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## **Manuscript Title**

Response dynamics of spiking network models to incoming seizure-like perturbation

## **Abbreviated Title**

Seizure-like propagation in spiking network models

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## **Author contribution**

DD and MC performed the research, analyzed data and wrote the paper, contributing equally; DD, MC and AD designed research and revised the paper.

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The authors declare no competing financial interests.

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## Abstract

Epilepsies are characterized by electrophysiological crises in the brain, which were first observed thanks to electroencephalograms. However, it is known that seizures originating from one or more specific regions may or may not spread to the rest of the brain, while the exact mechanisms are unclear. We propose three computational models at the neural network scale to study the underlying dynamics of seizure propagation, understand which specific features play a role, and relate them to clinical or experimental observations. We consider both network features, such as the internal connectivity structure and single neuron model, and input properties in our characterization. We show that a paroxysmal input leads to a dynamical heterogeneity inside the network, non-trivially related with its architecture, which may or may not entrain it into a seizure. Although hard to anticipate because of the intricate nature of the instability involved, the seizure propagation might be circumvented upon acting on the network during a specific time window. As we deal with a complex system, which seems to depend non trivially on various parameters, we propose a probabilistic approach to the propagative/non-propagative scenarios, which may serve as a guide to control the seizure by using appropriate stimuli.

**Significance:** Our computational study shows the specific role that the inhibitory population can have and the possible dynamics regarding the propagation of seizure-like behavior in three different neuronal networks. The study conducted in this paper results from the combination of structural aspects and time-continuous measures, which helps us unravel the internal dynamics of the network. We show the existence of a specific time window favorable to the reversal of the seizure propagation.

## 1 Introduction

Epilepsy is one of the most common neurological diseases (Beghi, 2019), which can take numerous forms. It is associated with the presence of electrophysiological seizures, usually recorded in humans using electroencephalogram (EEG). However, EEG recordings do not allow us to probe the activity of each neuron within the network. More recently, the recording carried out with microelectrode arrays made it possible to obtain spike information of the order of a hundred neurons (Peyrache et al., 2012; Dehghani et al., 2016).

It has then been observed that the neuronal activity does not necessarily

38 correspond to synchronized spikes of the whole neuron population, as previously  
39 modeled (*Computational Neuroscience in Epilepsy*, 2008) and can be modeled at  
40 different scales from cellular to whole-brain levels (Depannemaecker, Destexhe,  
41 Jirsa, & Bernard, 2021; Depannemaecker et al., 2020). In fact, it turns out that  
42 the dynamics of neural networks during seizures are more complex (Jiruska et  
43 al., 2013), and the mechanisms of propagation at different scales are poorly  
44 understood.

45 We take as a starting point examples of seizures where the inhibitory net-  
46 work is strongly recruited, while excitatory cells' firing is diminished. Fig.1  
47 shows three seizures from a patient who was recorded using Utah-arrays, be-  
48 fore resection surgery in a case of untractable epilepsy. From these intracranial  
49 recordings, 92 neurons have been identified and isolated and were classified  
50 into two groups: Fast-Spiking (FS) neurons and Regular-Spiking (RS) neu-  
51 rons, based on spike shape, autocorrelograms, and firing rates (Peyrache et  
52 al., 2012). Remarkably, direct cell-to-cell functional interactions were observed,  
53 which demonstrated that some of the FS cells are inhibitory while some of the  
54 RS cells are excitatory (see details in (Peyrache et al., 2012)). The three seizures  
55 shown in Fig.1 were taken from the analysis of (Dehghani et al., 2016) (see this  
56 paper for details), and are shown with the firing rate of each population of cells.  
57 During the seizure, we can observe a plateau of high activity of FS cells, and a  
58 strongly reduced activity of RS cells. This phenomenon of unbalanced dynamics  
59 between RS and FS cells was only seen during seizures in this patient (Dehghani  
60 et al., 2016). It shows that, in these three examples, the seizure was manifested  
61 by a strong "control" by the inhibitory FS cells, which almost silenced exci-  
62 tatory RS cells. It is interesting to see that a very different conclusion would  
63 be reached if no discrimination between RS and FS cells was performed, which  
64 underlies the importance of recording inhibitory cells during seizures.

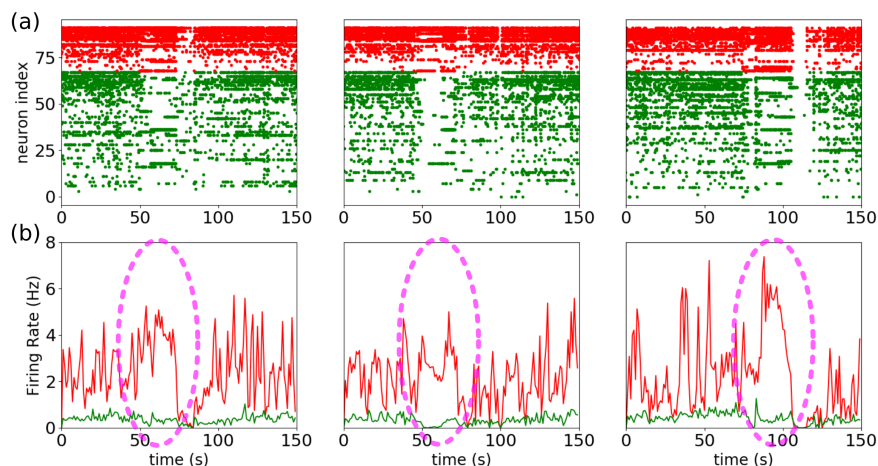


Figure 1: **Examples of inhibitory recruitment during seizures:** (a) Raster plot of three different seizures from the same patient, 92 neurones were identified 24 putatives inhibitory cells (red) and (68) putative excitatory cells (green) (b) Corresponding firing rate of the putative inhibitory population (red) and the putative excitatory population (green). A plateau of high activity of the putative inhibitory cells can be observed during the seizure (highlighted in dashed purple oval). Done with data from (Dehghani et al., 2016).

65 The region of the brain where the seizure starts is called the seizure focus,  
66 although in certain patients it is distributed over several foci (Nadler & Spencer,  
67 2014), then the seizure spreads to other regions of the brain. When another such  
68 region is reached, it can in turn display a seizure, or manage to control it, thus  
69 preventing its spread to further regions.

70 In order to gain understanding on the dynamics underlying this type of mech-  
71 anisms, we study the response of networks composed of three different neuron  
72 models (Adaptive exponential Integrate and fire (AdEx), Conductance-based  
73 Adaptive Exponential integrate-and-fire (CAAdEx), and Hodgkin-Huxley (HH)  
74 models) interacting through conductance-based synapses, to an incoming parox-  
75 ysmal (seizure-like) perturbation. We observe two types of behavior: one where  
76 the incoming perturbation transfers to the excitatory population, thus making  
77 its activity stronger than the input, and the other where only the inhibitory

78 population strongly increases its activity, thus controlling the perturbation. We  
79 then propose a more precise approach, based on the AdEx network, that mixes  
80 structural and dynamical ingredients in order to unravel key aspects of the  
81 mechanisms into play. Focusing on the different input connectivity profiles for  
82 each node in the network, we are able to build separate groups of neurons that  
83 display significantly different dynamics with respect to the perturbation. Fi-  
84 nally, we study the possibility of a proactive approach, based on the application  
85 of an extra stimulus with the aim of reversing the propagative behavior.

## 86 **2 Material and methods**

### 87 **2.1 Computational models**

88 We use for this study a mathematical model of electrophysiological activity  
89 based on ordinary differential equations, describing the dynamics of the neuron's  
90 membrane potential through their interactions.

91 Each model of neuron of the network is described by the equation (13) of  
92 the Adaptive Exponential integrate and fire (AdEx) model (Naud, Marcille,  
93 Clopath, & Gerstner, 2008).

$$\begin{aligned} C \frac{dV}{dt} &= g_L(E_L - V) + g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right) - w + I_{syn} & (1) \\ \tau_w \frac{dw}{dt} &= a(V - E_L) - w \end{aligned}$$

94 When the membrane potential crosses a threshold, a spike is emitted, and the

95 system is reset as in the equation (16).

$$\text{if } V \geq V_D \text{ then } \begin{cases} V \rightarrow V_R \\ w \rightarrow w + b \end{cases} \quad (2)$$

96 Parameters used for the excitatory (RS) and inhibitory (FS) populations are  
 97 respectively  $V_t = -50$  mV and  $V_i = -48$  mV,  $D_t = 2$  mV and  $D_i = 0.5$  mV,  
 98  $b = 100$  pA and  $b = 0$  pA, and  $\tau_w = 1000$  ms for RS. For both population:  
 99  $C_m = 200$  pF,  $g_l = 10$  nS,  $E_l = -65$  mV,  $a = 0$  nS,  $V_{reset} = -65$  mV,  
 100  $t_{refractory} = 5$  ms.

