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1 Expansion of epileptogenic networks via 2 neuroplasticity

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5 Abstract

6 Neuroplasticity refers to functional and structural changes in brain regions in response to healthy and
7 pathological activity. Neuroplasticity induced by epileptic activity can involve healthy brain regions into
8 the epileptogenic network by perturbing their excitation/inhibition balance. In this article, we present a
9 new neural mass model that accounts for neuroplasticity and that is used to investigate the possible
10 mechanisms underlying the epileptogenic network expansion. We formulate physiological calcium-
11 mediated synaptic plasticity and pathological structural plasticity in a multiple-timescale framework. The
12 model highlights that synaptic plasticity at excitatory connections and structural changes in the inhibitory
13 system can transform a healthy region into a secondary epileptic focus under recurrent seizures and
14 interictal activity occurring in the primary focus. Our results suggest that the latent period of this
15 transformation can provide a window of opportunity to prevent the expansion of epileptogenic networks,
16 formation of an epileptic focus, or other comorbidities associated with epileptic activity.

17 *Key words: epilepsy, synaptic plasticity, secondary focus, neural mass model, multiple timescale systems*

18 Author Summary

19 Repetitive epileptic activity leads to a large variety of plastic changes in brain. Understanding the
20 mechanism and its time course can indicate windows of opportunity for preventing the devastating

21 impact of focal epileptic activity on brain networks. Animal models of focal epilepsy underlined to role of
22 NMDA receptors and deregulations in the GABAergic system in the expansion of epileptic activity. Here
23 we develop a plastic neural mass model integrating physiological and pathologic plasticity. Our results
24 show that neuroplasticity mediated by epileptic activity increases synaptic efficacy between epileptic and
25 healthy regions, and causes irreversible changes in the GABAergic system in the healthy region. The
26 model gives mechanistic insights into the physio-pathological impact of focal epileptic activity on large-
27 scale networks and suggests that seizures may beget seizures.

28 Introduction

29 The most general definition of neuroplasticity is the ability of neural networks to reorganize over time,
30 which can take place under physiological and pathological conditions. Synaptic plasticity is the ability of
31 synapses to strengthen or weaken, in response to increases or decreases in their activity. Under
32 physiological conditions, it is accompanied by many regulatory mechanisms through which the
33 excitation/inhibition balance is preserved (for examples [1–6]). However, epileptiform discharges drive
34 not only physiologic synaptic plasticity but also pathological plasticity, which disturbs the
35 excitation/inhibition balance, and can cause expansion of epileptogenic networks during epileptogenesis
36 [7–9]. The aim of this article is to investigate the expansion of epileptogenic networks with a
37 neurophysiologically plausible mathematical model of physio-pathological plasticity under recurrent
38 epileptic activity.

39 Synaptic plasticity occurs on multiple timescales at both presynaptic and postsynaptic sites [10]. Short-
40 term plasticity (STP, in milliseconds) refers to transient changes in the probability of neurotransmitter
41 release at the presynaptic site [11]. Long-term synaptic plasticity (in hours or days), although generally
42 considered as postsynaptic alterations, is related to both (i) the insertion/removal of alpha-amino-3-
43 hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPA) at the postsynaptic site and (ii)
44 the change in the probability of neurotransmitter release at the presynaptic site [12].

45 Postsynaptic long-term potentiation (LTP) and long-term depression (LTD) depend on the calcium
46 concentration at the postsynaptic site [13]. In excitatory (glutamatergic) synapses, an increase in
47 postsynaptic calcium concentration through activation of synaptic N-methyl-D-aspartate (NMDA)
48 receptors (NMDARs), metabotropic glutamate receptors, voltage-gated calcium channels, etc. is
49 necessary and sufficient for synaptic plasticity (see [12,14] and references therein). Calcium-dependent
50 activation of secondary messengers, such as nitric oxide, endocannabinoids, etc., triggers presynaptic
51 long-term plasticity [15,16]. The late phase of long-term plasticity, referred to as maintenance or
52 consolidation, occurs via new protein synthesis and gene transcription [12].

53 Epileptic discharges that cause glutamatergic spillover have a twofold impact. First, epileptiform activity
54 strengthens excitatory synapses by increasing the number of alpha-amino-3-hydroxy-5-methyl-4-
55 isoxazolepropionic acid receptors (AMPA) [17,18], as in the physiological LTP. Second, a high amount of
56 glutamate released during epileptiform activity can activate extrasynaptic NMDARs that cause
57 pathological changes in GABAergic signaling, through inactivation of functional potassium chloride co-
58 transporters 2 (KCC2) and internalization of GABAergic receptors [19,20]. KCC2 controls the outflow of
59 the chloride ions entered the intracellular space through GABAergic channels to the extracellular and
60 maintains the GABAergic reversal potential. Calcium ions flowing through extrasynaptic NMDARs bind on
61 calpain that inactivates KCC2 [20–22]. Reducing the number of functional KCC2 results in the increase of
62 chloride concentration and changes GABAergic responses from inhibitory to excitatory. KCC2 dysfunction
63 is related to epileptic activity in the naive site [7], and it is one of the factors contributing to epileptic
64 activity in the mature brain [23].

65 The extrasynaptic NMDAR activity also affects tonic inhibition that is mainly mediated by the α_5 GABA_A
66 receptors in the hippocampus. Overexpression of GluN2B NMDA receptors, which are located mostly in
67 extrasynaptic regions, downregulates the expression of α_5 GABA_A receptors expression, promotes their
68 internalization, and therefore, reduces tonic GABAergic [24] (but see [25] for limbic epileptogenesis). We

69 refer to these two mechanisms, i.e. reduced KCC2 and internalization of extrasynaptic GABAR, as
70 *pathological plasticity*.

71 Physiological synaptic plasticity followed by pathological plasticity can increase the susceptibility of a
72 brain region to epileptic discharges, expand epileptic network, and generate a secondary (mirror) focus.
73 Secondary (mirror) focus refers to epileptogenesis in a naive area induced by repetitively uncontrolled
74 epileptic seizures from a primary seizure focus [26,27]. Independent epileptic activity in the contralateral
75 area in humans suggests that mirror focus develops via a kindling process mediated by the primary focus.
76 In animal models of epilepsy, for instance, under kindling [28] or kainite application [7] to one of the
77 hippocampi (primary focus), secondary focus appears in the contralateral hippocampus due to recurrent
78 epileptic activity in the primary focus. Khalilov's elegant work in the immature brain [7] showed that
79 activation of NMDARs and long-term alterations in GABAergic synapses are responsible for chronic
80 epileptogenesis in the secondary focus. Despite the key role of plasticity in expansion of epileptogenic
81 networks, there is a lack of computational modeling studies of neuroplasticity under epileptic activity.
82 Previous modeling studies of calcium-mediated postsynaptic LTP/LTD have mainly focused on cellular
83 activity [29–34] (see [35] for a mean-field approximation), as well as presynaptic long-term plasticity
84 [30,33,36,37]. Recently, Chindemi et al. [30] developed a detailed cellular model of the neocortex that
85 integrates the calcium-mediated presynaptic and postsynaptic plasticity mechanisms. However, the
86 literature related to modeling calcium-mediated plasticity with neuro-physiologically plausible neural
87 mass model (NMMs) remains limited. We identified two studies on this phenomenon in the context of
88 magnetic stimulation [38,39]. Our computational model concentrates on the physio-pathological
89 plasticity under epileptic activity in a network of two unidirectionally coupled NMMs [40], each
90 representing an epileptic and a non-epileptic brain region, where the epileptic one perturbs the non-
91 epileptic one. First, we study how synaptic connections evolve under epileptic activity. We then
92 investigate the pathological plasticity triggered by the physiological plasticity. The results suggest that the

93 interaction between physiological and pathological plasticity can explain the expansion of epileptogenic
 94 networks and the formation of secondary epileptic foci.

95 Methods

96 Mesoscopic model of physiological short- and long-term plasticity

97 The seminal study by Shouval et al. [29] has proposed a calcium control hypothesis for postsynaptic
 98 plasticity, in which intra-cellular calcium concentration controls the rate of change of synaptic efficacy.
 99 The proposed model in [29] was then developed to account for the synaptic consolidation in [32] by
 100 introducing a variable ρ that describes the state of the synaptic efficacy. We combine both formulations
 101 as:

$$\frac{d\rho}{dt} = \frac{1}{\tau_\rho} (-\rho(1-\rho)(\rho_* - \rho) + (1-\rho)\Omega_p([Ca]) - \rho\Omega_d([Ca])), \quad (1)$$

102 where τ_ρ is the time constant of the synaptic variations, $\rho_* = 0.5$ is the boundary between the depressed
 103 ($\rho = 0$) and potentiated ($\rho = 1$) states. The functions $\Omega_{p,d}([Ca])$ describe how the synaptic efficacy is
 104 controlled by the calcium concentration:

$$\Omega_{p,d}([Ca]) = \frac{\gamma_{p,d}}{1 + \exp(-\beta_{p,d}([Ca] - \theta_{p,d}))}, \quad (2)$$

105 where $\gamma_p > \gamma_d$ are potentiation and depression rates, $\beta_{p,d}$ are the slopes and $\theta_p > \theta_d$ are potentiation
 106 and depression boundaries (Fig 1A).

107 **Figure 1 Synaptic efficacy and activation functions.** (A) Calcium dependent synaptic efficacy function,
 108 $\Omega([Ca]) = -\Omega_d([Ca]) + \Omega_p([Ca])$ (2) for. (B) Activation function, $H(V_{post})$ (5) the parameter set
 109 given in Table 1.

110 The calcium concentration is controlled by the NMDAR-mediated current $I_{NMDA}^{[Ca]}$:

$$\frac{d[Ca]}{dt} = I_{NMDA}^{[Ca]} - \frac{[Ca]}{\tau_{[Ca]}}, \quad (3)$$

111 where τ_{Ca} is the decay time constant of calcium influx. The NMDAR-mediated calcium current $I_{NMDA}^{[Ca]}$
 112 depend on both the presynaptic activity via the kinetics of glutamate binding and the postsynaptic
 113 membrane potential [29] expressed as,

$$I_{NMDA}^{[Ca]} = G(FR_{pre})h_{Ca}H(V_{post}), \quad (4)$$

114 where $G(FR_{pre})$ formulates the kinetics of the glutamate binding depending on the firing rate of the
 115 presynaptic population, FR_{pre} . The function $H(V_{post})$ (Fig. 1B) formulates the relation between the
 116 NMDA currents and the postsynaptic (population level) depolarization:

$$H(V_{post}) = \frac{1}{1 + \exp(-\mu(V_{post} - V_{th}))}, \quad (5)$$

117 where μ is the slope at $V_{th} = V_{post}$. The function $H(V_{post})$ can be interpreted as the magnesium
 118 blockage at the population level. Parameter h_{Ca} is a scaling factor, which distinguishes the NMDAR-
 119 mediated postsynaptic depolarization from calcium entry.

