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Fragility in Networks: Application to the Epileptic Brain

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Abstract: Networks consist of interacting components that often function together to achieve a particular goal. For example, in the human cortex, populations of neurons in different layers continuously communicate and encode information about the subject's environment and cognitive state to govern behavior. In cortical networks, neurons (network nodes) can be structurally connected (through synapses) in addition to being functionally connected; and in epilepsy, structural connections in just a few nodes change to destabilize the network and cause seizures. We define these nodes as *fragile* and set out to quantify fragility in networks. We first consider arbitrary linear networks whose state-evolution matrices characterize functional connectivity. Nodal fragility is then computed as the minimum energy perturbation required on the node's functional connectivity to destabilize the network. We then apply our perturbation theory to a stable probabilistic nonlinear neural network model. We show how the destabilizing perturbation in functional connectivity translates to a perturbation on the structural connections between neurons, i.e., the synaptic weights. Our results suggest that the most fragile nodes in the network are excitatory neurons that become more active or inhibitory neurons that become less active. This is consistent with abnormal axonal sprouting of excitatory neurons and loss of inhibitory chandelier cells observed in epileptic cortical tissue. The simulated activity before and after seizure also highlight the heterogeneity observed in actual recordings from epilepsy patients, where parts of the network either increase or decrease baseline firing while the rest of the neurons become silenced.

Keywords: Networks, Stability, Perturbations, Connectivty, Epilepsy, Cortical Networks

1. INTRODUCTION

Epilepsy is a neurological disease that affects over 50 million individuals worldwide (de Boer et al., 2008), manifesting in recurrent seizures. During seizures, there is evidence of abnormal activity in cortical neurons including more heterogeneity in firing (Truccolo et al., 2011), transient increases or decreases in firing rate (Truccolo et al., 2011), and synchronization in population oscillations (Uhlhaas and Singer, 2003). The etiology of epilepsy is unclear - studies have implicated genetic anomalies (Jeffrey, 2003), axo-axonic gap junctions (Traub et al., 2001), neurotransmitter imbalance (Bradford, 1995), loss of inhibitory chandelier cells in cortex (DeFelipe, 1999), atypical axonal sprouting from Layer V pyramidal cells (Jin et al., 2006), physical injury (Annegers and Coan, 2000) or infection (Lancman and Morris, 1996). A common thread among these possible mechanisms is that the effective coupling between neurons or populations of neurons is altered. For this reason, epilepsy is understood to be a network phenomenon and network models are often used to study the relationship between structural connections and functional activity.

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Network models consist of a set of nodes with internal dynamics, connected by edges that define the nature of nodal interactions. For neural networks, nodes are neurons and edge weights represent synaptic connection strengths. Negative outgoing edge weights from a node indicate that neurons in that node are inhibitory, while positive outgoing weights from a node indicate that the neurons in that node are excitatory.

We posit that aberrant functional activity observed during seizures does not arise from random changes in network structure (edge weights), but from the disruption of the most *fragile* nodal connections in the network. Fragility of a network node is defined as the minimum energy perturbation (on functional connections to its neighbors) required to destabilize the network, and is computed here for a class of perturbations that affect a subnetwork topology consisting of incoming connections to a single node. Next, the structural modifications, or the changes in the synaptic weights of the most fragile node that achieves the functional perturbation, are derived. The theory is then applied to a probabilistic nonlinear neural network model. In its unperturbed state, if a small stimulus is applied to the network, the activation probability of each neuron responds transiently but eventually returns to the fixed point. When the perturbed network is destabilized, the activation probabilities shift to larger or smaller values indefinitely.

