Rhythmic Behavior Generated by Ensembles of Neurons

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Abstract

A method for analyzing the rhythmic behavior of biological neural networks is developed. The mathematical foundations, based on group theory and graph theory, is explicitly constructed, and examples are given to clarify the method. An application is made to the brainstem circuitry of the vestibular system. The physiological mechanisms involved in generating vestibular nystagmus are characterized, and predictions are made about the phase relations of identified vestibular neurons with eye movements. Comparisons with other models of vestibular circuitry are discussed and suggestions are made for improvements to previous models.

1 Introduction

The survival of any animal is dependent on its ability to recognize and generate patterns. The spatial and temporal patterns of sensory information impinging on the nervous system through many sensory modalities must be encoded in neural activity patterns to be useful for further processing. Movement is carried out by generating temporal patterns of motor neuron activity that are spatially distributed to coordinate various combinations of muscle groups. Sensorimotor organization can be characterized

by the task of integrating and transforming afferent neural patterns from sensory stimuli into efferent neural patterns for motor output. The process of sensorimotor organization will not be thoroughly understood until neural activity patterns can be recognized, their interactions identified, and the relationship between patterned activity and behavior clarified.

Neural activity patterns are influenced by the anatomy, physiology, and afferent input of each neural system and are distributed in space and time. Recurrent connections between different systems can interlock these patterns like cogs in dynamical wheels. The development and application of appropriate mathematical methods to known properties of the nervous system is needed to determine the patterns that each system will support, how the patterns interact, and to identify the signature of such patterns that could be detected with current experimental techniques.

The growing acceptance of the population coding paradigm of neural computation [5] has brought with it an increasing interest in how coding strategies are implemented in the brain. Synchronous activity of neurons in a distributed population is a dynamic and efficient means for encoding information in the nervous system [24]. Evidence of coherent, spatiotemporal patterns is accumulating in various regions of the brain including the visual cortex [1], the olfactory bulb [8], and the cerebellar cortex [19].

However, patterns of neural activity are only meaningful to the regions with which they communicate. A difficulty with searching for patterns in experimental data is that often the regularities are overlooked unless substantiated by theory [6]. The underlying regularities that constitute a pattern are easily washed out of complicated data by statistical averages unless the statistics are tuned by theoretical predictions. An important duty of the theoretician is to classify the regularities of phenomena as an aid to experimentalists in analyzing data from subsequent investigations.

The formalism introduced in [22] is able to select the output of any functional network [10] that may be a subset of the anatomical network by defining a rhythm to be a cycle, subject to the dynamics of the network, where each cell changes state exactly twice. The method uses two-state neurons and combines various cellular and synaptic properties to formalize transitions between states. A wide range of network behaviors can be modeled with this method to predict rhythmic behavior in dynamic biological networks. When modeling small neural networks, there is often a tradeoff between computational efficiency and biological details. Reducing the details of a model is not incompatible with maintaining biological realism because detailed biological models can be highly nonlinear in their predictions so that a small error in setting the values of model parameters can lead to very unrealistic predictions. The advantage of using efficient methods to predict network behavior is that a wide range of conditions can be tested.

The formalism used in the this article is able to scan the space of rhythms and identify the possibilities that can be generated by a given neural circuit. This approach is therefore independent of any specific choice of initial conditions and can be thought of as a technique to identify the global attractors of the network for rhythmic behaviors. A network may generate a large number of rhythms so that a measure on the space of rhythms is required to make comparisons and classify the variety of rhythmic output. The measure investigated in [21] guarantees that functionally similar patterns are in close proximity of each other and clusters of rhythms form around dominant patterns in rhythm space. The specific biological mechanisms responsible for differences between rhythmic classes (or clusters in rhythm space) can be identified to reveal factors important for maintaining temporal patterns generated by multiple pattern generators.

The inclusion of cellular properties along with synaptic connectivity allows the formalism to predict temporal patterns generated by biological networks [22]. By including physiologically realistic cellular properties such as endogenous oscillation and postinhibitory rebound, a computationally simple model was used to predict the neural activity of dynamic biological networks (an example such networks are discussed in [17]). The next step in such an analysis would be to understand what biological mechanisms are involved in generating rhythms, or under what conditions these rhythms might be observed. Since the mechanisms responsible for each transition are explicit in the formalism, the juncture points can be identified at which two rhythms diverge to establish their identity in different behavioral classes.

The purpose of this article is to establish a mathematical foundation for investigating the interactions among patterns of neural activity in sensorimotor organization. In contrast to conduction-based modeling, the details of the membrane conductances are discretized to greatly reduce the computational load while maintaining the essence of relevant biological mechanisms. We test for rhythmic behavior in biological neural networks, and develop a general method to *classify* the possible patterns generated by a given network with known synaptic connectivity and cellular properties. Upon defining a suitable metric, the set of patterns form a metric space where *functionally* similar patterns appear in clusters, and each cluster defines a functional mode of the system.

In the next section, the mathematical fundamentals are explained and basic definitions are given. The following section applies the formalism to rhythmic behavior of the vestibular system, and analyzes bilateral neural networks to provide a mechanism for the generation of vestibular nystagmus.

2 Mathematical Methods

In well studied biological networks, many of the transitions between patterns of neural activity are already known in the form of synaptic or cellular properties which induce changes in the firing patterns of cells in the network. Conceptual machinery will be developed in the following to help elucidate how these properties work together to generate the observed behavior of the network. Traditional modelling studies develop complicated systems of differential equations, and then probe the parameter space on a point-by-point basis to examine the behavior of the model. Here, we depart from traditional methods by examining *probabilities* of changes in the behavior determined by regions of the parameter space.

