A novel density-based neural mass model for simulating neuronal network dynamics with conductance-based synapses and membrane current adaptation

Chih-Hsu Huang¹ and Chou-Ching K. Lin^{1†*}

*For correspondence:

cxl45@mail.ncku.edu.tw (CKL)

Present address: [†]Department of Neurology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

¹Department of Neurology, National Cheng Kung University Hospital, College of Medicine,

Abstract Nowadays, building low-dimensional mean-field models of neuronal populations is still a critical issue in the computational neuroscience community, because their derivation is difficult for realistic networks of neurons with conductance-based interactions and spike-frequency adaptation that generate nonlinear properties of neurons. Here, based on a colored-noise population density method, we derived a novel neural mass model, termed density-based neural mass model (dNMM), as the mean-field description of network dynamics of adaptive exponential integrate-and-fire neurons. Our results showed that the dNMM was capable of correctly estimating firing rate responses under both steady- and dynamic-input conditions. Finally, it was also able to quantitatively describe the effect of spike-frequency adaptation on the generation of asynchronous irregular activity of excitatory-inhibitory cortical networks. We conclude that in terms of its biological reality and calculation efficiency, the dNMM is a suitable candidate to build very large-scale network models involving multiple brain areas.

22

23 Introduction

24 Instead of exploring spiking activity of individual neurons, sometimes, scientists are more interested
25 in the summed activity of a neuronal population, composed of thousands or ten thousands of
26 neurons, in response to external stimuli for several reasons. One reason comes from the accepted
27 concept that the collective activity of interconnected neurons within multiple brain areas is con-
28 sidered to account for brain functions, such as sensory, motor, and cognitive functions (*Gerstner*
29 *et al., 2014; Deco et al., 2015*). Another reason is that functional measurements of brain states,
30 for examples, recorded from functional magnetic resonance imaging and electroencephalography,
31 reflect the collective activity of thousands of neurons (*Deco et al., 2008; Breakspear, 2017*). In
32 addition, investigating network dynamics of neuronal populations at mesoscopic scales bridges the
33 microscopic states of individual neurons to the macroscopic global brain states (*Goldman et al.,*
34 *2019*). Building computational models of such neuronal populations thus has been one of the major
35 goals in computational neuroscience.

36 The computational modeling of neuronal populations can be achieved by means of bottom-up
37 theoretical modeling approaches, ranging from direct numerical simulations of extremely detailed
38 spiking neurons (*Izhikevich and Edelman, 2008; Markram et al., 2015*) to more coarse-grained
39 rate models (*Dayan and Abbott, 2001*), or neural mass models (*David and Friston, 2003; Moran*
40 *et al., 2013*). The direct numerical simulation of spiking neurons encompasses essential details
41 of individual neuronal and synaptic dynamics. Such a modeling approach thus requires huge
42 computational resources, and it is really difficult to analyze the dynamic behaviors of such a large
43 system of neural networks. Therefore, mathematical models directly describing the collective activity
44 of neuronal populations emerge under the mean-field assumptions to reduce the computational
45 demands (*Deco et al., 2008; Breakspear, 2017*).

46 The neural mass model (NMM) describes the mean activity of a neuronal population, which
47 is derived by assuming that in the presence of strong coherence among neurons, the collective
48 activity is sufficiently close to the mean so that the variance can be discarded (*Breakspear, 2017*).
49 Those mean quantities typically include population-average firing rates, mean membrane potentials
50 and mean synaptic state variables, whose dynamic behaviors are described by a single or small
51 number of ordinary differential equations and, in general, a sigmoid rate function transferring the

mean membrane potential into the population firing rate. The history of the NMM can be traced back to 70's (*Lopes da Silva et al., 1974; Zetterberg et al., 1978*), and it has been seen in many examples of simulating various EEG rhythms during both the wakefulness and sleep (*Cona et al., 2014*), the generation of resting-state functional magnetic resonance imaging data (*Deco et al., 2013*), or pathological activity of neurological diseases (*Suffczynski et al., 2004; Chiang et al., 2011; Bhattacharya et al., 2011*). Moreover, it is now incorporated in the Virtual Brain Project that aims to deliver the first open simulation of the human brain based on the large-scale connectivity of neurons (*Sanz-Leon et al., 2015*).

However, an opposing opinion criticizes that the NMM is essentially phenomenological, possibly only reproducing a part of the rich repertoire of dynamic responses seen in real neuronal tissues (*Coombes and Byrne, 2019*). Furthermore, despite of its success, some disadvantages of NMMs also have been demonstrated recently. For examples, NMM lacks systematic link to microscopic models at the level of spiking neurons (*Schwalger et al., 2017*). Second, it fails to correctly reproduce the firing rate responses of a population of neurons when the input changes rapidly, although it has good accuracy of predicting steady-state responses (*Deco et al., 2008; Gerstner et al., 2014*). Third, fluctuations of activity variables in NMMs are absent. Forth, the use of a sigmoid rate function for estimating population activity is not derived from a biophysically detailed description of spiking neurons (*Byrne et al., 2020*). Accordingly, a new version of NMMs is mandatory.

To be biologically realistic, we focused on the development of a novel NMM for the modeling of a population of adaptive exponential integrate-and-fire (aEIF) neurons (*Brette and Gerstner, 2005*), in which two critical neuronal features, i.e., adaptive behaviors of firing rate responses and nonlinear voltage-dependent synaptic interactions, were included. Experiments showed that slowly adapting spike-frequency responses, a pattern called regular spiking (RS), were generally observed in virtually all excitatory neurons in cerebral cortex, while inhibitory neurons often fired at higher frequencies with no adaptation, a pattern called fast spiking (FS) (*Connors and Gutnick, 1990*). Nonlinearity of voltage-dependent synaptic interactions also has been displayed to play a key role in network responses to external stimuli (*Paulus and Rothwell, 2016; Zerlaut and Destexhe, 2017; di Volo et al., 2019*). Such voltage-dependent synaptic interactions were modeled in a conductance-based manner in our study.

Our work was based on the so-called colored-noise population density method (csPDM), proposed by *Huang and Lin (2018)*, where the authors yielded a Fokker-Planck formalism to govern the

temporal evolution of the probabilistic distribution of membrane potential state variables across a population of exponential integrate-and-fire (EIF) neurons (*Fourcaud-Trocmé et al., 2003*), together with conductance-based synaptic interactions, and then, to evaluate the dynamic population firing rate behavior in response to external inputs. Here, we expanded it to the case where adaptation was included. It is well known that the solution of the Fokker-Planck formalism was shaped by a Gaussian density function which could be completely described by the associated statistical mean and variance (*Risken, 1996*). In other words, the distribution of membrane potential state variables in the csPDM could also be well characterized by the corresponding mean and variance values. As a result, by deriving the dynamic equations for evaluating the temporal evolution of the mean and variance from the Fokker-Planck formalism, the csPDM could be transformed into a type of NMMs together with a semi-analytic rate function. In this study, we illustrated the transformation from the csPDM into the NMM based on this idea. Owing to its inspiration from the csPDM, we named this novel NMM the density-based NMM (dNMM).

In addition to treating the drawbacks of conventional NMMs, our dNMM was designed also to tackle the problem of computational inefficiency of population density methods (*Tranchina, 2009*). When building a large-scale network model consisting of multiple neuronal populations, the population density method lost its advantage as a time-saving alternative to direct numerical simulations of detailed spiking neuron networks, even though certain dimension-reduction algorithms were employed for each single neuronal population (*Apfalter et al., 2006*). Under this circumstance, however, our dNMM remained highly efficient in calculation because the dynamic equations tracing state variables were in the forms of ordinary differential equations, rather than partial differential equations. As such, it could be expected that the dNMM reasonably fit in the whole brain model for simulating the resting-state behaviors seen in BOLD signals (*Deco et al., 2013*).

In the current study, the dNMM was demonstrated to have excellent accuracy to reproduce steady or transient firing rate responses of a single aEIF neuronal population with different strengths of spike-frequency adaptation. In particular, we utilized the dNMM to investigate the network dynamics of an excitatory-inhibitory network, namely, the standard minimal circuitry for cortical neuronal networks (*Okun and Lampl, 2008; Avermann et al., 2012*). The modeled dynamics focused on the regime of asynchronous irregular (AI) activity that was experimentally observed in mammalian cortex under awake states (*Matsumura et al., 1988; Brunel, 2000; Steriade et al., 2001; Destexhe et al., 2003; Lee et al., 2006; El Boustani et al., 2007*). We explored whether the

114 spike-frequency adaptation affected the extent of AI regimes in a parameter space spanned by two
115 control parameters, that is, the amplitude of external input and the relative strength of inhibitory
116 synaptic interactions. We showed that such adaptation enlarged the AI regime in the parameter
117 space, suggesting that the spike-frequency adaptation in the cortical neurons possibly played a
118 critical role in maintaining the AI activity under the fluctuation of external inputs and neuronal
119 properties.

120 Results

121 Dynamic equations of density-based neural mass models

122 We were interested in the firing rate dynamics of a large homogeneous population of N uncoupled
123 aEIF neurons in response to external excitatory and inhibitory Poissonian spike trains. The synaptic
124 interaction was handled by using conductance-based methods with the first-order kinetics of
125 synaptic conductances. In this case, the state of each aEIF neuron was described by four state
126 variables, i.e., the membrane potential, $V(t)$, adaptation current, $w(t)$, excitatory and inhibitory
127 synaptic conductances, $g_e(t)$ and $g_i(t)$, which temporally evolved in response to overall presynaptic
128 excitatory and inhibitory spike inputs. Assuming that the mean rates of the excitatory and inhibitory
129 Poisson spike inputs were $v_e(t)$ and $v_i(t)$, respectively, the dynamic equations of the dNMM were:

$$\frac{d}{dt}\mu_{g_e} = -\frac{1}{\tau_e}\mu_{g_e} + v_e(t) \cdot \Gamma_e, \quad (1)$$

$$\frac{d}{dt}\sigma_{g_e}^2 = -\frac{2}{\tau_e}\sigma_{g_e}^2 + v_e(t) \cdot \Gamma_e^2, \quad (2)$$

$$\frac{d}{dt}\mu_{g_i} = -\frac{1}{\tau_i}\mu_{g_i} + v_i(t) \cdot \Gamma_i, \quad (3)$$

$$\frac{d}{dt}\sigma_{g_i}^2 = -\frac{2}{\tau_i}\sigma_{g_i}^2 + v_i(t) \cdot \Gamma_i^2, \quad (4)$$

$$\frac{d}{dt}\mu_w = \frac{1}{\tau_w} [a(\mu_V^{\text{nf}} - E_L) - \mu_w] + b \cdot v_{\text{out}}, \quad (5)$$

