Gamma-range oscillations evoked by Optogenetic stimulation - an *in silico* study

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ABSTRACT
Gamma-range oscillations are repetitive neuronal activation in various regions of the brain, displaying prominent energy distribution in the 30-90 Hz frequency band. It is shown that these oscillations emerge through excitatory-inhibitory neuronal interplay, but their mechanisms and functions remain unknown. Therefore, it is necessary to simplify the *in vivo* complexity. This has been accomplished by the host laboratory, which reproduced these rhythms in an *in vitro* model of cortical microcircuitry using Optogenetic tools and suggested a simple firing-rate mathematical model. Since Optogenetics influences synaptic efficacy, I propose an extension of this mathematical model by dynamical properties of synaptic transmission.

Keywords
Gamma-range oscillations, excitatory-inhibitory neuronal interplay, synaptic transmission, optogenetics, noisy mean-field model

INTRODUCTION

Neuronal signals in the gamma frequency band (30-90 Hz) started to attract considerable attention in neurosciences since it was demonstrated to correlate with perceptual binding. Intriguingly, gamma-range oscillations (GROs) are often observed during waking and sleep states, but their function and mechanisms remain unknown despite a large amount of published studies. They have been reported in many regions of the neocortex[1-4], olfactory bulb[5], entorhinal cortex[6], hippocampus[7,8], amygdala[9,10], striatum[11,12], thalamus[13], and other regions; and they are evoked or induced by various stimuli or tasks. Diverse gamma-band oscillatory processes are involved in different functions, including but not limited to, perceptual binding[2], attention[14,15], arousal[16], object recognition[17,18] and language perception[19,20]. So GROs are not highly specific correlates of a single process, but rather linked with multiple functions. Hence, GROs might be important building blocks of brain's electrical activity and probably serve as an universal code of CNS communication[21]. Furthermore, gamma activity is altered in some diseases such as schizophrenia[22,23] and bipolar disorder[24]. Since GROs seem to be a fundamental and elementary process in the whole-brain operation, and affected in some neuropsychiatric disorders; it is of great importance to understand and predict the generation of gamma rhythms (GGR).

Besides controversies and debates on the mechanistic explanation of GROs' emergence, there is an agreement on the excitatory-inhibitory interplay (EII) and on the need to unravel it by simplifying the *in vivo* complexity. *In vitro* experimental preparations have been thus considered, but for many years it has not been clear how to reproduce GROs in an *in vitro* reduced model of the brain circuits. Recently, the host laboratory showed that brief wide-field photostimuli evoke and modulate oscillatory activity in cortical neurons. These robust reverberating spiking responses contained prominent oscillations in the gamma frequency band. By electrophysiology, pharmacology, and mathematical modelling, it was concluded that GROs emerge, as *in vivo*, from the EII and that the photostimuli can briefly facilitate the excitatory synaptic transmission. Furthermore, their mathematical model is a starting point for studying *in silico* the emergence of similar network-level phenomena[25]. Interestingly, Giugliano-Pulizzi model (GPM) is simple enough to explain emergence of GROs by EII, but synaptic short-term plasticity (STP), which is experimentally shown to be affected by optogenetics, was not included in the model and the model does not explain the spontaneous episodic synchronization of neurons across the network. In other words, the original model includes static and not dynamical synaptic transmission properties.

However, Tsodyks-Markram model (TMM) is capturing with great accuracy the phenomenon of synaptic STP. According to TMM , synaptic efficacy (SE) changes over time, reflecting earlier presynaptic activity. It induces temporary modification to the SE. Thus, if there was no presynaptic activity, the synaptic strength will quickly return to its resting value. This TMM contains 3 states, describing the conditions of the resources for neurotransmission at each synaptic boutons: effective (E), inactive (I) and recovered (R). Each presynaptic action potential activates a certain fraction of the R-state. Then, this E-state gets inactivated. Thereafter, the process of recovery takes place. All these transitions happen with a certain timescale (TS) (i.e. τ_e, τ_i, τ_r). Since the E-state is caused by influx of Ca^{2+} into the axon terminal, the variable τ_e is dependent on Ca^{2+} [26].