Neural States and Transitions.

The generation of temporal patterns in the central nervous system often drive in motor circuits that require sustained bursts of action potentials to control muscle activity. The neurons participation in these circuits utilize slow responding currents to generate plateau potentials, long depolarized states that produce a burst of action potentials [16]. The output states of model neurons in the approach used here will be described as McCulloch-Pitts neural units [20], c_n, where $n = 1, \ldots, N$, and N is the number of neural units in a given network. Each neuron Associated with it an indicator of the membrane potential that takes its values in a binary state space, $\tilde{c}_n \in \mathbf{Z}_2$, where here the excited state ($\tilde{c}_n = 1$) means that the neuron is firing a burst of action potentials.

A set of N 2-state neurons, in combination with synaptic connections and cellular properties, is called a *network*, and is denoted; $\mathcal{N} = \{c_1, c_2, \ldots, c_N; \mathcal{S}, \mathcal{C}\}$, where $\mathcal{S}$ is a set of synaptic connections and $\mathcal{C}$ is a set of cellular properties. The two states of individual neurons will be represented by the 2-dimensional vectors:

$$c_n = \begin{bmatrix} 1 \\ 0 \end{bmatrix} \text{ or } \begin{bmatrix} 0 \\ 1 \end{bmatrix}. \tag{2.1}$$

A *neural state* is defined by P.Getting [10] to be the spatial distributation of activity within the network at any given moment in time. For example, if the set of neurons are given as

$$\nu = \{c_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, c_2 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}, c_3 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \ldots, c_N = \begin{bmatrix} 1 \\ 0 \end{bmatrix}\}, \tag{2.2}$$

then neuron c_1 is in a depolarized state, c_2 is in a polarized state, etc. We will abbreviate the above neural state as $\nu^n = [101\ldots1]$. The superscript denotes which neural state so that in a network of

N neurons, $n = 1, \ldots, 2^N$. This set of 2^N neural states form the basis of a vector space, V_{sp}, that represents all possible neural states.

Operators may now be defined that act on the neural states. For each element of $\mathcal{S}$ and $\mathcal{C}$ there corresponds an operator, $\mathcal{O}$, which transforms each neural state into a linear combination of states, $\mathcal{O} : V_{sp} \to V_{sp}$,

$$\mathcal{O}\nu^i = \sum_{j=1}^{2^N} a_j \nu^j \tag{2.3}$$

The coefficients, a_j, are weighting factors that will be used to set the relative strengths of the synaptic and cellular properties. It should be noted that cellular and synaptic properties may have different time scales, so the coefficients can be time dependent. Since this is a collection of 2-state systems, the operators will be defined in terms of the standard Pauli spin matricies as given in [7]; σ_1, σ_2, σ_3, and the 2×2 identity matrix, $\mathbf{1}$. A convenient set of operators from which to build the synaptic and cellular operators are given by

$$\begin{aligned} \mathcal{H}^{\pm} &= \frac{1}{2}(\sigma_1 \mp i\sigma_2) \\ \mathcal{L}^{\pm} &= \frac{1}{2}(\mathbf{1} \pm \sigma_3) \end{aligned} \tag{2.4}$$

It should be noted that these operators do *not* commute so one must be careful with their ordering when constructing synaptic and cellular operators. The operator $\mathcal{H}^+$ may be considered as a hyperpolarization operator which turns off a neuron in the excited state, and it is paired with $\mathcal{H}^-$ which depolarizes resting a neuron:

$$\begin{aligned} \mathcal{H}_n^+[c_1 \ldots c_{n-1}\, 1\, c_{n+1} \ldots c_N] &= [c_1 \ldots c_{n-1}\, 0\, c_{n+1} \ldots c_N], \\ \mathcal{H}_n^-[c_1 \ldots c_{n-1}\, 0\, c_{n+1} \ldots c_N] &= [c_1 \ldots c_{n-1}\, 1\, c_{n+1} \ldots c_N]. \end{aligned} \tag{2.5}$$

The other operators are projection operators which measure whether a neuron is in an excited or resting state:

$$\begin{aligned} \mathcal{L}_n^+[c_1 \ldots c_{n-1}\, 1\, c_{n+1} \ldots c_N] &= [c_1 \ldots c_{n-1}\, 1\, c_{n+1} \ldots c_N], \\ \mathcal{L}_n^-[c_1 \ldots c_{n-1}\, 0\, c_{n+1} \ldots c_N] &= [c_1 \ldots c_{n-1}\, 0\, c_{n+1} \ldots c_N]. \end{aligned} \tag{2.6}$$

Suppose there is a synaptic connection between neurons m and n in the network N where c_m represents a presynaptic cell c_m represents a postsynaptic cell. One may then define the following synaptic operators:

- Inhibitory: $\mathbf{S}^I_{mn} = s^{mn}_I \mathcal{H}^-_n \mathcal{L}^+_m$
- Excitatory: $\mathbf{S}^E_{mn} = s^{mn}_E \mathcal{H}^+_n \mathcal{L}^+_m$
- Gap junction: $\mathbf{S}^G_{mn} = s^{mn}_G (\mathcal{H}^+_n \mathcal{L}^+_m + \mathcal{H}^-_n \mathcal{L}^-_m + \mathcal{H}^+_m \mathcal{L}^+_n + \mathcal{H}^-_m \mathcal{L}^-_n)$
- Rectifier junction: $\mathbf{S}^R_{mn} = s^{mn}_R (\mathcal{H}^+_n \mathcal{L}^+_m + \mathcal{H}^-_n \mathcal{L}^-_m)$

