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Modeling the Mesoscopic-Scale Spatial Evolution of the Epileptic Pre-Ictal and Ictal Phases

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Abstract

The spatial evolution of the epileptiform regime in neural networks can be alternatively described in terms of a statistical approach, dealing with average smooth, differentiable fields rather than discrete neural elements. After a brief review of mathematical methods for modeling epilepsy (the condensed matter vs. the neural mass models) together with their pros and cons, we introduce our continuous-space model for the pre-ictal scalar field and the ictal epileptiform vector flux in the form of the diffusion equation and Cattaneo's equation, correspondingly. For the radially symmetric case, we derive the exact analytical solution that describes the spread of seizures at the mesoscopic level. Then we study the long-range asymptotes of our solution. To conclude, we discuss the possibility of controlling the epileptiform spatial evolution and briefly focus on the future development of the proposed model.

Keywords

Modeling epilepsy; continuous-space approach; diffusion equation; Cattaneo's law; mesoscopic spatial dynamics; analytical solution

1. Introduction: Alternative Models for the Brain Dynamics

Developing alternative mathematical approaches for modeling the appearance and spatial evolution of epileptiform regimes in neural networks that mimic epileptic seizures in the human brain is a matter of great interest for modern neuroscience [1]. The spatial evolution of such seizures can be caused by several factors, including synaptic transmission, ionic diffusion, pure axonal conduction, or external electromagnetic fields generated by neurons [2, 3]. The seizure phase often appears at the microscopic scales where the number of neurons can be evaluated as 10^2-10^3 [4], or cover a greater scale of focal seizures [5, 6], and then spreads to the mesoscopic and macroscopic scales using the complex excitatory and inhibitory mechanisms in the brain [7-10], see also [11] for mice data.

By *mesoscopic scales*, we mean here such scales where the typical dynamical features of individual neurons can be averaged and treated as statistical variables [12]. One can compare this approach with condensed matter methods that focus on the collective properties of (quasi)particle ensembles, rather than on the individual dynamics of atoms or molecules [13]. Thus, neural network modeling is not the only possible mathematical approach, but it might be replaced with the neural population dynamics in the 2D space and time continuum.

The continuous-space approach can be a suitable choice for modeling real epilepsy, as it focuses on the *collective* neural spiking and bursting behavior rather than the specific dynamics of the network elements. Currently, a variety of experimental techniques are employed to study the biological and physiological mechanisms of epilepsy, ranging from traditional EEG and fMRI [14-17] to intracellular recording [18] and imaging [19, 20]. For this reason, the continuous-space approach may, probably, stimulate the further development of combined theoretical and experimental techniques for studying the spatial dynamics of epilepsy.

Before we formulate our model, let's have a brief review of the existing theoretical approaches to compare their pros and cons.

1.1 The Secondary Quantization Models

First of all, we should warn the readers that the 'secondary quantization' and the related condensed matter concepts are mentioned here only from the formal mathematical (not quantum physical) perspectives. We do not enter into the discussion of such topics as 'quantum neurons', 'quantum gravity in the brain microtubules' proposed by R. Penrose and others [21, 22]. In other words, we discuss here the application of mathematical methods of quantum statistical physics to modeling epileptic seizures in the human brain.

The pioneer of the approach, which copied the idea of secondary quantization in condensed matter and transferred it to neuroscience, was the Japanese physicist Hiroomi Umezawa, along with L. M. Ricciardi and other collaborators as early as 1967 [23]. The idea was to describe brain processes not from the point of neuron populations, but to look at them as a multi-body environment creating the collective quasiparticle-type modes, which Umezawa called 'corticons' (analog of phonons, polaritons, and other quasiparticles in physics).

Quasiparticles transfer the energy and momentum of the collective modes, and from that point they can be studied statistically as usual particles, but they do not transfer the matter itself. To spread, they need a medium (condensed matter), which in the brain is provided by the neural population.

Umezawa himself was mainly focused on the mechanisms of memory [24-27], while his younger collaborator Giuseppe Vitiello extended this concept for all kinds of information processes in the brain [28, 29]. For a review of the approach, refer to [30].

