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NEUROMODULATION AS A CONTROL TOOL FOR NEURONAL ENSEMBLES[1]

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Abstract. Control mechanisms for the rhythms of neuronal ensembles based on the neuromodulation effect are described and implemented. The biological mechanisms of neuromodulation are briefly outlined, and some aspects are highlighted to control the activity patterns of interconnected neurons forming ensembles. Within the suggested model, neuromodulation is a change in the neuron's properties responsible for its sensitivity to excitatory and inhibitory impacts (and, therefore, for its activity). This change is initiated by certain neurotransmitters (modulators), which indirectly influence the electrical activity of all neurons sensitive to them. The discrete asynchronous chemical interaction model of biological neurons in small neural networks is modified and extended to implement this control mechanism inherent in living organisms. The key effect of neuromodulation is the rapid functional reorganization of neural networks without changing their structural properties. Activity patterns are changed not via costly changes in the connections between neurons but by changing the chemical environment of the ensemble's neurons. The mechanism of neuromodulation is formalized. The new model is implemented in software, and several computational experiments are performed to change the gait of hexapods.

Keywords: neuron, neuromodulation, neurotransmitters, control, discrete modeling, generator of rhythmic activity.

INTRODUCTION

In neurobiology, there is the concept of a *central pattern generator* (CPG). It refers to a neuronal ensemble whose members jointly generate a certain motor program of the body. A motor program is understood as a time-ordered output activity transmitted to muscles, forcing them to contract and relax in a certain coordinated sequence that forms a motor pattern [1, 2]. Locomotor gaits are a good example of such patterns. For four legs, gallop, trot, amble, and step are often distinguished. The same neuronal ensemble is capable of generating different activity patterns. Some model examples in this paper will show how to switch between different patterns using the neuromodulation effect without restructuring the ensembles.

The neuromodulation effect is that neurotransmitters (chemical signaling molecules acting on neurons sensitive to them) can switch the network of interactions [3–6]. Anatomical connections between neurons indicate only the potential for their interactions. Real interactions are determined by molecules of neuromodulators, which change the composition and activity of neuronal ensembles [4]. In other words, anatomical connections are only a starting point for understanding the dynamics of ensembles [5]. An important role is also played by the fundamental diversity and heterogeneity of neurotransmitters and the types of neurons and their interactions [2, 7–9].

The overwhelming majority of biologically accurate mathematical models of neurons describe membrane potential dynamics [10–12]. The advantages of discrete models are interpretability and the reflection of neural interactions at a phenomenological level under a relatively low computational complexity. However, discrete models of biological neurons describing

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heterochemical interactions have not been developed so far.

The automata-based approach to modeling biological neurons was proposed in the monograph [13]. This paper presents an automaton model of a neuron that survives under conditions of limited nutrition. It is shown that when minimizing consumption, the system acquires memory and the mechanisms of behavior and feeling. The basic property of the neuron modeled below is its endogenous electrical activity: "A discharge in a neuron is needed by the neuron itself."

This paper modifies the discrete asynchronous chemical interaction model of neurons [14] to reproduce neuromodulation effects. In the previous version of the model, neurotransmitters only have an activating or inhibitory effect on neurons, i.e., increase or decrease the membrane potential. In the new version, two types of receptors are introduced for neurons as follows. The impact on the first-type receptors, as before, entails a change in the charge on the neuron membrane. The impact on the second-type receptors changes the sensitivity of the first receptors, thereby modulating the neuron's response to external impacts.

1. BIOLOGICAL MECHANISMS OF NEUROMODULATION

The main characteristic of neuron's activity is the electrical potential at its membrane. When the membrane potential exceeds some threshold, the neuron goes into an active, excited state. Excitation is transmitted from the neuron to other neurons and tissue cells via axons having terminals with synaptic endings. They contain neurotransmitter molecules whose function is to transmit signals between neurons chemically. When the excitement reaches the synaptic end, it undergoes rapid transformations, leading to the release of transmitters into the extracellular space. Near the synaptic end of the neuron that transmits the signal, there are dendrites or the body of the neuron that receives the signal. Their surface has receptors acting as signal receivers. The connection of a transmitter with a receptor sensitive to it causes a chemical reaction and intracellular transformations in the receiving neuron, which often change its membrane potential. Therefore, it is convenient to represent the nervous tissue at the cellular level as a network of electrically conductive elements. This approach to describing the nervous system is called electrophysiological. It resulted in many important discoveries and dominated neurosciences for the entire second half of the 20th century. The overwhelming majority of exact mathematical models of neurons are aimed precisely at describing membrane potential dynamics [10–12].