120 Plasticity of excitatory synapses is modeled at both presynaptic and postsynaptic levels. Presynaptic
 121 plasticity corresponds to variations in glutamate release probability, running on short- and long-
 122 timescales. The presynaptic STP rule follows [41]:

$$\frac{dr}{dt} = \frac{1-r}{\tau_r} - u r FR_{pre} \quad (6a)$$

$$\frac{du}{dt} = \frac{U_{se} - u}{\tau_f} + U_{se}(1-u)FR_{pre} \quad (6b)$$

123 where r is the amount of available neurotransmitters, u is the utilization factor, τ_r is the recovery
 124 timescale, τ_f is the facilitation timescale and U_{se} is the neurotransmitter release probability.

125 The presynaptic long-term plasticity is the long-term variations in the neurotransmitter release
 126 probability U_{se} controlled by the calcium-dependent retrograde signaling [30],

$$\frac{dU_{se}}{dt} = \frac{1}{\tau_{Use}}(U_{se,d} - U_{se} + \rho(U_{se,p} - U_{se,d})). \quad (7)$$

127 Parameters $U_{se,d}$ and $U_{se,p}$ represent the depressed and potentiated states of the release
 128 probability U_{se} , and $\tau_{U_{se}}$ is the time-constant of the presynaptic long-term plasticity.
 129 Postsynaptic long-term plasticity corresponds to an insertion/removal of glutamatergic AMPAR,

$$\frac{dC_{AMPA}}{dt} = \frac{1}{\tau_{C_{AMPA}}} (C_{AMPA,d} - C_{AMPA} + \rho(C_{AMPA,p} - C_{AMPA,d})). \quad (8)$$

130 Parameters $C_{AMPA,d}$ and $C_{AMPA,p}$ represent the depressed and potentiated states of the AMPAergic
 131 coupling strength $C_{AMPA}(t)$, and $\tau_{C_{AMPA}}$ is the time-constant of the postsynaptic long-term plasticity. For
 132 simplicity, we assume that presynaptic and postsynaptic long-term changes have the same timescales
 133 $\tau_{U_{se}} = \tau_{C_{AMPA}}$.

134 Whole model of pre- and postsynaptic plasticity reads as follows:

$$\frac{dr}{dt} = \frac{1-r}{\tau_r} - u r FR_{pre}, \quad (9a)$$

$$\frac{du}{dt} = \frac{U_{se} - u}{\tau_f} + U_{se}(1-u)FR_{pre}, \quad (9b)$$

$$\frac{d[Ca]}{dt} = I_{NMDA}^{[Ca]} - \frac{[Ca]}{\tau_{ca}}, \quad (9c)$$

$$\frac{d\rho}{dt} = \frac{1}{\tau_\rho} (-\rho(1-\rho)(\rho_* - \rho) + (1-\rho)\Omega_p([Ca]) - \rho\Omega_d([Ca])), \quad (9d)$$

$$\frac{dU_{se}}{dt} = \frac{1}{\tau_{U_{se}}} (U_{se,d} - U_{se} + \rho(U_{se,p} - U_{se,d})), \quad (9e)$$

$$\frac{dC_{AMPA}}{dt} = \frac{1}{\tau_{C_{AMPA}}} (C_{AMPA,d} - C_{AMPA} + \rho(C_{AMPA,p} - C_{AMPA,d})). \quad (9f)$$

135

136

Table 1: Parameters of (9) and their values unless otherwise stated

θ_d	depression threshold	0.1
θ_p	potentiation threshold	0.4
γ_d	depression amplitude	1

γ_p	potentiation amplitude	5
β_d	depression slope	80
β_p	potentiation slope	80
μ	slope of NMDA-dependent postsynaptic depolarization	1
V_{th}	threshold of NMDA-dependent postsynaptic depolarization	5 V
h_{Ca}	calcium current scaling factor	10
τ_d	presynaptic short-term depression time constant	0.200 sec
τ_f	presynaptic short-term facilitation time constant	0.05 sec
τ_{Ca}	the calcium influx decay time constant	0.05 sec
τ_ρ	synaptic efficacy time constant	50 sec
τ_{Use}	presynaptic long-term plasticity time constant	100 sec
$\tau_{C_{AMPA}}$	postsynaptic long-term plasticity time constant	100 sec
$U_{se,d}$	Value of depressed release probability	0.4
$U_{se,p}$	Value of potentiated release probability	0.8
$C_{AMPA,d}$	Value of depressed AMPAergic coupling strength	50
$C_{AMPA,p}$	Value of potentiated AMPAergic coupling strength	100

137

138 The revisited neural mass model

139 We revisited a minimal NMM of the CA1 region of the hippocampus [40] for obtaining an autonomous
140 model that can undergoes seizures for a fixed parameter set. The original model includes four interacting
141 neuronal subpopulations: two interconnected subpopulations of glutamatergic pyramidal neurons (P, P'),
142 and two subpopulations of GABAergic inhibitory interneurons (somatostatin positive (SOM+), and
143 parvalbumin positive (PV+), also called dendrite-projecting slow and soma-projecting fast interneurons,
144 respectively). The activity of each subpopulation is described by a "wave to pulse" function, $S(v) =$
145 $5/(1 + \exp(0.56(6 - v)))$, transforming the net membrane polarization in response to synaptic inputs

146 into a firing rate. The synaptic interactions between the subpopulations is described by a "pulse to wave"
 147 that converts the input average firing rate into a postsynaptic potential (PSP), which can be either
 148 excitatory – EPSP - or inhibitory - IPSP) at the input of each subpopulation, that is $h(t) = W /$
 149 $\tau_w t \exp(-t/\tau_w)$, where W represents the average PSP amplitude. The equations of an unconnected
 150 population i POP _{i} reads:

$$\frac{d^2 y_P^{(i)}}{dt^2} = \frac{A^{(i)}}{\tau_a} S[V_P^{(i)}] - \frac{2}{\tau_a} \frac{dy_P^{(i)}}{dt} - \frac{1}{\tau_a^2} y_P^{(i)}, \quad (10a)$$

$$\frac{d^2 y_{P'}^{(i)}}{dt^2} = \frac{A^{(i)}}{\tau_a} (p(t) + C_{P',P}^{(i)} S[C_{P,P'}^{(i)} y_P^{(i)}]) - \frac{2}{\tau_a} \frac{dy_{P'}^{(i)}}{dt} - \frac{1}{\tau_a^2} y_{P'}^{(i)}, \quad (10b)$$

$$\frac{d^2 y_{SOM}^{(i)}}{dt^2} = \frac{B^{(i)}}{\tau_b} S[C_{P,SOM}^{(i)} y_P^{(i)}] - \frac{2}{\tau_b} \frac{dy_{SOM}^{(i)}}{dt} - \frac{1}{\tau_b^2} y_{SOM}^{(i)}, \quad (10c)$$

$$\frac{d^2 y_{PV}^{(i)}}{dt^2} = \frac{G^{(i)}}{\tau_g} S[C_{P,PV}^{(i)} y_P^{(i)} - C_{SOM,PV}^{(i)} y_{SOM}^{(i)}] - \frac{2}{\tau_g} \frac{dy_{PV}^{(i)}}{dt} - \frac{1}{\tau_g^2} y_{PV}^{(i)}, \quad (10d)$$

151

152 Parameters $C_{k,p}^{(i)}$ scales the impact from subpopulation k to subpopulation p within the population POP _{i} .

153 The net polarization of P subpopulation of POP _{i} , $V_P^{(i)}$, reads,

$$V_P^{(1)} = \Sigma(C_{k,P}^{(1)} y_k^{(1)})$$

154 for POP₁, and,

$$V_P^{(2)} = \Sigma(C_{k,P}^{(2)} y_k^{(2)}) + \Sigma Input_{POP_1 \rightarrow POP_2}$$

155 for POP₂, which is subject to the excitatory AMPAergic and NMDAergic signals from POP₁ on its P

156 subpopulation, $\Sigma Input_{POP_1 \rightarrow POP_2}$. We consider $V_P^{(i)}$ as the model output, which is a simplified proxy for

157 the local field potential recorded by an extracellular electrode positioned in the neuronal population.

158 Intracranial recordings from epileptic patients with focal epilepsy show four distinct phases of activity:

159 interictal phase with sporadic spikes, preictal phase with periodic preictal spikes, low-voltage fast onset

160 marked by a gamma-band activity, and tonic discharges [42]. Recordings show sequential transitions

161 between these phases, that is, interictal, preictal, then, ictal phase (so-called *seizure*, which starts with a
162 tonic low-voltage fast onset phase followed by clonic discharges). For an appropriate choice of model
163 parameters, the transitions between these phases in (10) can be obtained by varying the IPSP amplitude
164 of the SOM interneurons, $B^{(i)}$, (e.g. [40,43]). Figure 2A shows the bifurcation diagram of (10) for POP_1 as
165 a function of $B^{(1)}$ with the parameter set in Table 2. The branch of equilibrium points undergoes four
166 Hopf bifurcations at $B^{(1)} \approx \{0.47, 2.66, 9.98, 32.14\}$ and saddle-node bifurcations at $B^{(1)} \approx$
167 $\{2.60, 2.92, 32.01, 50.38\}$. The gamma-band oscillations lie in $B^{(1)} \approx (2.66, 0.47)$ and the tonic lower
168 frequency oscillations in $B^{(1)} \approx (9.98, 32.14)$. Under a stochastic input, such as $p(t) = \mathcal{N}(p_m, p_s)$ in
169 (10b), the gamma-band oscillations can be observed for $0 < B^{(1)} < 4$, the tonic phase for $4 < B^{(1)} <$
170 32 . The low-frequency periodic preictal spikes and aperiodic interictal spikes can be located at the
171 boundary between tonic oscillations and stable equilibrium points for $32 < B^{(1)} < 50$.

172 **Figure 2 Dynamics of (10)-(11) in the interictal and ictal regimes.** (A-D) Dynamics of (10)-(11) in the
173 interictal regime for $b_{thr}^{(1)} = 34$. (A) Bifurcation diagram of (10) where the amplitude of $y_p^{(1)}$ is presented
174 as a function of $B^{(1)}$. The blue curve shows the branch of equilibrium points (bold for stable and dashed
175 for unstable equilibrium points). The red curves show the amplitude of $y_p^{(1)}$ in the oscillatory regime. The
176 Hopf bifurcations along the branch of equilibrium points are denoted by red dots and saddle-node
177 bifurcation by blue dots. The parameter regions correspond to the fast onset, ictal and interictal periods
178 are marked by purple, yellow and cyan patches, respectively. The time solution (black curve) is
179 superimposed on the bifurcation diagram. (B) Time trace for $V_p^{(1)}$ showing interictal spikes. (C) Phase
180 plane of (11) with the $B^{(1)}$ -nullcline (blue curve, bold for stable and dashed for branches) and the $n^{(1)}$ -
181 nullcline (orange curve). The parameter regions correspond to the fast onset, ictal and interictal periods
182 are marked by green, yellow and cyan patches, respectively. The time solution (black curve) is
183 superimposed on the bifurcation diagram. (D) Time trace for $B^{(1)}$. (E-H) Dynamics of (10)-(11) in the ictal
184 regime for $b_{thr}^{(1)} = 32$. Same color codes and markers in (A-D) is used. Arrows in panel (G) indicates the
185 direction of the trajectory (black curve) on the $(B^{(1)}, n^{(1)})$ -plane with double arrows indicating the fast

186 transitions. The fast onset, ictal and interictal periods are marked on the time traces of $V_p^{(1)}$ and $B^{(1)}$ on
 187 panels F and H, respectively.

