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COMBINATORIAL ASPECTS OF DYNAMICS IN BIOLOGICAL SYSTEMS

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I. INTRODUCTION

In biology it is common to represent the dynamics of complex interacting systems by N coupled first order ordinary differential equations

$$\frac{dx_i}{dt} = f_i(\vec{x}), \qquad i = 1, N \tag{I.1}$$

where the x_i are the variables (e.g. population densities, concentrations of metabolites, firing frequencies of neurons), the f_i give the interactions between the variables, and there are N variables of interest. The equation of motion (equation (I.1)) can in principle be integrated starting from any initial condition to give the N variables as a function of time. These solutions define continuous trajectories in N-dimensional Euclidean space. In many instances, and those which I discuss here, the variables are positive by definition so that the *phase space* is the positive orthant of N-dimensional Euclidean space. Since, the f_i will in general be nonlinear, and there may be a great many interacting species, "analytic solutions" of equation (I.1) are impossible. This observation has led to the development of methods to determine the properties of the solutions of equation (I.1) without numerically integrating the equation.

Statistical mechanics has played a prominent role. Volterra [*1*] assumed the f_i are

$$f_i = x_i \left[a_i - \sum_{\substack{j=1 \\ i \neq j}}^{N} \beta_{ij} x_j \right] \tag{I.2}$$

where the x_i are the population densities, the a_i give the growth of a single species in absence of all others, and the interaction coefficients β_{ij} are appropriate for predator-prey systems $\beta_{ij} = - \beta_{ij}$. With this choice of f_i the quantity

$$H = \sum_{i=1}^{N} [x_i(t) - x_i^o \ell n \; x_i(t)] \tag{I.3}$$

is conserved. Here, x_i^o is the steady state solution of equation (I.1) $dx_i^o/dt = 0$. The observation of a conserved quantity has led to the development of a statistical mechanics of equations (I.1) and (I.2), [2,3]. This approach has not only been applied to ecological systems [1-3] but also to metabolic cellular systems [4] and to neural networks [5] by choosing different (but also very special) functional forms for the f_i.

The major criticism of this statistical mechanical approach is that the theory depends on selection of special functional forms for the f_i [6]. Under arbitrary small perturbations to the f_i, the whole topological character of the solution curves to equation (I.1) and (I.2) changes. A set of differential equations is called *structurally stable* if the topological features of the dynamics remain invariant to small changes in the differential equations [7]. Several authors, particularly Thom, have stressed the importance of structural stability of mathematical models in biology [8]. Since the interactions between species are not *exactly* those described by equation (I.2), mathematical results which depend on this precise functional form lack robustness.

This article describes combinatorial methods which can be used to analyze qualitative aspects of flows in phase space. My approach has been motivated by the observation that despite differences in mathematical models of biological systems, the qualitative features of the dynamics are often identical. For example, in mathematical models of the predator-prey system with 2 species, one of two generic behaviors is typically observed [6]. In the limit $t \to \infty$, either trajectories approach a stable steady state, or trajectories approach a stable limit cycle, figure (1) (a *stable limit cycle* is a periodic solution to a differential equation which has the property that every point in phase space sufficiently close to the periodic solution approaches it in the limit $t \to \infty$)[*7*]. These two phase plane portraits should be compared with the nested closed trajectories observed in the structurally unstable Volterra-Lotka equation, equations (I.1) and (I.2) with N=2, figure (1) [*3,6,7*].

In this article I describe mathematical methods which can be used to classify biological systems on the basis of the *symmetries of the flows* in N-dimensional phase space (Section II). These methods are then used to classify a set of paradigm piecewise linear differential equations (called PL equations, Eqs. (III.1)) on the basis of the flows in phase space and also the interactions between the variables (Section III). Using this classification scheme, it has been possible to predict the existence of stable limit cycle oscillations in a large class of the PL equations (Section IV). Methods to study the uniqueness and the period of the cycles are introduced in Section V. The results are discussed in Section VI. The Appendix contains a brief survey of the combinatorial methods used in the text.

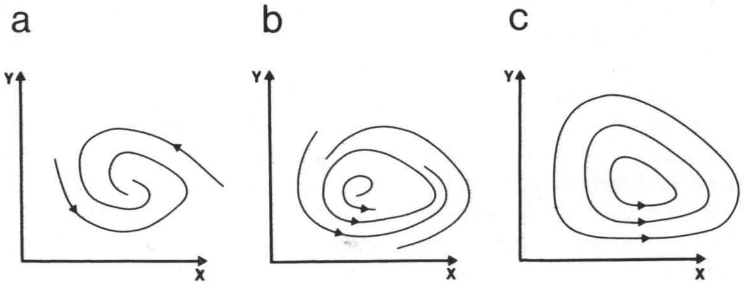

Figure 1 -- Typical dynamics found for predator-prey system. In (a) all trajectories approach a steady state in the limit $t \to \infty$. In (b) all trajectories approach a stable limit cycle attractor. In (c) the structurally unstable closed loop trajectories for the Volterra-Lotka equations is shown.

II. CLASSIFICATION OF COARSE GRAINED FLOWS IN PHASE SPACE [*9*]

The analysis is appropriate for biological systems in which

1) The phase space can be decomposed into 2^N volumes which are *homeomorphic* (topologically equivalent) to the 2^N orthants of N-dimensional Euclidean space.
2) Flows between each pair of *adjacent volumes* (volumes which share a common (N-1) dimensional boundary) are in one and only one direction.