Nevertheless, chemical interactions between neurons can induce a wide range of intracellular effects not expressible by a direct change in the value of the membrane potential. Chemical interactions between neurons, not associated or indirectly associated with changes in the membrane potential, have a huge impact on the behavior of both individual neurons and their populations. The rich variety of such impacts is called "neuromodulation" [3–6]. Often, neuromodulation does not directly affect membrane potential dynamics but modifies endogenous and exogenous patterns of electrical activity. In this regard, it is especially interesting when studying the mechanisms of the emergence and maintenance of rhythmic activity in the nervous system. Neuromodulation can significantly vary rhythm parameters (e.g., the duration of the phases of activity and silence) and even transfer the neuron to the rhythmic mode from the non-rhythmic one [15].

The specifics of existing approaches to modeling natural neural systems restrict the possibilities of reflecting neuromodulatory impacts. Biophysically accurate modeling requires measuring the microconcentrations of various substances very finely in extremely small volumes of space and considering the geometric features of the extracellular space on the nanometer scale. Currently, models of this level of accuracy exist only for local areas of a neuron [16] and are impossible in practice, even for small groups of neurons.

In this paper, we develop the asynchronous model of multitransmitter interactions [14, 17]. The model has the following features: a discrete approach is used to model the behavior of neurons, and the neurons in the model exchange chemical signals extrasynaptically–through the common extracellular space (all signals are broadcast). However, any impact on a neuron is reflected in this model directly by a change in the membrane potential. Hence, the expressive power of the multitransmitter approach is considerably restricted. This paper introduces an additional modus of neural interactions into the asynchronous model by adding another type of receptors that would directly affect not the membrane potential but the weights of other receptors, thereby changing the neuron's sensitivity to certain input signals. As shown below, the introduced modifications allow implementing a fast and low-cost mechanism for controlling motor rhythms.

2. BASIC NOTIONS OF DISCRETE ASYNCHRONOUS MODEL

The basic model and the principles of its functioning were formally described in [17]. Some model examples of the rhythms generated by the nervous systems of various mollusks were presented in [14]. In

this section, we briefly consider the model and the main definitions and notations used below.

A heterogeneous neural network is a system $\mathbf{S} = \langle \mathbf{N}, \mathbf{X}(t), \mathbf{C}, \mathbf{T} \rangle$ with the following notations: $\mathbf{N} = \{N_1, \ldots, N_n\}$ is the set of neurons; $\mathbf{X}$ is the extracellular space through which chemical neural interactions occur; $\mathbf{C} = \{c_1, \ldots, c_m\}$ is the set of transmitters; $\mathbf{T}$ denotes the continuous time in which the system is functioning.

The continuous time is divided into unequal intervals (time steps) by *events*. An event is a change in the state of at least one of the system's neurons (activation of a passive neuron or deactivation of an active neuron).

In each time step, neurons interact with the extracellular space $\mathbf{X}$. Transmitters from the space $\mathbf{X}$ influence the behavior of neurons, which can be expressed in a change in their state of activity. In turn, a change in the neuron's state changes the transmitter composition of the space $\mathbf{X}$. This approach allows describing both synaptic and nonsynaptic interactions [14].

2.1. Neuron Parameters

2.1.1. Receptors

Neuron N_i possesses many receptor slots, and each slot is characterized by sensitivity to some transmitter c_j and weight $w_{ij} \in \mathbf{R}$. A slot is a union of all receptors sensitive to transmitter c_j; its weight is the cumulative effect of these receptors. If the neuron is insensitive to transmitter c_j, it does not have a corresponding slot, and $w_{ij} = 0$. A weight $w_{ij} > 0$ ($w_{ij} < 0$) means that this transmitter has an excitatory impact (inhibitory impact, respectively) on the neuron. For all neurons, the receptor weights form the matrix $W = (w_{ij})_{n\times m}$.

2.1.2. Output activity of neurons

The activity of neuron N_i is given by a value $y_i(t) \in \{0, 1\}$: if $y_i(t) = 1$, the neuron is active in time step t; otherwise ($y_i(t) = 0$), the neuron is passive in time step t.