This approach, developed by physicists for an extended period, was viewed as marginal among neuroscientists. Partially, this could be due to the relatively sophisticated mathematical formulation of the secondary quantization method; another reason might be the focus on conceptual problems of brain modeling rather than on the needs of experimental neuroscience.

A significant step was taken in [12] for the microscopic-scale description, when the elements of the secondary-quantized field were derived based on the states of individual cells: activated, quiescent, and refractory phases, together with the corresponding master equations that describe the dynamics of the process. The neurons in certain states interacted with their network companions, spreading the activated phase in the cortical space.

Buice-Cowan's model had a good rapport with the experimental data. From another point of view, it was designed for the *microscopic* scale, producing the discrete-space solutions in the manner of cellular automata, like in the famous mathematical model 'Life' [31]. For the larger scales, especially for chaotic regimes like epilepsy, it faces many computational challenges.

1.2 The Neural Mass Models

An alternative approach, which we will mention here, is the concept of a neural mass model (NMM), which describes the dynamics of a neural cluster in the brain as a single entity [32]. It may correspond to the microscopic or mesoscopic level. Still, it originates from the discrete spatial structures based on a particular topology of the proposed neural network or its average characteristics [33].

Its typical representative is the K-set by Walter Freeman [34]. The hierarchy of the K-set (from K0 to KV) does not start from individual neurons, but from small neuron clusters (approximately 10^3-10^4 cells), and via the mesoscopic level, tends to cover the entire cortical part of the human brain. The topology of the neural network is described by defining excitatory and inhibitory clusters of neurons. This ambitious project encompasses the detailed modeling of the olfactory system, learning, and pattern classification (KIII), as well as the limbic system (KIV). The upcoming KV is intended to describe even some cognitive processes [35].

As a leading alternative to the condensed matter concept, NMMs have been intensively applied to study epilepsy. Among them, one should mention Wilson-Cowan's model [36, 37], Kuramoto's model [38, 39], the Epileptor [40-42], and others [43-45].

NMMs may provide good tools for practical studies of epilepsy. From our point of view, their main handicap is an arbitrary design of the network topology, which in the majority of cases is based not on the experimental data sets, but on quite a voluntarist choice of the authors. Even macroscopic NMM-based models strongly depend on the choice of such topology [46, 47].

1.3 Mesoscopic Continuous-Space Models for Epilepsy

A mesoscopic continuous-space modeling approach based on condensed matter methods, and ideologically following the 'secondary quantization' paradigm, describes the collective model of the perturbation in an environment. For the continuous-space approach, the microscopic details on the dynamics of elements (neurons in our case) forming the matter are not sufficient, just as the details of their microscopic topology. On the other hand, the collective perturbations contain some features of the 'quanta' that form the macroscopic medium, so that the properties of this medium cannot be deduced entirely from its macroscopic characteristics. Thus, the mathematical equations used to model collective modes are not derived from macroscopic first principles but are formulated in terms of implicit quantum collective features of the neural matter.

The introductory steps for modeling one-dimensional continuous spatial components of epileptiform behavior were done in [48, 49]. This one-dimensional spatial model was purely phenomenological and did not cover the mechanisms underlying the occurrence of different phases in the process of epilepsy spread.

1.4 Mathematical Models for the Epileptic Spatial Waves: Microscopic vs. Mesoscopic

Both approaches have their pros and cons.

At the *microscopic* level, the details of the neural interactions are studied in great detail based on different biophysical principles. Particularly, two mechanisms are believed to contribute to the spatial spread of the epileptic waves: *potassium diffusion* and *synaptic activit*y [50]. It is almost certain that the extracellular potassium concentration plays a vital role in neuronal excitability, just like in synaptic communication. The primary debates about the spatial evolution of epilepsy at the microscopic level is about the prevalence of different biological mechanisms contributing to the balance between the excitation and inhibition processes [51-53], which can be caused, apart from the diffusion and synaptic activity, by different factors: electric field interactions, some gap functions and others [54-56].

The criticisms of the potassium diffusion models are typically based on the simplification of ionic interactions [57], incorrect spatiotemporal dynamics describing individual neurons [58], and the neglect of the role of glial cells (e.g., astrocytes) [59, 60]. At the same time, the synaptic transmission models do not include electrical synapses (gap junctions), paracrine signaling [61], and synaptic plasticity [62].