Furthermore, ChR2 LC-TC (used variant of opsin for evoking GROs) has an enhanced Ca^{2+} selectivity in comparison to its wild type. The host laboratory observed an increase in presynaptic release probability after light stimulation, which was linearly correlated at its peak with the light pulse duration. This is reminiscent of Ca^{2+} accumulation in the presynaptic terminal, thus altering the SE. Consequently, Optogenetic stimulation has an unexpected impact on the strength of recurrent connectivity, so that in experimental design and interpretation one must consider a modulatory effect on synaptic physiology in addition to neuronal physiology[25]. Therefore, I propose an extension of GPM by dynamical properties of synaptic transmission as a first step to investigate the action of ChR2 LC-TC and involvement of dynamical SE in GGR in cortical circuits.

MATERIALS AND METHODS

Inspired by the TMM and by a model proposed recently by Masquelier and Deco (MDM), I considered again a Wilson-Cowan-like set of equations as in the paper by Gigante *et al.*

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Table 1: Network parameters (NP)

Parameter	Value
n_e / n_i	1600 / 400
c	0.2500
$\tilde{\tau}_E$ / $\tilde{\tau}_I$	10 / 2 ms
$\tau_E = \tau_I$	20 ms
$J_{ee} \pm \sigma_{J_{ee}}$	16.1800 ± 4.0400 mV
$J_{ei} \pm \sigma_{J_{ei}}$	-6.8000 ± 1.7000 mV
$J_{ie} \pm \sigma_{J_{ie}}$	24.6000 ± 6.1400 mV
$J_{ii} \pm \sigma_{J_{ii}}$	-7.1600 ±1.7880 mV
$J_{ext} \pm \sigma_{J_{ext}}$	8.3200 ± 2.0800 mV
v_{ext}	1.2500 kHz
dt	0.25 ms
V^{reset} / V^{thresh}	-70 / -55 mV
R_m	1
τ_v /$\tau_{refract}$	20 / 2 ms
T	60 000 ms
U	0.025

This table shows all the fixed NP during simulations run in MATLAB.

(GEAM), to be extended with short-term facilitation (STF) between excitatory-excitatory (EE) neurons[27-29]. Furthermore, the suggestion of Gigante and colleagues was taken into account to include spike-frequency adaptation (SFA) in the model. This led to a model assuming the following form for the mean and the variance of the excitatory current I_E (while the expression for the inhibitory current remained the same I_I as proposed by GEAM[27]). (Since I propose an extension of an existing model, only novel equations and variables are described here, for others consult[27].)

$$\mu_e = cn_e\tilde{v}_e w_{exc} J_{EE} r_e \tau_{STF}(u_e\,(1-U)+U) + cn_i\tilde{v}_i w_{inh}\,J_{EI} + v_{ext}J_{ext} - g_{SFA}c_e(t) \qquad (1)$$

$$\sigma_e^2 = cn_e\tilde{v}_e w_{exc}^2\left(J_{EE}^2+\sigma_{J_{EE}}^2\right)r_e^2\tau_{STF}(u_e(1-U)+U) + cn_i\tilde{v}_i w_{inh}^2\left(J_{EI}^2+\sigma_{J_{EI}}^2\right) + v_{ext}\left(J_{ext}^2+\sigma_{J_{ext}}^2\right) \qquad (2)$$