$$\begin{aligned} \frac{d}{dt}\mu_V^{\text{nf}} = & \left[\frac{-1}{C} (g_L + \mu_{g_e} + \mu_{g_i}) + \frac{2\tau_e\tau_{\text{eff}}}{\tau_e + \tau_{\text{eff}}} \frac{\sigma_{g_e}^2}{C^2} + \frac{2\tau_i\tau_{\text{eff}}}{\tau_i + \tau_{\text{eff}}} \frac{\sigma_{g_i}^2}{C^2} \right] \mu_V^{\text{nf}} \\ & + \frac{1}{C} (g_L E_L + \mu_{g_e} E_e + \mu_{g_i} E_i - \mu_w) - \frac{2\tau_e\tau_{\text{eff}} E_e}{\tau_e + \tau_{\text{eff}}} \frac{\sigma_{g_e}^2}{C^2} - \frac{2\tau_i\tau_{\text{eff}} E_i}{\tau_i + \tau_{\text{eff}}} \frac{\sigma_{g_i}^2}{C^2}, \end{aligned} \quad (6)$$

$$\begin{aligned} \frac{d}{dt} \sigma_V^{2,\text{nf}} = & \left[\frac{-2}{C} (g_L + \mu_{g_e} + \mu_{g_i}) + \frac{2\tau_e \tau_{\text{eff}}}{\tau_e + \tau_{\text{eff}}} \frac{\sigma_{g_e}^2}{C^2} + \frac{2\tau_i \tau_{\text{eff}}}{\tau_i + \tau_{\text{eff}}} \frac{\sigma_{g_i}^2}{C^2} \right] \sigma_V^{2,\text{nf}} \\ & + \frac{\sigma_{g_e}^2}{C^2} (\mu_V^{\text{nf}} - E_e)^2 + \frac{2\tau_i \tau_{\text{eff}} E_i}{\tau_i + \tau_{\text{eff}}} \frac{\sigma_{g_i}^2}{C^2} (\mu_V^{\text{nf}} - E_i)^2, \end{aligned} \quad (7)$$

where μ_* denoted the associated means of state variables, and σ_*^2 the variances; C was the mem-
brane capacitance, g_L the leak (resting) conductance, E_L the leak reversal potential. τ_{eff} was the
effective membrane time constant, τ_w the time constant of the adaptation current, τ_e the time
constant of the excitatory synaptic dynamics and τ_i the inhibitory one. Here, Γ_e and Γ_i stood for the
synaptic strengths, which were, respectively, the jump sizes of the excitatory and inhibitory synaptic
conductances caused by one presynaptic spike under the assumption of 1-exponential synaptic
kinetics (**Roth and van Rossum, 2009**). The mean adaptation current μ_w was controlled both by the
subthreshold adaptation parameter a and the spike-frequency adaptation parameter b . v_{out} was
the so-called population-average firing rate of the neuronal population. Notice that although the
neuronal model was conductance-based, v_{out} was computed by a current mapping algorithm, which
was given by:

$$\begin{aligned} v_{\text{out}}(t) = & \underbrace{\frac{d}{dt} R_{\text{act}}(t)}_{\text{if } \geq 0} + \bar{v}(t) R_{\text{act}}(t), \\ = & \bar{A} \left(\mu_V^{\text{nf}}, \sigma_V^{2,\text{nf}}, \frac{d\mu_V^{\text{nf}}}{dt}, \frac{d\sigma_V^{2,\text{nf}}}{dt} \right) + \bar{B} \left(\mu_V^{\text{nf}}, \sigma_V^{2,\text{nf}} \right), \end{aligned} \quad (8)$$

where

$$R_{\text{act}}(t) = \int_{V_{\text{th}}}^{\infty} \mathcal{N}(V | \mu_V^{\text{nf}}, \sigma_V^{2,\text{nf}}) dV, \quad (9)$$

$$\bar{v}(t) = \int_I f_{\text{EIF}}(I) \cdot \mathcal{N}(I | \mu_{I_{\text{tot}}}, \sigma_{I_{\text{tot}}}^2) dI, \quad (10)$$

$$\mu_{I_{\text{tot}}} = -\mu_{g_e} \left(\frac{V_r + V_T}{2} - E_e \right) - \mu_{g_i} \left(\frac{V_r + V_T}{2} - E_i \right) - \mu_w, \quad (11)$$

$$\sigma_{I_{\text{tot}}}^2 = \frac{2\sigma_{g_e}^2}{C} \frac{\tau_e \tau_{\text{eff}}}{\tau_e + \tau_{\text{eff}}} \left(\frac{V_r + V_T}{2} - E_e \right)^2 + \frac{2\sigma_{g_i}^2}{C} \frac{\tau_i \tau_{\text{eff}}}{\tau_i + \tau_{\text{eff}}} \left(\frac{V_r + V_T}{2} - E_i \right)^2. \quad (12)$$

Here, $\bar{A}(\cdot)$ accounted for transient changes of the firing rate in response to the rapidly changing
input, while $\bar{B}(\cdot)$ expressed the steady firing rate. $R_{\text{act}}(t)$ denoted the proportion of activated
neurons whose membrane potentials exceeded a certain threshold voltage V_{th} within the neuronal
population at the present time t . $\bar{v}$ was the estimate of the mean firing rate of those activated

neurons. $\mathcal{N}(*|\mu, \sigma^2)$ meant the Gaussian density function with the mean μ and variance σ^2 . $f_{\text{EIF}}(I)$ was the current-rate relationship of a single EIF neuron that mapped the current input into its mean output firing rate, which, in this study, was obtained numerically before running simulations. $\mu_{I_{\text{tot}}}$ denoted the total mean effective input current received by a neuron, and $\sigma_{I_{\text{tot}}}^2$ meant the variance of the effective input current. It should be noted that the superscript "nf" meant that the mean and variance of membrane potentials were estimated under the removal of spike-firing mechanisms of individual aEIF neuronal dynamics. In short, the dynamic equations of the dNMM included seven ordinary differential equations and a rate estimate function for evaluating the population-average output firing rate, together with a few auxiliary variables. All descriptions and derivations of the state variables and dynamic equations above are presented in the section of Methods and Materials.

Gaussian distributions of membrane potential state variables

A core assumption of the dNMM was the Gaussian distribution of membrane potential state variables across the neuronal population. We attempted to explore whether such an assumption was valid with respect to different synaptic strengths and input rates. Before this, the premise of the csPDM, i.e., the diffusion approximations of synaptic dynamics (*Huang and Lin, 2018*), were first checked. Such an approximating technique was often used in the computational studies of network dynamics for considering the fluctuations of synaptic interactions (*Fourcaud and Brunel, 2002; Richardson, 2004; Linaro et al., 2011; Augustin et al., 2013; Rosenbaum, 2016; Augustin et al., 2017*). In our cases, the steady distributions of synaptic conductances were postulated to be shaped by Gaussian density functions under diffusive limits, i.e., the input rate $v_{e,i} \gg 1$ and the synaptic strength $\Gamma_{e,i} \ll 1$. First, we checked the reasonable physiological ranges of synaptic strengths. As shown by the blue line in *Figure 1A*, the peak voltage jump Γ_V caused by individual excitatory presynaptic spikes revealed a linear relationship with the amplitude of the synaptic strength Γ_e . In particular, $\Gamma_V = 0.5$ mV (a typical value for a large network of 10,000 to 100,000 neurons (*El Boustani et al., 2007; Brémaud et al., 2007*)) when $\Gamma_e = 0.0025$ mS. So, we explored the distributions of excitatory synaptic conductances with three different synaptic strengths of 0.0025, 0.005 and 0.01 mS which gave rise to peak voltage jumps of 0.5, 1 and 2 mV, respectively. The input rate for each case was just at the half of v_c , which was the minimum input rate of an excitatory Poisson spike train whose mean input allowed the aEIF neuron to repeatedly emit spikes, given by

$$v_c = \frac{I_{rh}}{(E_e - V_T) \Gamma_e \tau_e}, \quad (13)$$

where I_{rh} was defined as the rheobase current that was the minimum constant current required to elicit a spike (see the Eq. (7) in *Touboul and Brette (2008)*).

The upper row in **Figure 1B** displays steady distributions of excitatory synaptic conductances from Monte-Carlo (MC) simulations, i.e., direct numerical simulations of synaptic dynamics as ground truths (shaded areas), and Gaussian density functions from diffusion approximations whose means and variances were given by equilibrium points of Eqs. (1) and (2) (blue lines). As expected, the diffusion approximation was in good agreement with the MC simulation only in the case of $\Gamma_e = 0.0025$ mS and $v_e = 0.56$ kHz, that is, under the condition of small synaptic strengths and large input rates. To highlight this, we quantitatively characterized the effectiveness of diffusion approximations by using the total variation of histogram probabilities, given by

$$d_{TV}(\mathbf{P}_{DA}, \mathbf{P}_{MC}) = \sum_{i=1}^{N_b} |p_{DA,i} - p_{MC,i}|, \quad (14)$$

where N_b was the number of bins, $\mathbf{P}_{DA}$ meant a histogram probability vector consisting of N_b elements, i.e., $p_{DA,i}$, where $i = 1, 2, \dots, N_b$, which was the histogram probability within the i -th bin obtained from the diffusion approximation; similarly, $\mathbf{P}_{MC}$ for MC simulations. We set $N_b = 100$ bins ranging from $\mu_{g_e} - 4\sigma_{g_e}$ to $\mu_{g_e} + 4\sigma_{g_e}$. In the case of $\Gamma_e = 0.0025$ mS and $v_e = 0.56$ kHz, d_{TV} was 0.1606. Through this observation, the diffusion approximation would reveal good estimations of synaptic conductances if d_{TV} was below 0.15. For the other two cases of $\Gamma_e = 0.005$ and 0.01 mS, the conductance distributions from MC simulations were markedly different from Gaussian functions, whose d_{TV} were 0.2416 and 0.4297, respectively.

We also checked the inhibitory synaptic dynamics. The inhibitory synaptic strength was determined according to the relative strength of effective inhibition, which was given by (*Kumar et al., 2008*):

$$S_{inhi} = \frac{\Gamma_i \tau_i |\bar{V} - E_i|}{\Gamma_e \tau_e |\bar{V} - E_e|}, \quad (15)$$

where $\bar{V}$ was set as $(V_r + V_T)/2$ (V_T was the spiking threshold voltage and V_r was the resetting voltage of the aEIF neuron). We let $S_{inhi} = 4$ in order to balance the excitatory and inhibitory recurrent current inputs because the ratio between the excitatory and inhibitory recurrent connections was four (*Brunel, 2000; Kumar et al., 2008*). Accordingly, Γ_i were 0.013, 0.026 and 0.051 mS, respectively, for $\Gamma_e = 0.0025, 0.005, 0.01$ mS. As shown in the bottom row in **Figure 1B**, we found that $d_{TV} > 0.2$ for all cases because of high synaptic jump sizes and small input rates (v_i was a quarter of v_e in all cases). In other words, the inhibitory synaptic dynamics could not be characterized by diffusion

approximations very well for these cases.