2. METHODS

2.1 Structural Connectivity and Functional Connectivity

Here, we elucidate the distinction between structural and functional connectivity. Consider a network of three nodes with directed edges from node 1 to 2, and from node 2 to 3. Each node has internal dynamics that are modulated by external inputs to produce outputs propagated along the directed edges. The structural connectivity, the physical connections that define adjacent nodes, can be represented as an adjacency matrix, $\mathbf{W}$, with two non-zero elements. The functional connectivity, the effect of one node's activity on another's, is different than the structural connectivity, however. While the activity of the second node depends only on the activity of the first, the activity of node 3 depends on the activity of both nodes 1 and 2 – the activity of node 1 is relayed through node 2 to affect node 3. The functional connectivity can be represented as an adjacency matrix, $\mathbf{J}$, with three non-zero elements (strictly lower triangular).

In the context of neurological diseases, what is of interest is not the structural connectivity per se, but the interdependence between the activity of nodes, the functional connectivity, that arises from the structural connectivity. In epilepsy, the obvious defect is in the functional connectivity, the aberrant behavior of neurons and populations that manifests during seizures, and the goal is to link this back to some abnormality in the structural connectivity. This is a non-trivial problem that depends strongly on both network topology and internal nodal dynamics.

2.2 Stability of Linear Networks

First consider a linear system that evolves in continuous time as (1) with state vector $\mathbf{x}(t) \in \mathbb{R}^N$, and state matrix $\mathbf{A} \in \mathbb{R}^{N\times N}$.

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) \tag{1}$$

The state matrix can be viewed as an adjacency matrix representation of the functional connectivity of a network of N nodes, whose dynamics are linear and captured in the evolution of the state vector. The elements in the state vector are some metric of the activity of each node. The system is said to be asymptotically stable about a fixed point, $\widehat{\mathbf{x}}$, if $\mathbf{x}(t)$ converges to $\widehat{\mathbf{x}}$ as $t \to \infty$ for all initial conditions. This implies that the activity of the nodes remains at a baseline value and responds transiently to external inputs before recovering. In terms of the matrix representation, stability is equivalent to the eigenvalues of $\mathbf{A}$ being in the open left hand plane i.e. $Re\{\lambda_i\} < 0$.

If $\max\{Re\{\lambda_i\} = 0\}$, the state settles somewhere along the first eigenvector based on initial conditions. Therefore, the network gets stuck in some pattern of activity instead of decaying to its baseline. If the elements in the state vector represent spiking rates, this may be analogous to tonic spiking or silenced neurons.

2.3 Perturbations and Network Fragility

A linear system becomes unstable if there is a change to the state matrix so that the conditions on the eigenvalues (real parts being negative) are no longer met. This change can be modeled as an additive perturbation, $\mathbf{\Delta}$, to the state matrix so that $\mathbf{A}+\mathbf{\Delta}$ replaces $\mathbf{A}$ in the state equation (1). In this section, we construct perturbation matrices that render the network unstable. A variety of perturbation matrices can push the original network into instability. Based on the structure of the perturbation, and which elements are preferentially affected, different perturbation strengths (measured by a matrix norm) are required to cause the perturbed system to become unstable. Network fragility is defined here as the magnitude of the minimum energy perturbation required to push the network to the brink of instability. If a large magnitude perturbation is required, the network is more robust, while small energy perturbations correspond to a fragile network. The elements that are modified by the minimum energy perturbation define the edges of the most fragile subnetwork. Here, we constrict ourselves to the treatment of perturbations with non-zero entries along a row, which correspond to disruptions of a single neuron's incoming edge weights. The column perturbation result is analogous. Subsequently, preliminary results from a row-perturbed model network are presented.

