Systems Methods and Concepts in Biology and Medicine

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ABSTRACT

Three different and independent approaches were utilized to measure the extent of application of systems theory to the biological and medical sciences, namely, literature surveys of computerized data bases, analysis of six case studies involving different levels of biological organization, and personal assessments by a working biologist who is also familiar with systems theory. Five categories of systems terms were selected for the literature search using a priori assumptions regarding their potential utility in detecting systems awareness in biology. Overall, the five clusters of systems terms show the same pattern in year-to-year trends from 1966 to 1981, namely, that systems analysis precedes systems-oriented holistic/theoretical modeling, concepts dealing with intra-system dynamics are used before concepts that indicate awareness of between-system dynamics, and most all categories of systems terms are enjoying increased usage in more recent years. Systems terms used as indicators of some of the new geometric modeling techniques potentially useful to biology showed little or no usage in the bio-literature. Altogether, the data indicates that roughly a twenty year lag period exists between the time when a concept becomes popular in systems circles, and when it is first used by biologists even in a cursory manner. The case study approach examined new biological discoveries in biochemistry and molecular biology, cellular biology, developmental biology, ecology, evolution, and neurobiology. In each of the six case studies analyzed, an incredible and unexpected complexity has appeared with man's increased factual knowledge of the natural phenomenon. This complexity is shown to be more easily understood, communicated, and its remaining issues resolved using a systems framework. This paper also tried to assess how robust current systems approaches are in interpreting and solving biological systems problems, and how widespread systems awareness actually is in the practicing community of biological scientists. Unfortunately, the assessment is negative on both counts with guarded optimism for the future. The most robust and optimistic assessment is reserved for the application of topological geometry to the prediction and modeling of bio-systems. The paper concludes with a discussion of four specific areas that are especially ripe for the application of systems theory to biology.

1.0 INTRODUCTION AND OBJECTIVES

Symposia in this conference were designed to review as comprehensively as possible the state-of-the-art of systems methodology/concepts in several conventional disciplines. The objective of this paper is to review the applications of systems theory to the biological and medical sciences. Systems methodology will be defined as broadly as possible for the purposes of this review. Systems analysis, systems theory, modeling and simulation, citation of systems concepts, and certain specific mathematical approaches will all be regarded as comprising systems methodology. One of the dangers inherent in writing a review, the adoption of too myopic and constrained a scope, will be partially avoided by using this expanded definition of systems methodology. Another immediate problem with reviews of such a generalized topic as this one involves how to measure as empirically as possible the usage of systems theory in biology. If an empirically-based approach isn't at least attempted, the review becomes merely anecdotal. On the other hand, using only an empirical approach may leave out important observations that only the experienced human mind can make. I intend to combine both of these complementary approaches in this review. First, I conduct a literature survey of two of the most complete and comprehensive computerized data bases representing the field of biology using keywords involving systems theory, methods, modeling, and mathematics to represent the general field of systems. Second, I explore in much greater depth than possible in mere keyword searches, one specific phenomenon in each of six different sub-specialties of biology. In each of these cases I try to show how some of the most recent developments portend an increased need for the use of systems concepts and methods, whether or not those methods are now in use. This helps develop a more clear

Citation: Troncale, L.R. (1985b) "Systems Methods and Concepts in Biology and Medicine. Proceedings of the 29th Annual Meeting. SGSR, Louisville, Kentucky, pp. 589-[redacted]
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distinction between "actual" usage of systems methods (which can be partially obtained from keyword searches), and "potential" usage (which is impossible to read from the more empirical, keyword searches). Finally, I try to answer some tough questions which hopefully cut to the heart of the issue of the usage of systems theory in biology. Some of the questions may make biologists uncomfortable. They ask where systems theory could be effectively used and yet is not used. Other questions may make systems investigators uncomfortable. They ask how robust the results really are when systems approaches are used. Throughout I try to make statements, where appropriate, on the differences between "active" and "passive" use of systems concepts and methods, and between reductionist-oriented systems analysis and integration-oriented systems theory. Finally, I would like to end this introduction with a note of caution. Although I term the data base searches "empirical" because they yield numbers for interpretation, it is clear that the numbers provided are only crude approximations of systems awareness across the wide sweep of the field of biology. Numbers have a dangerous tendency to appear more official and objective than they warrant. In this case, at least, the subjective/case study approaches may yield a more realistic picture than the numbers arising from an admittedly unrefined search strategy.

2.0 A LITERATURE SURVEY APPROACH

The computerized data base MEDLINE serves both the biological and the medical fields. MEDLINE analyzes as many as 2,558 periodicals per year. Each article of each issue of these periodicals is represented on-line by its title, bibliographic reference, and abstract. Over a quarter of a million articles were placed on-line in 1980 alone. The observations listed below were based on a composite, super-search for systems-oriented keywords in over three million articles appearing in the professional literature from 1966 to 1981. Table One shows the five major categories of systems keywords and the number of articles in which those words occur over the 16 year period covered by MEDLINE. The number of articles containing systems-oriented keywords is a very small percentage of the total number of articles searched. Even this number is inflated, however, because MEDLINE reviews a number of periodicals which are significant to medicine in general but cannot be considered part of the traditional discipline of biology. For example, systems keywords can be found in journals on psychiatry, psychology, social theory, and health care organizations, many of which are analyzed for MEDLINE, but none of which are considered solely biological. The raw data reported in Table One is incomplete for another reason. Even though a respectable sample of nineteen keywords was included in the search, this sample clearly does not represent all of the possible keywords associated with systems methodology. Still such searches are useful for the many titles they uncover in the international literature which are germane to the issue, and further because year-to-year searches reveal interesting trends in the levels of systems-awareness in biologists and physicians.

BIOSIS is a computerized data base of essentially the same periodicals as those covered in the more traditional Biological Abstracts. Biological Abstracts is a soft-bound publication of cross-referenced abstracts, published monthly and used by most working biologists for hands-on, unaided searches on a frequent basis. Again each article is represented by title, reference, and abstract. BIOSIS covers 8,580 periodicals per year, and the search reported here represents the occurrence of systems-oriented keywords in 3.3 million articles over the period 1969 to 1981. BIOSIS is more specifically oriented to the literature of the biological sciences than MEDLINE. Table One also shows the number of articles in the BIOSIS data base which contain our sample of systems-oriented keywords. Again the successful matches or "hits" represent a small, but significant percentage of the total data base.

The number of articles containing reference to systems methodological terms in BIOSIS and MEDLINE shown in Table One cannot simply be added together to obtain grand totals. MEDLINE and BIOSIS are independent data bases and overlap in their journal coverage. They are redundant. 79% of MEDLINE journals can be found in BIOSIS, and 24% of BIOSIS in MEDLINE. In comparing a listing of titles representing successful searches for the keyword "system"(w)theor?" in MEDLINE and BIOSIS, I found about 10% of the "hits" were the same articles in both data bases. A discrepancy was found between the totals of successful "hits" obtained using super-searches of composite/grouped years for the keywords, and the totals revealed by adding the year-to-year searches for the MEDLINE data base. At the time this article went to press, this discrepancy remained unresolved. Anomalous data for 1974 and 1979 led to omission of data for these years. These shortcomings reinforce the aforementioned caution that these numbers be used only to assess in a rough manner the usage of systems concepts in biology.

The five categories of keywords used in the searches were selected using a priori assumptions regarding their appropriateness for measuring the use of systems awareness in the study of bio-phenomena. Each category represents a different aspect of systems methods and so provides several independent "tests" of systems awareness, each expected to supply unique insights. A more detailed appraisal and analysis of each of the five categories of keyword-searches follows.

