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Modeling Focal and Multi-focal Epilepsy as a Qualitative Resonance in Networks of Chaotic Oscillators

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Abstract. We propose a modeling framework for (multi-) focal epilepsy aimed at identifying the most probable epileptic foci. We model the brain as an ensemble of neuronal macro-areas, each with electrical activity described by a chaotic oscillator. The connection strengths are normalized to obtain an asynchronous, complex (chaotic and high-dimensional) seizure-free activity. Seizures manifest as a resonance phenomenon, in which one (or more) oscillator receives a periodic stimulus (the elaboration of an external stimulus in reflex epilepsies, or the result of functional disorders or lesions), resonates with it, thus lowering the complexity of its behavior by following the stimulus, and passes the stimulus through the connections. As a result, part or the entire network tends to synchronize on a less complex (periodic-like and low-dimensional) regime, and by stimulating different oscillators one can identify the macro-areas most prone to act as epileptic foci. We exploit the "qualitative resonance" typical of oscillators with chaotic behavior organized by a homoclinic bifurcation (Shil'nikov-like chaos, as observed in reconstructed and modeled epileptic attractors). We test our framework on a simple network of three (e.g. frontal-parietal-occipital) Colpitts oscillators. Although further testing, with different oscillators and networks, seems promising, here we provide only qualitative results. Future developments will make use of more realistic neural mass models, EEG, MEG, or fMRI connectivity information, and will be tested against clinical data.

Keywords: Colpitts oscillator, Epilepsy, Homoclinic chaos, Networks of oscillators, Qualitative resonance, Synchronization.

1. Introduction

Epileptic seizures are classified into focal and multifocal depending on whether there is one or several (small) portions of the brain, typically in the cerebral cortex (foci), that serve as the "irritant" driving the epileptic response (see, e.g. [Berg et al., 2010]). They may arise spontaneously, as a result of functional disorders or lesions, or be triggered by an external stimulus (reflex epilepsy—photosensitive being the most common type [Berg et al., 2010]).

The nonlinear time-series analysis of human EEG [1] recordings (pioneered in [Babloyantz and Destexhe, 1986; Freeman, 1987]; see [Stam, 2005] for a review) suggests the normal (seizure-free) cortical activity to be chaotic, relatively high-dimensional (above ten during the awake stage—alpha waves—and REM[1] sleep; around 5 during deep sleep), and asynchronous across cortex macro-areas. By contrast, EEG recordings during seizure show remarkable synchrony on low-dimensional (periodic-like) attractors, characterized by a reduced mean frequency (around 3 Hz with respect to 10 Hz seizure-free mean frequency) and by repeated peak-wave cycles (a minor bursting activity followed by an ample long wave).

[1] Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; ODE, ordinary differential equation; REM, rapid eye movement.

Seizure attractors, reconstructed in the space of time delayed recordings (with 3D embedding), show the typical geometry organized by a homoclinic bifurcation (Shil'nikov-like chaos). The reconstructed state approaches (leaves) the saddle equilibrium by following the stable (unstable) manifold, so describing the long wave, and irregularly oscillates around the saddle before departing for the next wave. This is confirmed by the bifurcation analysis of the class of neural mass models [Freeman, 2000], where the Shil'nikov saddle-node homoclinic bifurcation is responsible of the observed chaotic behavior [Grimbert and Faugeras, 2006; van Veen et al., 2006; Spiegler et al., 2010].

Shil'nikov-like chaotic oscillators have an interesting resonance property (qualitative resonance after [De Feo, 2004]). When properly forced by one of the unstable (saddle) cycles composing the backbone of the attractor (hereafter generating cycle), they can synchronize with it, so that the cycle becomes the attractor of the forced oscillator. Here we make use of this property to build a modeling framework for focal and multi-focal epilepsy.

We model the brain as a directed, weighted network of neuronal macro-areas, each with similar electrical activity described by a Shil'nikov-like chaotic oscillator, and with influences on other macro-areas that can be estimated from the statistical or causal modeling analysis of EEG, MEG, and fMRI[1] recordings [Astolfi et al., 2007; Brookes et al., 2001; Friston, 2009]. We model each candidate epileptic focus, as a special node of the network that is forced by its generating cycle, thus limiting its activity to a low-dimensional (periodic-like) attractor around the generating cycle (the oscillator does not fully synchronize with the cycle due to the influence of the other nodes). The generating cycle naturally plays the role of the (physiologically processed) external stimulus in reflex epilepsies, but we also use it to describe the effects of localized functional disorders or lesions (i.e., the limited complexity of the node activity).

