Classification of Temporal Patterns in Dynamic Biological Networks

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Abstract

A general method is presented to classify temporal patterns generated by rhythmic biological networks when synaptic connections and cellular properties are known. The method is discrete in nature and relies on algebraic properties of state transitions and graph theory. Elements of the set of rhythms generated by a network are compared using a metric that quantifies the functional differences between them. The rhythms are then classified according to their location in a metric space. Examples are given and biological implications are discussed.

1 Introduction

The development of theoretical tools is essential for a thorough understanding of complex biological systems. Networks of interconnected neurons are systems that can display very complex dynamics. Much of the literature concerning neural networks focuses on the strengths of synaptic connections (Hebb, 1949) when analyzing network dynamics. The emphasis on synaptic currents tends to downplay other membrane properties of the neurons that make important contributions to the activity of biological networks (Llinás, 1988; Maynard, 1972; Mulloney and Selverston, 1974). In recent years it has become clear that the modulation of cellular properties is as important to the behavior of a

biological network as the efficacy of synaptic connections. In the ongoing behavior of an animal, neural modulation by hormones or neuropeptides is crucial to the maintenance and control of neuronal activity (Harris-Warrick et al., 1992). A formalism designed to aid in our understanding of biological neural systems should take into account such modulation for a thorough description of behavior in specific applications.

Recent experimental studies of central pattern generators have revealed that the rhythmic output of small neural circuits can switch between elements of a restricted group of stable patterns (Dickinson and Moulins, 1992). In fact, the idea of a pattern generator as an anatomically distinct unit has given way to considerations of *functional multiple*-pattern generators that are dynamically sculpted out of a fixed anatomical network (Getting, 1989). These dynamic biological networks appear to be controlled by both diffuse application of neuromodulators and direct synaptic stimulation of target cells.

Many modelling studies designed to explore the behavior of small neural networks have concentrated on the membrane conductances (Hodgkin and Huxley, l952) of the component neurons. In these models, the details of multiple membrane currents in the component neurons are simulated using coupled differential equations. Although these efforts reveal the behavior of a network under perturbations of system parameters, the computational overhead of these models forbids a full classification of rhythmic output. One may reduce the computational load while maintaining the essence of relevant biological mechanisms by discretizing the details of membrane conductances.

The logical complexity of *discrete* networks was first analyzed by McCulloch and Pitts (McCulloch and Pitts, 1942) in their study of neural networks. These early studies have since been expanded into a general study of discrete automata following technological advances in digital computers. A large class of discrete systems involves cellular automata (Wolfram, 1986; Kauffman, 1993) which have been shown to generalize to discrete neural network models (Garzon, l990). Methods to analyze these systems have proven useful in the study of general complex systems (Weisbuch, 1991), but such methods must be adapted to the idiosyncrasies of multiple-pattern generators.

Deterministic models, such as Boolean automata, have been used to make specific predictions about the relation between a network's architecture and its output. Classifications of networks have been made using these methods based on symmetries (Glass, l975a) and the output dynamics (Wuensche and Lesser, 1992) of deterministic networks. However, deterministic systems do not include multiple mechanisms that are needed to predict all *possible* output patterns of a given biological network. In order to scan the range of possibilities, one must study less tractable, *non-deterministic* networks.

In a non-deterministic automata, each state may make a transition to more that one final state. This implies that the mechanisms do not uniquely determine the outcome following any point in the

dynamics of the system. In terms of symbolic dynamics, these systems can be described by *shifts of finite type* (Lind and Marcus, 1995). Methods from automata theory have been applied to continuous state dynamical systems in order to analyze their computational complexity (Crutchfield, l994). Such methods have recently been applied to neural network models yielding insights into the mechanisms implied by their input/output behavior (Casey, l996), and applied to study the computations of biologically plausible networks. (Kentridge, l994).

However, the previous research has proven difficult to use by experimentalists who wish to know what temporal patterns a specific dynamic biological network is capable of generating. Although discrete methods have been applied to study central pattern generators (Caianiello and Ricciardi, l967; Glass and Young, l979; Huerta, l996), a method to classify rhythmic behavior in terms of relations between different temporal sequences is a necessary addition to the theoretician's toolbox.

The purpose of this letter is to introduce two new tools for the study of multiple-pattern generators. First, cellular properties of constituent neurons are expressed as discrete transitions on equal footing with synaptically induced transitions. Secondly, similarities between rhythmic patterns are quantified in order to *classify* the possible patterns generated by a given network with known synaptic connectivity and cellular properties. The set of rhythmic patterns form a metric space where *functionally* similar patterns appear in clusters, and each cluster defines a functional mode of the system. Significant biological mechanisms that differentiate clusters can then be investigated to help understand how the network navigates through behavioral options.

In the next section we make the necessary definitions for this approach and present the scheme for identifying rhythmic patterns. The following section investigates the properties of the space of rhythmic patterns followed by a section with examples of dynamic biological networks. We conclude with a discussion of some open mathematical questions and biological implications of this approach.

