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## ► To cite this version:

Mallory Carlu, Omar Chehab, Leonardo Dalla Porta, Damien Depannemaecker, Charlotte Héricé, et al.. A mean-field approach to the dynamics of networks of complex neurons, from nonlinear Integrate-and-Fire to Hodgkin-Huxley models. *Journal of Neurophysiology*, 2020, 123 (3), pp.1042-1051. 10.1152/jn.00399.2019 . hal-02414751

**HAL Id: hal-02414751**

**<https://inria.hal.science/hal-02414751>**

Submitted on 16 Dec 2019

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# A mean-field approach to the dynamics of networks of complex neurons, from nonlinear Integrate-and-Fire to Hodgkin-Huxley models

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## Abstract

We present a mean-field formalism able to predict the collective dynamics of large networks of conductance-based interacting spiking neurons. We apply this formalism to several neuronal models, from the simplest Adaptive Exponential Integrate-and-Fire model to the more complex Hodgkin-Huxley and Morris-Lecar models. We show that the resulting mean-field models are capable of predicting the correct spontaneous activity of both excitatory and inhibitory neurons in asynchronous irregular regimes, typical of cortical dynamics. Moreover, it is possible to quantitatively predict the populations response to external stimuli in the form of external spike trains. This mean-field formalism therefore provides a paradigm to bridge the scale between population dynamics and the microscopic complexity of the individual cells physiology.

**NEW & NOTEWORTHY (75 words max)** *Population models are a powerful mathematical tool to study the dynamics of neuronal networks and to simulate the brain at macroscopic scales. We present a mean-field model capable of quantitatively predicting the temporal dynamics of a network of complex spiking neuronal models, from Integrate-and-Fire to Hodgkin-Huxley, thus linking population models to neurons electrophysiology. This opens a perspective on generating biologically realistic mean-field models from electrophysiological recordings.*

## 1 Introduction

1 Brain dynamics can be investigated at different scales, from the microscopic cellular scale, describ-  
2 ing the voltage dynamics of neurons and synapses (Markram et al., 2015) to the mesoscopic scale,  
3 characterizing the dynamics of whole populations of neurons (Wilson and Cowan, 1972), up to the  
4 scale of the whole brain where several populations connect together (Bassett et al., 2018; Deco  
5 et al., 2015; Sanz Leon et al., 2013).

6 In their pioneering work (Wilson and Cowan, 1972), Wilson and Cowan describe the dynamics  
7 of a population of neurons through a well-known differential equation where the input-output gain  
8 function is described by a sigmoid function. This approach inspired a long lasting research in  
9 neuroscience where population models, usually called *rate models*, permit a qualitative insight  
10 into the dynamics of population of neurons (di Santo et al., 2018; Hopfield, 1984; Sompolinsky  
11 et al., 1988; Sussillo and Abbott, 2009).

12 Moreover, a large effort has been made in order to derive population descriptions from the  
13 specificity of the network model under consideration. This bottom-up approach permits to obtain  
14 a dimensionally reduced *mean field* description of the network population dynamics in different  
15 regimes (Amit and Brunel, 1997; Brunel and Hakim, 1999; Capone et al., 2019b; di Volo et al.,  
16 2014; El Boustani and Destexhe, 2009; Montbrió et al., 2015; Ohira and Cowan, 1993; Renart et al.,  
17 2004; Schwalger et al., 2017; Tort-Colet et al., 2019; Tsodyks and Sejnowski, 1995; Van Vreeswijk  
18 and Sompolinsky, 1996; Vreeswijk and Sompolinsky, 1998). On one hand *mean field* models  
19 permit a simpler, reduced picture of the dynamics of a population of neurons, thus allowing to  
20 unveil mechanisms determining specific observed phenomena (di Volo and Torcini, 2018; Jercog  
21 et al., 2017; Reig and Sanchez-Vives, 2007). On the other hand, they enable a direct comparison  
22 with imaging studies where the spatial resolution implies that the recorded field represents the  
23 average over a large population of neurons (i.e. a mean-field) (Capone et al., 2017; Chemla et al.,  
24 2019).

25 During awake states, cortical dynamics generally show asynchronous spiking activity, where  
26 individual neurons are characterized by an irregular (typically Poissonian) firing pattern (Burns  
27 and Webb, 1976; Deghani et al., 2016; Softky and Koch, 1993). In this dynamical regime, so-called  
28 Asynchronous Irregular (AI), the correlation of the network activity decays relatively quickly in  
29 time, making it possible to develop a Markovian formalism in order to obtain mean-field equations.  
30 The application of such a theory to binary neurons led to the derivation of dynamical equations  
31 for population rates (Ginzburg and Sompolinsky, 1994; Ohira and Cowan, 1993). More recently,  
32 such a theory has been extended to spiking neurons, permitting to obtain differential equations  
33 for neurons average activity and for higher-order moments (Buice et al., 2010; Dahmen et al.,  
34 2016; El Boustani and Destexhe, 2009). In the first order, these equations are formally the same  
35 as the *rate models*, like the Wilson-Cowan approach, although the function linking input-output  
36 properties of populations of neurons, namely the transfer function, is more complex than a sigmoid.  
37 Indeed, in this formalism, it encompasses internal properties of the neuronal models, together with  
38 the type of synaptic interactions under consideration, to yield a population scale description. In  
39 general, such function cannot be expressed in a closed form for complex neurons, especially if some  
40 realistic ingredients like conductance based interactions are taken into account.

41 In this article we present a general approach to determine the transfer function for complex  
42 models, from the Adaptive Exponential Integrate-and-Fire (AdEx) to the Hodgkin-Huxley (HH)  
43 and the Morris-Lecar (ML) models. As a result, we obtain mean-field equations for the population  
44 dynamics in AI regimes as observed in cortical regions for highly detailed models, creating a bridge  
45 between electrophysiology at the microscopic scale and the details of the famous transfer function  
46 first used by Wilson and Cowan as a sigmoid.

47 Finally, we test not only the ability of our mean-field models to describe spontaneous activity  
48 of the considered neuronal populations, but also their predictive power for network response to  
49 external stimuli. We show that, provided the stimuli are fairly slow, the mean field model gives  
50 good quantitative predictions.

## 51 2 Materials and Methods

52 We describe here the neuronal and network models used in this study. We also introduce mean-field  
53 equations describing population dynamics and the template to estimate the transfer function that  
54 we apply to all the neuronal models under consideration.