Most importantly, the microscopic models often underemphasize the critical role of inhibitory control [63] and details of the network topological structures [64]. Nevertheless, the integration of different types of microscopic approaches enables the creation of relatively simple yet highly effective models of epilepsy spread [50, 65].

The mesoscopic level approach, such as the *mean-field models* [53, 54, 66], focuses on the average collective activities of large neuron populations. Their main handicap, perhaps, is also their main advantage: they do not concentrate on the microscopic details of neurons. This often leads to the rejection of specialists from the fields of biology and medicine, as such models do not allow for a detailed understanding of the role of various biological processes in the spread of epilepsy. At the same time, such models allow for easy integration of different biological mechanisms implicitly.

To conclude, we briefly mention here the *network models*, such as coupled Epileptors [53] or data-driven networks [67], which are related to the *macroscopic* level. They consider the whole brain as a network of interconnected regions, and such an approach falls outside our topic of discussion.

1.5 Novel Continuous-Space Model for the Spatial Epileptic Waves at the Mesoscopic Level

Recently, we formulated the microscopic statistical approach for epilepsy dynamics in the form of master equations for the normal, pre-ictal, and ictal phases [68], and then proposed the advanced 1D model for the spatial components of the hyper-synchronized (ictal) phase [69].

Our approach has been inspired by the Buice-Cowan ideas [12], but reformulated for the mesoscopic level. That means that all particular details of the biological processes, such as ion diffusion and synaptic activities, are averaged for the whole neuron population, and we study the spatial evolution of epilepsy as waves in the *neuron-condensed*, *matted medium*.

In this paper, we develop our model for the two-dimensional case. We introduce two fields: the scalar field S, which in our interpretation corresponds to the pre-ictal phase, and the vector stream j, describing the spatial spread of the epileptiform (ictal) phase.

We focus on the analytical solution in the form of separated variables for the radially symmetric case. Then we study the long-range asymptotes of our analytical solution and make some remarks on its spatial properties. We conclude with some discussion items regarding the further development of our model.

2. Continuous-Space Two-Dimensional Mathematical Model

Our mathematical model is based on the continuous spatial and temporal formulation for the mesoscopic scale. It covers the pre-ictal synchronized phase S, which is spread in the two-dimensional cortical continuous space following the generalized telegraph equation. This scalar field S generates a vector flux j of the ictal (hyper-synchronized) phase, exhibiting heterogeneous propagation patterns [70]. A positive "diffusion coefficient" constant D serves as a fundamental phenomenological parameter of the model. A similar continuous-field approach has been used in [71] for spatio-temporal source localization of EEG and MRI data.

2.1 Interpretation of the Variables and Their Units

The basic idea behind our model is that in simplified case the spread of collective epileptiform activity can be described as a *three-state process*: the neuron population that does not participate in the collective activities (and they are not covered here), pre-ictal phase neurons represented with the scalar field S, and the ictal phase neurons. At the mesoscopic level, the pre-ictal phase spreads as a diffusion-type process (similar to many microscopic models, such as [50]), with a possible decay rate corresponding to the loss of pre-ictally excited cells and their return to the epileptically non-active phase. On the other hand, pre-ictal field stimulated the transition of the elements to the ictal phase that creates spreading spatially as a vector flux with some delay effect, which results in Cattaneo's equation. The ictal flux may also be lost due to the transition of the neurons back to the non-active or pre-ictal levels.

Thus, we formulate our model for the scalar field *S*, which represents the average collective activity of the neural population, accumulating all contributions of particular neurons to the pre-ictal regime. It does not have any specific units and remains a collective field (voltage) scaled by a typical potential constant to maintain dimensionless units.

The ictal flux *j*, by that, must have a unit of the inverse time. It describes the evolution of the collective ictal mode in the condensed matter medium formed by the neuron populations.

