NEW HORIZONS IN BIOSYSTEMS ANALYSIS AND CONTROL

Report of the
Workshop on Analysis, Control, and Adaptation of Dynamical Systems in Biology

November 13-15, 1995

FINAL DRAFT

September 12, 1996

National Science Foundation
Arlington, VA

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PREFACE

This workshop was convened under a special cross-directorate initiative of the National Science Foundation (NSF), the Biosystems Analysis and Control (BAC) Initiative. The BAC is a cooperative activity of the Directorates for Biological Sciences (BIO), Engineering (ENG), and Computer and Information Science and Engineering (CISE). It is one of several current cross-directorate efforts to address the control and modulation of biological (including neurological and cognitive) processes and the development of technologies that support the research. Activities to date under the BAC have focused on neuroscience and its interaction with engineering. Program directors in all three of the participating directorates believe that the time is now ripe for an expansion of these activities to areas other than neuroscience, potentially ranging from molecules to ecosystems. They convened a workshop of some 35 researchers in all relevant areas of biology and engineering, including both academic and industrial participants.

Over two days of deliberations, this highly diverse group of participants from many disciplines and many different realms of interest focused intensively and with admirable cooperation on the research needs in this emerging field and the possible collaborative research attacks on those problems. A subgroup spent a third day synthesizing the themes that emerged from the workshop and developing a tentative research agenda. The workshop organizers worked iteratively with the workshop participants to prepare this report, which we believe meets the goals of the workshop in its identification of specific areas for expansion of the BAC.

We would like to thank Drs. Kishan Baheti, Howard Moraff, and Bruce Umminger, of NSF, for taking the initiative in suggesting this workshop and asking us to organize it. We appreciate the excellent support provided by Ms. Alex Brudy, of the University of California at Berkeley, and Ms. Karen Propheter, of Courtesy Travel in Washington, DC, in making organizational arrangements for the workshop. Finally, we thank Mr. Courtland Lewis for his painstaking efforts in drafting much of the report.

Robert Full
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Organizers
Workshop on Analysis, Control, and Adaptation of Dynamical Systems in Biology

CONTENTS

I. SUMMARY

This workshop was one of a series of National Science Foundation-sponsored workshops that are attempting to lay the groundwork for expanded connections between the biological sciences and engineering/control theory, with a view to developing new approaches for systems modeling, analysis, and control that could benefit both biological and man-made systems. Much of the focus to date has been on promising interactions between neuroscience and engineering. The aim of this particular workshop was to expand that focus to address the challenges and uses of new conceptual and technological tools for the modeling, analysis, and control of biological systems over a range of scales, potentially from molecules to ecosystems.

Workshop participants determined that an expansion beyond "Computational Neuroscience" (the interaction between neuroscience and engineering) can fruitfully be made into four other broad areas of biology: ecology and organismal, cell, and molecular biology. The integration of biology with engineering in these four areas can be termed as:

- Ecology X Engineering = Biophysical Ecology
- Organismal biology + Engineering = Biocybernetics
- Cell biology + Engineering = Cytodynamics
- Molecular Biology + Engineering = Nanobiology.

These expansion areas may be thought of as new disciplines, or perhaps "interdisciplines." Expanded definitions and discussion of each area appear in the report.

An analysis of the outputs from the workshop resulted in a detailed correlation of (1) the most promising *approaches, paradigms, and methods* with (2) the most promising *technologies and technological advancements* applicable to the Analysis, Control, or Adaptation of complex dynamical systems in biology. These correlations are presented in the report in tabular form, in which likely *application areas* for each group of approaches and technologies are also identified.

To support the expansion of research and technology development into these new areas, the workshop participants recommend that NSF support a balanced, sustained approach to collaborative cross-disciplinary research in these areas. This would include support for a range of research structures, including pairwise collaborations between biologists and engineers, small groups, and research centers. Cooperation among the relevant NSF directorates is essential; and NSF program officers should look for opportunities to combine proposals under this and similar NSF initiatives. In addition, interagency cooperation is encouraged.