2 Neural States and Transition Graphs

Central pattern generators are often found in motor circuits that require sustained bursts of action potentials to control muscle activity. Many of the neurons that participate in pattern generation exhibit plateau potentials; long depolarized states that arise from a bistable membrane potential (Hartline, 1987). In the language of Rinzel (Rinzel, 1987), the methods developed here focus on the *slow* mechanisms involved in the generation of rhythmic behavior. Individual action potentials are considered to have only a secondary effect on pattern generation.

2.1 Neural States. We will describe the output state of our model neurons in terms of standard McCulloch-Pitts neural units (McCulloch and Pitts, 1942), c_n, where $n = 1, \ldots, N$, and N is the number of neural units under consideration. Associated with each neuron is 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 *network* $\mathcal{N}$ is a set of N 2-state neurons augmented with synaptic connections and cellular properties; $\mathcal{N} = \{c_1, c_2, \ldots, c_N; \mathcal{S}, \mathcal{C}\}$, where $\mathcal{S}$ is a set of synaptic connections and $\mathcal{C}$ is a set of cellular properties. Both $\mathcal{S}$ and $\mathcal{C}$ formalized as transitions between states and the elements of $\mathcal{S}$ sometimes take on additional parameters that denote their efficacy. A *neural state* (or *configuration* (Botelho and Garzon, l991)) is defined by Getting (Getting, 1989) to be the spatial distribution of activity within the network at any given moment in time. For example, if at time t neuron c_1 is firing a burst of action potentials, c_2 is silent, c_3 is silent, etc., then the neural state will be represented as $\nu(t) = [\tilde{c}_1\tilde{c}_2\tilde{c}_3 \ldots \tilde{c}_N](t) = [100\ldots](t)$. The set of time-independent neural states (ignoring the time component) is denoted by $\mathcal{V} = \{\nu_1, \ldots, \nu_h\}$, where $h = 2^N$. We have given the neural states a subscript to identify them without an explicit reference to time.

The cellular properties and synaptic connections provide the *mechanisms* (M) of the network that induce transitions between neural states. For each element M of $\mathcal{S}$ and $\mathcal{C}$ there corresponds a collection of ordered pairs of neural states that represent transitions, $\{M(\nu_1'|\nu), M(\nu_1'|\nu)\ldots\}$. In each transition, $M(\nu'|\nu)$, the initial state is given by ν, the final state is ν', and the mechanism that presently accounts for the transition is labeled by M.

2.2 Transition Graphs. The full set of transitions generated by all elements of $\mathcal{S}$ and $\mathcal{C}$ in the network $\mathcal{N}$ is denoted by $\mathcal{E}$. Together with the set of neural states $\mathcal{V}$, the transitions define a directed graph $G(\mathcal{V}, \mathcal{E})$ that represents the dynamics of the network (Carré, 1979). In the graphical representation, the set $\mathcal{V}$ contains the vertices and the set $\mathcal{E}$ contains the edges. Since there is typically more than one out-going edge from each vertex in $G(\mathcal{V}, \mathcal{E})$, the system is non-deterministic and can be thought of as a Markov chain where the precise values of the non-vanishing probabilities are not specified (sometimes called a *topological* Markov chain (Lind and Marcus, 1995)[1]).

We now define useful cellular properties and their associated transitions. Cellular properties are used here in the sense that there are transitions that individual neurons can undergo independently of external influences arising from synaptic connections. Depending upon the conductance properties of a biological membrane, individual neurons can either spontaneously terminate a plateau, remain tonically active, or oscillate between active and inactive states. The cellular property called *plateau*

[1]The author would like to thank John Taylor for pointing out the methods of symbolic dynamics.

termination is interpreted as follows: A neuron (c_n) that can terminate a plateau, but cannot activate from a resting state without external influence, will contribute exactly one transition to the set $\mathcal{E}$, $\mathbf{C}_n^{PT}(\nu'|\nu) \in \mathcal{E}$, where $\tilde{c}'_n = 0$ if $\tilde{c}_n = 1$.

Two other cellular properties, *tonic activity* and *endogenous oscillation* will be interpreted analogously as transitions. The first transition, $\mathbf{C}_n^{TA}(\nu'|\nu)$, works in the opposite direction as plateau termination, if the neuron c_n is inactive, then it becomes active. The second cellular property, $\mathbf{C}_n^{EO}(\nu'|\nu)$, results in one of two transitions, depending upon the initial state of neuron c_n. If $\tilde{c}_n = 1$ then $\tilde{c}'_n = 0$, otherwise $\tilde{c}'_n = 1$

The information about synaptic connectivity of the network adds more transitions to the set $\mathcal{E}$. Suppose there is a synaptic connection between neurons c_m and c_n in the network $\mathcal{N} = \{\ldots, c_m, \ldots, c_n, \ldots; \mathcal{S}, \mathcal{C}\}$ where c_n is the postsynaptic neuron. A synaptic transition associated with an inhibitory chemical synapse in $\mathcal{S}$ is denoted as $\mathbf{S}_{mn}^{I}(\nu'|\nu)$ where the activity of the presynaptic neuron can silence the activity of the postsynaptic neuron so that $\tilde{c}'_n = 0$, if $\tilde{c}_n = 1$ and $\tilde{c}_m = 1$. The transition associated with an excitatory chemical synapse, $\mathbf{S}_{mn}^{E}(\nu'|\nu)$, is defined in an analogous manner except that the postsynaptic neuron is excited from an inactive.

