

XXXIV. NEUROPHYSIOLOGY

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RESEARCH OBJECTIVES AND SUMMARY OF RESEARCH

1. Basic Theory

Research on the functional organization of the reticular core of the central nervous system continues, in collaboration with Dr. William L. Kilmer of Michigan State University.

Our problem is to construct a theory for the reticular system which is compatible with known neuroanatomy and neurophysiology, and which will lead to testable hypotheses concerning its operation.^{1,2}

Our first and second approaches to this problem³ were outlined in Quarterly Progress Report No. 76 (page 313).

We can report that we are embarked on a kind of iterative net statistical decision theory⁴ that is comprehensive, versatile, and penetrating enough to stand a reasonable chance of success.

The computer modeling is being done at the Instrumentation Laboratory, M. I. T., by members of Louis L. Sutro's group.

W. S. McCulloch

References

1. W. S. McCulloch and W. L. Kilmer, "Introduction to the Problem of the Reticular Formation," in Automata Theory (Academic Press, Inc., New York, 1966).
2. W. S. McCulloch, "What's in the Brain That Ink May Character?," Proceedings of the 1964 International Congress for Logic, Methodology and Philosophy of Science, Held in Jerusalem, August 26-September 2, 1964 (North-Holland Publishing Company, Amsterdam, 1965).

*This work was supported in part by the National Institutes of Health (Grants 5R01 NB-04985-04, NB-07576-01, NB-07501-01, and NB-07568-01), the U.S. Air Force (Aerospace Medical Division) under Contract AF33(615)-3885, and by a grant from Bell Telephone Laboratories Incorporated.

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3. W. L. Kilmer, "On Dynamic Switching in One-Dimensional Iterative Logic Networks," Inform. Contr. 6, 399-415 (1963).
4. W. L. Kilmer, "Topics in the Theory of One-Dimensional Iterative Networks," Inform. Contr. 7, 180-199 (1964).

2. Project Plans

a. The study of color vision and the coding of "dimming detectors" in frog optic nerve have led the group under Professor J. Y. Lettvin to propose a theory of the receptor process that yields in an extremely simple fashion not only the parameters necessary to account for their data, but also predicts the threshold behavior in human psychophysics. That is, the laws for absolute threshold, increment threshold, Barlow's law for small spots, and Alpern's and Rushton's law for contrast threshold seem to arise quite naturally. While this concordance does not, by any means, prove the theory, it does suggest further experimental exploration.

It appears that there are several transductive processes in the photoreceptors at least two of which are involved as automatic gain controls. This much is certainly true for the frog. The AGC with a fast-time constant applies to the signal current generation by activated rhodopsin in a proportional shunt generated by one of the intermediate breakdown products, while an additional signal of the same type seen after activated rhodopsin is generated by opsin itself.

b. Professor J. E. Brown, in collaboration with Dr. T. G. Smith, Jr., of the National Institutes of Health, has continued work on photoelectric potentials in response to flashes of bright light recorded from single visual receptor cells in the eyes of Limulus polyphemus. These photoelectric potentials have been shown to be generated across the cell membrane of the visual receptors and to have action spectrum resembling the absorption spectrum of Limulus rhodopsin. The response has been found to have two components which have differing dependences on membrane polarization and temperature.

The receptive field organization of rat retinal ganglion cells has been studied, in collaboration with L. D. Partridge, by the area-response criterion method. The results confirm the observation, based on less quantitative approaches, that there are receptive fields having no demonstrable antagonistic surrounds, as well as receptive fields with concentric antagonistic areas.

Investigation of the median ocellus of Limulus polyphemus has begun in collaboration with J. F. Nolte. Intracellular recordings have been taken from single receptor cells in the ocellus. Depolarizing generator potentials which seem to have the time course of other visual generator potentials in Limulus eyes have been recorded with monochromatic light flashes at 350 nm. The same cell shows a hyperpolarizing generator potential with light flashes of 525 nm. This is unlike all other visual phenomena in Limulus eyes, and the mechanism for this hyperpolarization is still unknown.