The consequence of these two assumptions is that a coarse-grained representation of the dynamics is possible on an N-cube, where each edge of the N-cube is directed (see Appendix). Each vertex of the N-cube corresponds to a volume of phase space and the directed edges give transitions between adjacent volumes. The N-cube with directed edges is called a *state transition diagram*. State transition diagrams have been constructed for a large number of mathematical models which have been proposed previously to represent dynamics in biological systems [*9*]. Two biological systems will be said to be in the same *structural equivalence class* if their state transition diagrams can be superimposed under a symmetry operation of the N-cube.

It is a simple matter to count the number of structural equivalence classes in 2 and 3 dimensions [*9*]. In 2 dimensions there are just 4 classes, shown in figure (2). Structure IV arises in situations in which there are stable oscillations, or where there is an oscillatory decay to a single stable steady state such as is shown in figure (1). Structure I arises in cases for which there are two stable steady states, such as occurs with mutually inhibitory interaction (competitive exclusion) or mutually activating interactions. In 3 dimensions the Polya enumeration theorem (see Appendix) can be used to count the number of structural equivalence classes. There are 112. One of the classes, shown in figure (3), has been of particular interest in studies of oscillations in biological and chemical systems. This structure was found [*10,11*] for the Field-Noyes model [*12*] of the Belousov-Zhabotinsky reaction (an oscillating chemical reaction) and also in mathematical models of feedback inhibition (the last element in a synthetic sequence inhibits synthesis of the first element) [*13-18*].

I have not tried to count the number of structural equivalence classes for N≥4. Although such computations should be possible, the number of classes is large and knowing the exact number does not seem to be terribly interesting.

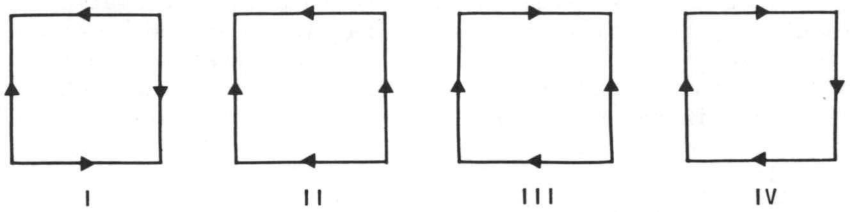

Figure 2 -- The four structural equivalence classes in 2 dimensions. Structure IV is the 2-dimensional cyclic attractor (see Sect. IV).

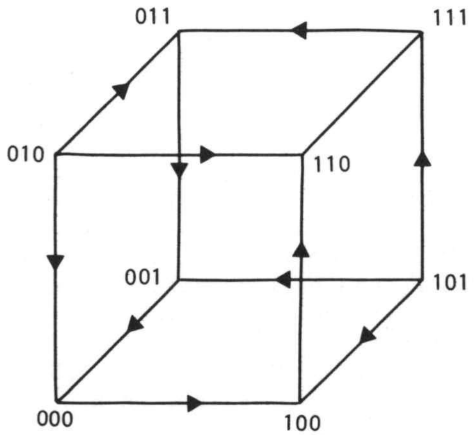

Figure 3 -- The structural equivalence class found for mathematical models of limit cycle oscillations in biological systems in 3 dimensions. This is the 3-dimensional cyclic attractor (see Sect. IV).

III. CLASSIFICATION OF PARADIGM PL EQUATIONS [11,16,17]

In neurobiology [19], cellular biology [20-23], and endocrinology [24] analogies have been drawn between control elements and discrete "switches." In this section, a system of piecewise linear ordinary differential equations (PL equations) is given which represents in a schematic fashion, potentially complex interactions between "switch-like" elements. These equations can be classified on the basis of their state transition diagrams using the technique described in the preceeding section. The PL equations are,

$$\frac{dx_i}{dt} = \lambda_i B_i[\tilde{x}_1\tilde{x}_2\ldots\tilde{x}_{i-1}\tilde{x}_{i+1}\ldots\tilde{x}_N] - \gamma_i x_i$$

$$x_i \geqslant 0; \quad i = 1,N; \quad N+1 = 1 \qquad \text{(III.1a)}$$

where

$$\tilde{x}_i = 1 \quad \text{if} \quad x_i > \theta_i$$

$$\tilde{x}_i = 0 \quad \text{if} \quad x_i < \theta_i \qquad \text{(III.1b)}$$

and

$$\lambda_i/\gamma_i > \theta_i \;. \qquad \text{(III.1c)}$$

The production constants λ_i, decay constants γ_i, and thresholds θ_i, are all taken to be positive numbers. Here each B_i is a Boolean function of (N-1) Boolean variables (see Appendix). The B_i can be represented in a truth table as in Table I. Each of the $b_{i,j}$ in Table I is either 0 or 1. The condition that B_i is not a function of i places restrictions on the entries in the truth table, $b_{1,1} = b_{1,2}$, $b_{1,3} = b_{1,4}$, $b_{2,1} = b_{2,3}$ etc. Since each B_i can be chosen in $2^{2^{N-1}}$ different ways, the total number of ways of choosing the B_i in equation (III.1) is $2^{N\times 2^{N-1}}$. The N threshold hyperplanes divide the positive orthant into 2^N hypervolumes. Each hypervolume is named by its Boolean state $(\tilde{x}_1\tilde{x}_2\ldots\tilde{x}_N)$ and in this way can be associated with a vertex of the N-cube (see Appendix). The Boolean states are called