2.1 A LITERATURE SURVEY ON SYSTEMS METHODS

The first cluster of keywords are those which denote some awareness of systems methods in the way that the authors present their study of biological phenomena. Table One shows the outcome of a simple search for the use of the root construct.... "system?". The question mark indicates that any suffix could appear with system- and still be graded as a "hit" (for example, systems, systematic, systematize, and systemic would be allowable). Although, this keyword yields the highest number of articles retrieved, fully 7.94% of the articles searched, it is useless for the purpose of this paper. The word system is used non-specifically in biology as in "organ system", or to designate an entire subspecialty as in "systematics" for taxonomy. These usages predate by 200 or more years the beginning of the field of systems analysis and systems theory, but do not connote a sophisticated knowledge of systems dynamics. In order to more closely assess the extent of systems awareness in biological research it was necessary to combine the generic word system? with such modifiers as "approach", "analysis", and "theor?". Using the more specific search strategy the number of articles found in MEDLINE becomes a small fraction of articles searched, namely .017% for Systems Approach, .055% for Systems Analysis, and .0084% for Systems Theor? (n = 540, 1702, and 258 respectively). The most frequently cited keyword was Systems Analysis, followed by Systems Approach, and then Systems Theory. A search of BIOSIS for the same words revealed the same pattern; Systems Analysis (n = 597) was the most frequent, Systems Approach the second in frequency (n = 349), and Systems Theory the least frequent (n = 202). The numbers were not the same in both data bases possibly indicating that they contain articles from a significant number of different journals. On the other hand the differences result from the difference in total years available for the search. The same order of frequency of usage is revealed in both despite the difference in numbers found. This may be construed to mean that a literature survey of such computerized data bases for the purpose of providing a crude estimate of systems awareness in biology is, indeed, a reasonable and reliable expectation.

"Systems Analysis" is found almost twice as frequently as "Systems Approach". This indicates that the inherently reductionist and analytical nature of this method is more compatible with the modus operandi of experimental biologists. It may also indicate that a great deal of information and empirical fact must be obtained about any sub-system in biology before the full nature of the interconnections between the sub-sub-systems within the sub-system reveal themselves and enable (or require) a systems approach to be utilized. The use of "Systems Theory" implies a more synthetic or integrative approach to a biological phenomenon. This is considerably removed from the day-to-day operational experiments of most bioscientists and may explain its low usage to date. Historically, one might predict the necessity of more than half a century of reductionist experiments before sufficient information is accumulated to enable a decade or two of systems analysis, before sufficient understanding is achieved to enable systems comparisons and true theoretical advances. And herein lies precisely the point of this essay. If a sufficiently detailed and proven general theory of systems was available, and if it were widely studied and respected by most reductionist workers, then the 150 years necessary to move from raw data to systems-theoretical levels of understanding might be considerably shortened. I. I. Rabi, the widely respected Nobel Laureate in Sub-atomic Physics, once compared science to a mining operation. He was delighted that hoardes of scientists so dedicatedly "mined" the rich ores from the bowels of Nature (analytical, reductionist experiments), but he bemoaned the fact that so very, very few did anything with the crude ores once mined. They merely piled up around the mouth of the mine. What was missing and was desparately needed was refinement of facts; in other words, their synthesis and integration into meaningful and comprehensive models of ever wider scope and generality; models capable of spawning theoretical predictions. I will return to this theme later.

Figure One is a graph of the year-by-year citations of "systems analysis", "systems approach" and "systems theory", in MEDLINE only. These are compared with the very gradual increase in the total number of articles contained in the data base. It is clear that the use of the term "systems analysis" in biology enjoyed a remarkable increase in the late sixties and continues to oscillate around the frequency achieved by 1970, throughout the seventies. By contrast "systems approaches" do not appear in the data base until the mid-seventies and they reach a plateau in the late seventies. "Systems theory" citations do not appear until the late seventies, and appear to be enjoying a rapid increase in the current literature. Figure One indicates that systems analysis precedes systems theory in usage and that there is a delay of almost twenty years between the use of a technique in the systems field and its spread to applied fields. Systems analysis first became popular in the forties in military and government operations. It appeared in biology in the sixties according to the graphed data. Systems theory led to the establishment of the Society for General Systems Research in the fifties, and systems theory is just now being used detectably in the biological literature of the seventies. It is important to note that I speak here of the attainment of a moderate level of usage and awareness. Undoubtedly, systems workers know of early and sporadic uses of systems concepts in biology that predate the wider usage revealed in the graphed data. I do not believe these early uses by specialists concerned mostly with systems theory constitute recognized usage by working biologists. Clearly, general systems theory is not even being used now by most working biologists.

An analysis of 242 titles retrieved from the MEDLINE and BIOSIS data bases from the years 1977 to 1981 and using the most conservative "hit" list, "systems theory", yields many useful titles for biologists and systems specialists. But, only 9% of the titles retrieved directly involved "general" systems theory, while 33% can be interpreted as systems analysis-oriented, and 17% are involved in disciplinary-oriented systems theory. For each of these categories, BIOSIS (a 5 year sample) retrieved roughly twice as many articles as MEDLINE (a 2 year sample). Further, the BIOSIS-retrieved titles were more germane to the topic of this paper than were the MEDLINE articles. Both of the above categories, systems analysis and specialty-restricted systems theory are certainly methodologies involving some systems concepts, but they clearly do not compare <u>across</u> widely different types of systems in the manner of true general systems theory. They may be the vanguard of the systems movement, but are significantly different in character, results, and potential from general systems approaches. I do not see how the use of the term "systems theory" is justified unless a transdisciplinary base of principles and patterns is incorporated into the theoretical construct. In contrast, the use of systems analysis and simulation in biology are not only based in a single discipline, but often involve only considerations of the single sub-specialty or phenomenon being modeled. This deprives the user of the most fertile qualities of a general theory of systems -- the opportunity to discover order in a new system more quickly by analyzing it using well-studied principles and patterns of systems optimization already known to be true of other systems. It is precisely this application of a "template model" of systems function that could lead to shortening the 150 years necessary for rediscovering the details of operation of each new system addressed by mankind. Doubtless, reductionist scientists would counter this dream with a sobering question aimed at how holists intend to verify the "template model" to insure that its application is justified. There is no answer for this question as yet. In any case, the field is so young at this time that a search for "systems theory" in these data bases yields articles indicating that this category is mixed in with entries which are actually systems analysis, with few, if any entries utilizing truly general systems methodologies. Ironically, those entries that are general systems oriented have been published in journals sponsored by our own professional societies in systems theory. I conclude that general systems theory has not yet penetrated the world of the average working biologist, while systems analysis has to a limited extent to be further elucidated in the case study section.