J. Y. Lettvin

A. FIORELLO*

The problem of re-entrance or circularity has obstructed the progress of Logic and Mathematics for two millennia, of Neurophysiology for 330 years, and of Engineering and Physics for at least 200 years. Warren McCulloch began worrying about it in 1917 and it became acute for him in 1923, when he conceived information flowing through ranks of formal neurons as Mendelian genes do in a hereditary net. But he could make nothing of it until he had the help of Walter H. Pitts with whom he worked for more than a year, chiefly on Part III of their paper of 1943, entitled "A Logical Calculus of the Ideas Immanent in Nervous Activity," which became an opening wedge for what is now called the Algebraic Theory of Finite Automata. They managed to prove, albeit obscurely, three theorems which depend, in a vague way, on the theory of relatively prime numbers. They concluded that neural nets without loops, provided with scanners and tape, were equivalent to Turing machines, and that nets with loops could compute, without scanners and tape, some of the numbers a Turing machine can compute, but not all of them, and no others. No new theorems concerning closed loops appeared until 1955, when David A. Huffman, working from prime polynomials on a Galois field, initiated the theory of linear Shift Registers, composed of delays and logical gates called "zero-sum-adders" that compute the exclusive or.

In the ensuing eleven years, many new theorems concerning them appeared, including a way of linearizing nonlinear cases by increasing the number of delays, and, in 1966, James L. Massey devised an algorithm generating the minimum linear shift register to produce a given sequence of digits. With his help, Jose L. Simões da Fonseca invented a way of mathematically linearizing any nonlinear shift register and an algorithm for its construction in minimal length which is never longer, and usually shorter, than the linear one. Unfortunately, shift registers of a given number of delays can compute only a handful of those computable by fully connected nets of the same number of neurons, each capable of computing any Boolean function of its inputs.

In 1965, McCulloch was working on the more general problem of what modes of oscillation a net of N neurons could embody. For one neuron, it is one mode; for two neurons, twenty modes; for three he could neither exhaust them nor count them. Carl P. J. Schnabel succeeded: It is the sum from $k=1$ to N of $(k-1)$ factorial times the combinations of 2^N taken k at a time, which is much more than $(2^N-1)!$ and hence grows fantastically as N increases. The mode of oscillation which the net will enjoy is uniquely determined by a constant input over a number of input lines equal to the logarithm to the base two of the number of possible modes.

*This work was done partly at the Instrumentation Laboratory under the auspices of DSR Project 55-257, sponsored by the Bioscience Division of National Aeronautics and Space Administration through Contract NSR 22-009-138.

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In the next year, Roberto Moreno-Diaz, using a theorem of Manuel Blum, proved that all possible modes, for a net of N neurons, could be realized by a single net with the same number of inputs. Then, thanks to Lewis Gilstrap's tensor representations of loop-free nets, we began two streams of study which have converged to produce the work we are about to report.

One stream concerns the stability of neural nets, solved by Roberto Moreno-Diaz, with suggestions from Manuel Blum, employing what is called – we believe erroneously – a "state transition matrix." This is a square array of zeros and ones at the intersections of rows defining states of the net at time t with columns defining the states at time $t+1$, under a given input. That diagonal in which the state at time t and the state at time $t+1$ are the same, for that input, is called the "principal diagonal." If it is composed of zeros alone, the network is obviously completely unstable for that input. If there is a one in at least one place, then it is stable when it reaches that state. From such considerations, the length of the transients can be computed for each input, from the appropriate transition matrix. If instead of using 1's and 0's, one uses probabilities, the probabilistic behavior of the net can be computed for each fixed input.