Finally, we assessed the distributions of membrane potentials under those synaptic conditions, where only excitatory inputs or combinations of excitatory and inhibitory inputs were delivered to the neurons. The interesting finding was that, even though, for some cases, the real steady distributions of synaptic conductances did not match Gaussian density functions, the steady distributions of membrane potentials V could be correctly captured by Gaussian distributions whose means and variances were estimated through Eqs. (6) and (7) for all cases. The results showed that d_{TV} was smaller than 0.15 in all cases (see **Figure 1C**). It was summarized that, when the synaptic strengths $\Gamma_{e/i}$ were within physiological ranges, the poor performance of diffusion approximations of synaptic conductances might not result in the violation of Gaussian distributions of membrane potential state variables of neurons. Consequently, the assumption of Gaussian density functions in Eqs. (9) and (10) seemed reasonable.

Mismatch of sigmoid rate functions on estimating population firing rates

The main discrepancy between NMM and dNMM was the different rate estimate functions used for determining population firing rates. The conventional NMM employed monotonic sigmoidal functions of mean membrane potentials to estimate population firing rates. That idea was ubiquitous throughout the modeling studies with NMMs, but the use of sigmoid rate functions did not come from a biophysically detailed descriptions of spiking neurons (*Byrne et al., 2020*). Furthermore, as shown in **Figure 2A**, where steady population firing rates obtained from MC simulations given by a series of combinations of different excitatory and inhibitory Poissonian input rates are displayed, the population firing rate did not only monotonically increase with the increased mean membrane potentials, but also depended on the standard deviations of membrane potentials across the population. So, the monotonic sigmoid rate function of only mean membrane potentials was insufficient to cover the whole scenario. On the other hand, the dNMM included the estimation of the standard deviation of membrane potentials to determine the firing rates, using Eq. (8). The upper plot in **Figure 2B** highlights the difference between the dNMM and NMM in the accuracy of estimating population firing rates, and their estimating errors by comparisons with those from MC simulations are shown in the bottom plot. As seen, the firing rates could be quantitatively correctly estimated by the dNMM. Maximum estimating error of up to ≈ 15 Hz occurred in the regimes where the mean membrane potential μ_V^{nf} was near the spiking threshold voltage ≈ -50 mV or at the extremely

A

B

C

Figure 1. Validity of diffusion approximations of synaptic dynamics. **(A)** Relationships of excitatory synaptic strengths Γ_e with the peak voltage jump sizes Γ_V caused by individual presynaptic spikes (left axis, the blue line) and the minimum input rates ν_e required to emit spikes (right axis, the red line). The black squares indicate the Γ_e chosen for validating diffusion approximations, and the corresponding ν_e are indicated by x notations. **(B)** Comparisons of steady distributions of postsynaptic conductances with Monte-Carlo (MC) simulations, i.e., direct numerical simulations of synaptic dynamics. The upper row is for excitatory conductances and the bottom row for inhibitory conductances. **(C)** Comparisons of steady distributions of membrane potentials with Monte-Carlo (MC) simulations of aEIF neuron networks. The upper row shows the distributions of membrane potentials of aEIF neurons only receiving excitatory input, while the bottom row shows the associated distributions where aEIF neurons receive excitatory and inhibitory inputs. The corresponding steady distributions of either excitatory or inhibitory postsynaptic conductances are shown in **B**.

activated region, that is, ≈ -10 mV. All results indicated that the sigmoid rate function, which had a poor estimating accuracy in our cases, was inadequate as an estimate function for determining firing rates. This was due to the fact that, as mentioned-above, it was not derived based on the biophysical understandings of spiking neurons.

Performance of simulating steady-state firing rate responses

Here, and in the next section, we further checked the accuracy of Eq. (8) in estimating population firing rates of neuronal populations with different strengths of spike-frequency adaptation. First, we explored steady-state responses, which were mainly dominated by $\bar{B}(\mu_V^{nf}, \sigma_V^{2,nf})$. The inhibitory input rates were scanned from 50 to 1000 Hz, and the excitatory input rates were scanned from the fluctuation-driven operating regime, namely, $v_e/v_c \approx 1$, in which synaptic-input fluctuations were the primary cause of neuronal firings, to the mean-driven operating one, $v_e/v_c \gg 1$, in which neuronal firings were determined primarily by driving inputs (Cai et al., 2012). Here, the values of spike-frequency adaptation parameters were set as 0, 0.02 and 0.1 for representing adaptation-free, weak adaptation and strong adaptation. As expected, larger spike-frequency adaptation lowered the steady output firing rates under the same input conditions (see the upper row in Figure 3). A counter-intuitive finding was that, under the same excitatory input rate, larger inhibitory input rate led to larger output firing rate. This was due to the increased fluctuations of membrane potentials originating from additional inhibitory input. As compared with those from MC simulations (see the bottom row in Figure 3), it was found that the estimation of firing rates had apparent errors of up-to ≈ 15 Hz when the neurons were driven under fluctuation-driven regimes. But, such errors were smaller for neurons with strong adaptation. The results also showed that under mean-driven operating regimes, the estimated steady-state output firing rates were comparable to those from MC simulations. In summary, the term $\bar{B}(\ast)$ could correctly capture the steady population firing rates under a wide range of input rates, except for the fluctuation-driven operating regimes where the fluctuation magnitude of membrane potentials dominated the accuracy of estimating firing rates.

Performance of simulating dynamic firing rate responses

In this section, we assessed the accuracy of Eq. (8) in estimating dynamic firing rates of a single neuronal population in response to time-varying stimuli. In particular, we shed light on the importance

Figure 2. Comparison of dNMMs with conventional NMMs in estimating population firing rates. **(A)** Nonmonotonic relationship of population firing rates with mean membrane potentials. The population firing rates are estimated by MC simulations, and different circles indicate the estimated firing rates with respect to different sets of excitatory and inhibitory Poissonian input rates. The colors of circles map the values of the standard deviations of membrane potentials across the population. ν_{out} : population firing rates; μ_V^{nf} : mean membrane potentials; σ_V^{nf} : standard deviations of membrane potentials. **(B)** Upper plot: steady population firing rates obtained from the dNMM (blue circles) and conventional NMM (orange circles) given by the same input rate in **A**. Lower plot: the corresponding estimating errors of the dNMM (blue circles) and NMM (orange circles) by comparisons with those from MC simulations. The sigmoid rate function was $\nu_{\text{out}} = \frac{1}{\tau_r} \frac{1}{1 + \exp[-(\mu_V^{\text{nf}} - \mu_s)/\sigma_s]}$, whose parameters were determined by an optimizing procedure (least squares methods) with data from MC simulations given only by excitatory input. Under this circumstance, $\mu_s = -23.165$ mV and $\sigma_s = 12.163$ mV.

Figure 3. Accuracy of the dNMM in estimating steady-state firing rates. Three different spike-frequency adaptation parameters $b = 0, 0.02$ and $0.01 \mu\text{A}$ were adopted for testing. The upper row shows the population-average output firing rates, ν_{out} , given by different combinations of excitatory and inhibitory input rates, ν_e and ν_i . Note that the scale of the excitatory input was normalized by ν_c , derived in Eq. (13), in those plots. The bottom row shows the corresponding estimation error by comparing with those from MC simulations.

of $\bar{A} \left(\mu_V^{\text{nf}}, \sigma_V^{2,\text{nf}}, \frac{d\mu_V^{\text{nf}}}{dt}, \frac{d\sigma_V^{2,\text{nf}}}{dt} \right)$ in Eq. (8) on estimating firing rates. Here, it was assumed that neurons only received nonstationary excitatory Poissonian spiking input, whose mean rate was described by an Ornstein-Uhlenbeck (OU) process,

$$\dot{v}_e = \frac{\bar{v} - v_e}{\tau_{\text{ou}}} + \sqrt{\frac{2}{\tau_{\text{ou}}}} \mathcal{V} \xi(t), \quad (16)$$

where τ_{ou} denoted the correlation time, $\bar{v}$ and $\mathcal{V}$ were the mean and standard deviation of the OU process, and $\xi(t)$ was a unit Gaussian white noise process. Here, we set $\bar{v}$ as $1.25\nu_c$ and $\mathcal{V}$ as $0.25\nu_c$, so that the input covered both the fluctuation- and mean-driven operating regimes. τ_{ou} was considered as the control parameter, which ranged from 10 to 100 ms. We adopted two performance measures, as in (Ostojic et al., 2011). One was the absolute difference between the estimated firing rates obtained from the dNMM and MC simulations, represented by root mean square (RMS) distance,

$$d_{\text{RMS}}(\nu_{\text{out}}^{\text{MC}}, \nu_{\text{out}}^{\text{dNMM}}) = \sqrt{\frac{1}{M} \sum_{k=1}^M (\nu_{\text{out}}^{\text{MC}}(t_k) - \nu_{\text{out}}^{\text{dNMM}}(t_k))^2}. \quad (17)$$

Here, $\nu_{\text{out}}^{\text{MC}}$ and $\nu_{\text{out}}^{\text{dNMM}}$ were respectively time series of the estimated firing rates from the MC simulations and dNMM, and each of them had M discrete elements over the calculating interval.

273 The other one was Pearson's correlation coefficient:

$$r(v_{\text{out}}^{\text{MC}}, v_{\text{out}}^{\text{dNMM}}) = \frac{\sum_{k=1}^M (v_{\text{out}}^{\text{MC}}(t_k) - \bar{v}_{\text{out}}^{\text{MC}}) \cdot (v_{\text{out}}^{\text{dNMM}}(t_k) - \bar{v}_{\text{out}}^{\text{dNMM}})}{\sqrt{\sum_{k=1}^M (v_{\text{out}}^{\text{MC}}(t_k) - \bar{v}_{\text{out}}^{\text{MC}})^2 \cdot \sum_{k=1}^M (v_{\text{out}}^{\text{dNMM}}(t_k) - \bar{v}_{\text{out}}^{\text{dNMM}})^2}}, \quad (18)$$

274 where $\bar{v}_{\text{out}}^{\text{MC}} = 1/M \sum_{k=1}^M v_{\text{out}}^{\text{MC}}(t_k)$ and $\bar{v}_{\text{out}}^{\text{dNMM}} = 1/M \sum_{k=1}^M v_{\text{out}}^{\text{dNMM}}(t_k)$ were time averages of discretely
275 given firing rates.