Our modeling framework is aimed at supporting the identification of the potential epileptic foci. Using proper chaotic oscillators, describing or mimicking the electrical activity of the neuronal macro-areas, and realistic connectivity information, one can test which are the macro-areas most prone to trigger the epileptic seizure. These correspond to the nodes that, when forced by their generating cycle, are able to resonate with it and force part or the entire network to do the same by transferring a similar stimulus through the network connections. Single - or multi-focal seizures can therefore be simulated.

The paper is organized as follows. Sect. 2.1 briefly describes the technicalities behind the qualitative resonance of Shil'nikov-like chaotic oscillators. In particular, we use the Colpitts oscillator because it is low-dimensional (3D), but yet generates irregular sine-like signals similar to reconstructed and modeled epileptic EEG recordings (see [Babloyantz and Destexhe, 1986, Fig. 2], [Freeman, 1987, Figs. 9 and 10], [Spiegler et al., 2011, Fig. 3]; in [Carmeli et al., 2005] the Colpitts oscillator is used to mimic EEG dynamics).

Sect. 2.2 presents our modeling framework by showing two simple numerical experiments on a three-node network of Colpitts oscillators (e.g. representing macro-areas in the frontal, parietal, and occipital cortex). The network has all-to-all topology (see Fig. 1), with high connection strength from node 1 to nodes 2 and 3, medium strength from nodes 2 and 3 to node 1, and low strength between nodes 2 and 3. In the first (second) experiment, the node 1 (2) is the epileptic focus (the red arrow represents the periodic forcing).

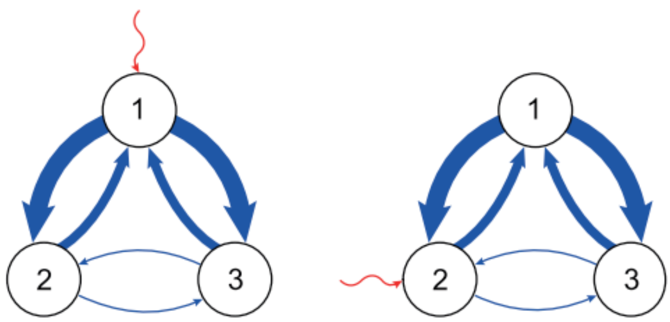

Figure 1. *Network connectivity i-to-j connection strengths w ij proportional to arrow thickness;* $w_{12} = w_{13} = 1$, $w_{21} = w_{31} = 0.5$, $w_{23} = w_{32} = 0.1$.

Not surprisingly (given our network connectivity), our results suggest oscillator 1 as the most probable epileptic focus. We close the paper discussing the results and the future developments in Sect. 3. This is a revised version of the paper appeared in the Proceedings of the 7th International Workshop on Biosignal Interpretation (BSI2012, [Barbieri et al., 2012]).

2. Material and Methods

2.1. Qualitative resonance of Shil'nikov-like chaotic attractors

The Colpitts oscillator is an ODE[1] model for an electronic device widely used in communication systems. Using suitable dimensionless variables, the model equations are:

$$\tau\dot{x}_1 = f_1(x) = \frac{g}{Q(1-k)}(1-\exp(-x_2)+x_3) \quad (1a)$$

$$\tau\dot{x}_2 = f_2(x) = \frac{g}{Qk}x_3 \quad (1b)$$

$$\tau\dot{x}_3 = f_3(x) = -\frac{Qk(1-k)}{g}(x_1+x_2)-\frac{1}{Q}x_3 \quad (1c)$$

where $x = (x_1, x_2, x_3)$ is the state vector and the positive time-scaling parameter τ is used to control the mean frequency of the oscillations. For realistic values of the parameters, the model has a global chaotic attractor organized by a Shil'nikov saddle-focus homoclinic bifurcation [De Feo et al., 2000].

The continuation [Dhooge et al., 2002] of the generating cycle of the (primary) homoclinic bifurcation [De Feo et al., 2000] is reported in Fig. 2, together with the wave-shape of the state variable x_2 close to the homoclinic bifurcation (the initial phase is set to have the minor peaks before the long wave).