101 In order to compare some of the results obtained with the AdEx model  
 102 we used two other models of neuronal activity. First the Conductance-based  
 103 Adaptive Exponential integrate-and-fire model (CAdEx), which solves some of  
 104 the limitation of the AdEx model (Górski, Depannemaecker, & Destexhe, 2021).  
 105 The equation are as follow:

$$C \frac{dV}{dt} = g_L(E_L - V) + g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right) + g_A(E_A - V) + I_s \quad (3)$$

$$\tau_A \frac{dg_A}{dt} = \frac{\bar{g}_A}{1 + \exp\left(\frac{V_A - V}{\Delta_A}\right)} - g_A$$

106 When the membrane potential crosses a threshold, a spike is emitted, and the  
 107 system is reset as in the equation (16).

$$\text{if } V \geq V_D \text{ then } \begin{cases} V \rightarrow V_R \\ g_A \rightarrow g_A + \delta g_A \end{cases} \quad (4)$$

108 Parameters used for inhibitory (FS) populations are:  $g_l = 10$  nS,  $E_l =$   
 109  $-65$  mV,  $V_T = -50$  mV,  $g_a = 0$ . nS,  $E_A = -70$  mV,  $\delta g_A = 0$  nS,  $C = 200$  pF,

110  $\Delta_T = 0.5$  ms,  $V_A = -45$  mV,  $I_s = 0.0$  nA, *refractory* = 5 ms,  $V_{reset} =$   
 111  $-65$  mV,  $\tau_{A} = 0.01$  ms,  $\Delta_A = 0.5$  mV and for the excitatory (RS):  $g_l = 10$  nS,  
 112  $E_l = -65$  mV,  $V_T = -50$  mV,  $\delta g_A = 1$  nS,  $E_A = -65$  mV,  $\delta g_A = 1$  nS,  
 113  $C = 200$  pF,  $\Delta_T = 2$  mV,  $V_A = -30$  mV,  $I_s = 0.0$  nA,  $t_{refractory} = 5$  ms,  
 114  $V_{reset} = -65$  mV,  $\tau_{A} = 1.0$  s,  $\Delta_A = 1$  mV

115 Then we use the Hodgkin-Huxley model (Hodgkin & Huxley, 1952), hereafter  
 116 denoted HH, with the following equations:

$$C_m \frac{dV}{dt} = -g_l(E_l - V) - g_K n^4(V - E_K) - g_{Na} m^3 h(V - E_{Na}) + I_{syn} \quad (5)$$

117 with gating variables (in ms):

$$\frac{dn}{dt} = \frac{0.032(15. - V + V_T)}{(\exp(\frac{15. - V + V_T}{5.}) - 1.)}(1. - n) - 0.5 \exp(\frac{10. - V + V_T}{40.})n \quad (6)$$

118

$$\frac{dh}{dt} = 0.128 \exp(\frac{17. - V + V_T}{18.})(1. - h) - \frac{4.}{1 + \exp(\frac{40. - V + V_T}{5.})}h \quad (7)$$

119

$$\frac{dm}{dt} = \frac{0.32(13. - V + V_T)}{(\exp(\frac{13. - V + V_T}{4.}) - 1.)}(1 - m) - \frac{0.28(V - V_T - 40.)}{(\exp(\frac{V - V_T - 40.}{5.}) - 1.)}m \quad (8)$$

120 With  $C_m = 200$  pF,  $E_l = -65$  mV,  $E_{Na} = 60$  mV,  $E_K = -90$  mV,  
 121  $g_l = 10$  nS,  $g_{Na} = 20$  nS,  $g_K = 6$  nS,  $V_{Texc} = -50$  mV,  $V_{Tinh} = -52$  mV.

122 For all types of neuron models, the parameters have been chosen in bio-  
 123 physical range (see (Naud et al., 2008; Górski et al., 2021; Hodgkin & Huxley,  
 124 1952; Hille, 1992)) in order to keep the basal asynchronous irregular activities  
 125 (Brunel, 2000) into a range of firing rate coherent with experimental observa-  
 126 tions (El Boustani, Pospischil, Rudolph-Lilith, & Destexhe, 2007).

127 The network is built according to a sparse and random (Erdos-Renyi type)  
 128 architecture where a fixed probability of connection between each neurons is set  
 129 to 5%. We considered a network model of ten thousand neurons, built according



130 to specific properties of the cortex. This network is made of an inhibitory  
131 (FS) and an excitatory (RS) population, respectively representing 20% and  
132 80% of the total size of the system as previously done in (Carlu et al., 2020) The  
133 communication between neurons occurs through conductance-based synapses.  
134 The synaptic current is described by the equation (21).

$$I_{syn} = g_E(E_E - V) + g_I(E_I - V) \quad (9)$$

135 Where  $E_E = 0$  mV is the reversal potential of excitatory synapses and  $E_I =$   
136  $-80$  mV is the reversal potential of inhibitory synapses.  $g_E$  and  $g_I$ , are respec-  
137 tively the excitatory and inhibitory conductances, which increase by quantity  
138  $Q_E = 1.5$  nS and  $Q_I = 5$  nS for each incoming spike. The increment of conduc-  
139 tance is followed by an exponential decrease according to the equation (22).

$$\frac{dg_{E/I}}{dt} = -\frac{g_{E/I}}{\tau_{syn}} \quad (10)$$

140 with  $\tau_{syn} = 5$  ms

141

142 The network thus formed receives an external input, based on the activity  
143 of a third population (excitatory) of the same size as the excitatory population.  
144 Each of its neurons is connected to the rest of the network according to the  
145 same rule as mentioned earlier (fixed probability of 5 % for each connection).  
146 This external population produces spikes with a Poissonian distribution at a  
147 given tunable rate. The external perturbation that mimics the incoming seizure  
148 occurs through the augmentation of this firing rate.

149 The shape of the latter is described by the equation (23).

$$\begin{aligned} v_{pert}(t) = & \beta + \alpha * (\exp(-(t - T_1)^2 / (2 * \tau_{on}^2)) * H(-(t - T_1)) \\ & + H(-(t - T_2)) * H(t - T_1) + \exp(-(t - T_2)^2 / (2 * \tau_{off}^2)) * H(t - T_2)) \end{aligned} \quad (11)$$

150 where  $H$  is the heaviside function and  $\beta = 6$  Hz is the basal constant input.  
151 This function takes the general form of a high plateau, where  $T_1$  and  $T_2$  are  
152 the times when the perturbation reach its beginning and end respectively, and  
153  $\alpha$  defines its maximal height.  $\tau_{on}$  and  $\tau_{off}$  are respectively time constants  
154 associated with the exponential rise and decay of the perturbation.

## 155 2.2 Coarse graining and continuous analysis

156 In order to analyse in details what mechanisms are at play in the network  
157 during a seizure-like event, we resort to a combination of two methods : a so-  
158 called *structural coarse-graining*, that is we gather neuron models in  $n$  groups  
159 according to their inhibitory in-degree (the number of inhibitory connections  
160 they receive, we justify this approach in the body), and we study their time  
161 evolution through statistics of their membrane potential (mean and alignment)  
162 over these groups. In other words, at each integration time step, we will obtain  
163  $n$  values of mean membrane potentials, one for each group, as well as  $n$  values  
164 of Kuramoto order parameter (measuring alignment in groups).

165 To obtain the Kuramoto order parameter, we first transform the single neu-  
166 rons membrane potentials into phase variables by applying a linear mapping  
167  $v_j \in [V_R, V_D] \rightarrow \theta_j^v \in [0, \pi]$ . Then the Kuramoto order parameter is computed  
168 through the equation (24).

$$R \exp i\Psi = \frac{1}{N} \sum_j \exp i\theta_j^v \quad (12)$$

169  $R \in [0, 1]$  gives the degree of “alignment” (if it persists in time, one would  
170 say synchronization) :  $R = 1$  implies full alignment , while  $R = 0$  implies no  
171 alignment whatsoever.  $\Psi \in [0, \pi]$  tells us the mean phase of the transformed  
172 variables (directly related to the mean membrane potential).

173 Let us mention one caveat here. The membrane potentials are not mapped  
174 on the full circle, to avoid artificial periodicity of the obtained angles: having  
175  $V = V_R$  is not the same as having  $V = V_D$ . One may thus ask why such a mea-  
176 sure is used instead of the usual measures of dispersion such as the standard  
177 deviation. We use the Kuramoto order parameter because it gives a naturally  
178 normalized quantity, thus allowing a direct comparison of what is happening at  
179 each time step. We acknowledge that it would be formally possible to use a nor-  
180 malized version of standard deviation, but the normalization procedure involved  
181 would not be as intuitive. Besides, the Kuramoto order parameter allows direct  
182 calculation of higher order types of alignment by using the generalized version:  
183 adding an  $n$  multiplier to the exponential would give a measure of the degree  
184 of partitioning into  $n$  clusters, which can turn out to be useful in subsequent  
185 studies.

## 186 2.3 Code Accessibility

187 The code/software described in the paper is freely available online at [URL  
188 redacted for double-blind review]. The code is available as Extended Data and  
189 is run on Linux operating system.

## 190 3 Results

191 In this section we show how, in networks of various neuron models, a parox-  
192 ysmal external stimulation can trigger a crisis or not, depending on various  
193 parameters. We show how the situations differ from model to model and what

194 are the common features. Then, we turn ourselves to a structural analysis based  
 195 on mean firing rates of individual neuron models to guide a particular coarse-  
 196 graining, which we use as a filter to observe the dynamics and gain further  
 197 understanding, from both qualitative and quantitative perspectives. Finally we  
 198 show how this study can guide proactive approach to reduce the chances of crisis  
 199 propagation.