276 We found that the dNMM with the complete rate function, i.e., Eq. (8), could accurately reproduce
277 the time series of firing rates $v_{\text{out}}^{\text{MC}}$: $d_{\text{RMS}} < 8$ Hz and $r > 0.95$ over the explored range of correlation
278 times τ_{ou} , regardless of spike-frequency adaptation strengths (see blue lines in **Figure 4A**). However,
279 when the term $\bar{A}(\ast)$ was ignored, the estimation accuracy became worse, especially for the cases
280 where $\tau_{\text{ou}} = 10$ ms (see red lines in **Figure 4A**). Smaller τ_{ou} meant more rapidly changes in input
281 rates. In other words, the term $\bar{B}(\ast)$ could not react quickly to rapidly changing inputs. As seen in
282 **Figure 4B**, especially for $b = 0$ μA , the time series of the estimated firing rates from the incomplete
283 rate function without $\bar{A}(\ast)$ had a phase lag as compared to that from MC simulations, while the
284 complete rate function encompassing $\bar{A}(\ast)$ as well $\bar{B}(\ast)$ matched much better with MC simulations.
285 Large spike-frequency adaptation ($b = 0.1$ μA) decreased the sensitivity of neuronal populations
286 reacting to stimuli, thus leading to increases in estimation accuracy of the incomplete rate function.
287 We also observed that the estimation accuracy of the incomplete rate function became better for
288 the case of $\tau_{\text{ou}} = 100$ ms because of the more smoothed variation of the time-varying input (see
289 **Figure 4C**). But, it still could not capture rapid changes of output firing rates in this case.

290 **Spike-frequency adaptation stabilized asynchronous irregular activity of cortical** 291 **networks**

292 In this section, we moved on to the cortical network dynamics orchestrated by both the excitatory
293 and inhibitory neuronal populations. Experiments showed that during the state of vigilance,
294 intracellular recordings of cortical neurons in the awake animal revealed irregular discharges,
295 and the neurons fire tonically at low firing rates (*Steriade et al., 2001; Destexhe et al., 2003*). In
296 the viewpoint of network dynamics, such a network activity was referred to as the hallmark of
297 the "asynchronous irregular" (AI) state, during which the population-average output firing rates
298 sustainedly remained constant (*Brunel, 2000*). Typically, during this state, the inhibitory neurons
299 had larger firing rates (around 30 Hz in average) compared to the excitatory neurons (around
300 10 Hz in average), which might result from the presence of spike-frequency adaptation in the

Figure 4. Accuracy of the dNMM in estimating dynamic firing rates in response to time-varying input represented by an OU process. **(A)** Root mean square distance, d_{RMS} , and Pearson correlation coefficient, r , between the firing rate time series, $\nu_{\text{out}}^{\text{MC}}$ from MC simulations and $\nu_{\text{out}}^{\text{dNMM}}$ from the dNMM, for different spike-frequency adaptation strengths and different correlation times of the delivered OU input rate. The blue lines denote the performance using the complete rate estimate function, i.e., Eq. (8), while the red ones denote the performance using the incomplete rate estimate function where $\bar{A}(\cdot)$ is ignored. **(B)** Examples of the time series of estimated firing rates. The upper row shows the delivered OU process with $\tau_{\text{ou}} = 10$ ms. The middle one shows the firing rate time series from MC simulations (gray line), dNMM with a complete rate function (blue line) and an incomplete rate function (red line) under $b = 0$ μA . The bottom one shows the time series under $b = 0.1$ μA . **(C)** Similar to **(B)**, except for $\tau_{\text{ou}} = 100$ ms. OU process: Ornstein-Uhlenbeck process.

excitatory neurons. This raised a question of whether the spike-frequency adaptation influenced the emergence of the AI states of cortical networks. Here, we attempted to study this question.

In this study, a local cortical networks was assumed to be characterized by a recurrent excitatory-inhibitory network composed of a pyramidal (PY) neuron population and an interneuron (IN) population, as in (Brunel, 2000; Kumar et al., 2008; Augustin et al., 2013). The details about the structure of this network is described in the section of Methods and Materials. We explored the network activity of such a recurrent cortical network as a function of two control parameters, the external excitatory input v_{ext} and the relative inhibitory strength S_{inhi} (i.e., Eq. (15)) by using the dNMM, and then detected the regime covered by the AI state in this parameter space. Results showed that the AI state emerged due to sufficiently strong S_{inhi} , and the presence of spike-frequency adaptation ($b > 0$) allowed the AI state to cover the regime of lower v_{ext} and S_{inhi} (color shaded areas in **Figure 5A**). Within the covered parameter space, the population firing rate of the PY population, $v_{\text{out,PY}}$, for the AI state ranged from 8 to 25 Hz in the absence of spike-frequency adaptation, while it ranged from 5 to 22 Hz for $b_{\text{PY}} = 0.02 \mu\text{A}$ and from 2 to 15 Hz for $b_{\text{PY}} = 0.1 \mu\text{A}$ (characterized by colors in **Figure 5A**). These magnitude levels of output firing rate roughly matched experimental observations of the AI network activity. Some examples of firing rate time series are shown in **Figure 5B** ($b_{\text{PY}} = 0.02 \mu\text{A}$) and **Figure 5C** ($b_{\text{PY}} = 0.1 \mu\text{A}$), showing that the dNMM gave a good estimation of AI cortical network activity comparable to MC simulations. Importantly, the presence of spike-frequency adaptation enlarged the regime covered by the AI state in the parameter space. This suggested that the spike-frequency adaptation in the excitatory neurons could stabilize the AI network activity in the presence of fluctuating neuronal or synaptic properties.

Discussions

In this study, we have developed a novel type of NMMs, termed dNMM, for simulating network dynamics of aEIF neuronal populations with biologically conductance-based synaptic interactions and adaptive behaviors of firing rate responses. Our study has demonstrated that, as compared to MC simulations, the dNMM gave accurate estimations of firing rate responses under both steady and time-varying input conditions. The dNMM could also correctly predict the activities of large scale neural networks consisting of multiple neuronal populations, such as the prediction of the regime having AI network activity of the cortical network shown in **Figure 5**. In the future, like conventional NMMs, we will test the applicability of the dNMM to simulate other electrophysiological

Figure 5. Characteristics of the AI state with respect to different spike-frequency adaptations. **(A)** Covered regimes of the AI state in a parameter space spanned by the external excitatory input ν_{ext} (normalized by ν_c) and the relative inhibitory strength S_{inhi} for $b_{PY} = 0, 0.02$ and $0.1 \mu A$ from left to right panel. Colored shaded areas: regimes covered by the AI state. Blank area: regimes covered by the non-AI state. $\nu_{out,PY}$: the population firing rate of the PY population. **(B)** and **(C)** show four examples of firing rate time series estimated by the MC simulations and dNMM during AI states for $b_{PY} = 0.02$ and $0.1 \mu A$, respectively. AI state is asynchronous irregular state.

331 measurements of neural systems, such as the emergence of various rhythms in electroencephalog-
332 raphy (*Ursino et al., 2010; Zavaglia et al., 2010; Cona et al., 2014*) or the changes of BOLD signals
333 in functional magnetic resonance imaging (*Deco et al., 2013; Friston et al., 2017*).

334 Our dNMM tackled two major issues in current computational neuroscience community. First,
335 the dNMM can be viewed as the next-generation of NMMs when one seeks new types of NMMs
336 with the adaptive property (*Coombes and Byrne, 2019; Byrne et al., 2020*). Because of the presence
337 of rigorously theoretic bottom-up frameworks based on the csPDM, dNMM overcomes drawbacks
338 in the existing NMMs. For example, it retains all parameters of the underlying neuron model, such
339 that one can explore which neuronal property predominates the superficial network dynamics,
340 such as the spike-frequency adaptation that plays an important role in determining the emergence
341 of AI network activity. A major discrepancy between the dNMM and other NMMs existing is the
342 different rate functions used for estimating the population-average firing rates. Unlike the sigmoid
343 rate function used in other NMMs, our rate function, i.e., Eq. (8), is based on the description of
344 detailed spiking neurons (see Methods and Materials). As shown in *Figure 2*, our rate function gives
345 more accurate estimations of steady-state firing rates when compared to the sigmoid rate function.
346 The dNMM, therefore unlike the convectional NMMs, is not just a phenomenological modeling
347 approach.

348 The dNMM was tested by comparing its estimations of firing rate responses to that of the
349 full spiking network model, i.e., the MC simulations, as shown in *Figure 3, Figure 4* and *Figure 5*,
350 and it gives accurate estimations. The rate function in the dNMM includes two terms: $\bar{A}(\ast)$ and
351 $\bar{B}(\ast)$. In physiological interpretation, the activity $\bar{A}$ arises as a result of threshold crossings by the
352 mean and variance of membrane potentials caused by time-varying input, whereas the activity $\bar{B}$
353 occurs due to threshold crossings by steady fluctuation- or mean-driven input. Similar forms of
354 such a rate function can also be seen in previous firing rate models (*Chizhov et al., 2007; Buchin*
355 *and Chizhov, 2010*), but they did not consider the threshold crossings by transient variances of
356 membrane potentials caused by the changing input. We find that $\bar{A}$ helps to quickly react to the
357 rapidly changing input, especially at the transition to the activated firing regimes from the non-firing
358 regimes (as seen in *Figure 4*).

359 It should also be noted that the estimation of v_{out} neglected the spike generation mechanism
360 of aEIF spiking models. That was acceptable because the quantity of interest was the population-
361 average firing rate determined by the number of the generated spikes of activated neurons, rather

than their spiking times determined by the spiking generation mechanism. Furthermore, re-crossing of the spiking threshold voltage for activated neurons was actually involved by the expression of $\bar{v}$ in the $\bar{B}(\ast)$.

The second issue tackled by dNMMs is the calculation inefficiency of PDMs (*Tranchina, 2009*). Due to the presence of only ordinary differential equations, the dNMM has excellent calculation efficiency on neural network modelings. In this study, we employed the trapezoidal method to solve all necessary ordinary differential equations and the midpoint method to calculate the population firing rates numerically. The function and constant that needed to be determined before simulation were the current-rate relationship of EIF neurons, $f_{\text{EIF}}(I)$, and the threshold voltage V_{th} . It took around 12 seconds to simulate 10-seconds activity of the two-population cortical network with a time step size of 0.1 milliseconds (implemented in C++ programming with a CPU: i5-6500, 3.20GHz).

Our work is based on the csPDM (*Huang and Lin, 2018*), which we have augmented by explicitly including the dynamics of adaptation through aEIF neuron models. Due to its ability to reproduce a variety of firing patterns (*Naud et al., 2008; Touboul and Brette, 2008*), the use of the aEIF neuron model allowed us to simulate the activity of some brain regions where neurons revealed other special firing patterns, rather than just RS or FS pattern. The thalamus, for example, was in general the simulated target for studying slow-wave oscillations during sleep (*Destexhe, 2009; Crunelli et al., 2012; Cona et al., 2014*), where thalamic nuclei exhibited strong low-threshold spiking bursts (*Destexhe and Sejnowski, 2003*). In addition, following the original csPDM where the short-term plasticity of synaptic dynamics was encompassed, it is thus expected that, by just adding associated dynamic equations of the short-term plasticity, dNMM also can be used to simulate specific network dynamics, for examples, the persistent activity in working memory models (*Barak and Tsodyks, 2014*), that is significantly influenced by the short-term plasticity between synaptic interactions.