2.2 Diffusion and Cattaneo Equations in 2D

The spatial evolution of the epileptiform phase takes place in the virtually flat cortical space of dimension 2. It is presented with the continuous differentiable hyper-synchronized scalar pre-ictal field $S(\mathbf{r},t)$ and the vector flux of the epileptiform (ictal) phase $\mathbf{j}(\mathbf{r},t)$, where $\mathbf{r} = (x,y)$. The pre-ictal field can be represented in the form of a *diffusion equation*:

$$\frac{\partial}{\partial t} S(\mathbf{r},t) = D \cdot \nabla^2 S(\mathbf{r},t), \tag{1}$$

where *D* is a positive constant.

The ictal flux is expressed via *Cattaneo's law* [72]:

$$\mathbf{j}(\mathbf{r},t) + \tau \frac{\partial}{\partial t} \mathbf{j}(\mathbf{r},t) = -D\nabla S(\mathbf{r},t). \tag{2}$$

Here the parameter τ stays for the time delay effect, as a result of the first order Taylor's extension.

If the principle of *conservation of energy* is satisfied for the system (1)-(2), it can be written in the form [73]:

$$\boldsymbol{T} \frac{\partial S(\mathbf{r},t)}{\partial t} + \nabla \mathbf{j}(\mathbf{r},t) = 0. \tag{3}$$

T here stands for a typical temporal scale parameter. Then by the substitution of **j** from (2) into (3), one gets:

$$T \frac{\partial S(\mathbf{r},t)}{\partial t} + \nabla \left(-\tau \frac{\partial}{\partial t} \mathbf{j}(\mathbf{r},t) - D\nabla S(\mathbf{r},t) \right) = 0. \tag{4}$$

Using (3), the flux can be excluded, and the partial differential equation for *S* takes a form of the *telegraph equation*:

$$\frac{\partial S(\mathbf{r},t)}{\partial t} + \tau \frac{\partial^2 S(\mathbf{r},t)}{\partial t^2} = \frac{D}{T} \nabla^2 S(\mathbf{r},t). \tag{5}$$

However, in our particular model discussed here, we *do not* assume conservation of energy in the process of epilepsy propagation.

The system we study here is not isolated in terms of energy processes. On the one hand, the highest neural activity is sustained from the neurotransmitter storage and neurotransmission efficacy provided by the astrocytes [74]; on the other hand, there are various mechanisms of

energy losses during the spread of epilepsy [75]. Thus, Eq. (5) is not valid to describe the epileptic special waves far away from their microscopic energy sources.

2.3 Analytical Solution to the Radially-Symmetric Case: Separation of Variables

We search for the solution in the factorized form for functions of the space coordinate **r** and time coordinate *t* separately:

$$S(\mathbf{r},t) = A(\mathbf{r})B(t). \tag{6}$$

Then:

$$\frac{\nabla^2 A(\mathbf{r})}{A(\mathbf{r})} = \frac{1}{D}\frac{dB(t)}{B(t)} = -k_1. \tag{7}$$

Here, k_1 is a separation constant.

To derive an analytical solution, let's suppose the radial symmetry of 2D evolution of the epileptiform case. Then the Laplace operator in the polar coordinates (r,ϑ) in RHS(1) takes the form:

$$\nabla^2 = \frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} + \frac{1}{r^2}\frac{\partial^2}{\partial \theta^2}. \tag{8}$$

In the case of radial symmetry the functions *S* and *j* do not depend on the angle variable ϑ.

Taking the separation constant as a negative value $-k_1$ (because the epileptiform phase must growth) in the system:

$$\frac{d^2S(r)}{dr^2} + \frac{1}{r}\frac{dS(r)}{dr} = -k_1 S(r); \quad \frac{dB(t)}{dt} = -k_1 DB(t), \tag{9}$$

one can easily get for the functions:

$$A(r) = c_1 J_0\left(\sqrt{k_1}r\right) + c_2 \mathrm{Y}_0\left(\sqrt{k_1}r\right); \quad B(t) = e^{Dk_1 t}; \quad k_1 > 0. \tag{10}$$

and for the field *S*:

$$S(r,t) = e^{Dk_1 t} \cdot \left[c_1 J_0\left(\sqrt{k_1}r\right) + c_2 \mathrm{Y}_0\left(\sqrt{k_1}r\right)\right]; \quad k_1 > 0. \tag{11}$$

Here, J_0 and Y_0 are the Bessel functions of the first and second types, respectively, and c_1 and c_2 stand for arbitrary coefficients.