The neurons in the model are transmitter-specific: upon activation, each neuron releases the same transmitter c_j into the extracellular space. In the model without neuromodulation, the release is determined by a constant d_{ij}.

The output is represented by the matrix $D = (d_{ij})_{n\times m}$, in which $d_{ij} \geq 0$ is the rate of release of transmitter c_j by neuron N_i. Note that $d_{ij} = 0$ if neuron N_i does not release transmitter c_j. Due to the transmitter-specificity of neurons, each row of the matrix contains exactly one nonzero element. The value d_{ij} is assumed to be invariable during the release process.

2.1.3. Internal state of neurons

Neuron N_i has the membrane potential $U_i(t)$, which varies within a range $U_i^0 \leq U_i(t) \leq U_i^{\max}$. The neuron in the model is active if its membrane potential $U_i(t)$ exceeds a threshold P_i, often smaller than $U_i^{\max}$. The values U_i^0, $U_i^{\max}$, and P_i are specific for each neuron.

2.1.4. Types of neurons

The neurons in the model are heterogeneous. Each neuron is determined by the following characteristics:

– the transmitter it releases (see subsubsection 2.1.2);

– the set of receptors and their weights;

– the nature of endogenous activity, i.e., the ability for activation without external impacts.

The model implements three types of neurons with different types of activity (Fig. 1):

- *Tonic neuron* has permanent endogenous activity in the absence of inhibition. In the model, permanent activity is understood as the regular generation of spikes (nerve impulses) in equal time intervals.
- *Burst* (o*scillator*) neuron generates spike bursts in definite time intervals in the absence of inhibition. The frequency of spikes in bursts exceeds the frequency of spikes generated by the tonic neuron (Fig. 1a, b).
- *Reactive* (*passive*) neuron has no endogenous excitation. It is activated only under an excitation reaching the threshold.

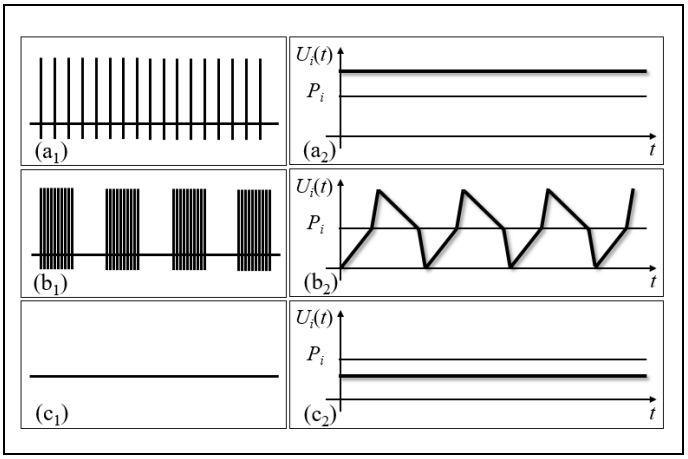

Fig. 1. Three types of endogenous activity. Diagrams with generated spikes (left column), and model approximations (right column):
(a_1) tonic neuron with regular spikes; (a_2) constant membrane potential $U_i(t)$ exceeding threshold P_i; (b_1) oscillator's spike bursts; (b_2) piecewise linear approximation by four endogenous rates of change of membrane potential: two rates above threshold, and two rates below; (c_1), (c_2) reactive neuron with membrane potential below threshold.

A neuron is activated if its membrane potential has exceeded a threshold specific for each neuron. Activation occurs due to either endogenous activity or external impacts when the sum of the responses of the receptors (considering their weights) exceeds the threshold. In this case, the neuron releases a transmitter. Differences in the activation rates of tonic and burst neurons are implemented by setting specifying different values of the rates of release d_{ij}; see subsubsection 2.1.2.

For all three types of neurons, the endogenous dynamics of the membrane potential are given by linear functions. The left column in Fig. 1 schematically shows the membrane potential dynamics of the neurons generating impulses; the right column, its linear approximations used in the model.

2.1.5. Membrane potential dynamics

During each time step, the membrane potential of neuron N_i changes (increases or decreases) linearly, i.e., with a constant total rate:

$$U_i(t) = v_{i\text{en}}^{\alpha}(t) + s_i(t),$$

where $v_{i\text{en}}^{\alpha}(t)$ is the *endogenous rate* of change of the membrane potential given by a piecewise linear function; α is a parameter depending on the neuron's type of electrical activity (each type of neurons has a specific set of endogenous rates of change) and the current range of the membrane potential in this time step; $s_i(t)$ is the *exogenous rate* of change, equal to the power of the external impacts:

$$s_i(t) = \sum_{j=1}^{m} w_{ij} x_j(t), \qquad (1)$$

where $x_j(t)$ is the concentration of the jth transmitter in the extracellular space (see subsection 2.2).