2.4 Structured Perturbation Problem

Problem: For a stable matrix $\mathbf{A} \in \mathbb{R}^{N\times N}$, and a family of row perturbations, $\Lambda_r = \mathbf{e_k}\mathbf{\Gamma}^T, \mathbf{\Gamma} \in \mathbb{R}^N$, solve for the minimum induced 2-norm perturbation, $\widehat{\mathbf{\Delta}} \in \Lambda_r$, so that $\lambda = 0$ is an eigenvalue of $\mathbf{A} + \widehat{\mathbf{\Delta}}$. $\mathbf{e_k} \in \mathbb{R}^N$ is the k^{th} elementary basis vector.

$$\begin{aligned}\widehat{\mathbf{\Delta}} = \underset{\mathbf{\Delta}\in\Lambda_r}{\operatorname{argmin}}\{\|\mathbf{\Delta}\|_2 \mid \exists i : \lambda_i(\mathbf{A}+\mathbf{\Delta}) = 0,\\ \forall i : Re\{\lambda_i(\mathbf{A})\} < 0, i \in 1\dots N, \mathbf{A} \in \mathbb{R}^{N\times N}\}\end{aligned} \tag{2}$$

Solution: Since 0 is an eigenvalue of $\mathbf{A}+\mathbf{\Delta}$, there exists a $\mathbf{v} \in \mathbb{C}^N$, $\mathbf{v} \neq \mathbf{0}$ such that

$$(\mathbf{A}+\mathbf{\Delta})\mathbf{v} = 0\mathbf{v} \tag{3a}$$
$$\left(\mathbf{A}+\mathbf{e_k}\mathbf{\Gamma}^T\right)\mathbf{v} = \mathbf{0} \tag{3b}$$

From the characteristic equation,

$$\left|\mathbf{A}+\mathbf{e_k}\mathbf{\Gamma}^T\right| = 0 \tag{4a}$$
$$|\mathbf{A}|\left|\mathbf{I}+\mathbf{A}^{-1}\mathbf{e_k}\mathbf{\Gamma}^T\right| = 0 \tag{4b}$$
$$\left|\mathbf{I}+\mathbf{A}^{-1}\mathbf{e_k}\mathbf{\Gamma}^T\right| = 0 \tag{4c}$$
$$\left|1+\mathbf{\Gamma}^T\mathbf{A}^{-1}\mathbf{e_k}\right| = 0 \tag{4d}$$
$$\mathbf{\Gamma}^T\mathbf{A}^{-1}\mathbf{e_k} = -1 \tag{4e}$$

This is just a minimization of an underdetermined least squares problem over k.

$$\widehat{k} = \underset{k}{\operatorname{argmax}}\{\left\|\mathbf{A}^{-1}\mathbf{e_k}\right\|_2\} \tag{5}$$

Then $\widehat{\mathbf{\Delta}} = \mathbf{e}_{\widehat{\mathbf{k}}}\widehat{\mathbf{\Gamma}}^T$ with

$$\widehat{\mathbf{\Gamma}} = \frac{-\mathbf{A}^{-1}\mathbf{e}_{\widehat{\mathbf{k}}}}{\mathbf{e}_{\widehat{\mathbf{k}}}^T\mathbf{A}^{-T}\mathbf{A}^{-1}\mathbf{e}_{\widehat{\mathbf{k}}}} \tag{6}$$

2.5 Probabilistic Neural Network Model

The row perturbation result above will be applied to destabilize a neural network model used in Benayoun et al. (2010). This model is attractive because it includes parameters analogous to physiological features like refractory periods, synaptic strengths and firing rates without involving the complexity of biophysical models. A diagram of the neural network model is given in Figure 1.

Consider node i to be a single neuron that exists in one of two states at some time, active ($x_i(t) = 1$) or quiescent ($x_i(t) = 0$). The state probability evolves as a Markov process, with rate constants as given below, for a small time interval dt.

$$\Pr\{x_i(t+dt) = 0 \mid x_i(t) = 1\} = \alpha dt \tag{7a}$$
$$\Pr\{x_i(t+dt) = 1 \mid x_i(t) = 0\} = f(s_i(t))\, dt \tag{7b}$$

The active state represents the action potential duration of a neuron including its refractory period. The input to neuron i is given by $s_i(t)$. The spiking propensity of a neuron therefore depends on the level of input it receives, but the inactivation propensity is fixed. $f(\bullet)$ is a non-linear response function, representing the expected firing rate when quiescent. A clamped hyperbolic tangent was used in simulations, i.e.