188 One can ensure an autonomous transition between the phases of epileptic activity by modeling $B^{(i)}$ as a
 189 variable that varies in the range where they are observed. Here, we introduce a slow-subsystem where
 190 the IPSP amplitude of the SOM interneurons $B^{(i)}$ is a variable:

$$\frac{dB^{(i)}}{dt} = \delta \left(n^{(i)} \right) \quad (11a)$$

$$- \left(- \frac{m_1(B^{(i)} - p_1)^2}{1 + \exp(-p_1 + B^{(i)})} + \frac{1}{1 + \exp(-p_2 + B^{(i)})} \right. \\ \left. + \frac{m_3(B^{(i)} - p_3)^2}{1 + \exp(-p_3 + B^{(i)})} \right),$$

$$\frac{dn^{(i)}}{dt} = \varepsilon \left(-n^{(i)} + n_k + \frac{n_p}{1 + \exp(-n_r(b_{thr}^{(i)} - B^{(i)})} \right). \quad (11b)$$

191

192 Parameters of the $B^{(i)}$ - and $n^{(i)}$ -nullclines can be adjusted with respect to the critical (bifurcation) points
 193 of (10), desired type and range of behavior. Parameters of (11) are given in Table 2. In this study, the
 194 parameter $b_{thr}^{(i)}$ is the main parameter controlling the excitability, hence, the susceptibility of seizing of
 195 POP_i.

196

Table 2: Parameters values for (10)-(15) unless otherwise stated

	Parameters of (10)	POP ₁	POP ₂
$A^{(i)}$	EPSP amplitude [mV]	5	5
$B^{(i)}$	IPSP _{SOM} amplitude [mV]	Variable	
$G^{(i)}$	IPSP _{PV} amplitude [mV]	20	2

τ_a	EPSP time constant [s]	0.01	0.01
τ_b	IPSP _{SOM} time constant [s]	0.03	0.03
τ_g	IPSP _{PV} time constant [s]	0.003	0.003
$C_{P,P'}^{(i)}$	$P \rightarrow P'$ coupling coefficient	135	135
$C_{P',P}^{(i)}$	$P' \rightarrow P$ coupling coefficient	108	108
$C_{SOM,P}^{(i)}$	SOM \rightarrow P coupling coefficient	35	35
$C_{PV,P}^{(i)}$	PV \rightarrow P coupling coefficient	200	200
$C_{P,SOM}^{(i)}$	P \rightarrow SOM coupling coefficient	25	25
$C_{P,PV}^{(i)}$	P \rightarrow PV coupling coefficient	200	200
$C_{SOM,PV}^{(i)}$	SOM \rightarrow PV coupling coefficient	120	120
	Parameters of (11)		
p_1	local maximum of the $B^{(j)}$ -nullcline	25	25
p_2	inflection point of the middle branch of the $B^{(j)}$ -nullcline	30	30
p_3	local minimum of the $B^{(j)}$ -nullcline	33	33
m_1	slope of the of the left branch of $B^{(j)}$ -nullcline	0.0015	0.0015
m_3	slope of the of the right branch of the $B^{(i)}$ –nullcline	0.003	0.003
n_k	minimum of the n -nullcline	-0.2	-0.2
n_p	maximum of the n -nullcline sigmoid	1.4	1.4
n_r	slope of the n -nullcline at the inflection point	2	2
$b_{thr}^{(i)}$	inflection point of the n -nullcline	34	44
δ	time-scale parameter	50	50
ε	time-scale parameter	0.05	0.05
	Parameter values of (12)-(15)		
$A_{AMPA}^{(2)}$	AMPAergic-EPSP amplitude [mV]	-	10

$A_{NMDA}^{(2)}$	NMDAergic-EPSP amplitude [mV]	-	2
$A_{NMDA,ext}^{(2)}$	Extrasynaptic NMDAergic-EPSP amplitude [mV]	-	1
τ_{AMPA}	AMPAergic-EPSP time constant [s]	-	0.005
τ_{NMDA}	NMDAergic-EPSP time constant [s]	-	0.02
$\tau_{NMDA,ext}$	Extrasynaptic NMDAergic-EPSP time constant [s]	-	0.04
C_{NMDA}	NMDAergic coupling coefficient	-	$C_{AMPA,min}$
τ_K	Extrasynaptic NMDA integration time constant	-	10

197

198 Note that the system (11) is a slow-fast system itself, where $B^{(i)}$ is the fast and $n^{(i)}$ is the slow variable.

199 The $B^{(i)}$ -nullcline of (11) has an N-shape with stable outer and unstable middle branches (Fig 3C). System

200 (10) governs the interictal and preictal phases for the $B^{(i)}$ values on the right branch $B^{(i)}$ -nullcline. The

201 $B^{(i)}$ values on the left and middle branches $B^{(i)}$ -nullcline correspond to the ictal phase (fast-onset and

202 tonic discharges) of (10). Depending on the position of the equilibrium point of (11), defined as the

203 intersection between the N-shaped $B^{(i)}$ -nullcline and sigmoidal $n^{(i)}$ -nullcline, the system (11) follows

204 either a steady state or an oscillatory solution. If the equilibrium point is close to the right fold point of

205 the $B^{(i)}$ -nullcline, then (11) is in an excitable state. If the equilibrium point is at the right handside of the

206 right fold, any perturbation on $B^{(i)}$ can trigger a jump to the left branch of the fast nullcline, which

207 corresponds to the ictal regime starting with the fast-onset activity. As the trajectory of (11) moves along

208 the left branch of the $B^{(i)}$ -nullcline, the system (10) undergoes the fast-onset, then tonic spiking before

209 jumping back to the right branch, that is the interictal regime.

210 Modeling plasticity with coupled neural mass models

211 We consider two populations POP_1 and POP_2 modelled by the NMM formulation given in (10)-(11). POP_2

212 receives excitatory inputs from POP_1 through AMPAergic and NMDAergic signaling. Let $FR_p^{(1)}$ be the

213 firing rate of the P subpopulation of the POP₁, $r^{(1)}(t)$ and $u^{(1)}(t)$ are the variables describing the
 214 presynaptic neurotransmitter release (6). Then the AMPAergic excitatory PSP (EPSP) is the solution of

$$\frac{d^2 y_{AMPA}}{d^2 t} = \frac{r^{(1)} u^{(1)} A_{AMPA}^{(2)}}{\tau_{AMPA}} FR_P^{(1)} - \frac{2}{\tau_{AMPA}} \frac{dy_{AMPA}}{dt} - \frac{1}{\tau_{AMPA}^2} y_{AMPA}, \quad (12)$$

215 where τ_{AMPA} is the synaptic time constant and $A_{AMPA}^{(2)}$ is the amplitude that is modulated by STP
 216 variables, $r^{(1)}(t)$ and $u^{(1)}(t)$. The NMDAergic-EPSP is the solution of

$$\frac{d^2 y_{NMDA}}{d^2 t} = \frac{r^{(1)} u^{(1)} A_{NMDA}^{(2)}}{\tau_{NMDA}} FR_P^{(1)} - \frac{2}{\tau_{NMDA}} \frac{dy_{NMDA}}{dt} - \frac{1}{\tau_{NMDA}^2} y_{NMDA}, \quad (13)$$

217 where τ_{NMDA} is the synaptic time constant and $A_{NMDA}^{(2)}$ is the amplitude. The NMDAergic EPSP are slower
 218 than the AMPAergic EPSP [44], thus $\tau_{AMPA} < \tau_{NMDA}$. The net depolarization of the postsynaptic
 219 subpopulation due to the activation of NMDAR depends on the postsynaptic potential, V_P^2 as well as the
 220 presynaptic entry $C_{NMDA} y_{NMDA}$, i.e. $C_{NMDA} y_{NMDA} H(V_P^2)$, with C_{NMDA} is the coupling strength.

221 The pathological plasticity is activated when both the probability of vesicle opening U_{se} and the AMPAR
 222 insertion C_{AMPA} are potentiated (9). Under this condition, an afferent epileptic spike from POP₁, which
 223 releases high levels of glutamate, activates the extrasynaptic NMDAR. The EPSP mediated by
 224 extrasynaptic NMDR, $y_{NMDA,ext}$, has slower kinetics than the EPSP mediated by synaptic NMDAR [45] (i.e.
 225 $\tau_{NMDA} < \tau_{NMDA,ext}$) and $y_{NMDA,ext}$ is the solution of the following equation

$$\frac{d^2 y_{NMDA,ext}}{d^2 t} = \frac{r^{(1)} u^{(1)} A_{NMDA,ext}^{(2)}}{\tau_{NMDA,ext}} FR_P^{(1)} - \frac{2}{\tau_{NMDA,ext}} \frac{dy_{NMDA,ext}}{dt} - \frac{1}{\tau_{NMDA,ext}^2} y_{NMDA,ext}, \quad (14)$$

226 with the postsynaptic depolarization $C_{NMDA} y_{NMDA,ext} H(V_P^2)$, . The net postsynaptic polarization the P
 227 subpopulation of the POP₂ then reads,

$$V_P^{(2)} = \Sigma \left(C_{k,P}^{(2)} y_k^{(2)} \right) + C_{AMPA} y_{AMPA} + C_{NMDA} (y_{NMDA} H(V_P^2) + y_{NMDA,ext} H(V_P^2))$$

228 with the plastic $C_{AMPA}(t)$ given in (12) and constant C_{NMDA} .