### 55 2.1 Network of spiking neurons

56 We consider a random directed network of  $N = 10^4$  cells, among which 80% are regular spiking  
57 (RS) excitatory (E) and 20% are fast spiking (FS) inhibitory (I) neurons. The connections between  
58 pairs of neurons are set randomly with a fixed probability ( $p = 0.05$ ). Unless otherwise stated,  
59 the same network and synaptic constants are used for all the neuronal models (Hodgkin-Huxley,  
60 Adaptive Exponential Integrate-and-Fire and Morris-Lecar). The dynamics of each node  $k$  follows:

$$\dot{\bar{x}}_k = F(\bar{x}_k) + I_{\text{syn}}, \quad (1)$$

61 where  $\bar{x}$  and  $F(\bar{x})$  represent the neuronal state and dynamics, the latter depending on the  
62 specific model (see Section 2.2). Note the notation  $\bar{x}_k$  which indicates that, in general, each neuron  
63 is characterized by a vector of variables. The synaptic current impinging on the postsynaptic  
64 neurons  $k$ ,  $I_{\text{syn}}$ , is modeled as:

$$I_{\text{syn}} = (E_e - v_k)G_{\text{syn}}^e + (E_i - v_k)G_{\text{syn}}^i, \quad (2)$$

65 where  $E_e = 0$  mV ( $E_i = -70$  mV) is the excitatory (inhibitory) reversal potential and  $G_{\text{syn}}^{(e,i)}$   
66 is the conductance modeled as a decaying exponential function:

$$G_{\text{syn}}^{(e,i)}(t) = Q_{(e,i)} \sum_n \Theta(t - t_{\text{sp}}(n)) e^{-\frac{t - t_{\text{sp}}(n)}{\tau}}, \quad (3)$$

67 where  $Q_e$  ( $Q_i$ ) is the excitatory (inhibitory) quantal conductance. The variable  $\tau = 5$  ms is the  
68 decay timescale of excitatory and inhibitory synapses and  $\Theta$  is the Heaviside step function. The  
69 summation runs over the over all the pre-synaptic spiking times  $t_{\text{sp}}(n)$ . For both Hodgkin-Huxley  
70 and Adaptive Exponential Integrate-and-Fire models we set  $Q_e = 1.5$  nS and  $Q_i = 5$  nS, while  
71 for Morris-Lecar model  $Q_e = 4$  nS and  $Q_i = 10$  nS. On top of inputs coming from other neurons  
72 in the network, each excitatory and inhibitory neuron receive an external drive in the form of a  
73 Poissonian excitatory spike train at a constant firing rate  $\nu_{\text{drive}} = 4$  Hz, if not stated otherwise.

## 74 2.2 Single neuron models

75 We describe here the neuronal models used in the rest of the paper, starting from the Integrate-  
76 and-Fire up to the Morris-Lecar and Hodgkin-Huxley models.

### 77 2.2.1 Adaptive Exponential Integrate-and-Fire model

78 The dynamics of each of the AdEx neurons  $i$  is described by the following 2D (here  $\bar{x}_i = (v_i, w_i)$ )  
79 differential equations (Brette and Gerstner, 2005) :

$$c_m \frac{dv_i}{dt} = g_L(E_L - v_i) + g_L \Delta e^{\frac{v_i - v_t}{\Delta}} - w_i + I_{\text{syn}}, \quad (4)$$

80

$$\frac{dw_i}{dt} = -\frac{w_i}{\tau_w} + b \sum_{t_{\text{sp}}(i)} \delta(t - t_{\text{sp}}(k)) + a(v_i - E_L), \quad (5)$$

81 where  $c_m = 150\text{pF}$  is the membrane capacity,  $v_i$  is the voltage of neuron  $i$  and, whenever  $v_i >$   
82  $v_t = -50$  mV at time  $t_{\text{sp}}(i)$ ,  $v_i$  is reset to the resting voltage  $v_{\text{rest}} = -65$  mV and fixed to this  
83 value for a refractory time  $T_{\text{refr}} = 5$  ms. The leak term has a fixed conductance of  $g_L = 10$  nS and  
84 the leakage reversal  $E_L = -65$  mV, if not stated otherwise. The exponential term has a different  
85 strength for regular-spiking (RS) and fast-spiking (FS) cells, i.e.  $\Delta = 2$  mV ( $\Delta = 0.5$  mV) for  
86 excitatory (inhibitory) cells. The variable  $w$  mimicks the dynamics of spike frequency adaptation.  
87 Inhibitory neurons are modeled according to physiological insights as the FS neurons with no  
88 adaptation while the excitatory RS neurons have a lower level of excitability due to the presence  
89 of adaptation. Here we consider  $b = 60$  pA,  $a = 4$  nS and  $\tau_w = 500$  ms, if not stated otherwise.

### 90 2.2.2 Hodgkin-Huxley

The dynamics of the Hodgkin-Huxley model (Hodgkin and Huxley, 1952) is given by the following  
5-dimensional system of differential equations (Pospischil et al., 2008):

$$c_m \frac{dv_i}{dt} = g_L(E_L - v_i) + g_{Na} m_i^3 h_i (E_{Na} - v_i) + \quad (6)$$

$$+ g_K n_i^4 (E_K - v_i) + g_M p_i (E_K - v_i) + I_{\text{syn}},$$

$$\frac{dn_i}{dt} = \alpha_n(v_i)(1 - n_i) - \beta_n(v_i)n_i, \quad (7)$$

$$\frac{dm_i}{dt} = \alpha_m(v_i)(1 - m_i) - \beta_m(v_i)m_i, \quad (8)$$

$$\frac{dh_i}{dt} = \alpha_h(v_i)(1 - h_i) - \beta_h(v_i)h_i, \quad (9)$$

$$\frac{dp_i}{dt} = (p_\infty(v_i) - p_i)/\tau_p(v_i), \quad (10)$$

91 with the gating functions,

$$\alpha_n(v) = \frac{-0.032(v - V_T - 15)}{\exp[-(v - V_T - 15)/5] - 1}, \quad \beta_n(v) = 0.5 \exp\left[\frac{-(v - V_T - 10)}{40}\right],$$

$$\alpha_m(v) = \frac{-0.32(v - V_T - 13)}{\exp[-(v - V_T - 13)/4] - 1}, \quad \beta_m(v) = \frac{0.28(v - V_T - 40)}{\exp[(v - V_T - 40)/5] - 1}, \quad (11)$$

$$\alpha_h(v) = 0.128 \exp[-(v - V_T - 17)/18], \quad \beta_h(v) = \frac{4}{1 + \exp[-(v - V_T - 40)/5]},$$

$$p_\infty(v) = \frac{1}{1 + \exp[-(v + 35)/10]}, \quad \tau_p(v) = \frac{\tau_{\text{max}}}{3.3 \exp[(v + 35)/20] + \exp[-(v + 35)/20]},$$

92 where  $v_i$  is the voltage and  $(n_i, m_i, h_i, p_i)$  are the corresponding gating variables of the  $i$ -th neuron.  
 93 We set the spike emission times  $t_{\text{sp}}(k)$  for this model to time steps in which the membrane potential  
 94  $v$  exceeded a voltage threshold of 10 mV. Unless stated otherwise, the membrane capacitance  
 95  $c_m = 200$  pF/cm<sup>2</sup>, the maximal conductance of the leak current  $g_L = 10$  mS/cm<sup>2</sup>, the sodium  
 96 current  $g_{Na} = 20$  mS/cm<sup>2</sup>, the delayed-rectifier potassium current  $g_K = 6$  mS/cm<sup>2</sup>, the slow  
 97 non-inactivating potassium current of the excitatory (RS) neurons  $g_M = 0.03$  mS/cm<sup>2</sup> and of the  
 98 inhibitory (FS) neurons  $g_M = 0$  mS/cm<sup>2</sup>, with corresponding reversal potentials  $E_L = -65$  mV,  
 99  $E_{Na} = 50$  mV,  $E_K = -90$  mV, the spiking threshold  $V_T = -53.5$  mV and  $\tau_{\text{max}} = 0.4$  s are the  
 100 fixed parameter values in Eqs. (6)-(11).

