S1 Text: The Model

A. The 5-dim Epileptor model

In order to take into account the timescale separation present in the seizure evolution, Jirsa et al. [1] used the theory of fast-slow systems in nonlinear dynamics [2] to develop a taxonomy of seizures. In addition, from experimental seizure data of various species, they identified a predominant class of bifurcation pairs, which resulted to be integrated into a phenomenological dynamic model called Epileptor. The Epileptor is a five-dimensional model and comprises three different timescales accounting for various electrographic patterns: on the fastest timescale, two state variables (x_1 and y_1) exhibit bistable dynamics between oscillatory activity, thus modeling fast discharges, and a stable node representing interictal activity. On the intermediate timescale two state variables (x_2 and y_2) model the spike and wave events. Finally, on the slowest timescale, the evolution of a very slow permittivity variable (z) guides the neural population through the seizures, including seizure onset and offset. In particular the permittivity variable captures the details of the autonomous slow evolution of interictal and ictal phases, as well as various details of seizure evolution during each phase. The activity in this model is autonomously switching between interictal and ictal states because of the slow permittivity variable accounting for the extracellular effects related to energy consumption and tissue oxygenation. In particular the activity is described by the following equations

$$
\begin{aligned}
&\dot{x}_1 = y_1 - f_1(x_1, x_2) - z + I_1, \qquad \dot{y}_1 = 1 - 5x_1^2 - y_1 \\
&\dot{z} = \frac{1}{\tau_0}\left[4(x_1 - x_0) - z\right] \\
&\dot{x}_2 = -y_2 + x_2 - x_2^3 + I_2 + 0.002g(x_1) - 0.3(z - 3.5), \qquad \dot{y}_2 = \frac{1}{\tau_2}(-y_2 + f_2(x_1, x_2)),
\end{aligned}
\tag{1}
$$

where

$$f_1(x_1, x_2) = \begin{cases} x_1^3 - 3x_1^2 & \text{if } x_1 < 0; \\ (x_2 - 0.6(z-4)^2)x_1 & \text{if } x_1 \geq 0. \end{cases}$$

$$f_2(x_1, x_2) = \begin{cases} 0 & \text{if } x_2 < -0.25; \\ 6(x_2 + 0.25)x_1 & \text{if } x_1 \geq -0.25. \end{cases}$$

$$g(x_1) = \int_{t_0}^{t} e^{-\gamma(t-\tau)} x_1(\tau) d\tau.$$

and the degree of epileptogenicity is represented by the value x_0. If we identify with x_c the critical value between the stable and unstable regime, for $x_0 < x_c$, the Epileptor autonomously shows seizure activity and is said to be epileptogenic while, for values of $x_0 > x_c$, the Epileptor is in its (healthy) equilibrium state. It is worth noticing that the distinction between excitation and inhibition in terms of explicit mechanistic realizations (for instance, GABA, Glutamate, etc.) is impossible in the model. These mechanisms are absorbed in the generic dynamics of the Epileptor model. The distinction of excitation and inhibition is, however, still preserved functionally, that is in terms of their role in the model linked to increase or decrease of state variables values. The functional distinction (as opposed to mechanistic) of excitation/inhibition persists through the mathematical expression of bifurcations in terms of the capability of generating oscillatory behavior (corresponding to the epileptogenic state) or not. A detailed mechanistic realization of the Epileptor model has been given in [3] where a correspondence between the emergent dynamic behaviors of this model and a network model of spiking neurons is investigated. In particular Naze *et al.* consider two neuronal populations, characterized by fast excitatory bursting neurons and regular spiking inhibitory neurons, embedded in a common extracellular environment represented by a slow variable: in this setup spike waves, including interictal spikes, are generated primarily by inhibitory neurons, whereas fast discharges during the wave part are due to excitatory neurons. The system is pushed into paroxysmal regimes by slow variations of global excitability, due to exogenous fluctuations from extracellular environment, and by gap junction communication. However the mechanistic realization shown in [3] is not unique and depends on the chosen spiking network model. It can be, for instance, easily demonstrated analytically that the system's oscillation amplitude depends only on the E/I balance and cannot isolate the individual contributions. There is an extensive general literature on the identifiability of model mechanisms, whose practical use is unfortunately limited to a

small number of degrees of freedom [4].