$S_1, S_2 \ldots S_{2^N}$ in Table I. From the truth table it is easy to determine the restrictions on the flows in phase space for any set of B_i. For example, consider the two vertices representing S_1 and S_2. If $b_{1,2}=b_{1,1}=1$ then the edge is directed from S_1 to S_2. This is because from equation (III.1) if $\tilde{x}_2=\tilde{x}_3=\ldots=\tilde{x}_N=0$, $(dx_1/dt)_{x_1=\theta_1}>0$. If $b_{1,2}=b_{1,1}$ $=0$ the edge is directed from S_2 to S_1. In similar fashion the orientation of each of the $N\times 2^{N-1}$ edges of the N-cube is specified by the truth table in Table I. The N-cube with directed edges is called the *state transition diagram* of equation (III.1). Given a state transition diagram, the process just described can be reversed so that mathematical models which reproduce observed patterns of coarse-grained flows can be generated. This process is used in the next section and also is discussed in detail elsewhere [*17*]. The remainder of this article deals with limit cycles in equation (III.1).

Table I

A tabular representation of the function B_i in equation (III.1). The elements $b_{i,j}$ are either 1 or 0. Using the restrictions discussed in the text, only $N\times 2^{N-1}$ of the $b_{i,j}$ can be chosen independently. Each of these choices corresponds to specifying one of the edges on the N-cube.

	$\tilde{x}_1$	$\tilde{x}_2$	$\tilde{x}_3$	$\ldots\tilde{x}_N$	B_1	B_2	...	B_N
S_1	0	0	0	...0	$b_{1,1}$	$b_{2,1}$	...	$b_{N,1}$
S_2	1	0	0	...0	$b_{1,2}$	$b_{2,2}$	...	$b_{N,2}$
S_3	0	1	0	...0	$b_{1,3}$	$b_{2,3}$	...	$b_{N,3}$
S_4	1	1	0	...0	$b_{1,4}$	$b_{2,4}$	...	$b_{N,4}$
.								
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S_{2^N-1}	1	1	1	...1	$b_{1,2^N-1}$	$b_{2,2^N-1}$	...	$b_{N,2^N-1}$
S_{2^N}	1	1	1	...1	$b_{1,2^N}$	$b_{2,2^N}$	...	$b_{N,2^N}$

IV. LIMIT CYCLES IN THE PL EQUATIONS

A. Cyclic Attractors Imply Limit Cycles [*16*,*17*]

I believe the dynamics of equation (III.1) are of interest not only in their own right, but also because they appear to offer a set of paradigm examples of interest in a biological context. For more than three interacting species it seems hopeless to try to examine every possible structural equivalence class. However, a method has been found which has been used to predict the existence of stable limit cycle oscillations for a large class of PL equations. The method is related to the combinatorial notion of snakes.

A *snake* in a graph G is a simple circuit C in G such that C has no chords in G, so that every edge in G which joins two vertices of C is an edge of C [*25*]. A *cyclic attractor* of a directed graph G' can be constructed from a snake C in the following way [*16*,*17*]. Every edge in G' which shares a common vertex with C is directed towards C. Every edge in C is directed so that the snake may be traversed by following the directed edges (figures 2 and 3). In the following I consider cyclic attractors on the N-cube. An *N-dimensional cyclic attractor* (or snake) is found on all M-cubes for $M \geq N$ but not for $M < N$. Two N-dimensional cyclic attractors which can be superimposed under a symmetry of the N-cube are called *equivalent*.

Conjecture [*17*] For $N \geq 3$, an N-dimensional cyclic attractor implies a stable limit cycle oscillation in the PL equations. This limit cycle oscillation passes through the same volumes in phase space in the same order as the cyclic attractor. All points in each volume through which the limit cycle passes tend to the limit cycle as $t \to \infty$.

Equation (III.1) was numerically integrated with $\lambda_i = \gamma_i = 1$, $\theta_i = 0.5$, $i = 1, N$ for all the different equivalence classes of cyclic attractors in 3, 4 and 5 dimensions, (22 cases in all). In every case a stable limit cycle oscillation was found. The patterns of oscillation in phase space satisfy the conjecture. Moreover, in any one case, the limit cycles appear to be unique as conjectured, since the asymptotic cycle was the same for several different initial conditions (but an extensive numerical study of this point was not undertaken). The periods of the limit cycles found for each case are different. These results are summarized in Table II.

The cyclic attractors in 3 and 4 dimensions were readily found using Gilbert's list of cycles on 3-cubes and 4-cubes [*26*]. It was necessary to find the 5-dimensional snakes since I was unable to find a complete listing of snakes or cycles on N-cubes, for $N \geq 5$. The next section describes this computation.

B. Snakes on 5-cubes

The *length* of a snake is equal to the number of vertices (or edges) that the snake passes through as the circuit is traversed. Let S(N) denote the length of the longest snake on the N-cube. A number of workers [*25*,*27*,*28*] have provided upper bounds for S(N). Using the result attributed to Larman [*28*] for $N \geq 5$

$$S(N) \leq 2^{N-1} - 2^{N-5} N^{-6}, \qquad \text{(IV.1)}$$

S(5) is computed to be 14.