$$f(s) = \max\{0, tanh(s)\} \tag{8}$$

Combining (7a) and (7b), the nodal probability, $p_i(t) = \langle x_i(t)\rangle = Pr\{x_i(t) = 1\}$, i.e. the probability of a neuron being active at some time, evolves according to the following non-linear rate equation.

$$\dot{p}_i(t) = -\alpha p_i(t) + f(s_i(t))(1 - p_i(t)) \tag{9}$$

Consider a network of N such nodes, connected according to a structural connectivity matrix, $\mathbf{W} = [w_{ij}]$, whose elements are positive if node j excites node i, negative if node j inhibits node i and zero if nodes i and j are physically unconnected. The input to node i, $s_i(t)$, is contingent on the state of the nodes which connect to it, the weights of these connections, and some constant external input, h_i. If node j is active, node i feels an incremental synaptic drive of w_{ij}.

$$s_i(t) = \sum_{j=1}^{N} w_{ij} x_j(t) + h_i \tag{10}$$

The state of all the nodes in the network at any time, the network state, is given by aggregating the nodal states, $x_i(t)$, into the Boolean vector $\mathbf{x}(t) \in \mathbb{R}^N$. Similarly, the nodal inputs, $s_i(t)$, can be aggregated to form the synaptic input vector $\mathbf{s}(t) \in \mathbb{R}^N$. It can be expressed in matrix form as follows where $\mathbf{h} \in \mathbb{R}^N$ is the aggregate vector of external inputs. Then (10) can be re-written as

$$\mathbf{s}(t) = \mathbf{W}\mathbf{x}(t) + \mathbf{h} \tag{11}$$

The network probability, $\mathbf{p}(t) \in \mathbb{R}^N$, formed by aggregating nodal probabilities, $p_i(t)$, therefore evolves according to a non-linear rate equation analogous to the nodal rate equation in (9).

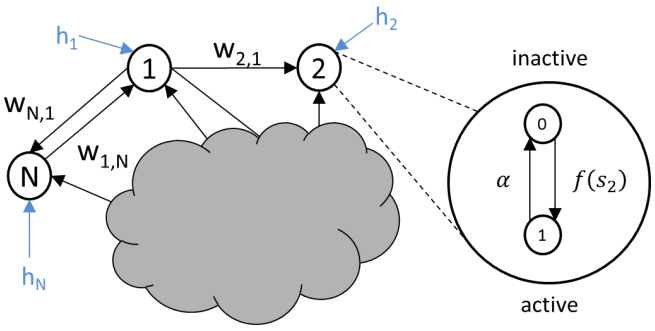

Fig. 1. Diagram of the probabilistic neural network model. Each node is a two-state Markov process, with an inactivation rate that is constant and an activation rate dependent on synaptic inputs, s_i. The synaptic input is the sum of an external input, h_i, and the synaptic weights, w_{ij}, from active upstream neurons.

$$\begin{aligned}\dot{\mathbf{p}}(t) &= -\alpha\mathbf{p}(t) + diag\{\mathbf{f}(\mathbf{W}\mathbf{p}(t) + \mathbf{h})\}(\mathbf{1} - \mathbf{p}(t)) \\ &\triangleq \mathbf{g}(\mathbf{p}(t); \mathbf{W})\end{aligned} \tag{12}$$

Determining Functional Connectivity Note that (12) explicitly forecasts the functional activity of the network, $\dot{\mathbf{p}}(t)$, given some network structure, $\mathbf{W}$, and so the notation $\mathbf{g}(\mathbf{p}(t); \mathbf{W})$ is used. Assume that the initial structural connectivity of the network gives rise to functional stability, so that there exists a unique stable fixed point, $\widehat{\mathbf{p}} \in \mathbb{R}^N$. Details on the existence of a stable fixed point are given in Benayoun et al. (2010) . This fixed point is a steady-state probability that satisfies (13) and therefore represents the baseline behavior of the network. The fixed point also depends on the network structure.