### 101 2.2.3 Morris-Lecar

102 The dynamics of the Morris-Lecar model (Morris and Lecar, 1981) is described by the system of  
 103 differential equations:

$$c_m \frac{dv_i}{dt} = g_L(E_L - v_i) + g_{Ca}M_{ss}(v_i)(E_{Ca} - v_i) + g_KN_i(E_K - v_i) + I_{\text{syn}} + I_0, \quad (12)$$

$$\frac{dN_i}{dt} = \frac{N_{ss}(v_i) - N_i}{\tau_N(v_i)}, \quad (13)$$

where  $c_m = 2\mu$  F/cm<sup>2</sup> is the membrane capacitance,  $v_i$  is the membrane potential in mV,  $N_i$  and  $M_{ss}$  are the fraction of open potassium and calcium channels, respectively. The current  $I_0 = 0.2$  nA/cm<sup>2</sup> is a reference DC external current. Spike emission times are established in the same way as for the HH model. The maximal conductances for the leakage current (L), calcium (Ca) and potassium (K) were fixed to  $g_L = 20$  mS/cm<sup>2</sup>,  $g_{Ca} = 80$  mS/cm<sup>2</sup> and  $g_K = 160$  mS/cm<sup>2</sup>, respectively. The reversal potentials are  $E_L = -50$  mV for excitatory RS neurons and  $E_L = -70$  mV for inhibitory FS neurons,  $E_{Ca} = 120$  mV and  $E_K = -84$  mV. The quantities  $M_{ss}$  and  $N_{ss}$  are modeled as:

$$M_{ss}(v) = \frac{1}{2} \left( 1 + \tanh \left[ \frac{v - V_1}{V_2} \right] \right), \quad (14)$$

$$N_{ss}(v) = \frac{1}{2} \left( 1 + \tanh \left[ \frac{v - V_3}{V_4} \right] \right), \quad (15)$$

with

$$\tau_N(v) = \frac{1}{2} \left( \phi \cosh \left[ \frac{v - V_3}{2V_4} \right] \right), \quad (16)$$

104 where  $V_1 = -1.2$  mV,  $V_2 = 18$  mV,  $V_3 = 2$  mV,  $V_4 = 30$  mV are tuning parameters that  
 105 determine the half activating voltage and slope of the activation curves for calcium and potassium  
 106 conductances. This choice of parameters is such that the ML neuron is set in a type II excitability  
 107 class, i.e. its response to a DC current is discontinuous and the neuron firing rate increases very  
 108 slowly with the injected current (data not shown).

## 109 2.3 Mean-field formalism

110 Mean-field theory scales the analysis of interacting point-wise neurons to their macroscopic, collec-  
 111 tive, dynamics based on the moment-statistics of the system, requiring a self-averaging hypothesis  
 112 for physical quantities. We make here an additional hypothesis that the biological neural network

113 is set to asynchronous irregular dynamical regime. The latter is chosen for its biological plausibility  
 114 (Destexhe et al., 2003) as observed in awake cortical states of adult mammalian brains.

115 We use here the master equation formalism reported by (El Boustani and Destexhe, 2009)  
 116 providing a system of ordinary differential equations that describe the evolution of the mean and  
 117 variance of the firing rate of excitatory and inhibitory neurons. The central argument for this  
 118 derivation is to consider the network dynamics as markovian on an infinitesimal (a time resolution  
 119  $T$ , typically 20ms) scale, as in Buice et al. (2010); Ginzburg and Sompolinsky (1994); Ohira and  
 120 Cowan (1993). Moreover, such a theory is based on the assumption that neurons emit maximum  
 121 one spike over the Markovian step  $T$ , meaning that the theory assumes relatively low firing rate  
 122 of neurons, lower than  $1/T \sim 50$  Hz (El Boustani and Destexhe, 2009), as typically is the case in  
 123 the asynchronous irregular regimes here investigated. The differential equations read:

$$T \frac{d\nu_\mu}{dt} = (F_\mu - \nu_\mu) + \frac{1}{2} c_{\lambda\eta} \frac{\partial^2 F_\mu}{\partial \nu_\lambda \partial \nu_\eta}, \quad (17)$$

$$T \frac{dc_{\lambda\eta}}{dt} = \delta_{\lambda\eta} \frac{F_\lambda(1/T - F_\eta)}{N_\lambda} + (F_\lambda - \nu_\lambda)(F_\eta - \nu_\eta) \\ + \frac{\partial F_\lambda}{\partial \nu_\mu} c_{\eta\mu} + \frac{\partial F_\eta}{\partial \nu_\mu} c_{\lambda\mu} - 2c_{\lambda\eta}, \quad (18)$$

124 where  $\mu = \{e, i\}$  is the population index (excitatory or inhibitory),  $\nu_\mu$  the population firing rate  
 125 and  $c_{\lambda\eta}$  the covariance between populations  $\lambda$  and  $\eta$ . The function  $F_{\mu=\{e,i\}} = F_{\mu=\{e,i\}}(\nu_e, \nu_i)$  is  
 126 the transfer function which describes the firing rate of population  $\mu$  as a function of excitatory  
 127 and inhibitory inputs (with rates  $\nu_e$  and  $\nu_i$ ). At the first order, i.e. neglecting the dynamics of  
 128 the covariance terms  $c_{\lambda\eta}$ , this model reduces to the well known Wilson-Cowan model, with the  
 129 specificity that the functions  $F$  need to be obtained according to the specific single neuron model  
 130 under consideration. We introduce this procedure in the next section.

## 131 2.4 Transfer function estimate

132 The transfer function relates the firing rate of a neuron's response to its presynaptic excitatory  
 133 and inhibitory firing rates. The particular form of the transfer function is related to the dynamics  
 134 describing neuronal activity. Deriving an analytical expression for the transfer function is a non-  
 135 trivial endeavor due to the nonlinear character of the dynamics, e.g. through conductance based  
 136 interactions. Therefore, we use here a semi-analytic approach to fit a family of plausible transfer  
 137 functions to the data obtained by means of numerical simulations with the desired neuron types.

138 This method, developed first by Zerlaut et al. (2016) on data from experimental recordings, is  
 139 based on the assumption that the transfer function depends only on the statistics of the subthresh-  
 140 old membrane voltage dynamics which is assumed to be normally distributed. These statistics are:  
 141 the average membrane voltage  $\mu_V$ , its standard deviation  $\sigma_V$  and auto-correlation time  $\tau_V$ . Under  
 142 these assumptions the neuronal output firing rate  $F_\nu$  is given by the following formula:

$$F_\nu = \frac{1}{2\tau_V} \operatorname{erfc} \left( \frac{V_{\text{thre}}^{\text{eff}} - \mu_V}{\sqrt{2}\sigma_V} \right), \quad (19)$$

143 where  $\operatorname{erfc}$  is the Gauss error function,  $V_{\text{thre}}^{\text{eff}}$  is an *effective* or *phenomenological threshold* accounting  
 144 for nonlinearities in the single-neuron dynamics. Note that when dealing with extremely high  
 145 spiking frequencies, e.g. in the case of Hodgkin-Huxley model close to depolarization block, a  
 146 multiplicative factor  $\alpha$  can be added in front of r.h.s. of Eq. (19) to permit the fitting procedure  
 147 to deal with such high frequencies. In the asynchronous irregular dynamical regime, investigated



148 in this work, neurons have relatively low firing rates (smaller than 30 Hz). Accordingly, we never  
 149 use this extension (i.e. the inclusion of the factor  $\alpha$ ) apart from the inset of Fig. 2b where we fit  
 150 the transfer function of the Hodgkin-Huxley model over a broad range of frequencies, including  
 151 those close to depolarization block where the firing rate is around 500-600 Hz. For this case we  
 152 used  $\alpha = 2$ . In the following section we introduce how the quantities  $\mu_V, \sigma_V, \tau_V$  can be expressed  
 153 as functions of the presynaptic excitatory and inhibitory firing rates  $\nu_E$  and  $\nu_I$ .