For example, if the synapse is inhibitory, then the operator acts on neural states as:

$$\begin{aligned} \mathbf{S}^I_{mn}[c_1 \ldots c_{m-1}\, 1\, c_{m+1} \ldots c_{n-1}\, 1\, c_{n+1} \ldots c_N] &= s^{mn}_I [c_1 \ldots c_{m-1}\, 1\, c_{m+1} \ldots c_{n-1}\, 0\, c_{n+1} \ldots c_N] \\ \mathbf{S}^I_{mn}[c_1 \ldots c_{m-1}\, 1\, c_{m+1} \ldots c_{n-1}\, 0\, c_{n+1} \ldots c_N] &= 0 \\ \mathbf{S}^I_{mn}[c_1 \ldots c_{m-1}\, 0\, c_{m+1} \ldots c_n \ \ldots c_N] &= 0. \end{aligned} \tag{2.7}$$

The real coefficients s^{mn}_I, s^{mn}_E, s^{mn}_G, and s^{mn}_R are useful to assign the strength of the mechanism represented by the operator, and these coefficients may be time dependent. The first two of the above operators are commonly associated with chemical synapses with time courses that are longer than the second two which represent electrical synapses. At the first stage of a rhythmic analysis, it is customary to set all of the operator coefficients to unity.

In a biological neural network, membrane currents may cause neurons to terminate a burst of action potentials spontaneously after a period of time, or remain tonically active. A third possibility is that a neuron may oscillate between quiescence and bursts. To each cell in the network we assign one of the following operators to reflect these properties.

- Plateau termination: $\mathbf{C}^{PT}_n = c^n_{PT} \mathcal{H}^-_n$
- Tonic Activity: $\mathbf{C}^{TA}_n = c^n_{TA} \mathcal{H}^+_n$
- Endogenous oscillations: $\mathbf{C}^{EO}_n = c^n_{EO} (\mathcal{H}^+_n + \mathcal{H}^-_n)$

One more cellular property plays a central role in many pattern generating networks. If a neuron is in a resting state and is concurrently subjected to a inhibitory current, often it will adapt to the added current, thus holding the membrane potential at a preferred value. If the inhibitory current is then removed, the cell may rebound to an excited state. This phenomenon is called postinhibitory rebound [3] and is assigned the following operator:

- Postinhibitory rebound: $\mathbf{C}^{PIR}_{mn} = c^{mn}_{PIR} \mathcal{H}^+_n \mathcal{L}^-_m$

There are two indices because it is presently assumed that inhibition is a result of a postsynaptic inhibitory current, and the operator $\mathcal{L}_m^-$ insures that the presynaptic cell is no longer in an excited state. This operator can only be applied in combination with an operator that silences the presynaptic neuron (c_m) which has been inhibiting the postsynaptic neuron (c_n).

In order to use these operators to analyse a biological neural net one takes a sum of all the synaptic and cellular properties and applies the resultant operator to any neural state. To show how this procedure is carried out in practice, we will take the not-so-realistic (though standard) example of two mutually inhibitory neurons (Fig. 1A). The operator for this network takes the form:

$$\mathcal{O} = \mathbf{S}_{12}^I + \mathbf{S}_{21}^I + \mathbf{C}_{12}^{PIR} + \mathbf{C}_{21}^{PIR} + \mathbf{C}_1^{PT} + \mathbf{C}_2^{PT} + \mathbf{C}_{12}^{PIR}\mathbf{C}_2^{PT} + \mathbf{C}_{21}^{PIR}\mathbf{C}_1^{PT} \tag{2.8}$$

This operator acts on the neural states, $[c_1, c_2]$ as follows.

$$\begin{aligned}
\mathcal{O}[11] &= (s_I^{12} + c_{PT}^2)[10] + (s_I^{21} + c_{PT}^1)[01] \\
\mathcal{O}[10] &= c_{PT}^1[00] \\
\mathcal{O}[01] &= c_{PT}^2[00] \\
\mathcal{O}[00] &= c_{PIR}^{21}[01] + c_{PIR}^{12}[10]
\end{aligned} \tag{2.9}$$

Thus, a list is generated of the transitions from each neural state under the influence of the connectivity and cellular properties. The probability of each transition is the coefficient divided by the sum of all the coefficients included in the sum. For instance, the transition probability for $[11] \to [10]$ is

$$\mathcal{P}([11] \to [10]) = \frac{s_I^{12} + c_{PT}^2}{s_I^{21} + c_{PT}^2 + s_I^{12} + c_{PT}^1}. \tag{2.10}$$

Physiological data may be used to set the values of these variable to determine the transition probabilities of each transition.

Rhythms and Rhythmic patterns.

The application of the synaptic and cellular operators on states of the network N generates a set of transitions between neural states. Each transition is denoted by $(\nu_i, \nu_f)_M$, where ν_i is the initial state of the transition, ν_f is the final state, and $M \in \{I, E, G, R, PT, TA, EO, PIR\}$ is the mechanism responsible for the transition. The set $\mathcal{E} = \{(\nu_i, \nu_f)_M, \text{ for any } M\}$ is formed by the set of unique directed edges such that the specification of the mechanism is suppressed. Combining this set with the set of neural states, $\mathcal{V}$, forms the transition graph of the network, $G(\mathcal{V}, \mathcal{E})$. The transition graph for the half-center oscillator is shown in Fig. 1B.