For different types of neurons, changes in the membrane potential were described in detail in [12].

2.2. Extracellular space

The state of the extracellular space in time step t is represented by a vector $X(t) = (x_1(t), \ldots, x_m(t))$, where $x_j(t) > 0$ is the total volume of transmitter c_j present during time step t; otherwise, $x_j(t) = 0$. The state of the extracellular space changes under each event: when a neuron is activated, the concentration of a neurotransmitter specific to it increases by d_{ij}; when deactivated, it decreases by the same value.

In what follows, we propose a modification of this model to reflect the neuromodulation effects.

3. FORMAL DESCRIPTION OF NEUROMODULATION

As shown in subsubsection 2.1.1, the receptor weights w_{ij} in the basic model are constant values. They contribute to the rate of change of the membrane potential according to formula (1). For reflecting the neuromodulation effect in the model, we introduce additional receptors responsible for neuromodulatory impacts. For neuron N_i, the weight of the modulatory receptor will be denoted by w_{ijk}^{β}, where the superscript β indicates the receptor's type. The weight w_{ijk}^{β} is the value by which the weight w_{ij} changes in the presence of transmitter c_k. We write the set of receptor weights of neuron N_i receptors responsible for neuromodulatory impacts as the matrix

$$\mathbf{W}_i^{\beta} = (w_{ijk}^{\beta})_{m\times m}.$$

Then the jth row of this matrix is a vector containing the weights of all receptors, sensitive to transmitter c_j, that change under the impact of transmitter c_k, $k = 1, \ldots, m$.

Formula (1) for calculating the external impact on a neuron (1) will be modified to

$$s_i(t) = \sum_{j=1}^{m} \left(w_{ij} + \sum_{k=1}^{m} w_{ijk}^{\beta} x_k(t) \right) x_j(t), \qquad (2)$$

Using $\mathbf{W}_i = (w_{ij})_{1\times m}$ and $\mathbf{X}(t) = (x_j(t))_{1\times m}$, it can be written in the matrix form

$$s_i(t) = \mathbf{W}_i \mathbf{X}^{\mathbf{T}}(t) + \mathbf{X}(t)\mathbf{W}_i^{\beta}\mathbf{X}^{T}(t).$$

This means that before calculating the contribution of the jth transmitter to the external impact s on neuron N_i, the weight w_{ij} is summed up with the product of the jth row of the matrix $\mathbf{W}_i^{\beta}$ and the transmitter concentration vector $\mathbf{X}(t)$. All receptor types respond to the same set of transmitters. Such changes allow introducing interactions that modify the neuron's response to transmitters by specifying indirect impacts on the membrane potential.

All model parameters described in Sections 2 and 3 are illustrated Fig. 2a, b.

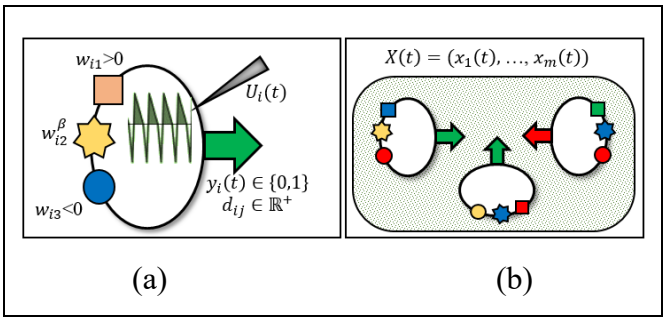

Fig. 2. (a) Neuron and its model parameters: excitatory, inhibitory, and modulatory receptors with weights $w_{i1} > 0$, $w_{i3} < 0$, and w_{i2}^{β}, respectively; each receptor is sensitive to transmitter of one type; type of endogenous activity: dynamics of membrane potential type $U_i(t)$; neuron's release: type of neurotransmitter c_j and rate of release d_{ij}. (b) Interaction of neurons through common intercellular space characterized by neurotransmitter concentration vector.