The premise of our dNMM is the Gaussian distribution of membrane potential variables, a solution of Fokker-Planck equation. This assumption can be seen in the prediction of the proportion of activated neurons (Eq. (9)) and of the effective current input to neurons (Eq. (10)). In turn, it also dominates the estimation of population firing rates. This is why the firing rate can be correctly estimated if such a premise is satisfied, even though the fluctuation of synaptic conductances cannot be well described by using diffusion approximations (see in *Figure 1*). However, the satisfaction of this premise may depend on the choice of spiking neuron models. It is an adequate assumption for the integrate-and-fire neuron models, but does not guarantee its applicability to the integrate-and-

393 fire-or-burst neuron models (*Smith et al., 2000*) or Izhikevich's models (*Izhikevich, 2003*), which do
394 not result in Fokker-Planck formalisms.

395 Using low-dimensional mean-field models to simulate large scale neural networks is a current
396 trend in the computational neuroscience community (*Breakspear, 2017*). In terms of performance
397 measures, d_{RMS} and r , the accuracy of the dNMM is comparable to other mean-field models, such
398 as linear-nonlinear models (*Ostojic et al., 2011*), spectral models (*Augustin et al., 2017*) and master
399 equation formalisms (*di Volo et al., 2019*), when, in general, $d_{\text{RMS}} < 10$ Hz and $r > 0.95$. However,
400 synaptic interactions in the models by *Ostojic et al. (2011)* and *Augustin et al. (2017)* were current-
401 based, which did not take the nonlinearity resulting from voltage-dependent synapses (*Paulus and*
402 *Rothwell, 2016; Zerlaut and Destexhe, 2017*) into account. And the model by *di Volo et al. (2019)*
403 only formulated the dynamics of firing rates, but did not include other state variables such as
404 membrane potentials that might be relevant to electroencephalographical signals.

405 **Methods and Materials**

406 In this section, the cortical excitatory-inhibitory network of aEIF neurons and details about aEIF
407 neuron models were described, and the dynamic equations of the dNMM were derived step by
408 step, starting from the description of the csPDM.

409 **The recurrent cortical network model**

410 As proposed by *Brunel (2000)*, here, a local cortical network was hypothesized to consist of both
411 the excitatory PY and the inhibitory IN neuronal populations, in which the probability of connection
412 between two neurons was 5%. The block diagram of this network circuit is shown in *Figure 6*. We
413 set there were totally $N = 10000$ neurons in this network. Eighty percent of them were considered
414 to be excitatory, and the rest were inhibitory. So, each neuron received recurrent inputs from
415 400 excitatory PY neurons and 100 inhibitory IN neurons. In addition, each neuron also received
416 excitatory inputs outside the network through 400 connections. We considered that the excitatory
417 input was mediated through AMPA-receptors, and the inhibitory one was mediated through GABAa-
418 receptors. The time scales of dynamics of both types of receptors were assumed to be short, at
419 the level of milliseconds or tens of milliseconds (*Dayan and Abbott, 2001*). In this study, we set
420 the strength of external excitatory inputs and the relative strength of recurrent inhibitory input as
421 control parameters to explore the network activity. The delayed time for delivering spikes between

neuronal populations was set as 2 ms.

The spiking neuron model

Each neuron in the cortical network was modeled by using aEIF model (*Brette and Gerstner, 2005*), which combined the exponential integrate-and-fire (EIF) spiking neuron model (*Fourcaud-Trocmé et al., 2003*) with an adaptation current for capturing adaptive firing responses. The resulting dynamic equations were:

$$C \frac{dV}{dt} = -g_L (V - E_L) + g_L \kappa \exp \left[(V - V_T) / \kappa \right] - w + I_{\text{syn}}(V, t), \quad (19)$$

$$\frac{dw}{dt} = \frac{1}{\tau_w} [a (V - E_L) - w] + b \sum_k \delta(t - t_k^f), \quad (20)$$

where $C = 1 \mu\text{F}$ was the membrane capacitance, $g_L = 0.05 \text{ mS}$ was the leak (resting) conductance, $E_L = -65 \text{ mV}$ was the leak reversal potential, $\kappa = 2.5 \text{ mV}$ was the steepness of the exponential driving force to threshold, and $V_T = -50 \text{ mV}$ was the spiking threshold voltage. Regarding the spike generation, when the membrane potential V reached the threshold, a spike was emitted, and V was then instantaneously reset to the resetting voltage $V_r = -65 \text{ mV}$ and clamped for a refractory period of $\tau_r = 2.5 \text{ ms}$. w was the adaptation current variable, with a time constant $\tau_w = 600 \text{ ms}$. The strength of the adaptation current was controlled by two parameters: $a = 0.005 \text{ mS}$ for sub-threshold adaptation and b (in μA) for spike-frequency adaptation. The value of b was set as zero for IN neurons that had no spike-frequency adaptation. In this study, the value of b for PY neurons was a control parameter to explore its associated effect on the types of network activity.

I_{syn} was the postsynaptic current, accounting for synaptic interactions induced by the presynaptic spikes. We modeled it as the sum of excitatory and inhibitory currents, given by:

$$I_{\text{syn}} = -g_e (V - E_e) - g_i (V - E_i), \quad (21)$$

where $E_e = 0 \text{ mV}$ and $E_i = -80 \text{ mV}$ were the excitatory and inhibitory reversal potentials, respectively. Here, we employed voltage-dependent conductance-based synaptic currents. g_e and g_i were synaptic conductance variables. We modeled their dynamics as first-order kinetics, in which the conductance was an exponentially decaying function that took instant jumps of amount Γ_e (Γ_i) at each excitatory (inhibitory) presynaptic spike. Their dynamic equations could be written by (*Roth and van Rossum, 2009*):

$$\frac{d}{dt} g_e = -\frac{1}{\tau_e} g_e + \Gamma_e \sum_j \delta(t - t_j^e), \quad (22)$$

Figure 6. Block diagram of a local cortical network. The network consists of pyramidal (PY) and interneuron (IN) populations, both represented by aEIF models. Each neuron receives external excitatory input through AMPA-mediated synapses, and, meanwhile, receives excitatory and inhibitory recurrent connections from PY and IN populations, respectively, through AMPA- and GABA-mediated synapses. K_{mn} means the average number of connections from the m population to the n one, with m, n assuming 1 (PY) and 2 (IN). K_{ext} means the number of connections from the external sources, and v_{ext} is the mean rate of Poissonian input spike trains. In the dNMM the dynamics of each neuronal population is characterized by a serial combination of synaptic dynamics, describing time-varying means (denoted by μ_{gs} , $s \in \{1, 2, 3, 4, 5, 6\}$) and variances (denoted by σ_{gs}^2 , $s \in \{1, 2, 3, 4, 5, 6\}$) of synaptic conductances, membrane dynamics, describing the time-varying means (denoted by $\mu_{V_m}^{nf}$) and variances (denoted by $\sigma_{V_m}^{2,nf}$) of membrane potentials, adaptation dynamics, describing the time-varying means (denoted by μ_{wm}) of adaptation currents, and an estimator of the population-average output firing rate (denoted by $v_{out,m}$).

446 and

$$\frac{d}{dt}g_i = -\frac{1}{\tau_i}g_i + \Gamma_i \sum_j \delta(t - t_j^i), \quad (23)$$

447 where $\tau_e = 5$ ms and $\tau_i = 10$ ms were synaptic time constants, t_j^e indicated the arrival time of the j -th
448 presynaptic spike along the excitatory synaptic connections, and t_j^i for inhibitory synaptic input. We
449 considered that the arrival times, t_j^e and t_j^i , were governed by homogeneous or inhomogeneous
450 stochastic Poisson processes. This assumption of Poissonian spike trains was in agreement with
451 the findings of Poisson-like inter-spike interval distributions of cortical neurons under awake states
452 (*Bédard et al., 2006; El Boustani et al., 2007*).

453 **The colored-noise population density method**

454 Rather than the activities of individual neurons, dNMM offered a mean-field description of the
455 collective activity of a sparsely connected random network of aEIF neurons as defined by Eqs.
456 (19)-(23). Its derivation started from the so-called csPDM, in which the distribution of membrane
457 potentials and the population firing rate could be calculated using the Fokker-Planck equation
458 in the mean-field limit, i.e., $N \gg 1$. A core assumption of the csPDM was that the synaptic
459 dynamics operated under the diffusive limit, under which, in the presence of finite synaptic time
460 constants, the stochastic fluctuating synaptic conductances could be approximated by nonstationary
461 Gaussian colored noises. The corresponding dynamic equations for their means and variances
462 were (equations (31) and (32) in *Huang and Lin (2018)*):

$$\frac{d}{dt}\mu_{g_{e/i}} = -\frac{1}{\tau_{e/i}}\mu_{g_{e/i}} + v_{e/i}(t) \cdot \Gamma_{e/i}, \quad (24)$$

463 and

$$\frac{d}{dt}\sigma_{g_{e/i}}^2 = -\frac{2}{\tau_{e/i}}\sigma_{g_{e/i}}^2 + v_{e/i}(t) \cdot \Gamma_{e/i}^2, \quad (25)$$

464 where $\mu_{g_{e/i}}$ stood for the mean of the fluctuating conductance and $\sigma_{g_{e/i}}^2$ for the variance (**Figure 6,**
465 **Synapses**); $v_e(t)$ ($v_i(t)$) denoted the time-varying mean rate of excitatory (inhibitory) presynaptic
466 spike trains.

467 In order to follow the original idea of csPDM, where individual neurons were characterized by
468 using the EIF spiking neuron model without adaptation, an adiabatic approximation was made
469 on the adaptation current (*Augustin et al., 2013*). The adiabatic approximation was applicable if
470 the time scale of the adaptation current was much slower than that of the membrane potential,
471 i.e., $\tau_w \gg \tau_m = C/g_L$. Under this approximation, every neuron within the population had the same

adaptation current, whose amplitude was approximated by its average over the population $\mu_w(t)$.
Accordingly, we yielded a new spiking neuron model equation when $\mu_w(t)$ was substituted into Eq. (19), given by

$$C \frac{dV}{dt} = -g_L (V - E_L) + g_L \kappa \exp \left[\frac{(V - V_T)}{\kappa} \right] - \mu_w + I_{\text{syn}}(V, t). \quad (26)$$

It turned out that Eq. (26) could be considered as a form of EIF neuron models if μ_w was viewed as an additional current input. We therefore could directly apply the csPDM to Eq. (26). How to calculate μ_w is described later in the Eq. (43). After applying the csPDM, we had the following partial differential equation to govern the temporal evolution of the density function (denoted by $\rho_V(V, t)$) of the distribution of the membrane potential variables within the population:

$$\frac{\partial}{\partial t} \rho_V = -\frac{\partial}{\partial V} \left[F(V, t) \rho_V - D(V, t) \frac{\partial \rho_V}{\partial V} \right] + v_{\text{out}}(t - \tau_r) \cdot \delta(V - V_r), \quad (27)$$

where

$$F(V, t) = \frac{1}{C} \left[-g_L (V - E_L) + g_L \kappa \exp \left(\frac{(V - V_T)}{\kappa} \right) + \mu_w - \mu_{g_e} (V - E_e) - \mu_{g_i} (V - E_i) \right], \quad (28)$$

$$D(V, t) = \frac{1}{C^2} \left[\frac{\tau_e \tau_{\text{eff}}}{\tau_e + \tau_{\text{eff}}} \cdot (V - E_e)^2 \sigma_{g_e}^2 + \frac{\tau_i \tau_{\text{eff}}}{\tau_i + \tau_{\text{eff}}} \cdot (V - E_i)^2 \sigma_{g_i}^2 \right]. \quad (29)$$

v_{out} denoted the population-average output firing rate of the neuronal population, τ_r was the refractory period of individual neurons, and τ_{eff} was defined as the effective time constant of membrane potentials of conductance-based spiking neurons (Gerstner et al., 2014), given by

$$\tau_{\text{eff}} = \frac{C}{g_L + \mu_{g_e} + \mu_{g_i}}. \quad (30)$$

The details of derivations of these equations can be found in the paper of Huang and Lin (2018). In summary, the dynamic equations of the csPDM included a partial differential equation and a few ordinary differential equations, through which the population dynamics of a population of aEIF neurons receiving external excitatory and inhibitory inputs was described. It can be imagined, therefore, that, as compared to that for ordinary differential equations, most effort was made to solve the partial differential equation numerically when using the csPDM. This is one of the major motivations to develop dNMM.