### 200 3.1 Propagative and Non-propagative behaviors

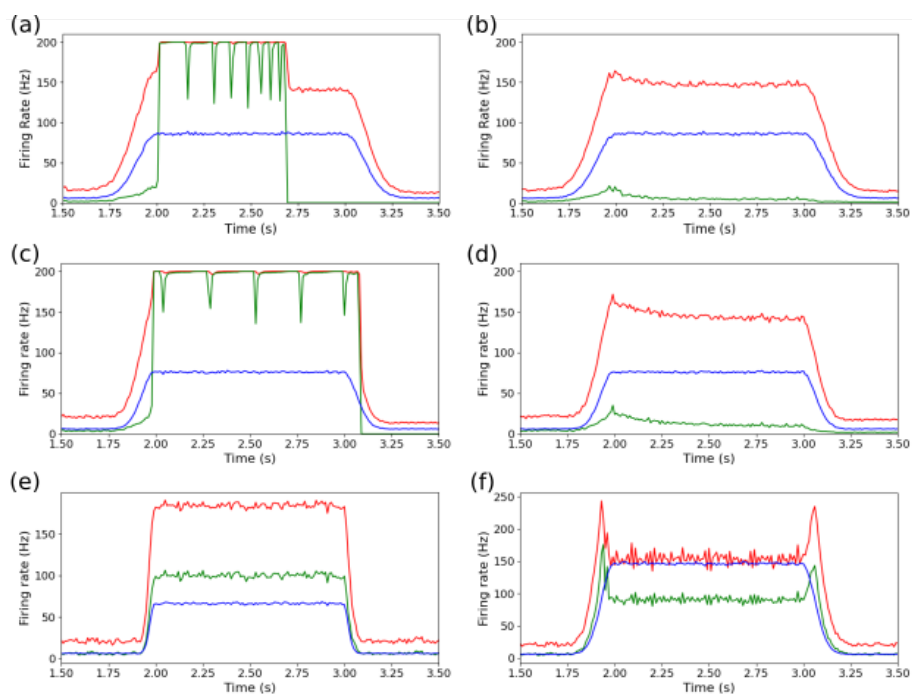


Figure 2: **Firing rate of the network populations in response to a perturbation:** propagative and non-propagative behaviors (respectively left and right columns) for AdEx model ((a) and (b)), with amplitude of perturbation  $\alpha = 80Hz$  and  $\tau_{slope} = 100ms$  ; CAdEx model ((c) and (d)) with  $\alpha = 70Hz$  and  $\tau_{slope} = 80ms$  ; HH model (e) with  $\alpha = 60Hz$  and  $\tau_{slope} = 60ms$  and (f) with  $\alpha = 140Hz$  and  $\tau_{slope} = 60ms$ . [FIGURE MODIFIED]

201 In this study we assume that the networks depicted in the previous section

202 represent a small cortical area receiving connections from an epileptic focus.  
203 Specifically, the arrival of the seizure is modeled by a sudden rise in the firing  
204 rate of the external (afferent) Poisson region where the crisis comes from, or  
205 originates. In other words, we are not concerned with how crises *originate*  
206 (epileptogenesis), but how they can *propagate*. Therefore, we will frame our  
207 analysis into two main behaviors : *propagative*, *i.e* the network develops an  
208 excitatory firing rate greater than the input, which makes it able to propagate  
209 the crisis to efferent regions, and *non-propagative* behavior where the excitatory  
210 firing rate is lower than the input, thus attenuating the incoming signal.

211 As mentioned (and detailed) in the method section, the perturbation starts  
212 with an exponential growth followed by a plateau and ends with an exponential  
213 decrease, going back to the basal level, see blue curves in Fig.2). We show  
214 in this figure the response of the various networks to this type of disturbance.  
215 Here we can distinguish between two classes of macroscopic differences between  
216 propagative and non-propagative scenarios : one where the difference is binary  
217 (AdEx and CAdEx), *i.e* the network either features

218 a very strong increase in the firing rate of the inhibitory *and* excitatory  
219 populations, either the sharp increase in the firing rate concerns the inhibitory  
220 population only, thus strongly limiting the activity of the excitatory population  
221 (consequently preventing the disturbance from spreading to the next region).  
222 From this perspective, the propagative scenario can be understood as a loss  
223 of balance between excitatory and inhibitory firing rates, which the network  
224 struggles to find once the excitatory population has exploded. Interestingly  
225 these two scenarios can occur for the same global shape of the perturbation  
226 but changing only the noise and network realizations. It must be noted that  
227 the 200Hz maximum frequencies measured here are the results of the temporal  
228 binning of the global spiking dynamics, taken as  $T = 5ms$ , which corresponds to

229 the refractory time of the single neurons in Adex and CAdEx. Upon choosing  
 230 a shorter binning, *e.g.*  $T = 1ms$ , higher frequency peaks are observed, going  
 231 up to  $800Hz$ , thus hinting at overall faster dynamics. The second class (HH)  
 232 shows a rather continuous difference between propagative and non-propagative  
 233 behaviors, depending on the amplitude of the perturbation (this will become  
 234 clearer in the next section). This said, there is still some degree of stiffness in  
 235 the HH scenario, where the non-propagative case shows peaks of both excitatory  
 236 and inhibitory activities at the beginning and end of the plateau.

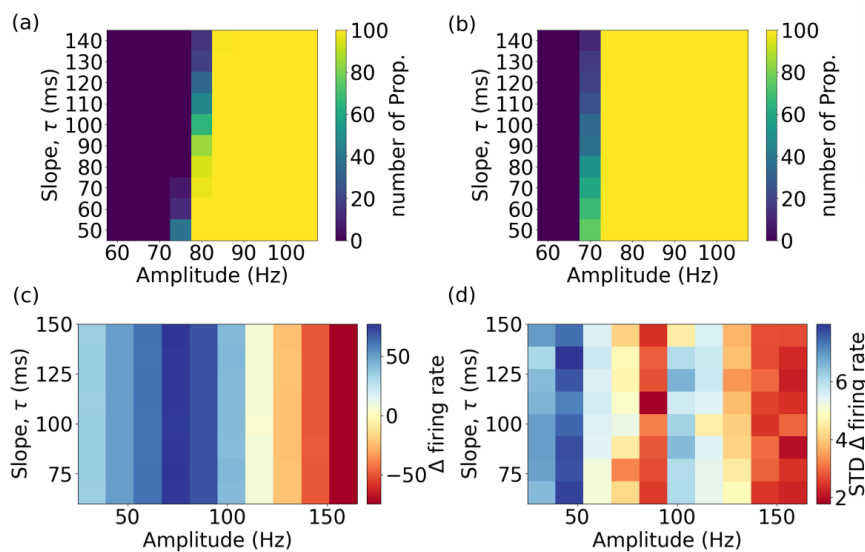


Figure 3: **Grid search on the amplitude and slope of the incoming perturbation for each network.** Panels (a) and (b) show the number of realizations which propagate, respectively for Adex and CAdEx networks. Panels (c) and (d) show respectively, for HH networks, the means and standard deviations (over realizations) of the difference of firing rates between excitatory and Poisson populations ( $\Delta \text{ firing rate} = \nu_e - \nu_{Pois}$ ), averaged over the length of the plateau. [FIGURE MODIFIED]

## 237 3.2 Parameter search

238 To study how the shape of the perturbation affects the networks response, we  
239 screened different time constants of the exponential growth rates and maximum  
240 amplitude of the plateau with 100 seeds (for both network and noise realizations)  
241 for each couple of values, see Fig.3)

242 and probed, in the case of AdEx and CAdEx (respectively (a) and (b),  
243 the number of realizations which *did not* yield propagative behavior. In the  
244 HH case, the perspective is a little different : we chose to show two figures,  
245 displaying means and standard deviations over realizations of the difference  
246 in firing rate between excitatory and Poisson populations (averaged over the  
247 plateau),  $\Delta \text{ firing rate} = \nu_e - \nu_{Pois}$  rate (respectively (c) and (d)). As can  
248 be expected, for all networks (AdEx, CAdEx and HH) the amplitude of the  
249 perturbation plays a determinant role in the type of scenario we eventually find  
250 (propagative or not), however in opposite directions and of different nature.  
251 Indeed, for both AdEx and CAdEx, increasing the amplitude increases the  
252 chance of having a propagative scenario for a fixed slope, in a binary fashion,  
253 while in the case of HH the contrary is observed, and in a continuous fashion.  
254 Furthermore, in AdEx and CAdEx networks, we observe that when the arrival  
255 of the disturbance is abrupt (i.e. small time constant for exponential growth),  
256 it is systematically propagative, no matter which amplitude is considered in the  
257 range [60 – 120Hz]. On the other hand, if the perturbation rises sufficiently  
258 slowly (i.e. large exponential time constant), it does not significantly affect  
259 the excitatory population of the network. These observations show that we are  
260 dealing with a phenomenon where dynamics play a crucial role. Also, we observe  
261 a slight coupling effect between slope and amplitude : for higher amplitudes,  
262 the propagation range extends to slower perturbations. On the contrary, in  
263 the HH network, it seems that the slope does not play any major role, hinting

264 at a much less dynamical effect : the difference manifest themselves as local  
265 equilibria of the networks under considerations, reached no matter the time  
266 course. Moreover, the standard deviations, besides showing no clear dependence  
267 on neither amplitude nor slope, are very small compared to the means, thus  
268 evidencing that noise neither plays any significant part here. These observations  
269 highlight once again deep differences between the two types of network and their  
270 respective phenomenology.

271 Interestingly, in the case of AdEx and CAdEx, there exists a limit, bi-stable  
272 region where the perturbation may or may not propagate in the network, de-  
273 pending on the noise realisation. Thus, the global scenario does not trivially  
274 depend on the amplitude and time constants of the perturbation in this region,  
275 which, besides being of primary importance in the case of seizure propagation,  
276 also makes it a perfect candidate to study more deeply the internal mechanisms  
277 at play, and will thus be the main focus of the remainder of this paper.