Remark. Formula (2) has a quadratic term, which generally increases the number of parameters from $O(nm)$ to $O(nm^2)$. As a result, the problem of choosing appropriate parameters for implementing the system's desired behavior acquires a higher complexity. This paper will be restricted to studying a particular case in which modulatory impacts completely disable some receptors; see Section 4. One modulatory transmitter is added to zero the weights of given receptors. In this statement, the problem's dimension remains the same.

Fig. 3 illustrates the modulation of the impact of neuron N_2 on neuron N_1 by neuron N_3. Without the impact of neuron N_2, the membrane potential dynamics of neuron N_1 do not change.

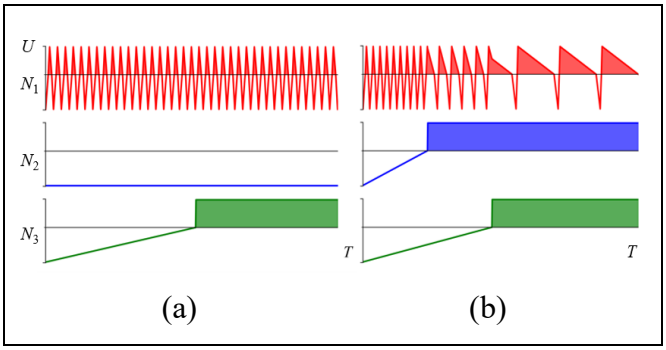

Fig. 3. Change in membrane potential under modulatory impact. Neuron N_3 modulates impact of neuron N_2 on neuron N_1.
(a) Modulatory impact changes the weight of receptor of neuron N_1 to the transmitter of neuron N_2; when neuron N_2 is silent, modulation does not affect the membrane potential of neuron N_1. (b) Neuron N_2 is activated earlier than neuron N_3 and slows down the oscillations of membrane potential of neuron N_1; when neuron N_3 is connected, oscillations slow down even more due to modulatory impact. Ordinate axis corresponds to membrane potential and abscissa axis to time.

4. OBJECT OF MODELING

Let us describe the gait switching mechanism of an abstract six-legged walking (hexapod) robot using neuromodulation. The motor programs that control walking differ in the number of legs on the ground at a given time. For example, four legs lean on the ground under a four-legged gait, and two are taking a step. As a rule, one, two, or even three legs take a step simultaneously. The more legs are involved, the higher the speed of movement will be. A three-legged (tripod) gait is considered optimal since the robot has three support points at each time, which provides stability.

The motor programs of hexapods are biologically inspired: insects are six-legged animals and have a fairly simple nervous system. Therefore, it is possible to study the mechanisms that control their walking [18, 19]. Figure 4 shows the three-legged gait of the fruit fly *Drosophila melanogaster*.

The tetrapod gait is similar: four legs are always on the ground, and two take a step. The idealized step alternation diagrams of these gaits are presented in Fig. 5.

5. GAIT SWITCHING USING NEUROMODULATION

Each leg of the animal performs two groups of mutually exclusive actions: moves the animal forward when it is on the ground, or steps forward. These groups consist of several simpler actions corresponding to flexion, extension, and movement of the limbs in different planes. In animals, the actions mentioned are implemented by contractions of various muscle groups; in robots, by switching on various servos.

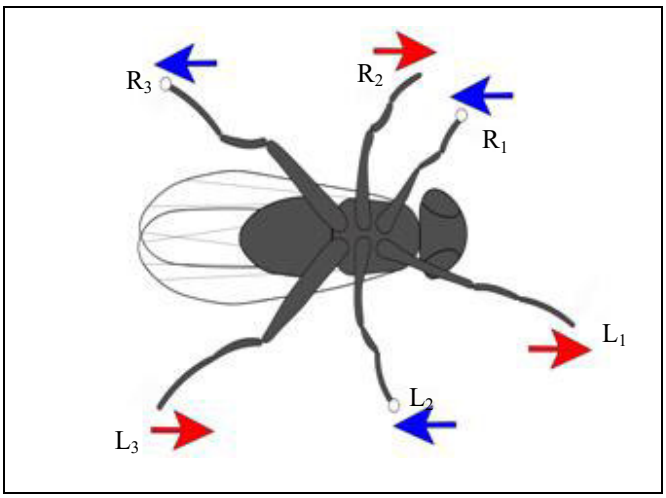

Fig. 4. Tripod gait of Drosophila, bottom view:
front and back right (R_1, R_3) and middle left (L_2) legs are on ground; front and back left (L_1, L_3), and middle right (R_2) feet take step.