The density-based neural mass model

In this section, we moved on to the core work of this paper, i.e., the derivation of the dNMM based on the csPDM mentioned-above. First, we neglected the spike generation mechanism of individual

neurons and, thus, defined a function $\rho_V^{\text{nf}}(V, t)$, which described the distribution of membrane potential variables under this circumstance. Such a new density function evolved along with the time also according to a partial differential equation, similar to Eq. (27):

$$\frac{\partial}{\partial t} \rho_V^{\text{nf}} = -\frac{\partial}{\partial V} \left[F'(V, t) \rho_V^{\text{nf}} - D(V, t) \frac{\partial \rho_V^{\text{nf}}}{\partial V} \right], \quad (31)$$

except for the removal of the re-entering source term, i.e., the last term in the Eq. (27). The boundary conditions of this equation were $\rho_V^{\text{nf}} = \frac{\partial \rho_V^{\text{nf}}}{\partial V} = 0$ at both boundary sides of membrane potentials. Notice that in the Eq. (31), $F(V, t)$ was replaced by

$$F'(V, t) = \frac{1}{C} [-g_L (V - E_L) + \mu_w - \mu_{g_e} (V - E_e) - \mu_{g_i} (V - E_i)], \quad (32)$$

in which the exponential term was removed in order to avoid the mathematical divergence of the membrane potential when the spike generation mechanism was not taken into account. Finally, Eq. (31) was a typical form of nonlinear Fokker-Planck equations with state-dependent drift and diffusion coefficients. In other words, the solution $\rho_V^{\text{nf}}(V, t)$ should be a nonstationary Gaussian function (Risken, 1996) which was characterized perfectly by its mean and variance.

According to the definition of the mean value $\mu_V^{\text{nf}} = \int V \cdot \rho_V^{\text{nf}} dV$, we yielded

$$\begin{aligned} \frac{d}{dt} \mu_V^{\text{nf}} &= \frac{d}{dt} \int V \cdot \rho_V^{\text{nf}} dV = \int V \cdot \frac{\partial}{\partial t} \rho_V^{\text{nf}} dV = \int -V \cdot \frac{\partial}{\partial V} \left[F' \rho_V^{\text{nf}} - D \frac{\partial \rho_V^{\text{nf}}}{\partial V} \right] dV \\ &= -V \cdot \left[F' \rho_V^{\text{nf}} - D \frac{\partial \rho_V^{\text{nf}}}{\partial V} \right] \Big|_V + \int F' \rho_V^{\text{nf}} - D \frac{\partial \rho_V^{\text{nf}}}{\partial V} dV \quad (\text{integration by parts}) \\ &= \int F' \rho_V^{\text{nf}} dV - \int D \frac{\partial \rho_V^{\text{nf}}}{\partial V} dV \quad (\text{BCs}) \\ &= \int F' \rho_V^{\text{nf}} dV - D \rho_V^{\text{nf}} \Big|_V + \int \frac{\partial D}{\partial V} \rho_V^{\text{nf}} dV \quad (\text{integration by parts}) \\ &= \int F' \rho_V^{\text{nf}} dV + \int \frac{\partial D}{\partial V} \rho_V^{\text{nf}} dV \quad (\text{BCs}) \\ &= \left[\frac{-1}{C} (g_L + \mu_{g_e} + \mu_{g_i}) + \frac{2\tau_e \tau_{\text{eff}}}{\tau_e + \tau_{\text{eff}}} \frac{\sigma_{g_e}^2}{C^2} + \frac{2\tau_i \tau_{\text{eff}}}{\tau_i + \tau_{\text{eff}}} \frac{\sigma_{g_i}^2}{C^2} \right] \mu_V^{\text{nf}} \\ &\quad + \frac{1}{C} (g_L E_L + \mu_{g_e} E_e + \mu_{g_i} E_i - \mu_w) - \frac{2\tau_e \tau_{\text{eff}} E_e}{\tau_e + \tau_{\text{eff}}} \frac{\sigma_{g_e}^2}{C^2} - \frac{2\tau_i \tau_{\text{eff}} E_i}{\tau_i + \tau_{\text{eff}}} \frac{\sigma_{g_i}^2}{C^2} \end{aligned} \quad (33)$$

as the dynamic equation governing the time-dependent mean value $\mu_V^{\text{nf}}(t)$. Similarly, we yield

$$\begin{aligned}
 \frac{d}{dt}\mu_{V^2}^{\text{nf}} &= \frac{d}{dt} \int V^2 \cdot \rho_V^{\text{nf}} dV = \int V^2 \cdot \frac{\partial}{\partial t} \rho_V^{\text{nf}} dV = \int -V^2 \cdot \frac{\partial}{\partial V} \left[F' \rho_V^{\text{nf}} - D \frac{\partial \rho_V^{\text{nf}}}{\partial V} \right] dV \\
 &= -V^2 \cdot \left[F' \rho_V^{\text{nf}} - D \frac{\partial \rho_V^{\text{nf}}}{\partial V} \right] \Big|_V + 2 \int V \cdot \left[F' \rho_V^{\text{nf}} - D \frac{\partial \rho_V^{\text{nf}}}{\partial V} \right] dV \quad (\text{integration by parts}) \\
 &= 2 \int V F' \rho_V^{\text{nf}} dV - 2D \cdot \rho_V^{\text{nf}} \Big|_V + 2 \int \frac{\partial D}{\partial V} \cdot \rho_V^{\text{nf}} dV \quad (\text{BCs, integration by parts}) \\
 &= 2 \int V F' \rho_V^{\text{nf}} dV + 2 \int \frac{\partial D}{\partial V} \cdot \rho_V^{\text{nf}} dV \quad (\text{BCs}) \\
 &= \frac{2}{C} \left[-g_L (\mu_{V^2}^{\text{nf}} - E_L \mu_V^{\text{nf}}) + \mu_{\text{w}} \mu_V^{\text{nf}} - \mu_{\text{ge}} (\mu_{V^2}^{\text{nf}} - E_e \mu_V^{\text{nf}}) - \mu_{\text{gi}} (\mu_{V^2}^{\text{nf}} - E_i \mu_V^{\text{nf}}) \right] \\
 &\quad + \frac{4\tau_e \tau_{\text{eff}} (\mu_V^{\text{nf}} - E_e) \frac{\sigma_{\text{ge}}^2}{C^2}}{\tau_e + \tau_{\text{eff}}} + \frac{4\tau_i \tau_{\text{eff}} (\mu_V^{\text{nf}} - E_i) \frac{\sigma_{\text{gi}}^2}{C^2}}{\tau_i + \tau_{\text{eff}}} \quad (34)
 \end{aligned}$$

507 for governing the time-dependent mean value of the square of the membrane potential variable.

508 Next, according to the identity $\sigma_V^{2,\text{nf}} = \mu_{V^2}^{\text{nf}} - \mu_V^{\text{nf}^2}$, the dynamic equation for governing the variance

509 $\sigma_V^{2,\text{nf}}$ is given by

$$\frac{d}{dt}\sigma_V^{2,\text{nf}} = \frac{d}{dt}\mu_{V^2}^{\text{nf}} - 2\mu_V^{\text{nf}} \frac{d}{dt}\mu_V^{\text{nf}}. \quad (35)$$

510 Replacing $\frac{d}{dt}\mu_{V^2}^{\text{nf}}$ and $\frac{d}{dt}\mu_V^{\text{nf}}$ in the above equation with Eqs. (33) and (34), we then had

$$\begin{aligned}
 \frac{d}{dt}\sigma_V^{2,\text{nf}} &= \left[\frac{-2}{C} (g_L + \mu_{\text{ge}} + \mu_{\text{gi}}) + \frac{2\tau_e \tau_{\text{eff}} \frac{\sigma_{\text{ge}}^2}{C^2}}{\tau_e + \tau_{\text{eff}}} + \frac{2\tau_i \tau_{\text{eff}} \frac{\sigma_{\text{gi}}^2}{C^2}}{\tau_i + \tau_{\text{eff}}} \right] \sigma_V^{2,\text{nf}} \\
 &\quad + \frac{2\tau_e \tau_{\text{eff}} \frac{\sigma_{\text{ge}}^2}{C^2}}{\tau_e + \tau_{\text{eff}}} (\mu_V^{\text{nf}} - E_e)^2 + \frac{2\tau_i \tau_{\text{eff}} \frac{\sigma_{\text{gi}}^2}{C^2}}{\tau_i + \tau_{\text{eff}}} (\mu_V^{\text{nf}} - E_i)^2. \quad (36)
 \end{aligned}$$

511 As a result, the partial differential equation, i.e., Eq. (31), was turned into two coupled ordinary

512 differential equations, one for tracing the mean value and the other one for tracing the variance

513 (**Figure 6, Membrane**). The next step was to calculate the output firing rate of neurons (**Figure 6,**

514 **Firing**).