An important subgraph of $G(\mathcal{V}, \mathcal{E})$ for the study of rhythmic behavior is the graph that is generated by introducing current thresholds for the neurons of the network, and eliminating those transitions

that violate a rule based on the sum of currents in each cell [20]. For instance, if the network is in a state where one of the neurons is heavily inhibited by synaptic currents, then it is biologically implausible that the cell would undergo a transition from a silent state to firing a burst.

If postsynaptic currents are labeled by integers, $i_n \in \mathbf{Z}$, for each neuron n, then $i_n > 0$ represents an excitatory and $i_n < 0$ an inhibitory postsynaptic current. A value C may be assigned to each type of transition such that $C > 0$ implies that the transition in which a neuron changes from an inactive to an active state and $C < 0$ otherwise. A transitions is eliminated by the *synaptic* constraint if

$$\begin{aligned} C + \sum_n i_n &\geq \theta, \text{ for } C < 0 \\ C + \sum_n i_n &\leq -\theta, \text{ for } C > 0 \end{aligned} \tag{2.11}$$

where θ is a threshold and the sum is over all active presynaptic neurons.

In order to study complicated rhythms in all but the simplest of networks, we will need a notation to keep track of cycles on the transition graph and aid in the classification of multiple rhythms. The definition of rhythm will be formalized using techniques found in [4], resulting in a method to generate the functional rhythms of a network. The first step is to define what is meant by a path on the transition graph (for an alternative approach, see [13]). Let $\mathcal{E}^*$ be the set of finite sequences of elements of $\mathcal{E}$ juxtaposed; $\mathcal{E}^* = \{(\nu_{f_1}|\nu_{i_1})(\nu_{f_2}|\nu_{i_2})(\nu_{f_3}|\nu_{i_3})\cdots(\nu_{f_k}|\nu_{i_k}) : (\nu_{f_a}|\nu_{i_a}) \in \mathcal{E}, a \in \mathbf{Z}^+\} \cup \epsilon$, where ϵ represents the null sequence. A *path* on the transition graph is an element of $\mathcal{E}^*$ where the transitions are contiguous so that $\nu_{f_a} = \nu_{i_{a+1}}$ for all juxtaposed elements. We now need a function that acts on elements of $\mathcal{E}^*$ which will count how many times each cell of the network has changed state, and what the nature of that change is. Let N be the number of neurons participating in the functional network. We define the *label* function $\ell : \mathcal{E}^* \to \mathbf{Z}^N \times \mathbf{Z}^N$: If $(\nu_f|\nu_i) \in \mathcal{E}$, where $\nu_i = [\tilde{c}_1 \ldots \tilde{c}_N]$, and $\nu_f = [\tilde{c}'_1 \ldots \tilde{c}'_N]$, then $\ell(\nu_f|\nu_i) = (b_1^+ \ldots b_N^+; b_1^- \ldots b_N^-)$, where

$$\begin{aligned} b_n^+ &= \begin{cases} 1 \text{ if } c'_n - c_n = 1 \\ 0 \text{ otherwise} \end{cases} \\ b_n^- &= \begin{cases} 1 \text{ if } c'_n - c_n = -1 \\ 0 \text{ otherwise} \end{cases} \end{aligned} \tag{2.12}$$

The function ℓ is extended to all of $\mathcal{E}^*$ as follows:

$$\ell(S_1 S_2) = \ell(S_1) + \ell(S_2) \tag{2.13}$$

for $S_1, S_2 \in \mathcal{E}^*$ and '+' is vector addition in $\mathbf{Z}^N$. Since the transition operators have been defined to allow only one neuron to change with each transition, the function ℓ given by eq.(2.12) maps elements of $\mathcal{E}$ to vectors with all components equal zero except one that is unity.

We next introduce a *path algebra* which is a set P with two binary operators, a join operation and multiplication obeying the rules below [4]. For our present purposes, the set P is the power set of $\mathcal{E}^*$; the set of sets of elements of $\mathcal{E}^*$. The binary operators are defined as follows:

- The join operation ($\vee$) is idempotent, commutative, associative, and is taken here to be set union.
- Multiplication ($\cdot$) is associative, and distributive over $\vee$, and is defined here for $S_1, S_2 \in P$ by concatenation:

$$S_1 \cdot S_2 = \{\pi_1\pi_2 \; : \quad \text{for all } \pi_1 \in S_1, \pi_2 \in S_2 \text{ and} \\ \ell(\pi_1\pi_2) = (b_1^+ \ldots b_N^+; b_1^- \ldots b_N^-), b_n^{\pm} \leq 1 \text{ for all } n\}, \tag{2.14}$$

This rule allows only two changes of state on the path for each neuron. A path algebra has, by definition, a zero element which is the empty set:

$$\begin{aligned} \phi \vee S &= S \qquad \text{for all } S \in P \\ \phi \cdot \; S &= \phi = S \cdot \phi \quad \text{for all } S \in P. \end{aligned} \tag{2.15}$$

In addition, a path algebra contains a multiplicative identity element which is the null path $\epsilon \in \mathcal{E}$:

$$\epsilon \cdot \; S = S = S \cdot \epsilon \qquad \text{for all } S \in P. \tag{2.16}$$