Table 1: Fit Parameters AdEx Neurons (in  $mV$ )

Cell Type	$P_0$	$P_{\mu V}$	$P_{\sigma V}$	$P_{\tau V}$	$P_{\mu V}^2$	$P_{\sigma V}^2$	$P_{\tau V}^2$	$P_{\mu V \sigma V}$	$P_{\mu V \tau V}$	$P_{\sigma V \tau V}$
RS-Cell	-49.8	5.06	-23.4	2.3	-0.41	10.5	-36.6	7.4	1.2	-40.7
FS-Cell	-51.5	4.0	-8.35	0.24	-0.50	1.43	-14.7	4.5	2.8	-15.3

Table 2: Fit Parameters Hodgkins-Huxley Neurons (in  $mV$ )

Cell Type	$P_0$	$P_{\mu V}$	$P_{\sigma V}$	$P_{\tau V}$	$P_{\mu V}^2$	$P_{\sigma V}^2$	$P_{\tau V}^2$	$P_{\mu V \sigma V}$	$P_{\mu V \tau V}$	$P_{\sigma V \tau V}$
RS-Cell	-48.1	3.2	10.9	-0.32	0.98	1.1	-1.2e-3	-1.4	3.9	-0.11
FS-Cell	-51.2	1.8	-6.1	-0.86	1.6	-0.70	-11	-0.18	1.2	-1.2

Table 3: Fit Parameters Morris-Lecar Neurons (in  $mV$ )

Cell Type	$P_0$	$P_{\mu V}$	$P_{\sigma V}$	$P_{\tau V}$	$P_{\mu V}^2$	$P_{\sigma V}^2$	$P_{\tau V}^2$	$P_{\mu V \sigma V}$	$P_{\mu V \tau V}$	$P_{\sigma V \tau V}$
RS-Cell	339	-218	-570	-1204	41.2	970	1724	297	186	-155
FS-Cell	-0.615	-2.56	-17.6	-164	0.83	-55	108	-7.4	24.6	288

#### 154 2.4.1 From input rates to sub-threshold voltage moments

155 We start by calculating the averages ( $\mu_{G_e, G_i}$ ) and standard deviations ( $\sigma_{G_e, G_i}$ ) of the conductances  
 156 given by Eq. 3 under the assumption that the input spike trains follow the Poissonian statistics  
 157 (as is indeed the case in asynchronous irregular regimes here considered). In such case we obtain  
 158 (Zerlaut and Destexhe, 2017a):

$$\begin{aligned}
 \mu_{G_e}(\nu_e, \nu_i) &= \nu_e K_e \tau_e Q_e, \\
 \sigma_{G_e}(\nu_e, \nu_i) &= \sqrt{\frac{\nu_e K_e \tau_e}{2}} Q_e, \\
 \mu_{G_i}(\nu_e, \nu_i) &= \nu_i K_i \tau_i Q_i, \\
 \sigma_{G_i}(\nu_e, \nu_i) &= \sqrt{\frac{\nu_i K_i \tau_i}{2}} Q_i,
 \end{aligned} \tag{20}$$

159 where  $K_{i,e}$  is the average input connectivity received from the excitatory or inhibitory population  
 160 (in our cases typically  $K_e = 400$  and  $K_i = 100$ ) and in our model  $\tau_e = \tau_i = \tau$  (see Eq. 3).

161 The mean conductances will control the total input of the neuron  $\mu_G$  and therefore its effective  
 162 membrane time constant  $\tau_m^{\text{eff}}$ :

$$\begin{aligned}
 \mu_G(\nu_e, \nu_i) &= \mu_{G_e} + \mu_{G_i} + g_L, \\
 \tau_m^{\text{eff}}(\nu_e, \nu_i) &= \frac{c_m}{\mu_G}.
 \end{aligned} \tag{21}$$



163 Here we make the assumption that the subthreshold moments ( $\mu_V$ ,  $\sigma_V$ ,  $\tau_V$ ) are not affected by the  
 164 dynamics of the currents coming into play at the spiking time (e.g. sodium channels dynamics or  
 165 the exponential term of the AdEx model). We thus consider, for all neurons, only the leakage term  
 166 and the synaptic input in order to estimate subthreshold moments. Accordingly, we can write the  
 167 equation for the mean subthreshold voltage:

$$\mu_V(\nu_e, \nu_I) = \frac{\mu_{Ge} E_e + \mu_{Gi} E_i + g_L E_L}{\mu_G}. \quad (22)$$

The final formulas for  $\sigma_V$  and  $\tau_V$  follow from calculations introduced in Zerlaut et al. (2018) and they read:

$$\sigma_V(\nu_e, \nu_i) = \sqrt{\sum_s K_s \nu_s \frac{(U_s \cdot \tau_s)^2}{2(\tau_m^{\text{eff}} + \tau_s)}}, \quad (23)$$

$$\tau_V(\nu_e, \nu_i) = \left( \frac{\sum_s (K_s \nu_s (U_s \cdot \tau_s)^2)}{\sum_s (K_s \nu_s (U_s \cdot \tau_s)^2 / (\tau_m^{\text{eff}} + \tau_s))} \right), \quad (24)$$

168 where we defined  $U_s = \frac{Q_s}{\mu_G} (E_s - \mu_V)$  and  $s = (e, i)$ . Notice that neglecting all the spiking currents  
 169 becomes a poorer assumption as the neuron activity increases. Nevertheless, we consider here AI  
 170 dynamics where neurons have typically low firing rates (of the order few Hz). Moreover, as we  
 171 show in the following sections, the fitting procedure will account for discrepancies in the actual  
 172 evaluation of voltage moments by permitting an accurate prediction of neuron output firing rate.

#### 173 2.4.2 From sub-threshold voltage moments to the output firing rate

174 The quantities  $\mu_V$ ,  $\sigma_V$  and  $\tau_V$ , obtained in the previous section, can now be plugged into Eq. 19  
 175 when an additional relation is taken into account. This relation follows from theoretical and  
 176 experimental considerations (Zerlaut et al., 2016) showing that the voltage effective threshold  
 177  $V_{\text{thre}}^{\text{eff}}$  can be expressed as a function of  $(\mu_V, \sigma_V, \tau_V)$ . In Zerlaut et al. (2016) the phenomenological  
 178 threshold was taken as a second order polynomial in the following form:

$$V_{\text{thre}}^{\text{eff}}(\mu_V, \sigma_V, \tau_V^N) = P_0 + \sum_{x \in \{\mu_V, \sigma_V, \tau_V^N\}} P_x \cdot \left( \frac{x - x^0}{\delta x^0} \right) + \sum_{x, y \in \{\mu_V, \sigma_V, \tau_V^N\}^2} P_{xy} \cdot \left( \frac{x - x^0}{\delta x^0} \right) \left( \frac{y - y^0}{\delta y^0} \right), \quad (25)$$

179 where we introduced the quantity  $\tau_V^N = \tau_V G_l / c_m$ . We evaluated  $\{P\}$  through a fit according to  
 180 simulations on single neurons activity setting first  $\mu_V^0 = -60$  mV,  $\sigma_V^0 = 0.004$  mV,  $(\tau_V^N)^0 = 0.5$ ,  
 181  $\delta\mu_V^0 = 0.001$  mV,  $\delta\sigma_V^0 = 0.006$  mV and  $\delta(\tau_V^N)^0 = 1$ . By the fitting procedure we find the values of  
 182 the P parameters for the three neuronal models considered here (additionally for each model we  
 183 consider two neuronal types: RS and FS) and we report the results in Table 3. In the first part of  
 184 the Results section we describe the goodness of this procedure for the three considered neuronal  
 185 models.