where c is the probability of two neurons being synaptically connected; n_e and n_i are the number of neurons respectively in excitatory and inhibitory population; and $\tilde{v}_e$ and $\tilde{v}_i$ denote the instantaneous firing rates. Furthermore, J_{EE} (J_{EI}) is the average SE from an excitatory (inhibitory) pre-synaptic neuron to an excitatory one, and σ_J^2 represents the variance of the J-distribution, while w_{exc} and w_{inh} indicate synaptic connection weights respectively for excitatory and inhibitory neurons. Moreover, τ_{STF} is the TS needed to transition from R to E. In addition, there is external current assumed with spike rate of v_{ext} and SE of J_{ext}. In this equation, r_e ($0 < r_e < 1$) represents the available fraction of synaptic resources for the response of an excitatory synapse to a pre-synaptic spike. This fraction is time-dependent and evolves following dynamics of STP:

$$\dot{r}_e = \frac{(1-r_e)}{\tau_{STD}} - r_e\tilde{v}_e(u_e(1-U)+U) \qquad (3)$$

where τ_{STD} denotes TS needed to transition from I to R. Most importantly, u_e denotes the running value of SE while U is SE belonging to the first action potential in a spike train. The dynamics of u_e can be described as follows:

$$\dot{u}_e = \frac{-u_e}{\tau_{STF}} + U(1-u)\tilde{v}_e \qquad (4)$$

Finally, the last term in eq. 1 is caused by SFA, whereby g_{SFA} represents conductance; while c_e can be interpreted as the cytoplasmatic [Ca^{2+}] and can be described as follows:

$$\tau_{SFA}\frac{dc_e}{dt} = -c_e + v_{n_e} \qquad (5)$$

whereby τ_{SFA} can be interpreted as TS needed for cellular recovery and v_{n_e} is caused by a random process using a Poisson-distributed random variable, capturing the finite-size network effects. ***Table 1*** shows all the fixed parameters used during simulations in MATLAB. The aim is to find the right set of modifiable parameters to mimic *in vitro* GROs (burst frequency (BF) = [0.5-1 burst/s] and burst duration (BD) = [0.1-0.4s]), so that eventually the effect of optogenetics in GGR can be studied by altering U and u_e.

RESULTS

Examining the effect of g_{SFA} using MDM's parameters for TSs ($\tau_{STD} < \tau_{STF} < \tau_{SFA}$)

MDM assumes for network spontaneous "bursting" events the following conditions on the kinetic parameters: τ_{STD} (800 ms) < τ_{STF} (1600 ms) < τ_{SFA} (4000 ms). Noteworthy, only excitatory neurons were included in their model[29]. In the beginning, I used these constants to study the effect of other modifiable parameters. For the sake of simplicity, w_{exc} and w_{inh} are set to 1. In this procedure, g_{SFA} is changed stepwise (***Fig. 1*** shows only some of the outputs). It seems like there is a threshold value for g_{SFA} needed to simulate repetitive bursts. When g_{SFA} is below this threshold, BD is too long. Increasing above threshold g_{SFA} leads to shorter BD and longer inter-burst-intervals (IBIs).

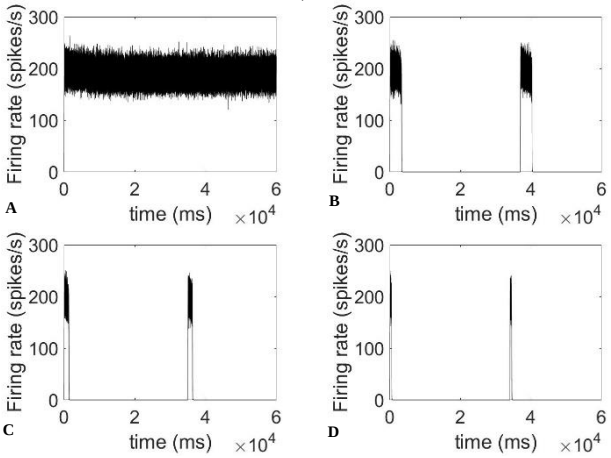

Figure 1: The effect of g_{SFA}. Time course of network firing rate is represented. A burst is a sudden increase in the firing rate. To examine the effect of g_{SFA} on the firing rate all parameters are kept constant, while changing g_{SFA}. Increasing g_{SFA} leads to shorter BD and longer IBIs. **A)** g_{SFA} = 50 **B)** g_{SFA} = 100 **C)** g_{SFA} = 200 **D)** g_{SFA} = 500.