515 **Gerstner et al. (2014)** defined the population-average output firing rate v_{out} as

$$v_{\text{out}} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \frac{n_s(t; t + \Delta t)}{N}, \quad (37)$$

516 which was calculated through counting the number of spikes $n_s(t; t + \Delta t)$ in a small time interval

517 Δt and dividing it by N and Δt . Here, we assumed that the spikes within the interval Δt came

518 from two parts: (1) the initial firing of non-activated neurons from below the threshold, and (2) the

519 re-enforced firing of activated neurons escaping from refractoriness if the input was still sufficiently

520 large. Accordingly, v_{out} was calculated by

$$v_{\text{out}} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \frac{\underbrace{N (R_{\text{act}}(t + \Delta t) - R_{\text{act}}(t))}_{\text{if } \geq 0} + N \Delta t \bar{v}(t) R_{\text{act}}(t)}{N}$$

$$= \underbrace{\frac{d}{dt} R_{\text{act}}(t)}_{\text{if } \geq 0} + \bar{v}(t) R_{\text{act}}(t). \quad (38)$$

521 $R_{\text{act}}(t)$ meant the proportion of activated neurons whose membrane potentials exceeded a thresh-
522 old voltage V_{th} at time t , which was calculated as

$$R_{\text{act}}(t) = \int_{V_{th}}^{\infty} \mathcal{N}(V | \mu_V^{\text{nf}}, \sigma_V^{2,\text{nf}}) dV, \quad (39)$$

523 where $\mathcal{N}(\cdot | \mu_V^{\text{nf}}, \sigma_V^{2,\text{nf}})$ was a Gaussian density function with the corresponding mean μ_V^{nf} and
524 variance $\sigma_V^{2,\text{nf}}$. $\bar{v}(t)$ in Eq. (38) was assumed to be the mean firing rate of an activated neuron, and,
525 as a result, $N \Delta t \bar{v}(t) R_{\text{act}}(t)$ was the total number of spikes produced by activated neurons within
526 the time interval Δt . Here, $\bar{v}(t)$ was estimated through a current-mapping algorithm. We assumed
527 that the effective input current received by an activated neuron was characterized by a stochastic
528 Gaussian process, whose mean was

$$\mu_{I_{\text{tot}}} = -\mu_{g_e} \left(\frac{V_r + V_T}{2} - E_e \right) - \mu_{g_i} \left(\frac{V_r + V_T}{2} - E_i \right) + \mu_w, \quad (40)$$

529 and whose variance was

$$\sigma_{I_{\text{tot}}}^2 = \frac{2\sigma_{g_e}^2}{C} \frac{\tau_e \tau_{\text{eff}}}{\tau_e + \tau_{\text{eff}}} \left(\frac{V_r + V_T}{2} - E_e \right)^2 + \frac{2\sigma_{g_i}^2}{C} \frac{\tau_i \tau_{\text{eff}}}{\tau_i + \tau_{\text{eff}}} \left(\frac{V_r + V_T}{2} - E_i \right)^2. \quad (41)$$

530 Assuming $f_{\text{EIF}}(I)$ was the current-rate relationship of the EIF neuron, then $\bar{v}(t)$ was given by

$$\bar{v}(t) = \int_I f_{\text{EIF}}(I) \cdot \mathcal{N}(I | \mu_{I_{\text{tot}}}, \sigma_{I_{\text{tot}}}^2) dI. \quad (42)$$

531 The calculations of R_{act} and $\bar{v}$ are illustrated in **Figure 7**. What remained unknown was the dynamics
532 of the mean adaptation current μ_w (**Figure 6, Adaptation**). According to the derivation in (**Augustin**
533 **et al., 2013**), its dynamic equation was

$$\frac{d}{dt} \mu_w = \frac{1}{\tau_w} [a (\mu_V^{\text{nf}} - E_L) - \mu_w] + b \cdot v_{\text{out}}. \quad (43)$$

534 We have stated all necessary dynamic equations of the dNMM, i.e., Eqs. (24), (25), (33), (36) and
535 (43), and the estimate function of population-average output firing rate, i.e., Eq. (38), based on
536 a single population of aEIF neurons. The idea of dNMM can be easily extended to random and
537 sparsely connected neural networks consisting of multiple neuronal populations, like the cortical
538 network mentioned above.

Figure 7. Illustrations of the proportion of activated neurons (R_{act}) and the calculation of the average firing rate of activated neurons ($\bar{v}$).

Notice that we did not directly consider the spike threshold voltage, V_T , of the aEIF neuron as the threshold voltage for determining R_{act} because that the nonlinear exponential term and the spike generation mechanism were neglected. We hoped that these mismatches could be compensated by a careful choice of V_{th} . So, in the present study, the value of V_{th} was determined through optimally minimizing the error of estimating steady-state output firing rates given by a series of inputs. In our simulated cases, we set $V_{th} = -50.790$ mV for the case of $b = 0$ μA , $V_{th} = -50.907$ mV for $b = 0.02$ μA and $V_{th} = -51.133$ mV for $b = 0.1$ μA .

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References

- Apfalter F**, Ly C, Tranchina D. Population density methods for stochastic neurons with realistic synaptic kinetics: Firing rate dynamics and fast computational methods. *Network: Computation in Neural Systems*. 2006; 17(4):373–418. doi: <https://doi.org/10.1080/09548980601069787>.
- Augustin M**, Ladenbauer J, Baumann F, Obermayer K, Litke A, Chichilnisky E. Low-dimensional spike rate models

554 derived from networks of adaptive integrate-and-fire neurons: Comparison and implementation. PLOS
555 Computational Biology. 2017; 13(6):e1005545. doi: <https://10.1371/journal.pcbi.1005545>.

556 **Augustin M**, Ladenbauer J, Obermayer K. How adaptation shapes spike rate oscillations in recurrent neuronal
557 networks. Frontiers in Computational Neuroscience. 2013; 7:9. doi: <https://10.3389/fncom.2013.00009>.

558 **Avermann M**, Tomm C, Mateo C, Gerstner W, Petersen CCH. Microcircuits of excitatory and inhibitory neu-
559 rons in layer 2/3 of mouse barrel cortex. Journal of Neurophysiology. 2012; 107(11):3116–3134. doi:
560 <https://10.1152/jn.00917.2011>.

561 **Barak O**, Tsodyks M. Working models of working memory. Current Opinion in Neurobiology. 2014; 25:20–24.
562 doi: <https://10.1016/j.CONB.2013.10.008>.

563 **Bédard C**, Kröger H, Destexhe A. Does the $1/f$ Frequency Scaling of Brain Signals Reflect Self-Organized Critical
564 States? Physical Review Letters. 2006; 97:118102. doi: <https://10.1103/PhysRevLett.97.118102>.

565 **Bhattacharya BS**, Coyle D, Maguire LP. A thalamo-cortico-thalamic neural mass model to study alpha rhythms
566 in Alzheimer's disease. Neural Networks. 2011; 24(6):631–645. doi: <https://10.1016/j.neunet.2011.02.009>.

567 **Breakspear M**. Dynamic models of large-scale brain activity. Nature Neuroscience. 2017; 20(3):340–352. doi:
568 <https://10.1016/j.neunet.2011.02.009>.

569 **Brémaud A**, West DC, Thomson AM. Binomial parameters differ across neocortical layers and with different
570 classes of connections in adult rat and cat neocortex. Proceedings of the National Academy of Sciences. 2007;
571 104(35):14134–14139. doi: <https://doi.org/10.1073/pnas.0705661104>.

572 **Brette R**, Gerstner W. Adaptive Exponential Integrate-and-Fire Model as an Effective Description of Neuronal
573 Activity. Journal of Neurophysiology. 2005; 94(5):3637–3642. doi: <https://doi.org/10.1152/jn.00686.2005>.

574 **Brunel N**. Dynamics of Sparsely Connected Networks of Excitatory and Inhibitory Spiking Neurons. Journal of
575 Computational Neuroscience. 2000; 8(3):183–208. doi: <https://10.1023/A:1008925309027>.

576 **Buchin AY**, Chizhov AV. Firing-rate model of a population of adaptive neurons. Biophysics. 2010; 55(4):592–599.
577 doi: <https://10.1134/S0006350910040135>.

578 **Byrne Á**, O'Dea RD, Forrester M, Ross J, Coombes S. Next-generation neural mass and field modeling. Journal of
579 Neurophysiology. 2020; 123(2):726–742. doi: <https://doi.org/10.1152/jn.00406.2019>.

580 **Cai D**, Tao L, Shkarayev MS, Rangan AV, McLaughlin DW, Kovacic G. The role of fluctuations in coarse-grained
581 descriptions of neuronal networks. Communications in Mathematical Sciences. 2012; 10:307–354. doi:
582 <https://dx.doi.org/10.4310/CMS.2012.v10.n1.a14>.

583 **Chiang CC**, Ju MS, Lin CCK. Description and computational modeling of the whole course of status
584 epilepticus induced by low dose lithium-pilocarpine in rats. Brain research. 2011; 1417:151–162. doi:
585 <https://doi.org/10.1016/j.brainres.2011.08.045>.

- 586 **Chizhov AV**, Rodrigues S, Terry JR. A comparative analysis of a firing-rate model and a conductance-based
587 neural population model. *Physics Letters A*. 2007; 369(1-2):31–36. doi: <https://10.1016/j.physleta.2007.04.060>.
- 588 **Cona F**, Lacanna M, Ursino M. A thalamo-cortical neural mass model for the simulation of brain rhythms during
589 sleep. *Journal of Computational Neuroscience*. 2014; 37(1):125–148. doi: [https://doi.org/10.1007/s10827-013-](https://doi.org/10.1007/s10827-013-0493-1)
590 [0493-1](https://doi.org/10.1007/s10827-013-0493-1).
- 591 **Connors BW**, Gutnick MJ. Intrinsic firing patterns of diverse neocortical neurons. *Trends in neurosciences*. 1990;
592 13(3):99–104. doi: [https://doi.org/10.1016/0166-2236\(90\)90185-D](https://doi.org/10.1016/0166-2236(90)90185-D).
- 593 **Coombes S**, Byrne Á. Next generation neural mass models. In: Torcini A, Corinto F, editors. *Nonlinear Dynamics*
594 *in Computational Neuroscience* Springer, Cham; 2019.p. 1–16.
- 595 **Crunelli V**, Lorincz ML, Errington AC, Hughes SW. Activity of cortical and thalamic neurons during the slow (<1 Hz)
596 rhythm in the mouse in vivo. *European Journal of Physiology*. 2012; 463(1):73–88. doi: [https://10.1007/s00424-](https://10.1007/s00424-011-1011-9)
597 [011-1011-9](https://10.1007/s00424-011-1011-9).
- 598 **David O**, Friston KJ. A neural mass model for MEG/EEG:: coupling and neuronal dynamics. *NeuroImage*. 2003;
599 20(3):1743–1755. doi: <https://10.1016/j.neuroimage.2003.07.015>.
- 600 **Dayan P**, Abbott LF. *Theoretical neuroscience: Computational and mathematical modeling of neural systems*. 1
601 ed. MIT Press; 2001.
- 602 **Deco G**, Jirsa VK, Robinson PA, Breakspear M, Friston K. The dynamic brain: From spiking neu-
603 rons to neural masses and cortical fields. *PLoS Computational Biology*. 2008; 4(8):e1000092. doi:
604 <https://10.1371/journal.pcbi.1000092>.
- 605 **Deco G**, Ponce-Alvarez A, Mantini D, Romani GL, Hagmann P, Corbetta M. Resting-state functional connectivity
606 emerges from structurally and dynamically shaped slow linear fluctuations. *The Journal of Neuroscience*.
607 2013; 33(27):11239–52. doi: <https://10.1523/JNEUROSCI.1091-13.2013>.
- 608 **Deco G**, Tononi G, Boly M, Kringelbach ML. Rethinking segregation and integration: contributions of whole-brain
609 modelling. *Nature Reviews Neuroscience*. 2015; 16(7):430–439. doi: <https://10.1038/nrn3963>.
- 610 **Destexhe A**. Self-sustained asynchronous irregular states and Up–Down states in thalamic, cortical and
611 thalamocortical networks of nonlinear integrate-and-fire neurons. *Journal of Computational Neuroscience*.
612 2009; 27(3):493–506. doi: <https://10.1007/s10827-009-0164-4>.
- 613 **Destexhe A**, Rudolph M, Paré D. The high-conductance state of neocortical neurons in vivo. *Nature Reviews*
614 *Neuroscience*. 2003; 4(9):739–751. doi: <https://10.1038/nrn1198>.
- 615 **Destexhe A**, Sejnowski TJ. Interactions Between Membrane Conductances Underlying Thalamocortical Slow-
616 Wave Oscillations. *Physiological Reviews*. 2003; 83(4). doi: <https://doi.org/10.1152/physrev.00012.2003>.

