Dynamical modeling of the biphasic GABA actions

Kenji Morita[†], Kunichika Tsumoto[‡], and Kazuyuki Aihara[‡*]

†Department of Complexity Science and Engineering, Graduate School of Frontier Sciences, The University of Tokyo
5-1-5 Kashiwanoha, Kashiwa, Chiba 277-8561, Japan
‡ ERATO Aihara Complexity Modelling Project, JST
Maeda Building, 45-18 Oyama, Shibuya-ku, Tokyo 151-0065, Japan
* Institute of Industrial Science, The University of Tokyo
4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan
Email: morita@sat.t.u-tokyo.ac.jp, tsumoto@aihara.jst.go.jp, aihara@sat.t.u-tokyo.ac.jp

Abstract– Recent electrophysiological experiments have revealed that GABA, originally known as inhibitory neurotransmitter in the mammalian central nervous system, could actually have biphasic actions depending on the timing of its application relative to other excitatory synaptic inputs. We explore the dynamical foundations of these GABA actions using a conductance-based neuron model. Based on a bifurcation analysis on this neuron model receiving two kinds of periodic input trains, excitatory ones and GABAergic ones, we propose a novel putative mechanism of neural coding transformation such that the phase difference between these two periodic inputs is transformed into a graded response of the output neuron's firing rate.

1. Introduction

GABA (γ - aminobutyric acid) is one of the principal neurotransmitters in the mammalian brain. GABA released from a pre-synaptic neuronal terminal binds to the receptors on a membrane of a post-synaptic neuron. Among two types of GABA receptors, the GABA$_A$ receptor acts as an ion channel by itself: chloride ion can pass through it if and only if GABA is binding to it. When the GABA$_A$ receptor-channel is open, chloride-ionic flow through it makes the membrane potential close to its *reversal potential* (Nernst's equilibrium potential). In the mature mammalian's cerebral cortex, this reversal potential has long been thought to be nearly equal to the neuron's resting potential that is considerably lower than the threshold of the action potential generation, and thus GABA has been considered to have only an inhibitory action because it always prevents an elevation of the membrane potential. However, recent elaborative experiments, which took the disturbance of anion's concentration by recording electrodes into account for the first time, have revealed that GABA$_A$ reversal potential is actually higher than what has so far been thought to be: it is about 10 mV higher than the resting potential though it is still lower than the firing threshold [1]. As a consequence, GABA could have an excitatory action such that it facilitates the action potential generation in cooperation with other excitatory synaptic inputs according to circumstances [1]. We examine the conditions for GABA to have an excitatory or inhibitory action using a conductance-based neuron model through a bifurcation analysis. We explore the extended case in which the neuron receives periodic excitatory glutamatergic and input trains and GABAergic ones, showing that the phase difference between these two periodic inputs is coded into a graded response of the output neuron's firing rate. We discuss the possibility that such a mechanism is used for a kind of coding transformation in the brain.

2. Model

We use the conductance-based model of neocortical regular spiking neurons proposed by Wilson [3]:

$$\frac{dV}{dt} = -g_{Na}(V)(V - E_{Na}) - cR(V - E_K) + I_{syn}$$

$$\frac{dR}{dt} = \frac{1}{\tau}(-R + f(V))$$

(1)

V : the membrane potential, R : the inactivation variable, c : a certain constant, E_{Na} and E_K : the reversal potentials of sodium and potassium channels associated to action potential generation, $g_{Na}(V)$ and $f(V)$: the voltage dependence of the sodium channel conductance or the inactivation variable, τ : the time constant of the inactivation variable. The exact values of the parameters and the shapes of $g_{Na}(V)$ and $f(V)$ were determined by Wilson: $g_{Na}(V) = 17.81 + 47.58V + 33.8V^2$; $f(V) = 1.29V + 0.79 + 3.3(V + 0.38)^2$; $E_{Na} = 48$ (mV); $E_K = -95$ (mV); $\tau = 5.6$ (ms); $c = 26$. I_{syn} represents the inward current through synaptic channels:

$$I_{syn} = -g_{Glu}(t)(V - E_{Glu}) - g_{GABA}(t)(V - E_{GABA})$$

(2)