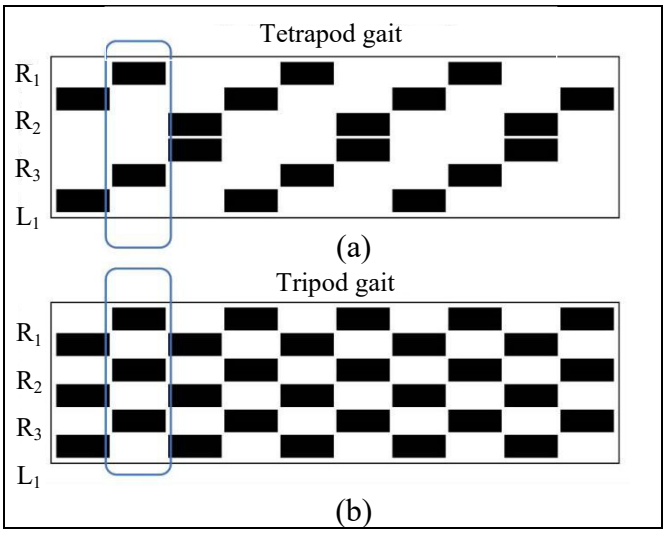

Fig. 5. Step alternation diagrams for Drosophila:
(a) tetrapod gait and (b) tripod gait.
(– ground, – step).

Since the action sequences for each leg are stereotyped, the asynchronous model will reproduce four- and three-legged gaits after assigning two neurons for each leg: one is active when the leg is on the ground, the other when the leg oversteps.

Let the neuron responsible for the movement of the supporting leg be *tonic* (active in the absence of external impacts), and the stepping one be *silent* (reactive). For their anti-phase activity, we create an excitatory connection from the support tonic neuron (*Supp*) to the step silent neuron (*Step*) and an inhibitory connection from the step neuron to the support one; see Fig. 6.

The membrane potential of such a pair of neurons will change as shown in Fig. 7. Tonic neuron *Supp* activates silent neuron *Step*. Neuron *Step* reaches the threshold, is activated, immediately inhibits neuron *Supp*, and remains active for some time, while its membrane potential decreases under the influence of endogenous forces, approaching the threshold from above. When neuron *Step* becomes silent, the inhibitory impact on neuron *Supp* is eliminated: it is activated, and the time step repeats.

Next, we build six pairs of such neurons with necessary connections so that the excitation pattern corresponds to the diagram of a four-legged gait (Fig. 5*a*).

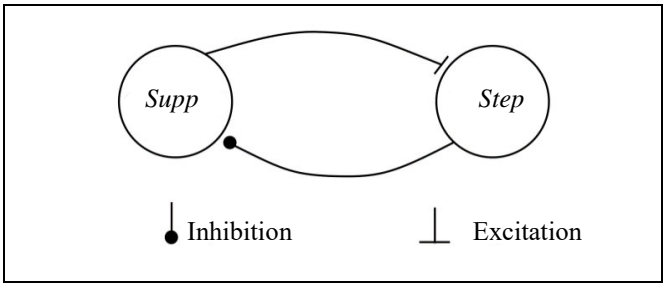

Fig. 6. Connection diagram of two antagonistic neurons controlling movements of one leg.

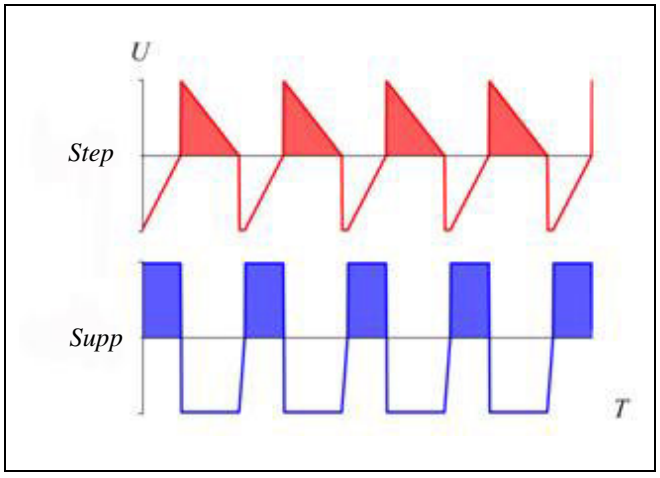

Fig. 7. Graphs of the membrane potential of model neurons with anti-phase excitation.
Ordinate axis corresponds to membrane potential and abscissa axis to time.