Electrical synaptic connections cause the neurons to equalize their membrane potential so they either excite or inhibit, depending on the state of the presynaptic neuron. If the synapse is a *gap junction*, then either neuron can take the role of postsynaptic and presynaptic neuron. Suppose that $\tilde{c}_n = 1$ and $\tilde{c}_m = 0$. Then two transitions are associated with this connection: one with final state $\tilde{c}_n = 1$ and $\tilde{c}_m = 1$, and the other with final state $\tilde{c}_n = 0$ and $\tilde{c}_m = 0$.

Important subgraphs of $G(\mathcal{V}, \mathcal{E})$ for the study of rhythmic behavior result from the elimination of edges that do not satisfy certain constraints. 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 neuron would undergo a transition from a silent state to firing a burst of action potentials. One may introduce thresholds for the neurons of the network and eliminate those transitions that violate a rule based on the sum of ionic currents in each neuron (McCulloch and Pitts, 1942).

Let $i_n \in \mathbf{Z}$ be a postsynaptic current due to activity of neuron n where $i_n > 0$ for an excitatory and $i_n < 0$ for an inhibitory postsynaptic current. Assign a value C to each type of transition such that $C > 0$ if the transition represents a neuron changing from an inactive to an active state and $C < 0$ otherwise. A transitions is eliminated by the *synaptic* constraint if

$$\begin{aligned} C + \sum_n i_n &\geq \theta, \text{ for } C < 0 \\ C + \sum_n i_n &\leq -\theta, \text{ for } C > 0 \end{aligned} \tag{2.1}$$

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

3 Rhythms and Rhythm Space

We will concentrate on the *functional* output of a given anatomical network of distinguishable neurons because dynamic biological networks tend to reconfigure themselves to alter their output. The emphasis on functional output is achieved by defining a *rhythm* as a cycle through the transition graph, $G(\mathcal{V}, \mathcal{E})$, where each neuron participating in the functional network changes state exactly twice, and the states of all other neurons in the anatomical network are held fixed. This definition contains the simplification that makes our analysis possible, and there are several plausible reasons for why allowing only two state changes for each neuron is not too restrictive. Double bursts within a cycle of central pattern generators appear to be quite uncommon. In observed cases from the literature (see e.g. (Miller, 1987)) it can be argued that an observed double burst is actually a long plateau that has its spikes suppressed by inhibitory input during the middle of the plateau. A good reason for allowing only one burst for each neuron per cycle is that plateau mechanisms are slow (Rinzel, 1987) so that small neural networks complete a full cycle before any neuron has recovered from its last burst. Larger networks may have a tendency to breakup into smaller functional sub-networks, but this issue requires more detailed investigation.

In order to count the maximum possible number of rhythms generated by a network of a given size N, let us consider the extreme case where each state shares an edge with exactly N other states. This would be the transition graph of a network composed of N endogenous oscillators. Each rhythm of the network is a $2N$-cycle of transitions. To count these rhythms, the number of orderings of these transitions is equal to the number of permutations of $2N$ elements $(2N!)$. Dividing out the redundancy by rotations through the each cycle yields $(2N-1)!$ rhythms.

A classification of cyclic dynamics on transition graphs corresponding to networks has been carried out previously (Glass, l977). Every cyclic path is associated with to a *coordinate sequence* (Gilbert, 1958) that is the sequence of neurons that change state at each time step. According to this scheme, any two cycles that have the same coordinate sequence are equivalent by a symmetry of the transition graph. In dynamic biological networks, the assignment of cellular properties to individual neurons breaks this symmetry so that another method must be devised for classification.

3.1 Distances Between Rhythms. The functional similarity relevant to many neural systems is the sequence of bursts generated by the composite neurons. Comparisons between rhythms will be accomplished by introducing a distance function onto the set of rhythms to quantify the functional

differences between them. Two rhythms are defined to be neighbors if their coordinate sequences differ by the transposition of adjacent elements. For instance, if a rhythm contains the following sequence of neural states,

$$\cdots[\ldots\tilde{c}_m\ldots\tilde{c}_n\ldots][\ldots\tilde{c}'_m\ldots\tilde{c}_n\ldots][\ldots\tilde{c}'_m\ldots\tilde{c}'_n\ldots]\cdots \tag{3.1}$$

then its coordinate sequence contains the elements $(\ldots mn\ldots)$. A neighboring rhythm shares all the states in the cycle but one,