The Biological Sciences Directorate of NSF should sponsor research directed at the development and application of technology and instrumentation. Explicit requests should be issued in a program announcement, perhaps jointly with the Engineering Directorate.

It is important to stimulate individual, personal interaction between biologists and engineers, and between empiricists and theorists, through conferences and workshops, summer study programs, and cross-disciplinary research projects. Interdisciplinary training grants, graduate and faculty fellowships and internships that permit working in other departments or in industry, and sabbaticals that involve an intensive self-education in the fundamentals of another discipline should all be used to ensure that more researchers learn to "speak more than one scientific language."

Undergraduate education in biology should be broader, with in-depth exposure to at least two different disciplines. Graduate education in biology also should be cross-disciplinary, with significant course requirements in at least one other discipline outside the major field.

The time is ripe for an exploration of many areas of potential interplay between biology and engineering/control theory. The Foundation already has begun this exploration with a series of related cross-directorate initiatives focusing on different areas of possible interaction. Other workshops have discussed connections with learning, cognitive science, developmental psychology and education, mathematics, chemistry, and physics. It would be worthwhile to examine these initiatives in order to integrate their various suggested lines of inquiry into a single broad, multivariate, and intellectually cohesive initiative.

II. CONTEXT AND PURPOSE

Background: The BAC Initiative

The Biosystems Analysis and Control (BAC) initiative of the National Science Foundation (NSF) began in FY 1993 and is now in its third year. This is a cross-directorate activity within NSF — involving the Directorates for Biological Sciences (BIO), Engineering (ENG), and Computer and Information Science and Engineering (CISE) — that fosters the interplay between biological sciences and engineering/control theory (including artificial intelligence) to stimulate the development of new approaches for systems modeling, analysis, and control that could benefit both biological (natural) and man-made (artificial) systems. (Please see the List of Key Terms at the end of the report for definitions of recurring terms.)

The BAC initiative emerged as a result of a 1990 NSF Workshop on Biocontrol by Neural Networks.* Judging by the response of the scientific community, BAC addresses an area ripe for collaborative research, as engineers increasingly are attracted to biology and biologists increasingly are addressing questions of modulation and control mechanisms for cellular, organismal, and neuronal function.

The goal of the cross-disciplinary focus of BAC is to develop innovative techniques to analyze and control complex dynamic systems by extending our understanding of how biological systems interpret sensory signals, control physiological processes, and adaptively monitor and control bioprocesses. As presently conceived, proposal topics that fall under this thrust include, but are not limited to, the following:

- Development and application of innovative dynamic system modeling techniques to analyze and characterize biological systems.
- The use of information obtained from biological systems to further develop novel systems and control engineering methods.
- Elucidation of the capabilities of natural biological systems as flexible general control devices.
- Development of new engineering adaptive control system architectures based on biological prototypes.
- Application of biologically inspired control strategies in either biological or non-biological systems.
- Development of highly innovative artificial neural network designs which could function as potential models of vertebrate neural systems.
- Development of models of uncertainty in system representation, adaptation, and learning based on information obtained from the nervous system.
- Improved methods for identifying, representing, and analyzing hierarchical and self-organizing systems.

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* NSF. 1990. Biocontrol by Neural Networks — Summary of a Workshop Supported by the National Science Foundation, May 1990 (G. Bekey & P. Katona, eds.). Washington, DC.

- Elucidation of the capabilities of natural biological systems as flexible general computing devices.
- Development of models of neural circuits/structures involved in signal and information processing and/or the control of behavior.