229 The changes in GABAergic activity caused by the activation of extrasynaptic NMDAR is modeled via an
 230 auxiliary variable $K(t)$,

$$\frac{dK}{dt} = \frac{1}{\tau_K} \left(-K(0.5 - K)(1 - K) - C_{NMDA} y_{NMDA,ext} H(V_P^{(2)}) \right). \quad (15)$$

231 When extrasynaptic NMDAR is inactive (i.e. $y_{NMDA,ext} = 0$, (14) has three equilibrium points at
 232 $K^* = \{0, 0.5, 1\}$. The extrasynaptic NMDAR activation (i.e. $y_{NMDA,ext} \neq 0$) can lead to a saddle-node
 233 bifurcation of the equilibria $K^* = 0.5$ and $K^* = 1$ leaving (15) with a single equilibrium point at
 234 $K^* \approx 0$. The variable $K(t)$ modulates the excitability of POP_2 as,

$$b_{thr}^{(2)}(t) = b_{thr}^{(2)} - k_B^{(2)}(1 - K(t)),$$

235 where the parameter $k_B^{(2)}$ scales the impact of $K(t)$ on the excitability. Since the gamma-band activity
 236 observed at the seizure onset can be obtained by increasing the IPSP amplitude of PV interneurons
 237 [40,43], $K(t)$ modulates $G^{(2)}$ as

$$G^{(2)}(t) = G^{(2)} + k_G^{(2)}(1 - K(t)),$$

238 where the parameter $k_G^{(2)}$ scales the impact of $K(t)$ on the IPSP amplitude. We assumed that, in the
 239 absence of extrasynaptic NMDAR activity, $K(t) = 1$, for which IPSP amplitude is too small for yielding a
 240 gamma-band activity in (10) and the equilibrium point of (11) is far from the critical point of the seizure
 241 transition (i.e. the $n^{(2)}$ -nullcline intersects the $B^{(2)}$ -nullcline on its right branch). As $K(t) \rightarrow 0$ with the
 242 activation of the extrasynaptic NMDAR, $G^{(2)}(t)$ increases to a suitable level for obtaining gamma-band
 243 activity, whereas $b_{thr}^{(2)}(t)$ decreases and drives the equilibrium point of (10) towards the critical point of
 244 seizure transition in (10)-(11). In other words, how far (11) is from a Hopf bifurcation, hence how far (10)
 245 is from seizing, is controlled by the extrasynaptic NMDAR activity.

246 The parameter values of equations (10)-(15) are given in Table 2. Stochastic differential equations were
 247 iterated using Euler-Maruyama method with a step size $dt = 10^{-5}$ second. Bifurcation analysis was done
 248 with AUTO-07p [46].

249 Results

250 Physiological plasticity

251 The model of physiological plasticity includes presynaptic STP, calcium-driven pre- and postsynaptic
 252 LTP/LTD and consolidation (Eq (9), Figure 1A). All these mechanisms have distinct timescales, and
 253 therefore the system describing the physiological plasticity (9) is a multiple timescale system with
 254 $(\tau_d, \tau_f) < \tau_{Ca} < \tau_\rho < \tau_{Use} = \tau_{C_{AMPA}}$. We assume that the slow regime is governed by the variables
 255 concerning LTP/LTP and consolidation, e.g. (ρ, U_{se}, C_{AMPA}) . In the slow regime, the fast variables
 256 describing STP, $r^{(1)}$ and $u^{(1)}$, are slaved to the slow variables, as:

$$r^{(1)s} = \frac{1}{1 + \tau_d u^{(1)s} FR_p^{(1)}}, \quad u^{(1)s} = \frac{U_{se}(1 + \tau_f FR_p^{(1)})}{1 + \tau_f U_{se} FR_p^{(1)}}$$

257 where superscript $(.)^s$ indicates the slow regime. The NMDA-mediated calcium dynamics in the slow
 258 regime is given by

$$[Ca]^s = \tau_{Ca} G\left(FR_p^{(1)}\right) h_{Ca} H(V_p^2) = \tau_{Ca} C_{NMDA} y_{NMDA}(t) h_{Ca} H(V_p^2).$$

259 The NMDAergic-EPSPs $y_{NMDA}(t)$ can be approximated by $y_{NMDA} \approx \tau_{NMDA} A_{NMDA}^{(2)} r^{(1)s} u^{(1)s} FR_p^{(1)}$. If
 260 similar is applied for the AMPAergic synapses, $y_{AMPA} \approx \tau_{AMPA} A_{AMPA}^{(2)} r^{(1)s} u^{(1)s} FR_p^{(1)}$, then
 261 postsynaptic potential $V_p^{(2)}$ is given by

$$V_p^{(2)} = \Sigma\left(C_{k,p}^{(2)} y_k^{(2)}\right) + C_{AMPA} \tau_{AMPA} A_{AMPA}^{(2)} r^{(1)s} u^{(1)s} FR_p^{(1)} + C_{NMDA} \tau_{NMDA} A_{NMDA}^{(2)} r^{(1)s} u^{(1)s} FR_p^{(1)}.$$

262 For the NMDA-mediated calcium entry and postsynaptic depolarization to occur, the postsynaptic
 263 membrane should be sufficiently depolarized, i.e. $V_p^{(2)} > V_{th}$. This depolarization depends on the
 264 AMPAergic input. Assuming that the postsynaptic system is balanced for $FR_p^{(1)} = 0$ and intra-population
 265 interactions are independent of the external input, i.e. $\Sigma\left(C_{k,p}^{(2)} y_k^{(2)}\right) = 0$, the postsynaptic polarization in
 266 response to the AMPAergic input from POP_1 can be reduced to

$$V_p^{(2)} \approx C_{AMPA} \tau_{AMPA} A_{AMPA}^{(2)} r^{(1)s} u^{(1)s} FR_p^{(1)},$$

267 calcium concentration to

$$[Ca]^s = C_{NMDA} \tau_{NMDA} A_{NMDA}^{(2)} r^{(1)s} u^{(1)s} FR_p^{(1)} h_{Ca}, \text{ if } V_p^{(2)} > V_{th}, \text{ otherwise } [Ca]^s \approx 0$$

268 As the fast variables ($r^{(1)}, u^{(1)}, [Ca]$) are expressed as a function of the slow variables, (ρ, U_{se}, C_{AMPA}),

269 the reduced (slow) system reads:

$$\frac{d\rho}{d\bar{t}} = (-\rho(1-\rho)(\rho_* - \rho) + (1-\rho)\Omega_p([Ca]) - \rho\Omega_d([Ca])), \quad (16a)$$

$$\frac{dU_{se}}{d\bar{t}} = \frac{\tau_\rho}{\tau_{U_{se}}} (U_{se,d} - U_{se} + \rho(U_{se,p} - U_{se,d})). \quad (16b)$$

$$\frac{dC_{AMPA}}{d\bar{t}} = \frac{\tau_\rho}{\tau_{C_{AMPA}}} (C_{AMPA,d} - C_{AMPA} + \rho(C_{AMPA,p} - C_{AMPA,d})). \quad (16c)$$

270 where $\bar{t} = \frac{t}{\tau_\rho}$. If $\frac{\tau_\rho}{\tau_{U_{se}}} = \frac{\tau_\rho}{\tau_{C_{AMPA}}} \ll 1$, then we can take them to zero limit and thread them as

271 parameters to investigate the variation of ρ under plasticity, which is the variable that controls the long-

272 term variations in the neurotransmitter release probability, U_{se} , and the AMPARergic coupling strength,

273 C_{AMPA} . For a simple investigation of ρ (16a) for $\frac{\tau_\rho}{\tau_{U_{se}}} = \frac{\tau_\rho}{\tau_{C_{AMPA}}} = 0$, we assume that $C_{AMPA} \approx$

274 $C_{AMPA,min} + \kappa U_{se}$, ($\kappa > 0$), which is a reasonable assumption since both C_{AMPA} and U_{se} depend on ρ

275 in the same manner. Figure 4(A) and (B) shows $V_p^{(2)}$ and $[Ca]^s$ as a function of $FR_p^{(1)}$ and U_{se} with the

276 parameter set given in Table 1. The postsynaptic subpopulation depolarizes monotonically for increasing

277 $FR_p^{(1)}$ and U_{se} (Fig 4(A)). The change in the calcium concentration follows a sigmoidal shape (Fig 4(B)). It

278 remains close to zero for low values of U_{se} and $FR_p^{(1)}$. It increases sharply for medium values of U_{se} and

279 $FR_p^{(1)}$, then slowly for higher values of U_{se} and $FR_p^{(1)}$ as it approaches a plateau.

280 **Figure 3 Physiological plasticity at presynaptic and postsynaptic sites.** (A) Presynaptic glutamatergic

281 release and subsequent postsynaptic depolarization results in calcium influx via NMDARs. Calcium

282 signaling activates independent biochemical pathways, leading to postsynaptic and presynaptic long-term

283 changes due to the insertion of new AMPARs and an increase in vesicle release probability. Under

284 physiological conditions, excitation is balanced by sufficient chloride trafficking through GABAR and KCC2.
 285 (B) Pathological plasticity at postsynaptic site. When the released glutamate is too high to be used by
 286 synaptic AMPAR and NMDAR, it diffuses to the extrasynaptic site and activates the extrasynaptic NMDAR.
 287 Activation of NMDAR causes internalization of extrasynaptic GABAR. Calcium influx via the extrasynaptic
 288 NMDAR activates calpain that perturbs the KCC2 functioning.

289

290 **Figure 4 Postsynaptic depolarization, calcium concentrating and long-term plasticity in sow regime.** (A)
 291 Postsynaptic polarization $V_p^{(2)s}$ and (B) calcium concentration $[Ca]_s$ as a function of $(FR_p^{(1)}, U_{se})$ for the
 292 parameter set given in Table 1 and $\gamma_p = 1$. (C) Equilibrium points of (16a) as function of $(FR_p^{(1)}, U_{se})$ for
 293 different values of (θ_p, θ_d) .

294 We then investigate the variation of ρ under plasticity. For this, we compute the equilibrium points of
 295 (16) for $\frac{dU_{\{se\}}}{d\bar{t}} = \frac{dC_{AMPA}}{d\bar{t}} = 0$. In particular, (16a) has three equilibrium points at $\rho^* = \{0, 0.5, 1\}$ if the
 296 variations in U_{se} and $FR_p^{(1)}$ are not sufficient to change, meaning that depressed synapses will remain
 297 depressed, and the potentiated ones will remain potentiated. If U_{se} and $FR_p^{(1)}$ are in a region where
 298 they can induce any change in ρ , (16a) has a single stable equilibrium point. If $\rho^* \in [0, 0.5)$ then the
 299 synapses will depress, if $\rho^* \in (0.5, 1]$ then the synapses will potentiate. Figure 4(C) shows ρ^* as a
 300 function of $(FR_p^{(1)}, U_{se})$ as the LTD and LTP thresholds, θ_d and θ_p , vary on this calcium concentration
 301 surface. The dark blue regions indicate that (16a) has three equilibrium points at $\rho^* = \{0, 0.5, 1\}$,
 302 therefore, the synapses do not change. When the potentiation threshold θ_p is too high ($\theta_p = 1.5$, upper
 303 panels), synapses either do not change or become depressed for moderate to high input firing rates
 304 $FR_p^{(1)}$ and release probability U_{se} depending on the depression threshold θ_d . A decreasing difference
 305 between θ_d and θ_p widens the $(FR_p^{(1)}, U_{se})$ region for which (16a) has three equilibria. Consequently,
 306 both synapses preserve their values for a low presynaptic firing rate. Lowering the potentiation threshold
 307 expands the range of LTP. In this case, increasing θ_d shrinks the LTD range.