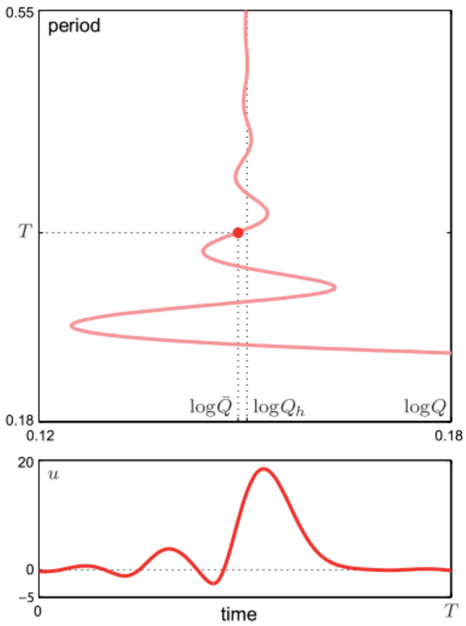

Figure 2. *A. Continuation of the generating cycle of the (primary) homoclinic bifurcation in the Colpitts oscillator. B. Wave-shape of the variable $u = x_2$ corresponding to the red dot (logQ = 0.15, period T = 0.35sec). Other parameter values: τ = 0.0137, log(g) = 0.5, k = 0.5.*

The qualitative resonance in the Colpitts oscillator has been obtained in [De Feo, 2004] by perturbing the second equation at time t by the discrepancy between the state variable $x_2(t)$ and the value $u(t)$ assumed by x_2 in the generating cycle at the same time t (with phase set as in Fig. 2), i.e.,

$$\tau\dot{x}_2 = f_2(x) - \alpha(x_2 - u) \quad (2)$$

The result is reported in Fig. 3, where the unforced (resp. forced) attractor is shown in green (resp. blue) and the side panel confirms synchronization with the generating cycle.

The qualitative resonance of Shil'nikov-like chaotic oscillators works as follows. The generating cycle is an unstable (saddle) cycle contained in the unforced chaotic attractor, and is also a solution for the forced oscillator, since the forcing vanishes when $x_2(t) = u(t)$ (i.e., the oscillator is fully synchronized, both in phase and amplitude, with the generating cycle; in this sense, resonance is quantitative rather than qualitative, but see below).

By suitably perturbing the unforced oscillator (see Eq.(2)), one can feedback (locally) stabilize the generating cycle [Bittanti and Colaneri, 2009], so that, if the oscillator state $x(t)$ becomes sufficiently close to and in phase with the generating cycle at some time t (i.e., $\|x(t) - U(t)\|$ becomes sufficiently small, where $U(t) = U(t + T) \in \mathbf{R}^3$ is the periodic vector describing the generating cycle), then synchronization is achieved. The trick behind qualitative resonance is the random-like phase shifts that occur when the state passes close to the saddle equilibrium. Thus, sooner or later, the oscillator will be sufficiently in phase with the generating cycle, while sufficient amplitude synchronization is guaranteed by the structure of the chaotic attractor.

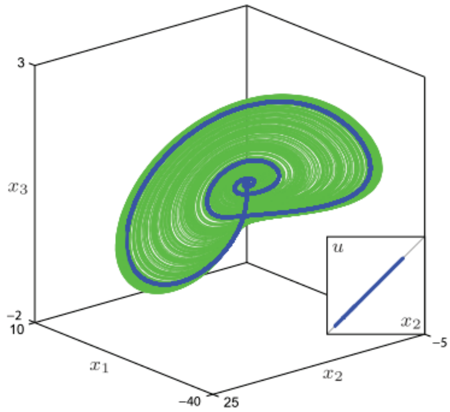

Figure 3. *Qualitative resonance in the Colpitts oscillator. Unforced (α = 0, green) and forced (α = 1, blue) attractor. The side panel shows that the forced attractor is synchronized in amplitude and phase with the generating cycle of Fig. 2.*

Qualitative resonance is a rather robust phenomenon, it qualitatively works (i.e., the forced oscillator works on a chaotic attractor that develops in a neighborhood of the generating cycle) even if the generating cycle is obtained for different, but similar, parameter settings, or roughly (piecewise linear or harmonic) approximated [De Feo, 2004].