Across the three directorates, NSF programs currently involved in the support of BAC research include the following:

- ENGINEERING -- 5 programs:
  — Biochemical Engineering,
  — Biotechnology
  — Biomedical Engineering and Research to Aid Persons with Disabilities
  — Engineering Systems
  — Dynamic Systems and Control

- COMPUTER AND INFORMATION SCIENCE AND ENGINEERING -- 2 programs:
  — Interactive Systems
  — Robotics and Machine Intelligence

- BIOLOGICAL SCIENCES -- 1 program (Neuroscience), with 6 themes:
  — Behavioral Neuroscience
  — Computational Neuroscience
  — Developmental Neuroscience
  — Neuroendocrinology
  — Neuronal and Glial Mechanisms
  — Sensory Systems

Synopses of the full scope of research supported under these programs are presented in Appendix A. A number of cross-disciplinary research projects are already underway within the BAC (see Exhibit 1); in the short period of its existence the initiative has stimulated the development of an increasingly cohesive research program in its area of focus.

EXHIBIT 1

Proposals Funded by the Biosystems Analysis
and Control Initiative (as of 1/96)

- Perceptual and Motor Control Mechanisms in Visual Tracking
- Cooperation and Coordination of Two Arms in Biological and Robotic Systems
- Neural Network Control of Oscillatory Movements of Multi-segmented Musculoskeletal Systems
- Signal Processing and Target Images for Spatial Perception in Bat Sonar
- Adaptive Control of Pheromone-Guided Locomotion
- Neural Optimization Algorithms in Respiratory Control
- Silicon Neuromorphs II: Activity-Dependent Plasticity and Voltage-Dependent Dendritic Channels
- Design and Control of Electromagnetic Orthotic Actuators Which Behave as Hill's Model of Human Muscles Predicts
- Neural Strategies in Eye Movement Control
- Analog-VLSI and Parallel-Computer Modeling of Intersegmental Coordination
- Development of a Biologically Motivated Model for Adaptive, Multi-input Multi-output Control of Human Balance
- Sensory Feedback and Control of Legged Locomotion: Biological Simulation and Robotic Implementation
- Analysis of Insect Flight Dynamics
- Intelligent Computing for Analysis of Metabolic and Physiological Systems
- Systems Modeling of Endothelial Cell Migration and Proliferation
- Analysis and Control of Mammalian Cell Motility and Proliferation

Recent, Related Activities

Since the BAC was founded, a number of related initiatives and other activities have been undertaken by NSF. One, the initiative on "Learning and Intelligent Systems," focuses on the overlaps between neuroscience, engineering and systems/control theory, computer science, cognitive science, and education. A cross-directorate task group of program officers from all seven research directorates, including CISE, ENG, and BIO, is coordinating the initiative. An initial workshop was held in

September 1995,[*] and a cross-directorate Program Guideline for "Collaborative Research on Learning Technologies" was issued in April 1996. The workshop reported here is the second in this series. A third workshop within this initiative, on "Information Processing in Biological and Artificial Intelligent Systems," was held in April 1996. A planned World Wide Web homepage for the Learning and Intelligent Systems initiative, located under the NSF homepage, will provide links to information on these activities and to relevant publications.

Within the BIO Directorate alone, a cross-disciplinary workshop on the "Impact of Emerging Technologies on the Biological Sciences" was held in June 1995. The aim of this workshop was to identify promising technologies, both new and existing, whose application to biological research will accelerate scientific progress. The report identifies more than 30 such technologies, many of which are directly applicable to the analysis and control of biological systems and processes.[*]

In December 1995, NSF announced a new research program entitled, "Integrating Enabling Technologies into Neuroscience Research: Opportunities for Planning and Initiation of Collaborative Research in Neuroscience, Computer and Mathematical Sciences and Engineering." The specific focus here is research on the application of information, modeling, visualization, and other tools to the mapping of function onto the structure of the brain.

The current workshop can be seen as an attempt to sweep across these boundaries and lay out the participants' vision of new research opportunities in biosystems analysis and control

Goals of This Workshop

All these activities and initiatives represent interrelated efforts to address the control and modulation of biological (including neurological and cognitive) processes and the development of technologies that support the research. In the case of the BAC, however, the focus to date has been restricted to neuroscience and its interaction with engineering. The success of the program thus far makes it evident that areas of biology other than neuroscience would benefit from a systems approach, involving both engineers and biologists, to understand biological control at all levels.