Equations 1 describe the dynamics of a single, uncoupled phenomenological model of epileptiform neural activity. Using again time-scale separation as well as evidences from SEEG recordings, Proix *et al.* [5] introduced a nonlocal interareal permittive coupling between Epileptors and they suggested to consider seizure recruitment among brain regions on a slow time scale. Such a coupling function can be expressed as a linear difference coupling term, assuming first order deviations from the homeostatic equilibrium of the slow permittivity variable. In particular it is possible to approximate the effect of fast neuronal discharges as a homeostatic perturbation of the slow permittive variable z of the Epileptor in the target region. Therefore the distant discharges at remote location j are transmitted via axons to target region i and can be seen as a perturbation of the homeostatic equilibrium of the region i. This disturbance of ion homeostasis will depend on both local and distant neuronal discharges and can be schematized as a coupling term $C_{i,j}(x_{1,i}, x_{1,j}) = \frac{1}{\tau_0}\sum_{j=1}^{N} k_{ij}(x_{1,j} - x_{1,i})$ that influences the rate of change of the permittivity variable z_1 of the region i, for $i, j = 1, ..., N$, where N is the number of regions of interest. Under these considerations, the final model equations for N-coupled Epileptors with permittive coupling read as follows:

$$
\begin{aligned}
&\dot{x}_{1,i} = y_{1,i} - f_1(x_{1,i}, x_{2,i}) - z_i + I_1, \qquad \dot{y}_{1,i} = 1 - 5x_{1,i}^2 - y_{1,i} \\
&\dot{z}_i = \frac{1}{\tau_0}\left[4(x_{1,i} - x_{0,i}) - z_i\right] - \frac{1}{\tau_0}\sum_{j=1}^{N} k_{ij}(x_{1,j} - x_{1,i}) \\
&\dot{x}_{2,i} = -y_{2,i} + x_{2,i} - x_{2,i}^3 + I_2 + 0.002g(x_{1,i}) - 0.3(z_i - 3.5), \quad \dot{y}_{2,i} = \frac{1}{\tau_2}(-y_{2,i} + f_2(x_{1,i}, x_{2,i})),
\end{aligned}
\tag{2}
$$

where $\tau_0 = 2857$, $\tau_2 = 10$, $I_1 = 3.1$ and $I_2 = 0.45$; f_1, g and f_2 are defined as above.

B. Two dimensional reduction of the Epileptor

To study the recruitment effects on the slowest timescale of the permittivity variable, and in particular to investigate large scale brain networks, it is possible to apply averaging methods to the coupled Epileptor equations, in order to reduce the dimension of the original model. Numerical analyses of the full system demonstrate that the effect of the second neuronal ensemble ($x_{2,i}$ and $y_{2,i}$) is negligible under this approximation, hence we can neglect it. Then the Epileptor equations (2) become

$$\begin{aligned}\dot{x}_{1,i} &= -x_{1,i}^3 - 2x_{1,i}^2 + 1 - z_i + I_i \\ \dot{z}_i &= \frac{1}{\tau_0}\left[4(x_{1,i} - x_{0,i}) - z_i - \sum_{j=1}^{N} K_{i,j}(x_{1,j} - x_{1,i})\right].\end{aligned} \tag{3}$$

For the sake of simplicity of our analysis, we also drop the subscripts $_1$ in the previous equations. Finally, the model used to mimic the dynamics of the single node coupled in a network reads

$$\begin{aligned}\dot{x}_i &= -x_i^3 - 2x_i^2 + 1 - z_i + I \\ \dot{z}_i &= \frac{1}{\tau}\left[4(x_i - x_{0,i}) - z_i - \sum_{j=1}^{N} K_{ij}(x_j - x_i)\right],\end{aligned} \tag{4}$$