308 Physiological plasticity under epileptic activity

309 In our model, long-term plasticity depends on the time lag between the interictal spikes of POP₁ and
310 POP₂, as well. In this section we assume that only the physiological synaptic plasticity mechanism (Fig 1A)
311 is active. Figure 5 exemplifies how ρ changes in response to single spikes of POP₁ and POP₂ elicited by a
312 pulse stimulation when ρ is initiated at $\rho(0) = 0.5$. The synaptic variable ρ potentiates regardless of the
313 pulse delay for $(\theta_d, \theta_p) = (0.6, 0.7)$, depresses $(\theta_d, \theta_p) = (0.1, 0.7)$ (Fig 5A). We obtain a depression-
314 potentiation-depression curve of $\Delta\rho$ for $(\theta_d, \theta_p) = (0.3, 0.7)$, for which the system response is shown in
315 Figure 5B-D. When POP₂ spikes $\Delta t = 0.02 \text{ sec}$ before POP₁, the calcium concentration stays between
316 (θ_d, θ_p) and ρ decreases (Fig 5B). When POP₂ and POP₁ spike simultaneously, the calcium concentration
317 exceeds θ_p and ρ increases (Fig 5C). Finally, when POP₂ spikes $\Delta t = 0.02 \text{ sec}$ after POP₁, ρ decreases
318 since the calcium concentration stays between (θ_d, θ_p) (Fig 5D).

319 **Figure 5 Change in synaptic efficacy under epileptic spikes.** (A) Rate of change in the synaptic efficacy
320 variable ρ under single epileptic spike in in Pop1 and Pop2 when the system (9)-(10) is initialized from
321 $\rho(0) = 0.5$ with $(U_{se}, C_{AMPA}) = (U_{se,min}, C_{AMPA,min})$. Epileptic spikes are triggered by a pulse
322 stimulation applied with a time delay of Δt (sec) for $(\theta_d, \theta_p) = (0.1, 0.7)$ (green line), $(\theta_d, \theta_p) =$
323 $(0.3, 0.7)$ (orange line) and $(\theta_d, \theta_p) = (0.1, 0.7)$ (blue line). (B-D) Pre- and post-spiking is triggered by a
324 single pulse with $\Delta t = -0.2 \text{ sec}$ in (B), $\Delta t = 0$ in (C) and $\Delta t = 0.2$ in (D) for $(\theta_d, \theta_p) = (0.3, 0.7)$.
325 The corresponding behaviour of $[Ca]$ and ρ are shown in the middle and bottom panels, respectively.
326 The orange dotted and green dotted lines in the middle panels mark θ_d and θ_p , respectively.

327 Depending on the potentiation and depression thresholds, and intrinsic dynamics of the interacting
328 populations, aperiodic but continuous interictal epileptic discharges can cause long-term changes in the
329 presynaptic release probability and coupling strength between the interacting populations (Fig 6). Here,
330 we assume that POP₁ is in interictal spiking mode as in Fig 2B, and the less excitable POP₂ responds to
331 POP₁ by generating spikes. If the potentiation threshold is high, then initially depressed synapses
332 between POP₁ and POP₂ remain depressed (Fig 6A). For a lower potentiation threshold, the

333 depolarization in POP₂ is high enough to increase the calcium concentration above θ_p , hence causing a
334 positive change in the synaptic variable ρ ($\Delta\rho > 0$). If this regime is maintained long enough and (θ_d, θ_p)
335 are in a suitable range for LTP, ρ can cross the threshold separating depressed to potentiated states, and
336 a pre- and postsynaptic LTP occurs (Fig 6B). Because of the LTP, the time lag between the POP₁ and POP₂
337 spikes decreases. In the same configuration but with potentiated synapses, increasing the difference
338 between θ_d and θ_p causes pre- and postsynaptic LTD since the calcium concentration remains in (θ_d, θ_p)
339 (Fig 6C). Consequently, the time lag between the POP₁ and POP₂ spikes increases. If both depression and
340 potentiation thresholds are high, despite the interaction between POP₁ and POP₂, synaptic variables do
341 not change (Fig 6D).

342 **Figure 6 Physiological plasticity under inter-ictal epileptic discharges.** (A) No change in depressed
343 synapses for $(\theta_d, \theta_p) = (0.3, 0.7)$. (B) Potentiation of initially depressed synapses for $(\theta_d, \theta_p) =$
344 $(0.3, 0.4)$. (C) Depression of initially potentiated synapses for $(\theta_d, \theta_p) = (0.1, 1.5)$ (D) No change in
345 potentiated synapses for $(\theta_d, \theta_p) = (1.2, 1.5)$.

346 Experimental studies suggest that high rate of synchronized activity, during an epileptic seizure for
347 instance, increases the glutamate release. Indeed, the model also suggests that an increased firing rate
348 during a seizure in POP₁ can drive the calcium concentration above θ_p , and cause LTP, while the interictal
349 activity with the same values of (θ_d, θ_p) does not change synaptic efficacy (Fig. 6A vs 7A). Alternatively, if
350 calcium concentration is already above θ_p , then the increased firing rate can accelerate LTP in POP₂ (Fig.
351 6B vs 7B). In Figure 7 the repeated seizures in POP₁ are triggered by a stochastic input to $B^{(1)}$ variable.

352 **Figure 7 Impact of seizure to physiological plasticity.** Potentiation of depressed synapses for $(\theta_d, \theta_p) =$
353 $(0.3, 0.7)$ (A) and for $(\theta_d, \theta_p) = (0.3, 0.4)$ (B).

354 Expansion of the epileptogenic network

355 Physiological plasticity alone increases coupling strength by increasing the probability of
356 neurotransmitter release at the presynaptic site and inserting AMPAR at the postsynaptic site. Unless the

357 extrasynaptic NMDAR are activated at the postsynaptic site, the postsynaptic population can preserve its
 358 excitation/inhibition balance, hence, does not undergo seizures. However, the extrasynaptic NMDAR
 359 activation triggers different processes that disturb the excitation/inhibition balance by reducing the
 360 effect of the GABAergic activity [7,47,48] (Fig 3B).

361 We assumed that the extrasynaptic NMDAR (14) is activated after the synapses are potentiated, i.e. for
 362 $U_{se} > 0.7$. The extrasynaptic NMDAR activity changes the amplitude of the PV INs $G^{(2)}(t)$ and the
 363 excitability $btr^{(2)}(t)$ of POP₂ via the auxiliary variable $K(t)$ (15). We investigate the impact of these
 364 changes in the whole model given by (9)-(15). We simulate the whole system (9)-(15) starting from the
 365 last point of the solution in Fig 7B for $(\theta_d, \theta_p) = (0.3, 0.4)$. When POP₁ undergoes seizures since low
 366 value of $btr^{(1)}$, and POP₂ responds by epileptic spikes since POP₂ has a low excitability because $btr^{(2)}(t)$
 367 is initially high. Activation of the extrasynaptic NMDAR drives the variable $K(t)$ to 0 as it causes
 368 "structural" changes within POP₂. In particular, the amount of the GABAergic loss in POP₂, which is
 369 represented by the parameter $k_B^{(2)}$, can decrease the excitability threshold of POP₂ and cause seizures in
 370 POP₂. The relation between the GABAergic loss and seizure in POP₂ is represented in the phase space of
 371 $(B^{(2)}, n^{(2)})$ in Fig 8A, and the time traces are shown in Fig 8B. For $0 \leq k_B^{(2)} < 8$ the equilibrium point of
 372 the $(B^{(2)}, n^{(2)})$ –subsystem remains on the right handside of the critical point of the seizure transitions.
 373 In this regime, POP₂ responds to the seizures of POP₁ by spiking only, For $8 \leq k_B^{(2)}$, the variable $B^{(2)}$
 374 crosses the critical point and jumps to the left branch of the $B^{(2)}$ -nullcline, meanwhile POP₂ responds to
 375 the seizures of POP₁ with a seizure. POP₂ undergoes spontaneous and periodic seizures for $10 \leq k_B^{(2)}$.

376 **Figure 8 Effect of the pathological plasticity on POP₂.** (A) Phase portrait of $(B^{(2)}, n^{(2)})$ -subsystem
 377 showing the effect of the parameter k_B on the excitability of POP₂. POP₂ crosses the critical point as k_B
 378 increases. (B) Time traces of $B^{(2)}$ shown in (A). (C) Normalized PSD of $V_p^{(2)}$ during seizures shows the
 379 effect of $k_G^{(2)}$ for $k_B = 9$. Gamma-band activity appears for $k_G^{(2)} > 8$. (D-E) Example time trace of (9)-(15)

380 for (E) $(k_B, k_G) = (0,0)$ and (F) $(k_B, k_G) = (9, 20)$. POP₂ undergoes a complete seizure in $t =$
381 $(180, 230)$.

382 One of the markers of the seizure onset zone is the gamma-band activity observed at the seizure onset.

383 Parameter $k_G^{(2)}$ scales the impact of the variable $K(t)$, hence of the activation of extrasynaptic NMDAR,

384 on the fast GABAergic interneurons. POP₂ undergoes a gamma-band activity at the seizure onset for

385 $k_G^{(2)} > 8$ as demonstrated in the power spectral density (PSD) of $V_p^{(2)}$ during a seizure triggered by POP₁

386 for $k_B^{(2)} = 9$ (Fig 8C). Figure 8E and F show the response of POP₂ for $(k_B^{(2)}, k_G^{(2)}) = (0, 0)$ and

387 $(k_B^{(2)}, k_G^{(2)}) = (9, 20)$ for the epileptic spikes and seizure on POP₁, respectively. POP₂ undergoes a seizure

388 at $t = (180, 230)$ after spiking as a response to a seizure in POP₁ at $t = (160, 190)$.

389 Resection of the epileptic zone

390 The activation of extrasynaptic NMDAR induces irreversible structural changes in POP₂, in particular, in its

391 GABAergic structure. If the GABAergic loss is important, despite a completely silent POP₁, POP₂ continues

392 to undergo epileptic activity. Figure 9 shows an example where at $t = 250 \text{ sec}$ POP₁ is silenced by

393 setting $A^{(1)} = 0$ but POP₂ continues seizing.

394 **Figure 9 Resection of the primarily focus.** After the cessation of any form of activity in POP₁ at $t = 250$

395 (A), POP₂ continues to undergo spontaneous seizures (B).

