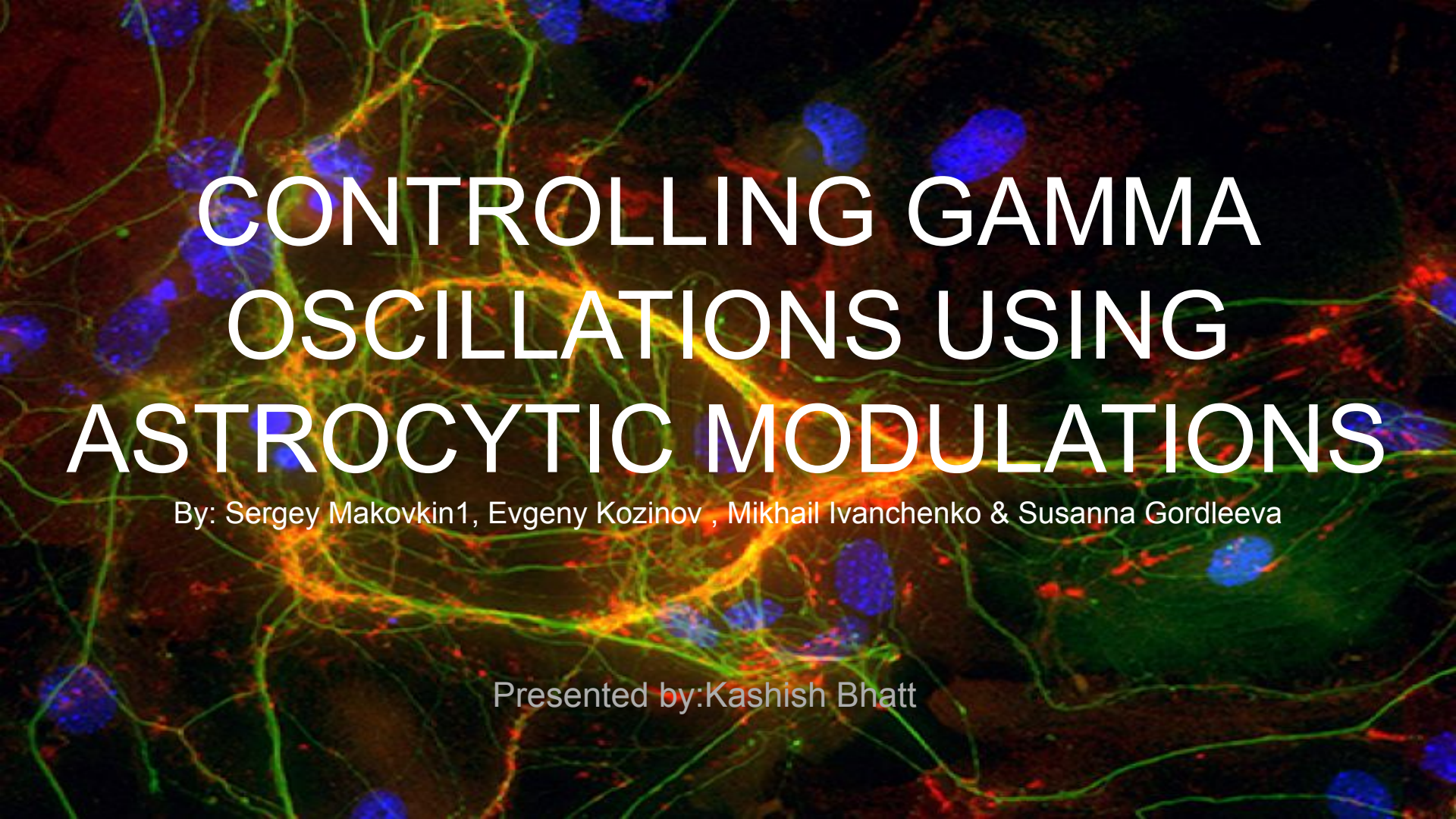


CONTROLLING GAMMA OSCILLATIONS USING ASTROCYTIC MODULATIONS

By: Sergey Makovkin1, Evgeny Kozinov , Mikhail Ivanchenko & Susanna Gordleeva

Presented by:Kashish Bhatt

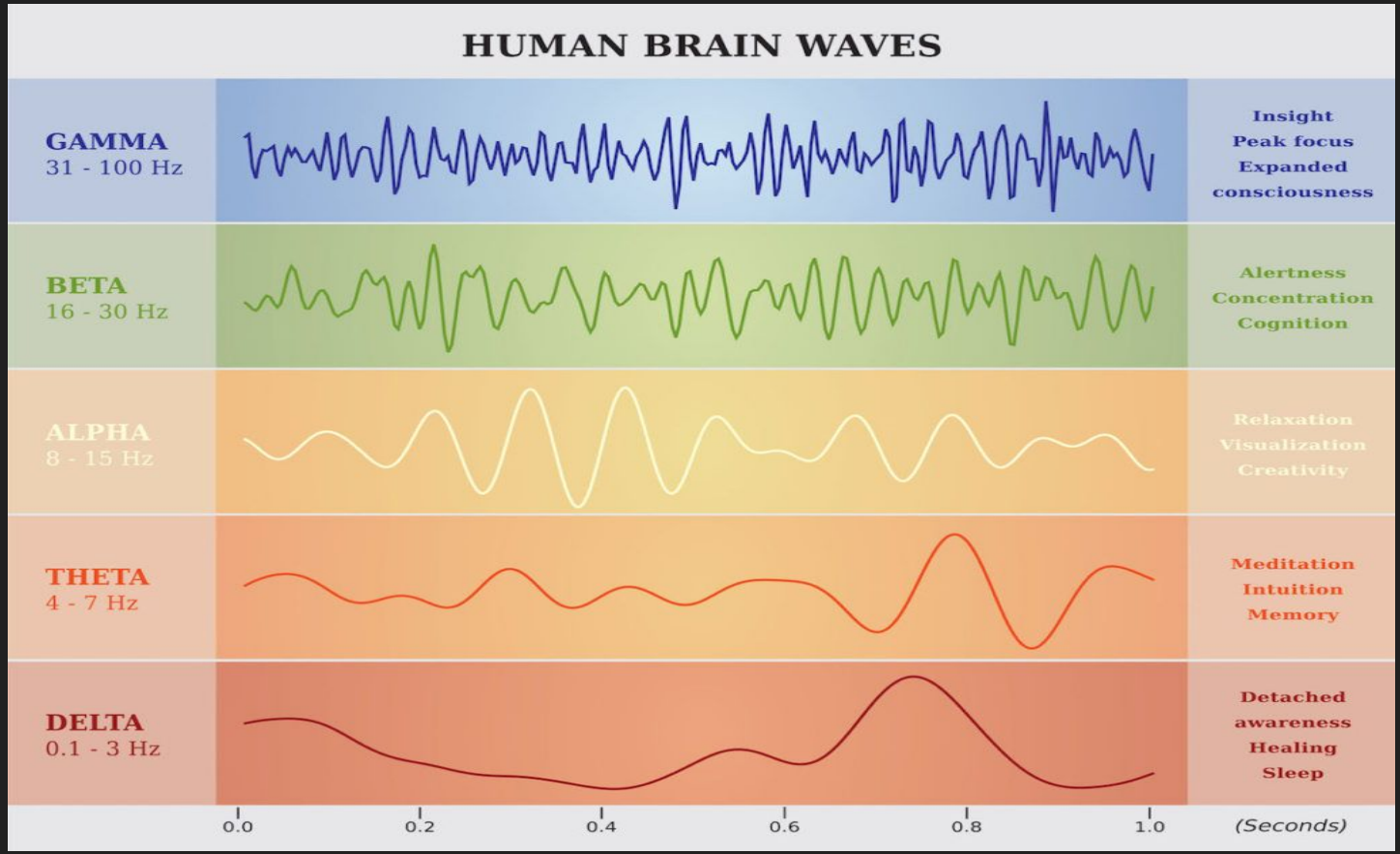


Figure 1: Shows the different types of brainwaves and their functions.[13]

Introduction

- Gamma (γ) Cortical Oscillations:
  - γ 20–80 Hz
  - Sensory Processing, learning, memory and storage[1]
  - Alzheimer's disease, Parkinson's disease, and schizophrenia
  - generation of γ network oscillations:
    - Theoretical and Experimental studies:
      - Rhythmic activity of the intergenic GABAergic interneurons [3]
    - Previous experimental Findings:
      - fast-spiking basket cells (BCs), can generate γ activity in vitro and in vivo [4]

Introduction

- Major Issues In Previous studies:
  - synchronized gamma activity only produced when the heterogeneity of the input drive is low and the amplitude is high [5]
  - Heterogeneity can be reduced by implementing realistic synaptic properties in the model [6]

- Specific Aim:
  - Astrocytic regulation of signal transmission between neurons improves the fring synchrony and extends the region of coherent oscillations in the biologically relevant values of synaptic conductance.

Astrocytes

- Type of Glial Cells
- Previously shown that Astrocytic vesicular release is necessary to maintain functional gamma oscillations [7]
- Integrate Neuronal Activity by responding with intracellular calcium elivations[9]

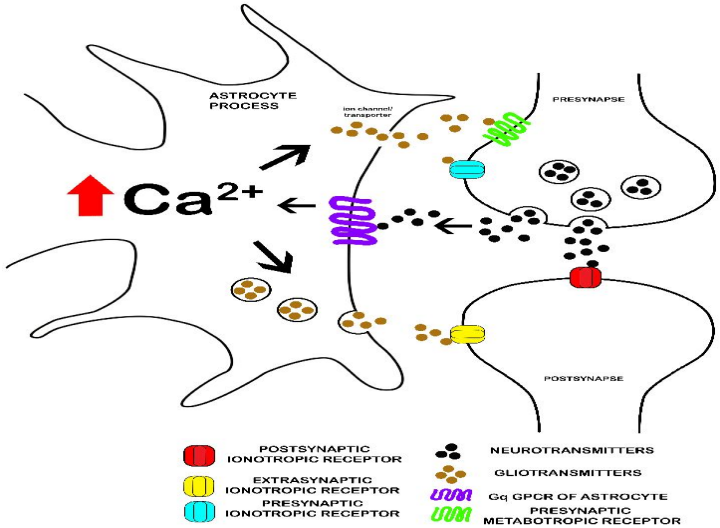


Figure 1: shows the mechanisms of how neurotransmitters work and how astrocytes modulate the process, [11]