	KEYWORD SEARCHED	MEDLINE (1966-1981) TOTAL SEARCHED= 3,082,188 TOTAL RETRIEVED	RETRIEVED: $ OF TOTAL	BIOSIS (1969-1981) TOTAL SEARCHED= 3,309,142 TOTAL RETRIEVED	RETRIEVED: $ OF TOTAL
SYSTEMS METHODS	SYSTEM?	244,595	7.94	166,722	5.04
	SYSTEM? (W) APPROACH	540	.017	349	.01
	SYSTEM? (W) ANALYSIS	1,702	.055	597	.018
	SYSTEM? (W) THEOR?	258	.0084	202	.006
SYSTEMS MODEL BUILDING	BIOLOGIC? (W) MODEL	120	.004	101	.003
	MOLECUL? (W) MODEL	1,993	.065	242	.007
	STRUCTUR? OR FUNCTION? (W) MODEL	192	.006	437	.013
INTRA SYSTEMS CONCEPT	STABILIT?	19,096	.62	15,153	.458
	EQUILIBRI?	16,269	.53	13,265	.40
	FEEDBACK	9,024	.3	7,022	.212
	SYNERG?	16,903	.55	5,206	.157
TRANSITIONAL SYSTEMS CONCEPTS	HIERARCH?	769	.025	1,311	.04
	STATE PHASE?	21	-	67	.002
	ENTROP?	776	.025	1,063	.023
	DUAL?	2,547	.083	3,123	.094
	AUTOPOIET?	2	-	5	-
NEW MATH APPROACHES	TOPOLOG?	372	.012	596	.018
	BIFURCAT?	924	.03	429	.013
	BIFURCAT? (W) THEOR?	7	-	15	-
	CATASTROPH? THEOR?	21	-	73	.002

TABLE ONE: Results of Keyword Searches for Five Categories of Systems Terms Using Two International, Computerized Data Bases.

2.2 USE OF SYSTEMS CONCEPTS IN BIOLOGY

I selected nine terms as keywords to monitor the depth of systems awareness in Biology. Table One shows that two subgroups of terms emerge from the data. Well-established terms such as feedback, stability, and equilibrium are also the most commonly encountered in Biology. They occur in three-tenths

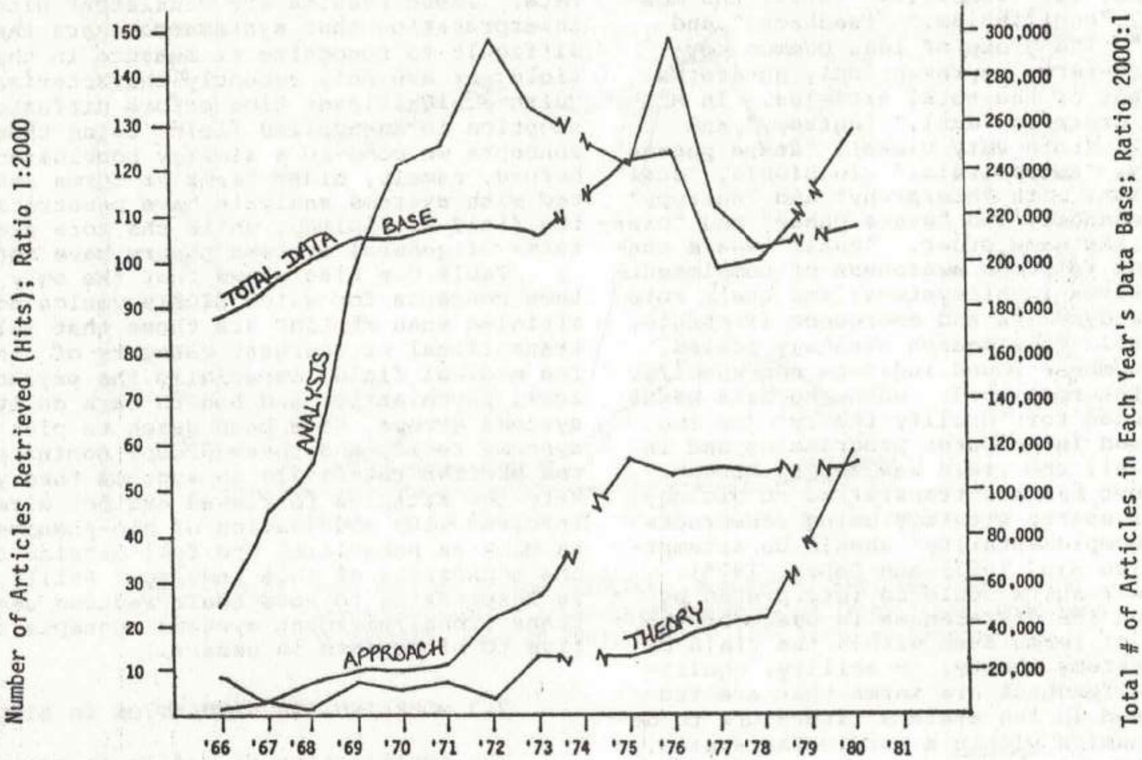

FIGURE ONE: MEDLINE, Year-By-Year Numbers of Articles Using Keywords on Systems Methods, 1966 to 1981, 3.08 Million Articles Searched.

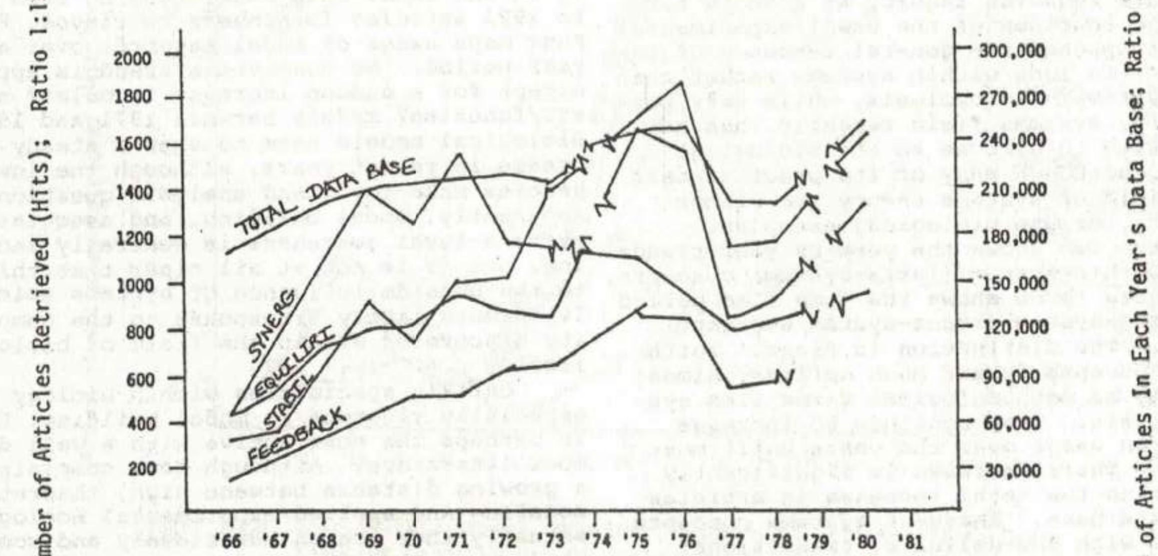

FIGURE TWO: Year-By-Year Search, MEDLINE. Numbers of Articles Found Using Keywords on Intra-Level Dynamics of Systems, 1966 to 1981, 3.08 Million Articles Searched.

to six-tenths of 1% of the total articles, the most encountered so far. In MEDLINE, the order of frequency is "stability" (most common), "synergy," "equilibrium," and "feedback" (least common). In BIOSIS, the order of frequency is: "stability" (still the most frequent), "equilibrium," "feedback," and "synergy." The group of less common keyword-search-terms represent only hundreths of a percent of the total articles. In MEDLINE, the order is "dual," "entropy" and "hierarch?" (both very close), "state phases" and lastly, "autopoiesis." In BIOSIS, "dual" is also high, with "hierarchy" and "entropy" now interchanged, and "state phase" and "hierarchy" in the same order. "Dual?" was a construct used to probe awareness of complementary dualitites in biosystems, and their role in systems dynamics and emergence (Troncale, 1972, 1978). This search strategy failed. The high numbers found indicate non-specific usage of the root word. When the data bases were searched for "duality theory" (as the term is used in computer programming and in mathematics), the yield was zero. Either this concept has not transferred to biology, or another search strategy using constructs such as "complementarity" should be attempted,(see also Siu, 1957; and Capra, 1975).