The second stream began with an understanding of Charles Saunders Peirce's representations of the logic of relations. For diadic relations in extenso, he has a square array, the intersections of whose rows and columns signify individuals between whom the relation exists by a 1, and does not exist by a 0. This representation enabled him to form relative products, such as "A loves someone who serves B," and it is on those relative products that the important theorems of the Logic of Relations depend. These are not matrices in the full sense, since the relative sum "Take any individual, then A loves him, or he serves B," does not belong to the matricial calculus. The "state transition matrices" for each input appear, thus, to be representations of binary relations in extenso. Peirce's individuals in the relations correspond to the states of the net.

But the relation that we seek to represent is fundamentally triadic, and only appears diadic by restriction to a fixed input. We defined a mint as a three-dimensional array in which are stacked all of the two-dimensional state transitional representations for each of the possible inputs. Mints enjoy relative sums and relative products, and we have used them as Peirce defined them. Thus, our vertical dimension comprises the inputs.

Please note that, in the mint, the intersections of any three orthogonal lines are only 1's or 0's, and hence are directly applicable to deterministic nets.

This type of triadic relation among state, input, and new state is a particular type of triadic relation in which the vertical dimension comprises individuals (the inputs) of a nature different from the states. In this case, by looking down through the mint, we can form what we call a "functional matrix" in which every position contains a functional expression of the input variables. Each takes the value 1 or 0 for each value of

the inputs, according to what the value, 1 or 0, of that position was in the original mint. The functional matrix is then a two-dimensional projection of the truly triadic relation. Thus, every position in the "functional matrix," for deterministic nets, is a Boolean function of Boolean or non-Boolean variables (the input variables) or, expressed in the language of the theory of relations, it is a triadic relation projected into a binary relation by using the third subscript, or blank, as a parameter.

When one wants to extend his theory to nondeterministic nets, all that is necessary is to replace the functional expressions by multivalued or probabilistic functions of the inputs, as McCulloch and his co-workers did in answer to the challenge in probabilistic logic posed by John von Neuman. It follows that one can handle such nets as if they were deterministic, receiving their inputs from the appropriate encoder. This complements the work of Shmoul Winograd and Jack D. Cowan on reliable computation in the presence of noise, but in no sense replaces it.

Just as a universal Turing Machine can be made specific for the computation of a particular number by having a portion of its tape serve as a program, so can a "universal net" of N neurons be made specific to embody any net of N neurons (with or without loops), by a proper encoding of its inputs. Its composition may seem trivial. It is. To construct it, form a mint by stacking all possible state transition matrices of a given dimension, and, by the method indicated above, form the corresponding functional matrix from which the universal net is to be synthesized. Its realization in a neuronal net follows immediately. The encoder is a net without loops, and thus a degenerate case of the theory. Its functional representation is such that all functions in each column are the same. The same is true for a decoder. A network followed by a one-to-one decoder, which samples every neuron of the net, is then equivalent to an alphabetical permutation of the neurons of the net.

Neither the logic of relations, nor the theory of neural nets is fully developed. We expect both to bear fruit in due season, and have only reported their present flowering.

R. Moreno-Diaz, W. S. McCulloch

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B. RANDOM NETS OF FORMAL GENES

Genes switch each other on and off. A bacterium with 2000 interacting genes, let alone Man with 2,000,000 per cell, is too large a control net to be analyzed in detail biochemically. Were it done, we would still want a theory to deduce the behavior of cells, not merely an accurate catalogue of their particular acts. Original proto-organisms must have aggregated their control nets at random, hence study of the behavior of randomly assembled switching nets should reveal the basic organization of the behavior of living systems, regardless of how evolution has selected the surviving forms.