396 Discussion

397 In this study, we presented a neurophysiologically plausible NMM of physiological and pathological

398 plasticity under epileptic activity. Physiological plasticity takes into account short- and long-term

399 variations in the glutamatergic interactions at both presynaptic and postsynaptic sites. Pathological

400 plasticity considers GABAergic modulations at the postsynaptic site. Under epileptic activity, increased

401 connectivity strength resulting from the physiological plasticity triggers the pathological plasticity, which

402 causes a secondary focus. These mechanisms have been implemented in an autonomous (self-driven)
403 NMM, which generates the typical focal seizure pattern from interictal to seizure termination.

404 Physiological synaptic plasticity in the model integrates three main mechanisms. The first one is the
405 presynaptic STP. The second one is the calcium-mediated long-term synaptic plasticity that changes the
406 probability of glutamate release at the presynaptic site and insertion of AMPAR at the postsynaptic site.
407 The third mechanism is the consolidation of long-term plasticity. Although the description of
408 consolidation remained phenomenological as in [30,32], its integration into the model allowed for a
409 sustained change in synaptic connectivity.

410 We assumed that presynaptic and postsynaptic long-term plasticity are proportional. While this
411 simplified assumption is true for retrograde nitric oxide signaling, retrograde endocannabinoid release
412 works in the opposite direction. Costa et al. [37] suggested a phenomenological model integrating the
413 effects of opposing proteins on long-term presynaptic plasticity. Such effects can be integrated in our
414 model, for instance, by introducing a second variable to track the calcium variations, which modifies the
415 neurotransmitter release probability.

416 Our approach of modeling NMDA currents is quasi-physiological, similar to [38], but without explicitly
417 modeling the magnesium gate. Yet, it does include the essential ingredients mediating the NMDAR
418 activity, which are the presynaptic release and postsynaptic potentiation. Conductance-based modeling
419 of synaptic receptors in the neural mass formulation has been proposed in [49], and more recently, in
420 [50]. While the conductance-based neural mass formulation may provide a more physiological way of
421 modeling neural dynamics, we argue that our approach is consistent with the neural mass formulation
422 we considered and captures the key ingredients necessary for the problem studied.

423 The pathological plasticity under epileptic activity includes disruption of the GABAergic pathway caused
424 by the activation of the extrasynaptic NMDAR. The model captures possible changes without detailing
425 the process, such as how calcium entry through the extrasynaptic NMDAR acts on calpain, how a
426 decreasing number of KCC2 changes the GABA reversal potential, or how GABAR expression is

427 downregulated, etc. Rather, the impact of the extrasynaptic NMDAR activation is reflected by an auxiliary
428 variable that acts on perisomatic and dendritic GABAergic interneurons of the NMM. The former mimics
429 the effect of KCC2 downregulation that induces a gamma-band activity, which is considered a signature
430 of an epileptogenic zone in focal seizures. The latter mimics the effect of GABAR downregulation that
431 reduces the excitability threshold of the population targeted by the epileptic population. Indeed, the
432 dendritic SOM interneurons control the calcium dynamics, for instance by directly inhibiting calcium
433 influx [51–53]. Low dendritic SOM projection may lead to accumulation of intracellular calcium and
434 aggravate KCC2 dysfunctions.

435 In this study we extended a widely used model of the hippocampus [40] for ensuring autonomous
436 epileptic activity from interictal to ictal and seizure termination. Essentially, this was achieved by
437 introducing a slow subsystem that modulates the IPSP amplitude of the slow GABAergic interneurons. In
438 other words, we introduced a basic slow-fast process for obtaining an autonomous interictal-to-ictal
439 activity. Except for very few studies [54,55], the modulation has been performed manually to obtain ictal
440 activity. In both studies, the main agent driving system to seizure is the IPSP amplitude of the slow
441 GABAergic INs. In [55,56] a dynamic chloride accumulation in pyramidal neurons caused by GABAergic
442 activity modulates the IPSP amplitude. However, the authors of [55] do not propose a mechanism for
443 seizure termination. In [54] this modulation was obtained through feedback from the activity of the
444 pyramidal cells. Our approach is similar to the phenomenological approach of [54], except the feedback
445 from the pyramidal neurons and the dimension of the slow subsystem. In the transition to seizures, not
446 only pyramidal neurons but also interneurons can play a critical role [57]. Our model can be improved
447 further to reflect the involvement of specific cellular and network mechanisms by considering
448 appropriate feedback mechanisms. Furthermore, the fast-system representing neuronal subpopulations
449 and the slow-subsystem controlling the excitability and the IPSP amplitude have the essential ingredients
450 for studying different bifurcation types, which can be inherent to specific seizure types (absence seizures,
451 focal seizures with different seizure onset patterns [42]). Furthermore, the slow-fast system can be used

452 to study the effect of electrical stimulation that is a general procedure in clinics to understand the
453 excitability of the brain region to identify epileptogenic networks.

454 Our study confirms the so-called *seizure can beget seizures* phenomena: epileptic activity in one brain
455 region can recruit healthy regions and cause the formation of a complex epileptic network [58]. The
456 model suggests that epileptic seizures boots physio-pathological plasticity, as suggested in the literature
457 [8,59]. Once a healthy zone is driven to the critical point, then it generates epileptic discharges and/or
458 seizures. Therefore, the timing of interference with epileptic activity may be critical. Indeed, in clinical
459 practice, acute symptomatic seizures are treated with anti-seizure medication [60]. In addition to the role
460 of epileptic activity in epileptogenesis, epileptic activity can interfere with physiological oscillatory activity
461 in distributed neural networks and cause cognitive comorbidity [61–65]. Generalizing our model to
462 personalized dynamic brain network modeling for planning the treatment of epilepsy is a future research
463 direction [66].

464 On the other hand, epilepsy is a complex and patient-specific disease, and it is challenging to propose a
465 “one-fits-all” theory. The “seizure beget seizure” phenomenon has been questioned recently [67],
466 especially in the light of clinical data [68]. Our model has many limitations to address this challenge. First,
467 it only considers glutamatergic plasticity mediated by epileptic activity between unidirectionally coupled
468 neuronal populations. A growing body of literature suggests that inhibitory GABAergic synapses exhibit
469 long-term plasticity, which can have a protective role against the expansion of epileptogenic networks
470 [69,70]. The model does not address mGLUR mediated plasticity [71,72], homeostatic effects [73] or
471 other mechanisms, such as epigenetic changes [74]. In addition, the considered NMM is the simplest
472 formulation for the CA1 region of the hippocampus. A laminar NMM can be considered for the distant
473 synaptic rules related to dendritic location, which can be useful for studying the plasticity induced in
474 neocortical regions by non-invasive brain stimulation. Modeling experimental recording will be an asset.
475 Finally, the model simulates epileptiform discharges, whereas the physiological plasticity is also mediated

476 by theta rhythm and theta-gamma oscillations in the hippocampus [75]. These points will be addressed in
477 future works.

478 Conclusion

479 We have proposed a framework based on neural mass modeling for studying physio-pathological
480 plasticity under epileptic activity. We have shown how increased connectivity between an epileptic and
481 non-epileptic brain regions leads to GABAergic dysfunctions in the latter, and it forms an epileptogenic
482 network. Our study can benefit the development of *plastic* large-scale brain models for studying the
483 expansion of epileptogenic networks, formation of secondary foci, and the design of invasive or non-
484 invasive brain stimulation protocols to control the epileptogenic networks.

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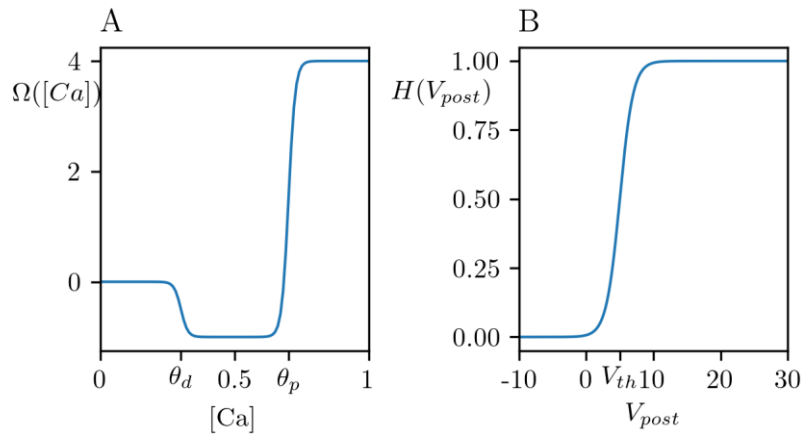
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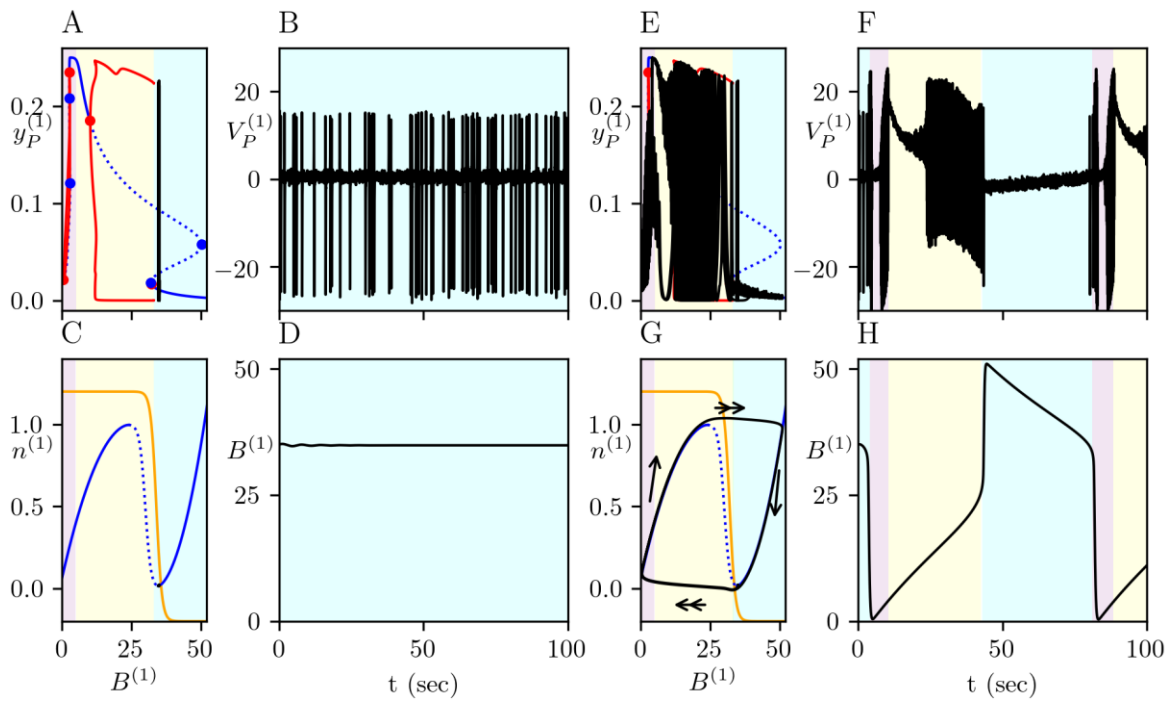
674 Figure 1