$$\cdots[\ldots\tilde{c}_m\ldots\tilde{c}_n\ldots][\ldots\tilde{c}_m\ldots\tilde{c}'_n\ldots][\ldots\tilde{c}'_m\ldots\tilde{c}'_n\ldots]\cdots \tag{3.2}$$

and has a coordinate sequence with two adjacent elements transposed, $(\ldots nm\ldots)$. Since these two rhythms differ by only one neural state, it is natural to consider them as neighbors in the set of rhythms. Our definition of distance is as follows: *The distance between rhythm r_1 and r_2 is the minimum number of adjacent transpositions of coordinate sequence elements that transforms r_1 into r_2.* This operation is symmetric with respect to the rhythms and satisfies the triangle inequality so it qualifies as a distance. Thus, we may define a *rhythm space*, $\mathcal{R}$, as a set of rhythms R along with metric, $d : R \times R \to \mathbf{Z}^+ \cup \{0\}$ as defined above. Note that this definition of distance differs from the Hamming distance (Hamming, 1986) which measures the overlap between two strings of binary numbers; the distance function introduced here involves the adjacent transitions to the neural states that do not overlap.

Two neighboring rhythms have a strong functional similarity because most of the activation sequence is preserved under translation by one step in rhythm space. This observation is particularly important when considering networks that consist of motor neurons or a network that *drives* motor neurons. The sequence of neuronal activation will translate into a sequence of muscle contractions. Two rhythms that lie far apart in rhythm space will correspond to very different movement patterns, and neighboring rhythms will generate similar movements.

4 Rhythmic examples

Examples of rhythm generating networks are presented in this section to illustrate the concepts of rhythm space. The following two examples are simple oscillator networks that generate all possible rhythms when no constraints are applied to the transition graphs. These examples demonstrate the complex geometric structure of rhythm space. The last example is from a well known biological system (Getting, 1989) that has given rise to modern conceptual approaches to central pattern generators.

The network is of interest here because it contains multicomponent synapses, and our analysis reveals the specific components that are necessary for the generation of viable rhythms.

4.1 Oscillator Networks. The simplest rhythm generating network to be investigated here is an abstract 2-neuron network where the maximum number of rhythms is $(2N-1)! = 6$. An example of such a network would be two endogenous oscillators connected by excitatory chemical synapses, $\mathcal{N} = \{c_1, c_2; \{\mathbf{S}^E_{1,2}, \mathbf{S}^E_{2,1}\}, \{\mathbf{C}^{EO}_1, \mathbf{C}^{EO}_2\}\}$ as shown at the top of Fig. 1A. The transition graph is shown in middle of Fig. 1A. The six rhythms are are represented by the following sequences of states, followed by their associated coordinate sequences.

$$\begin{array}{llll} r_1 & : [10][00][01][00], (1221) & r_2 & : [11][10][00][01], (2121) \\ r_3 & : [11][01][00][01], (1221) & r_4 & : [10][11][01][00], (2121) \\ r_5 & : [11][10][11][01], (2211) & r_6 & : [10][11][10][00], (2211). \end{array} \tag{4.1}$$

Although rhythms are cyclical, we have adopted the convention of writing the rhythm beginning with the transition in which the first neuron change state from 0 to 1. The structure of r_1 tells us that it has two neighbors because there are only two transpositions of adjacent coordinate sequence elements that transform the rhythm. The transposition of the first coordinate sequence element with the second transforms r_1 into r_4. Thus, the distance from r_1 to r_4 is $d(r_1, r_4) = 1$. These two rhythms are superimposed on the transition graph of . The transposition of the last two coordinate sequence elements yields r_2. Continuing in this manner one is able to map out the rhythm space as shown at the bottom of Fig. 1A. It is interesting to note that r_2 and r_4 are oriented in that they make a loop through the states in opposite directions, while the other four rhythms are non-oriented since they double back onto themselves. Thus, the distance from r_2 to r_4 must be greater than one since the transformation must pass through a non-oriented rhythm in order to switch the orientation.

A similar network that generates only one rhythm is shown in Fig. 1B for comparison. Here the cellular properties have been changes from endogenous oscillation to plateau termination so that there is no mechanism that can excite either neuron if the neural state is [0 0]. Thus, the rhythm space consists of a single rhythm. These two example show how changes in the cellular properties can change the potential behavior of anatomically equivalent networks.

The distances between rhythms generated by a 2-neuron network are never great enough to illustrate the differences between rhythms that are separated by a large distance in rhythm space. Connecting a third oscillating neuron with gap junctions to our example network demonstrates the complexity of rhythm space. Cycles on the transition graph of a 3-neuron network may be depicted by cyclical paths on cubes (Glass, l975a; Glass, l975b) as shown in Fig. 2A. The figure shows an

arbitrary cluster of rhythms in the space of rhythms generated by three oscillating neurons. Each line between cubes represents a distance of one so that the rhythms form a contiguous set in rhythm space. The figure is organized so that the rhythms on each row are members of *dynamical equivalence classes* determined by symmetries of the cube (Glass, l975a). In the classification scheme presented here, rhythms are considered *similar* if they are near neighbors in rhythm space as shown in the figure.