The typical behavior of the spatial components for $A(r)$ is represented in Figure 1: J_0 component (red) and Y_0 component (green), the magnitude of the separation parameter k_1 = 1, and the constants for the components $c_1 = c_2 = 1$. One should remember that the plot in Figure 1 also has the temporal exponentially increasing factor $\exp\{Dk_1 t\}$.

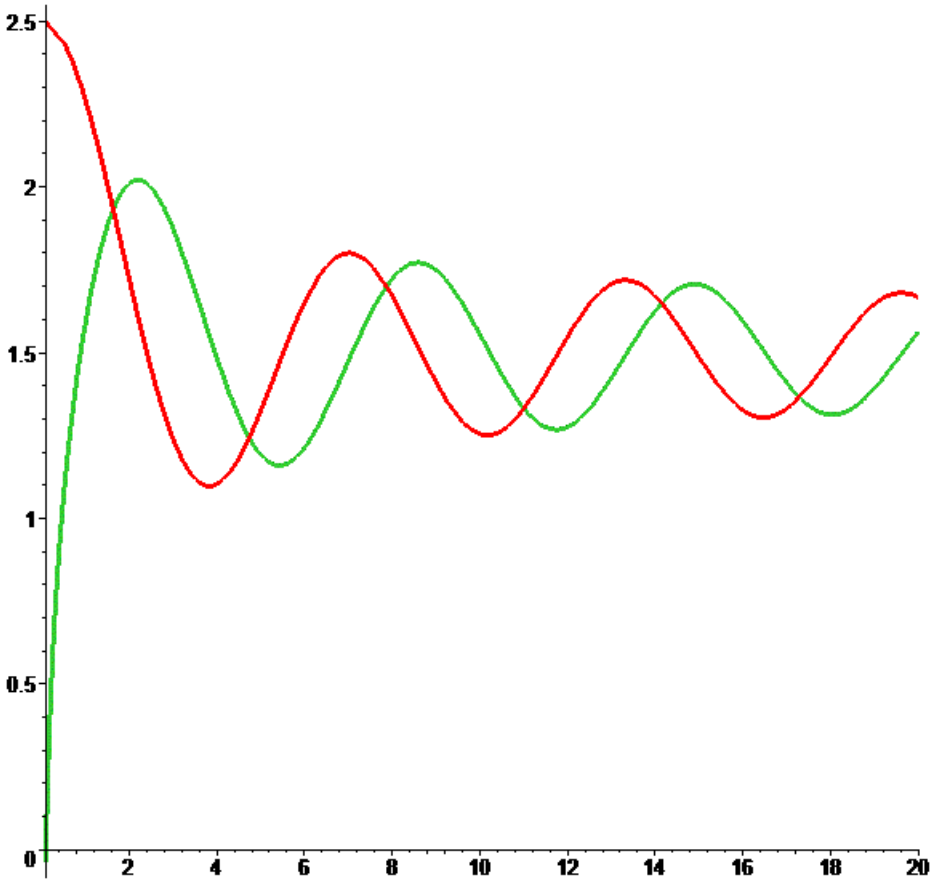

Figure 1 Typical behavior of the radial spatial components for Eq. (11) (the vertical axis) versus *r* (the horizontal axis).

Solution (11) explicitly shows that in our model, the epileptiform behavior at the mesoscopic level demonstrates oscillating features, which are defined by the separation parameter k_1. In the case of being a control parameter in the model, this variable can serve as a 'handle' for the manipulation of the spatial scales of epilepsy.