### 278 **3.3 Influence of structural aspects on the dynamics**

279 In the following, we turn our attention to the bi-stable region of AdEx and  
280 CAdEx networks, where the two behaviors are present, and investigate what  
281 can be the source of the divergence. There are two main differences between  
282 the simulations under consideration: the realization of the network structure  
283 and the realization of the external input, as both rely on random number gener-  
284 ators. We have therefore successively fixed each of them, and observed that the  
285 two behaviors were still present. Also, the global scenarios were indistinguish-  
286 able from those showed so far. First, this allows us to fix the network structure  
287 (which will become determinant in this part) without losing the richness of the  
288 phenomenology. Second, this tells us that what shapes the distinction between  
289 the two phenomena is more complex than a single question of structure, or real-



290 ization of the input. Another perspective is then needed to explore the internal  
291 dynamics of the network in both scenarios. As the models into consideration  
292 have very large number of dimensions, as well as quite intricate structures, brute  
293 force analytical approaches are simply not conceivable.

294 Let us then take a step back and investigate the relationship between the  
295 firing rate of each neuron and its number of afferent (input) connections of  
296 the three kinds: excitatory ( $N_{inp}^{Exc}$ ), inhibitory ( $N_{inp}^{Inh}$ ) and Poissonian ( $N_{inp}^{Pois}$ ).  
297 Fig.4(a) shows the average firing rates ( $\nu_E^{NP}$  and  $\nu_I^{NP}$ ) measured over the whole  
298 non-propagative (NP) scenario for each neuron in the AdEx network (simply  
299 defined as the total number of spikes divided by the total integration time,  
300 after having discarded a transient), plotted as a function of the three different  
301 connectivity profiles.

302 Note here that averaging over simulations for the sake of robustness might  
303 be a delicate matter, as we might lose constitutive differences in the process.  
304 As we are dealing with highly variable situations, we have to make compro-  
305 mises between generalizability and relevance. Therefore, we start with a single  
306 realization to then guide larger and more systematic investigations.

307 Interestingly, we see a much stronger influence coming from the inhibitory  
308 in-degree than from the Poissonian and excitatory ones. Counter-intuitively,  
309 it even seems that excitatory in-degree has barely any effect at all on total  
310 measured firing rates. Indeed, from the point of view of Pearson's correlation,  
311 inhibitory in-degree is much more (anti)-correlated with the firing rate than the  
312 excitatory in-degree (almost no correlation) or the Poissonian in-degree (little  
313 correlation). Note that we observe the same structure for propagative situations  
314 (results not shown). This said we can compile the previous results and analyze  
315 whether the most salient in-degrees (inhibitory and Poissonian) has any influ-  
316 ence on the *difference* between propagative and non-propagative situations, see

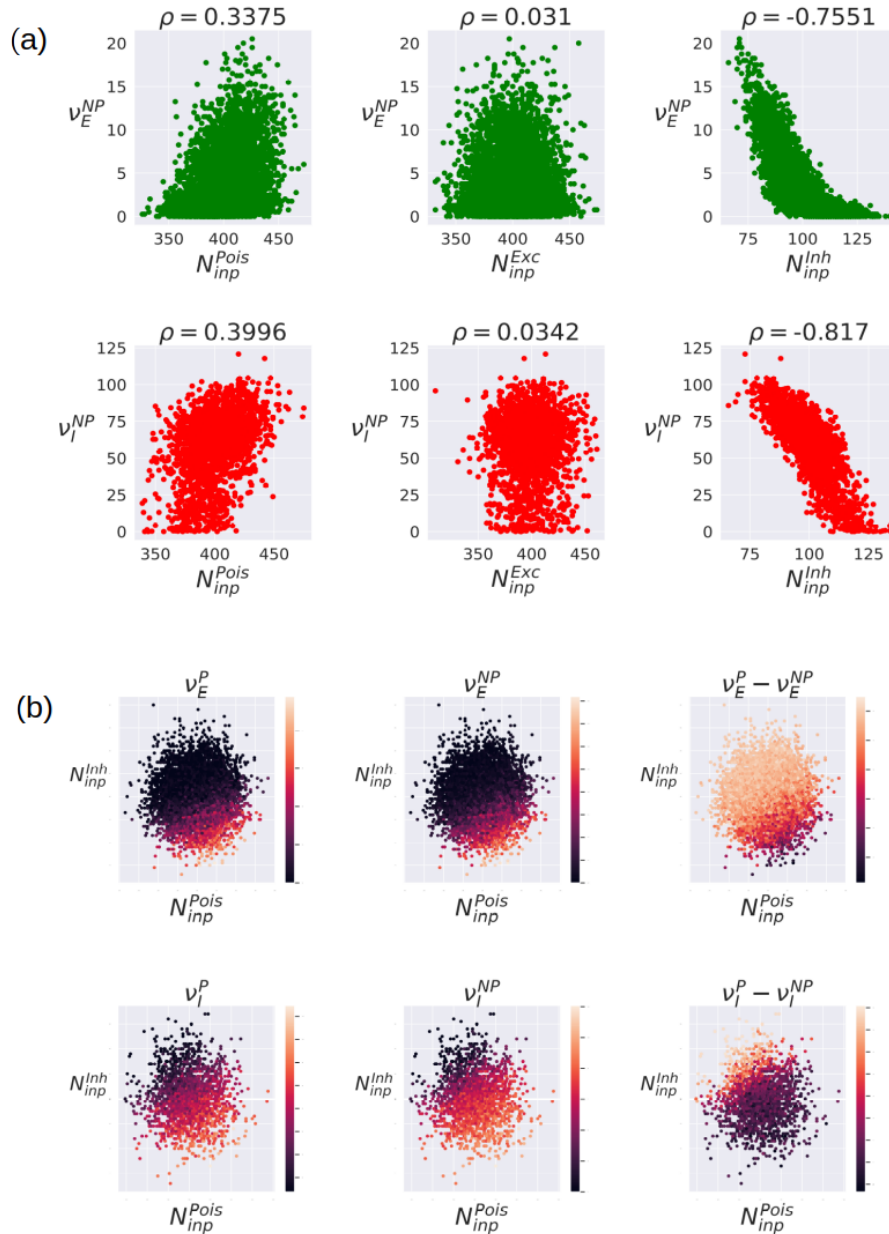


Figure 4: **Influence of connectivity on single neurons firing rates:** (a) Influence of poissonian ( $N_{inp}^{Pois}$ ), excitatory ( $N_{inp}^{Exc}$ ) and inhibitory ( $N_{inp}^{Inh}$ ) input connectivity on the firing rates of excitatory neurons ( $\nu_E^{NP}$ ), and inhibitory ones ( $\nu_I^{NP}$ ) in non-propagative scenario (NP) of the AdEx network. The standard pearson correlation coefficient  $\rho$  is estimated. (b) Time averaged single neuron firing rates and differences in propagative vs non-propagative regimes, as a function of both inhibitory and poissonian in-degrees. [FIGURE MODIFIED]

317 Fig.4(b).

318 Here we see that the global dependency of the average single neuron firing  
319 rates on inhibitory and Poissonian connectivity does not qualitatively change  
320 between propagative and non-propagative regimes. However, the difference dis-  
321 plays an inverse dependency on both variables: despite maintaining the same  
322 general hierarchical structure, the crisis tends to compensate a little bit for it.  
323 In other words, the neurons that are initially less firing, due to their struc-  
324 tural properties, are the most impacted by the crisis. Furthermore, it must be  
325 noted that, although there is no correlation between inhibitory and Poissonian  
326 in-degrees (as can be expected from random connectivities), we still see a slope  
327 of the firing rate in the 2D+color representation, highlighting that they both  
328 play a role in the single neurons long term dynamics.

329 Although these results are not sufficient to explain the propagation or non-  
330 propagation behaviors, it is already worth pointing that, not only they establish  
331 a first link between structure and dynamics, but give insight on how *differences*  
332 of dynamics are correlated with structure, hence giving interesting leads on pos-  
333 sible ways of analyzing time-series. Indeed one can think of deploying algorithms  
334 to infer structural or functional connectivity from the spiking regimes of single  
335 neurons in both “nominal” and crisis dynamics, as well as their difference.

336 However, it seems necessary from our current perspective to go deeper into  
337 the temporal evolution. In order to probe whether the differences in the indi-  
338 vidual mean firing rates give single neurons specific roles in the dynamics, we  
339 now start classifying in the AdEx network the indices of the neurons in the  
340 raster plot according to the total number of spikes they emit during the whole  
341 simulation. We chose for this purpose a representative propagative scenario for  
342 two reasons : 1) it is clearly the most consequential case in the context of seizure  
343 dynamics and spreading, hence 2) if no distinction is visible here, the previous

344 static approach (in the sense “time-averaged”) would be of little dynamical rel-  
345 evance. The sequence of propagation of the perturbation then appears visually,  
346 see Fig.5(a). We observe, in the case of propagation a fast cascade, which is con-  
347 sistent with the experimental observations (Neumann et al., 2017): the model  
348 shows that some neurons are quickly ”entrained” in a sequence at the onset of  
349 the seizure. In addition, there is no perfect synchronization of the action poten-  
350 tials of all neurons. This is an interesting result, coherent with the observations  
351 on epilepsy in the last decade (Jiruska et al., 2013).