We may now state the definition of an N-rhythm as an $2N$-cycle of transitions

$$\mu = (\nu_{f_1}|\nu_{i_1})(\nu_{f_2}|\nu_{f_1}) \ldots (\nu_{i_1}|\nu_{i_{2N}}) \tag{2.17}$$

such that

$$\ell(\mu) = (1, \ldots 1; 1, \ldots, 1). \tag{2.18}$$

Every graph $G = (\mathcal{V}, \mathcal{E})$ with h vertices and the path algebra P has an associated *adjacency matrix*, $A = [a_{if}]$ where $i, f = 1, 2, \ldots, h = 2^N$ and the entries are defined by;

$$a_{if} = \begin{cases} \{(\nu_f|\nu_i)\} & \text{if } (\nu_f|\nu_i) \in \mathcal{E} \\ \phi & \text{if } (\nu_f|\nu_i) \notin \mathcal{E} \end{cases} \tag{2.19}$$

The adjacency matrix is useful for calculating paths on the graph G. The definition of the path algebra given above is designed to calculate rhythms of a network. Matrix multiplication is defined

in terms of the path algebra in analogy to matrices of real numbers where sums are replaced by the join operator so that the result is a matrix whose elements are members of P. By taking powers of the matrix A^k, the entries along the diagonal represent k-cycles satisfying the rule that no neuron has changed state more than twice. Thus, the set of N-rhythms containing the neural state ν_i is given by the i^{th} entry on the diagonal of the matrix A^{2N}:

$$R_i = \bigvee_{j_1,j_2,\ldots,j_{2N-1}} \{(\nu_{j_1}|\nu_i)\} \cdot \{(\nu_{j_2}|\nu_{j_1})\} \cdots \{(\nu_{j_{2N-1}}|\nu_{j_{2N-2}})\} \cdot \{(\nu_i|\nu_{j_{2N-1}})\}. \tag{2.20}$$

where $\bigvee_{j_1,j_2,\ldots,j_{2N-1}}$ represents the join of all values of the indices.

The set R of all N-rhythms generated by a network is given by the join $R = \bigvee_i R_i$. Because the join operator is idempotent, the duplicate cycles drop out of the series. Two rhythms are considered equivalent if the sequences of their neural states are identical. The maximum number of possible rhythms that can be generated by a network containing N neurons can be computed by considering that each state in the transition graph shares an edge with exactly N other states. Each rhythm of the network is a $2N$-cycle of transitions because each transition has a label with a single 1 in the appropriate position. Thus, each rhythm can be associated with a cycle of $2N$ such labels, and in fact, there is a one-to-one correspondence between the rhythms in the given network and the cycles consisting of all $2N$ labels that have a single 1. To count these cycles, the number of orderings if these labels is equal to the number of permutations of $2N$ elements $(2N!)$. Since there is a symmetry of rotations through the cycles, the final answer of $(2N-1)!$ rhythms is arrived at by dividing out the symmetry.

Most networks will generate a large number of rhythms so it is useful to have a means of comparing different rhythms of a fixed number of neurons. By comparing similar rhythms we will then be able to classify the patterns generated by a given network into groups that reflect a similar property. The functional similarity relevant to many neural systems is the sequence of bursts generated by the composite neurons. Comparisons between rhythms can be accomplished by introducing a distance function onto the set of rhythms to quantify the functional differences between them. For each rhythm, there is a sequence of $2N$ *transition vectors*, $p_i \in \mathbf{Z}_2^N$, $i = 1, \ldots, N$, which are N-tuples of zeros and a 1 in the location of the neuron that changed state. Note that different sequences of neural states may have the same sequence of transition vectors so that the transition vectors do not uniquely determine a rhythm. It is often convenient to write rhythms with the transition vectors inserted between the states as in the following where we show only 3 states of a rhythm;

$$\cdots[\ldots\tilde{c}_m\ldots\tilde{c}_n\ldots]p_m[\ldots\tilde{c}'_m\ldots\tilde{c}_n\ldots]p_n[\ldots\tilde{c}'_m\ldots\tilde{c}'_n\ldots]\cdots \tag{2.21}$$

We may transform this rhythm into another by transposing the vectors p_m and p_n, changing the intervening neural state accordingly;

$$\cdots[\ldots\tilde{c}_m\ldots\tilde{c}_n\ldots]p_n[\ldots\tilde{c}_m\ldots\tilde{c}'_n\ldots]p_m[\ldots\tilde{c}'_m\ldots\tilde{c}'_n\ldots]\cdots \tag{2.22}$$

Since these two rhythms differ by only one neural state, it is natural to consider them to be neighbors in the set of rhythms. Thus, distance in rhythm space is defined as: *The distance between two rhythms is the minimum number of adjacent transpositions of transition vectors that transforms one rhythm into the other* [22]. It should be stressed that this kind of distance differs from the Hamming distance which measures the overlap between two strings of binary numbers. All rhythms that are neighbors in rhythm space would have a Hamming distance of two.

The reason for choosing this definition is that it implies that two neighboring rhythms have a strong functional similarity. Except for where they differ, they share all of the same transitions, and thus the same temporal pattern. The difference is the detour through the transition graph where their paths separate for a single neural state in the sequence, and then rejoin after the following transition. One is often interested in the activity of motor neurons, or neurons that drive motor neurons, so that similarities in rhythm space translates into similarities in movement patterns of the organism.