Lowering the numerical value of τ_{SFA}

Importantly, it was experimentally shown that $GABA_A$ receptors are necessary for the evoked GROs[25], so that one cannot ignore inhibition in GGR as MDM does. In MDM, SFA is the only mechanism ending the bursts[19]. But in my model, inhibition is taken into account. Therefore, τ_{SFA} has been systematically lowered in its numerical value while keeping other parameters constant. This results in longer BD and shorter IBIs. Also, when τ_{SFA} is below a certain value (dependent on used parameters), the BD lasts too long compared to typical experimental recordings (not shown).

The effect of remaining modifiable parameters

To investigate the individual impact of remaining modifiable parameters, i.e. w_{exc}, w_{inh}, τ_{STF}, τ_{STD}, all parameters are kept constant (w_{exc} = 1, w_{inh} = 1, g_{SFA} = 1000, τ_{STD} = 800 ms, τ_{STF} = 1600 ms, τ_{SFA} = 400 ms) while increasing one of the modifiable parameters at a time. First, strengthening w_{exc} causes longer BD while IBIs remain almost the same, hence lower BF. Furthermore, enhancing w_{inh} results in shorter BD and shorter IBIs, hence higher BF. In addition, augmenting τ_{STF} leads to longer BD and longer IBIs, hence lower BF. Finally, increasing τ_{STD} induces shorter BD and shorter IBIs, hence higher BF (not shown).

Relative TSs combined with other modifiable parameters

Since the aim is to mimic experimentally observed GROs with the dynamical noisy mean-field model (DNMFM), the set of parameters are searched to simulate bursts with BF = [0.5-1 burst/s] and BD = [0.1-0.4 s], so that this could be used

as baseline for simulations. By logical reasoning, there are six possibilities to set the TSs: (1) $\tau_{STD} < \tau_{STF} < \tau_{SFA}$, (2) $\tau_{STD} < \tau_{SFA} < \tau_{STF}$, (3) $\tau_{STF} < \tau_{STD} < \tau_{SFA}$, (4) $\tau_{STF} < \tau_{SFA} < \tau_{STD}$, (5) $\tau_{SFA} < \tau_{STD} < \tau_{STF}$, (6) $\tau_{SFA} < \tau_{STF} < \tau_{STD}$. Given ***Table 2*** and the *in vitro* observations of GROs, one can figure out that there is a need of relatively high τ_{STD} and relatively low τ_{STF}, meaning $\tau_{STF} < \tau_{STD}$. Hence, possibility 1, 2 and 5 can be ruled out. First of all, case 1 cannot be assumed in my model, because although it is possible to match the required BD, it is impossible to meet the required BF. The latter requires a lot of inhibition in the model which ultimately is impossible to reach with reasonable high amount of w_{inh} (***Fig. 2A-B***). One can argue that augmenting τ_{STD} will probably help, but even then, it is impossible within the boundaries defined by possibility 1. Also, possibility 2 can be ruled out, because this case demands very strong inhibition and it does not fulfil the requirement of long-TS short-term depression (STD) (***Fig. 2C-D***), otherwise BD would be too long (not shown). The same applies to possibility 5 (not shown). To prove this, some simulations are run.