1. Genetic Model

Under these assumptions, the gene is modeled as a binary device capable of realizing any one of the possible Boolean functions of its inputs. The activity of a formal gene, for brevity, gene, at any moment is either 1 or 0. If the genetic value of the i^{th} gene at time t is 1, then the value of all of its output lines at time $t+1$ is 1 simultaneously. Thus, the state of the outputs of a gene at $t+1$ depends on its activity at time t alone. For our logical analysis, it is sufficient to allow time to be discrete. Our formal GENETIC NET consists of a set of N formal genes, each receiving just K inputs, one from each of the K formal genes of N . Inputs arise only from members of N . We choose the K inputs to each gene randomly, and assign to each gene one of the 2^{2^K} Boolean functions of its K inputs in an equally unordered way. Thereafter these doubly disorderly formal nets are deterministic. We assume that all genes compute one step in one time unit. In a homogeneous medium, a single bacterium passes through its changes, and the sea urchin develops from a zygote through a sequence of states. We have therefore studied the autonomous behavior of such nets.

We are concerned with the lengths of modes of oscillation of these nets, the expected number of oscillatory modes in one net, and the length and number of transients leading to each mode. We define a stable state as a cycle length 1. By the difference between states we mean their Hamming distance. We have used this as a measure of the dissimilarity along and between transients and cycles. We have studied the effect of disruption of any state by one Hamming unit. This perturbation introduces an asymmetric probability of transition between cycles, between transients, and between transients and cycles in both directions. We did not investigate mutations, which are equivalent to changes in the functions and connections of the net.

2. Totally Connected Nets

State transitions in nets in which each element receives inputs from all elements, but functions are assigned randomly, are equivalent to random mappings of a set of

2^n integers into itself, and are known to have state cycles whose average length is approximately the square root of the number of states. For a net with 200 binary elements to realize its cycles of 10^{30} states, the age of the universe in microseconds is far too small. The number of its cycles, however, is small, $\sim .35N$. Thus, with high probability, the system will be on its way to or in one of a small number of cycles. Hamming distances per state transition average $.5N$.

3. One-Connected Nets

Nets in which each element receives just one input are no more biologically reasonable than those that are totally connected. State cycles arise which are common multiples of loop lengths in the structure of the net. These state cycles may approach 1,000,000 in length for nets comprising 100 elements. For larger nets, the cycle lengths rapidly become astronomically large, and capable of realization by no earthly organism.

4. Two-Connected Nets, $K = 2$

Nets in which each element receives just two inputs from other elements have the shortest cycles and appear most biologically reasonable. $K = 2$ nets of 15, 50, and 100 elements have been simulated at the University of California Medical Center and gave promising results. Nets of 64, 191, 400, 1024, 4096, and 8191 elements have been

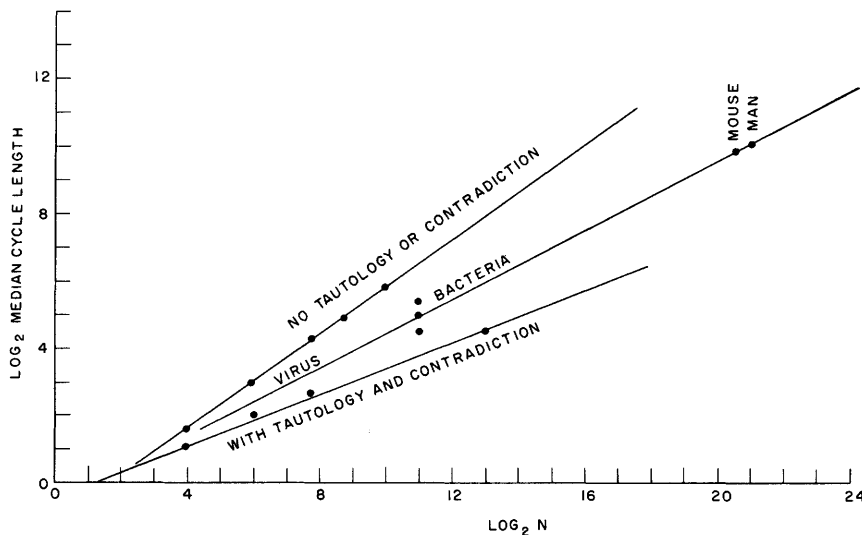


Fig. XXXIV-1. A log-log plot of the median cycle length against the size of the formal genetic $K = 2$ net, both with and without tautology and contradiction. Mean cycle lengths were always longer, and modal cycle lengths shorter, than the corresponding median length. The middle line plots the cell replication time (in minutes) of various organisms.

