A Functional Model of the Olivocerebellar System that Produces Rhythmic Activity at Gamma Frequency

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***Abstract*- This article presents a simplistic but biologically plausible functional model of the olivocerebellar neural circuitry to investigate its capability to generate rhythmic activity at gamma frequency (40 Hz). The design of the model has a general organization corresponding to that hypothesized by neurobiologists. The cerebellar circuitry is modeled as a dynamical system using cell prototypes similar to the ones used in artificial neural networks, whereas the olivary cells were represented with simple 'on/off' units. The model works as a unit that converts the irregular and low frequency spikes originating from the olivary cells into regular spikes at 40 Hz at the level of the dentate cells. The success of the model indicates that the olivocerebellar circuitry has the physiological properties to be able to generate such rhythmic activity.**

***Keywords*- Cerebellum;EEG;gamma frequency ;gap junctions;oscillations**

I. INTRODUCTION

Until recently, neuroscientists have all argued that the EEG was a background noise activity to be rejected from the recordings. However, brain scientists have finally recognized the importance of such oscillatory phenomena and functional EEG [1]. According to Basar, the EEG is one of the most important signals of the brain in order to understand brain functionality [1]. It is now known that the EEG contains a few dominant frequencies at around 10 Hz (alpha), 20 Hz (beta), and 40 Hz (gamma).

Although it is not possible to give an exact relationship between single unit activity and gross activity (EEG signal), measurements showed neuronal activities in similar frequency channels as in the EEG; i.e., around 10 Hz, 20 Hz, and 40 Hz. Synchronized rhythms can arise as an emergent property of a network of neurons, which fire in a non-rhythmic manner individually. These rhythmic activities have been measured not only from the cortical layers but also from subcortical structures including the cerebellum [2]. The work in this paper aims to provide insight about the capability of the olivocerebellar circuitry to produce such rhythmic activity at gamma frequency, i.e. at 40 Hz. The gamma activity have been proposed to have a role in feature binding and object segmentation [3].

II. BIOLOGICAL BACKGROUND

The membrane potentials of olivary cells (OCs) intrinsically develop subthreshold sinusoidal oscillations within the 5-10 Hz range [4,5,6,7,8,9]. However, in order to develop such oscillations, a large number of OCs has to be coupled through gap junctions [10,11]. Such coupling is dynamically controlled by GABAergic input, which almost exclusively originates from the inhibitory cerebellar nuclear cells [12,13,14]. The electrotonic coupling serves to generate groups of synchronously active OCs. Moreover, the interaction between the coupled cells, their selective activation, and inhibitory feedback from the cerebellum yield to phase differences between different cell groups [15,16].

The membrane potential oscillations of OCs are mostly at subthreshold levels, and, therefore, in order to be able to fire, these cells need to be depolarized by external stimulation. Such input mostly come from the mesodiencephalic regions of the brain, where the red nucleus is located [12]. These subthreshold sinusoidal oscillations of membrane potentials can produce rhythmic firing by combining with prolonged depolarization in such a way that the wave peaks reach firing threshold [9]. However, individual OCs does not necessarily fire at every peak of the oscillations; most of the time, these cells fire irregularly at some peaks with very low firing frequencies around 1 Hz. But upon receiving strong depolarizing input, the firing rates of individual OCs could increase up to 4 Hz [17].

The axons of the OCs, i.e. climbing fibers, constitute a mechanism whereby the cerebellum is parceled into different anatomical modules. The Purkinje cells (P-cells) in a certain module converge on a specific group of cerebellar nuclear cells and form a different functional unit [18,19,20]. The climbing fiber input always causes a P-cell to produce a complex spike, which has a different effect on the target nuclear cells than that of a simple spike: A nuclear cell normally fires irregularly depending on the strength of the mossy fiber input. However, strong inhibitory input created by a complex spike leads to considerable hyperpolarization of this cell for a period of 20-25 ms. At the return of the membrane potential to the resting level, the cell displays rebound activity, i.e. one or more action potentials. The rebound spikes are in turn transmitted as inhibitory input onto the gap junctions between the OCs and as excitatory input to the rest of the nervous system.

Another effect of the climbing fibers on the functionality of the cerebellum is to suppress the simple spike activity of the P-cells indirectly by strongly exciting the Golgi cells. These cells in turn inhibit the granule cells, the only group of cells that causes P-cells to produce simple spikes [23]. It has been argued that Golgi cell inhibition of a granule cell lasts for a period of 100 *ms* [24]. As a result, the rate of simple spike production by P-cells decreases enormously.