A circuit on an N-cube can be specified by giving the sequence of vertices the cycle passes through as the cycle is traversed. The circuit in figure 3 can be given

$$(000,\ 100,\ 110,\ 111,\ 011,\ 001,\ 000\ \ldots)\ . \qquad \text{(IV.2)}$$

The *coordinate sequence* gives a listing of the coordinates which change as the circuit is traversed [*26*]. For a circuit of the length L the coordinate sequence is an L-tuple, for example the circuit in equation (IV.2) is designated (123123).

Consider the circuit that passes through the vertices

$$(010,\ 110,\ 100,\ 101,\ 001,\ 011,\ 010\ \ldots). \qquad \text{(IV.3)}$$

This circuit is obtained from equation (IV.2) by complementing the second coordinate (see Appendix). The coordinate sequences of equations (IV.2) and (IV.3) are identical, and the two cycles are in the same equivalence class. Similarly given a coordinate sequence for any circuit, potentially 2^N different orientations of the circuit on the

Table II

Snakes in 2,3,4 and 5 dimensions. For each snake is given the coordinate sequence; interval sequence; the span (S); the period of the associated limit cycle in equation (III.1) with $\lambda_i=\gamma_i=1$, $\theta_i=0.5$, $i=1,N$; the predicted period ($T=kS^{\alpha}$) with $k=0.65576$ and $\alpha=0.47485$ (see Sections IV and V).

Dimension	Coordinate Sequence	Interval Sequence	S	Period of Limit Cycle	$T=kS^{\alpha}$
2	1212	(11)(11)	8	-	-
3	123123	(22)(22)(22)	27	2.88727	3.13644
4	12341234	(33)(33)(33)(33)	64	4.87502	4.72521
	12341243	(33)(33)(42)(42)	62	4.77749	4.65451
	12314324	(24)(42)(24)(24)	60	4.67046	4.58260
5	1234512345	(44)(44)(44)(44)(44)	125	6.56256	6.49347
	1234512354	(44)(44)(44)(53)(35)	123	6.52185	6.44393
	1234513254	(44)(53)(35)(53)(35)	121	6.47949	6.39396
	1234512534	(44)(44)(53)(53)(26)	119	6.42957	6.34355
	1234521534	(53)(35)(53)(53)(26)	117	6.38316	6.29270
	1234512543	(44)(44)(62)(44)(26)	117	6.37605	6.29270
	1234513524	(44)(62)(35)(53)(26)	115	6.33490	6.24139
	1234521543	(53)(35)(62)(44)(26)	115	6.32712	6.24139
	1234531524	(53)(62)(26)(53)(26)	111	6.23048	6.13734
	1231435425	(26)(62)(26)(26)(26)	105	6.05948	5.97751
	----------	--------------------	---	-------	-------
	123145123145	(2222)(55)(55)(55)(55)	180	7.57853	7.72106
	123145123154	(2222)(55)(55)(64)(46)	178	7.55154	7.68019
	123145132154	(2222)(64)(46)(64)(46)	176	7.52381	7.63910
	123142153145	(2222)(37)(55)(55)(37)	172	7.47991	7.55616
	123142154135	(2222)(37)(73)(37)(37)	164	7.37034	7.38718
	------------	----------------------	---	-------	-------
	12314251231425	(2323)(3232)(66)(66)(66)	243	8.71866	8.90362
	12314215321425	(2233)(3322)(57)(66)(57)	243	8.71342	8.90362
	12314215231425	(2233)(3232)(66)(66)(57)	243	8.71276	8.90362

N-cube can be generated by considering all possible complementations of the coordinates. Therefore, it simplifies matters to consider the coordinate sequences for circuits, rather than listing the vertices the circuit passes through.

Any listing of coordinates will generate a path on the N-cube. It is simple to find the criteria that give paths which are circuits and snakes. The two conditions that a list of coordinates must satisfy to represent a circuit of length L and not contain a shorter circuit are [*26*]:

1. Each coordinate in the L-tuple must appear an even number of times.
2. For any sequence of consecutive steps of length shorter than L, at least one coordinate must appear an odd number of times.

The coordinate sequence also makes it easy to spot circuits which are snakes. In addition to conditions 1 and 2, for a snake of length L ($L \geq 6$)

3. Every sequence of consecutive digits of length I, where I is an odd integer $3 \leq I \leq L-3$, must contain at least 3 coordinates which appear an odd number of times.

For example, the coordinate sequence for (IV.2) does represent a snake, whereas, the coordinate sequence (121323) represents a circuit which is not a snake.