These results could be interpreted by focusing on the differences in usage of the two types of terms even within the field of general systems theory. Stability, equilibrium, and feedback are terms that are frequently used in the systems literature to describe dynamics within a particular system. As such they may be more easily utilized by practitioners who focus on a single real system and by reductionists who have to concentrate on a delimited area for purposes of controlled experimentation. Terms such as hierarchy and entropy involve dynamics and emergence across or between systems (Troncale, 1978, 1981). This requires an awareness of an added dimension of dynamics which may be less easy to grasp by empiricists. The concept of hierarchy, for example, by its very nature requires inquiry at a scope far beyond the confines of the usual experimental plan. It opposes the general tendency of the empiricist to look within systems rather than beyond systems. Autopoiesis, while very popular in the systems field recently, has not had the time to diffuse to the biological sciences, although many of its practitioners in the field of systems theory are either biologists, or use biological examples.

Figure Two shows the year-by-year trends for the within-system (intra-system) concepts, while Figure Three shows the same time period for between-system (trans-system/emergent) concepts. The distinction is clear. Intra-systems concepts appear much earlier, almost as quickly as methodological terms like systems analysis. They continue to increase slightly in usage over the years until most recently. Their increase is significantly greater than the total increase in articles in the data base. Emergent systems concepts that deal with the delicate, transitional states of systems, do not appear to increase in the bio-medical literature until the mid-seventies and then show a modest increase until recently. Autopoiesis is not even shown in Figure Three because of its low occurrence rate. These results are consistent with the interpretation that systems concepts that are difficult to recognize or measure in the system field, or are only recently characterized, require a significant time before diffusion and adoption in an applied field. Using these key concepts we come to a similar conclusion as before, namely, older terms or terms associated with systems analysis have penetrated into the field of biology, while the more exotic terms of general systems theory have not.

Table One also shows that the only systems concepts for which BIOSIS yields more articles than MEDLINE are those that fall in the transitional or emergent category of concepts. The medical field, especially the psychological, psychiatric, and health care delivery systems groups, have been quick to pick up systems terms, and these groups dominate the MEDLINE retrievals on systems theory. Yet, the articles retrieved are not directly involved with elucidation of bio-phenomena as much as behavioral and fall outside the the boundaries of this inquiry. Still, it is interesting to note their reduced use of transitional/emergent systems concepts relative to biologists in general.

2.3 MODELING AND SIMULATION IN BIOLOGY

The construction of models in biology involves the use of systems techniques ranging from computer simulation to simple diagrams of networks of multiple/simultaneous causes and effects. Keyword searches for model building (Table One) show that "molecular models" were the most frequent in MEDLINE followed by "structural/functional models." The reverse was true for BIOSIS. "Biologic?(w)model" scored low in both. These retrieved items amounted to only hundreths to thousandths of 1% of the total data base, ranging from 101 to 1993 articles in numbers retrieved. Figure Four maps usage of model keywords over a 16 year period. No consistent trend is apparent except for a sudden increase in molec? and str/function? models between 1971 and 1977. Biological models seem to show a steady increase in recent years, although the low frequencies make any trend analysis questionable. Apparently, model building, and associated systems-level awareness is generally increasing, but it is not at all clear that this is due to the outside influence of systems science. It is more likely a response to the complexity discovered within the field of biology itself.

Certain specialties within biology are especially vigorous in model building. Ecology is perhaps the most active with a well developed literature. Although some complain of a growing distance between high, theoretical modeling and applied/experimental ecology, actually they are rather closely and cooperatively coupled compared to other biological

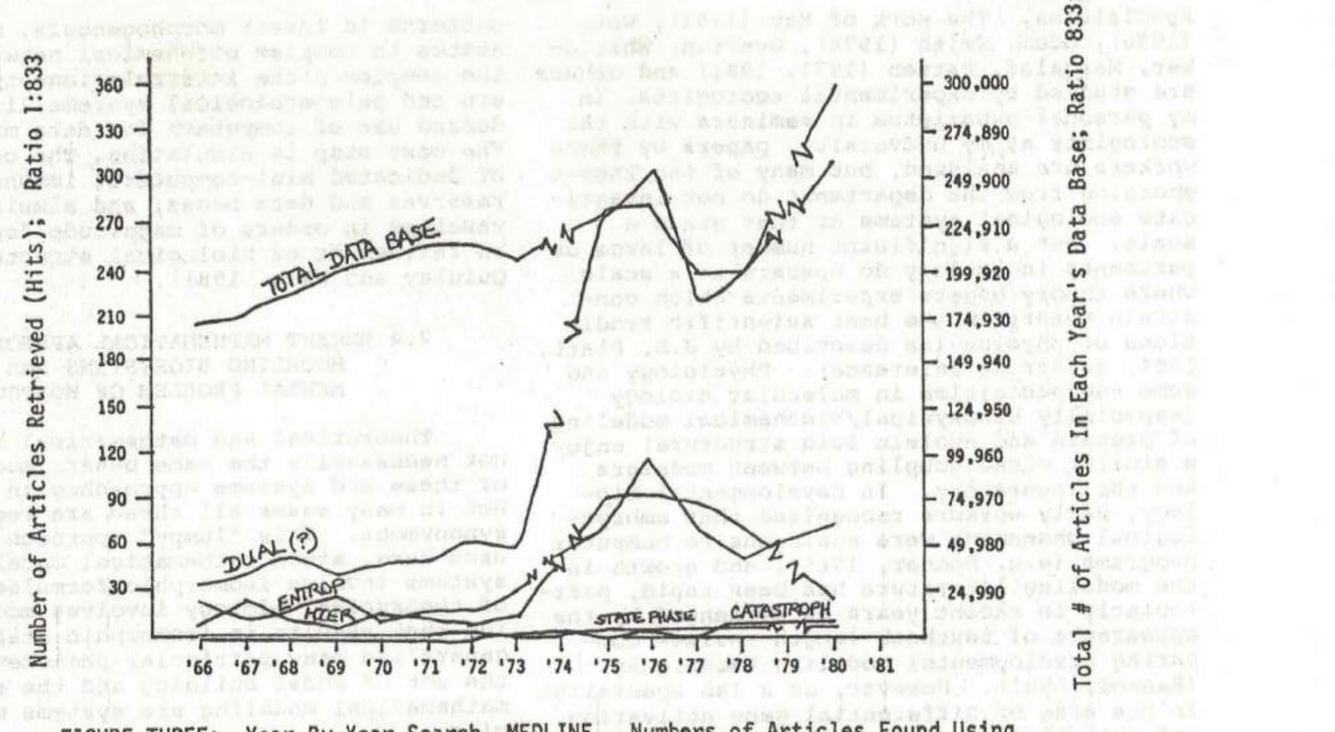

FIGURE THREE: Year-By-Year Search, MEDLINE. Numbers of Articles Found Using Keywords Denoting Inter-Level Dynamics or Transitional Phenomena of Systems, 1966 to 1981, 3.08 Million Articles Searched.