2.2. Qualitative resonance in networks of similar oscillators: Preliminary results

Here we propose our modeling framework. We consider a directed, weighted network ($w_{ij} \geq 0$ is the i-to-j connection strength; $w_{ii} = 0$, $i, j = 1, \ldots, N$, N being the number of nodes) of Colpitts oscillators, with linear, diffusive coupling, i.e.,

$$\tau\dot{x}^{(i)} = f(x^{(i)}) + d\sum_{j\neq i} w_{ji} H x^{(j)} - d\sum_{j\neq i} w_{ij} H x^{(i)}. \quad (3)$$

where the coupling profile H is a 3×3 nonnegative matrix that connects only the second variable of the oscillators($h_{22} = 1$, all other elements being zero) and d modulates the coupling.

If all oscillators are identical (same parameter settings), the connection strengths can be such that the network can fully synchronize on the attractor of the unforced oscillator: the sum of the outflow strengths $\Sigma_j\, w_{ij}$ should equal the sum of the inflow strengths $\Sigma_j\, w_{ji}$ for each $i = 1, \ldots, N$ [Boccaletti et al., 2006]. However, there is no reason why this should be the case of the cerebral cortex, so that with similar oscillators and generic connectivity, weaker (i.e., qualitative) forms of synchronization are expected for increasing coupling d.

To test whether node i is a potential epileptic focus, we add the periodic forcing to its second variable, i.e.

$$\tau\dot{x}_2^{(i)} = f_2(x^{(i)}) + d\sum_{j\neq i} w_{ji} H x_2^{(j)} - d\sum_{j\neq i} w_{ij} H x_2^{(i)} + \alpha u. \quad (4)$$

Note that this is a simple forcing of the second equation of node i, without the state feedback $-\alpha x_2^{(i)}$ present in Eq.(2). However, the outflow term gives a similar feedback, hence qualitative resonance could still occur in node i when the ratio α/d is close to the sum of the outflow strengths $\Sigma_j\, w_{ij}$ and the inflow is small. Then, the regularized dynamics of node i acts as a driving signal for the other connected nodes $j \neq i$, whose second equations read

$$\tau\dot{x}_2^{(j)} = f_2(x^{(j)}) + \cdots + d w_{ij} x_2^{(i)} - d\sum_{k\neq j} w_{jk} x_2^{(j)}. \quad (5)$$

Again, the structure is similar to Eq.(2), as $x_2^{(i)}$ is synchronized with the forcing u, so qualitative resonance can spread in the network.

Fig. 4 reports two simple numerical experiments on the network of Fig. 1. The unforced (forced) network attractors are shown in green (blue) and the generating cycle is added in red to the 3D oscillators' subspaces.

3. Results and Discussion

Fig. 4 shows that node 1 is the most probable epileptic focus in the network of Fig. 1. As discussed in Sect. 2, node 1 is in the proper conditions to resonate with the forcing. Fig. 4a shows imperfect synchronization with the generating cycle (red) on a low dimensional, periodic-like attractor (blue) due to the imperfect balance between the α/d ratio ($\simeq$ 5.55) and the sum of the outflow strengths ($w_{12} + w_{13} = 2$), and to the inflow strengths ($w_{21} = w_{31} = 0.5$). Figs.4b,c show that the 1-2 and 1-3 connections properly work as forcing for nodes 2 and 3, which also reach imperfect synchronization. The bottom panels (d–f) refer to the experimental settings of Fig. 1 (right) and show that node 2, as well as node 3 by symmetry, are less able to trigger the epileptic seizure.