Model

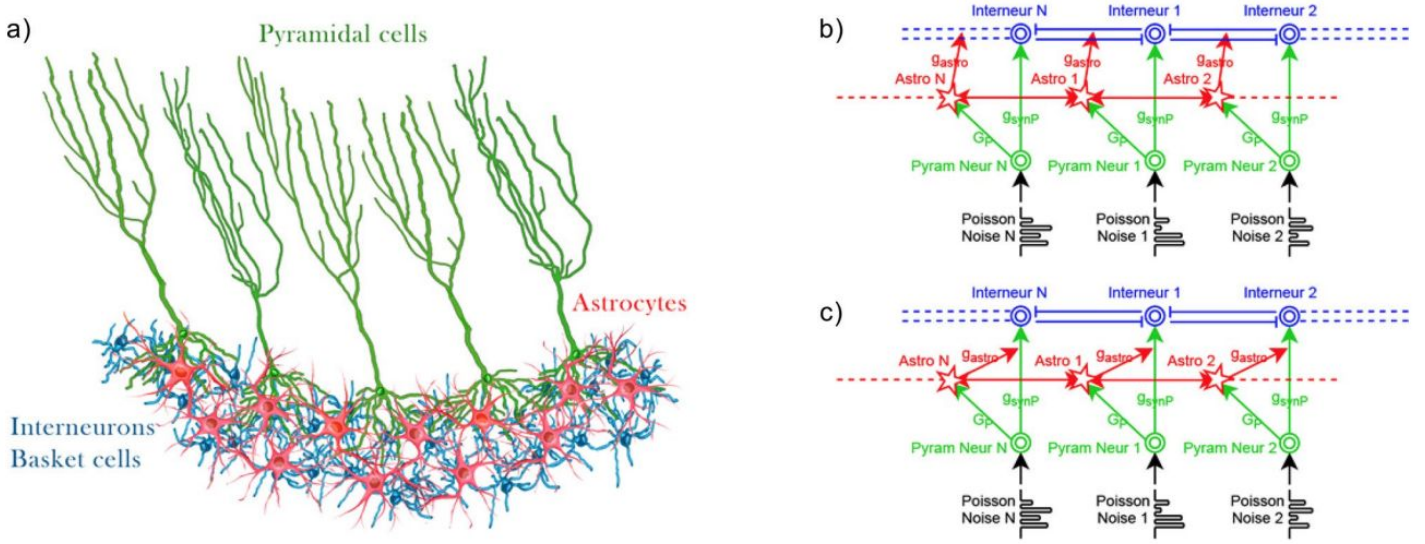


Figure 1a: Depicts the organization of modeled BCs-pyramidal cells-astrocytes network in hippocampal area CA1
Figure 1b and 1c: Architecture of the neuron-astrocyte network model.
(b) inhibitory synaptic transmission in the interneuron network
(c) excitatory synaptic transmission from pyramidal neurons to interneurons.

Methods

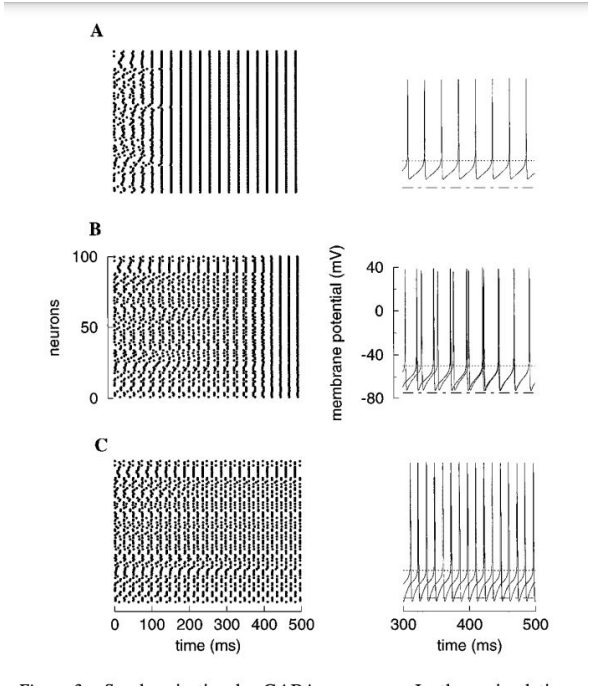
- Used a previous model of interneuron network model of 200 neurons arranged on a virtual ring[10]
- Each interneuron was randomly connected to 100 nearest neighbors by inhibitory chemical synapses with probability of 0.5
- Each astrocyte is connected to the two nearest neighboring astrocytes through gap junctions
- Focus of this paper:
  - 2 types of modulations:
    - astrocyte-induced modulation of inhibitory synaptic transmission in an interneuron network
    - excitatory synaptic transmission from pyramidal neurons to interneurons

Paper Comparison

- Followed the basic Hodgkin-Huxley Model

$$C_m \frac{dV}{dt} = -I_{\mathrm{Na}} - I_{\mathrm{K}} - I_{\mathrm{L}} - I_{\mathrm{syn}} + I_{\mathrm{app}}, \qquad (2.1)$$

- Focus on the results was to create oscillating neurons, by changing the $GABA_A$ synaptic maximal conductance, synaptic decay time constant, or the mean external excitatory drive to the network,



Mathematical Steps Involved

- Hodgkin and Huxley Equation:

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_{\mathrm{K}} n^4 (V_m - V_K) + \bar{g}_{\mathrm{Na}} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l),$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

Modifications Made

- Hodgkin and Huxley Equation with Mainen modification:

$$\begin{cases} \dfrac{dV_i}{dt} = \dfrac{1}{C}\left(I_{channel\,i} + I_{app} + I_{P\,i} + I_{syn_i}\right), \\ \dfrac{dx_i}{dt} = \alpha_x(1 - x_i) - \beta_x x_i,\ x = m, n, h; \\ I_{channel\,i} = g_{Na} m_i^3 h_i (E_{Na} - V_i) + g_K n_i (E_K - V_i) + g_{Leak}(E_{Leak} - V_i), \end{cases}$$

  - Non-linear functions with gated variables:

$$\alpha_m = \frac{0.182(V_i + 35)}{1 - e^{\frac{-(V_i+35)}{9}}}; \quad \beta_m = \frac{-0.124(V_i + 35)}{1 - e^{\frac{(V_i+35)}{9}}};$$

$$\alpha_n = \frac{0.02(V_i - 25)}{1 - e^{\frac{-(V_i-25)}{9}}}; \quad \beta_n = \frac{-0.002(V_i - 25)}{1 - e^{\frac{(V_i-25)}{9}}};$$

$$\alpha_h = 0.25 e^{\frac{-(V_i+90)}{12}}; \quad \beta_h = 0.25 \frac{e^{\frac{V_i+62}{6}}}{e^{\frac{V_i+90}{12}}}.$$

$$I_{syn_i} = \sum_{j}^{N} \frac{\tilde{g}_{syn}(V_i - E_{syn_j})}{1 + e^{\frac{-V_j}{k_{syn}}}};$$

$$\tilde{g}_{syn} = \begin{cases} g_{syn}(1 + g_{astro}[Ca^{2+}]_i), & \text{if } [Ca^{2+}]_i \geq 0.3\ \mu\text{M}, \\ g_{syn}, & \text{otherwise} \end{cases}$$