Now we can define the separation of variables for the flux *j*:

$$j(r,t) = F(r)G(t). \tag{12}$$

By (2) it becomes:

$$\frac{G(t) + \tau \frac{dG(t)}{dt}}{B(t)} = -\frac{D}{F(r)}\frac{dA(r)}{dr} = k_2, \tag{13}$$

with a separation non-zero constant k_2. The system:

$$F(r) = -\frac{D}{k_2}\frac{dA(r)}{dr}; \quad \tau\frac{dG(t)}{dt} + G(t) = k_2 B(t) \tag{14}$$

Possesses the solution:

$$F(r) = \frac{D\sqrt{k_1}}{k_2}\left[c_1 J_1(\sqrt{k_1}r) + c_2 Y_1(\sqrt{k_1}r)\right]; \quad G(t) = c_3 e^{-t/\tau} + \frac{k_2}{1 + Dk_1\tau} e^{Dk_1 t}, \tag{15}$$

with the Bessel functions J_1 and Y_1, and the constant of integration c_3. Correspondingly,

$$j(r,t) = \frac{D\sqrt{k_1}}{k_2}\left(c_3 e^{-t/\tau} + \frac{k_2}{1 + Dk_1\tau} e^{Dk_1 t}\right)\left[c_1 J_1(\sqrt{k_1}r) + c_2 Y_1(\sqrt{k_1}r)\right]. \tag{16}$$

A typical spatial behavior for the flux (16) is represented in Figure 2: J_1 component (red) and Y_1 component (green). The numerical parameters are the same as for Figure 1, $k_2 = 1$, $c_3 = 1$.

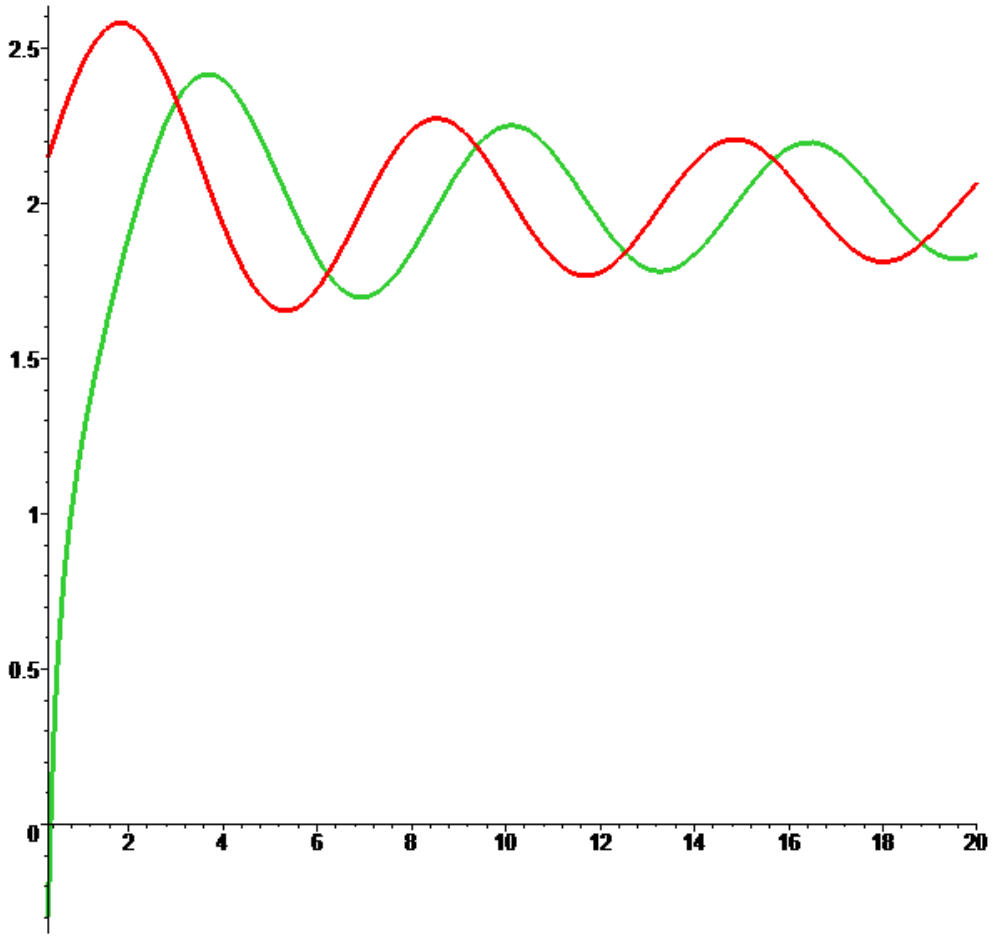

Figure 2 Typical behavior of the radial spatial components for the flux *j* (the vertical axis) versus *r* (the horizontal axis).