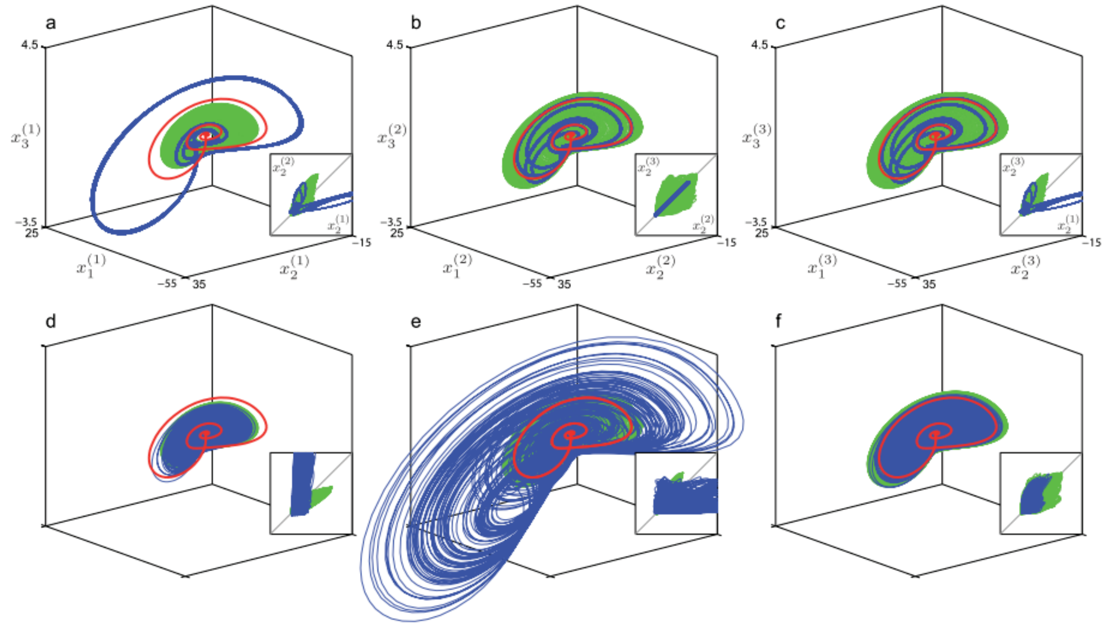

Figure 4. *Qualitative resonance in the two experimental settings of Fig. 1 (left), panels a–c, and Fig. 1 (right), panels d–f (with same variables on the axes). Unforced (α = 0, green) and forced (α = 1, blue) network attractor (projections in the 3D oscillators' subspaces). The generating cycle (Fig. 2) is reported in red for comparison. The side panel shows that the forced attractor is synchronized in amplitude and phase with the generating cycle of Fig. 2. Nodes synchrony is reported in the side panels. Coupling: d = 0.18; other parameters as in Figs. 1 and 2.*

Previous models of epileptic seizures make use of neural mass models [Freeman, 2000], which are able to reproduce realistic seizure and seizure-free EEG dynamics, but for different parameter settings. In contrast, our framework generates both dynamics for the same parameter setting, as a response to the periodic forcing.

The seizure dynamics reach regime after a transient from the normal activity (not drawn in Fig. 4) showing an initial decrease in synchronization. This is in line with clinical data [Mormann et al., 2003] (and has been exploited for seizure prediction [Mormann et al., 2007]). Then, on the seizure regime, the low dimensional, periodic-like activity is more synchronous across the network (see the side panels in Fig. 4) and typically has wider amplitude than the normal activity (see, e.g., [Babloyantz and Destexhe, 1986, Fig. 1]). Eventually, the seizure ends with a transient that starts as soon as the forcing ceases and brings the network back to normal activity (the transient duration depends on both the oscillators and the coupling).

4. Conclusions

Our modeling framework suggests as the most probable epileptic foci, those nodes that most easily trigger the qualitative resonance in a significant part of the network. Although the candidate epileptic foci might be identified based on the connectivity analysis alone [Astolfi et al., 2007; Brookes et al., 2001; Friston, 2009]—as in our simple network where causality goes from node 1 to nodes 2 and 3—our approach can play a relevant role when this is not feasible. Here we have presented only preliminary results showing that the idea can work, but systematic and more detailed analyses on more realistic oscillators and networks are required. Realistic networks (with connectivity estimated from EEG, MEG, or fMRI data in normal and epileptic subjects) of similar Colpitts oscillators, with parametric fitting to match the seizure-free activity of the various macro-areas, will be first investigated.

Then, the more realistic (and higher-dimensional) neural mass models will be used. There, it is interesting to see if the qualitative resonance phenomenon (observed and investigated in [De Feo, 2004] for Shil'nikov attractors organized by a saddle-focus homoclinic bifurcation) also occurs close the Shil'nikov saddle-node homoclinic bifurcation References that is responsible of the EEG chaotic attractors in the neural mass models [Grimbert and Faugeras, 2006; van Veen et al., 2006; Spiegler et al., 2010].

Eventually, our framework could be tested against clinical data of seizures for which the epileptic foci are known by direct observations (e.g., stereo-EEG).

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