- 617 **El Boustani S**, Pospischil M, Rudolph-Lilith M, Destexhe A. Activated cortical states: Experiments, analyses and
618 models. *Journal of Physiology-Paris*. 2007; 101(1-3):99–109. doi: <https://10.1016/j.jphysparis.2007.10.001>.
- 619 **Fourcaud N**, Brunel N. Dynamics of the Firing Probability of Noisy Integrate-and-Fire Neurons. *Neural Compu-*
620 *tation*. 2002; 14(9):2057–2110. doi: <https://10.1162/089976602320264015>.
- 621 **Fourcaud-Trocmé N**, Hansel D, van Vreeswijk C, Brunel N. How Spike Generation Mechanisms Determine the
622 Neuronal Response to Fluctuating Inputs. *Journal of Neuroscience*. 2003; 23(37):11628–11640.
- 623 **Friston KJ**, Preller KH, Mathys C, Cagnan H, Heinze J, Razi A, Zeidman P. Dynamic causal modelling revisited.
624 *NeuroImage*. 2017; doi: <https://10.1016/j.NEUROIMAGE.2017.02.045>.
- 625 **Gerstner W**, Kistler WM, Naud R, Paninski L. *Neuronal dynamics: From single neurons to networks and models*
626 *of cognition*. 1 ed. Cambridge University Press; 2014.
- 627 **Goldman JS**, Tort-Colet N, di Volo M, Susin E, Bouté J, Dali M, Carlu M, Nghiem TA, Górski T, Destexhe A.
628 Bridging Single Neuron Dynamics to Global Brain States. *Frontiers in Systems Neuroscience*. 2019; 13:75. doi:
629 <https://10.3389/fnsys.2019.00075>.
- 630 **Huang CH**, Lin CCK. An Efficient Population Density Method for Modeling Neural Networks with Synaptic
631 Dynamics Manifesting Finite Relaxation Time and Short-Term Plasticity. *eNeuro*. 2018; 5(6):ENEURO.0002–
632 18.2018. doi: <https://10.1523/ENEURO.0002-18.2018>.
- 633 **Izhikevich EM**. Simple model of spiking neurons. *IEEE Transactions on Neural Networks*. 2003; 14(6):1569–1572.
634 doi: <https://10.1109/TNN.2003.820440>.
- 635 **Izhikevich EM**, Edelman GM. Large-scale model of mammalian thalamocortical systems. *Proceedings of the*
636 *National Academy of Sciences*. 2008; 105(9):3593–8. doi: <https://10.1073/pnas.0712231105>.
- 637 **Kumar A**, Schrader S, Aertsen A, Rotter S. The high-conductance state of cortical networks. *Neural Computation*.
638 2008; 20(1):1–43. doi: <https://10.1162/neco.2008.20.1.1>.
- 639 **Lee AK**, Manns ID, Sakmann B, Brecht M. Whole-cell recordings in freely moving rats. *Neuron*. 2006; 51(4):399–
640 407. doi: <https://doi.org/10.1016/j.neuron.2006.07.004>.
- 641 **Linaro D**, Storace M, Giugliano M. Accurate and Fast Simulation of Channel Noise in Conductance-Based
642 Model Neurons by Diffusion Approximation. *PLoS Computational Biology*. 2011; 7(3):e1001102. doi:
643 <https://10.1371/journal.pcbi.1001102>.
- 644 **Lopes da Silva FH**, Hoeks A, Smits H, Zetterberg LH. Model of brain rhythmic activity. *Kybernetik*. 1974;
645 15(1):27–37. doi: <https://10.1007/BF00270757>.
- 646 **Markram H**, Muller E, Ramaswamy S, Reimann MW, Abdellah M, Sanchez CA, Ailamaki A, Alonso-Nanclares
647 L, Antille N, Arsever S, Kahou GAA, Berger TK, Bilgili A, Buncic N, Chalimourda A, Chindemi G, Courcol JD,

- 648 Delalondre F, Delattre V, Druckmann S, et al. Reconstruction and Simulation of Neocortical Microcircuitry.
649 Cell. 2015; 163(2):456–492. doi: <https://10.1016/j.cell.2015.09.029>.
- 650 **Matsumura M**, Cope T, Fetz E. Sustained excitatory synaptic input to motor cortex neurons in awake animals
651 revealed by intracellular recording of membrane potentials. Experimental brain research. 1988; 70(3):463–469.
652 doi: <https://doi.org/10.1007/BF00247594>.
- 653 **Moran R**, Pinotsis DA, Friston K. Neural masses and fields in dynamic causal modeling. Frontiers in Computa-
654 tional Neuroscience. 2013; 7:57. doi: <https://10.3389/fncom.2013.00057>.
- 655 **Naud R**, Marcille N, Clopath C, Gerstner W. Firing patterns in the adaptive exponential integrate-and-fire model.
656 Biological Cybernetics. 2008; 99:335. doi: <https://10.1007/s00422-008-0264-7>.
- 657 **Okun M**, Lampl I. Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked
658 activities. Nature Neuroscience. 2008; 11(5):535–537. doi: <https://10.1038/nn.2105>.
- 659 **Ostojic S**, Brunel N, Thirbon D, Luscher H, Senn W. From Spiking Neuron Models to Linear-Nonlinear Models.
660 PLoS Computational Biology. 2011; 7(1):e1001056. doi: <https://10.1371/journal.pcbi.1001056>.
- 661 **Paulus W**, Rothwell JC. Membrane resistance and shunting inhibition: where biophysics meets state-dependent
662 human neurophysiology. The Journal of Physiology. 2016; 594(10):2719–2728. doi: <https://10.1113/JP271452>.
- 663 **Richardson MJE**. Effects of synaptic conductance on the voltage distribution and firing rate of spiking neurons.
664 Physical Review E. 2004; 69(5):051918. doi: <https://10.1103/PhysRevE.69.051918>.
- 665 **Risken H**. The Fokker-Planck Equation. Berlin: Springer; 1996.
- 666 **Rosenbaum R**. A Diffusion Approximation and Numerical Methods for Adaptive Neuron Models with Stochastic
667 Inputs. Frontiers in Computational Neuroscience. 2016; 10:39. doi: <https://10.3389/fncom.2016.00039>.
- 668 **Roth A**, van Rossum M. Modeling Synapses. In: Erik De Schutter, editor. *Computational Modeling Methods for*
669 *Neuroscientists* MIT Press; 2009.p. 139–159. doi: <https://10.7551/mitpress/9780262013277.003.0007>.
- 670 **Sanz-Leon P**, Knock SA, Spiegler A, Jirsa VK. Mathematical framework for large-scale brain network modeling in
671 The Virtual Brain. NeuroImage. 2015; 111:385–430. doi: <https://10.1016/j.neuroimage.2015.01.002>.
- 672 **Schwalger T**, Deger M, Gerstner W. Towards a theory of cortical columns: From spiking neurons to in-
673 teracting neural populations of finite size. PLoS Computational Biology. 2017; 13(4):e1005507. doi:
674 <https://10.1371/journal.pcbi.1005507>.
- 675 **Smith GD**, Cox CL, Sherman SM, Rinzel J. Fourier analysis of sinusoidally driven thalamocortical relay neurons
676 and a minimal integrate-and-fire-or-burst model. Journal of Neurophysiology. 2000; 83(1):588–610. doi:
677 <https://doi.org/10.1152/jn.2000.83.1.588>.
- 678 **Steriade M**, Timofeev I, Grenier F. Natural waking and sleep states: a view from inside neocortical neurons.
679 Journal of neurophysiology. 2001; 85(5):1969–1985. doi: <https://doi.org/10.1152/jn.2001.85.5.1969>.

- 680 **Suffczynski P**, Kalitzin S, Lopes Da Silva FH. Dynamics of non-convulsive epileptic phenom-
681 ena modeled by a bistable neuronal network. *Neuroscience*. 2004; 126(2):467–484. doi:
682 <https://10.1016/j.neuroscience.2004.03.014>.
- 683 **Touboul J**, Brette R. Dynamics and bifurcations of the adaptive exponential integrate-and-fire model. *Biological*
684 *Cybernetics*. 2008; 99(4-5):319–334. doi: <https://doi.org/10.1007/s00422-008-0267-4>.
- 685 **Tranchina D**. Population Density Methods in Large-Scale Neural Network Modelling. In: Laing
686 C, Lord GJ, editors. *Stochastic Methods in Neuroscience* Oxford: Oxford University Press; 2009. doi:
687 <https://10.1093/acprof:oso/9780199235070.003.0007>.
- 688 **Ursino M**, Cona F, Zavaglia M. The generation of rhythms within a cortical region: Analysis of a neural mass
689 model. *NeuroImage*. 2010; 52(3):1080–1094. doi: <https://doi.org/10.1016/j.neuroimage.2009.12.084>.
- 690 **di Volo M**, Romagnoni A, Capone C, Destexhe A. Biologically Realistic Mean-Field Models of Conductance-
691 Based Networks of Spiking Neurons with Adaptation. *Neural Computation*. 2019; 31(4):653–680. doi:
692 https://10.1162/neco_a_01173.
- 693 **Zavaglia M**, Cona F, Ursino M. A neural mass model to simulate different rhythms in a cortical region. *Compu-*
694 *tational Intelligence and Neuroscience*. 2010; 2010. doi: <https://doi.org/10.1155/2010/456140>.
- 695 **Zerlaut Y**, Destexhe A. Enhanced Responsiveness and Low-Level Awareness in Stochastic Network States.
696 *Neuron*. 2017; 94(5):1002–1009. doi: <https://10.1016/j.neuron.2017.04.001>.
- 697 **Zetterberg L**, Kristiansson L, Mossberg K. Performance of a model for a local neuron population. *Biological*
698 *cybernetics*. 1978; 31(1):15–26. doi: <https://doi.org/10.1007/BF00337367>.