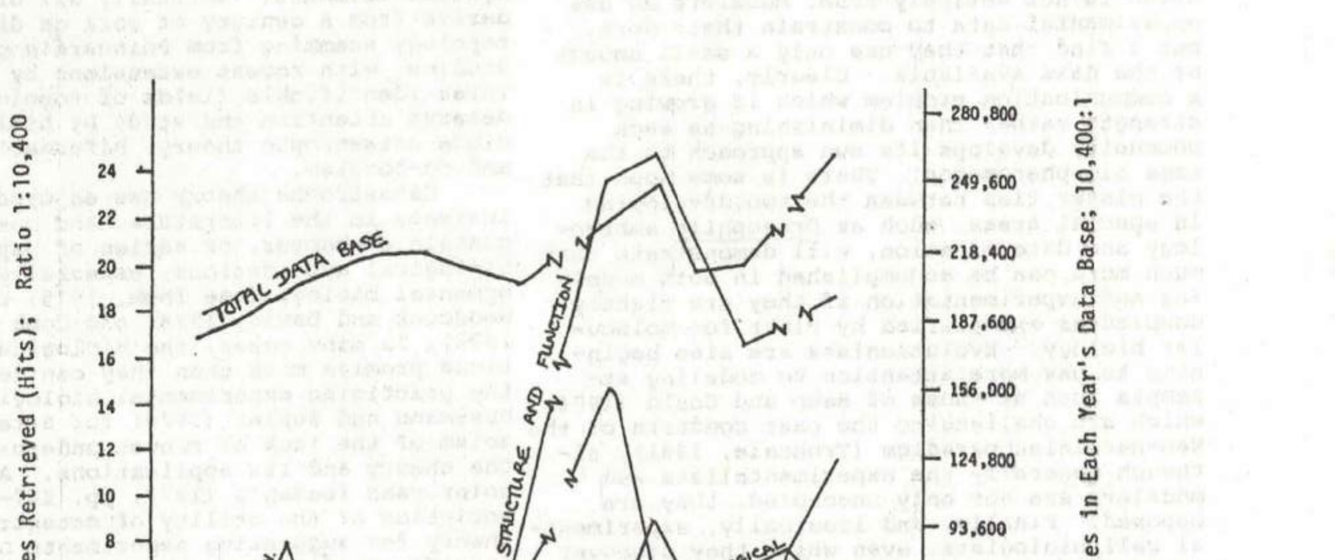

FIGURE FOUR: Year-By-Year Search, MEDLINE. Numbers of Articles Found Using Keywords Denoting Use Of Systems-Level Modeling Techniques from 1966 to 1981, 3.08 Million Articles Searched.

specialties. The work of May (1981), Watt (1966), Odum, Smith (1974), Overton, Whittaker, Margalef, Patten (1971, 1981) and others are studied by experimental ecologists. In my personal experience in seminars with the ecologists at my university, papers by these workers are analyzed, but many of the theses emerging from the department do not investigate ecological systems at that grand a scale. But a significant number of large departments in ecology do operate at a scale where theory begets experiments which constrain theory in the best scientific traditions of physics (as described by J.R. Platt, 1964, as Strong Inference). Physiology and some subspecialties in molecular biology (especially biophysical/biochemical modeling of protein and nucleic acid structure) enjoy a similar close coupling between modelers and the laboratory. In developmental biology, early workers recognized that embryological phenomena were analogous to computer programs (e.g. Bonner, 1965), and growth in the modeling literature has been rapid, particularly in recent years as evidenced by the appearance of textbook length reviews comparing developmental modeling techniques (Ransom, 1981). However, as a lab specialist in the area of differential gene activation, and cell biology, I find that the majority of experimentalists are rather isolated from the attempts of the healthy modeling community. Their experiments are designed with little study of modeling attempts. Their literature is uncoupled. The contrary situation is not entirely true. Modelers do use experimental data to constrain their work, but I find that they use only a small amount of the data available. Clearly, there is a communication problem which is growing in strength rather than diminishing as each community develops its own approach to the same bio-phenomenon. There is some hope that the closer ties between the two, developing in special areas such as <u>Drosophila</u> embryology and determination, will demonstrate that much more can be accomplished in both modeling and experimentation if they are tightly coupled as exemplified by Platt for molecular biology. Evolutionists are also beginning to pay more attention to modeling attempts such as those of Raup and Gould (1974) which are challenging the past comforts of the Neo-Darwinian paradigm (Troncale, 1981), although generally the experimentalists and modelers are not only uncoupled, they are opposed. Finally, and ironically, experimental cell biologists, even while they discover incredible complexity within the cell, remain the most uncoupled from modeling attempts. More detailed appraisal of each of these disciplines may be found in the case study section.

I believe the prognosis is extremely good for systems modeling in biology. The amount of information appearing in fields as diverse as base sequences in genetics, X-ray diffraction data on DNA structure, cell epiboly states in developing embryo's, cell interaction potentials, cell clone growth patterns in insect morphogenesis, metastable states in complex biochemical networks, and the complex niche interrelationships in modern and paleoecological systems literally demand use of computers for data management. The next step is simulation. The combination of dedicated mini-computers, immense data reserves and data bases, and simulation has resulted in orders of magnitude "speed-up's" in refinement of biological structures (see Quigley and Wang, 1981).

2.4 RECENT MATHEMATICAL APPROACHES TO MODELING BIOSYSTEMS AND THE FUNDAMENTAL PROBLEM OF MORPHOGENESIS.

Theoretical and mathematical biology are not necessarily the same beast, much less both of these and systems approaches in biology. But in many cases all three are regarded as synonymous. This "lumpy" approach will be used here, since mathematical models of biosystems involve isomorphic formulae, and much of theoretical biology involves model building that results in isomorphic statements that generalize many particular phenomena. Thus, the act of model building and the act of mathematical modeling are systems methodologies.

Several new tools have appeared which hold promise for modeling the elusive concept of "form" in biosystems. The tools result from the efforts of mathematicians who are not themselves identified specifically with the systems movement. Virtually all of the tools derive from a century of work on differential topology stemming from Poincaré's pioneering studies, with recent extensions by Rene Thom. Three identifiable fields of topology which deserve attention and study by biologists include catastrophe theory, bifurcation analysis, and co-bordism.

Catastrophe theory has enjoyed a rapid increase in the literature, and most selections contain a chapter, or series of papers on biological applications, especially in developmental biology (see Thom, 1975; Zeeman, 1977; Woodcock and Davis, 1978; and Cobb and Ragade, 1978). In many cases, the biological applications promise more than they can deliver to the practicing experimental biologist. See Sussmann and Zahler (1978) for a telling criticism of the lack of robust underpinnings to the theory and its applications. As counterpoint, read Zeeman's (1977, pp. 267-286) description of the utility of catastrophe theory for suggesting experiments by making specific predictions that are testable by the working biologist. Overall, catastrophe theory seems to be more successful in biological applications relating to development and differentiation of form, than to other less morphogenetic phenomena. Benham and Kozak (1978) extend catastrophe theory to stochastic-based considerations of macromolecules. If their application is used to model protein monomers, not in solution, but in autocatalytically-produced organelles, where N may be considered quite large, and where two different metastable states of a mixed multimeric functional protein complex can be demonstrated, then the catastrophe model might be linked to the function of the organelle. One protein conformation would be most stable for entrance of the multimer into the structure, while the other metastable conformation might be the altered conformation characteristic of the altered organelle performing its function. In this applic., one has modeled the chemical-mechanical transition at the very basis of the function of the organelle (after Katchalsky). But it is precisely this transition that all structural organelles utilize to do their work, as well as many non-structural enzymes and carriers in the cell (e.g. hemoglobin). Still, the problem pointed out by Sussmann and Zahler remains.....the catastrophe model is rather uncoupled from the parameters of the actual system under study. Few, if any, convincing and robust correspondence principles exist between the two, and until they are discovered, so that the model can predict a wide range of apparently unrelated phenomena, at a sufficiently deep level, catastrophe theory will be of limited value to the benchbound biologist.