Therefore, the primary goal of this workshop was to determine how the Biosystems Analysis and Control initiative might be expanded from its current form to address the challenges and uses of new conceptual and technological tools for biological systems over a range of scales, potentially from molecules to ecosystems.

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[*] Gentner, D., M.C. Linn, K.S. Narendra, P. Smolensky, and E. Soloway. 1996. The Science and Systems of Learning: Augmenting Our Ability to Learn and Create (C.S. Lewis, ed.). Draft Report of the Workshop on Collaborative Research Into Learning and Intelligent Systems, September 17-19, 1995. National Science Foundation, Arlington, VA.

[*] Carnegie Mellon University. 1996. Impact of Emerging Technologies on the Biological Sciences: Report of a Workshop. Sponsored by the Directorate for Biological Sciences, National Science Foundation. Pittsburgh, PA: Carnegie Mellon University Press.

Expansion of the BAC activity is synergistic with BIO interests in computational and theoretical biology and with ENG and CISE interests in intelligent systems and learning. Thus, there is the potential for such an expansion to lead eventually to merging of the BAC initiative with other current NSF cross-disciplinary initiatives involving these three directorates. However, the focus of this workshop was strictly on the expansion of the BAC to programs in BIO.

Across the Biology Directorate, there are three science Divisions— Molecular and Cellular Biosciences (MCB), Integrative Biology and Neuroscience (IBN), and Environmental Biology (DEB) — which offer opportunities for BAC-related work within their program areas. Figure 1 depicts the Directorate's organizational chart. Apart from Neuroscience, there are eight research "clusters," each of which includes a number of pertinent research themes or topic areas:

- Under MCB -- 3 clusters:
  — Biochemistry and Molecular Structure and Function
  (themes: Metabolic Biochemistry, Molecular Biochemistry, and Molecular Biophysics)
  — Cell Biology
  (themes: Cellular Organization, and Signal Transduction and Regulation)
  — Genetics and Nucleic Acids
  (themes: Microbial Genetics, Eukaryotic Genetics, and Biochemical Genetics)

- Under IBN -- 2 clusters:
  — Physiology and Behavior
  (themes: Animal Behavior, Ecological and Evolutionary, Integrative Animal Biology Physiology, and Integrative Plant Biology)
  — Developmental Mechanisms

- Under DEB -- 3 clusters:
  — Systematics and Population Biology
  (themes: Population Biology, and Systematics)
  — Ecological Studies
  (themes: Ecosystems and Ecology)
  — Long-Term Projects in Environmental Biology
  (themes: Long-Term Ecological Research (LTER), Long-Term Research in Environmental Biology (LTREB), Land-Margin Ecosystem Research (LMER), Research Collections in Systematics and Ecology, and Biotic Surveys and Inventories)

Appendix B presents synopses of the scope of research supported in these areas.