Figure 1: This is the formula used to calculate the total synaptic current received by neuron i from N presynaptic neurons

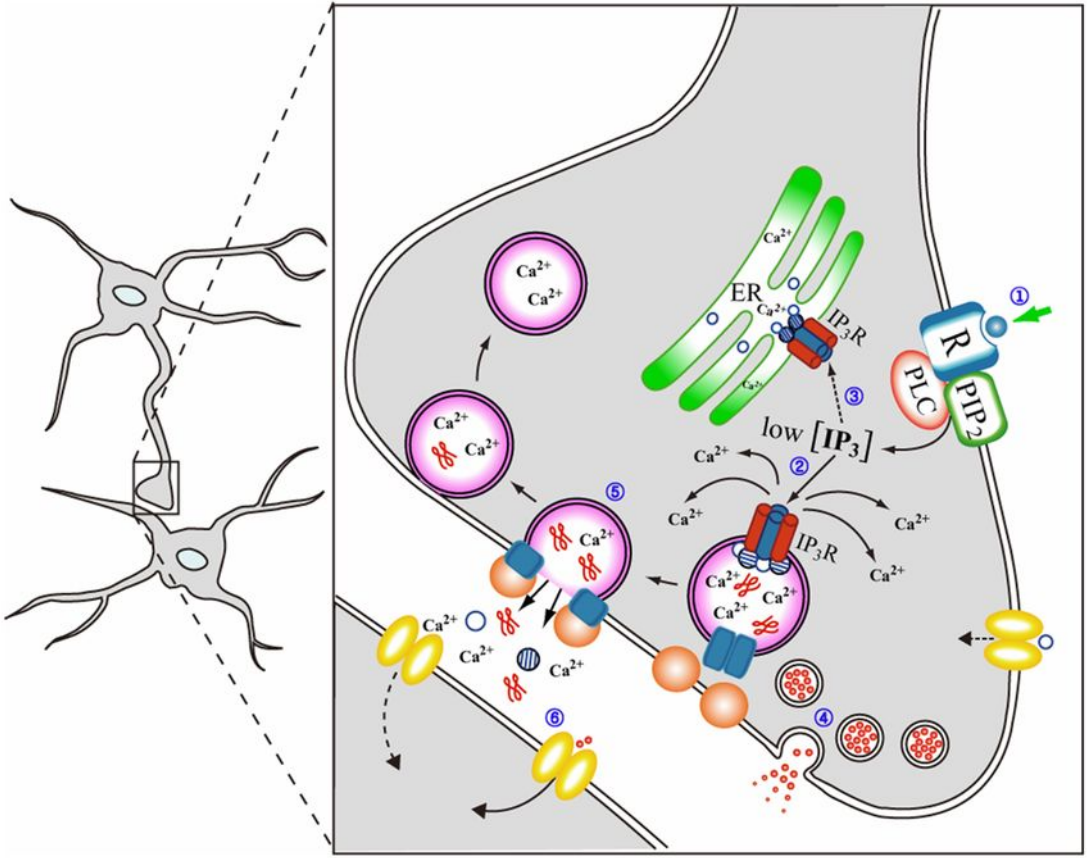
Astrocytic Network

- Each astrocyte tracks the activity of pyramidal neurons,
- Generates the elevation of the intracellular concentration of IP3 then Calcium pulse in response to changes in neurotransmitter (glutamate) concentration in the synaptic cleft
- When the pyramidal cell i generates an action potential it causes the release of glutamate from the synapse

Glutamate Concentration Equation

$$\frac{dG_i}{dt} = -\alpha_G G_i + \beta_G \frac{1}{1 + e^{(-\frac{V_i}{0.5})}},$$

Where α_G = 25 s−1 and β_G = 500 s−1 denote the relaxation and production rates of glutamate.


Ca2+
Ca2+
ER
IP3R
R
PLC
PIP2
low [IP3]
①
②
③
④
⑤
⑥

Intracellular concentration of IP3 Dynamics

- Glutamate binds to the metabotropic glutamate receptors on the astrocytic membrane and activates IP3 signaling in the astrocyte

$$\frac{dIP3_i}{dt} = \frac{IP3^* - IP3_i}{\tau_{IP3}} + J_{PLCi} + J_{IP3diff_i} + J_{Glui},$$

$$J_{PLCi} = v_4\left([Ca^{2+}]_i + (1-\alpha)k_4\right)/([Ca^{2+}]_i + k_4),$$

$$J_{IP3diff_i} = d_{IP3}(IP3_{i-1} + IP3_{i+1} - 2IP3_i);$$

$$J_{Glui} = \frac{\alpha_{Glu}}{1 + e^{\frac{-(G_i - 0.25)}{0.01}}}.$$

$$\begin{cases} \dfrac{d[Ca^{2+}]_i}{dt} = J_{ERi} - J_{pump_i} + J_{leaki} + J_{ini} - J_{outi} + J_{Cadiff_i}, \\ \dfrac{dz_i}{dt} = a_2 \left(d_2 \dfrac{IP3_i + d_1}{IP3_i + d_3}(1 - z_i) - [Ca^{2+}]_i z_i \right), \end{cases}$$

$$J_{ERi} = c_1 \nu_1 IP3_i^3 [Ca^{2+}]_i^3 z_i^3 \left(\frac{c_0}{c_1} - (1 + \frac{1}{c_1})[Ca^{2+}]_i \right) / \left[(IP3_i + d_1)([Ca^{2+}]_i + d_5) \right]^3;$$

$$J_{pump_i} = \nu_3 [Ca^{2+}]_i^2 / (k_3^2 + [Ca^{2+}]_i^2);$$

$$J_{leaki} = c_1 \nu_2 \left(\frac{c_0}{c_1} - (1 + \frac{1}{c_1})[Ca^{2+}]_i \right);$$

$$J_{ini} = \nu_5 + \nu_6 IP3_i^2 / (k_2^2 + IP3_i^2);$$

$$J_{outi} = k_1 [Ca^{2+}]_i;$$

$$J_{Cadiff_i} = d_{Ca}([Ca^{2+}]_{i-1} + [Ca^{2+}]_{i+1} - 2[Ca^{2+}]_i).$$

Results- Influence of Astrocytic Modulation of the inhibitory Gamma oscillations in the interneuron network

