinear signal recorded from patient's EEG displaying seizure-like events, in particular or in the area of the brain infected by epilepsy, in general. Doing that, one may then, be able to regulate seizures amplitudes. This achievement is confirmed by Fig. 6 depicting the synchronization of systems (3.10) and (3.11).

Interestingly, both systems perfectly synchronize over a very short range of time. Meanwhile, further studies are made in this work to model the dynamical behaviors of  $N$ -coupled neural networks as shown by Eqs. (3.10) and (3.11), based on phase synchronization, but for simplicity, we limited ourselves to two coupled epileptors, i.e.,  $N=2$  for our simulations. We considered

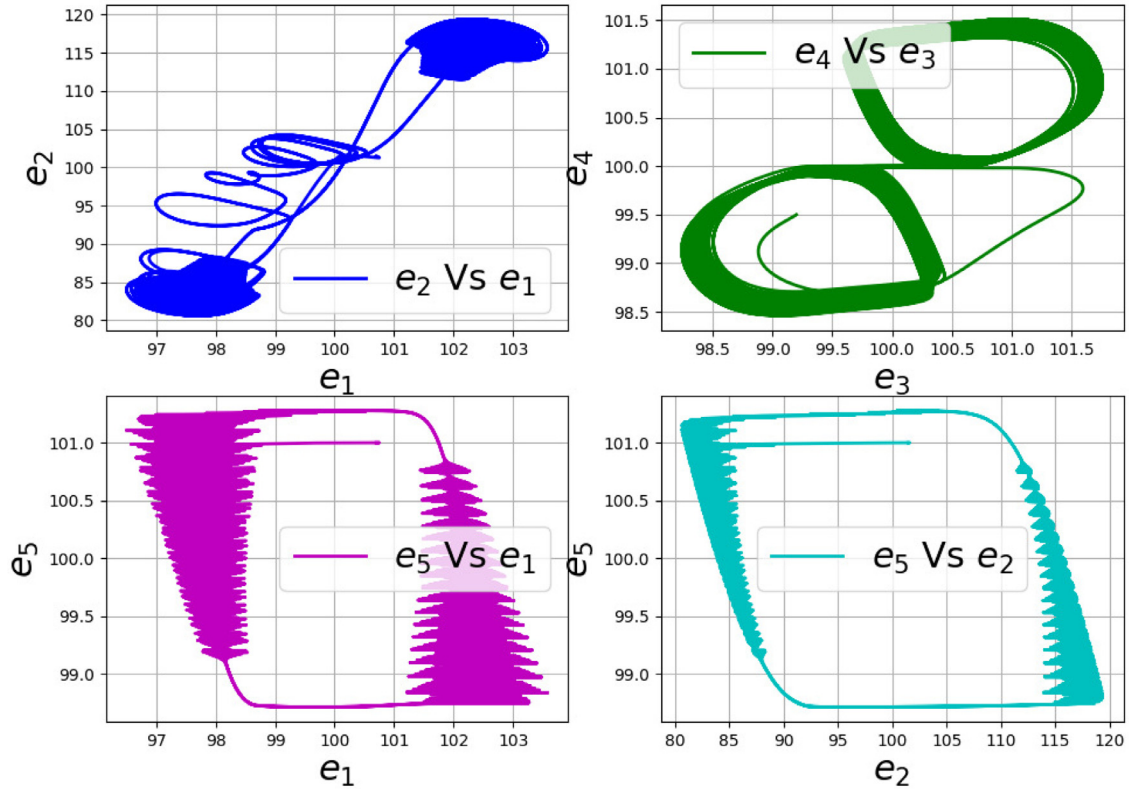


**Fig. 4.** Phase portrait of the error dynamics between two identically coupled epileptors with fractional-order derivatives ( $\alpha = 0.98$ ) taking as initial conditions  $x_{1,0}, y_{1,0}, x_{2,0}, y_{2,0}, z_0, x_{11,0}, y_{11,0}, x_{21,0}, y_{21,0}, z_{1,0} = (0, -5., 0, 0, 3., 0, 0.7, -3, -0.8, -0.5, 4)$ , the coupling constant  $K = 0.7$ .