The coordinate sequence does not help very much in identifying equivalent snakes under permutations (see Appendix) of the coordinates, particularly if different starting vertices are listed first in the different coordinate sequences. For example, the coordinate sequences

$$(12314251231425) \qquad \text{(IV.4a)}$$

$$(12314351231435) \qquad \text{(IV.4b)}$$

represent equivalent snakes. The *change number* n_i of the *i*-th coordinate gives the number of times the *i*-th coordinate appears in the coordinate sequence [*26*]. The *interval sequence* $(a_{i1}a_{i2}\ldots a_{in_i})$ of the *i*-th coordinate is an n_i tuple giving the number of coordinates intervening between each successive appearance in the coordinate sequence 1 in (IV.4a) is (2323). For a circuit of length L

$$\sum_{j=1}^{N} a_{ij} + n_i = L, \quad i = 1, N. \qquad (IV.5)$$

Provided cyclic permutations of interval sequences are allowed, the interval sequence of a given element is invariant to both permutations of labellings as well as starting points on the cycle. Consequently, by determining the interval sequences for each element of two snakes, permutations in labellings and starting points can be rapidly found. For example, the interval sequences for (IV.4a) and (IV.4b) are (2323)(3232)(66)(66)(66) and (2323)(66)(2323)(66)(66) respectively. If equation (IV.4b) is rewritten (31435123143512) and the coordinates are relabelled 3→1, 1→2, 4→3, 5→4, 2→5, the equivalence of equations (IV.4a) and (IV.4b) is established. In general, a necessary but not sufficient condition that two snakes are equivalent is that the set of interval sequences for one snake are in one to one correspondence with the set of interval sequences of the second snake, where the interval sequence for any one coordinate can be cyclically permuted.

A systematic procedure was developed for finding all the snakes in 5 dimensions. The technique will be briefly indicated. Without any loss of generality, the first three digits of the coordinate sequence can be given as (123 ...). Using the criteria for snakes discussed above, it is easy to see that the fourth digit can either be 1 or 4. Given the first four digits, there are restrictions placed on the fifth digit, so that the only possibilities for the first five digits for snakes on 5-cubes are (12341 ...), (12342 ...), (12345 ...) and (12314 ...). Note that only the last possibility need be considered for snakes of length 12 and 14. In similar fashion, all the possibilities for the remaining digits consistent with the three criteria discussed above were generated. Since each snake appears several times, these long lists of coordinate sequences were then winnowed down by computing the set of interval sequences for each snake and searching for permutations which led to equivalences with other snakes. This search for equivalences was facilitated by integrating equation (III.1). Equivalent snakes always led to limit cycles of identical periods, as they must if the limit cycles are unique as conjectured.

V. THE PERIODS OF LIMIT CYCLES IN THE PL EQUATIONS

A. The Span of the Cyclic Attractors

An examination of Table II shows that the periods of the limit cycles change in approximate "quanta", where the size of the quanta gets smaller as the period gets longer. I have observed a correlation between the period of the cycle and a number, which I call the *span* of the cycle, denoted S, which can be computed by considering the entire set of vertices that the cycle passes through. The *span* of a cycle is equal to the sum of distances between all pairs of vertices on the cycle, where the distance between any two vertices is only counted once. For example, the span of the cycle in equation (IV.1) is 27. I have fit the period of the cycles listed in Table II to the equation

$$T = kS^{\alpha} \tag{V.1}$$

The computation was performed by taking the logarithm of both sides and doing a least squares fit. The computed values of k and α are $k=0.65576$ and $\alpha=0.47485$. The predicted cycle periods using these values of k and α in equation (V.1) are listed in Table II. Agreement between predicted and observed periods is excellent (except for the 3-dimensional snake, it is better than 3%).

B. Uniqueness and Period for Two Classes of Limit Cycles

Here I derive polynomial expressions for the periods of the limit cycles for two classes of cyclic attractors of equation (III.1). For an N-dimensional system, the polynomial is of order (N-1). In the limit $N \to \infty$, the period is explicitly computed. This computation can be used to give values for k and α in equation (V.1) for each class of cycles in the asymptotic high dimension case. Moreover, certain uniqueness properties of the limit cycle solutions of equation (III.1) can be deduced by considering the roots of the polynomials.

The two classes of cycles which I consider are specified by the coordinate sequences

$$123 \ldots M123 \ldots M \qquad \text{(V.2a)}$$

$$2M \text{ terms} \qquad M \geq 2$$

and

$$(1M)(21)(32) \ldots (M,M-1) \qquad \text{(V.2b)}$$

$$M \text{ doublets} \qquad M \geq 3$$

The coordinate sequences in equations (V.2) produce M-dimensional snakes of length 2M. The spans of both classes of snakes can be computed and are M^3 and $6M^2-9M$ for equations (V.2a) and (V.2b) respectively. For an M-dimensional snake of length 2M, equation (V.2a) gives the snake of greatest span and equation (V.2b) gives the snake of smallest span. The coordinate sequence in equation (V.2a) gives the coordinate sequence for a system of equations analogous to N-dimensional feedback inhibition [*15*,*18*]. In 3 dimensions both (V.2a) and (V.2b) give snakes equivalent to the snake in equation (IV.2). In 4 dimensions the snakes are different. One of the snakes for equation (V.2a) passes through the vertices

$$(0000,1000,1100,1110,1111,0111,0011,0001,0000 \ldots) \qquad \text{(V.3a)}$$

while one of the 4-dimensional snakes for equation (V.2b) passes through the vertices

$$(0001,1001,1000,1100,0100,0110,0010,0011,0001, \ldots) \qquad \text{(V.3b)}$$

Truth tables which produce the snakes in equations (V.3) are given in Table III.

Polynomial expressions for the period of the cycles are computed for a special case of equation (III.1) in which

$$\lambda_i = 1, \ \gamma_i = 1, \ \theta_i = 0.5, \qquad i = 1, N. \qquad \text{(V.4)}$$

The computations are simplified by transforming the variables. If

Table III

Truth tables which generate two of the 4-dimensional cyclic attractors. Case A gives equation (V.3a) and Case B gives equation (V.3b).