The full rhythm space for three oscillating neurons contains 120 rhythms and exhibits a complicated topology with several loops and interconnections between dynamical equivalence classes. Since the paths on the transition graph are defined to be cycles of length $2N$, the rhythms may also be represented by hexagons (or $2N$-gons for N-neuron networks). Each hexagon in Fig. 2B represents a symmetry class of rhythms where the inscribed solid lines connect coordinate sequence elements involving the same neuron. Beside each hexagon is a representative example of the class from Fig. 2A, and the letters surrounding the hexagons correspond to coordinate sequence elements of each example rhythm. The symmetry classes extend laterally to form loops in rhythm space through neighboring members of adjacent symmetry classes. The number of members in each symmetry class is given beside the corresponding hexagon and is computed by counting the symmetries of the inscribed figure in each hexagon, modulo rotations.

4.2 Multicomponent Synapses in a Biological Network. The escape reflex of the marine mollusk *Tritonia diomedea* is a swimming response generated by a rhythmic neural network (see (Getting, 1989) for review). Swimming consists of alternating dorsal and ventral flexions correlated with bursts of activity in two motor neuron pools. The alternating bursts of motor neurons are driven by a premotor central pattern generator (Dorsett et al., l976) that consists of three neuronal types interconnected with both inhibitory and excitatory chemical synapse. An interesting aspect of the pattern generator is that it contains multicomponent synapses (Getting, 1983); synapses that generate both excitatory and inhibitory postsynaptic potentials on different time courses (Fig. 3A).

There are three populations of premotor interneurons: the dorsal swim interneurons (DSI) that drive the dorsal motor pool, the ventral swim interneurons (VSI) that drive the ventral motor pool, and C2 interneurons that aid in generating a functionally appropriate rhythmic pattern. For a viable swim response, the DSI and VSI must fire out of phase with each other during some portion of the swim cycle. Otherwise the dorsal and ventral muscles will simply co-contract, immobilizing the mollusk.

An external source drives the DSI neuron to tonic excitability, thus initiating the swimming response. There are no identified pacemaker neurons, thus the pattern is generated completely by

the synaptic interactions. The properties of this network can be investigated using the methods of this article by carrying out the analysis on the circuit diagram in Fig. 3A. The network will be represented by $\mathcal{N}_{Tritonia} = \{DSI, VSI, C2; \mathcal{S}, \{\mathbf{C}^{TA}_{DSI}, \mathbf{C}^{PT}_{VSI}, \mathbf{C}^{PT}_{C2}\}\}$. There are two approaches that one may take when dealing with the multicomponent synapses. First, both excitatory and inhibitory synapse may be included to represent the multicomponent synapse,

$$\begin{aligned}\mathcal{S} = \{ \quad & \mathbf{S}^{I}_{\text{DSI, VSI}}, \mathbf{S}^{I}_{\text{C2, DSI}}, \mathbf{S}^{I}_{\text{C2, VSI}}, \mathbf{S}^{I}_{\text{VSI, DSI}}, \\ & \mathbf{S}^{E}_{\text{DSI, VSI}}, \mathbf{S}^{E}_{\text{C2, DSI}}, \mathbf{S}^{E}_{\text{C2, VSI}}, \mathbf{S}^{E}_{\text{DSI, C2}}\}\end{aligned} \tag{4.2}$$

where in $\mathbf{S}^{I}_{\text{M, N}}$, M is the presynaptic neuron and N is the postsynaptic neuron. Alternately, several analyses may be run with different combinations of a single synapse representing each multicomponent synapse to determine which components are necessary for the pattern generation:

$$\begin{aligned}\mathcal{S}(a_1, a_2, a_3) = \{ \quad & \mathbf{S}^{a_1}_{\text{DSI, VSI}}, \mathbf{S}^{a_2}_{\text{C2, DSI}}, \mathbf{S}^{a_3}_{\text{C2, VSI}}, \\ & \mathbf{S}^{I}_{\text{VSI, DSI}}, \mathbf{S}^{E}_{\text{DSI, C2}}\}\end{aligned} \tag{4.3}$$

where $a_i = I$ or E.

The first approach generates a large contiguous cluster of 44 rhythms which can be compared to the experimental results (Getting, 1983). Only one or two of the rhythms represent the sequence of neural state transitions that are observed in the biological network, and in 9 rhythms VSI fires only in phase with DSI leading to the inappropriate motor behavior described above. One may try to reduce the number of rhythms by applying the synaptic constraint (eq. 2.1), but if the threshold is set at $\theta = 0$, then no rhythms survive the constraint, and with $\theta = 1$, all 44 of the rhythms survive. The reason for this "all or nothing" result from the constraint is that our method does not take into account the time courses of the multicomponent synapses. The constraint counts the currents of all synaptic conductances simultaneously, thus eliminating more than is realistic when the threshold is set low. Otherwise, all of the synaptic currents can act without regard to temporal ordering to generate many spurious rhythms that do not follow from the synaptic time courses of the biological network.