Also stemming from the creative work of Poincaré are the theorems of bifurcation analysis. A modest literature on biological applications has appeared (see the cluster of five papers in Gurel and Rossler, 1979, and their references). In this collection, R. Rosen clarifies the question of the reducibility of biological descriptions to physical descriptions using bifurcation theory, and others explore development of embryo's and branching in plants, oscillatory states in biochemical networks, pathological instabilities in organismic physiology, and an interesting discussion by Decker of a key/critical question concerning the origin of life that experimental biologists have been unable to decipher......how did the first self-replicating, information storage system initially appear and stabilize itself?(see also Eigen et. al., 1981 for a more biological description of the work). Part V of the Gurel and Rossler volume on this conference sponsored by the N.Y. Academy of Science contains a further five papers on ecosystem stability, modeling, prey-predator relationships, oscillatory behaviors, and ecosystem complexity. I was delighted to see the last paper authored by the eclectic R.M. May who may be expected to bring applications of bifurcation theory to the field biologists that follow his work quite closely. Thus, the prognosis for use of this mathematical approach, which is clearly respected by mathematicians as more deep and robust than catastrophe theory, seems very good with several bioapplications already under development.

Co-bordism approaches to modeling biosystems are rare as yet, to my knowledge. The papers by Antonelli and Voorhees (SGSR Proceedings, 1982, Troncale, ed.) could serve as an introduction and review of the possibilities this approach has in elucidating bio-phenomena, esp. in developmental biology. These authors hope that co-bordism may have important applications in modeling hierarchical structure in general, and the emergence of form. Both are difficult problems long ignored by biologists because of the absence of an appropriate tool. Geometric approaches such as the three just cited may give them that "handle" in the next generation.

Other mathematical approaches, not as closely related to each other as the above three, have also appeared and been applied to modeling bio-systems. The aspects of biophenomena that include non-equilibria and dissipative processes arising from their biophysical and biochemical sub-systems may be elucidated by application of the work of Prigogine (1980). Certain aspects of morphology are modeled by application of Fibonacci sequences and their associated theorems. I am looking forward toward more linking theorems between these and stochastic processes to describe variations in types to populate a level of structure once it emerges from a previous level of structure (see horizontal proliferation in Troncale, 1972 and 1978). Hartman and High (1976) use Bernard's phenomenon, Rayleigh numbers, and Turing theorems to approach morphogenesis. The new book by Winfree (1980) on the geometry of biological time has received encouraging reviews and complements some of the above mentioned approaches. Finally, Mandelbrot's creative work on fractals (1977), especially in its characterization of clustering phenomena and Browninan motion, undoubtedly has some significant bio-modeling applications beyond the obvious one's related to rivers and islands.

In the literature survey of computerized data bases, it is interesting to note that many of the aforementioned, geometric modeling techniques were found to yield more articles in BIOSIS thanMEDLINE, although Figure Four shows their frequencies in all cases are rather low compared to usage of systems concepts. This may reflect the chasm that remains between practicing biologists and mathematical modelers. The only solution for the future may be the initiation of rigorous, interdisciplinary programs that train new biologists as mathematicians, or vice versa, fully doubling the preparation time required for work in the combined fields.

2.5 EXEMPLAR JOURNALS AND TEXTBOOKS.

Exemplar's are described by T.S. Kuhn as examples of method, process, or application that embody the paradigm of a field of study. Their practical use is in the initiation of entrants into the field with a minimum of effort. The field of systems theory in biology is too young to have its own paradigm or exemplar's, but I thought inclusion of a set of candidate exemplar books and periodicals might be useful.

The following section on case studies contains some exemplar books and articles pertaining to each specific field. This section concentrates on more general exemplars of the systems approach to biology and medicine.

The appearance of textbooks on the application of systems theory to biology began in the sixties. Examples include Waterman and Morowitz (1965) on Theoretical and Mathematical Biology and Mesarovic's edited volume of proceedings on Systems Theory and Biology. Provocative titles bearing on the subject continue to appear through the seventies although contributions are diverse in purpose and depth. Literature searches of data bases produce titles like Blesser's A Systems Approach to Biomedicine and Varju's Systems Theory for Biologists and Physicians, sound interesting but I could not obtain copies in time for this review. The only other article reviewing this same subject appears in the unlikely periodical Biology of Human Affairs (Pickup, 1976). Some book length treatments are actually totally mathematical, as, for example, the plethora of textbooks in any library on systems analysis (generally engineering oriented) and on biological control systems analysis (still engineering oriented). Rosen's books are very mathematical, but often with accompanying text explanations that contain carefully reasoned arguments accessible, in part, to non-mathematicians, for example (1970) Dynamical Systems Theory in Biology and (1972) Foundations of Mathematical Biology. Other teaching textbooks on this subject have appeared, for example, Smith (1971) Mathematical Ideas in Biology, and Gold's Mathematical Modeling of Biological Systems (1977). This latter is a teaching guidebook indicating that a sufficient number of students need introduction to the subject that publishers are now prepared to finance mass-media introductory works-surely a good sign for the future of the approach. Perhaps the most eclectic, massive, and not-overly-technical work on the application of systems theory to biology has to be Miller's thousand-page opus Living Systems (1978). It has received wide attention (the director of the National Science Foundation, a mathematician and computer specialist no less, was reading it and asked about it at a recent meeting), and good reviews.

The following list includes some of the journals in which articles are sometimes found on some aspect of systems theory applied to biology (abbreviations are standard):

BIOPHYS J.	ACTA BIOTHEOR (Neth.)
AM. J. PHYSIO.	PALEOBIOLOGY
BIOPHYS. CHEM.	KYBERNETES
BULL. MATH. BIO.	MATHEMAT. MODELING
J. THEOR. BIOL.	BIOSYSTEMS
J. MOL. BIOL.	BIOL. CYBERN.
PHYS. MED. BIOL.	MATH. BIOSCI.
ZH. OBSHCH. BIOL.	J. ENVIRON. SYSTEMS
SIMULATION	J. OF CYBERN.
INT. J. SYS. SCI.	INFO. SCI.
IEEE TRANS. ON SYS., MAN, & CYBERN.	

The journals sponsored by the S.G.S.R., Int. J. for General Systems and Behavioral Science, as well as the General Systems Yearbook are also good sources. A 241 page bibliography on Basic and Applied General Systems Research edited by G. Klir and G. Rogers, S.U.N.Y., Binghamton, N.Y. contains a computerized permutation of author's list, key-word list, subject list that surveys about 1500 articles, many on biological subjects.

In conclusion of this section, it appears that the literature on systems theory applied to biology is healthily developing and already has more entries and greater diversity than any one specialist can handle. Still, the degree of coupling between modelers and experimentalists is much less than desirable and may be increasing because of the increase in complexity of techniques used in modeling. A significant lag time between use of systems concepts and tools in systems theory and their application by practitioners of the target discipline is still in evidence, and may be aggravated in the future by division s developing between theoretical and applied approaches.

3.0 A CASE STUDY APPROACH TO MEASURING THE APPLICATION OF SYSTEMS THEORY TO BIOLOGY.

The forgoing literature survey tried to measuring what is happening in the interface between systems approaches and bio-research. It could not measure the potential work that could be accomplished in biology using systems techniques. That is the purpose of this section. By case study, I mean the discussion of a very specific phenomenon within each of several sub-specialties of biology in order to project areas where the systems approach may be useful to the field in the future.