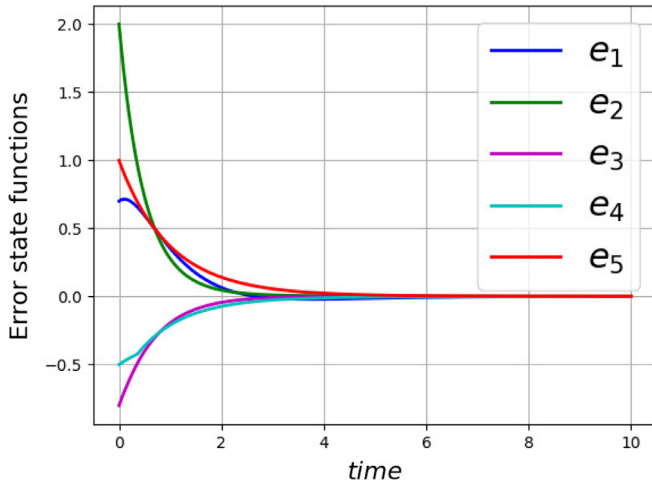


**Fig. 5.** Time history of the error state function of two identically coupled epileptors with fractional-order derivatives ( $\alpha = 0.98$ ), the coupling constant  $K = 0.7$  under the following initial conditions,  $x_{1,0}, y_{1,0}, x_{2,0}, y_{2,0}, z_0, x_{11,0}, y_{11,0}, x_{21,0}, y_{21,0}, z_{1,0} = (0, -5., 0, 0, 3., 0, 0.7, -3, -0.8, -0.5, 4)$ .

the first population to be infected by epilepsy (meaning that, in Eq. (3.10), we consider  $|x_{01}| < 2.91$ ) which, as we mentioned earlier, is the excitability parameter, chosen so that the epileptor shows seizure activities autonomously and is said to be epileptogenic and the epileptor is in its (healthy) equilibrium state for the value of  $|x_{02}| > 2.91$ , which is the case for the second population. Upon this assumption, we expect both populations, with different initial conditions  $x_{1,0}, y_{1,0}, x_{2,0}, y_{2,0}, z_0, x_{11,0}, y_{11,0}, x_{21,0}, y_{21,0}, z_{1,0} = (0, -5., 0, 0, 3., 0, 0.7, -3, -0.8, -0.5, 4)$ , to behave similarly as the time increases if the control inputs  $U_{1j}(t), U_{2j}(t), U_{3j}(t), U_{4j}(t)$  and

$U_{5j}(t)$  are applied. Under these conditions, we evaluated the Local Field Potential (LFP) associated to the activity of each neuron ( $\Psi_1(t) = x_{1,1}(t) + x_{2,1}(t)$  for neuron (1) and  $\Psi_2(t) = x_{1,2}(t) + x_{2,2}(t)$  for neuron (2), respectively). We simulated the PLV as defined in Section 3.3 associated to both activities as a function of the coupling constant  $K_{21} = K$ , given that  $K_{12} = 0$ . In an ideal case, where the evolution of the synchronization with respect to the coupling constant was linear, the expected graph would be a straight line from zero (no coupling) to 1 (strong coupling). In this case, there is perfect synchronization. However, Fig. 7 shows that the behavior of the PLV is nonlinear with respect to the coupling. It turns out from this figure that, the PLV increases and tends to 1 when the coupling becomes strong. This result is extremely important as it shows that there is a kind of information transfer between both populations through the coupling constant  $K$ . In the theory of control point of view, one can confirm that, using suitable values of the coupling constant  $K$ , we are able to control epileptic crisis. In addition, this figure is typically showing that as the coupling constant increases, a healthy population of neurons might become infected and vis-versa. Furthermore, to obtain more insights on the contribution of the order of the derivative, we simulated the behavior of PLV with respect to time as a function of  $\alpha$  the derivative order which is represented by Fig. 8.

We observe that the PLV, for  $\alpha = 0.92$ , as well as that for  $\alpha = 0.96$  (fractional-order derivatives epileptor), goes more quickly to 1 as the time increases compared to the PLV for  $\alpha = 1$  (integer-order epileptor). This observation is quite interesting and probably one of the main results of this work, since it is actually confirming our prediction for which fractional-order differentiation induces quick synchronization, compared to integer-order. Similar results were found in our previous contributions on the synchronization of the Hindmarsh-Rose neuronal model, where by simulating the synchronization time of the system for different values