## 186 3 Results

187 We present here the results of a comparison between mean-field predictions and direct simulations.  
 188 We first test the technique to estimate the transfer function of single cells in AdEx, Hodgkin-Huxley  
 189 and Morris-Lecar models and then compare theoretical predictions of the mean-field to numerical  
 190 simulation of sufficiently large networks of neurons.

### 191 3.1 Transfer function for integrate-and-fire models

192 The transfer function of a simple AdEx neuron can be straightforwardly estimated by numerical  
 193 simulations. As we report in Fig. 1 its shape is very similar to a sigmoidal function (as in the  
 194 seminal paper by Wilson and Cowan) but its specific parameters

195 follow from a complex combination of microscopic information, e.g. neurons resting potential.  
 196 See the black and blue dots in Fig. 1 for different values of the leakage reversal potential  $E_L$ . Two  
 197 main spiking modes can be distinguished in the neuronal dynamics. One, characterized by low  
 198 output firing rate, where spikes are strongly driven by the membrane voltage fluctuations, namely  
 199 fluctuation driven mode (see the bottom inset in Fig. 1). The second mode is characterized by  
 200 a highly deterministic and regular firing observed at very high output firing rates (larger than  
 201 40 – 50 Hz, top inset).

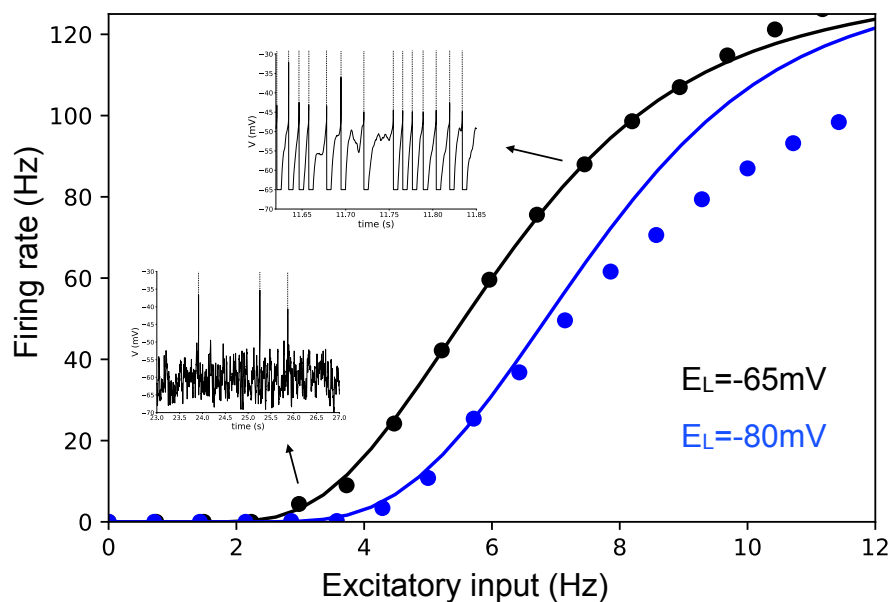


Figure 1: **Transfer function for an Exponential Integrate-and-Fire model** Dots indicate the results of the numerical simulation of the Exponential Integrate-and-Fire model (FS cell, see Materials and Methods). The continuous line illustrates the results based on the semi-analytic fitting. The inhibitory Poissonian spike train used here has a fixed rate,  $r_I = 8$  Hz, while we show neuron average output Firing rate as the function of the Poissonian excitatory input spike train of rate  $r_E$ . In the insets we show two exemplary voltage time traces corresponding to high (top inset) and low (bottom inset) firing rate. Colors stand for different values of the leakage reversal potential as indicated in the bottom-right corner of the figure.

202 By employing the semi-analytic approach to predict the transfer function we observe a very  
 203 good agreement with direct simulations (see continuous lines in Fig. 1, showing predictions based  
 204 on this approach) as it has been shown by El Boustani and Destexhe (2009); Zerlaut et al. (2016).  
 205 The agreement remains very good for relatively low neuronal activity (up to 50 Hz). This is a direct  
 206 consequence of the semi-analytic approach that assumes that neurons fire in an irregular manner  
 207 (as observed in cortical dynamics) strongly driven by fluctuations around the mean membrane

208 voltage. In this work we only consider Asynchronous Irregular population dynamics for which the  
 209 activity of neurons is low, irregular and strongly fluctuation driven.

### 210 3.2 Transfer function for complex models.

211 We report here the application of the techniques described in the Materials and Methods section  
 212 to evaluating the transfer function of more complex neuronal models. To this end we consider  
 213 the well-known Hodgkin-Huxley (HH) model and the Morris-Lecar (ML) models (see Materials  
 214 and Methods). These models permit to describe the details of Sodium and Potassium channels  
 215 dynamics neglected in the simpler Integrate-and-Fire model and reproduce time evolution of the  
 216 action potential. The semi-analytic approach to fit the numerical transfer function can be applied  
 exactly in the same way as for AdEx models (as discussed in the Materials and Methods section).

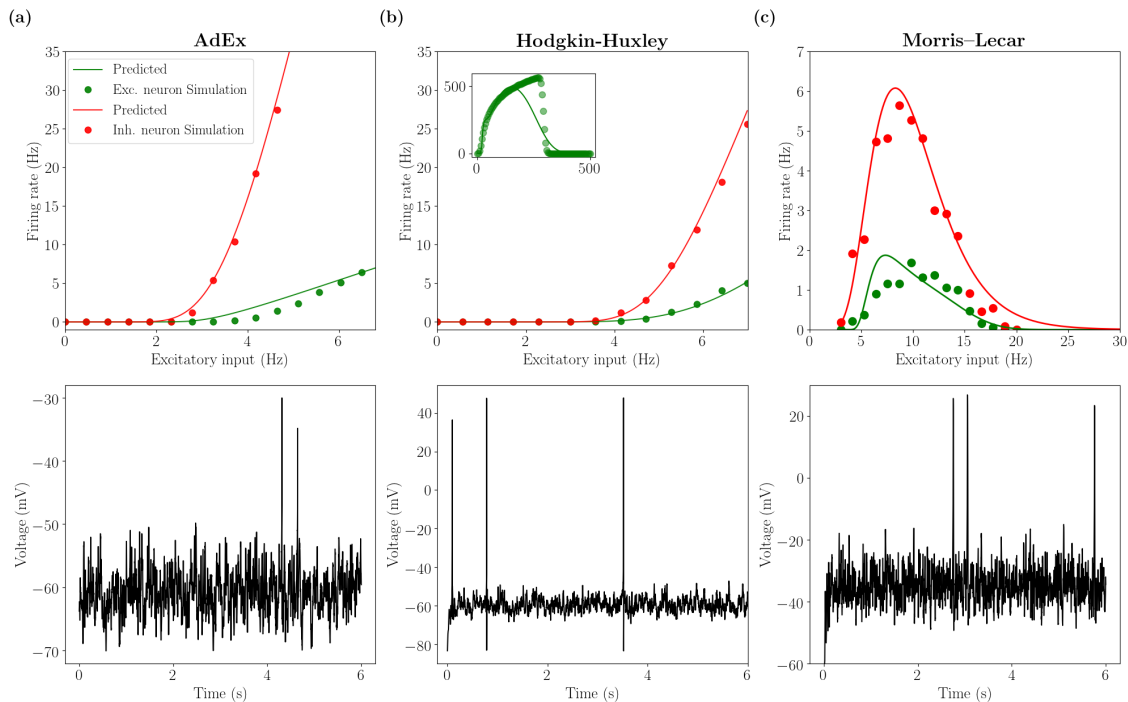


Figure 2: **Transfer function for RS and FS cells: AdEx, HH and ML.** We report the output firing rate for excitatory RS ( green) and inhibitory FS (red) cells obtained from numerical simulation (dots) and from the semi-analytic approach for the transfer function (continuous line). The inhibitory Poissonian spike train has a fixed rate,  $r_I = 8$  Hz. The bottom panels shows the time traces of the membrane voltage of an RS cell for an excitatory input equal to 4 Hz. Left column is obtained for the AdEx model, middle column for the HH model and right column for the ML model (see Materials and Methods). In the inset of panel (b) we report the transfer function for the RS cell estimated over very large values of input rates. In this case a separate fit by considering a broad input frequency range has been performed ( see Materials and Methods).