E_{Glu} and E_{GABA} : the reversal potentials of the channels coupled with the glutamate (non-NMDA type) and GABA$_A$ receptors at the synapses. We set $E_{Glu} = 0$ (mV) as usual, but set $E_{GABA} = -64$ (mV) that is about 11 mV higher than the resting potential of this model according to the recent experimental results [3]. $g_{Glu}(t)$ and $g_{GABA}(t)$ represent the time dependent conductance of these channels, and described by alpha-functions:

$$g_{Glu}(t) = \hat{g}_{Glu} \frac{t}{\tau_{Glu}} e^{1 - \frac{t}{\tau_{Glu}}} , \quad g_{GABA}(t) = \hat{g}_{GABA} \frac{t}{\tau_{GABA}} e^{1 - \frac{t}{\tau_{GABA}}}$$

Here $\hat{g}_{Glu}$ and $\hat{g}_{GABA}$ represent the maximum conductances of the channels, and τ_{Glu} and τ_{GABA} represent the times of these maximum conductances.

3. Results

3.1. Transient inputs

In this section, we show that Wilson's neuron model with alpha-function inputs reproduces the experimentally observed excitatory and inhibitory actions of GABA, and examine the conditions under which GABA has each of those actions.

3.1.1. Numerical simulation

At first, we consider the case in which the neuron receives isolated excitatory (glutamatergic) input and GABAergic input. Specifically, we consider either a single subthreshold ($\hat{g}_{Glu}=1.7$) or a suprathreshold ($\hat{g}_{Glu}=1.8$) glutamatergic input, and examine the effects of a single GABAergic input on the action potential generation. If a GABAergic input evokes an action potential in cooperation with a subthreshold glutamatergic input, it is said to have an excitatory action. On the other hand, if a GABAergic input inhibits spike generation by a suprathreshold glutamatergic input, it is said to have an inhibitory action. We examine under what conditions GABAergic inputs have excitatory or inhibitory actions. For example, a GABAergic input that is of the same strength as a subthreshold glutamatergic one and precedes it by 8 ms evokes an action potential (Fig. 1a), whereas another GABAergic input that is coincident with a suprathreshold glutamatergic one prevents spike generation (Fig. 1b). As summarized in Fig. 1c, GABAergic inputs that preceed a glutamatergic input by more than 2.5 ms have the excitatory actions (gray in Fig. 1c) while those arrive within ±2 ms of a glutamatergic input have the inhibitory actions (black in Fig. 1c).

(a) **(b)** **(c)**

△ Glutamergic input:
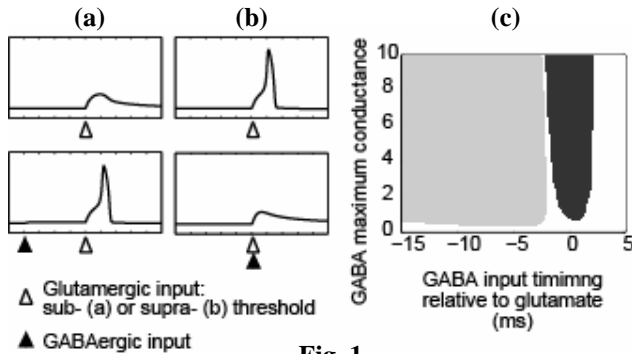sub- (a) or supra- (b) threshold
▲ GABAergic input

Fig. 1

3.1.2. Bifurcation analysis

Next, we examine the dynamics of the interaction between a glutamatergic input and a GABAergic one by a bifurcation analysis [2][4]. However, since it is generally difficult to compute the bifurcation sets for a dynamical system with such a transient (non-periodic) driving force, we assume that the neuron receives periodic inputs, whose period is substantially long compared to the membrane time constants so that each cycle can be regarded as practically independent. Specifically, we assume that $g_{Glu}(t)$ and $g_{GABA}(t)$ in Eq. 2 are periodic alpha-function trains with the period $T=100$ (ms), which we refer as the "quasi-transient" inputs.