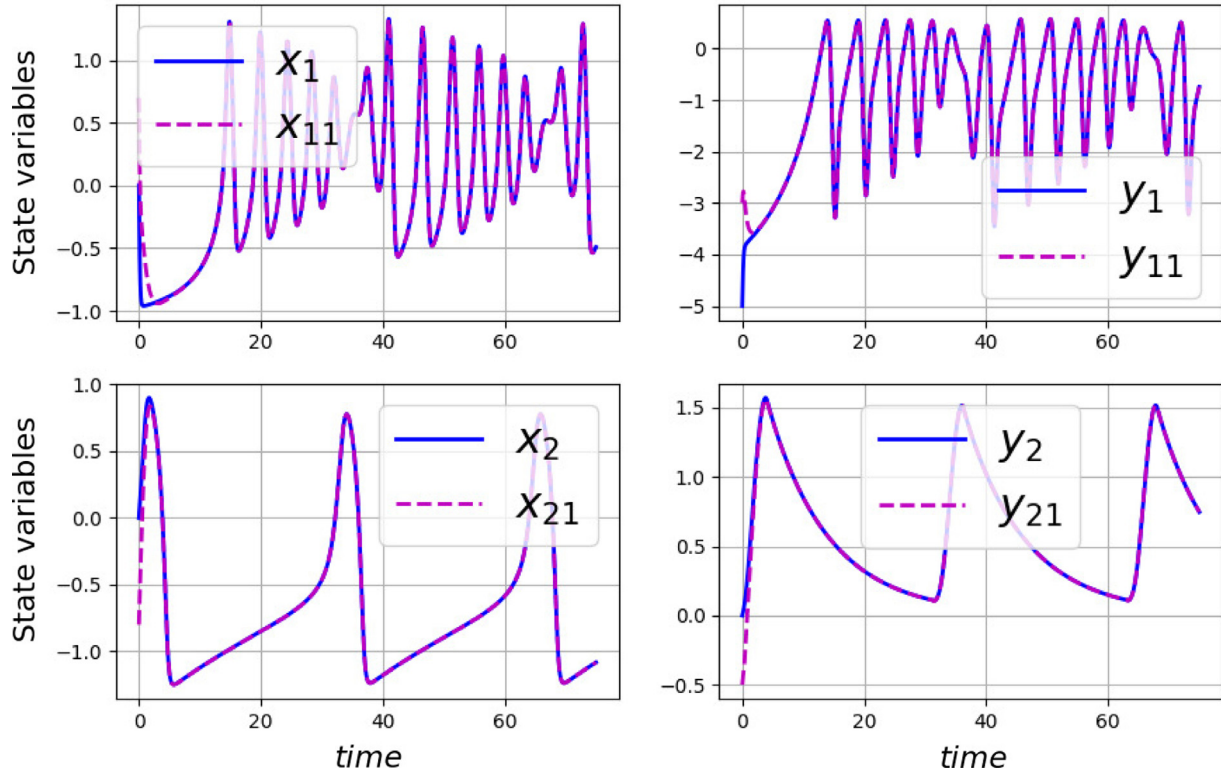


**Fig. 6.** Generalized synchronization of two identically coupled epileptors with fractional-order derivatives ( $\alpha = 0.98$ ) with the initial conditions  $x_{1,0}, y_{1,0}, x_{2,0}, y_{2,0}, z_0, x_{11,0}, y_{11,0}, x_{21,0}, y_{21,0}, z_{1,0} = (0, -5., 0, 0, 3., 0, 0.7, -3, -0.8, -0.5, 4)$ , the coupling constant  $K = 0.7$ . The synchronization is achieved by the GYC partial region stability theory under the controller inputs  $U_{1j}(t), U_{2j}(t), U_{3j}(t), U_{4j}(t)$  and  $U_{5j}(t)$ , as given by Eqs. (3.15)–(3.19).

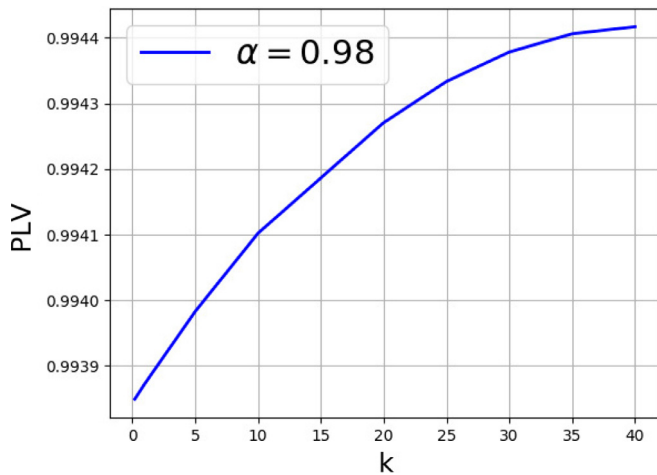


**Fig. 7.** Synchronization measure through Phase Locking Value (PLV) with respect to the coupling constant between two epileptors with fractional-order derivatives ( $\alpha = 0.98$ ).