An interesting example is provided by the network shown in Fig. 2A [18, 14]. Since this network is anatomically symmetric under cyclic rotations of the neurons, we may use the dynamical equivalences classes [11] in addition to the functional classification presented here. This is also a good example to demonstrate the variation of rhythmic behavior under changes of cellular properties.

Let the network be defined by $\mathcal{N}_4 = \{1, 2, 3, 4; \mathcal{S}, \mathcal{C}\}$ where

$$\begin{aligned}\mathcal{S} = \{ \quad & \mathbf{S}^I_{1,\,4}, \mathbf{S}^I_{4,\,3}, \mathbf{S}^I_{3,\,2}, \mathbf{S}^I_{2,\,1}, \\ & \mathbf{S}^I_{1,\,3}, \mathbf{S}^I_{3,\,1}, \mathbf{S}^I_{2,\,4}, \mathbf{S}^I_{4,\,2}\}\end{aligned} \tag{2.23}$$

and

$$\mathcal{C}^{TA} = \{\mathbf{C}^{TA}_1, \mathbf{C}^{TA}_2, \mathbf{C}^{TA}_3, \mathbf{C}^{TA}_3\}. \tag{2.24}$$

Without the application of constraints, this network generates 1715 rhythms. This number should be compared with the maximum of $7! = 5040$ rhythms that can be generated by a 4-cell network. Since the network is highly inhibitory, constraints will greatly reduce this number. Under the synaptic constraint with the threshold $\theta = 0$, the network generates one rhythm as shown in Fig. 2B. Note that the rhythm is symmetric under cyclical permutations of the neurons.

Instead of allowing the network to be driven by tonically active neurons, we may investigate the results of postinhibitory rebound as a driving mechanism. In this case we let the set of cellular properties be described by the set,

$$\begin{aligned}\mathcal{C}^{PIR} = \{ \quad & \mathbf{C}_1^{PT}, \mathbf{C}_2^{PT}, \mathbf{C}_3^{PT}, \mathbf{C}_3^{PT}, \\ & \mathbf{C}_1^{PIR}, \mathbf{C}_2^{PIR}, \mathbf{C}_3^{PIR}, \mathbf{C}_3^{PIR}\}. \end{aligned} \tag{2.25}$$

With these cellular properties, the network generates 204 rhythms without constraints and, if constrained with $\theta = 0$, then we find 16 rhythms that fall into 12 clusters. Due to the symmetry of the network, we may classify these clusters into 5 dynamical equivalence classes [11, 12] of whose members are equivalent under cyclical rotations of the neurons. Representatives of each equivalence are shown in Fig. 2C, where rhythms 1a and 1b form a cluster of two. Classes 2 and 5 have only one member, classes 1 and 3 have 4 members each, and class 4 has 2 members.

In the above example, we have defined clusters in rhythm space to be sets of rhythms that fill contiguous regions with a neighborhood of one surrounding each rhythm. In larger networks, it becomes advantageous to expand the neighborhood to larger distances between neurons when defining clusters. This is because in large networks there become so many ways two rhythms may differ that functional similarity may be preserved over greater distances in rhythm space. The rhythms of Fig. 2C are marked for both nearest neighbors (solid line between 1a and 1b) an

3 Application: Vestibular Nystagmus

The method described in this article has been previously used to predict the temporal pattern generation of small biological networks in invertebrate preparations [22, 21]. This approach to temporal pattern generation is also useful for vertebrate system with large numbers of neurons arranged in parallel circuits because of the probabilistic interpretation of the clusters in rhythm space. In a single small neural network, a cluster of rhythms is interpreted as variations on the rhythm that the network generates, and if there are many similar variations, a large cluster, that there are many reinforcing mechanisms at work to stabilize the temporal pattern.

In an ensemble of neurons where there are many parallel neural modules, then the clusters in rhythm space represent similar rhythms that occur simultaneously. These types of parallel neural modules are ubiquitous in the central nervous systems of vertebrates. The rhythm space method has successfully predicted the synchrony of cerebellar climbing responses due to gap junctions in

the inferior olive [23]. In the following, the circuitry in the brainstem that is involved in generating vestibular nystagmus is investigated, and the essential elements of the circuit are revealed.

Rhythmic patterns of bilateral vestibular circuitry.

The activity of neurons in the vestibular nuclei drive ocular-motor neurons to stabilize gaze during movements of the head. A sudden change of the input level from the vestibular end-organs, such as a complete loss of input following a lesion in the eighth nerve containing primary vestibular afferents, causes a rhythmic movement of the eyes, or nystagmus. Most studies concerning vestibular nystagmus treat the two phases of the behavior separately. Here we explore the possibility of brain stem circuitry that is responsible for generating the full rhythm.

In order to investigate whether a bilateral circuit exists that contributes to the maintenance of vestibular nystagmus, we evaluate the rhythmic patterns supported by the circuit consisting of the vestibular nuclei carrying head velocity information, the trochlear nucleus, and the inferior oblique division of the oculomotor nucleus. This circuit has been known to be instrumental in producing oblique nystagmus [2].

The space of rhythms for this vestibular circuit (Fig. 3A) was scanned to determine the potential rhythmic behavior that it could sustain. Functionally similar rhythms are manifest as the most prominent clusters in rhythm space. Rhythm space analysis shows the kind of rhythmic behavior that is dependent on the specifics of the functional networks, and which networks, if any, are common to several functional states of the system.