with $\tau = 2857$, $I = 3.1$. The timescale difference is guaranteed by $\tau \gg 1$. Even in the reduced model $x_{0,i}$ represents the degree of epileptogenicity and its value is chosen according to the relationship $\Delta x_{0,i} = x_{0,i} - x_c$, with $x_c = -2.1$ being the critical value between a stable and an epileptogenic Epileptor. If $\Delta x_{0,i} > 0$, a brain region is epileptogenic and seizures are triggered autonomously. Otherwise, $\Delta x_{0,i} < 0$ and regions are in an equilibrium state. $K_{i,j}$ represents the coupling matrix between the brain populations; the structural connectivity matrix of single patients is used with 88 populations describing the main regions in the brain. The entries in the matrix are rescaled with the value of the maximal entry. Finally, since we will mainly analyze the epileptic spread, which is determined by the slow dynamics of the permittivity coupling, we can further take advantage of time scale separation, thus focusing on the slower time scale and neglecting time delays due to the tract propagation, even though they can be of crucial importance for the study of synchronization [6].

C. Linear stability analysis: eigenvectors vs Lyapunov vector

From a numerical point of view the fixed point solution $(\bar{x}_i, \bar{z}_i)$ $\forall i \in [1, N]$ of the system can be found by setting $\dot{x}_i = 0, \dot{z}_i = 0$ and by implementing the Newton's function, a one-dimensional root-finding routine which is also called the Newton-Raphson method. While all the healthy nodes are subject to a constant motion in x_i, the epileptogenic node shows a periodic motion and, a priori, its stable state cannot be restricted to a simple fixed point

solution in order to calculate the Linear Stability Analysis around it. However this operation is justified by the time scale separation. In particular it is always possible to compute the stability around the stable manifold: this is called dissection analysis and holds if two separate time scales are present [7]. Once the fixed point is found, its stability is determined by calculating both the eigenvalues and eigenvectors of the Jacobian matrix. The Jacobian matrix J is calculated according to the following system:

$$\begin{aligned} \delta\dot{x}_i &= -3x_i^2\delta x_i - 4x_i\delta x_i - \delta z_i \\ \delta\dot{z}_i &= \frac{4}{\tau}\delta x_i - \frac{\delta z_i}{\tau} - \sum_{j=1}^{N} K_{ij}(\delta x_j - \delta x_i) \end{aligned} \tag{5}$$

and it is given by

$$J = \left(\begin{array}{cccc|cccc} -3x_1^2 - 4x_1 & 0 & \dots & 0 & -1 & 0 & \dots & 0 \\ 0 & -3x_2^2 - 4x_2 & 0 & \vdots & 0 & -1 & 0 & \dots \\ \vdots & \ddots & \ddots & 0 & \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & 0 & -3x_{88}^2 - 4x_{88} & 0 & \dots & 0 & -1 \\ \hline \frac{1}{\tau}\left(4 + \sum_{j=1}^{N} K_{1j}\right) & \frac{-K_{1,2}}{\tau} & \dots & \frac{-K_{1,88}}{\tau} & -1/\tau & 0 & \dots & 0 \\ \frac{-K_{2,1}}{\tau} & \frac{1}{\tau}\left(4 + \sum_{j=1}^{N} K_{2j}\right) & \frac{-K_{2,3}}{\tau} & \vdots & 0 & -1/\tau & 0 & \dots \\ \vdots & \ddots & \ddots & \frac{-K_{87,88}}{\tau} & \vdots & \ddots & \ddots & 0 \\ \frac{-K_{88,1}}{\tau} & \dots & \frac{-K_{88,87}}{\tau} & \frac{1}{\tau}\left(4 + \sum_{j=1}^{N} K_{88j}\right) & 0 & \dots & 0 & -1/\tau \end{array}\right)$$

The eigenvalues indicate the stability of the system (4): positive eigenvalues correspond to an unstable system and in this case we expect a seizure to propagate along the network. On the other hand if the eigenvalues are non-positive the system is stable and the seizure should not be able to propagate.