For this purpose, we introduce inhibitory connections from each step neuron on the right and left sides to two other step neurons on the same side. The corresponding diagram is shown in Fig. 8.

Here groups of neurons on the right and left sides are not connected with each other, and they are synchronized using the system parameters. They can be easily synchronized by making all support neurons silent and introducing one tonic neuron to excite them. However, this approach would considerably complicate the connection diagram, and Fig. 8 and 10 offer a simplified version.

Mutual inhibitory connections of the step neurons ensure that only one of them will be active on the left and right sides in each gait phase. The activation order is determined by the simulation parameters. The program-generated graphs of the membrane potentials of neurons are shown in Fig. 8. L_3*Step* is the first neuron activated on the left side. While active, it inhibits all other neurons *Step* on the left side. According to the simulation parameters, when the activity period of neuron L_3*Step* ends, L_2*Step* is activated first among the remaining step neurons. During the entire activity period, it inhibits the neighbors. Then neuron L_1*Step* switches on, and at the end of its activation period, the time step repeats. The order for the right side is symmetrical, with the only difference that neuron R_2*Step* is activated first.

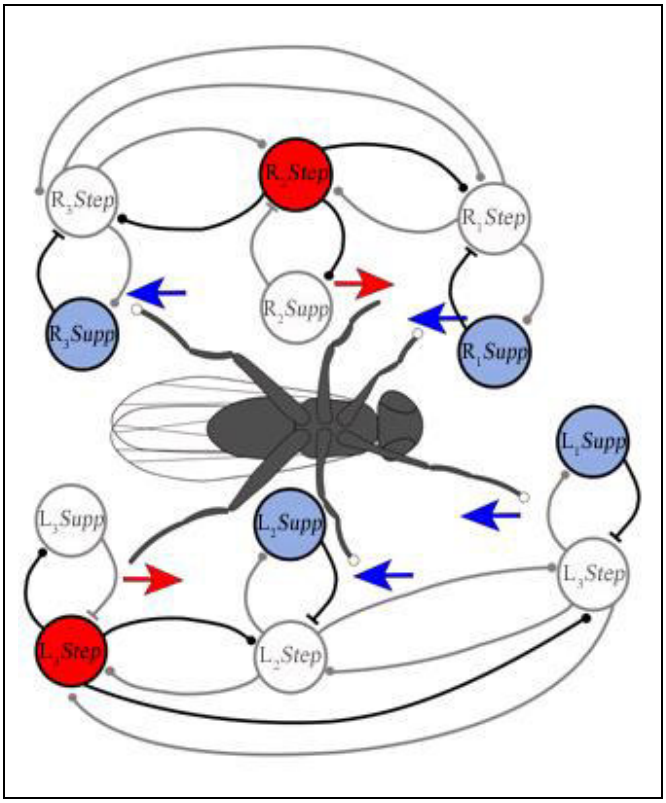

Fig. 8. Diagram of connections and activation of neurons in tetrapod gait phase.

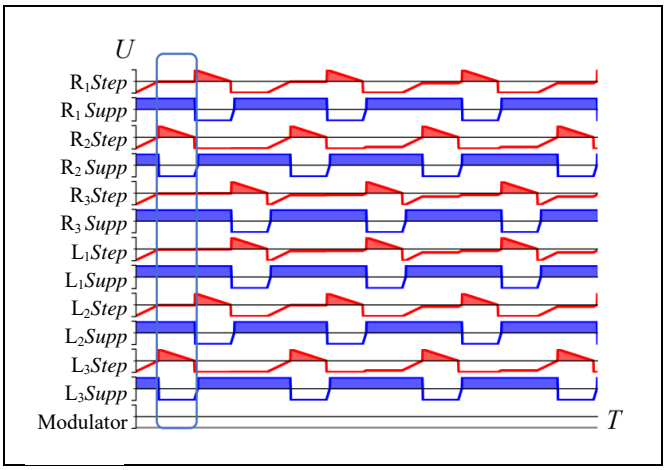

Fig. 9. Membrane potentials of neurons under tetrapod trait.
In each phase, only one step neuron is active on each side: two legs take step, and four are on ground. Modulatory neuron (silent) is required to adjust to tripod gait. Ordinate axis corresponds to membrane potential and abscissa axis to time.