For the subthreshold or the suprathreshold glutamatergic inputs, we perform the bifurcation analysis on the parameter plane consisting of the time difference of glutamatergic and GABAergic inputs (Δ ms) and the magnitude of GABAergic conductance ($\hat{g}_{GABA}$). As shown in Fig. 2, in both cases there exist mainly two types of solutions. One of them is a stable limit cycle (shaded in Fig. 2a and 2b) that corresponds to an action potential of the neuron, and the other one is a stable fixed point (white in Fig. 2a and 2b) that means the neuron does not evoke an action potential. The region of a stable limit cycle in the subthreshold glutamatergic case (shaded in Fig. 2a) well matches the "excitatory action" region of Fig. 1c (gray), while the region of a stable fixed point in the suprathreshold glutamatergic case (white in Fig. 2b) resembles the "inhibitory action" region of Fig. 1c (black). Therefore, the borderline of the excitatory or inhibitory actions of GABA can be characterized as the bifurcation curves at the edges of the stable solutions corresponding to the firing or the non-firing responses.
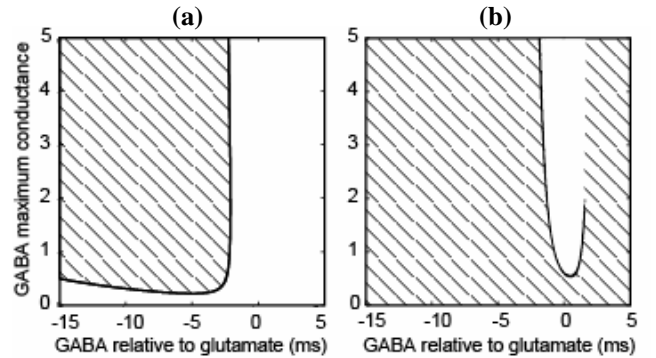

Fig. 2

As for these results, please note that the boundary between the region of a stable limit cycle and that of a stable fixed point is actually not a single bifurcation curve. That is to say, as the parameters change continuously, a stable limit cycle corresponding to an action potential does not bifurcate to be a stable fixed point at a single point on the parameter plane. Rather, it is suggested by numerical calculations of the bifurcation set that there exist a lot of extra bifurcation curves in the extremely narrow vacancy between the limit cycle region and the fixed point region, although they cannot be drawn in Fig. 2. These bifurcation curves are literally extra in the current context dealing with the quasi-transient inputs, since they are considered to be generated due to the substitutive usage of long-period periodic (quasi-transient)

inputs in stead of genuine transient inputs for the purpose of the bifurcation analysis. However, this observation suggests that various types of solutions, and thus a wide variety of responses, might exist if the neuron actually receives periodic glutamatergic and GABAergic inputs with not a so long period. Indeed, this conjecture will be successfully confirmed in the followings.

3.2. Periodic inputs

In this section, we explore the effects of the interaction of periodic glutamatergic and GABAergic synaptic inputs on the postsynaptic neuron's firing properties, especially the firing rate. Physiologically, these periodic inputs would come from synchronized oscillatory activities of presynaptic neural populations.

3.2.1. Only excitatory inputs

At first, we examine the neural responses to periodic glutamatergic inputs in the absence of GABAergic ones. Assume that $g_{Glu}(t)$ in Eq. 2 is a periodic alpha-function train with the period $T = 25$ (ms) (*i.e.* the frequency is 40 (Hz)), which is in the range of gamma oscillation. We analyze bifurcations with respect to $\hat{g}_{Glu}$ (maximum conductance) and τ_{Glu} (peak time). As shown in Fig. 3a, there exist two predominant regions occupying large portions of the parameter plane, and between them, a lot of curving stripe-like regions separated each other by a series of bifurcation curves. The upper-right region corresponds to "1:1" response in which the neuron evokes a single spike per one cycle of the periodic inputs, whereas the bottom-left region corresponds to "non-firing" response in which the neuron does not evoke spikes at all. The other regions sandwiched by those two regions correspond to various kinds of firing responses. Among them, the region corresponding to "1:2" response, that means one spike generation per two cycles of inputs, appears to be predominant. Fig. 3b shows the relationship between the magnitude of glutamatergic inputs and the output firing rate for $\tau_{Glu} = 1, 2, 3, 4$ (right to left). As the input magnitude increases, the firing rate increases. The longest plateau at the frequency of 20 (Hz), the half of the input frequency, corresponds to the predominant "1:2" response region on the parameter plane.
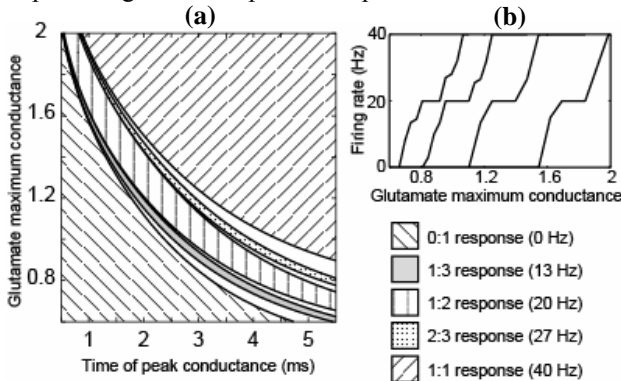