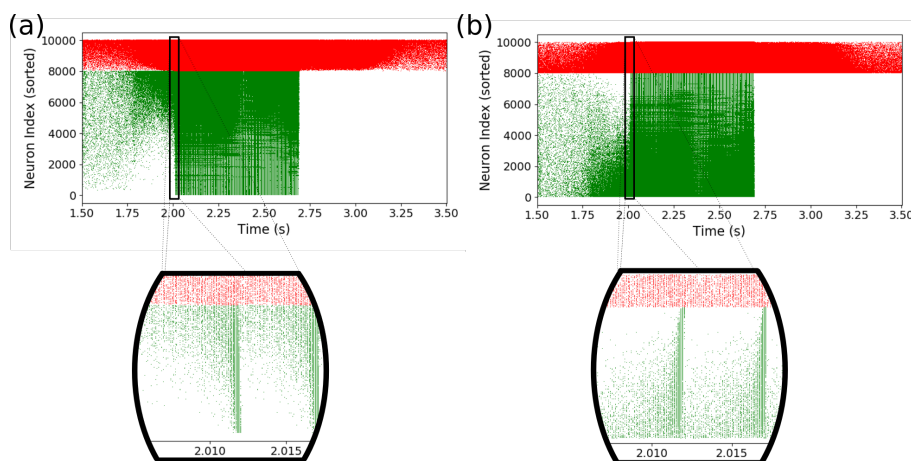


Figure 5: **Dynamics in propagative situation (AdEx):** (a) Raster plot of a simulation with propagative behavior, neuron indices are sorted according to the number of spikes during the simulation. A ”cascade” phenomenon can be observed when zooming on the onset of the perturbation propagation in the excitatory population. (b) The same cascade phenomenon is observed when neuron indices are sorted in function of the number of inhibitory inputs received.

352 Secondly, we examine the same situation, but sorting neuron indices as a  
353 function of the number of inhibitory inputs they receive (as shown Fig. 5(b), as  
354 it is the most influential structural feature we observed. Here too, the cascade  
355 phenomenon is clearly visible, showing that the inhibitory input connectivity  
356 has a central influence on the dynamics at play during the perturbation.

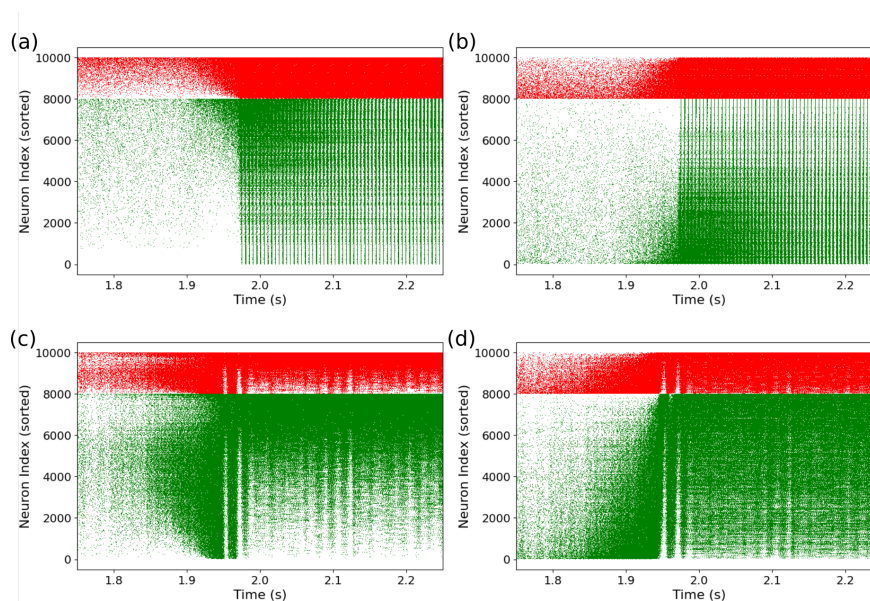


Figure 6: **Dynamics in propagative situation (CAdEx and HH)**: Same plot as previously shown but for CAdEx network ((a) spike-sorting, (b) inhibitory in-degree sorting) and HH network ((c) spike-sorting, (d) inhibitory in-degree sorting). Cascade phenomena are still observable in panels (a),(b) and (d), hence showing its robustness, but not in (c), where propagation takes a slightly different form, highlighting the contrast induced by different perspectives on a single complex dynamics.[NEW FIGURE]

357 Fig.6 shows the same pictures for CAdEx and HH networks. We see here  
358 that CAdEx network's behaviors are very similar to AdEx : sorting with firing  
359 rate or inhibitory in-degree give very similar structures and we can distinguish  
360 here too the cascading effect at the onset of the perturbation, following the  
361 indices. HH networks show quite a different phenomenology. First the two  
362 sorting do not show the same structures, which hints at a more subtle mapping  
363 between inhibitory in-degree and long-term single neuron model dynamics. In  
364 the firing rate sorting, we can still distinguish 3 blocs of distinct activity, and  
365 thus of populations, corresponding to the 3 key periods of the simulation : before  
366 stimulation, at the onset, and during the stimulation. Interestingly it seems that  
367 before and during the stimulation different populations of neuron models are

368 distinctly mobilized. While before the stimulation, the central neurons (with  
369 respect to their indices) are active, a double cascade contaminates the rest  
370 of them (towards higher and lower indices) at the onset, ending in a general  
371 surge of activity. This must be contrasted with the in-degree sorting panel,  
372 where the cascade is more unidirectional, as the main activity slides from low  
373 connectivity indices (less connected) to the higher ones, until all neurons fire.  
374 This emphasizes the importance of the perspective chosen to analyse complex  
375 behavior.

376 Altogether these results show the relevance of adopting a perspective based  
377 on the inhibitory in-degree : it yields interesting insights on the internal or-  
378 ganisation of the network before and during the paroxysmal event. In the  
379 next section, we push further this analysis by comparing propagative and non-  
380 propagative scenario, and make use of the continuous measures introduced in  
381 Material and Methods.

### 382 **3.4 Continuous measures on subgroups of neurons**

383 We now move to a deeper investigation of the AdEx networks behavior, in  
384 order to better grasp the internal dynamical structure into play. We chose this  
385 model among the three because : 1) it is the simplest, which 2) reduces the  
386 computational burden for a more systematic analysis, although 3) it can still  
387 yield various types of single neuron dynamics (which makes it a relevant model  
388 per se) and 4) is widely use for neuronal network simulations. To achieve so, we  
389 first consider groups of neurons defined by their inhibitory in-degree. These are  
390 somewhat artificial, as they are only statistical reflections of topological aspects  
391 of the network (i.e, there is no reason to think a priori that all neurons having  
392  $n$  inhibitory inputs would have more privileged links among themselves than  
393 with those having  $n + 1$ ). However, they allow in principle a variable degree

394 of categorization, based upon the sampling of the inhibitory in-degree distri-  
395 bution, which eventually leads to different levels of (nonlinear) coarse-graining  
396 (although we will consider only one such sampling here). This is a first bottom-  
397 up step towards a coarser description of the system, and hence, may guide  
398 reliable modeling attempts at larger scales. Secondly, we switch our analysis to  
399 continuous variables, which allow a finer and more systematic analysis of the  
400 dynamics, as they don't depend on spike times. Indeed, although spike tim-  
401 ings are the most accessible collective measures in real-life systems, which make  
402 them the most fitted candidates for "transferable" studies, we want here to take  
403 advantage of the virtues of mathematical modeling to probe the insides of these  
404 simulations, to then be able to draw conclusions on more accessible observables.  
405 We focus here uniquely on membrane potentials, as they are the closest proxy  
406 of the firing dynamics in the network and chose to use two main measures based  
407 on them: the mean  $\mu_V$  and a modified Kuramoto order parameter  $R$ , which  
408 gives a naturally normalized measure of instantaneous alignment (or similarity)  
409 of the membrane potentials. Both are defined in time, over a class of neurons.  
410 Note here that the network connectivity *is still* held fixed, as these calculations  
411 require a lot of time and computational power, especially as we always consider  
412 50 noise realizations. We will give evidence of the robustness of our observations  
413 in the next part.

414

#### 415 **Mean membrane potential in time**

416 We show in Fig.7(a)-(b) the mean membrane potential  $\mu_V$  defined for each  
417 group of excitatory (RS) and inhibitory (FS) neurons in time, averaged over  
418 realizations (top row), and standard deviation over realizations (bottom row),  
419 in propagation (a) and non-propagation (b) scenarios. The different realizations  
420 refer here to the incoming noisy input, while the network structure is held fixed.

421 All the data presented from now are obtained by regrouping neurons having  
422 the exact same inhibitory in-degree, thus corresponding to a discrete one-to-one  
423 sampling of the input distribution. Note that, given the network architecture  
424 under consideration, the mean number of afferent inhibitory synapses, defined  
425 over both populations of neurons, is defined by  $\mu_i = N_i \times p_{connect} = 2000 \times$   
426  $0.05 = 100$ , where  $N_i$  is the total number of inhibitory neurons and  $p_{connect}$  is the  
427 connection probability, while the standard deviation is  $\sigma_i = \sqrt{N_i \times p_{connect}} =$   
428  $10$ . Besides, the groups are defined operationally, by grouping in the range  
429  $n \in [0, 200]$  the neurons receiving  $n$  inputs. Thus, if no neuron receives  $n$  inputs,  
430 the group is not represented. Accordingly, having approximately 60 groups tells  
431 us that we sample the distribution from around  $\pm 30$ , that is  $3\sigma_i$ .

432 We see from this figure that the inhibitory in-degree profile seems to play a  
433 major role in the overall dynamics. Indeed, as the perturbation is growing, we  
434 can first observe a strong effect on the mean membrane potential of every ex-  
435 citatory neuron, then followed by a low-potential cascade initiated from weakly  
436 coupled neurons and following the group structure. This latter effect is much  
437 clearer in the case of inhibitory neurons, where the cascade follows very well the  
438 input profile, in both propagative and non-propagative scenarios. Note that the  
439 low-potential area can be easily understood as a high-firing regime: neurons fire  
440 as soon as they leave their resting potential, thus displaying very low values of  
441 membrane potential when calculated (and sampled) over time.