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677 Figure 2



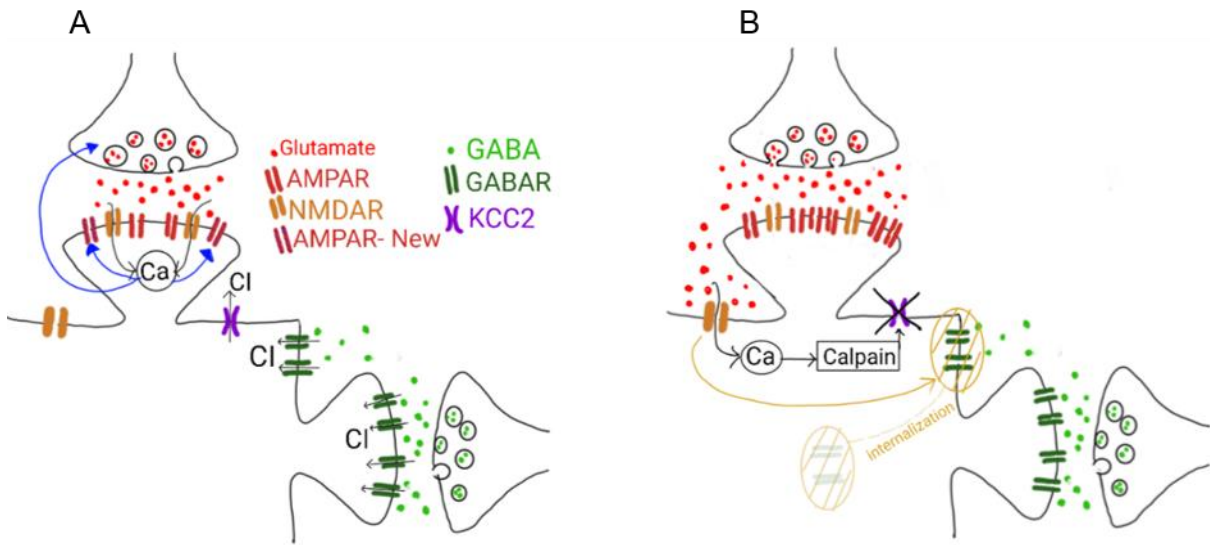
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682 Figure 3



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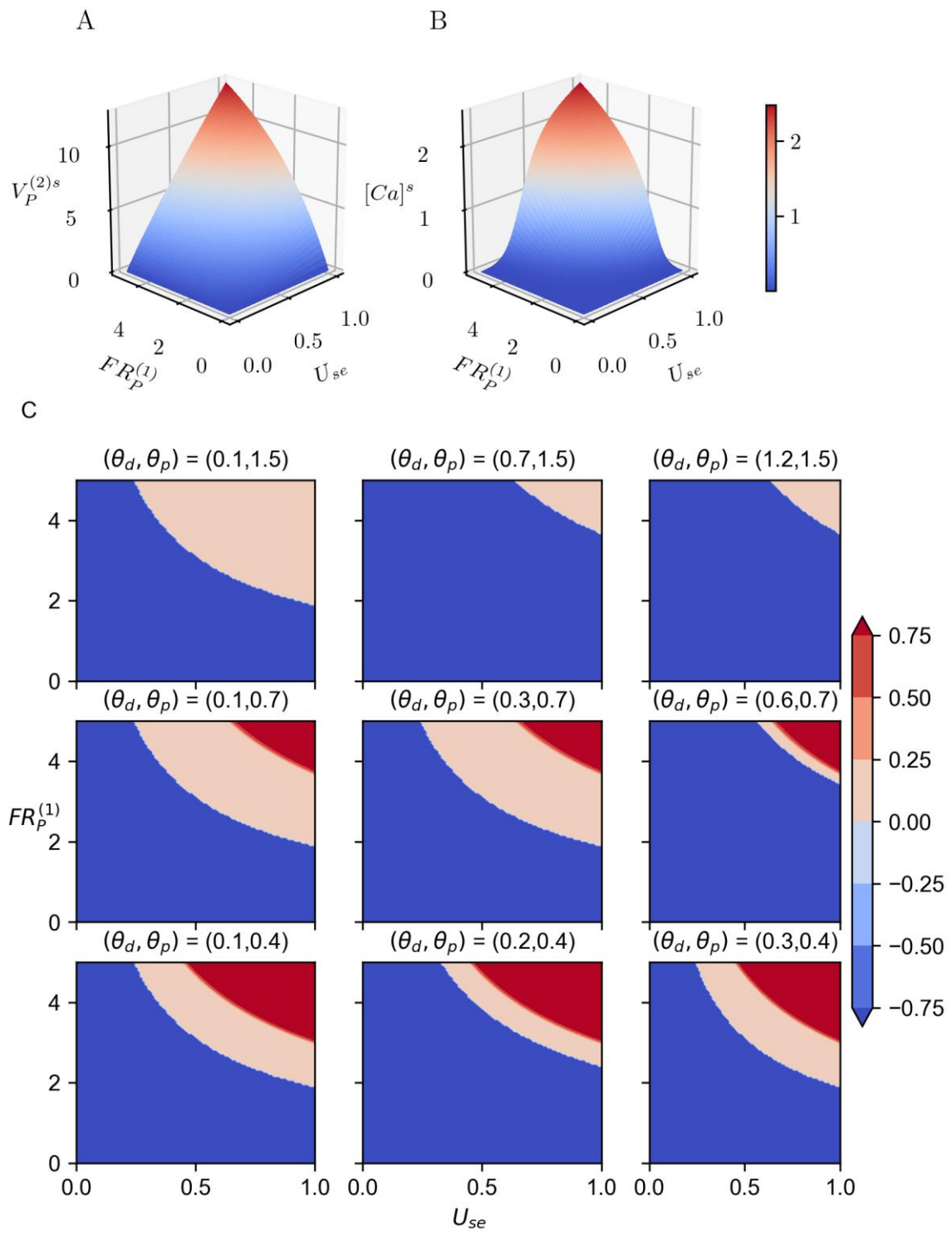
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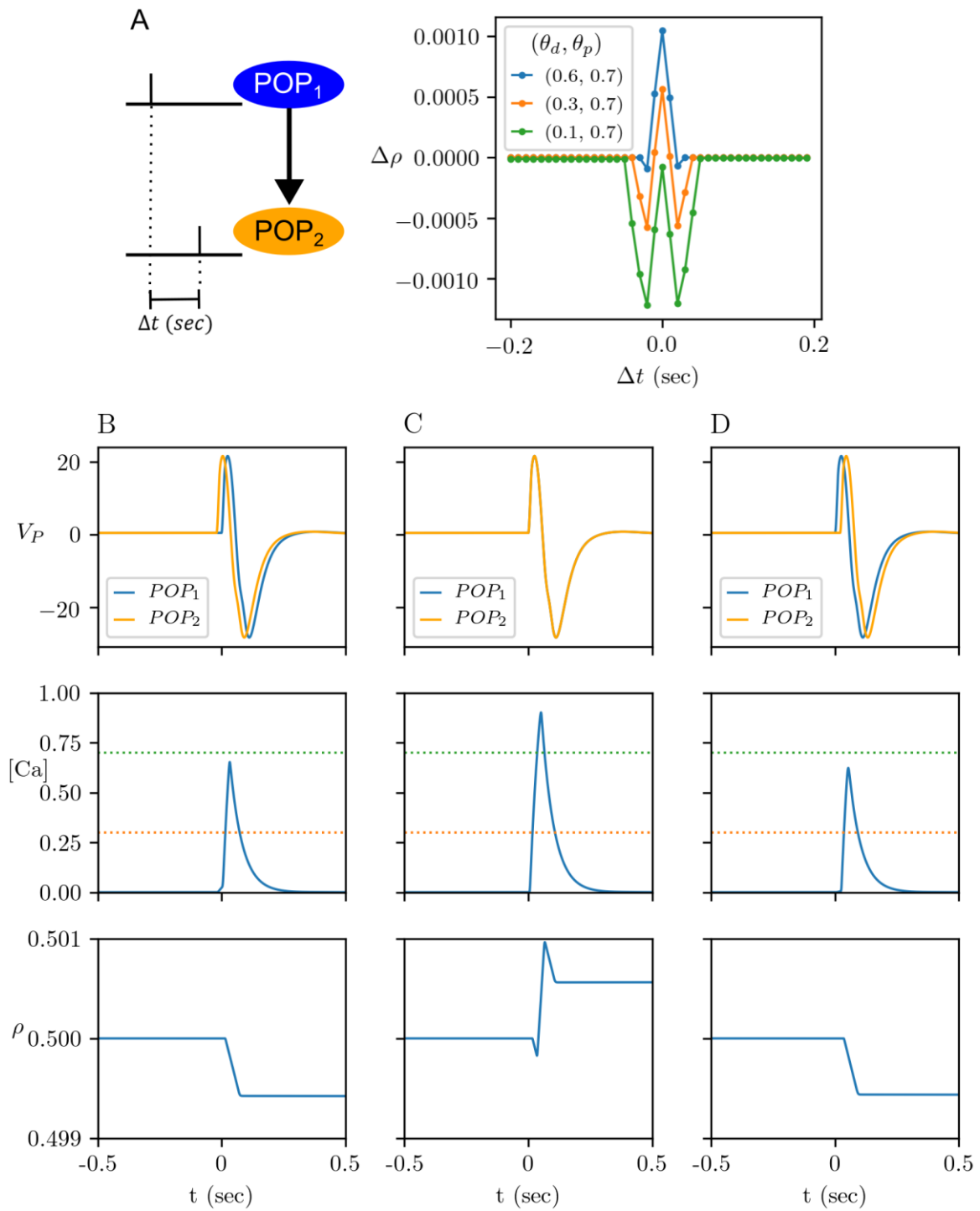
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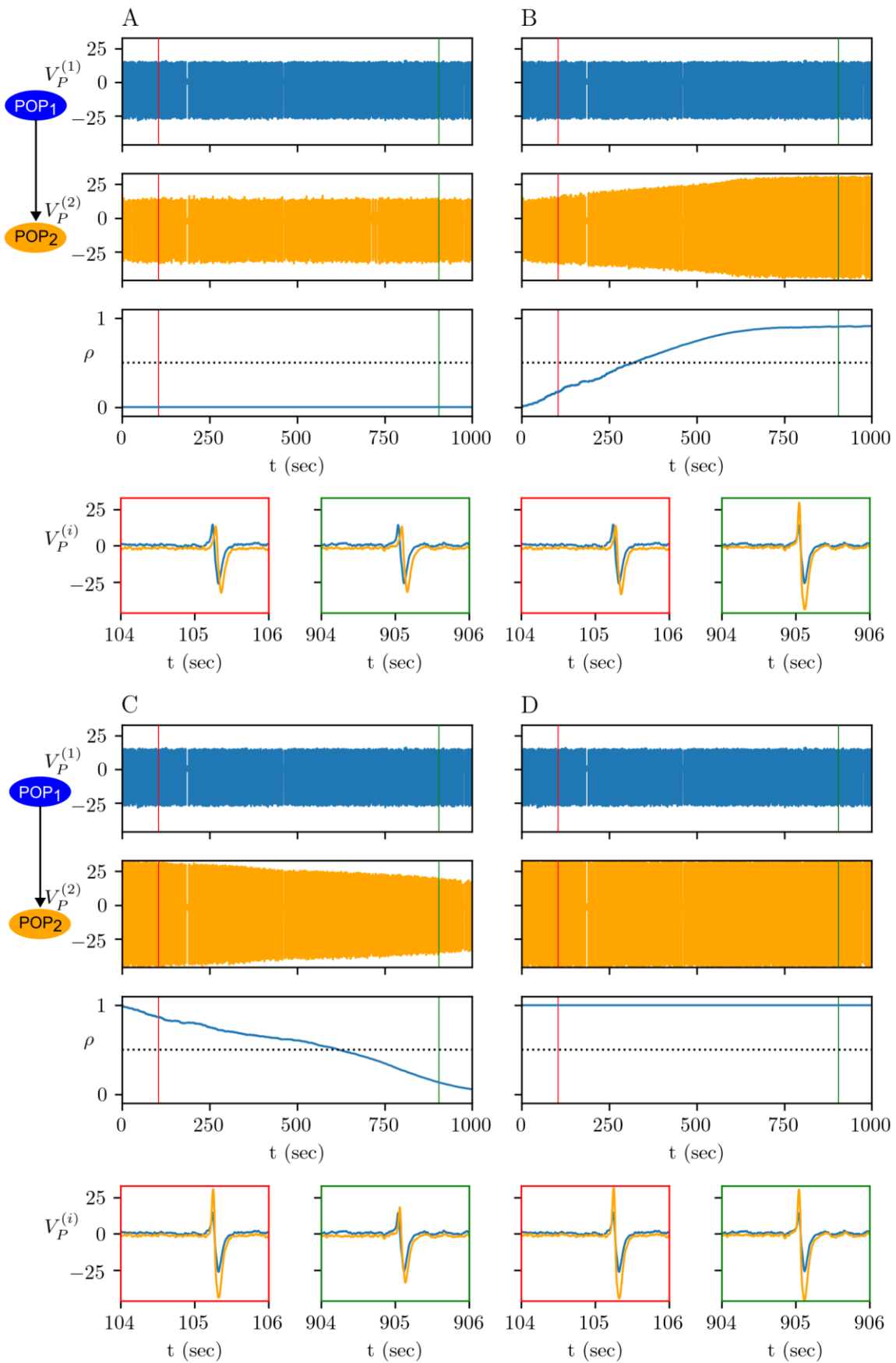