3.1 CASE STUDY: BIOCHEMISTRY AND MOLECULAR BIOLOGY

Discoveries in the area of molecular genetics in the past decade have been dramatic. As recently as 1977 two major experimental findings caused a complete paradigm shift in the field of gene structure. For two decades it had been assumed that the cistrons for a protein were continuous nucleotide sequences colinear with the information sequence of amino acids they specified. This left a number of observations unaccounted for such as the presence in the cell of very long transcripts of RNA made off the DNA called heterogeneous (Hn) RNA. Now it is known that almost every gene sequenced so far actually has non-transcribing, nonsense, spacer sequences of DNA in between and separating the meaningful parts of a cistron. These are called intervening sequences or "introns" (noncoding parts). The meaningful parts, called "exons", must be cut-out of the transcribed RNA copy and then reassociated to get a meaningful messenger RNA that will code for a protein. For example, the gene for ovalbumin contains about 7,700 base pairs, whereas its mRNA contains only about 1,859 bases. Fully seven introns must be cut out before the eight meaningful exons can be tied together for the smaller mRNA to be formed. Some genes have been found that have 52 nonsense, non-coding introns separating their meaningful message into pieces!

Why would evolution allow, in fact select for such an intolerably expensive and messy system! Clearly, application of Ockham's razor did not allow man to hypothesize such a situation before it was discovered. That is why molecular biologists and biochemists were so surprized. Why doesn't the cell lose pieces of important DNA? Why would it risk doing this and cost itself so much energy to reassociate the meaningful pieces? The exact answer is not yet known, but other discoveries suggest an answer. Transposons are mobile elements of genes that have "sticky ends". They have nucleotide sequences at one end that are repeated at the other end. This helps them insert themselves in other linear sequences of DNA. The entire field of genetic engineering emerges from the occurrence of these mobile, jumping genes. It is thought that genes-in-pieces and jumping genes so speed up the process of gene evolution that it is worth the cell's expense in specific enzymes, energy, and possible loss to erect such a complicated processing systems for RNA. The discoveries also explain clearly why Hn RNA exists--it is merely the primary transcript before introns are excised. Rapid evolution and variation is so important to future survival of a cellular system that a system of many more parts than the best of minds forsaw is necessary. The genes-in-pieces not only explains formerly unexplained observations like Hn RNA but also how new proteins can appear rather suddenly (discontinuously) by mixing and matching of parts of genes representing the functional domains of the tertiary and quaternary structure of proteins. And the whole process is built on a lower level discontinuity--the discontinuous sequence of meaningful and nonsense base pairs of DNA. The complexities and potentials that emerge from this newly-discovered mechanism will require the techniques of modeling used in systems theory. Already it is clear that they have significant information theory impacts. When one considers the time element, the element of discontinuity, and the evolutionary component, this system has many interesting features for study by the systems oriented specialist.

To prove that simulation is of utility to investigators at this level of biology one need only look to the field of physiology. Several textbook length studies or proceedings have appeared. Savageau (1976) reviews the fundamentals of enzymatic/metabolic interactions, linear, non-linear systems analysis, and computer simulation then applies these to studies of feedback inhibition in biosynthetic pathways, control functions in end-product inhibition, to branched metabolic networks, cascaded enzyme mechanisms, mechanisms of gene action, and contrasting inducible and repressed systems. Basar (1976) applies the techniques of systems analysis to circulatory regulation, muscle contraction, brain activity, sensory systems, and outlines a general biological systems analysis program in biophysics. Carson, Cobelli, and Finkelstein (1982) (and also, SGSR Proceedings, Troncale, ed.) have produced a general modeling survey of metabolic and endocrine systems. A related earlier work is Lieberstein's (1973) Mathematical Physiology and an entire volume of collected papers on clinical pharmacology and systems theory edited by Inoue (1976).

Systems analysis is very successful in physiology. One example suffices. In a recent paper by Edelson (1981) he points out that an unexplained result in simulation of chemical reaction kinetics producing anomalous behavior was first explained by application of the ideas of negative feedback, complementary (dual) opposing reactions, and steady state transitions. Clearly, awareness of systems concepts aided in modeling the systems. Further, once the behavior is explained it can be used as a generic behavior and applied to other similar systems.

I have already mentioned the utility of computer modeling of DNA structure to the elucidation of the newly-discovered "Z"-DNA form of DNA (Quigley and Wang, 1981). But, it is not only structure and physiological networks that are amenable to systems approaches in biology. Laufer (1975) and Prigogine (1980) have contributed to understanding of the role of thermodynamic and non-classical thermodynamic, energy-based modeling of biosystems.

Finally, the use of information theory in studying the organization of biosystems appears in the work of Gatlin (1972), Rosen, and in terms of a hierarchical approach in Troncale (1982, SGSR Proceedings, 26th Mtg.). These studies pre-date the above cited case study on the structure of the gene which should revolutionize time-dependent, information based modeling of bio-systems.

3.2 CASE STUDY: CELLULAR BIOLOGY

Of all the specialties of biology, cell biology is the least tutored in systems theory. I could only find two works remotely related. In 1979 a proceedings was published with the interesting title Systems Theory and Immunology, certainly a complicated phenomenon in cell biology worthy of the approach. One might add to the list Beckers' work on analyzing the cell according to its bioenergetics. My own Ph.D. thesis, A Theoretical Study of the Cyberkinins, was a systems model of a family of nucleoprotein subunits forming heterologous multimers and involved in a fundamental control mechanism for cell division and differentiation. The reaction of empiricists to this model was predictably negative considering the absence of systems concepts in the field of cell biology. Yet several of its predictions have been experimentally verified in the ensuing decade while it still suggests experiments which are useful to conduct in modern cell biology.

The case study in cell biology which may be used to project the potential of systems theory in this specialty involves the new discoveries of the cytoplasmic matrix, or cytoskeleton by Porter and colleagues, and the discovery of a nuclear matrix by Berezney, Coffey, and my own largely unrecognized report (Troncale, 1972). The cell skeleton is described variously but usually consists of microtrabeculae, or proteinaceous, filamentous structures coursing throughout the cytoplasm of a cell. Some workers like to include the contractile microfilaments, as attached to the traceculae and the plasma membranes, as part of the system. Others even include the microtubules. Each of these is a multimeric-based, organellar system in itself. Yet each bears considerable interaction with the others (Troncale, 1970). The structure of the cytoskeleton has been implicated in numerous cell-systems-level phenomena of great import such as cell motility, cell division, cell epiboly in differentiation and development, and cell response to infection. If one was to model the various components of the cytoskeleton, and their multifarious variations in different cell types to accomplish the different functions of terminally differentiated or phylogenetically differentiated cells, one would have a complicated systems model of great explanatory power.

But the cytoplasm is the slave of the nucleus which possesses its own matrix of proteinaceous fibrils. These are separated from, and different from the cytoskeleton trabeculae, yet they cooperate in differentiation and control of the cell metabolism. The nuclear matrix has been implicated by various experiments in the maintainance of structural integrity of chromatin, the replication of DNA as a control site, the transcription of RNA as a control site, alterations in volume of the nucleus, and differential gene activation. None are proven. But if even some are, the complexity is worthy of a systems modeling attempt.

Then a super-systems model of the interaction of the cytoplasmic and nuclear matrices would be warranted. And then a super-super-systems model of their evolutionary changes thru time leading to an understanding of the phylogeny of cell types, or, contrariwise, of the ontogeny of cell types in the development of a multicellular embryo. Clearly, despite the resistance of cell biology as a field to systems modeling, the use of systems concepts in explaining cell phenomena is ripe for exploration.