(a)   **(b)**

Glutamate maximum conductance (vertical axis) vs Time of peak conductance (ms) (horizontal axis)

Firing rate (Hz) vs Glutamate maximum conductance

0:1 response (0 Hz)
1:3 response (13 Hz)
1:2 response (20 Hz)
2:3 response (27 Hz)
1:1 response (40 Hz)

Fig. 3

3.2.2. Excitatory and GABAergic inputs

Come to here, we are ready to examine the effects of periodic GABAergic inputs, which have the same frequency as the glutamatergic ones but have a certain phase (time) difference. Specifically, assume that $g_{GABA}(t)$ as well as $g_{Glu}(t)$ in Eq. 2 are periodic alpha-function trains with the same period $T = 25$ (ms) (40 Hz). The phase (time) difference between them is denoted by Δ $(-\frac{T}{2} \leq \Delta < \frac{T}{2})$ (ms) so that $\Delta < 0$ means that the GABAergic inputs precede the glutamatergic inputs, and vice versa. According to the above result for the only gutamergic input case, we choose the value of $\hat{g}_{Glu}$ so that the neuron gives the "1:2" response (20 Hz) to the glutamatergic inputs only: $\hat{g}_{Glu} = 4.0$ for $\tau_{Glu} = 1$. Then we perform the bifurcation analysis with respect to the phase difference (Δ) and the magnitude of the GABAergic inputs ($\hat{g}_{GABA}$) in the cases of $\tau_{Glu} = \tau_{GABA} = 1$.

As shown in Fig. 4a, there exists several predominant regions in the parameter plane. Among them, the most predominant one corresponds to the "1:2" response. The regions corresponding to the "1:1" response and the "0:1" response (*i.e.* no firing) are also predominant. The vacancy between the "1:2" response region and the "1:1" response region is wide, and it is suggested by numerical calculations of the bifurcation sets that there exist a series of bifurcation curves in this vacancy. Only two of them sandwiching the "2:3" response region are drawn in Fig. 4a. Fig. 4c shows the relationship between the input phase (time) difference and the output firing rate for a fixed magnitude of GABAergic inputs ($\hat{g}_{GABA} = 4$). Roughly speaking, the output firing rate takes mainly three different values corresponding to the three predominant regions in the parameter plane: i) when the GABAergic inputs precede the glutamatergic inputs for $4 \sim 8$ ms, the neuron shows "1:1" response and so the firing rate is twice as high as the value without GABA, ii) if the time difference is within ±2 ms, the neuron ceases firing, iii) otherwise the firing rate is not affected by the GABAergic inputs. In this way, the periodic GABAergic inputs, whose reversal potential is higher than the resting potential, can modulate the neuron's firing rate to both directions depending on their phase difference from the glutamatergic inputs.