Although the unilateral circuit given in [2] does not support rhythmic behavior, a bilaterally symmetric version of it generated two clusters of rhythms shown in Fig. 3B. The rhythm clusters appear when there is an asymmetry between the right and left primary afferent vestibular input. In the clusters, there is an asymmetry in the length of activation of the neurons driving the inferior oblique motor neurons. This asymmetry corresponds to and contributes to the asymmetry of the fast phase verses the slow phase in nystagmus. The two rhythm clusters show a difference in motor neuron phasing (Fig. 3C).

More recently, a bilateral model by Galiana and Oterbridge (1984) based on physiological data has proven successful for predicting the linear dynamics of the slow phase of vestibular nystagmus [25, 15]. Although this bilateral model [9] is presently considered as the standard in bilateral modeling of the brainstem circuitry responsible for the dynamics of vestibular nystagmus, a rhythm space analysis finds that no rhythms are generated by this model without modification.

The necessary modification are found upon closer inspection of the bilateral version of the Baker

and Berthoz (1974) model. The essential pattern generating circuit is shown in Fig. 4A, where the other neurons in the previous figure only follow the activity of this circuit. One cluster in rhythm space is generated by this circuit, as shown in Fig. 4B. A comparison with the bilateral circuit given in Smith and Galiana (1991) reveals the missing element. Although there is a recurrent excitatory input to the vestibular nuclei representing "efferent copy", the missing internal detail within the vestibular nuclei lacks inhibitory interneurons. These interneurons provide essential hyperpolarization in the rhythmic model so that rebound properties of other neurons in the vestibular nuclei drive the rhythmic cycle of the vestibular nystagmus.

4 Discussion

This article has developed a method to analyze rhythmic patterns that are generated by neural circuits. The activity of a network is represented by neural states that are capable of transitions to a finite set of other states. Cycles on the graph of transitions are used defined rhythms that represent the temporal activity patterns of neural circuits. This method can be used to predict the rhythmic behavior of small networks found in invertebrates [22, 21] or ensembles of neurons found in vertebrates [23]. The difference is in the interpretation of the rhythm clusters generated by the method.

The analysis of brainstem circuitry responsible for vestibular nystagmus reveals the utility of this approach in the study on the neural basis for motor behavior. Linear approaches to vestibular reflexes do not predict the switching from the slow phase of the nystagmus to the fast phase. But here the vestibular nystagmus is treated as a whole rhythm and physiological mechanisms of the switching between phases are revealed. Although each phase of the nystagmus recruits different subsystems of the visual system, the imbalance of vestibular input that is known to be responsible for nystagmus is shown to involve circuitry within the vestibular nuclei to switch between each phase.

A deeper analysis would require further data to estimate the transition probabilities and the likelihood of each rhythm and cluster. This further analysis would predict the neural activity that would be recorded in the vestibular nuclei following a lesion to the eighth nerve in animal preparations. In the present form of the analysis given above, the phase response of GABAergic interneurons in the medial vestibular nuclei during vestibular nystagmus has been predicted for the first time.

A limitation of this approach is that the details of eye movements during each phase of nystagmus are absent. The rhythm space method is most concerned with the nonlinear switching between neural states, and the cyclical patterns that result. The dynamics of the slow phase has been analyzed using linear systems approaches (see, for example [25]) and the present study only addresses the rhythmic

character of vestibular nystagmus.

The most important contribution of this approach will be for revealing of synaptic connections and cellular properties in neural systems where exact experimental data is lacking. For instance, the observation of phase relations between recordings of bursts of action potentials from single cell recordings can be compared with motor activity as in the previous section. New, unrecognized synaptic connections to recorded neurons can be implied from these methods by deducing the necessary mechanisms for the generation of observed rhythms.

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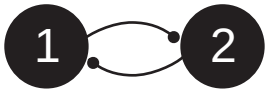
Figure 1: *Half-center oscillator.* (A) Network of 2 neurons with mutual inhibitory synaptic connections. (B) Transition graph of the half-center oscillator with the two types of transitions: Plateau termination (PT) and postinhibitory rebound (PIR).

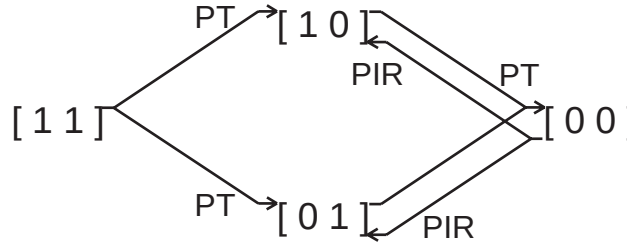
Figure 2: *Model rhythm generating network.* (A) Network of 4 neurons with inhibitory synaptic connections. (B) The rhythm generated by the network under synaptic constraints ($\theta = 0$) and each neuron is tonically active. (C) Representative rhythms of the network driven by postinhibitory rebound (see text for details). Solid lines between rhythms indicate a distance of one in rhythm space and broken lines indicate a distance of two.

Figure 3: *Rhythmic patterns supported by a bilateral vestibular circuit are responsible for oblique nystagmus.* The circuit (A) is the bilaterally symmetric version of the schematic diagram given in [2] describing the pathways responsible for oblique nystagmus. The circuit supports two rhythm clusters (B). One cycle of the rhythm is shown in each case, with increasing activity being indicated by darker shading. Neurons of the right (left) medial nucleus (R(L)M) and the right (left) superior nucleus (R(L)S) are driven by the eight nerve (VIII). These neurons interact through interneurons found in the right (left) medial nucleus (R(L)MI). The rhythms of the vestibular nuclei drive the left trochlear (LTRO) and right inferior oblique (RIO) motor neurons. The asymmetry between RS and LS contribute to the difference between the fast phase and slow phase of nystagmus. The two rhythm clusters have a slight difference in motor neuron phasing, as shown in (C).