III. DESIGN OF THE MODELS

The olivocerebellar model presented in this work consists of three distinct brain regions: the lateral cerebellum, the principal olive, and the parvocellular red nucleus (PRn). The reason for constructing the model using these specific regions is that they are known to have both anatomical and

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Abstract

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physiological interconnections and the closd loop among them was supposed to play role in cognitive functions [25]. Moreover, the lateral cerebellum has connections with the higher cortical areas of the frontal cortex. The activation of the proposed model is supposed to be controlled by a frontal cortical region. Correspondingly, when a need arises for this system to operate, the cortical region sends a mossy fiber volley to the lateral cerebellum region. Upon receiving such input, dentate cells fire simultaneously and strongly depolarize the corresponding PRn cells, which, in their turn, become active and excite the OCs in the principal olive region. Being depolarized, the peaks of the subthreshold oscillations of the membrane potentials of OCs reach firing thresholds resulting in firing at some of these peaks. Whereas the models of inferior olive and cerebellar circuitries are constructed with cell prototypes as described below, the functionality of the PRn region was represented by allowing the OCs to fire at higher frequencies.

A. The Model of the Inferior Olive

The intrinsic capability of the membrane potentials of the OCs to develop subthreshold sinusoidal oscillations and the existence of phase differences between these oscillations constitute the basis of the olivary model. The model consists of four different groups of OCs, each of which is referrred to as an olivary group (OG). These groups are juxtaposed with uniform distances and each OG is connected to the next one through gap junctions. The shunting of these junctions is controlled by the input from inhibitory dentate cells. Due to the existence of gap junctions, certain phase differences would occur between each OG. However, because of the uniform distances between the groups, the phase differences would be the same. 10 Hz was chosen as the oscillation frequency of the OCs in all groups, therefore the phase differences between the groups are 100 / 4 = 25 *ms*. Each OG, in its turn, contains four OCs that are also connected to each other through gap junctions. These junctions, however, do not receive any cerebellar input; therefore, the OCs in a certain group are always fully coupled to each other. This means that membrane potentials of OCs in a certain OG would oscillate synchronously, i.e. with no phase delay. Because of the 25 *ms* phase difference between each OG, if the oscillations of the cells of the first OG reach their peaks at t=T *ms*, then those of the second group would reach at t=T+25 *ms*, those of the third group at t=T+50 *ms*, and those of he fourth group at t=T+75 *ms*. Then every 100 *ms*, this pattern would repeat itself (Fig. 1).

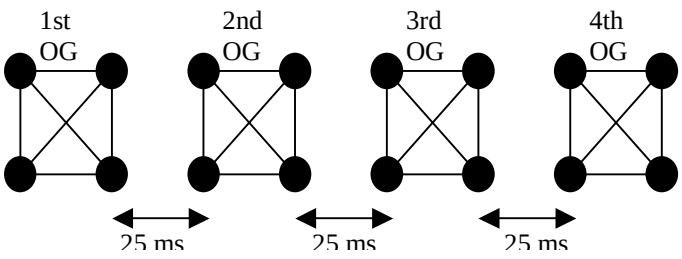

Fig. 1. The olivary model consists of 4 OGs connected to each other through gap junctions.

Each OC is modeled as a simple unit with two distinct states: ‘on’ and ‘off’. ‘On’ state represents the firing of the cell, while the ‘off’ state is used for the silence of the cell. Each OC is allowed to fire only at the peaks of the oscillations but not necessarily at every peak. It was also assumed, for simplicity, that only a single OC in a cell group would fire at a certain peak. However, the order of the firing of the cells is not important for the proper functioning of the model as long as there is an OC firing at each peak. Because of this firing mechanism, the average firing rate of OCs in a certain OG would be 10/4=2.5 Hz although the exact firing rates of individual OCs could be different from that value and from each other.

B. The Model of the Cerebellum

The cerebellum, which has the largest number of cells among all brain subdivisions, exhibits a simple and regular internal organization in which many modules with identical neural structure are juxtaposed. The modules differ only in the signals they receive as input and produce as output. Therefore, it is possible to model the cerebellum as a group of similar modules with input and output that tailor the modules to carry out the proposed functionality. Each cerebellar cell is modeled using a cell prototype similar to simple threshold units used in artificial neural networks. The output of unit k is found by (1).

$$u_k = (\sum_{j=1}^{p} w_{kj} x_j) + \theta \qquad (1)$$

where x_j are the input signals; w_{kj} are the synaptic weights of unit *j*; u_k is the output of the unit *k*; θ is its threshold. Therefore if the net input of the unit is above the threshold, then it would fire, i.e. its output would become 1; otherwise it would not fire and its output would be 0. On the other hand, a complex spike, which consists of a train of spikes, is modeled as a series of 1`s and 0`s for a period of 7 *ms*. The hyperpolarization of a nuclear cell by a complex spike is assumed to last 25 ms.