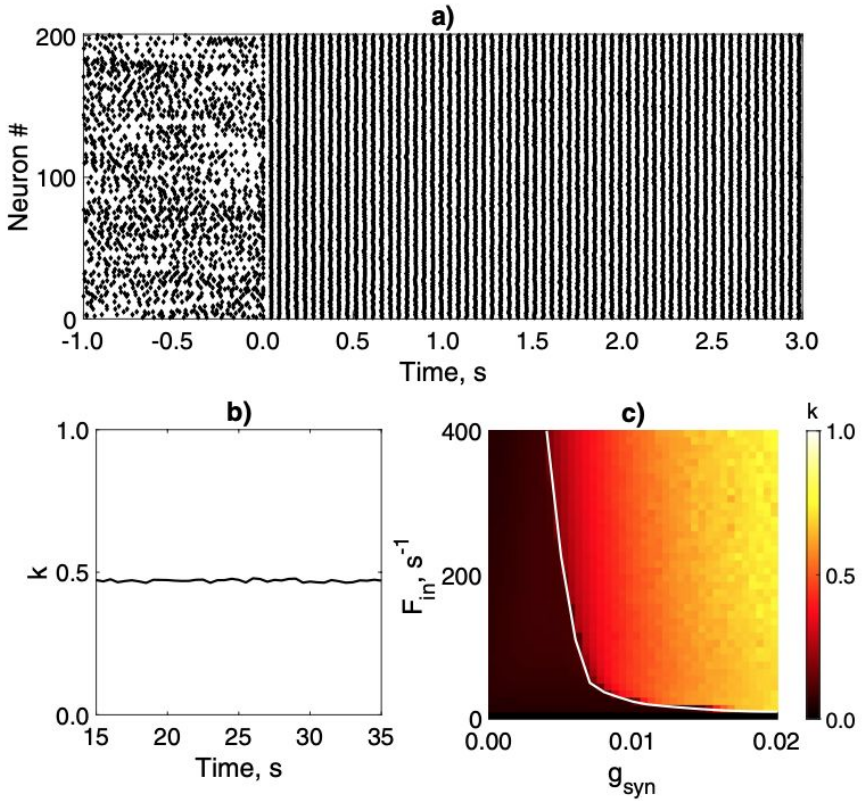


Figure 2. γ oscillations in the interneuron network model. (**a**) Raster plots of the interneuron network activity with default parameter settings. Synapses were activated at 0 s ($g_{syn} = 0.01$ mS/cm^2, $F_{in} = 260$ s^{-1}). (**b**) Coherence (k) is determined in 500-ms windows for the network oscillations shown on (**a**). (**c**) Mean network coherence (k) is plotted against the frequency of excitatory inputs (F_{in}) and the synaptic weight between interneurons (g_{syn}). The white line corresponds to the border of the synchronization region with $k = 0.4$. Each pixel represents an average of over 10 simulations.

curve (g_{syn}, F_{in}) determines the occurrence of synchronization shifts to lower values of g_{syn} for the entire range of $F_{in} > F_{in\ min}$ (Fig. 4b,d).

Results

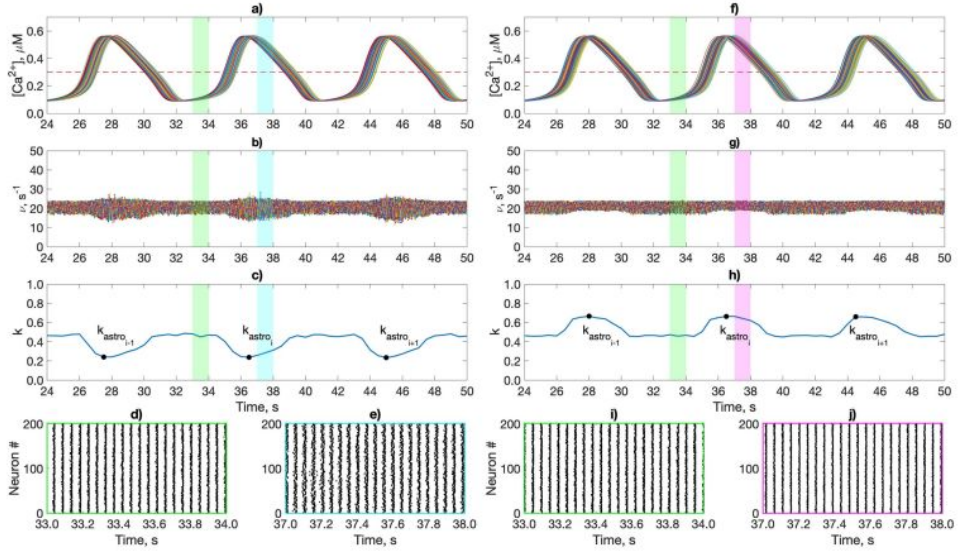


Figure 3. The astrocytic calcium dynamics induced by the activity of pyramidal neurons and its influence on γ oscillations in the interneuron network through astrocyte-mediated modulation of the inhibitory synaptic weights. (**a**,**f**) The intracellular Ca^{2+} concentration in the astrocytic network. (**b**,**g**) Instantaneous firing rates of interneurons. (**c**,**h**) Coherence network (k) dynamics. (**d**,**e**,**i**,**j**) Raster plots of an interneuron network activity. The dotted lines show the threshold Ca^{2+} concentration for the astrocytic modulation of the synapse $[Ca^{2+}]$ = 0.3 μM. Color coding of the 1 second long fragments of network activity: green—without astrocytic influence; blue—astrocyte-mediated depression of the inhibitory synapses ($g_{astro} = -0.8$); magenta—astrocyte-mediated facilitation of the inhibitory synapses ($g_{astro} = 1.2$). An example of used minimum/maximum values of the interneurons coherence during the Ca^{2+} elevations in astrocytes marked with dots k_{astro}. $F_{in} = 260\ s^{-1}$; $g_{syn} = 0.009$ mS/cm^2; $g_{syn_P} = 0.7$ mS/cm^2.