In order to tease out the important components of the synaptic dynamics, we take the second approach of using a single synaptic connection to represent each multicomponent synapse. A systematic study of the network with synaptic connections $\mathcal{S}(a_1, a_2, a_3)$ reveals that only a limited set of components are necessary for rhythm generation. With no synaptic constraints applied, $\mathcal{S}(I, E, I)$ and $\mathcal{S}(I, I, I)$ generate no rhythms. Under the synaptic constraint with $\theta = 0$, three of the synapse sets generate rhythms. These are $\mathcal{S}(E, I, E)$, $\mathcal{S}(E, I, I)$, and $\mathcal{S}(I, I, E)$ which generate the rhythms

shown in Fig. 3B. The rhythms generated by $\mathcal{S}(E, I, E)$ are numbered 1, 2, and 3, the network defined by $\mathcal{S}(E, I, I)$ generates 1, 4, and 5, and $\mathcal{S}(I, I, E)$ generates number 3. The rhythm most consistent with neurophysiological recordings (Getting, 1983) is number 2, while rhythm 3 may be consistent with the last cycle of the escape response.

Taken together these rhythms form a single cluster in rhythm space showing that all three connectivity sets generate functionally similar rhythms. Yet upon closer inspection it becomes clear that rhythm 5 is does not allow DSI and VSI to fire out of phase with each other. Note that this rhythm lies furthest from the rhythms consistent with physiological recordings. This example shows the functional meaning of the measure used in rhythm space. The rhythms that are within a distance of 1 or 2 to the rhythm that represents normal activity of the swim cycle are still able to generate a viable escape response. Further away the system generates rhythms that are *functionally distant* in the sense that the viable response is not adequately performed. This analysis tells us that certain phases of the synaptic responses are more important that others for generating viable rhythms.

5 Discussion

The main objective of this work is to fashion tools that are useful in the study of biological neural networks that exhibit complicated behavior. Rather than utilizing a continuous approach of dynamical systems, discrete methods have been chosen so that a classification theorem for rhythmic networks begins to emerge. This will help to fill the gap between simulation studies of biological networks and a global understanding of the systems. The lack of classification theorems for nonlinear dynamical systems in higher dimensions leaves one to probe the parameter space of a conduction-based simulation to gain an overall mapping of the expected behavior. The intent here is not to develop another method to analyze coupled oscillators, but to develop a way of understanding the behavior of complex automata with a rule base that can be tailored to biological problems. The result uncovers some interesting mathematical questions as well as opens the door to some potentially useful biological applications. A software implementation of the concepts presented here is available by anonymous ftp at `reed.edu/reed/users/proberts`.

An important mathematical question relates to the structure of rhythm space. We have been unable to derived a simple formula to measure the distance between two rhythms as described above. The calculations have been done in an iterative fashion by finding the nearest neighbors of the rhythms of interest and continuing until a region of rhythm space large enough to contain all of the rhythms is mapped out. Since the number of elements in rhythm space increases as $(2N-1)!$, this method

becomes impractical for any but the smallest networks. Another open question is what the greatest distance between two rhythms is in terms of the number of neurons. Rhythm space appears to have a rich and regular structure, and more research is needed to resolve these issues.

Once a network has been analyzed to classify the rhythms so that their positions in rhythm space have been determined, it might be useful to rate the rhythms in terms of probabilities from the most likely to the least. At every state from which there is more than one transition possible, a probability may be assigned to each transition dependent on cellular and synaptic factors. Such an assignment has already been introduced in the constraints where we eliminated transitions by effectively deeming them "impossible." This approach could be made more precise leading to the product of the transition probabilities in a rhythm to compute the relative probability of each rhythm. Such a ranking would be useful for predicting observations in real biological networks, estimating changes that need to be made to alter the output sequence, and what rhythmic changes can be expected as certain transition probabilities are varied.

The introduction of probabilities can also help to compare rhythms that involve different numbers of neurons. In its present form, rhythm space is useful only for comparing rhythms involving the same number of neurons. This is due to the restriction that in a rhythm each neuron changes state exactly twice. One could allow a rhythm to be expanded with sub-rhythms involving subsets of the neurons considered in the main rhythm. Such an expansion would convert an N-rhythm into an $N + N'$ rhythm where $N' \leq N$ is the number of neurons in the sub-rhythm. Due to the large number of possible expansions, the introduction of probabilities would help to choose only the most prominent rhythms for comparison. We expect that after considerations of each neurons burst length and recovery period, there is a certain optimum rhythmic period that would suppress most of the generated rhythms.