442 Interestingly these pictures show that, up to the decisive point of the crises,  
443 the continuous measures look very similar, thus hinting at an instantaneous  
444 finite-size fluctuation causing the whole network to explode. Also, it is note-  
445 worthy that the new “hierarchy” set by the cascade is conserved in the non-  
446 propagative regime, while propagation seems to have an overall reset effect.

447 Also, we see from these graphs that there is a particular time window where



448 the variance of the mean membrane potential is larger for the most inhibitory-  
449 connected neurons, in both RS and FS populations (although it appears clearer  
450 for RS ones here, because of the need to rescale the FS colorbar to have com-  
451 parable results). We found that this time window defines the period when the  
452 network can actually switch to propagation: the high variance corresponds to  
453 different times when various realizations “explode”, and thus defines a region of  
454 instability.

455 A central point to raise here is that what makes the difference between  
456 propagative and non-propagative scenarios is most likely *not* an *infinitesimal*  
457 instability defined from a macroscopic perspective, i.e, that is due to a positive  
458 eigenvalue of a Jacobian defined from a large scale representation (Mean-Field  
459 for example), otherwise the non-propagative behavior would simply not be ob-  
460 servable (as, except for chaotic dynamics, we do not observe unstable trajec-  
461 tories in phase space). Indeed, what differs between the various simulations is  
462 the noise realization of the external input, which may, or may not, bring the  
463 system to a point of instability. The external Poissonian drive, with *finite-size*  
464 fluctuations is thus constitutive of the scenarios we observe.

465 To gain more insight into the diversity of dynamics across neuron groups,  
466 we turn our attention to a measure of alignment, or synchronisation, namely  
467 the Kuramoto order parameter  $R$ .

#### 468 **Kuramoto order parameter**

469 We show in Fig.8(a)-(b) the Kuramoto order parameter  $R$  defined for each  
470 group of excitatory (RS) and inhibitory (FS) neurons in time, averaged over  
471 realizations (top row), and standard deviation over realizations (bottom row),  
472 in propagation (a) and non-propagation (b) scenarios.

473 The cascade previously observed is clearly visible for the average  $R$ , in the  
474 form of a “desynchronization cascade”. We note here that this illustrates a

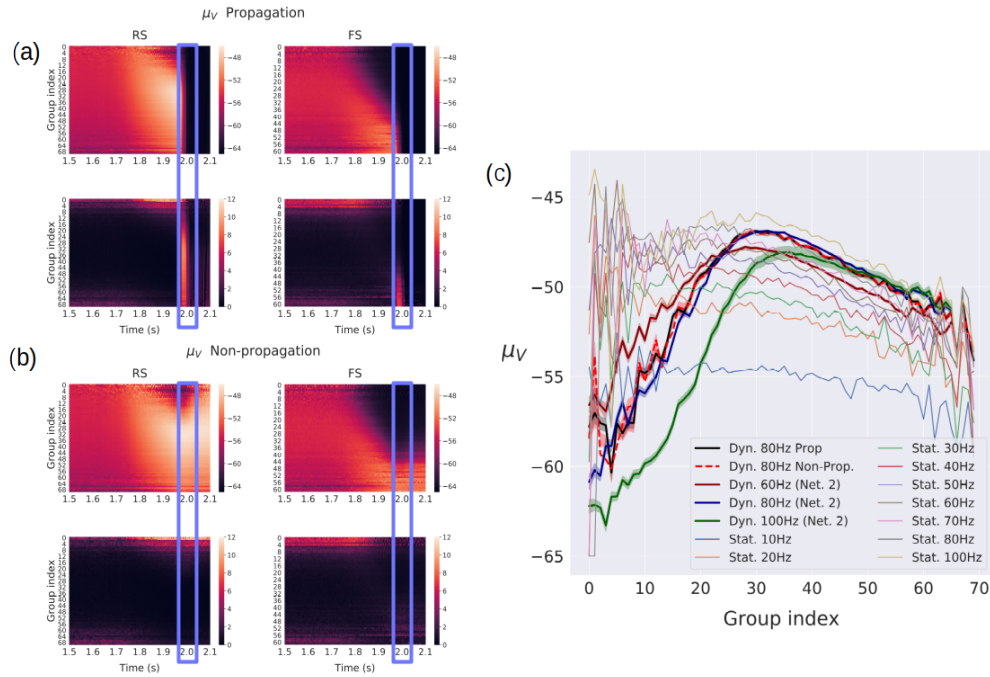


Figure 7: Mean membrane potential over subgroups of neurons for each group defined as a function of their incoming inhibitory connections, averaged over 50 noise realizations (17 non-propagative and 33 propagative). Color maps correspond for each group to the average membrane potential (top) and standard-deviation (bottom) across noise realizations in the propagative situations (a) and non-propagative situations (b) for both excitatory (RS) and inhibitory (FS) populations. The blue windows highlight the (time) region where the system either switches to a propagative regime, or remains stable. (c) Steady-state profiles (for fixed external input) of  $\mu_V$  for RS neurons, together with various profiles for different amplitudes of perturbation, captured right before typical time of crisis, at respectively 1950ms (60Hz), 1950ms (80Hz), 1930ms (100Hz, as the crisis develops *before* 1950ms). Networks are the same as previously analyzed, except when stated Net. 2. Standard errors estimated over noise realizations are shown in shaded areas.[FIGURE MODIFIED]

475 *recruitment* process between two radically different regimes having nonetheless  
476 similar alignment features : a fluctuation-driven asynchronous irregular (AI)  
477 dynamics, where membrane potentials are mostly conditioned by the balance  
478 of inhibitory versus excitatory inputs, and a crisis characterized by high spik-  
479 ing and membrane potentials clamped by refractoriness. The desynchronization  
480 cascade thus establishes a strict limit between them, while showing a significant  
481 degree of symmetry : the times right before or right after the cascade are in-  
482 distinguishable, from the point of view of the inhibitory neurons, except at the  
483 end of the non-propagative regime. Interestingly in this case, it appears that  
484 the misalignment of the neuron groups finally attained is constantly fueled by  
485 the network, thus hinting at a fundamentally out-of-equilibrium steady state.  
486 From the standard deviation perspective, two main features are worth pointing.  
487 First, we can again clearly observe the instability window, characterized by high  
488 standard deviation between realizations in propagative scenarios. Secondly, we  
489 can observe a significant variability between the various cascades observed in ex-  
490 citatory cells (particularly the low indices), while a very weak one for inhibitory  
491 ones. In other words, the excitatory cascade may take various forms in both  
492 propagative and non-propagative scenarios, while the inhibitory one remains  
493 quite robust, even with respect to the non-equilibrium state mentioned before.

### 494 **3.5 Dynamic versus static approach**

495 We have seen that changing the slope and the amplitude of the signal may  
496 trigger (or not) a crisis, thus hinting that the time evolution of the perturbation  
497 is central. Then we observed a hierarchical structure setting in from the point of  
498 view of continuous measures, following the perturbation. However, fundamen-  
499 tal questions remain: how much of this latter phenomenon is actually dynamic?  
500 Would we find the same structures if we bombarded the network with a fixed

501 input at, say,  $80\text{Hz}$ ? Can we observe the same structures for scenarios which  
502 are always, or never, propagative (no matter the noise realization) ? This would  
503 indicate that the structures observed thus far might have little to do with the  
504 crisis phenomenology itself but would either be the mere results of strong condi-  
505 tioning of the network by the level of input (if static structures are similar), or  
506 simply not yield any explanation for the instability we observe (if always/never  
507 propagative scenarios show similar features).

508 We now turn our attention to Fig.7(c), which displays the static  $\mu_V$  profiles  
509 in RS population obtained for fixed external inputs (Stat. curves), together with  
510 the profiles captured at the typical onset of the crisis, for various amplitudes:  
511  $60\text{Hz}$  (never propagative),  $80\text{Hz}$  (sometimes propagative) and  $100\text{Hz}$  (always  
512 propagative). The network realization is the same as previously analyzed, except  
513 when explicitly stated (Net. 2), where we refer to another connectivity. For the  
514  $80\text{Hz}$  scenarios with the first network (the one we have been investigating so  
515 far), we kept the splitting of the realizations between propagative and non-  
516 propagative, to highlight the potential differences of structures.

517 First, as previously observed, the profiles obtained for propagative versus  
518 non-propagative regimes are very similar at the onset. Then, we clearly see  
519 that the  $\mu_V$  profiles extracted from the dynamical situations (hereafter called  
520 the dynamical profiles) are very different from the static ones.

521 Besides, it is worth pointing that the profile obtained for a  $80\text{Hz}$  amplitude  
522 with a different random realization of the network (where all 50 noise realiza-  
523 tions are put together, based on the previous observation that propagative and  
524 non-propagative scenarios show very similar structures) is very similar to those  
525 already shown, with small standard error, which, together with the previous  
526 observation that noise and network realizations seem to play similar roles, un-  
527 derlie a robust network phenomenology. Furthermore, we see that the profiles

528 obtained for 60Hz, 80Hz and 100Hz amplitudes *are different*. The nature of  
529 their differences is of great interest for low indices, where we observe that 60Hz  
530 and 100Hz profiles are located on opposite sides of the central 80Hz profile: their  
531 ordering in this region is consistent with that of their degree of instability we  
532 have observed so far. This said, the dynamical profiles yet show similar qual-  
533 itative features : they all are non-monotonous and display two well-separated  
534 parts. Indeed, for low indices (until 30)  $\mu_V$  is increasing with values starting  
535 around the lowest of the static profiles ( 10Hz), while their high indices part  
536 is more aligned with high static profiles. Interestingly, we see that for 60Hz  
537 and 80Hz the right part is well aligned with the static profile obtained for sim-  
538 ilar inputs. This does not seem to be the case for 100Hz, although the static  
539 input simulation displays some instability, which makes their comparison less  
540 relevant. Although it is not straightforward to link  $\mu_V$  with the instantaneous  
541 regime, we have seen that low values can be associated with high firings (the  
542 neurons spending most of their time clamped at  $-65\text{mV}$ ). This would help un-  
543 derstanding what is happening here: for higher values of amplitude, the less  
544 inhibitory-connected neurons are firing more, and can thus entrain the rest of  
545 the network.