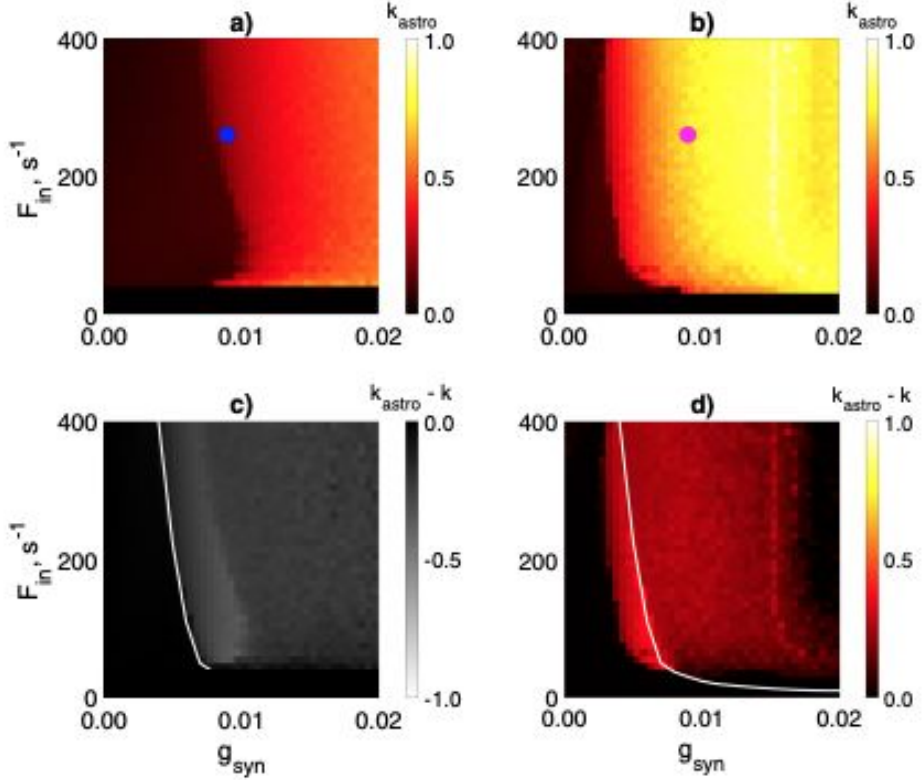


Figure 4. Influence of the astrocyte-induced modulation of the inhibitory synaptic transmission on the interneuron network coherence. Mean network coherence (k_{astro}) during astrocytic regulation of synaptic transmission is plotted against the frequency of excitatory inputs (F_{in}) and the synaptic weight between interneurons (g_{syn}) for astrocyte-mediated depression, $g_{astro} = -0.8$, (**a**) and facilitation, $g_{astro} = 1.2$, (**b**) of the inhibitory synapses. Filled circles indicate the parameter settings used in the simulations shown in Fig. 3. (**c**) Difference between (**a**) and Fig. 2c. (**d**) Difference between (**b**) and Fig. 2c. The white line corresponds to the border of the coherence region in the interneuron network without astrocyte (Fig. 2c). Each pixel represents an average of over 10 simulations. $g_{synp} = 0.7$ mS/cm^2.

Results- Influence of Astrocytic Modulation of the Synaptic Transmission on Gamma Rhythm Frequency in Interneuron