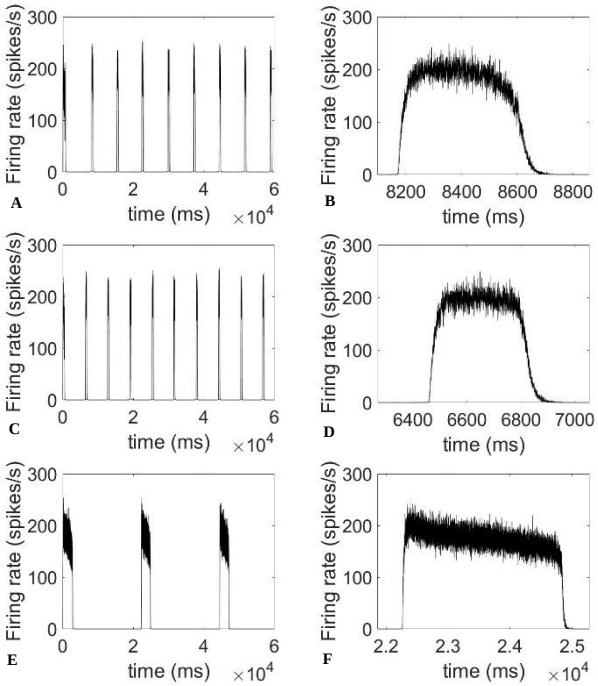

Figure 2: Ruled out cases: One representative of multiple simulations for each case is shown. **Possibility (1): $\tau_{STD} < \tau_{STF} < \tau_{SFA}$.** This case cannot be assumed in my model, because although it is possible to match the required BD, it is impossible to meet the required BF, even not when w_{inh} is massively increased and τ_{STD} augmented within the boundaries defined by possibility 1. **A)** The simulation is run with: τ_{STD} = 1500 ms < τ_{STF} = 1600 ms < τ_{SFA}= 2000 ms, g_{SFA} = 100, w_{exc} = 1, w_{inh} = 100,. **B)** Zoom of the second burst of A. **Possibility (2): $\tau_{STD} < \tau_{SFA} < \tau_{STF}$.** This case can be ruled out, because it demands immensely high inhibition and it does not fulfil the requirement of long TS STD. **C)** The simulation is run with: τ_{STD} = 1400 ms < τ_{SFA}= 1500ms < τ_{STF}= 1600 ms, w_{exc} = 1, w_{inh} = 100, g_{SFA} = 100. **D)** Zoom of the second burst of C. **Possibility (3): $\tau_{STF} < \tau_{STD} < \tau_{SFA}$.** This case can be ruled out because the criteria, as well as for BD as for BF, cannot be met. Interestingly, NSs within the burst are declining really subtle. **E)** The simulation is run with: τ_{STF}= 1000ms < τ_{STD} = 2400 ms < τ_{SFA} = 3000ms, w_{exc} = 1, w_{inh} = 1, g_{SFA} = 25. **F)** Zoom of the second burst of E.

So far, the remaining possibilities are 3, 4 and 6. Furthermore, the relative amount of τ_{SFA} and g_{SFA} cannot be predicted based on ***Table 2***, but it is clear that when one is increased the other must be decreased. So, further investigation is realised with case 3 (***Fig. 2E-F***). In this case, the criteria as well as for BD as for BF cannot be met. Interestingly, network spikes (NSs) within the burst are declining really subtle. Then, possibility 4 is examined. Intriguingly, when BD meets the criteria, the BF does not. More importantly, bursts are fading out gradually over time (***Fig. 3A-B***). This is required to simulate GROs. Furthermore, when BD is longer than desired, some oscillations are observed (***Fig. 3C-D***). Finally, possibility 6 is studied (***Fig. 3E-F***). To this endeavour, τ_{STF} and τ_{STD} are set to relatively low values. After trial-and-error, the parameters required to meet the given criteria are found, they lead to 44 bursts/60s = 0.73 Hz lasting ~0.4s. Next, τ_{STF} and τ_{STD} are modified together with w_{inh} and w_{exc}. Again, after trial-and-error, the combination of parameters leading to oscillations are established. However, the problem this time is, the inability to gradually fade out the bursts.