546 Fig.8(c) shows the Kuramoto counterpart of the latter figure. Here the  $R$   
547 profiles display structures quite different from those observed for  $\mu_V$ . Indeed,  
548 the various static profiles do not display such clear variability as for  $\mu_V$ , al-  
549 though little differences can still be observed: high inputs seem to show more  
550 variability in low indices, while ending at higher values for higher indices. More  
551 importantly, the dynamical profiles are here too very different, from the static  
552 ones, and among themselves. Besides, propagative and non-propagative simu-  
553 lations show little differences here too, and the profiles corresponding to same  
554 amplitude (80Hz) and different network architecture (Net. 2) also overlap here.

555 Interestingly we can also observe that the 60Hz and 100Hz profiles are different  
556 and located apart from the 80Hz, although they also show different magnitudes  
557 of their inverted peaks. Given that the ordering of these magnitudes are not  
558 consistent with the various degrees of instability, we suggest that the *position*  
559 of the peak might be the relevant criterion. This would be consistent with the  
560 observations we made thus far, and confirm our previously suggested scenario:  
561 as the more we approach the center group, the more neurons are considered  
562 (gaussian distribution), the green peak (100Hz) tells us that more neurons have  
563 undergone the desynchronization cascade we mentioned earlier, that is, more  
564 neurons have already “switched side” and entered a high firing regime, thus  
565 giving more inertia to the cascade phenomenon. The middle scenario (80Hz)  
566 would then sit on a *tipping point*, that is a point separating two radically dif-  
567 ferent dynamical regimes of the system.

568 These latter observations show that, from the perspective of both mean  
569 membrane potential and Kuramoto order parameter calculated inside the groups  
570 formed from inhibitory in-degree, we are in the presence of a structured behavior  
571 which emerges from an intricate interaction between dynamics and architecture,  
572 and which cannot be recovered from static approaches. Moreover, the various  
573 sizes of the groups and their impact on the phenomena we observe highlight  
574 that multiscale dynamics is a hallmark of the observed scenarios.

### 575 **3.6 Can seizure propagation be controlled by external in-** 576 **puts?**

577 Now that we have established how the structure of the dynamics allows or  
578 not the propagation of the paroxysmal perturbation (although the proximal  
579 cause relies on noise fluctuations), we investigate whether we could use the pre-  
580 vious finding of a strong instability window for the 80Hz dynamical scenario to

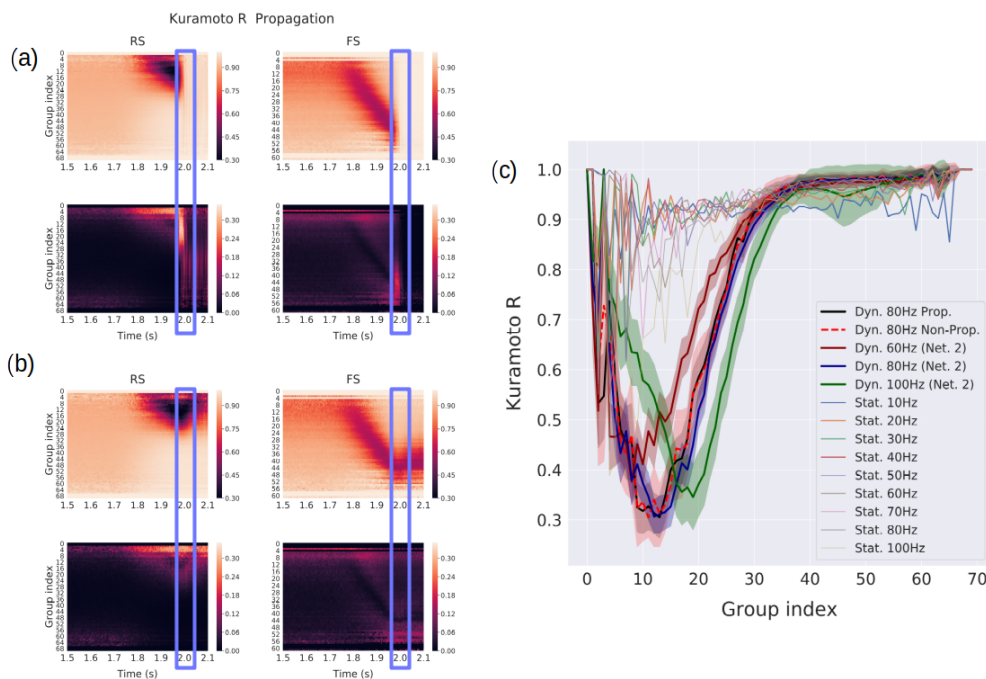


Figure 8: **Kuramoto  $R$  of membrane potentials over subgroups of neurons** for each group defined as a function of their incoming inhibitory connections, averaged over 50 noise realizations (17 non-propagative and 33 propagative). Color maps correspond for each group to the average membrane potential (top) and standard-deviation (bottom) across noise realizations in the propagative situations (a) and non-propagative situations (b) for both excitatory (RS) and inhibitory (FS) populations. The blue windows highlight the (time) region where the system either switches to a propagative regime, or remains stable. (c) Steady-state profiles (for fixed external input) of  $R$  for RS neurons, together with various profiles for different amplitudes of perturbation, captured right before typical time of crisis, at respectively 1950ms (60Hz), 1950ms (80Hz), 1930ms (100Hz, as the crises develops *before* 1950ms). Networks are the same as previously analyzed, except when stated Net. 2. Standard errors estimated over noise realizations are shown in shaded areas.[FIGURE MODIFIED]

581 alter the fate of the AdEx network dynamics. This approach is based on the  
582 following reasoning : we have observed, with a detailed analysis, the existence  
583 of a particular time window in the network under consideration (Net. 1) in  
584 this scenario, which implies a strong uncertainty on its global response. Thus,  
585 we want to design a stimulation protocol to reduce the chance of crisis propa-  
586 gation, based on this observation, *but which does not require the same level of*  
587 *analysis*, hence making it applicable inline and without the need of extensive  
588 computational power.

589 To achieve so, we apply a Gaussian stimulation, with 10 ms time constant,  
590 two different amplitudes (1Hz and 5Hz), positive or negative, *through a vari-*  
591 *ation* of the external excitatory input. For simulations performed under the  
592 same conditions, the stimulations were applied at different times as detailed in  
593 Tables 1(a)-(b). These tables show, for a total number of 100 simulations (with  
594 same network structure but different noise realizations), among which 72 were  
595 propagative, what relative percentage of simulations has undergone a triggering  
596 and a cancellation of crisis respectively.

597 We see that it is possible to somewhat “reverse” the situation, thanks to  
598 (or because of) the stimulation: in certain cases, it triggers a crisis propagation  
599 when none was initially occurring (Table 1(a)), and in other cases, it prevents  
600 one (Table 1(b)). We observe that if the possibility of “triggering” the propaga-  
601 tion by stimulation can take place for different times of peak, it remains more  
602 important when it occurs in the time window identified previously. This effect  
603 is even more visible in the reverse situation, in which propagation is prevented.  
604 A notably interesting case is that more than 50% of the crises are prevented  
605 if a stimulation of -5 Hz is applied in the same time window. This could open  
606 interesting leads in furthering qualitative comparisons between computational  
607 simulations and real-life situations, and eventually guide future interventions.



(a)	time of peak	+1Hz	+5Hz	-1Hz	-5Hz
	t = 1500ms	0.25	0.1786	0.2857	0.25
	t = 1850ms	0.178	0.1786	0.2143	0.2143
	t = 1950ms	0.0357	0.6071	0.2143	0.5
	t = 1975ms	0.7143	1.0	0.25	0.28572
	t = 2000ms	0.6071	1.0	0.0	0.0714
	t = 2500ms	0.0	0.0	0.0	0.0

(b)	time of peak	+1Hz	+5Hz	-1Hz	-5Hz
	t = 1500ms	0.1806	0.1944	0.1528	0.1389
	t = 1850ms	0.1389	0.1944	0.0972	0.1528
	t = 1950ms	0.1528	0.2361	0.125	0.0694
	t = 1975ms	0.0972	0.0	0.3472	0.3889
	t = 2000ms	0.0139	0.0	0.25	0.5556
	t = 2500ms	0.0	0.0	0.0	0.0972

Table 1: **Triggered and prevented events:** (a) Percentage of triggered propagation events, from an initial number of 38 non-propagative behaviors. Highlight in blue  $\geq 25\%$  and in red  $\geq 50\%$ . (b) Percentage of prevented events, from 72 initially propagative behaviors. Highlighted in blue  $\geq 25\%$  and in red  $\geq 50\%$ . The time of peak corresponds to the moment where the maximum of the stimulus is reached, the amplitude corresponds to a variation of the external input (see the main text)

## 608 4 Discussion

609 In this computational work we studied the response of various spiking neu-  
610 ral networks to paroxysmal inputs. We observed that the same networks can  
611 display various types of responses, depending on its nature (the neuron model  
612 used at its nodes), the shape of the perturbation (here we analysed particularly  
613 a plateau-like input with various slopes and amplitudes) and the realization of  
614 the random number generator. In the case of AdEx and CAdEx, two radically  
615 different responses to a qualitatively similar incoming excitatory perturbation  
616 are observed. Indeed, the latter could either contaminate the excitatory popu-  
617 lation and thus allow the crisis to propagate to efferent areas, or be “controlled”  
618 by the activity of the inhibitory population, keeping the excitatory population  
619 at a low activity level, thus preventing further propagation. The response of the

620 network depends not only on the amplitude of the perturbation but also on the  
621 “speed” at which it occurs. This is consistent with experimental observations.  
622 Interestingly, in the case of a HH network, our investigations show very different  
623 network responses, where only the amplitude of the perturbation plays a role  
624 and where no variability on noise realizations is observed.