C. The Architecture of the Cerebellar Circuitry

The cerebellar model consists of 4 different modules, each of which is referred to as a cerebellar group (CG). The P-cells that receive climbing fibers from a certain OG align in the rostracaudal direction and belong to a specific cerebellar group. As such, there is a corresponding CG for each OG. Since there are four OGs in the olivary model, the cerebellar model comprises four CGs. Each climbing fiber that originates from a specific OC makes numerous contacts with a single P-cell; therefore, each CG consists of four P-cells. In addition to P-cells, a CG also comprises four basket cells. Other than these cells, the cerebellar model also contains 10 mossy fibers, 120 granule cells, a single Golgi cell, and eight dentate cells - four excitatory and four inhibitory (Fig. 2).

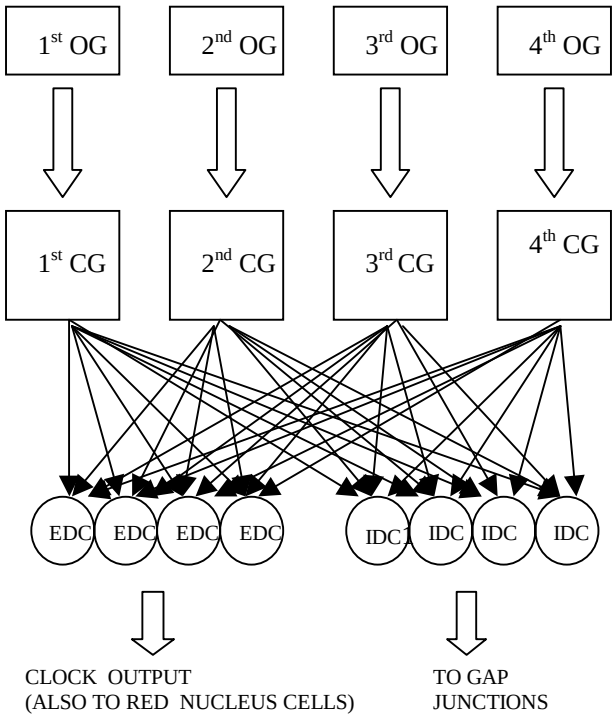

Fig. 2. The olivary model consists of 4 OGs connected to each other through gap junctions. OG, olivary group; CG, cerebellar group; EDC, excitatory dentate cell; IDC, inhibitory dentate cell.

The signal reaching the cerebellar cortex via mossy fibers is fed to all 120 granule cells through a codon mechanism, in which each granule cell receives input from a different set of three mossy fibers. Each granule cell in turn gives way to a parallel fiber, which contacts a single basket and a single P-cell in each group. However, the P- and basket cells in the model would also receive input from 120 additional parallel fibers originating from granule cells not included in the model. As a result of this connection mechanism, since there are 240 parallel fibers each synapsing with four basket and P-cells, each basket and P-cell receives input from a different set of 240 / 4 = 60 parallel fibers. While the output of a basket cell inhibits all P-cells in the same CG, the output of each P-cell inhibits all dentate cells. In addition to parallel fiber input, each P-cell is also contacted by a distinct climbing fiber. Although each climbing fiber contacts a single P-cell, the single Golgi cell in the model receives input from all climbing fibers. The Golgi cell also receives input from all parallel and mossy fibers, and, in turn, suppresses the activity of 120 granule cells included in the model. The output of the excitatory dentate cells forms the output of the system, while that of the inhibitory ones is used to control the shunting of the gap junctions between the olive groups.

IV. Calculation of the System Parameters

After the design of the cerebellar model had been finished, the next step was the determination of the range of the system parameters, i.e. weights and firing thresholds of each cell type, with which the model would function properly. The model would operate as a rhythmic system if the parallel fiber input to the P-cells is suppressed strongly. Such an effect would largely decrease the probability of simple spike production by the P-cells considerably. As a result, only complex spikes would be produced by P-cells. This situation would have a major effect on the functionality of the nuclear cells due to the fact that these cells would receive a new complex spike every 25 *ms.* In addition the powerful hyperpolarizations cerated by a complex spike lasts 20-25 *ms.* Therefore the dentate cells would most of the time be experiencing a strong inhibition due to the complex spikes. The relatively weak depolarizations created at these cells by direct mossy fiber input would be negligible because of this strong hyperpolarization. The most important factor in the proper operation of such a mechanism is the powerful inhibition of the granule cells by the Golgi cell, which would be firing at higher-than-normal rates because of the climbing fiber input it receives every 25 *ms*.