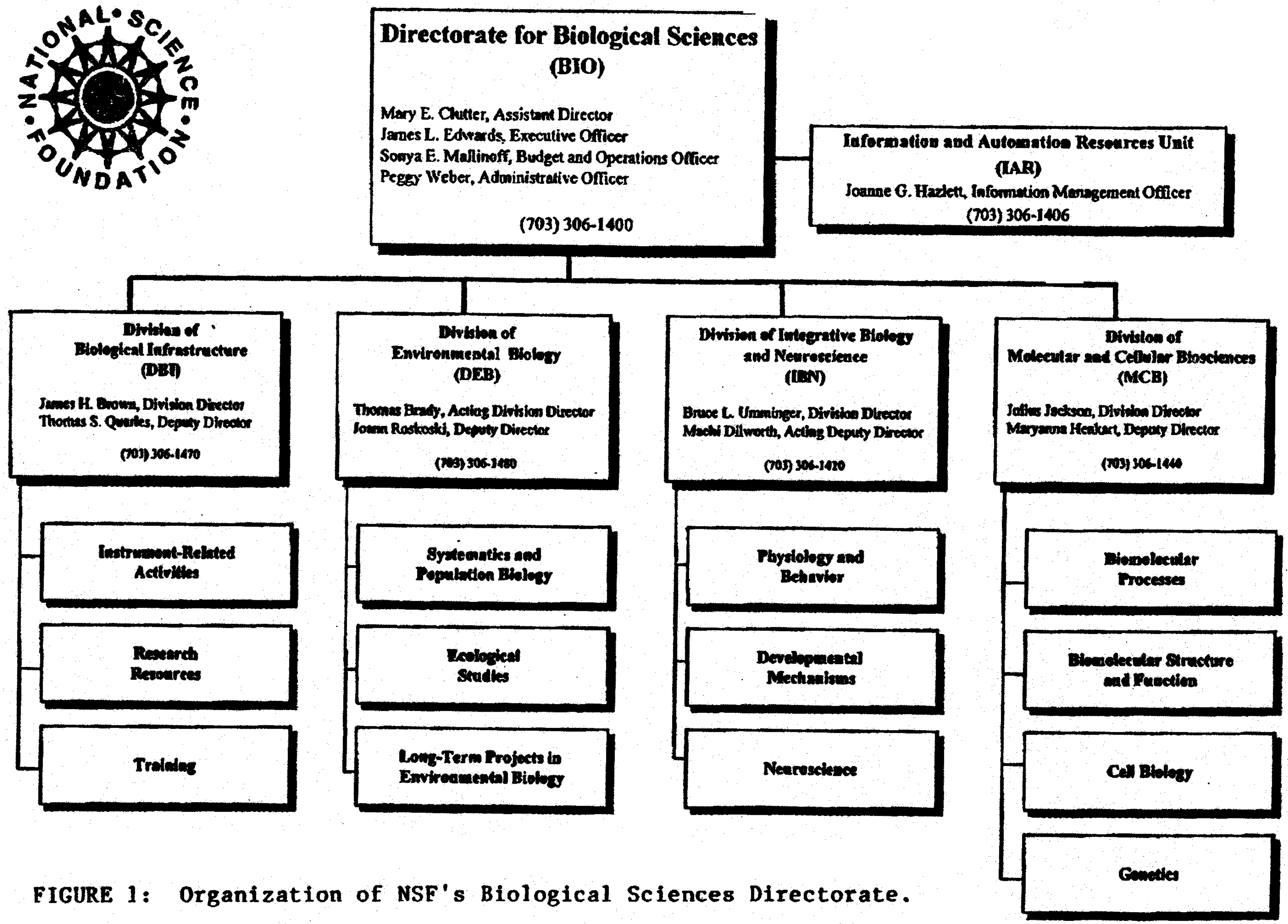

FIGURE 1: Organization of NSF's Biological Sciences Directorate.

Effective June 7, 1996

Study Approach

The nearly forty participants in this two-day workshop (see list on pg. i) were chosen for their ability to provide insightful advice not only relating to their own research interests, but also more broadly with respect to the goals of the workshop. Specific selection criteria were as follows:

- Exceptional recommendation from NSF Program Officers
- Multidisciplinary vision, encompassing:
  - biology and engineering
  - engineering breadth
  - integrative biologists (molecules to ecosystems)
- Leadership in their field, with extraordinary research programs (Nobel prize nominees, MacArthur Foundation Fellows)
- Both theorists and experimentalists
- Individuals funded by the BAC (looking outward toward expansion)
- Individuals not funded by the BAC (looking toward incorporation).

Thus, special care was taken to ensure that the participants represented a balanced range of points of view.

About half of the participants had agreed to make short presentations on their specific areas of research, which fell into four broad categories: New Technologies for Natural and Artificial Systems; Adaptation and Learning; Control at the Molecular to Cellular Level; and Control at the Organ Level to Ecosystems Level. These presentations stimulated surprisingly unfettered discussions among the diverse group of scientists, as they explored the potential applicability of concepts from different fields to the research under discussion.