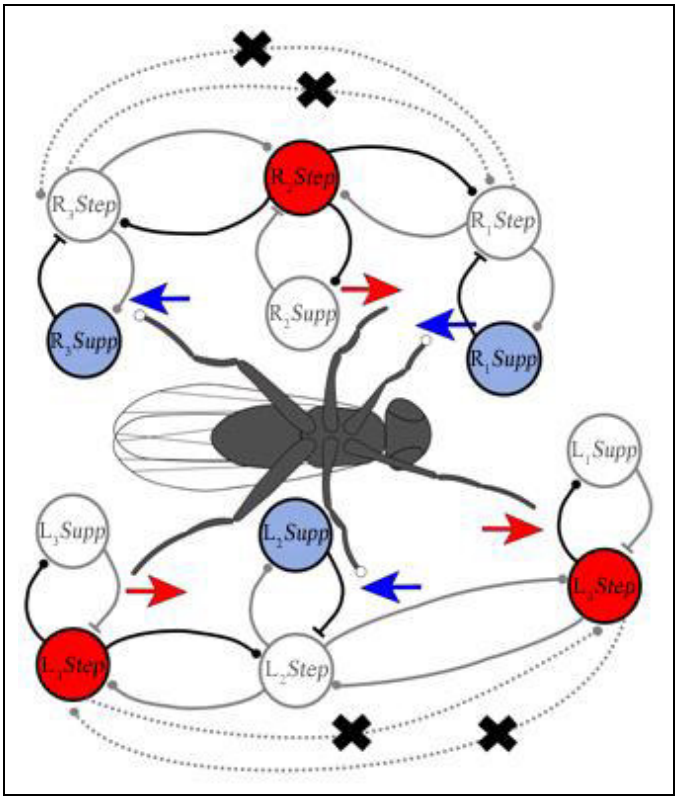

Fig. 10. Modulatory impact suppresses inhibitory connections between first and third neurons.

To harmonize this rhythm with the tripod gait diagram (Fig. 5*b*), it suffices to switch off the inhibitory connections between the first and third neurons on each side. This can be achieved by introducing a modulatory neuron, the transmitters of which switch off inhibitory receptors between the first and third neurons on each side (Fig. 10). As a result, the first and third neurons begin to activate synchronously, and the diagram corresponds to the tripod gait (Fig. 11).

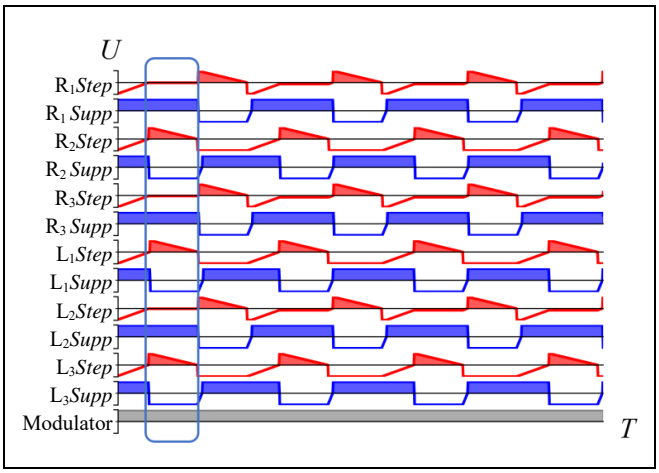

Fig. 11. Membrane potentials of neurons under tripod trait.
In each phase, three neurons are active on both sides. Modulatory neuron releases transmitter suppressing inhibitory connections between first and third neurons throughout operation. Ordinate axis corresponds to membrane potential and abscissa axis to time.

CONCLUSIONS

This paper has proposed a formal description of the neuromodulation mechanism within the discrete asynchronous model of heterochemical neural interactions and demonstrated the results of switching the gait of hexapods.

The main and extremely significant neuromodulation effect is the rapid functional reconfiguration of neuronal circuits (both natural and artificial) without changing their structural properties. Thus, activity patterns can be changed not by long and costly changes in connections between neurons and not by switching between different neuronal circuits to perform different actions but by changing the chemical composition of the intercellular space within one neuronal ensemble. In the model, this is done by changing a single parameter. This mechanism greatly simplifies the control of gaits and other types of motor activity.

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