If the parameter τ in (2) is zero, then $G(t) = k_2\exp\{Dk_1 t\}$.

2.4 Long-Range Asymptotes of the Analytical Solutions and the Typical Scales

To find the long-range asymptotes of the solutions (11) and (16), let's present the Bessel functions for large *r* as. For the large spatial scale *x*:

$$x >> \left|\alpha^2 - \frac{1}{4}\right|, \tag{17}$$

where α denotes the order of the Bessel functions (in our case it is 0 and 1). Then the Bessel asymptotes are given by [76]:

$$J_\alpha(x) = \sqrt{\frac{2}{\pi x}}\cos\left(x - \frac{\alpha\pi}{2} - \frac{\pi}{4}\right); \quad Y_\alpha(x) = \sqrt{\frac{2}{\pi x}}\sin\left(x - \frac{\alpha\pi}{2} - \frac{\pi}{4}\right). \tag{18}$$

Then (11) becomes:

$$S(r,t) = e^{Dk_1 t}\sqrt{\frac{2}{\pi\sqrt{k_1}r}}\left[c_1\cos\left(\sqrt{k_1}r - \frac{\pi}{4}\right) + c_2\sin\left(\sqrt{k_1}r - \frac{\pi}{4}\right)\right]. \tag{19}$$

Similarly, for (16) one gets:

$$j(r,t) = D\sqrt{k_1}\left(\frac{c_3}{k_2}e^{-\frac{t}{\tau}} + \frac{e^{Dk_1 t}}{1 + Dk_1\tau}\right)\sqrt{\frac{2}{\pi\sqrt{k_1}r}} \times \left[c_1\cos\left(\sqrt{k_1}r - \frac{3\pi}{4}\right) + c_2\sin\left(\sqrt{k_1}r - \frac{3\pi}{4}\right)\right]. \tag{20}$$

To study the behavior of the asymptotic solutions at the large scales, let's define the typical temporal and spatial parameters:

$$T = \frac{1}{Dk_1}; \quad L = \frac{2\pi}{\sqrt{k_1}}. \tag{21}$$

Then (19) can be represented as:

$$S(r,t) = \frac{1}{\pi}e^{t/T}\sqrt{\frac{L}{r}}\cdot\left[c_1\cos\left(2\pi\frac{r}{L} - \frac{\pi}{4}\right) + c_2\sin\left(2\pi\frac{r}{L} - \frac{\pi}{4}\right)\right]. \tag{22}$$

Eq. (20) becomes:

$$j(r,t) = \frac{LT}{2\pi^2}\left(\frac{c_3}{k_2}e^{-t/\tau} + \frac{e^{t/T}}{1 + \frac{\tau}{T}}\right)\sqrt{\frac{L}{r}}\cdot\left[c_1\cos\left(2\pi\frac{r}{L} - \frac{3\pi}{4}\right) + c_2\sin\left(2\pi\frac{r}{L} - \frac{3\pi}{4}\right)\right]. \tag{23}$$

Thus, the spatial component of S behaves at the large scale r as $(L/r)^{1/2}$, while j behaves as $L(L/r)^{1/2}/T$, in other words, j behaves as:

$$j \propto \frac{1}{2\pi}\cdot\frac{L}{T}\cdot S. \tag{24}$$

The parameters c_1, c_2, and the ratio c_3/k_2 do not have units.

3. Discussion

The effects of the *long-term spatial influence of pre-ictal and inter-ictal phases* on the ictal phases have been observed in the EEG data in [77]. More critically, quite similar results for the

relation between pre-ictal and ictal phases have been observed in [78], where intracranial EEG signals were analyzed using the connectivity algorithm of PageRank centrality, the Google version of the EigenCentrality algorithm [79].

3.1 Spatial Patterns of the Epileptic Waves

Two basic features of the proposed analytical solutions can be observed in Eqs. (22)-(23): their *oscillating spatial pattern* and the *spatial wave decay*.