For simplicity, all the cells of a certain type were assumed to have the same parameter values. The parameters of the Golgi and P-cells had to be assigned values in such a way that, upon receiving climbing fiber input, their firing would be guaranteed. In order to achieve this, the firing threshold of these cells were all assigned 1.0, whereas the weights of the climbing fiber-P-cell and climbing fiber-Golgi cell synapses were given the value of 1.1. In addition, the inhibition of a granule cell by the Golgi cell was assumed to last 50-100 *ms*.

Since the activity of all the parallel fibers originating from the granule cells of the model would always be inhibited by the Golgi cell, the maximum number of parallel fibers that could depolarize a certain P-cell occurs when the granule cells not located in the model fire simultaneously. Since only one-fourth, i.e. 30, of such parallel fibers synapse with a certain P-cell, the maximum number of parallel fibers that could excite a P-cell simultaneously is 60 / 2 = 30. Therefore, in order for these cells not to fire even if they receive input from all of thse 30 parallel fibers simultaneously, the weights had to be assigned values less than 1.0 / 30 = 0.33. The weights of the mossy fiber-dentate cell synapses were assigned arbitrary small weights in order to guarantee that the depolarization created by such input would be negligible compared to the strong hyperpolarization of dentate cells by complex spikes. The operation of the model with the assigned parameters was tested with a simulation program written by the author in C language. Fig. 3 shows the output of the system, i.e. the output of the dentate cells, for a period of 200 *ms* using discrete time steps of 1 *ms.*

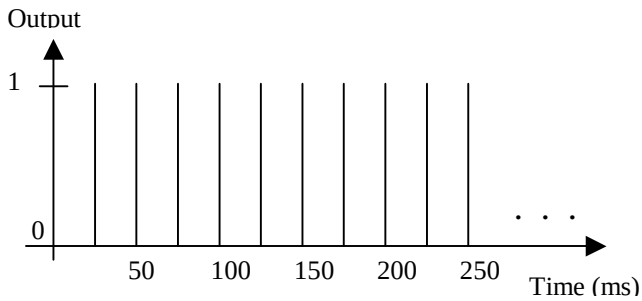

Fig. 3. The output signal of the model obtained from the simulation study for a period of 200 *ms.*

V. Discussion

In this study, a functional model of the olivocerebellar circuitry that generates rhythmic pulses by combining low frequency spikes produced by the olivary cells into regular spike sequences at the output of the dentate cells was presented. Various anatomical and physiological facts about these cells were taken into consideration during the design. Therefore, though simplistic, the model is sufficient to investigate the olivocerebellar circuitry from a higher level of organization. The results obtained show that the proposed model is able to produce rhythmic activity at 40 Hz.

Many biological and experimental findings about the cerebellar anatomy and physiology were also taken into account in the design of the cverebellar model. Beside the cerebellum, two other brain structures, i.e. the inferior olive and the parvocellular part of the red nucleus, were also modeled. The functionality of the model is based on several biological findings. Two of them are related to olivary cells: (1) the ability of the membrane potentials of these cells to develop subthreshold sinusoidal oscillations and (2) the existence of phase differences between different cell groups. The first property allowed the firing of olivary cells to occur at specific instants, i.e. at the peaks of the oscillations. The second property yielded to a design where different groups exist with certain phase differences between them. Another biological observation that played an important role in the design of the model is the intrinsic property of the cerebellar nuclear cells to produce rebound spikes. The dentate cells were modeled assuming that they would produce a rebound spike upon being hyperpolarized by a complex spikes.

One of the key elements in the proper operation of model is the Golgi cell, which repeatedly continously receives a new climbing fiber input every 25 *ms.* In addition, the inhibition of a granule cell by the Golgi cell is assumed to last 50-100 *ms*. Due to such mechanism, all the granule cells included in the model would most of the time be inhibited. Therefore the functionality of the dentate cells is completely determined by the activity of the complex spikes.

The model can be criticized in that such a rhythmic system within the olivocerebellar system has yet to be found. Nevertheless this fact does not conflict with the results of this study. The findings of this study do not prove that the lateral cerebellum, inferior olive and parvocellular part of the red nucleus form a rhythmic system; instead, it shows that these brain structures have all the properties to behave like a one. This does not imply that such a system do necessarily exist within the brain. Furthermore, even if such a system existed, it could be very hard to locate because it would occupy very small areas in these brain structures.

It is hoped that this study will contribute to advance the current knowledge about the functionality of the olivocerebellar system by providing theoretical support for its possible role in the oscillatory activity of the human brain reflected in EEG signals. The next step of this work will be to design different functional models that would produce rhythmic activities at other EEG frequencies. The ultimate goal is to design a single model which would be capable of producing rhythmic activities at multiple EEG bands.

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