The participants were divided in loosely random fashion into five discussion groups which met on the afternoon of the first day to identify *the most promising technologies and technological advancements* affecting Biosystems Analysis and Control. For each technology, they were asked to identify the areas of BAC expansion that it would affect most. At the end of the day, group leaders summarized the results of each group's findings.

On the afternoon of the second day, the participants again met in five discussion groups with the aim of identifying *the most promising approaches, paradigms, and methods* in Biosystems Analysis and Control and the areas of BAC expansion that these would most affect. Group leaders again summarized the results.

In addition, each participant filled out a survey form in which he or she identified, described, and prioritized the most promising technologies and approaches from an individual standpoint.

The day after the workshop concluded, the workshop organizers met to consider and analyze these various results. Based on an intensive review of the small-group and individual outputs, they formulated an integrated concept for expansion of the BAC to new areas of biology. This formulation is presented in the following Section III.

III. THE PROPOSAL: PROMISING APPROACHES AND TECHNOLOGIES

Overview of the Expanded BAC

Figure 2 presents an overview of the proposed expansion. The interaction between neurobiology and engineering already underway in the BAC initiative may be termed, "Computational Neuroscience." The engineering contribution to this collaboration is encompassed (in broad terms) by the technologies and approaches listed in the box at the left in the figure. These consist of methods supporting analysis (e.g, modeling and data representation) and strategies and techniques relating to control (including adaptive control).

An analysis of the outputs from the workshop resulted in a detailed correlation of (1) the most promising APPROACHES, PARADIGMS, AND METHODS with (2) the most promising TECHNOLOGIES AND TECHNOLOGICAL ADVANCEMENTS applicable to the Analysis, Control, or Adaptation of complex dynamical systems in biology. These correlations are presented in Table 1. The right-hand column of the table then lists likely APPLICATION AREAS for each group of approaches and technologies.

Promising New Areas

Next, Figures 3-6 depict individually the proposed areas for expansion of the BAC. The detail within the figures is derived in aggregated fashion from the table. At each level – ecological, organismal, cellular, and molecular – the contributions (areas of involvement) of both biology and engineering are listed. The labels on the arrows connecting the boxes represent specific areas of overlap that may be formulated as subdisciplines.

We have designated the broad expansion areas themselves (i.e., the overall area of integration or overlap between biology and engineering) as:

- **Biophysical Ecology (ecology and engineering)**
- **Biocybernetics (organismal biology and engineering)**
- **Cytodynamics (cell biology and engineering)**
- **Nanobiology (molecular biology and engineering).**

These expansion areas may be thought of as new disciplines, or perhaps "interdisciplines." Along with Computational Neuroscience (the overlap between neurobiology and engineering), these five areas comprise the "fully expanded" BAC initiative as the workshop participants envision it. Although the diagrams are largely self-explanatory, a brief definition of the four new expansion areas may be useful.