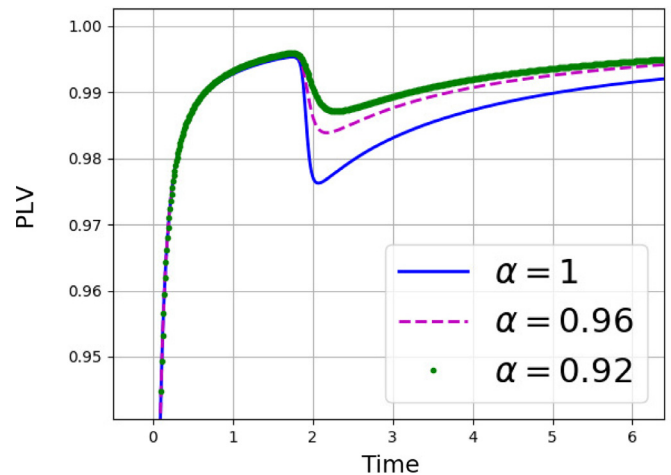


**Fig. 8.** Time evolution of the Phase Locking Values (PLV) as synchronization measurement between coupled epileptors for different order of the derivative: the dot line corresponds to  $\alpha = 0.92$ , the dash line to  $\alpha = 0.96$  and the solid line to  $\alpha = 1$  (epileptor with integer-order derivatives).

of the derivative order, we discovered that as the order of derivative decreases, the synchronization time (time where two signals get into synchronization) decreases too [22,23]. Practically, this result means that fractional-order differentiation provides better interpretation and excellent advantage of neural networks activities. Moreover, as epilepsy requires randomly and persistence occurrence of seizures from a particular region of the brain before spreading to other regions, the notion of time becomes very interesting when looking for treatment. In that respect, by modeling seizures

with fractional-order derivatives, this may provide some quick solutions which in most of the cases will help in avoiding drug resistant patients with epilepsy.

#### 4. Concluding remarks

In summary, the generalized synchronization of partial seizure dynamics, with fractional-order derivatives, has been investigated. Two main goals have been addressed: (i) we have proposed our

selves to show that epileptic seizure dynamics with fractional-order derivatives may display chaotic behaviors. Since several experiments proved that dynamical properties of EEG recordings from patients with epilepsy display complex nonlinear behaviors, we have therefore studied epileptic seizure dynamics from chaos theory point of view. To achieve this, the usual Lyapunov theory has been used and we have observed, from the stability analysis, that the system presents three equilibrium points, where two of them are unstable. The LLE has been simulated and we have realized that it increases from negative to strictly positive values after a given period of time. In addition, phase portraits analysis displays attractor points. From these three main observations, we can conclude effectively that epileptic seizure dynamics, with fractional-order derivatives, exhibits chaotic behaviors. (ii) We had to prove that by achieving the synchronization of epileptic seizure dynamics, we may be able to control the system, which might provide therapeutic solutions to the disease. For this reason, we have modeled the system as  $N$ -coupled populations of neurons and have focused on two of them, where we considered the first population to be infected by epilepsy and the second population to be healthy. Based on the generalized GYC partial region stability theory, we have realized the synchronization of both populations under the control inputs  $U_{1j}(t)$ ,  $U_{2j}(t)$ ,  $U_{3j}(t)$ ,  $U_{4j}(t)$  and  $U_{5j}(t)$ , kindly designed. We have also evaluated the PLV, which measures the phase synchronization of both populations and simulated its behaviors with respect to the coupling constant on one hand, and with respect to the time for different values of derivative order, on the second hand. Two main effects have been detected: (1) The PLV increases with the coupling constant from zero (no coupling) to 1 (strong coupling), meaning that under our controller inputs, we have been able to make infected population of neurons behave as the healthy one. This result may find interesting applications in medicine as it may be applied to regulate the seizure amplitude in epileptic drug resistant patients. (2) The time evolution of the PLV tends more quickly to 1 (perfect synchronization) when we decrease the value of  $\alpha$  implying that if therapeutic solutions to epilepsy disease is to be considered based on control theory, we strongly recommend experimentalists to model epileptic seizure dynamics with fractional-order derivatives as it will provide quick synchronization compared to integer-order derivative. Similar results were also found in our previous investigations on the Hindmarsh-Rose neuronal model [22,23] when computing the approximated synchronization time for different values of the order parameter. However, we mainly focused on two populations of neurons in our investigations and we considered both populations to be communicating only through the slowest variable related to the homeostatic equilibrium. It might then be of interests to consider a case where more than two populations of neurons interact via potential activities, which is the concern of a forthcoming work.

### Declaration of Competing Interest

None.

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