				Case A				Case B			
x_1	x_2	x_3	x_4	B_1	B_2	B_3	B_4	B_1	B_2	B_3	B_4
0	0	0	0	1	0	0	0	1	1	1	1
0	0	0	1	0	0	0	0	1	0	0	1
0	0	1	0	1	0	0	1	0	0	1	1
0	0	1	1	0	0	0	1	0	0	0	1
0	1	0	0	1	0	1	0	0	1	1	0
0	1	0	1	0	0	1	0	0	0	0	0
0	1	1	0	1	0	1	1	0	0	1	0
0	1	1	1	0	0	1	1	0	0	0	0
1	0	0	0	1	1	0	0	1	1	0	0
1	0	0	1	0	1	0	0	1	0	0	0
1	0	1	0	1	1	0	1	0	0	0	0
1	0	1	1	0	1	0	1	0	0	0	0
1	1	0	0	1	1	1	0	0	1	0	0
1	1	0	1	0	1	1	0	0	0	0	0
1	1	1	0	1	1	1	1	0	0	0	0
1	1	1	1	0	1	1	1	0	0	0	0

$$y_i = 2(x_i - 0.5)$$
$$B'_i = 2(B_i - 0.5)$$
$$\theta'_i = 2(\theta_i - 0.5) \qquad (V.5)$$

then for the values of the parameters in equation (V.4), equation (III.1) can be rewritten

$$\frac{dy_i}{dt} = B'_i[\tilde{y}_1\tilde{y}_2\cdots\tilde{y}_{i-1}\tilde{y}_{i+1}\cdots\tilde{y}_N] - y_i$$
$$i = 1, N; \quad y_i \geqslant -1; \quad N+1 = 1 \qquad (V.6a)$$

where

$$\tilde{y}_i = 1 \quad \text{if } y_i > 0,$$
$$\tilde{y}_i = 0 \quad \text{if } y_i < 0. \qquad (V.6b)$$

The transformation does not alter the period of the limit cycles. Numerical integration of equation (V.6) in 4 dimensions for the two snakes in equation (V.3) gives the limit cycles in Table IV. These limit cycles are termed "symmetric" since they fully reflect the symmetry of the piecewise linear vector fields. The arguments which follow derive periods for such symmetric solutions of equations (V.6), but do *not* exclude the possibility of asymmetric solutions [*18*]. The periods for the two classes of snakes will be computed separately. y_{max} is the maximum value of y and y_{min} is the minimum value.

Case A. (Coordinate sequence given in equation (V.3a))

By integrating equation (V.6), we find in M-dimensions

$$y_{max} = y_{min}e^{-M\tau} + (1-e^{-M\tau})$$
$$0 = y_{min}e^{-\tau} + (1-e^{-\tau})$$
$$y_{max} = -y_{min} \qquad (V.7)$$

where the period of the cycle is $2M\tau$. Calling

$$w = e^{-\tau} \qquad (V.8)$$

equation (V.7) can be reduced to the polynomial

Table IV

The limit cycle oscillations found in equations (V.6) for the truth tables in Table III. The limit cycle can be constructed by joining neighboring points on the cycles by straight lines in the four dimensional phase space.

IVa

Time	y_1	y_2	y_3	y_4
0.000	0.000	-0.839	-0.704	-0.456
0.609	0.456	0.000	-0.839	-0.704
1.219	0.704	0.456	0.000	-0.839
1.828	0.839	0.704	0.456	0.000
2.437	0.000	0.839	0.704	0.456
3.047	-0.456	0.000	0.839	0.704
3.656	-0.704	-0.456	0.000	0.839
4.266	-0.839	-0.704	-0.456	0.000
4.875	0.000	-0.839	-0.704	-0.456

IVb

Time	y_1	y_2	y_3	y_4
0.000	0.408	-0.903	-0.689	0.000
0.644	0.689	0.000	-0.837	-0.475
1.168	0.000	0.408	-0.903	-0.689
1.811	-0.475	0.689	0.000	-0.837
2.335	-0.689	0.000	0.408	-0.903
2.979	-0.837	-0.475	0.689	0.000
3.503	-0.903	-0.689	0.000	0.408
4.146	0.000	-0.837	-0.475	0.689
4.670	0.408	-0.903	-0.689	0.000

$$w^m - 2w + 1 = 0 \qquad \text{(V.9)}$$

where the only roots of interest lie in the interval (0,1]. There is one root at $w=1$. This is a trivial solution of zero period. Factoring this root from equation (V.9) yields the equation

$$F(w) = \sum_{i=1}^{M-1} w^i - 1 = 0 \,. \qquad \text{(V.10)}$$

Since $F(0) = -1$ and $F(1) = (M-1)$, there must be at least one root of $F(w)$ in (0,1). However, since $F'(w) > 0$ for $0<w<1$ the root is unique. Therefore, there is a unique symmetric limit cycle for Case A. This result was found in *reference 18* using a somewhat different method. For $M=3$, $T = -6 \,\ell n (-0.5 + 5^{1/2}/2) = 2.88727$. In the limit $M \rightarrow \infty$, the root in the interval (0,1) can be computed by summing the geometric series in equation (V.10). This gives

$$\frac{w}{1-w} - 1 = 0 \qquad \text{(V.11)}$$

which has the root $w=0.5$. Consequently in the limit $M \rightarrow \infty$ the period is $T_A = 2M \,\ell n 2$. Since for this case $S = M^3$, we compute the values $k=1.38630$ and $\alpha=0.33333$ in equation (V.1).