217  
 218

We consider two kinds of neurons in agreement with neurophysiological information about cor-

219 tical cells: excitatory neurons modeled as RS cells with a lower gain of the transfer function and  
220 inhibitory neurons modeled as FS cells with a higher gain. A different gain of the transfer func-  
221 tion can be obtained by changing the excitability of the cells through their resting potential, or  
222 increasing the adaptation strength (see Materials and Methods for details).

223 By comparing the theoretical prediction with numerical simulation we observe that, for the three  
224 models considered here, the transfer function is correctly estimated both for inhibitory neurons  
225 (FS cells) and excitatory neurons (RS cells). This result shows that, even by considering a much  
226 more complicated model than AdEx it is possible to have access to a semi-analytic form of its  
227 transfer function and, importantly, to modify neurons excitability in the way allowing to obtain a  
228 similar transfer function (of excitatory RS and inhibitory FS cells) between different models.

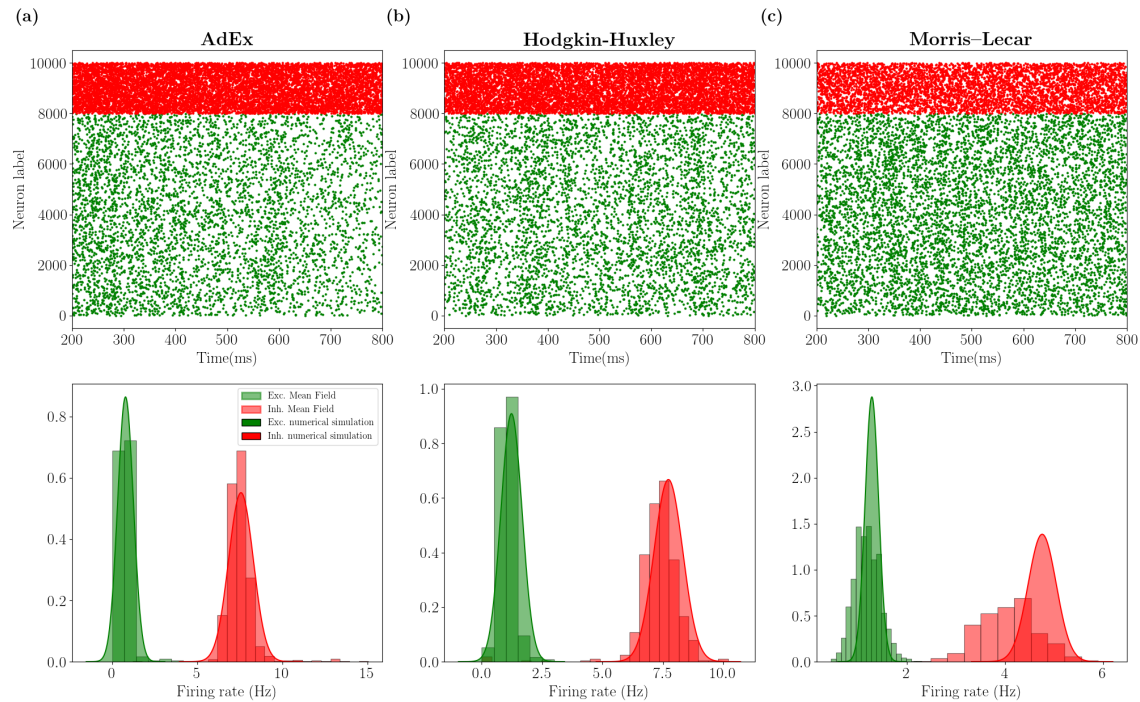
229 Notice that the ML model shows a decrease of firing rate at frequencies higher than 8 Hz (i.e. no  
230 voltage oscillations and thus no firing activity), as reported previously for this model by Kim and  
231 Nykamp (2017). This is a consequence of the depolarization block (DB) observed at high input  
232 frequencies (i.e. high average external current). Accordingly, we obtain a bell shaped transfer  
233 function, well predicted by our semi-analytical formalism. In previous studies this effect was taken  
234 into account in the context of Wilson-Cowan equations by using a Gaussian transfer function,  
235 instead of a sigmoidal Meijer et al. (2015), permitting to study the effect of the depolarization  
236 block in focal seizures at the population scale. In our model this shape, resembling a Gaussian,  
237 follows directly from Morris-Lecar equations, through the semi-analytical fitting. More specifically,  
238 in Meijer et al. (2015) the DB was studied in the Hodgkin-Huxley model. Indeed, also the HH  
239 model shows a DB but, at variance with the Morris-Lecar case, it appears in our parameters setup  
240 at very high firing rates, around 600-700 Hz (see the inset of Fig. 2b). In our simulations we do not  
241 consider this dynamical regime, being far from the dynamics typical of neurons in asynchronous  
242 irregular regimes. Moreover, as described in Fig.1, the semi-analytic fitting procedure works well  
243 for low firing rates and discrepancies appear at high rates, also in the case of the simpler AdEx  
244 model. Nevertheless, we report here that, when performing the fitting over a wide range of input  
245 and output rates (see Methods), it is possible to obtain an overall good fit of the bell-shaped  
246 transfer function (see the inset of Fig. 2b).

247 Beyond the methodological point, our results show that even if the details of the mechanisms  
248 that generate a specific transfer function are very different, it is possible to adjust neurons param-  
249 eters (e.g. excitability) in a way allowing to obtain similar transfer functions (at least in the region  
250 before entering a depolarization block). As a consequence, according to the mean-field theory,  
251 where what matters for the population dynamics is only the transfer function, we expect different  
252 models to have a comparable emergent dynamics at the population (collective) scale.

### 253 3.3 Asynchronous irregular dynamics and mean-field predictions

254 In this section we compare the mean-field predictions of the emergent dynamics of networks of  
255 AdEx, HH and ML neurons, in the setup described in the previous section. In particular, we  
256 simulate a sparse network of RS and FS cells (see Fig. 2) coupled through conductance based  
257 interactions (see Materials and Methods for details). By looking at Fig. 2 we observe that, before  
258 reaching the DB, all three models have similar transfer functions, with FS neurons having a higher  
259 gain with respect to RS neurons, approximately of factor 3–4. As a result, we expect the population  
260 activity in the three models to fall within a similar dynamical regime, as a natural consequence of  
261 the mean-field’s sole dependence on transfer functions, previously stated.