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simulated on the PDP-6 computer by Project MAC (M. I. T.). When all 16 Boolean functions of 2 variables are used with equiprobability, the cycle lengths obtained are very short indeed: With 64 elements, the median cycle length was 4; with 1024 elements, 12; for any value of N , the distribution of cycle lengths about the median is highly skewed toward shorter lengths, with rare cycles of lengths approximately 100 times the median.

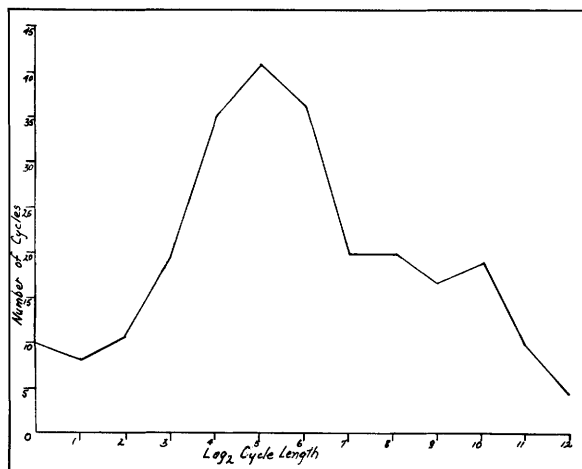


Fig. XXXIV-2.

Distribution of cycle lengths in $K=2$ nets of 400 elements, with neither tautology nor contradiction used. A \log_2 scale is used as the base to accommodate the data. Note that even with log scaling, the distribution is skewed toward short cycle lengths.

Among the 16 Boolean functions of 2 variables, two are tautology and contradiction, each of which yields a constant output. It might be thought that short cycle lengths are due to these foci of constancy, but this is untrue. If neither tautology nor contradiction is allowed, and the remaining 14 functions are used equiprobably, short cycle lengths are still obtained, although the median length for any value of N is a little greater than the condition with tautology and contradiction included. (See Figs. XXXIV-1 and XXXIV-2.)

For nets of a given size, the length of a transient appears to be uncorrelated with the length of the cycle to which it runs (see Fig. XXXIV-3). For nets of a given size the longest transients found were approximately the same length as the longest cycles found in nets of that number. The distribution of transients is highly skewed toward short lengths, but bounded below by the search procedures of the program.

Let the system be released from a randomly chosen initial state. With $N = 100$, the Hamming distance per state transition falls rapidly as the system approaches a cycle, from $\sim .4N$ change during the first transition, to approximately from 0 to $1N$ change for the state that enters the cycle. The curve of Hamming distance per state transition is nearly fitted by a negative exponential with a half-decay requiring 3-4 state transitions. For larger nets, the half-decay should require more transitions.