Case B. (Coordinate sequence given in equation (V.3b))

By integrating equation (V.6) we find

$$y_{max} = y_{min}\, e^{-(2\tau_1 + \tau_2)} + [1 - e^{-(2\tau_1 + \tau_2)}]$$

$$y_{min} = y_{max}\, e^{-[(M-2)\tau_1 + (M-1)\tau_1]} - [1 - e^{-[(M-2)\tau_1 + (M-1)\tau_2]}$$

$$0 = y_{min}\, e^{-\tau_1} + (1 - e^{-\tau_1})$$

$$0 = y_{max}\, e^{-\tau_2} - (1 - e^{-\tau_2}) \qquad \text{(V.12)}$$

where the period is $M(\tau_1 + \tau_2)$. Calling

$$w = e^{-(_1 + \tau_2)} \tag{V.13}$$

after some algebra we find

$$w^M - 2w^{M-1} - 2w^2 + 4w - 1 = 0 \tag{V.14}$$

$w = 1$ is a root of equation (V.14). Factoring out $w = 1$, we find

$$F(w) = w^{M-1} - \sum_{i=2}^{M-2} w^i - 3w + 1 = 0. \tag{V.15}$$

Now $F(0)=1$ and $F(1)=2-M$. Since $F(0) > 0$ and $F(1) < 0$ there must be at least one root in the interval $(0,1)$. Differentiating equation (V.15) we find

$$F'(w) = (M-1)w^{M-2} - \sum_{i=2}^{M-2} (iw^{i-1}) - 3 = 0. \tag{V.16}$$

For $M=4$, $F'(w)=3w^2-2w-3$. Since $F'(0)<0$, $F'(1)<0$ and $F'''(w)>0$, $F'(w)<0$ for $0<w<1$ and consequently there is one symmetric solution for $M=4$. We now consider the cases where $M \geqslant 5$. Here

$$F'(w) < w^{M-4}\, g(w) \tag{V.17}$$

where

$$g(w) = (M-1)w^2-(M-2)w-(M-3). \tag{V.18}$$

Since $g(0)<0$, $g(1)<0$ and $g''(w)>0$, $g(w)<0$ for $0<w<1$. Therefor $F'(w)$ is negative for $0<w<1$ and there is a unique symmetric solution to Case B for $M \geqslant 5$. In the limit $M \to \infty$, the positive root in the interval $(0,1)$ is given by

$$-\frac{w^2}{1-w} - 3w + 1 = 0 \tag{V.19}$$

from which $w=1-\sqrt{2}/2$. Consequently in the limit $M \to \infty$, the period for Case B is $T_B = -M\, \ell n(1-\sqrt{2}/2)$. Since for this case

$S=6M^2-9M$ we compute the values $k=0.50131$ and $\alpha=0.5000$ in equation (V.1).

VI. DISCUSSION

The methods which have been discussed are interesting from a mathematical and biological perspective. The theory of qualitative dynamics of nonlinear differential equations in 3 or more dimensions is not in very good shape. It has been particularly difficult to demonstrate uniqueness and local and global stability for limit cycle oscillations (but see *references 29-31*). If unique stable limit cycle oscillations in high dimensions can be generated at will as conjectured, a sharp challenge to prove the conjecture will be posed to theoreticians. A numerical computation which demonstrates the conjecture for the snake in equation (V.2a) with the parameters in equation (V.3a) is in *reference 18*. However, since the argument relied on explicit algebraic computations made possible by the symmetries of the vector field, the technique cannot be easily extended to the general case. All attempts to date to find an appropriate topological approach have failed.

Although in this article I have only discussed the dynamics in a class of piecewise linear equations, I believe the results are of much more general interest. The PL equations were devised only after several numerical studies based on hypothetical mechanisms for biological control systems indicated that qualitative features of the numerical solutions did not change provided the same underlying "logical" structure was preserved [*22*,*32*,*33*]. Any one PL equation can be taken to represent a paradigm example for a large class of nonlinear ordinary differential equations. Also partial differential equations, in which the N variables are considered to be localized catalysts interacting by diffusion, give dynamics which are typified by the PL equations [*34-36*]. A formal procedure for generating nonlinear ordinary differential equations from the PL equations is given in *reference 17*, along with several examples. One technique for analyzing nonlinear problems is to search for a piecewise linear limit where explicit results can be found [*16*, *18*, *31*, *37*]. It is then necessary to demonstrate invariance of qualitative dynamics as the limiting piecewise linear case was reached. There has recently been progress in this direction [*31*].

The mathematical techniques which have been presented can be used to relate the qualitative dynamics of experimental biological systems, expressed as relative phases of activity of variables in a coarse grained phase space, to the underlying interactions which generate these observed patterns of activity. As noted, for many simple systems with 2 or 3 interacting species, observed patterns of activity can be classified using the techniques described. The geometric and conceptual simplicity of the mathematics should enable biologists to employ these techniques in an experimental situation to help analyze the mechanisms generating and controlling biological oscillations.