625 A rich literature shows that seizures can be classified according to their  
626 onset/offset features described by bifurcation types (Saggio et al., 2020; Saggio,  
627 Spiegler, Bernard, & Jirsa, 2017; Jirsa, Stacey, Quilichini, Ivanov, & Bernard,  
628 2014). The most observed bifurcation at the onset of a seizure is a saddle-node  
629 bifurcation (Saggio et al., 2017), which is characterized by an abrupt change in  
630 the baseline of the electrophysiological signal (Jirsa et al., 2014). We observed in  
631 the current work that perturbations are always propagative in AdEx and CAdEx  
632 networks when they rise abruptly in the network. There is here an interesting  
633 correspondence revealing the importance of the onset of seizure dynamics, as  
634 it has been shown from a clinical point of view (Lagarde et al., 2018). It is  
635 worth noting that the absence of such phenomenology in HH networks (for the  
636 scenarios we considered) raises interesting questions in the modeling of seizure  
637 dynamics, but also more generally in neuronal networks : how the quantitative  
638 differences (number of variables) and qualitative differences (types of processes  
639 taken into account) in the single neuron models affect the global dynamics ?  
640 Are more precise models always the best in all respects ? This places back  
641 the importance of the the choice (of model, of parameters) in the center of the  
642 discussion : by modeling a neuronal network and observing a phenomenon which  
643 resembles reality, *we are not* testing whether the specific ingredients we chose  
644 are *constitutive* of this phenomenon, but *how they would be* if they were chosen  
645 *a priori*. It is only the systematic *cross-model observations and comparisons*,  
646 that can yield such answer as necessary and sufficient ingredients to observe a

647 phenomenon.

648 Note that, in clinical observations, the most accessible measurements are  
649 made on a macroscopic scale. In the study proposed here, we observe the  
650 activities at a smaller descriptive scale by building a network of neuron models.  
651 We thus have a complex system of very high dimension, rendering a priori  
652 impossible to obtain a simple description of the dynamics, which motivates the  
653 statistical approach proposed here. With this type of analysis, we were able to  
654 track in time key features of the underlying dynamics, especially those supported  
655 by the structure of the network : inhibitory in-degree can be mobilized to *explain*  
656 global differences in network response. Indeed, we proposed a coarse-grained  
657 description of the network dynamics based on inhibitory in-degree, allowing us  
658 to capture internal processes that were not visible at first, and which play a  
659 significant role in the global out-of-equilibrium dynamics. This opens the way  
660 to a flexible modeling framework of internal subpopulations, whose precision  
661 can be adapted to the most significant level of description, depending on the  
662 context and the questions asked.

663 We have also established that not only this structure matters, but also its  
664 interaction with instantaneous finite-size fluctuations of the noise and the time  
665 evolution of the *global* dynamics. These are all constitutive of the observed  
666 behaviors, and none can be neglected to understand them, which after all, is a  
667 universal feature of *complex systems*.

668 Also, our results showed that, for the AdEx network, there exists a time  
669 window, characterized by a high variance across noise realizations, during which  
670 it is possible to reverse the behavior by applying an appropriate stimulation.  
671 The use of a stimulus to interrupt a seizure has been applied in the past in the  
672 case of absence seizure (Rajna & Lona, 1989). These results have been used as  
673 bases of computational studies at the scale of the EEG (Taylor et al., 2014).

674 Computational work on the response of a network model to stimuli to disrupt  
675 seizure-like activities has shown the importance of the precise timing of the  
676 stimulation (Anderson, Kudela, Cho, Bergey, & Franaszczuk, 2007). Then, the  
677 use of electrode stimulation has been developed in rodents (Pais-Vieira et al.,  
678 2016). These different approaches have been implemented, including deep brain  
679 stimulation, vagus nerve stimulation (Boon, Cock, Mertens, & Trinka, 2018) and  
680 magnetic stimulation (Ye & Kaszuba, 2019). However, experimental recordings  
681 of the response to stimuli do not allow us to understand the mechanisms of  
682 large populations of neurons. Indeed, even if progress in calcium imaging or in  
683 multi-electrode arrays has made it possible since this last decade to record a  
684 large number of neurons simultaneously, we do not yet have access to the exact  
685 structure of the network they constitute. The study presented here is thus a  
686 proof of concept, based on a specific network model.

687 This said, the advantage of such a computational study is two-fold. On  
688 the one hand, linking internal structure with measured dynamics could foster  
689 more systematic interactions between experimentalists and theoreticians, with  
690 the constant goal of refining models to render them closer to reality and/or  
691 better at predicting real-life situations. On the other hand, it can shed lights  
692 on possible guidance for the design of new experimental protocols aimed at  
693 preventing the spread (or generalization) of epileptic seizures.

694 Generally speaking, our models describe an interesting variety of network  
695 dynamics in relation to the propagation of strong incoming perturbations. The  
696 studies on the dynamics of “crises” in networks of neuron models are a recent de-  
697 veloping field (*Computational Neuroscience in Epilepsy*, 2008; Naze, Bernard, &  
698 Jirsa, 2015; Rich, Hutt, Skinner, Valiante, & Lefebvre, 2020; Depannemaecker et  
699 al., 2021). Another approach proposes to study computationally how a network  
700 can be stabilized by the means of an external modulatory stimulus and internal

701 noise, and consequently, avoid the seizure-like regime (Rich et al., 2020). They  
702 also show the specific implications of the inhibitory population. Thus recent  
703 studies are complementary to offer an understanding of the different facets of  
704 this phenomenon of seizure.

705 Future work should examine the large-scale consequences of these properties,  
706 and for this, it will be necessary to design macroscopic population models that  
707 capture the propagative/non-propagative aspects of the seizure, while taking  
708 into account internal heterogeneities of the network (work in progress).

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## 835 Equations

### Adex model:

$$C \frac{dV}{dt} = g_L(E_L - V) + g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right) - w + I_{syn} \quad (13)$$

$$\tau_w \frac{dw}{dt} = a(V - E_L) - w$$

$$\text{if } V \geq V_D \text{ then } \begin{cases} V \rightarrow V_R \\ w \rightarrow w + b \end{cases} \quad (14)$$

### CAdEx model:

$$C \frac{dV}{dt} = g_L(E_L - V) + g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right) + g_A(E_A - V) + I_s \quad (15)$$

$$\tau_A \frac{dg_A}{dt} = \frac{\bar{g}_A}{1 + \exp\left(\frac{V_A - V}{\Delta_A}\right)} - g_A$$

836 (16).

$$\text{if } V \geq V_D \text{ then } \begin{cases} V \rightarrow V_R \\ g_A \rightarrow g_A + \delta g_A \end{cases} \quad (16)$$

### HH model:

$$C_m \frac{dV}{dt} = -g_l(E_l - V) - g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) + I_{syn} \quad (17)$$

837 with gating variables (in ms):

$$\frac{dn}{dt} = \frac{0.032(15. - V + V_T)}{\left(\exp\left(\frac{15. - V + V_T}{5.}\right) - 1.\right)} (1. - n) - 0.5 \exp\left(\frac{10. - V + V_T}{40.}\right) n \quad (18)$$

838

$$\frac{dh}{dt} = 0.128 \exp\left(\frac{17. - V + V_T}{18.}\right) (1. - h) - \frac{4.}{1 + \exp\left(\frac{40. - V + V_T}{5.}\right)} h \quad (19)$$

$$\frac{dm}{dt} = \frac{0.32(13. - V + V_T)}{\left(\exp\left(\frac{13. - V + V_T}{4.}\right) - 1.\right)}(1 - m) - \frac{0.28(V - V_T - 40.)}{\left(\exp\left(\frac{V - V_T - 40.}{5.}\right) - 1.\right)}m \quad (20)$$

839

840

841 **Conductance-based synapses:**

$$I_{syn} = g_E(E_E - V) + g_I(E_I - V) \quad (21)$$

$$\frac{dg_{E/I}}{dt} = -\frac{g_{E/I}}{\tau_{syn}} \quad (22)$$

842 **External perturbation:**

$$\begin{aligned} \nu_{pert}(t) = & \beta + \alpha * \left(\exp(-(t - T_1)^2 / (2. * \tau_{on}^2)) * H(-(t - T_1))\right) \\ & + H(-(t - T_2)) * H(t - T_1) + \exp(-(t - T_2)^2 / (2. * \tau_{off}^2)) * H(t - T_2) \end{aligned} \quad (23)$$

843 **Kuramoto order parameter:**

$$R \exp i\Psi = \frac{1}{N} \sum_j \exp i\theta_j^v \quad (24)$$