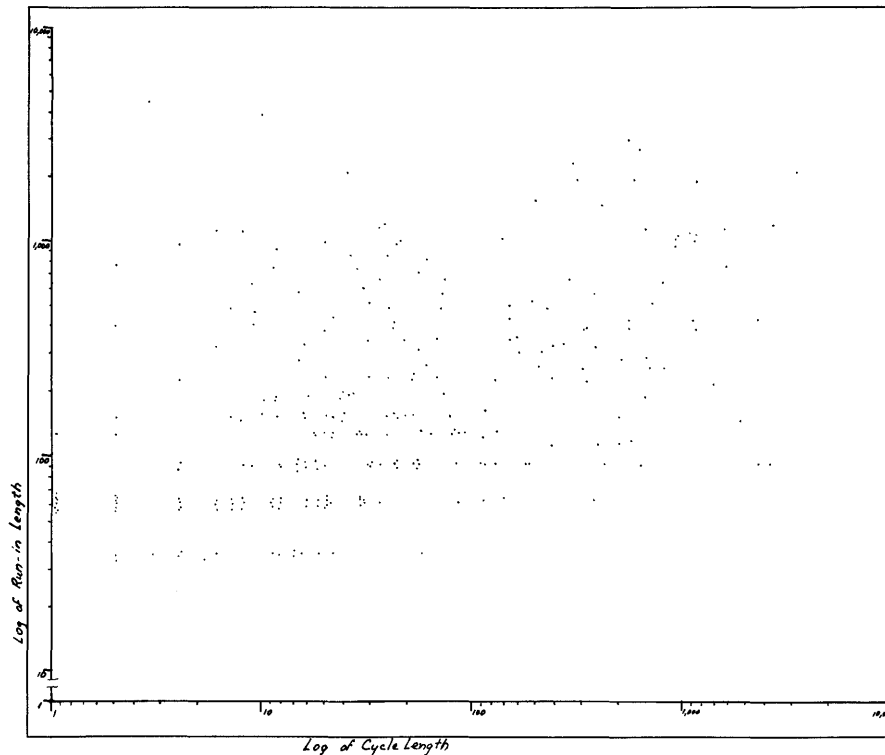


Fig. XXXIV-3. A scattergram of the length of a transient and the length of the cycle to which it led, in nets of 400 elements using neither tautology nor contradiction. Log-log paper was used to accommodate the data. The absence of transients shorter than 30 is due to the search procedure of the program.

Thus, as the system approaches a cycle, states become progressively more similar. We would therefore expect that all states differing from cycle states by a Hamming distance of 1 would themselves be located very few state transitions from cycles.

The number of formal genes that change value during the course of a cycle varies between 0 and 25 in nets with $N = 100$. Thus, most genes are constant throughout the cycle, and cycle states are greatly similar.

During the sequence of states comprising a transient, the number of times different genes change is bimodal; approximately $.3N$ -. $.5N$ elements rarely or never change value, the bulk of the remainder change value almost every second state transition.

The number of cycles per net is as surprisingly low as cycle lengths are short. By simulation on the PDP-6 computer, nets of 16, 64, 191, and 400 elements, with neither tautology nor contradiction used, have been explored by picking 50 initial states in each net. The median number of cycles discovered for $N = 16$ was 2;

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$N = 64, 4$; $N = 191, 6$; and $N = 400, 10$ (see Fig. XXXIV-4). Data from larger nets are now being obtained. Since 200 run-ins per net rarely produced more than one additional cycle than 50 run-ins had, we may expect that medians obtained with 50 run-ins per net serve as a good guide for the comparison of numbers of cycles per net in nets with different values of N .

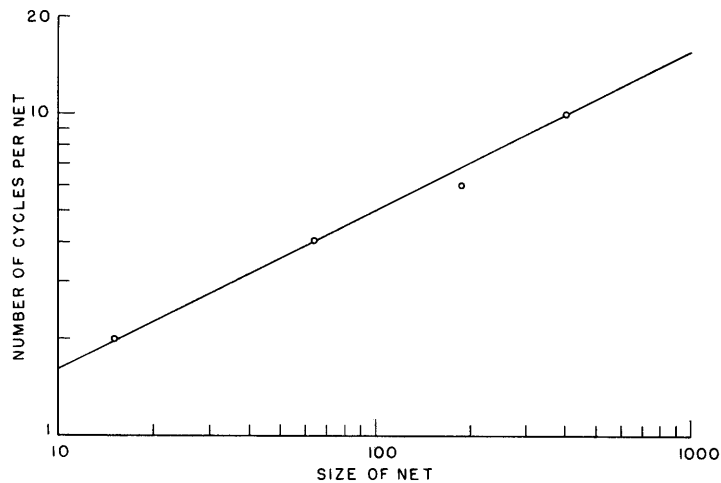


Fig. XXXIV-4. Median number of cycles disclosed on 50 run-ins to each net, plotted against the size of the net. Distributions about the median were skewed toward few cycles. These values are from nets with neither tautology nor contradiction used; their inclusion in nets of 400 has not influenced the median.