APPENDIX [*26, 38, 39*]

To understand this article it is necessary to see the connections between Boolean states, Euclidean N-space and N-dimensional cubes, called *N-cubes*. A *Boolean variable* is either 1 or 0. In this article Boolean variables are designated by a tilda, as in $\tilde{x}_i$. If there are N variables, a *Boolean state* is an N-tuple of 1s and 0s. For N variables, there are 2^N Boolean states.

In N dimensional Euclidean space, the equation $x_i=0$ determines an N-1 dimensional hyperplane called the *coordinate hyperplane*. In N-dimensions there are N coordinate hyperplanes. The N coordinate hyperplanes partition Euclidean space into 2^N hypervolumes, called *orthants*. Each orthant can be named by the Boolean N-tuple $(\tilde{x}_1\tilde{x}_2..\tilde{x}_N)$, where $\tilde{x}_i=0$ if $x_i<0$ and $\tilde{x}_i=1$ if $x_i>0$. Figure 4a shows the partition of Euclidean 2-spaces into 4 orthants (called *quadrants* in 2 dimensions). An N-cube can be constructed by:

1) Selecting a single point from each of the 2^N orthants. These points are the vertices of the Boolean N-cube and can be labelled by a Boolean N-tuple designating the orthant from which they came.
2) Drawing an edge between each pair of vertices coming from orthants which share a common (N-1) dimensional boundary. From this construction it is clear that there are $(N\times 2^N/2)$ edges on the N-cube.

The 2-cube with its vertices labelled is shown in figure 4b.

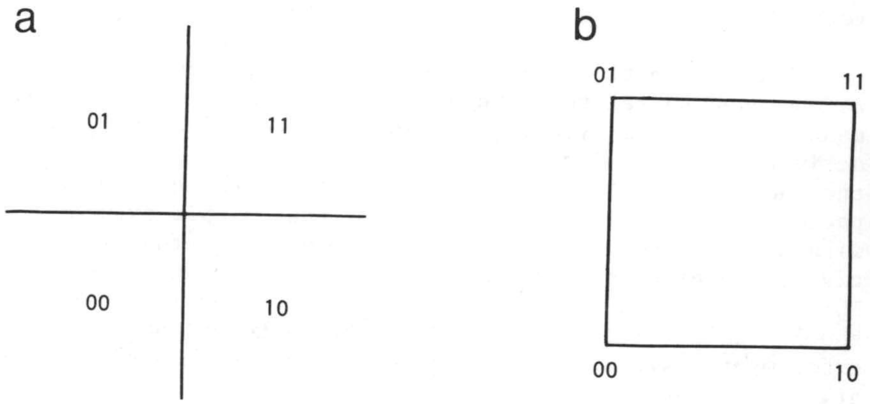

Figure 4 -- (a) 2 dimensional Euclidean space.
(b) The geometric dual of (a) - the 2-cube.

In Section V, I refer to the distance between 2 Boolean states. The *distance* between 2 Boolean states is equal to the number of loci which differ in the 2 states. Geometrically, the distance corresponds to the minimum number of edges which must be traversed on the N-cube to go from one vertex to another.

Equation (III.1) incorporates Boolean functions in a differential equation. A *Boolean function* of N Boolean variables designates a 1 or 0 to each of the 2^N states of the variables. There are 2^{2^N} Boolean functions of N-variables. A Boolean function of N-variables can be neatly represented on the N-cube. If the Boolean function associates a 1 (or 0) to a state, the vertex corresponding to that state is colored black (or white).

A classical combinatorial problem is to count the number of equivalence classes of Boolean functions under the symmetry group of the N-cube, called the *hyperoctahedral group*, O_N [*38*,*39*]. The number of elements (*order*) of O_N is equal to $N!\ 2^N$. Knowing the symmetry type of a Boolean function is of practical interest since two logic elements in the same symmetry class can be constructed out of the same hardware. Extensive listings of the symmetry classes of Boolean functions of 2,3, and 4 input variables have been compiled [*39*].

Polya has invented a technique to count the number of symmetry classes under a group without listing the classes [*38*,*39*]. If S is a finite set, h_i is an element of a group H, n is the order of H and $I(h_i)$ is the number of elements of S left invariant under h_i, the number C of equivalence classes in S under H is

$$C = \frac{1}{n} \sum_{i=1}^{n} I(h_i) \ .$$

This result has been used to count symmetry classes of Boolean switching networks, and also in Section II to count the symmetry classes of state transition diagrams.

There are two ways of thinking about the group elements of 0_N. A geometric approach will be familiar to those with standard training in chemistry and physics. The group elements of 0_N are the reflections, rotations and combinations of rotations and reflections which leave the N-cube invariant [*38*]. It is difficult to use the geometric definitions for $N \geq 4$ and an algebraic approach is often used [*39*]. Consider an N-cube in which the vertices are labelled by Boolean states, as in figures 3 and 4. The elements of 0_N generate all possible relabellings of the N-cube consistent with the constraint that vertices whose distance is 1 share a common edge. The elements of 0_N can therefore be seen to comprise that N! permutations of the coordinates, the 2^N complementations of the coordinates (changing a 1 to 0, and 0 to 1) and combinations of permutations and complementations. The discussion in Section IV makes use of this algebraic description of the elements of 0_N.

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