Moreover the computation of the eigenvectors allow us to identify the pathways along which the seizure propagates. In particular it is possible to identify the biggest components of the maximal eigenvector, i.e. the eigenvector related to the maximal eigenvalue, as the most unstable directions able to convey the propagation in the entire network. In other words the elements with the biggest components of the maximal eigenvector will be the most probable

to be recruited during the propagation. On this basis we estimated the Propagation Zone (PZ) by identifying the elements with the biggest amplitude: these elements represent the dominating sub-networks involved in the transition towards the seizure state. These results can be compared with the PZ which is empirically obtained by neurosurgeons or during the data analysis of the time series of the cortical and implanted EEG electrodes [8].

In order to support our analysis of the most unstable directions identified via the Linear Stability Analysis, we have compared the prediction obtained via the maximum eigenvector with the localization of the maximum Lyapunov vector. Lyapunov vectors describe the characteristic expanding and contracting directions of a dynamical system. These vectors are defined along the trajectories of a dynamical system: in particular, if the system can be described in terms of a n-dimensional state vector, $\mathbf{x} \in R^n$, the Lyapunov vectors $\mathbf{v}^k(x)$, $(k = 1 \dots n)$ point in the directions in which an infinitesimal perturbation will grow asymptotically, exponentially at an average rate given by the Lyapunov exponents. When expanded in terms of Lyapunov vectors, a perturbation asymptotically aligns with $\mathbf{v}^1$, i. e. the Lyapunov vector in that expansion corresponding to the largest Lyapunov exponent, as this direction outgrows all others. Therefore almost all perturbations align asymptotically with the Lyapunov vector corresponding to the largest Lyapunov exponent in the system. In order to numerically calculate $\mathbf{v}^1(x(t))$, we computed the exponential growth rate of the maximum Lyapunov exponents along the 2N-1 independent directions in tangent space. The Lyapunov exponents has been numerically estimated by implementing the standard algorithm [9] on the time-dependent set of eqs. (5). Finally the localization $\mathcal{L}$ of the maximal Lyapunov vector is obtained averaging in time the square modulus of the vector itself: $\mathcal{L} =< \sum_{i=1}^{n} v_i^1(t) * v_i^1(t) >_t$.

In this system the Lyapunov spectrum does not show any level of chaoticity (the exponents are usually non-positive) and the localization of the maximal Lyapunov vector allows us to understand the origin of the instability responsible for the seizure spreading, thus making possible to detect the direction of maximum instability of the system. The directions of maximum instability coming out from the localization analysis are the same as the ones previously calculated via the Linear Stability Analysis and reported in Fig. 5(b). The comparison between the two analyses is shown in S1 Fig., where both the localization of $\mathbf{v}^1$ and the maximum eigenvector are reported; in particular the dashed lines highlight the

common maximum elements, that represent the directions along which the seizure spreads.

A priori this is not obvious since Lyapunov vectors are not usually identical with the local principal expanding and contracting directions, i.e. the eigenvectors of the Jacobian. In fact, while the latter require only local knowledge of the system, the Lyapunov vectors are influenced by all Jacobians along a trajectory, thus representing a measure of the instability of the dynamics of the system, not related to any particular fixed point or initial stable solution.

D. Prospects for personalized spatial propagation zones

The knowledge of PZ and EZ, estimated by medical doctors, can be easily implemented in the model eqs. (1, 2) and in the analysis, by simply defining three different levels of excitability x_0: $x_0 < x_c$ for the epileptic zone nodes, $x_0 \gg x_c$ for the healthy nodes, and $x_0 > x_c$, where $x_0 - x_c \ll 0$ for the healthy nodes in the propagation zone where the epileptic activity can spread. On the other hand, only two different levels of the degree of epileptogenicity x_0 are necessary to enter in eq. (5), thus directly affecting its solutions, i. e. fixed points $(\bar{x}_i, \bar{z}_i)$ $\forall i \in [1, N]$. In particular for the reduced system it is not necessary to take a different level of epileptogenicity for the nodes in the propagation zone to describe the recruitment mechanism. Furthermore, the Jacobian matrix is an explicit function of the fixed points of the reduced epileptor, meaning that the eigenvector and eigenvalues obtained from the Linear Stability Analysis will also be influenced. Henceforth, a similar comparison like above can be performed for the more realistic scenarios that involve the PZ, and the outcomes of different lesioning strategies can be also computed and compared.

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