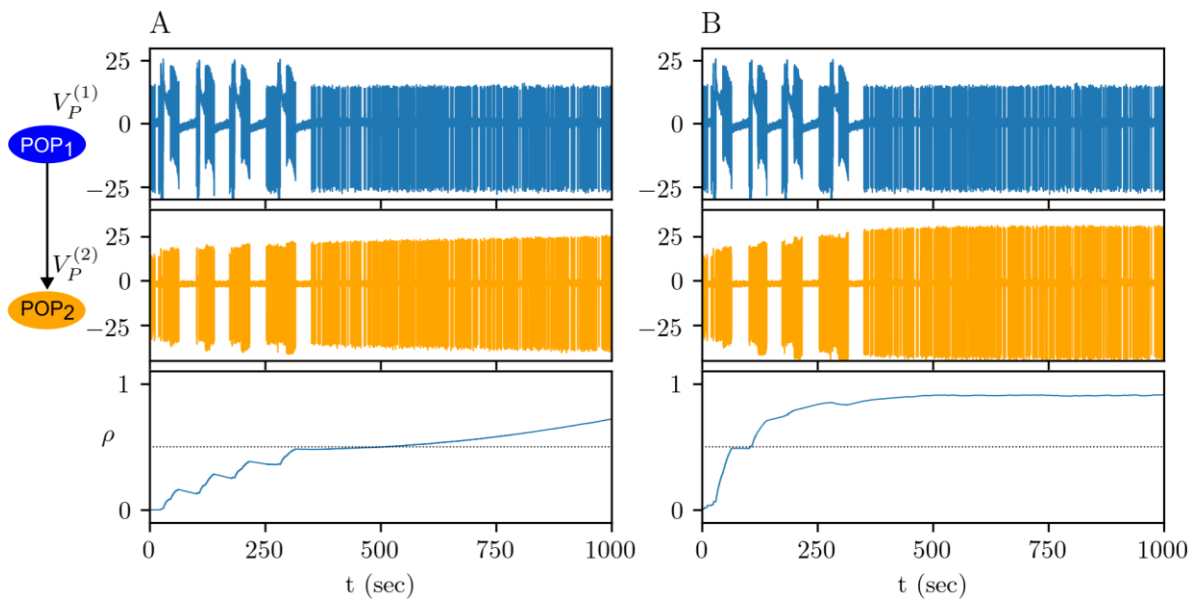
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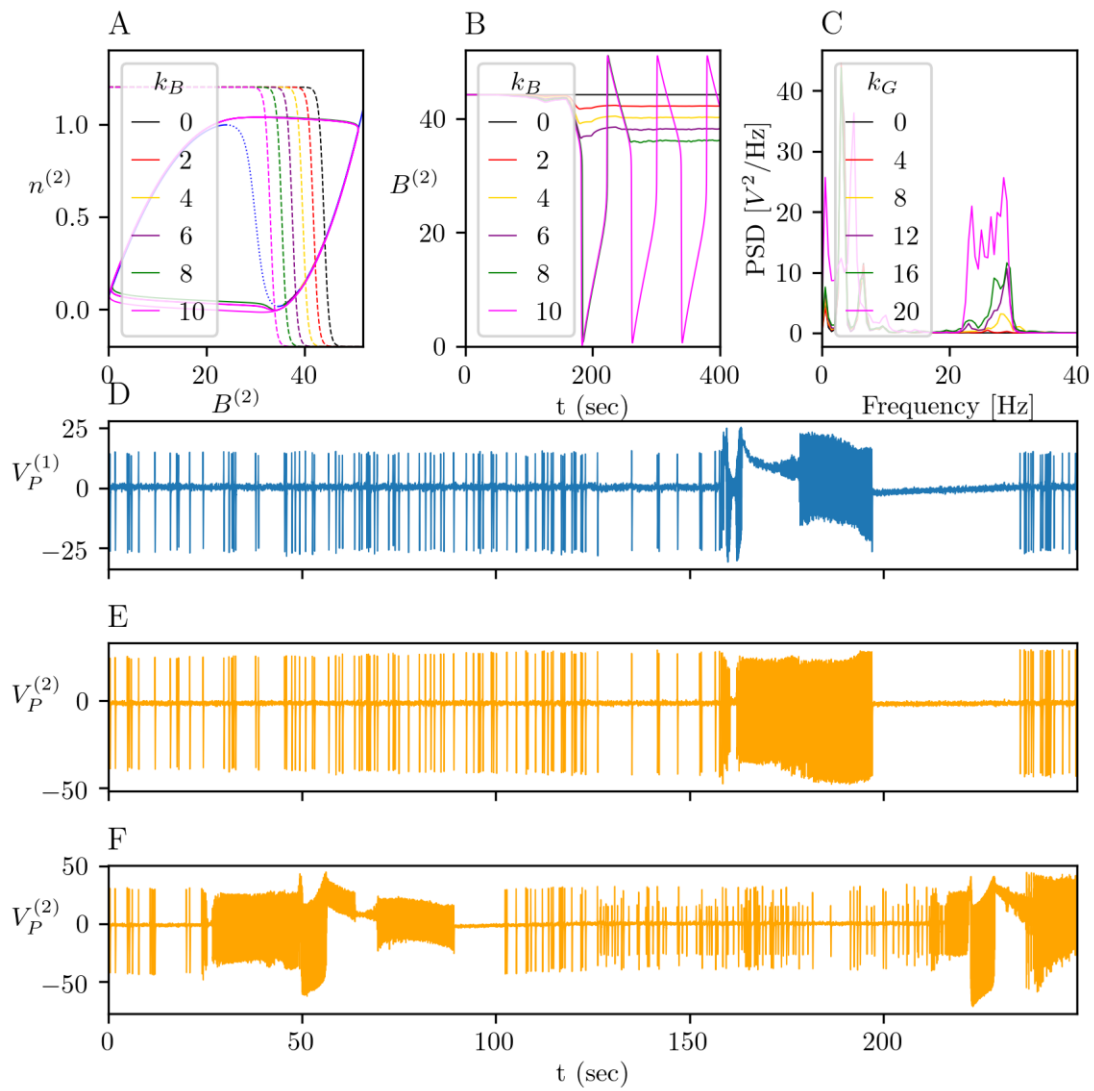
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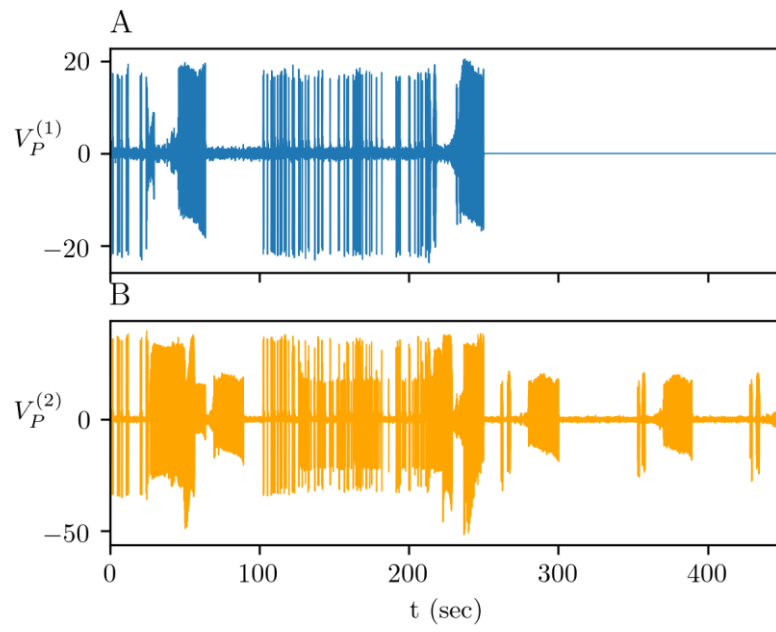
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717 Figure 9



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