The minimum Hamming distance between cycles is commonly 1 or 2, but may be as large as $.3N$. When a net embodies several cycles, say 20, these form sets within which each cycle usually is a minimum Hamming distance of 1 or 2 from at least one or two other members of the set. Between sets, the minimum distance is greater, and may be as large as $.3N$.

The effects of perturbation to all states with a Hamming distance of one from each state of each cycle has been studied for nets of 64, 191, and 400 elements. The system returned to the perturbed cycle 90% of the time, shifted to surprisingly few (1-5) other cycles with probabilities of .02 to .05, and shifted to 4 or 5 further cycles with probabilities between .001 and .005.

One of the nets which was studied is presented in Fig. XXXIV-5. In these nets, the matrix of transition probabilities embodies a Markov Chain. Such chains are characterized by ergodic sets, transient states, and absorbing states. If we consider each CYCLE in a net as a STATE of a Markov chain, then an ergodic set of states is defined as a set in which each state can reach all other states IN the set, but never a state outside the set; a transient state lies in no ergodic region, thus once the system has

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	103	2	16			8	1																							
2		289			2		11																							
3	92	20	976		9	2	1					46	5																	
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5	6	24	6		1076										39															
6	46	1	2			324	6								3	1														
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13	9	18	9										1060			56														
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17					8	1	7							32	10		322						2			1				
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19	37		12	2		6			18	9		2						1	939			6		80		39				
20					8	1				32					10			7		322		2						2		
21	27		6	18		3		1	2		86										949		43						5	
22			3							1	43							6		3	2	315								1
23									18		9		35			1			9			917					106	53	3	
24	3			1		9		6			2						3				43		315							2
25	12		37	18		2		1	2			6		9					80						939	40		6		
26	2		6	1				6				11				3									40	313				2
27	6		2			11			1									6	40								313		2	
28				18				0					35		1						9	106		9			917	4	53	
29													1			11		6				3	53				3	4	303	
30								6					1			11							4	3		3		53		303

Fig. XXXIV-5. A matrix composed of one row for each cycle perturbed, which lists the number of times the system returned to that cycle or shifted to each other cycle. Conversion to transition probabilities yields the corresponding Markov chain.

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reached an ergodic region, it cannot return to the transient states. An absorbing state is an ergodic region consisting of only one state. Markov chains may, of course, have more than one ergodic region; each or all may be accessible from a single or several transient states.

No simulation of a genetic net has disclosed more than one ergodic region. Many have had transients to the ergodic region, however. As can be seen in Fig. XXXIV-5, the probability of transition within each of two sets of cycles is high, between them it is low. One would expect that in systems with several hundred cycles, more than a single ergodic region would be found.

[Note: Mutation, the permanent silencing or switching on of an element in the net, will have less effect on nets with two inputs than for any other connectivity. Since only approximately 10% of the elements change value during a cycle, it is apparent that permanently fixing the behavior of any of the remainder either on or off has 50% probability of having no effect on the cycle behavior of the system. The net is well buffered against such structural noise. If mutation is effective, the state-cycle structure is altered, and a state that formerly was part of a cycle may become part of a transient sequence of states running into a newly formed cycle. No data are available on this.]

Beyond simulation, we want a theory in closed form, but we have not achieved it.