$$\mathbf{g}(\widehat{\mathbf{p}}; \mathbf{W}) = \mathbf{0} \tag{13}$$

Solving for $\widehat{\mathbf{p}}$ analytically using (12) and (13) is not generally possible, but gradient descent algorithms can be used instead. Equation (12) can be linearized around this fixed point, where $\mathbf{J}(\widehat{\mathbf{p}}; \mathbf{W})$ is the Jacobian evaluated at the fixed point (Strogatz, 1994).

$$\delta\dot{\mathbf{p}}(t) \approx \left(\frac{\partial \mathbf{g}(\mathbf{p}; \mathbf{W})}{\partial \mathbf{p}}\right)_{\mathbf{p}=\widehat{\mathbf{p}}} \delta\mathbf{p}(t) \tag{14a}$$
$$= \mathbf{J}(\widehat{\mathbf{p}}; \mathbf{W})\, \delta\mathbf{p}(t) \tag{14b}$$

The general form of the Jacobian is as follows. δ_{ij} is the Kronecker delta.

$$J_{ij}(\mathbf{p}; \mathbf{W}) = \frac{\partial g_i(\mathbf{p}; \mathbf{W})}{\partial p_j} \tag{15a}$$
$$= f'(\mathbf{w_i}^T\mathbf{p} + h_i)\, w_{ij}(1 - p_i) - \delta_{ij}(\alpha + f(\mathbf{w_i}^T\mathbf{p} + h_i)) \tag{15b}$$

Since $\widehat{\mathbf{p}}$ is a stable fixed point, $Re\{\lambda_i(\mathbf{J}(\widehat{\mathbf{p}}; \mathbf{W}))\} < 0$, so $\mathbf{J}(\widehat{\mathbf{p}}; \mathbf{W})$ is the stable adjacency matrix for a CT system

operating about $\widehat{\mathbf{p}}$. $\mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right)$ is therefore also the functional connectivity of a linearized network, with a given structural connectivity, $\mathbf{W}$. Row i of $\mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right)$ captures how the probability of any node being active affects the probability of node i being active. Column j indicates how the active probability of node j affects the active probability of other nodes.

Since the network has been linearized about $\widehat{\mathbf{p}}$, the minimum row perturbation, $\mathbf{\Delta_J}\left(\mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right)\right)$, required to cause CT instability is given by the result derived in Section 2.4. The unstable functional connectivity, $\tilde{\mathbf{J}}\left(\widehat{\mathbf{p}};\mathbf{W}\right)$, therefore has the following form where $r \in \{1,2,\ldots,N\}$ is the perturbed row.

$$\tilde{\mathbf{J}}\left(\widehat{\mathbf{p}};\mathbf{W}\right) = \mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right) + \mathbf{\Delta_J}\left(\mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right)\right) \tag{16a}$$

$$= \mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right) + \mathbf{e_r}\mathbf{\Gamma_J}^T\left(\mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right)\right). \tag{16b}$$

Disrupting Structure to Destabilize the Network Note that in (15b) the entries in row i of the functional connectivity matrix depend only on entries in row i of the structural connectivity matrix. That means the effect of inbound activity is facilitated at the structural level wholly by the weight of inbound connections. Therefore, if a row perturbation is applied to $\mathbf{J}\left(\widehat{\mathbf{p}};\mathbf{W}\right)$, this can be accounted for solely through modifications to the corresponding row of $\mathbf{W}$, interpreted as modifications to incoming synaptic strengths. The perturbed structural connectivity required to produce the unstable functional connectivity is necessarily of the following form.

$$\tilde{\mathbf{W}} = \mathbf{W} + \mathbf{\Delta_W} \tag{17a}$$

$$= \mathbf{W} + \mathbf{e_r}\mathbf{\Gamma_W}^T \tag{17b}$$

This perturbed structural connectivity should give rise to a new functional connectivity, $\mathbf{J}\left(\widehat{\mathbf{p}};\tilde{\mathbf{W}}\right)$, identical to the unstable one computed from the original network configuration.