262 Indeed, by looking at Fig. 3 we observe that in the different networks the dynamics stabilizes  
263 on an asynchronous regime. In all cases, this regime is characterized by irregular microscopic  
264 dynamics (neuron’s spiking statistics are Poissonian, data not shown) and represents the typical  
265 spiking patterns recorded during awake states in cortical regions (the autocorrelation function of  
266 population rate decreasing to zero in the time scale of tens of milliseconds). Moreover, as expected,



**Figure 3: Mean-field predictions and spontaneous activity: AdEx, HH and ML** Top panels show raster plots for excitatory (green dots) and inhibitory (red dots) neurons, i.e. the spiking times for each neuron. Bottom panels shows histograms (obtained on a time length  $T_w = 10$  s) of population firing rate for excitatory (green) and inhibitory (red) populations. The Gaussian distribution has been plotted from mean-field predictions giving access to average firing rate and its variance. The left column (a) is obtained for the AdEx model, the middle column (b) for the HH model and the right column (c) for the ML model (see Materials and Methods).

267 inhibitory FS cells fire at a higher frequency with respect to RS cells. Through the mean-field model  
 268 it is possible to measure both the average population rate and its covariance (second order mean-  
 269 field, see Materials and Methods). As reported in Fig. 3 we show that the mean-field model gives a  
 270 good quantitative prediction of both quantities when they are compared to the histogram obtained  
 271 by sampling the population rate in the network simulation. The higher discrepancy we observe  
 272 for the complex neuronal models (e.g. HH and ML case) is related to a higher mismatch of the  
 273 transfer function linked to the higher complexity of the model.

### 274 3.4 Network response to external stimuli

275 In order to complete the comparison between the mean-field model and the network dynamics,  
 276 we study the response of the system to external stimuli. In particular, we consider an incoming  
 277 Poissonian train of spikes characterized by time-varying frequency and targeting both excitatory  
 278 and inhibitory cells according to the following equation:



$$\nu(t) = A \left( \Theta(t_0 - t) e^{-\frac{(t-t_0)^2}{T_1^2}} + \Theta(t - t_0) e^{-\frac{(t-t_0)^2}{T_2^2}} \right), \quad (26)$$

279 where  $\Theta$  is the Heaviside function, and  $T_1$  and  $T_2$  are the rise and decay time constants,  
 280 respectively. In Fig. 4 we report the comparison between the mean-field prediction and the network  
 281 dynamics.

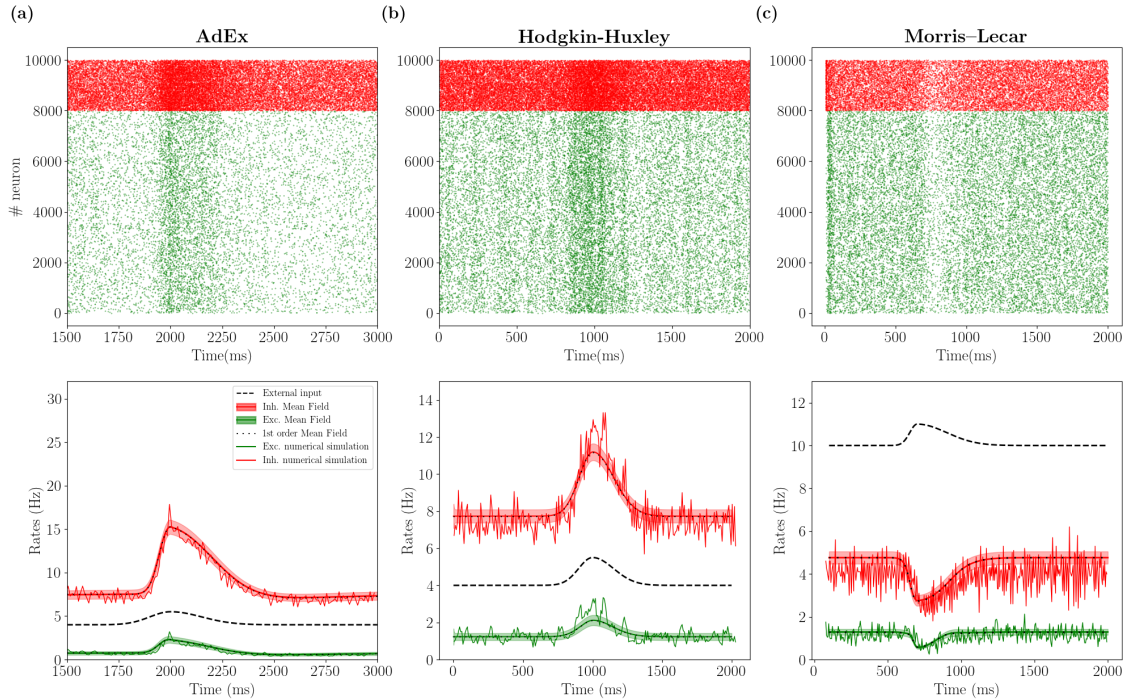


Figure 4: **Population response to external stimuli: AdEx, HH and ML** Top panels show the raster plot for excitatory (green dots) and inhibitory (red dots) neurons in response to an external excitatory stimulus (black dashed line in lower panels). Lower panels show the corresponding population rate (noisy line) together with the mean and standard deviation over time predicted by the the second order mean field model (red for inhibition and green for excitation). Superimposed the result obtained for the mean-field at the first order (black dots), which are almost coincident with results at the second order. Left column is obtained for the AdEx model, middle column for the HH model and right column for the ML model. Parameters are the same as in Fig. 3 and the external input (see Eq. (26)) has parameters  $A = 2$  Hz,  $T_1 = 100$  ms,  $T_2 = 150$  ms for AdEx and HH and  $A = 2$  Hz,  $T_1 = 100$  ms,  $T_2 = 150$  ms for ML, with  $t_0 = 2$  s.

282 By looking first at the AdEx and HH models, we observe that both mean-field models under  
 283 investigation compare favorably with their corresponding network dynamics. We also verified, as  
 284 it has been shown in (di Volo et al., 2019), that the faster the input dynamics is, the worse the  
 285 agreement becomes. Indeed, for the Markovian hypothesis to hold, we need the time scale  $T$  to be  
 286 much larger than the autocorrelation time in the spontaneous activity  $T \sim \tau_m \sim 10$  ms.

287 Considering now the case of the ML model, we observe that by looking at Fig. 2 a relatively

288 strong input would bring single neurons to a depolarization block, which appears at relatively low  
289 activity levels. According to this difference with respect to AdEx and HH models, we would expect  
290 the population dynamics to show different properties in response to external perturbations. Indeed,  
291 as reported in Fig. 4c, the response to an external stimulus is very different from the one observed  
292 in the HH and AdEx models. In fact, in this case the excitatory stimuli turns out to inhibit both  
293 population activities. This anti-correlation between population input and output is well captured  
294 in its time course also by the mean-field model. This result shows that also for a more complex  
295 and highly non-linear setup the mean-field model is capable of predicting the ongoing activity and  
296 the time course of the response of a network of neurons operating in the asynchronous irregular  
297 dynamical regime.

298 Finally, we compare the results of the first and second order mean field on average population  
299 rates. In Fig. 4 we superimpose the continuous green (red) line for excitatory (inhibitory) rate  
300 obtained with the second order mean field with the results obtained with the first order (black dots).  
301 We observe that the two quantities almost overlap (the difference is too small to be appreciated  
302 at this scale). Nevertheless, it is worth noticing that the second order mean field permits to  
303 obtain non-trivial information on the population dynamics and its fluctuations in time, with good  
304 quantitative predictions of the covariance of population rates (see the histograms in Fig. 3 and  
305 shadows in Fig. 4)).