5. Discussion

Random formal nets of low connectivity entail short stable cycles. We suggest that the converse face of the high molecular specificity required for life is the low connectivity of the resulting molecular net. Among cell cycles, none is more conspicuous than replication. Estimates of the time for switching a real gene on or off vary between 5 and 90 sec, call it a minute per state transition. If we plot the cell replication time in minutes of various organisms against the number of their genes, they are comparable to the behavior of $K=2$ nets of formal genes. Fig. XXXIV-1 shows that cell replication times lie midway between the median cycle lengths of nets with and without tautology and contradiction.

Figure XXXIV-2 shows the unimodal distribution of cycle lengths in nets of 400 elements, with neither tautology nor contradiction used. With nets of 1024, cycle lengths bunch together between 10 and 120, and rarely scatter up to 2000 or 3000. Bacteria, possessing between 2000 and 4000 genes, bunch their replication times between approximately 20 and 100 minutes, and scatter them to 1000.

The number of elements changing value during a state cycle is approximately one in 10. Brian Goodwin has pointed out to us that the number of genes whose products undergo oscillatory change during cell cycles is also approximately one in 10.

Cells behave stably in noisy environments. $K = 2$ switching nets, receiving single Hamming units of noise, also behave with stability; perturbation shifts a system from any cycle only approximately one in 10 times. No data are available for nets larger

than 400 or for the simultaneous perturbation of more than a single gene's value.

Cells are thought to differ because the genes that are active in them differ. It is reasonable to identify each temporal pattern of activity in a formal genetic net with one type of cell. Perturbations of genetic nets cause transitions from any cycle to, at most, a few other cycles with probabilities between .02 and .05; a few more may be reached with probabilities \sim .002 to .005. Throughout phylogeny, no cell, neoplastic or normal, differentiates directly into more than a few cell types.

The median number of cycles per net, with neither tautology nor contradiction used, at 64 is 4, and at 400 is 6, and, we may expect, at 2000 will be \sim 25, and at 2,000,000, \sim 1000. This should correspond roughly to the number of discrete metabolic modes of behavior in a bacterium, and cell types in Man.

Stable cell differentiation does not arise in organisms with only 2000-3000 genes. Stable difference will not arise in the behavior of a formal genetic net that embodies a single ergodic region. We hope to show that nets with 2000 elements, like those with 400, commonly disclose a single ergodic region when perturbed by one or slightly more Hamming units of noise; also, we hope to show a correspondence between the number of genes in an organism with more than one stable cell type, and the size of the formal genetic nets with that many ergodic regions.

We plan to develop the following model of differentiation: A fixed level of noise to a formal genetic net introduces asymmetric probabilities of transition between cycles, forming a Markov chain among the cycles. Let the number of cycles be large enough that the Markov chain contains more than a single ergodic region. Pick a cycle that is a Markovian transient able to reach most ergodic regions. Call the Markovian transient cycle the zygote. Then the zygote is totipotent with respect to all of its accessible ergodic sets of cycles. We may explain the origin of differentiation: The zygote is on a Markovian transient cycle and must eventually leave. We may explain the cessation of differentiation: The system will enter one of the ergodic sets of cycles and be trapped. As the system moves through successive cycles, perturbed by noise, from the zygote toward some ergodic region, it passes branch points to other ergodic regions. Before reaching a branch point, no noise will move it to that ergodic region; while passing, noise will so move it; after passing, it will not be able to respond to noise and reach that ergodic region. Hence we expect the competence to be of limited duration, the efficacy and reliability of noise as the stimulus for induction, and the progressive loss of totipotence as branch points are passed. As the system replicates during this goading by noise, a predetermined number of cells will pass down each transition from each cycle, and the appropriate number reach each ergodic region, replicate in each, and occupy each allowable ergodic cycle with the appropriate probability. Amend this to include noise biased by the particular cycles and their spatial locations. Grant death to some, a steady-state population of various cell types arises.

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We conclude that life requires no preordained harmony, only the inevitable consequences of chance and number.

We wish to thank T. Knight for his loyal help in programming Project MAC's PDP-6 computer, without which this work would have been impossible.

S. A. Kauffman, W. S. McCulloch