Regarding the oscillating spatial pattern, first, we can infer the role of interictal discharges in the seizure onset zone (SOZ). As [80] notes, they can exhibit spatiotemporal patterns that maintain temporal differences between different locations. These interictal discharge time sequences demonstrate fine spatial organization in the SOZ, with consistent and repetitive patterns of propagation observed over long periods. This phenomenon may create a certain degree of spatial regularity in the activity preceding the attacks. Another source of non-random spatial organization of seizures can originate from the presence of an anteroposterior gradient in closeness centrality connectivity of fast ripple hubs during spasms [81], or from other sources of inhibitory dynamics [82].

The attenuation of spatial patterns is an entirely normal phenomenon in the physics of waves that do not have a significant energy supply far from their source. In two-dimensional space, energy is dissipated along the increasing contour of the wave front. In addition, a gradual reduction in the excitatory currents can be caused by a weakening ictal wavefront. In contrast, the microscopic dynamics of the neurons of the ictal core lead up to the seizure self-termination [66].

3.2 The Bessel Function Patterns

Presently, there is not much experimental evidence for the spatial patterns based on the Bessel functions. Nevertheless, as early as [83, 84], it has been demonstrated that the intermittency between a regular (including inter-ictal) and chaotic (including pre-ictal and ictal) regimes can be successfully modeled with the Bessel-type coupled oscillators.

For the epileptic dynamics, the seizure occurrence from interictal and preictal transitions demonstrates spatiotemporal patterns based on the Bessel representation [85].

The closest data related to our theoretical prediction that we found are in [86]. The numerical model covered the electric potential diffusion equation associated with the geometry of dendritic links. The radial spatial components of the signals captured the tracks of the Bessel functions up to their 3rd order. From our point of view, the most crucial part in [86] is the 'noisy' experimental set with a precise Bessel-type shape in its opposition to the smoothed data, as we believe, this set summarizes the complex effects of the spatial patterns beyond the dendritic mechanism. Although the results in [86] are based on the patch-clamp recording used to study ionic currents in individual isolated living cells, they give a clue for the behavior at sufficiently larger scales due to the spatio-temporal collective hypersynchronous modes of many neurons. Also, the macropatch technique allows the recording of macroscopic currents as the accumulation of multiple channels from a large membrane area [87].

3.3 Further Research Proposals

Further *analytical investigations* of our proposed model could be conducted using various mathematical methods, including local radial basis functions [88], Caputo derivatives [89], Bayesian inference [90], and others.

The *numerical development* of the model should be improved based on experimental and numerical analyses of the traveling wave parameters, including their speed and magnitude [50, 51, 54, 55, 66, 91]. The detailed investigation of the time and space dynamics of epileptic waves within the proposed model will enable a comparison of the numerical results with the spatiotemporal mapping of interictal spike propagation [92-100].

Implementation of the microscopic-range sources to the system (1)-(2) to model the appearance of epilepsy at the micro-level is our primary focus for future research. It naturally takes the model extension to the application of *control methods*, which are very well developed for such equations [101, 102]. The interesting perspective of our model development is studying the influence of a feedback control embedded at the microscale level for the detection and suppression of seizures at a local point $\mathbf{r}_c$ (practically, this corresponds to the control via external electrode stimulation or optogenetic driving).

Such microscopic control over a small neighborhood in the system as we performed in [68] can cause a drastic change in the whole mesoscopic dynamics due to the exponential growth of different regimes from micro to upper scale levels. This feature can produce a highly efficient tool for the practical study of epilepsy, enabling the *control* of epileptic wave *detection and suppression* at the micro- and mesoscopic scales.

4. Conclusions

The proposed model enables the study of the spatial evolution of the mesoscale epileptiform regime, along with its temporal dynamics, through a set of ordinary differential equations that model the pre-ictal and ictal phases.

Our approach has a few essential features:

- It does not demand a sufficient computational cost, as is usually the case for artificial neural networks.
- It does not depend on the topology of the network.
- It allows reproducing the exact analytical results for the spatial wave components.
- It reproduces the spatial harmonic components predicted in some EEG experiments.

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Author Contributions

The author did all the research work for this study.

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Competing Interests

The author has declared that no competing interests exist.

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