## 306 4 Discussion

307 In this manuscript, we have reviewed a formalism to derive mean-field models from networks of  
308 spiking neurons and we have applied it to different complex neuronal models. The key to derive  
309 such “biologically realistic” mean-field models is to be able to obtain the transfer function of  
310 complex neuronal models. The approach we followed used a mean-field formalism based on a  
311 Master Equation and which is applicable to every neuron, provided the transfer function is known  
312 (El Boustani and Destexhe, 2009). More recently, we have shown that the usual mathematical  
313 form of the transfer function, known analytically for the Integrate-and-Fire model, can capture  
314 more complex neuronal models (Zerlaut et al., 2018, 2016). This gave rise to a “semi-analytic”  
315 approach, where the transfer function is parameterized and fit numerically to the neuron model,  
316 while the mean-field remains analytic as only the parameters are obtained from the fitting. This  
317 approach was applied to the AdEx model (di Volo et al., 2019; Zerlaut et al., 2018), and we extend  
318 it here to more complex models, namely the Morris-Lecar and the Hodgkin-Huxley models.

319 It is important to note that we limited here to “simple” firing patterns, i.e. neurons fire tonically  
320 in response to an external stimulus. In this setup the transfer function is well defined as the neuron’s  
321 firing rate defines completely the spiking pattern. In cases where neurons exhibit different kind  
322 of activity, e.g. bursting, a different approach needs to be employed (see (Ostojic and Brunel,  
323 2011)). Nevertheless, in the context of tonic neuronal activity the method is shown to be able to  
324 capture the response function of highly realistic models. We have studied here the predictions of  
325 the considered mean-field models on networks dynamics of excitatory RS and inhibitory FS cell  
326 populations during asynchronous irregular regimes, as observed in awake cortical activity. The  
327 results positively compare in the case of Morris-Lecar and Hodgkin-Huxley models for both the  
328 average and the variance of network population activity.

329 The good predictions at the population levels in the framework of the asynchronous irregular  
330 regimes is strongly dependent on the goodness of the fitting procedure for single neurons transfer  
331 functions. Even if such procedure works very well for neurons working in a low rate regime,  
332 whenever the firing rate becomes very high (higher than 100 Hz) the quantitative agreement gets  
333 worse. A more refined technique for the evaluation of the transfer function in different states (low  
334 and high rates activity) is an important topic for future research (recent work has addressed this



335 issue in AdEx model (Capone et al., 2019a)). A step forward in this direction can be important  
336 when dealing with neurons entering depolarization block at high firing rates, a mechanism playing  
337 an important role in focal seizures (Meijer et al., 2015) or in dopaminergic neurons under normal  
338 condition or under drugs assumption (Di Volo et al., 2019; Dovzhenok and Kuznetsov, 2012). Both  
339 in Morris Lecar and Hodgkin-Huxley model, the semi-analytic fitting is found to give quite good  
340 predictions on the presence of depolarization block, especially in the Morris Lecar case as this  
341 setup does not consider very high spiking frequencies. Even if work remains to be done in order to  
342 extend this framework to obtain a more reliable quantitative prediction on the depolarization block  
343 at very high frequencies, these preliminary results indicate the possibility to use these mean field  
344 techniques to connect the physiology at the cellular scale with pathological states at the population  
345 level, as the case of focal seizures.

346 We also reported that, in the framework of the Asynchronous regimes here considered, correc-  
347 tions to first order mean field due to second order terms (see Eq. (17)-(18)) were relatively small  
348 but gave a good quantitative indication on the covariance of population rates (see histograms in  
349 Fig. 2). Nevertheless, in the case of dynamical regimes with higher neuronal correlation with re-  
350 spect to the ones here considered, we expect the second order mean field (taking explicitly into  
351 account the dynamics of covariances), to play an important role in the prediction of population  
352 average collective dynamics.

353 Let us point out that the goodness of the mean-field prediction depends also on the emergent  
354 dynamics of the network, i.e. in a highly synchronous dynamical regime the Markovian hypoth-  
355 esis fails and the mean-field model cannot give accurate predictions. Nevertheless, even if light  
356 synchronization is considered, e.g. during slow waves sleep, the mean-field models has been shown  
357 to correctly predict such collective oscillations (di Volo et al., 2019). In this case it is however  
358 necessary to consider a mean-field model that includes the slow dynamics of spike frequency adap-  
359 tation or that of the  $I_M$  current in the case of Hodgkin-Huxley model. The possibility to include  
360 a conductance based adaptation to this formalism, e.g. by considering the slow dynamics of  $I_M$   
361 current, is a stimulating perspective for future works and will permit to obtain mean-field models  
362 for realistic neuronal models beyond the asynchronous irregular regime.

363 Moreover, beyond the input-output transfer function used here, a more complex transfer func-  
364 tion has been used in order to take into account other features of neuron response, e.g. response  
365 in frequency (Ostojic and Brunel, 2011). The addition of variables to account for a richer spiking  
366 pattern is an interesting direction, in case one is interested in modeling brain regions character-  
367 ized by non-tonic firing of neurons (e.g. bursting cells in the thalamus). The general framework pre-  
368 sented here could be extended in this direction, as it has been done to account for spike frequency  
369 adaptation yielding slow oscillations at the population scale.

370 Another possible extension is to apply the same formalism to complex neuronal models that  
371 include dendrites. A first attempt has been made in this direction (Zerlaut and Destexhe, 2017b) by  
372 considering simple “ball and stick” neuron models, where some analytic approximation is possible.  
373 In principle, it should be possible to apply this approach to models based on morphologically-  
374 reconstructed neurons, and calculate the transfer function of such models (work in progress).  
375 This will lead to mean-field models based on morphologically realistic neuronal models. However,  
376 the presence of dendritic voltage-dependent currents complicates this approach, and should be  
377 integrated in the formalism. This constitutes an exciting future development of our approach.

378 Finally, the positive results obtained here for complex models, by showing the generality of our  
379 approach, motivate the future step of the application of this technique directly to experimental  
380 data. To this end, neurons must be recorded intracellularly in the absence of network activity (as  
381 typically *in vitro*), and many combinations of excitatory and inhibitory inputs must be injected as  
382 conductances (using the dynamic-clamp technique). The first attempt of this sort was realized on  
383 the Layer 5 neurons from mouse primary visual cortex (Zerlaut et al., 2016), where the transfer

384 function could be reconstructed for a few dozen neurons. The same dynamic-clamp experiments  
385 should be done in the future to characterize the transfer function of inhibitory interneurons. Based  
386 on such experiments, it will be possible to obtain a mean-field model based on the properties of real  
387 neurons. Such a model will evidently be more realistic than the models we have presented here,  
388 which must be considered as a first step towards a quantitative population modeling of cerebral  
389 cortex and other brain regions.

## 390 5 Acknowledgments

391 This research resulted from student projects during the Spring School of the European Insti-  
392 tute of Theoretical Neuroscience ([www.eitn.org](http://www.eitn.org)), of which the participating students signed as  
393 co-first authors here. Research supported by the CNRS and the European Union (Human Brain  
394 Project H2020-720270 and H2020-785907). M.J. acknowledges support from the European Re-  
395 search Council under the European Union’s Seventh Framework Programme (FP/2007-2013)/ERC  
396 Grant Agreement No. 616268 F-TRACT and the European Unions Horizon 2020 Framework Pro-  
397 gramme for Research and Innovation under Specific Grant Agreement No. 785907 (Human Brain  
398 Project SGA2).

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