As parameters such as transition probabilities are introduced into the formalism, one moves away from formal classification and into biological modeling. To be sure, a *rhythm* as defined above is not what one observes in recordings of neuronal activity in dynamic biological networks. In order to convert rhythms into a form that can be compared with data, the time courses of the transition mechanisms must be considered. Each time step of a rhythm lasts as long as the time course of the next transition. Varying degrees of precision can be introduced until the converted rhythm best matches observations within experimental error. An application to the stomatogastric ganglion (Johnson and Hooper, 1992) using this approach has led to experimental predictions (Roberts, 1997) revealing the existence of mechanisms that would not be obvious from the study of a single rhythm. Thus, the formalism presented here not only treads upon some rich mathematical territory, but can

aid our understanding of the mechanisms involved in dynamic biological networks.

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Figure 1: *Two neurons.* (A) Top: A network of two neurons connected by excitatory chemical synapses. Each neuron is an endogenous oscillator. Middle: The transition graph associated with the network. The path through the transition graph of two rhythms generated by this network are shown. If the transition that silences neuron 1 in r_1 is transposed with an adjacent transition that excites neuron 2, then rhythm r_1 is changed into rhythm r_2. Bottom: Rhythm space of the network. (B) Top: The same anatomical network as (A), but here the neurons exhibit plateau termination. Middle: The transition graph for this network including the only cyclic path that represents rhythm r_5. Bottom: The rhythm space contains only one point.

Figure 2: *The structure of rhythm space.* (A) Each cube displays a cycle that represents a rhythm of the 3-oscillator network described in the text. Solid lines between cubes represent a distance of one in rhythm space. (B) A hexagonal representation of rhythms and the associated path on the cube. Numbers quantify the members in each dynamical equivalence class.

Figure 3: *Rhythms of the swim response network.* (A) The pattern generating network studied in the text. Filled circles are inhibitory synapses and T-bars are excitatory synapses. Mixed synapses indicate multiple components. (B) Five rhythms generated by 3 different choices of synaptic components. Connecting lines represent a distance of one in rhythm space. (C) The same rhythms as (B) represented by cycles on cubes.

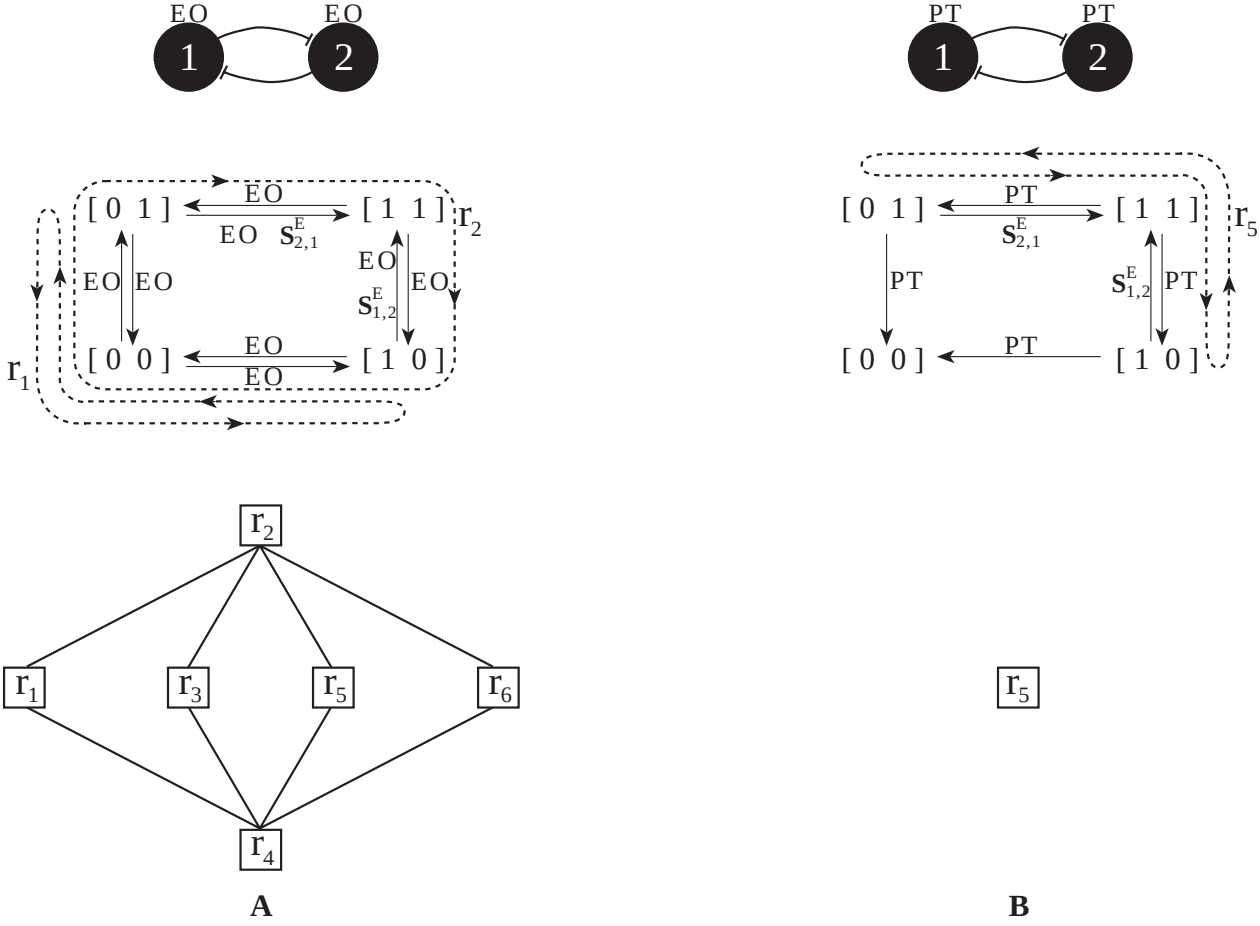
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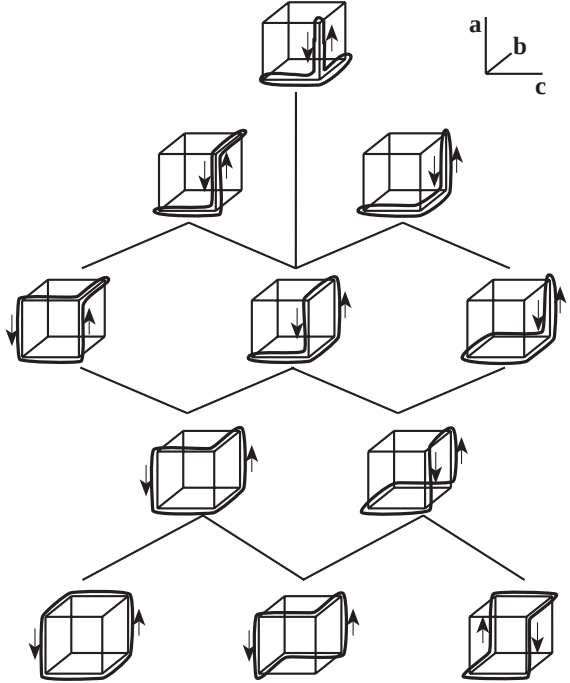
Fig. 1