Results

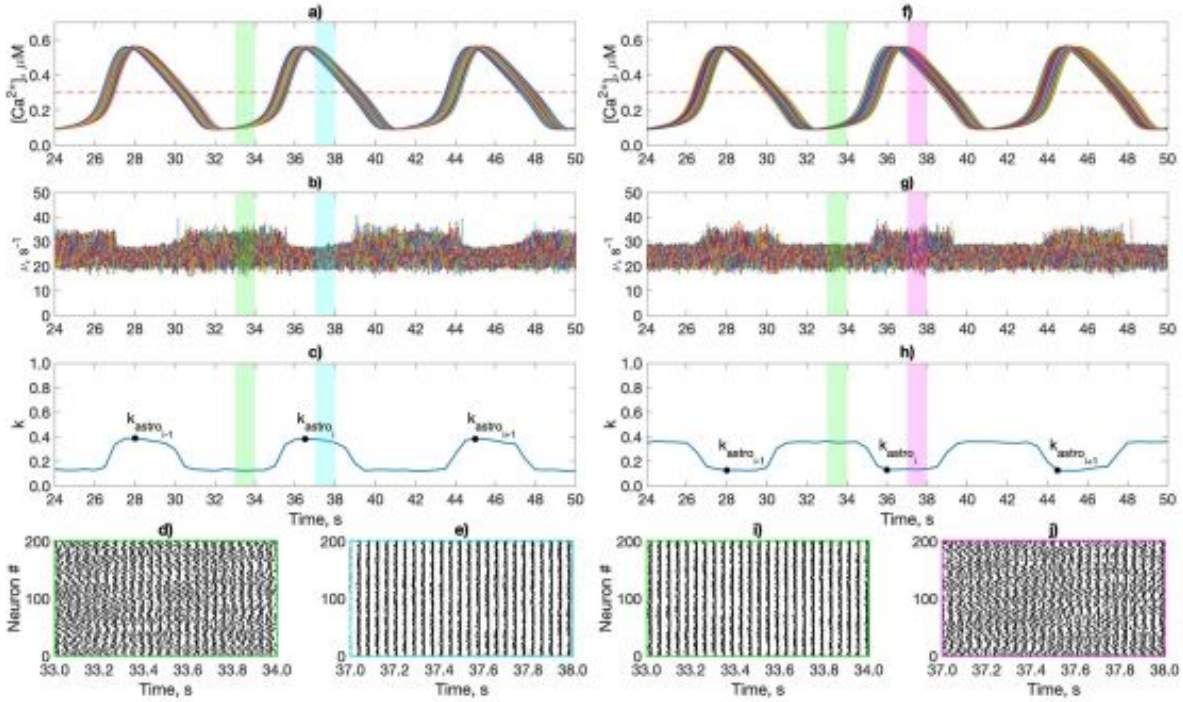
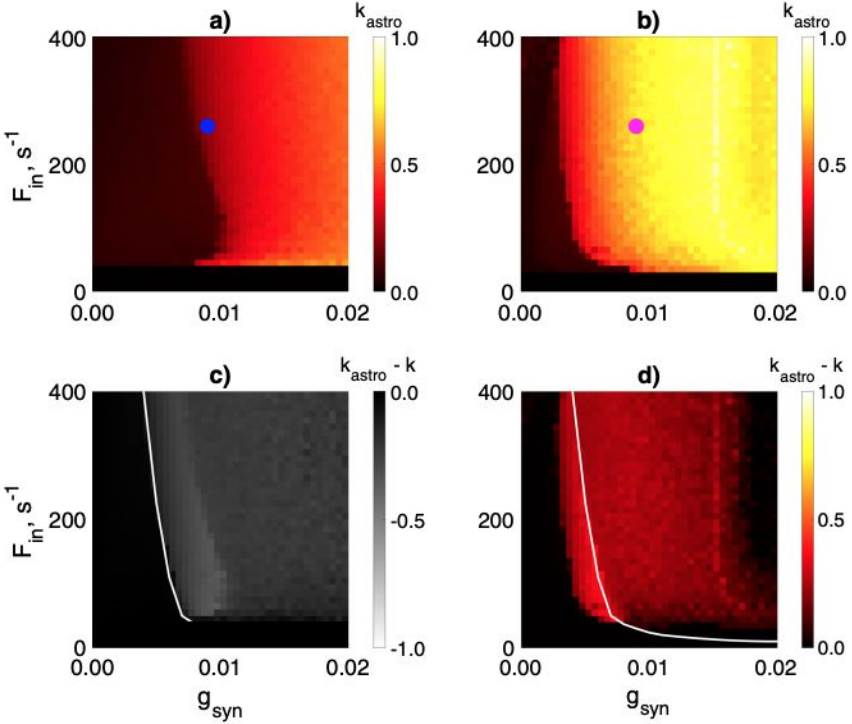


Figure 6. Dynamics of the astrocytic influence on γ oscillations in the interneuron network through regulation of the excitatory synaptic drive. (**a**,**f**) The intracellular Ca^{2+} concentration in the astrocytic network. (**b**,**g**) Instantaneous firing rates of interneurons. (**c**,**h**) Coherence network (k) dynamics. (**d**,**e**,**i**,**j**) Raster plots of an interneuron network activity. The dotted lines show the threshold Ca^{2+} concentration for the astrocytic modulation of the synapse $[Ca^{2+}] = 0.3$ μM. Color coding of the 1 second long fragments of network activity: green—without astrocytic influence; blue—astrocyte-mediated depression of the excitatory synaptic transmission ($g_{astro} = -0.4$; $g_{syn_E} = 1.2$ mS/cm^2); magenta—astrocyte-mediated facilitation of the excitatory synaptic transmission ($g_{astro} = 0.4$; $g_{syn_E} = 0.8$ mS/cm^2). Minimum/maximum values of the interneurons coherence during the Ca^{2+} elevations in astrocytes are marked with dots k_{astro}. $F_{in} = 260$ s^{-1}; $g_{syn} = 0.01$ mS/cm^2.

Results



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Comparisons:

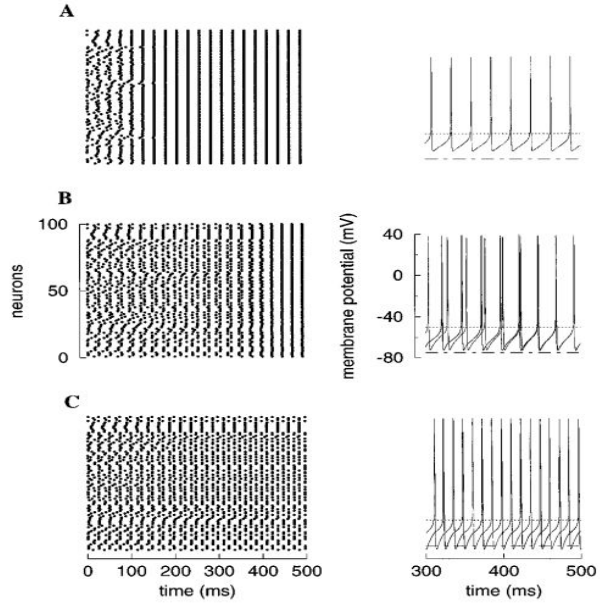


Figure 3. Synchronization by $GABA_A$ synapses. In these simulations, neurons are identical and coupled in an all-to-all fashion. *Left panels*, Rastergrams; *right panels*, membrane potentials of two cells (*dotted line*, −52 mV). The synchrony is realized when the spike AHP of the cells does not fall below the synaptic reversal potential $E_{syn} = -75$ mV (*dot-dashed* line on the *right panels*). From *A* to *C*, $\phi = 5$, 3.33, and 2 respectively; $I_{app} = 1$, 1.2, and 1.4 $\mu A/cm^2$ accordingly to preserve a similar oscillation frequency. With smaller ϕ values, I_K is slower and the AHP amplitude (V_{AHP}) is more negative. When $V_{AHP} < E_{syn}$, the full synchrony is lost (*C*).