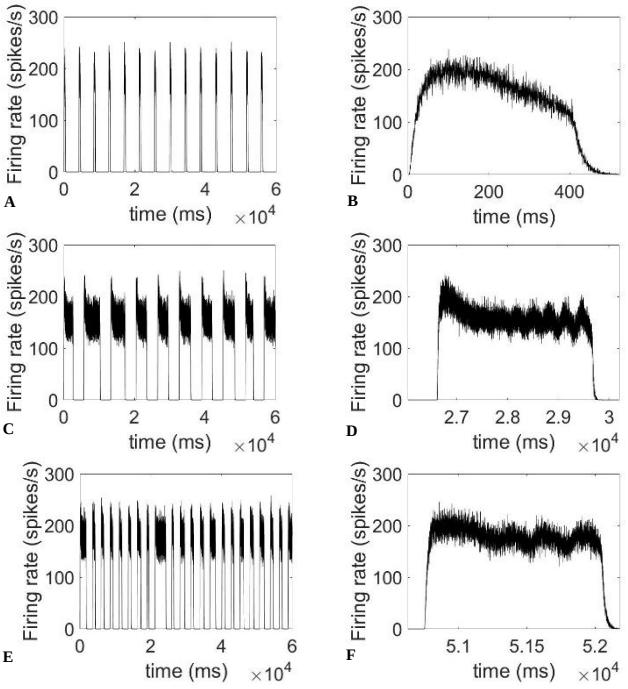

Figure 3*: *Remaining cases: Some representatives of multiple simulations for each case is shown. **Possibility (4): $\tau_{STF} < \tau_{SFA} < \tau_{STD}$.** In this case, when BD meets the criteria, the BF does not. More importantly, bursts are fading out gradually over time. Furthermore, when BD is longer than desired, some oscillations are observed. **A)** The simulation is run with: τ_{STF}= 325 ms < τ_{SFA} = 600 ms < τ_{STD} = 2400 ms, w_{exc} = 2, w_{inh} = 1, g_{SFA} = 80. **B)** Zoom of the first burst of A. **C)** The simulation is run with: τ_{STF}= 340 ms < τ_{SFA} = 450 ms < τ_{STD} = 2450 ms, w_{exc} = 3, w_{inh} = 2, g_{SFA} = 85. **D)** Zoom of the fifth burst of C. **Possibility (6): $\tau_{SFA} < \tau_{STF} < \tau_{STD}$.** In this case, it is possible to simulate oscillations; but impossible to gradually fade them out as in the experiments. **E)** The simulation is run with: w_{exc} = 2, w_{inh} = 0.8, g_{SFA} = 1000, τ_{SFA} = 200 ms < τ_{STF}= 660 ms < τ_{STD} = 800 ms. **F)** Zoom of the fourth last burst of E.

Table 2: The effect of all modifiable parameters

	BD	IBIs	BF
g_{SFA} ↑	↓	↑	↓
τ_{SFA} ↑	↓	↑	↓
w_{exc} ↑	↑	/	↓
w_{inh} ↑	↓	↓	↑
τ_{STD} ↑	↓	↓	↑
τ_{STF} ↑	↑	↑	↓

This table summarises the effect of every modifiable parameter which is mentioned above. ↑ indicates the increase of the parameter, while ↓ denotes the decrease of it. / means it does not affect the variable.

DISCUSSION

Ideally, to simulate GROs, a regime between possibilities 4 and 6 is needed. In case 4 ($\tau_{STF} < \tau_{SFA} < \tau_{STD}$), the bursts are fading out gradually, which is a condition necessary to mimic the *in vitro* observed GROs. However to generate oscillations, longer BD is required, compared with case 6. Furthermore, oscillations of case 6 do not fade out gradually as *in vitro* data. Rather, it is as if they are reaching an equilibrium, and then finally, they end abruptly. In contrast to possibility 4, it is impossible to gradually fade out the

bursts in case 6 ($\tau_{SFA} < \tau_{STF} < \tau_{STD}$). But in this condition, it is possible to generate oscillations within shorter BD compared to case 4. In both conditions, low-frequency delta (2-3,33 Hz) oscillations are generated (***Fig. 3***). Thus, my model offers a possible mechanism for delta oscillations.