3.3 CASE STUDY: DEVELOPMENTAL BIOLOGY

In the sections on mathematical approaches, several workers and techniques were cited which indicate how fertile the use of mathematical modeling has been in the study of developmental biology. The question of how form arises in the embryo is one which involves many phenomena on the cellular level which have not yet been appropriately understood. For example, the aforementioned role of the nuclear matrix in controlling cistron activation is poorly known, much less how the alterations in the cytoplasmic matrix and associated plasma membrane may change the dynamics of cell association and cell movement, which themselves are essential to knowing how the embryo forms. Developmental modelers consequently focus on parts of the phenomena such as diffusion of chemical signals, cell division and growth patterns, that we do know about cell movement patterns, and the actual forms created by those movements. Ransom (1981) is the most current and comprehensive review of the subject I have found. But the tradition goes back to the incredibly fertile ideas of D'Arcy Thompson, L.L. Whyte, Bertalanffy, and most recently Waddington (see 1977), J. Bonner (1965), and Jantsch. Where these workers speculated on the problem rather philosophically (except Waddington, <u>the</u> recognized empiricist for many years), the modern workers in the field have developed some significant new tools in geometric topology to challenge the empiricists with predictions for testing (see section 2.4, this paper). Two interesting examples of this modeling approach are Goodwin (1980) on cleavage as a field phenomenon, and the paper on cobordism approaches to modeling bio-systems by Antonelli and Voorhees (in Troncale, 1982). These linneages of work indicate that developmental biology is a prime area for systems approaches, but as in most other cases, it is still not entirely clear how much help this is to the practicing biologist. The most specific and successful predictions emerging from models have come from physiological and control systems analysis first, and second from developmental biology. If the utility of systems modeling is to prove itself, it will be in these fields, and ecology.

3.4 CASE STUDY: ECOLOGY

There is no need for exposition of a single phenomenological example in depth in this field to prove the worth of systems approaches. By its very nature ecology studies the interactions of organisms. It has been systems oriented from its inception. By now, classic texts in the field such as May's edited collection on <u>Theoretical Ecology: Principles and Applications</u>, which has a mathematical and systems conceptual orientation, are in their second edition (May, 1981). Patten's series on <u>Systems Analysis and Simulation in Ecology</u> has multiple volumes (1971, First Vol.). Some of the reigning textbooks in the field, such as that by K.E.F. Watt have a decidedly systems flavor. Watt (1966) has also edited on collection entitled <u>Systems Analysis in Ecology</u>. Lately, a number of introductory texts have appeared on mathematical and systems theoretical modeling of ecosystem level biology, for example, Smith (1974), Pantell (1976), Jeffers (1978), Berryman (1981), and Vandermeer

(1981). Patten and Auble (1981) recently published a paper in the American Naturalist on interpretation of the ecological niche concept using systems theory. This is illustrative of the position systems approaches enjoy in this field. This journal is the major periodical in the field yet the systems studies is a cornerstone concept of the field. Just last night a past student of mine now studying for his Ph.D. at Cornell mentioned in a phone conversation that Odum, a standard-bearer of ecological studies, pushed for greater use of general systems theory in ecology at a major symposium, a theme he has already stated in writing (Odum, 1977). All of these are signs that the use of systems concepts are not only accepted; they are fundamental to the field of ecology. An interesting question would be whether or not they use the same set of concepts and techniques when doing systems analyses and theoretical studies as the other robust fields in biology. Only a careful comparative systems analysis, as described in the introduction to these proceedings, would detect similarities and differences of usage, and so potential areas of cross-fertilization.

3.5 CASE STUDY: EVOLUTION

The study of evolution is such a gigantic field that it is supplied by data and supported by the empirical results of every one of the fields of biology previously mentioned. Still, model building is late in coming to this field. Recently, computer modeling has been used by such practitioners as Raup to examine the role of stochastic processes in evolution. Much to the surprize of Neo-Darwinian evolutionists, he found that random-based processes were quite successful in emulating the same morphogenetic changes in an simulated trilobite linneage as those known to have occurred in the fossil record! (American Scientist). But generally modeling approaches such as these bear much less weight than empirical studies from several fields that indicate the primacy of the role of environmental selection in the changes of morphology seen in linneages. Yet his result directly challenges the empirical position.

His is not the only study. Some time ago Gould of Harvard University began to challenge the established Neo-Darwinian concept that all evolutionary changes happen according to a very slow, gradual, cumulative process. The discoveries of genetics since Mendel's rediscovery in 1900 had all been consistent with the interpretation of genetic production of variants on a continuous, random and unpredictable basis. Population genetics followed with proof of alteration in gene frequencies in natural populations. But all evolutionists were not biologists--some were paleontologists who became uncomfortable with the neo-darwinian interpretations. They have repeatedly found instances of very good stratigraphic sequences that conclusively show species stasis for long periods of time. Rather than a gradual change, as predicted by neo-darwinism, the fossil specie remains the same for very long geological timespans, then rather abruptly as geo-time goes, they see the appearance of a new species. This has been called macroevolution by Gould, and is unrelated in description from the old, saltationist macroevolution of DeVries and Goldschmidt. Both Raup and Gould (1974) and Riedl (1977) have used stochastic simulation and systems analytical approaches, respectively, to elucidate macroevolution. The debate between phyletic gradualism (microevolution) and the seemingly heretical punctuated equilibrium (macroevolution) models of evolutionary processes is central to modern biology, is attracting much attention in major journals like Science and and Nature, and is utilizing some systems concepts to study the issue. It is interesting to note how impervious most classically trained empiricists are to the dynamic arguments they are meeting from the macroevolutionists. In some cases, it appears to me that they cannot perceive the basis of the argument because it rests on systems sensitivity.

4.0 CONCLUSION/PROGNOSIS

I should avoid ranking the specialties according to their degree of usage of systems concepts and techniques, but if you will recognize that this ranking is a subjective one limited to my experience, I will rank them from most successful to least. I rank systems analysis in physiology and chemical kinetics the highest, not because it is used as extensively as others, but because the predictions of the models and simulations are closest to the phenomena, have good correspondence principles, and are the most verifiable and falsifiable. Ecology ranks next, not because of verifiability, but because of the extensive use systems concepts enjoy in the field such that students of the general field must actually train in systems theory to become practioners of the field. Molecular biology ranks third, in my list, because of verifiability, not frequency of usage. Neurobiology in terms of nerve impulse modeling ranks fourth but would rank much lower if brain modeling (a much more difficult task) were considered. Developmental biology, despite the new topological modeling techniques appearing, must rank fifth because of the deep chasm of non-communication between the modelers and most experimentalists. It has the most potential, however, for leaping up to an advanced position in the near future, and a most exciting potential to stimulate breakthroughs. Evolution I would rank sixth, both because of the difficulties its systems approaches face as regards verifiability and the separation of theorists from experimentalists. And lastly, seventh, my own field of cell biology, which like developmental biology and evolution has great potential for systems theoretical approaches in the future, but has not yet begun to harvest them.

Both by the measure of use of systems concepts in the literature and by the measure of case studies of several specialties in biology, it is clear that systems theory in biology may expect to grow in applications over the next few decades. The lack of communication between modelers, theoreticians, and analysts working on systems-level concerns and their counterparts working on the experimental level remains the main obstacle. The varying degrees of sophistication and numbers of systems concepts and tools used by the many different specialties of biology utilizing the systems approach create a definite gradient of potential for cross-fertilization that could best be realized by careful studies in a new field called comparative systems analysis.

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