$$\mathbf{J}\left(\widehat{\mathbf{p}};\tilde{\mathbf{W}}\right) = \tilde{\mathbf{J}}\left(\widehat{\mathbf{p}};\mathbf{W}\right) \tag{18}$$

Note however that changes in the structural connectivity ($\mathbf{W} \rightarrow \tilde{\mathbf{W}}$) may change the fixed point, which in turn alters all rows of the functional connectivity so that $\mathbf{J}\left(\widehat{\mathbf{p}};\tilde{\mathbf{W}}\right)$ cannot reproduce $\tilde{\mathbf{J}}\left(\widehat{\mathbf{p}};\mathbf{W}\right)$ which differs only by a single row. This is to be expected since $\mathbf{\Delta_J}$ is computed for a functional connectivity at a given fixed point. Therefore, $\tilde{\mathbf{W}}$ must be restricted to be invariant on the fixed point of the unperturbed system so that

$$\widehat{\mathbf{p}}\left(\tilde{\mathbf{W}}\right) = \widehat{\mathbf{p}}\left(\mathbf{W}\right) = \widehat{\mathbf{p}} \tag{19}$$

This can be accomplished only if the probability flux in (12) remains at zero while the structural connectivity is changed so that the fixed point does not move.

$$\mathbf{g}\left(\tilde{\mathbf{W}};\widehat{\mathbf{p}}\right) = \mathbf{g}\left(\mathbf{W};\widehat{\mathbf{p}}\right) = \mathbf{0} \tag{20}$$

Note that $\mathbf{g}\left(\mathbf{W};\widehat{\mathbf{p}}\right)$ is used instead of $\mathbf{g}\left(\widehat{\mathbf{p}};\mathbf{W}\right)$ as before, since the fixed point is now the constant and structural connectivity the variable. Inspection of (12) reveals conditions required to satisfy (20) element-wise.

For $i \neq r$:

$$\mathbf{e_i}^T\,\tilde{\mathbf{W}} = \mathbf{e_i}^T\mathbf{W} \implies g_i\left(\mathbf{W};\widehat{\mathbf{p}}\right) = g_i\left(\tilde{\mathbf{W}};\widehat{\mathbf{p}}\right) = 0 \text{ always} \tag{21}$$

For $i = r$:

$$g_r\left(\tilde{\mathbf{W}};\widehat{\mathbf{p}}\right) = 0 \iff \mathbf{w_r}^T\widehat{\mathbf{p}} = f^{-1}\left(\frac{\alpha\widehat{p}_r}{1-\widehat{p}_r}\right) - h_r = \tilde{\mathbf{w}}_\mathbf{r}^T\widehat{\mathbf{p}} \tag{22a}$$

$$\implies \left(\tilde{\mathbf{w}}_\mathbf{r} - \mathbf{w_r}\right)^T\widehat{\mathbf{p}} = 0 \tag{22b}$$

The modified row of the structural connectivity, $\tilde{\mathbf{w}}_\mathbf{r}^T$, can be computed using a constrained gradient descent in a manner analogous to the fixed point discovery.