However, because of the lack of time it was not possible to exhaustively study my model. But, my findings suggest that the following criteria must be met to possibly generate (gamma) oscillations: (I) the product of g_{SFA} and τ_{SFA} must be low to meet the required BF and BD, whereby τ_{SFA} is long enough to gradually fade out the bursts. Hence, τ_{SFA} is accompanied by weak g_{SFA}. (II) On the one hand, there are two mechanisms promoting bursts: recurrent excitation and STF. On the other hand, there are five mechanisms to quench or silence bursts: mutual inhibition, reciprocal excitation and inhibition, STD and SFA. Hence, w_{exc} must be bigger than w_{inh}. (III) As a result, there is need of relatively long-TS STD and short-TS STF. This is incongruent with MDM, because MDM ignores inhibition[29] whereas my model takes inhibition into account which is experimentally shown to be necessary in GGR[25].

My observations can be due to different reasons. First of all, the model has been extended and studied in very short amount of time (9 days). Therefore, it was impossible to perform exhaustive research on both cases. As it can be insinuated, the output of simulations are determined by combination of parameters. Since there are a lot of simultaneously modifiable parameters, it is hard to predict the output of the simulation. This reflects the need of exhaustive *in silico* research. Secondly, my model does not only deal with the EII; but it also takes dynamical processes, such as STP and SFA, into account. Consequently, this results in a complex model yet considering the reality; so that once the right set of modifiable parameters are found, one can study the effect of optogenetics in GGR, by altering U and u_e. Thirdly, the extension was inspired by MDM, TMM and GEAM[27-29]. In other words, it is a generalization of MDM. But clearly, further investigation and/or extension is required to mimic GROs. Now, there is STP between EE neurons, but there is no STP between EI neurons, which may have an impact on GROs. This can be the reason for not observing oscillations and gradually fading out of bursts simultaneously. However, my model is already complex the way it is; including extra dynamical forces will make it even more complex to predict the output by reasoning. This will require even more exhaustive research on the modifiable parameters. Nonetheless, this approach will be more accurate than mine. Even though it seems more complex, one could go even further by including STP between inhibitory-inhibitory neurons. Therefore, there is a need of heuristic approach instead of exhaustive. Once, one succeeds to mimic experimentally observed GROs, one could examine the effect of optogenetics on SE in GGR by altering U and u_e.. Therefore, there is a need on mathematical dynamical firing-rate model for GROs; hence, further investigation and/or extension of my DNMFM.

CONCLUSION

The current observations suggest that creating possibly oscillations *in silico*, embedded in each spontaneous burst requires (I) medium-TS τ_{SFA} with weak g_{SFA}, whereby $g_{SFA} . \tau_{SFA}$ is low; (II) w_{exc} must be bigger than w_{inh}, (III) a relatively short-TS STF and long-TS STD. These findings are incongruent with the MDM[29]. My mathematical DNMFM must be further investigated and/or extended (as described before in discussion) to completely capture GROs as occurring spontaneously in the bursting activity of the network. Eventually, this can be used to study the effect of optogenetics on GROs by altering U and u_e. This is important to understand and predict the GGR which seems to be a fundamental and elementary process in the whole-brain operation; and affected in some neuropsychiatric disorders.

ROLE OF THE STUDENT

Meriam Malekzadeh was an undergraduate student working under the supervision of Prof. Dr. Michele Giugliano when the research in this report was performed. The topic was proposed by the supervisor. Furthermore, the investigation of the model and the processing of the results as well as formulation of the conclusions and the writing were done by the student.

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