Figure 4: *The essential circuitry for generation of the vestibular nystagmus.*(A) The bilateral circuit in Fig. 3A without the follower motor neurons. Unilateral input from the left eighth nerve (VIII) excites secondary neurons of the left medial (LM) vestibular nucleus. An excitatory projection of these neurons crosses the midline and makes contact with interneurons of the right medial vestibular (RMI) nucleus that in turn inhibit the secondary neurons of the right medial nucleus (RM) that receive excitatory input from the right eighth nerve, but that input is absent in this case. These neurons send an excitatory projection across the midline to interneurons in the left medial (LMI) nucleus that inhibit the LM neurons. (B) The cluster in rhythm space generated by the circuit in (A) contains 7 rhythms. Without vestibular input, the only way for the RM neurons to fire action potentials is by rebounding after release from inhibition by the RMI neurons. Thus, without postinhibitory rebound, no rhythms are generated by the circuit. (C) The bilateral model of Galiana and Oterbridge (1984). Neurons of the left (right) vestibular nuclei (L(R)V) inhibit neurons of the left (right) abducens nucleus (L(R)A), that inhibit motor neurons of the left (right) oculomotor nucleus (L(R)O). Excitatory connections are made across the midline. The self excitation of the LV and RV neurons represent efferent copy. To generate rhythmic oculomotor behavior, such as vestibular nystagmus, the circuit requires inhibitory interconnections within the vestibular nuclei.

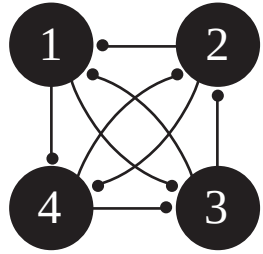


A



B

Fig. 1



A

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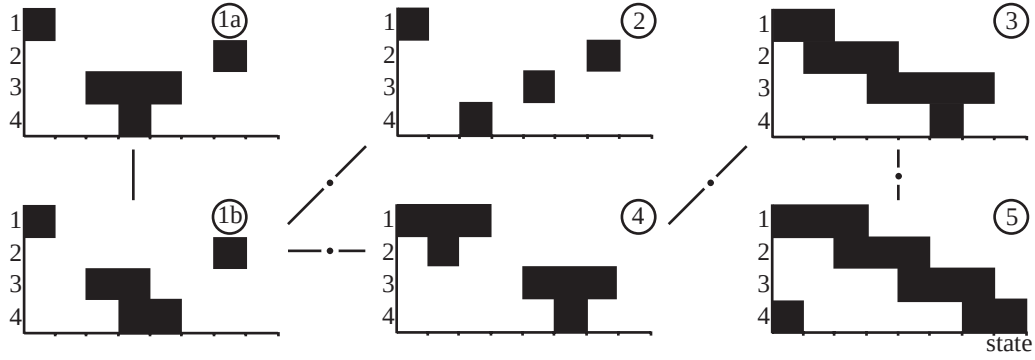
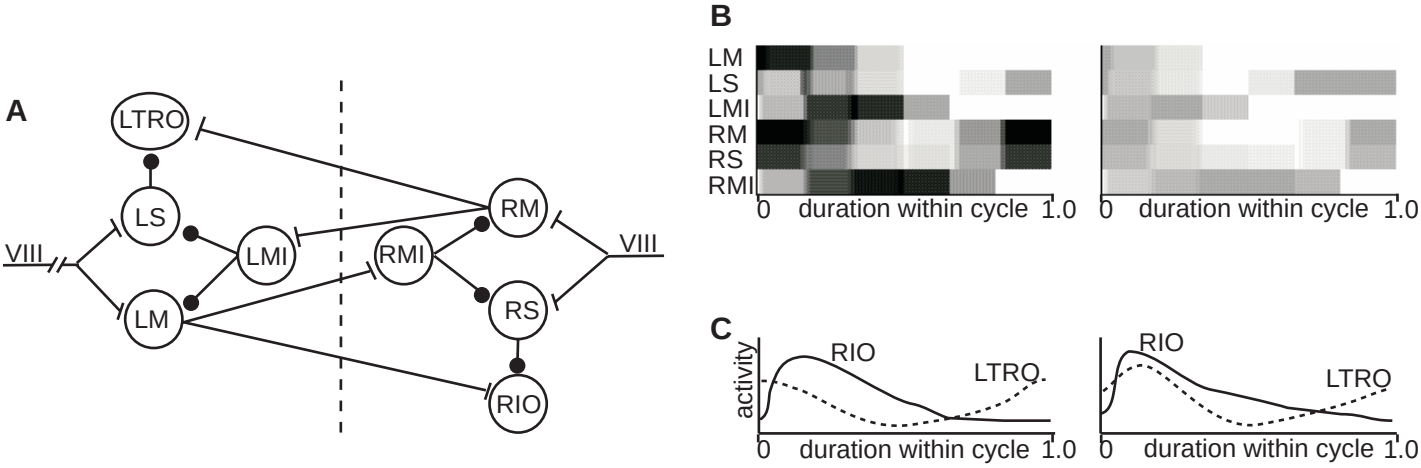


C

Fig. 2


A
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duration within cycle
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1.0
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Fig. 3