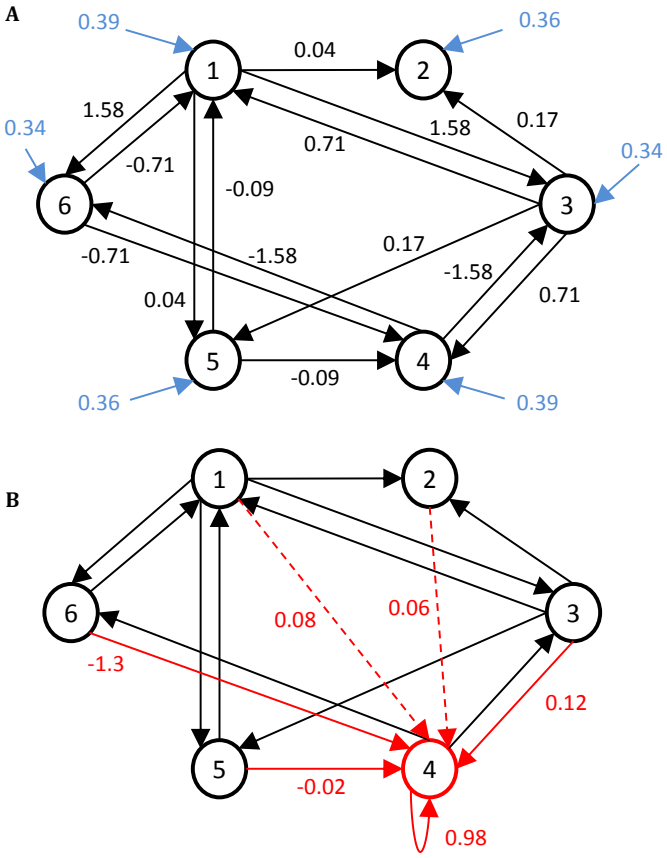

Fig. 2. Graph representation of a neuronal network with six nodes. **(A)** The original structural connectivity of the network. The blue arrows indicate the external inputs, h_i. Black arrows represent synaptic weights, w_{ij}, between nodes. **(B)** The perturbed structure of the network after a row perturbation is applied at 0 Hz (the minimum energy perturbation). The most fragile node and subnetwork is highlighted in red. Solid red arrows indicate existing connections with modified strengths. Dotted arrows indicate new connections. The black arrows have weights identical to the original network structure. The external input is also the same and omitted for clarity.

3. RESULTS

The network model is a probabilistic one and so far its average behavior has been described. To simulate realizations of the stochastic process, the Gillespie algorithm (Gillespie, 1977) can be used as in Benayoun et al. (2010). It is an exact algorithm that generates stochastic realizations faithful to the underlying distribution. Simulation results are presented for a sample network designed with only a few nodes to allow for easy visualization. The structure and function of the network in its stable state is described first, followed by its properties after destabilization.

3.1 Stable Network

A schematic of the original, stable network is shown in Figure 2A. The network has 6 neurons, and 14 connections. The decay rate, α, is set to 100 Hz, which caps the neuronal firing rates at that value. This network was simulated using MATLAB.

Raster plots of 1 second segments from 10 stochastic realizations are shown in Figure 3A. The spike times are marked as the instant when a node switches from quiescent to active. Firing rates are therefore closely related to the active state probabilities at the fixed point. All nodes fire fairly regularly in the raster plot.

3.2 Perturbed Network - DC Instability

The behavior of the perturbed network is now highlighted. The functional connectivity is computed by evaluating (15b) at the fixed point. Then, using the perturbation result, the minimum energy row perturbation for the system is computed and the corresponding structural perturbation that would manifest as this specific functional instability is computed. The structure of the perturbed network is shown in Figure 2B. The most fragile subnetwork corresponds to the incoming edges to node 4, an inhibitory neuron.

Figure 3B shows a segment of 10 stochastic realizations of the network activity after the structural perturbation is applied. The network is operating away from the baseline behavior at its fixed point with node 4 spiking less frequently. When the linearized system is perturbed so that an eigenvalue is moved to the origin, a stable manifold is on the cusp of becoming unstable. In a deterministic system, the emergence of an unstable manifold implies that for almost all initial conditions, the trajectory will grow without bound along the unstable manifold, at a rate proportional to the eigenvalue. In this system, since probabilities are being modeled, there are necessarily upper and lower bounds. The firing rates too are therefore capped. Furthermore, since the system is stochastic, trajectories do not indefinitely follow the unstable manifold but are kicked away and then recycled to the saddle point by the stable manifolds. This mechanism may explain the heterogeneity in firing rates seen during seizure activity, as trajectories veer about this fixed point.