Figure 1: Depicts the results from the Wang XJ, Buzsáki G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. This was the inspiration for my interest in my topic. According to the previous research the neurons were synchronized by $GABA_A$ synapses. This Model, as opposed to the model we used in our presentation only took into account the basic hodgkin and Huxley model with modifications made in the model by adding a Synaptic current, which represented the $GABA_A$ synapse. Here we can see the synchronization of the neurons. If we compare our raster models, the synchronicity here reaches easily but loses it when E_{syn} is greater than V_{AHP}. [1]

1.) Wang XJ, Buzsáki G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. J Neurosci. 1996 Oct 15;16(20):6402-13. doi: 10.1523/JNEUROSCI.16-20-06402.1996. PMID: 8815919; PMCID: PMC6578902.

Comparisons: Network Coherence (K)

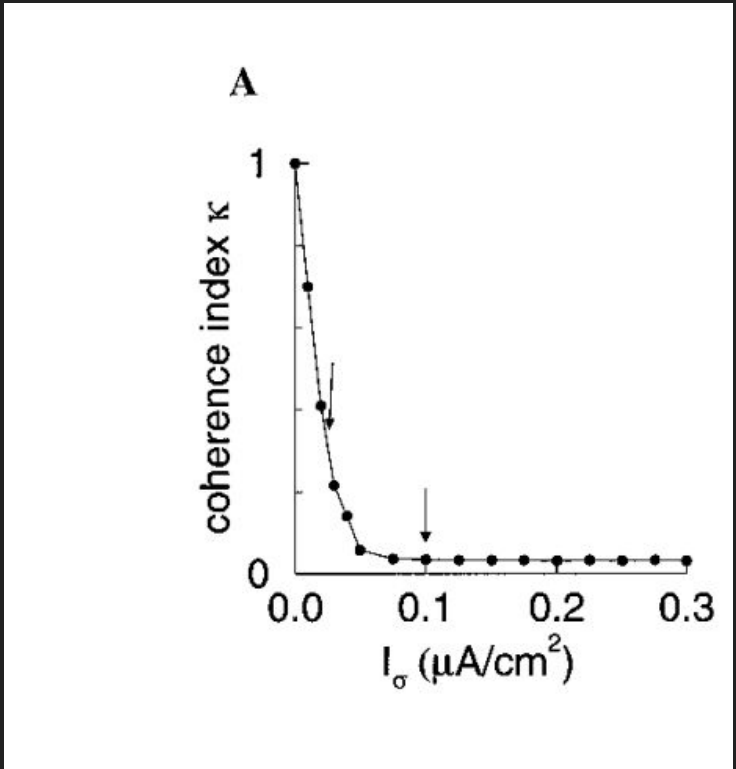
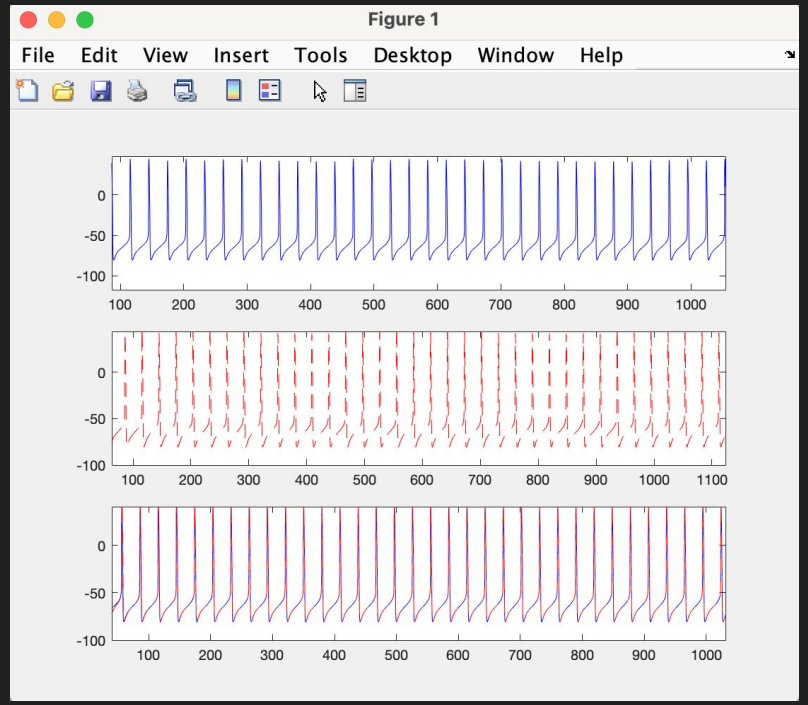


Figure 2: Like the the model in our research presentation the network coherence is very similar to the K_{astro} , where the coherence shows synchronicity at > 0.5 Current in the stated research paper and frequency in the research paper presented. In the research paper presented the coherence happens in both Astrocytic Modulation of the inhibitory Gamma oscillations in the interneuron network and Astrocytic Modulation of the excitatory Gamma oscillations in the interneuron network.[2]

2.) Wang XJ, Buzsáki G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. J Neurosci. 1996 Oct 15;16(20):6402-13. doi: 10.1523/JNEUROSCI.16-20-06402.1996. PMID: 8815919; PMCID: PMC6578902.

My Attempt At Modeling



Here my attempt was to see if I can create a synchronized neuron spiking using the paper by Wang XJ, Buzsáki G. and Gamma. I used their model, because it did not add the biophysical aspect. I used the basic Hodgkin and huxley model but added the parameters used in the research paper. The goal was to mimic the model in figure 1C (2 slides back). As seen here the model works well, and synchronization is achieved between the two neurons using those parameters.

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