A

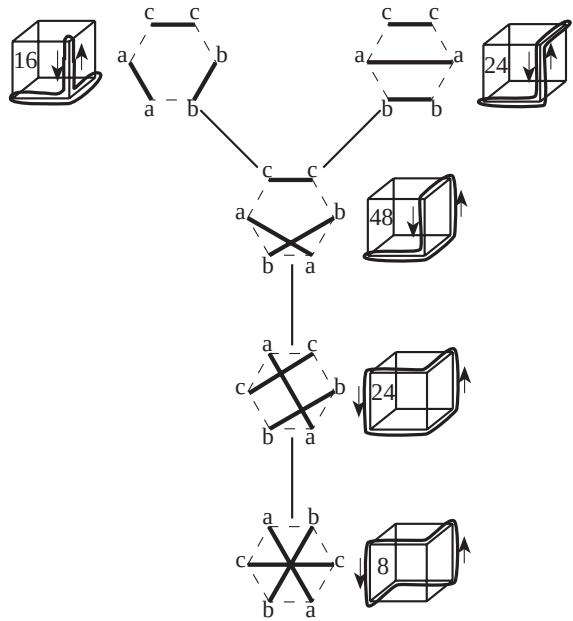


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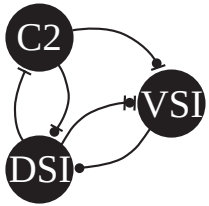
Fig. 2



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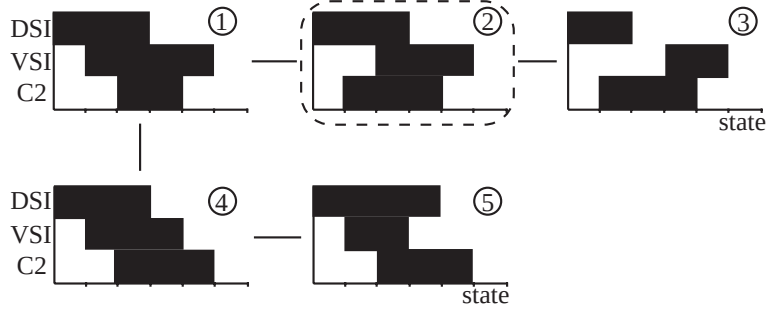

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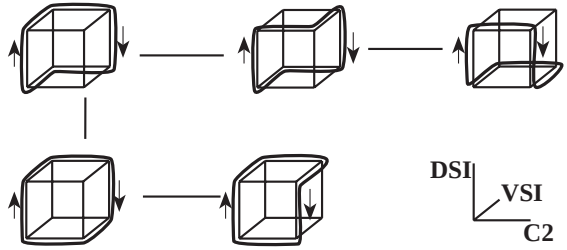

C

Fig. 3