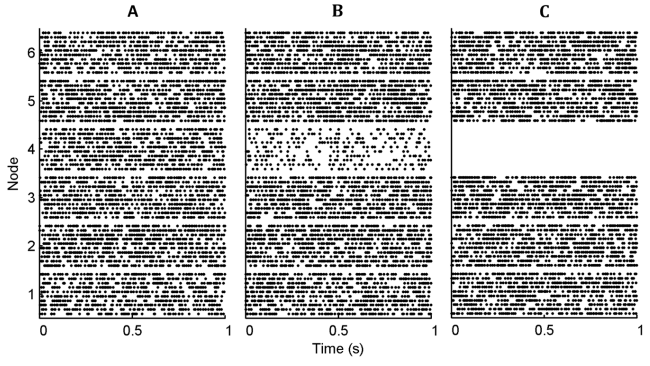

Fig. 3. Raster plots of 10 stochastic realizations of neural activity from **(A)** the original stable network, **(B)** the unstable network perturbed at 0 Hz with $\lambda = 0ms^{-1}$, and **(C)** $\lambda = 1ms^{-1}$. Node 4 is eventually silenced.

As the eigenvalue is set to be more positive, the trajectories follow the unstable manifold more strongly, the noisy resetting mechanism occurs less frequently and the active probabilities saturate at the boundaries more consistently during simulations, so that the nodes either approach tonic spiking or become silent (see Figure 3C). Inhibitory node 4 (where the perturbation is applied) is eventually silenced, and there is increased activity in nodes 3 and 6, which originally felt the strongest inhibition from node 4 prior to the perturbation. Cortical neurons from epilepsy patients show a similar increase or decrease in firing rates during seizure. Compare Figure 3 to the preictal and ictal spiking patterns respectively in Figure 4.

4. CONCLUSIONS

This study explored the relation between structure and function in a neuronal network model. The concept of network fragility was introduced and the minimum energy perturbation required to destabilize a linear network was derived. A procedure for linking structural connectivity to functional connectivity was developed for a probabilis-

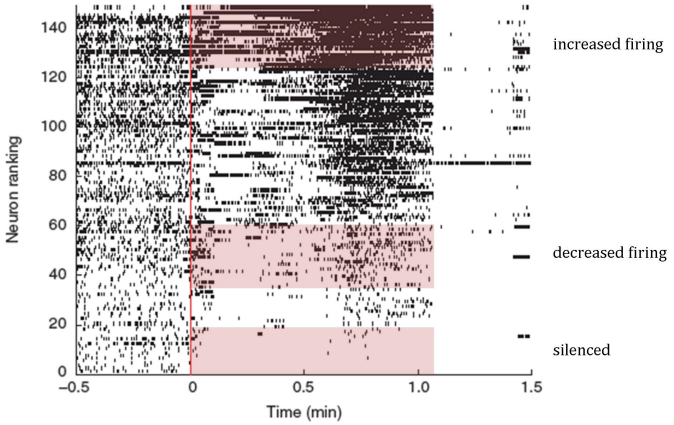

Fig. 4. Raster plot of cortical neurons sorted by mean spiking rate during seizure. The spiking rate of any given neuron is fairly uniform before seizure onset (marked by the vertical red line) suggesting a stable baseline behavior. During seizure, some neurons are silenced, a few fire almost tonically throughout, while others fire in bursts that appear as short streaks in the raster plot. Reprinted by permission from Macmillan Publishers Ltd: Nature Neuroscience (Truccolo et al., 2011), copyright 2011.

tic neuronal network so that a given functional instability could be reproduced by appropriate modifications to synaptic weights. These results were used to perturb a neuronal network with a stable baseline behavior to cause atypical functional activity. The mechanism by which aberrant activity was produced, namely wandering trajectories around a fixed point with an unstable manifold, may be indicative of neuronal or population dynamics in seizure.

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