So far we fixed the peak times of input conductances as $\tau_{Glu} = \tau_{GABA} = 1$. These parameters ($\tau_{Glu}$ and τ_{GABA}) can be considered to represent a degree of temporal precision of presynaptic neural activities. As τ_{Glu} and τ_{GABA} increase, the interaction between glutamatergic inputs and GABAergic ones becomes stronger. As a result, there appear a wider variety of solutions, as shown in Fig. 4b for the case of $\tau_{Glu} = \tau_{GABA} = 4$. In this case, the phase-rate response curve becomes smoother (Fig. 4d), realizing the more informative transformation from the input phase difference into the output firing rate in a certain range.
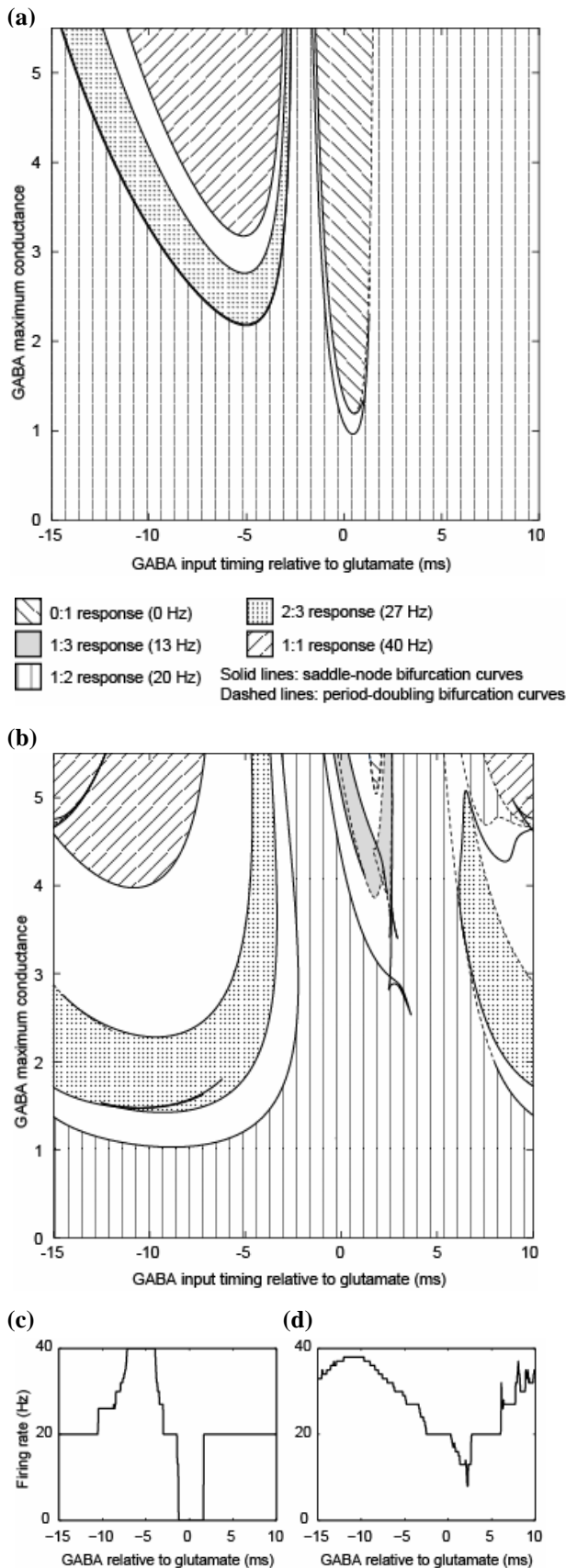
(a)

Legend:
- 0:1 response (0 Hz)
- 1:3 response (13 Hz)
- 1:2 response (20 Hz)
- 2:3 response (27 Hz)
- 1:1 response (40 Hz)
- Solid lines: saddle-node bifurcation curves
- Dashed lines: period-doubling bifurcation curves

(b)

(c)   **(d)**

Fig. 4

4. Discussion

Although how the information is coded in the brain is still elusive, it is widely respected that there are two basic coding schemes, firing-rate coding and temporal-spike coding. The brain seems to use each of them, or sometimes both of them, according to brain regions, types of the information, or other circumstances. Therefore, there must exist some mechanisms that transform the temporal-spike code into the firing-rate code or *vice versa*. As we have shown in the previous sections, when the neuron receives two kinds of periodic inputs, glutamatergic ones and GABAergic ones whose reversal potential is higher than the resting potential, the phase difference between them is encoded into a graded response of the neuron's firing rate. This can be a putative mechanism of the coding transformation from a kind of temporal-spike code (phase difference) into the firing-rate code. Even if the $GABA_A$ reversal potential is equal to the resting potential, as has so far been thought to be, GABAergic inputs do affect the firing rate. But in that case the effect is restrictive: GABAergic inputs with a small phase difference from glutamatergic ones reduce the firing rate, but otherwise GABAergic inputs do not affect the firing rate (results not shown). Therefore, it can be said that depolarized (high) value of $GABA_A$ reversal potential enables an effective transformation from the input phase difference into the output firing rate.

Acknowledgments

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