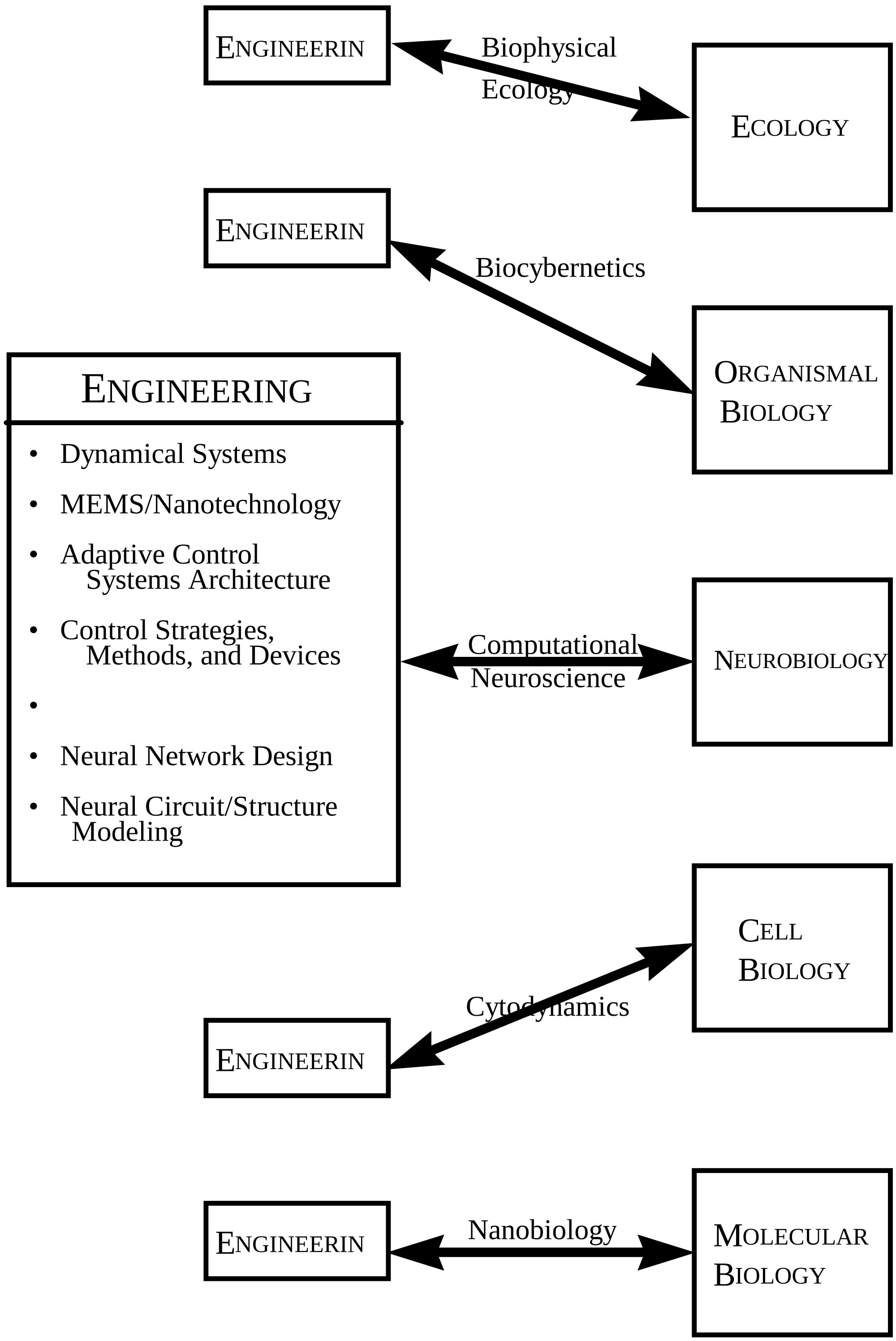

FIGURE 2: Workshop goal: Expansion of the BAC Initiative in to integrate other fields of biology (beyond with engineering.

TABLE 1: PROMISING APPROACHES AND TECHNOLOGIES IN BIOSYSTEMS ANALYSIS, CONTROL, AND ADAPTATION

APPROACH/PARADIGM/METHOD	TECHNOLOGY ADVANCEMENT/NEED	APPLICATION AREA(S)
<u>Analysis</u> of Complex Dynamical Systems		
System (machine/organism/population)-environment interactions	• Interfacing various models (e.g., dynamical models, human motor control, motion perception, language models, speech recognition, organism energetics & behavior) • User-friendly advanced visualization tools • On-chip biochemical analysis • Non-invasive biosensors, microchips • Remote sensing of large numbers of organisms or molecular events • Imaging devices & signal processing • Physiological monitoring • Population response imaging	• Predicting growth, reproduction potential • Management, control, and assessment of individual or organismal behavior
Biomimetic engineering (e.g., of neural, musculoskeletal, biochemical systems), using biomimetics as both an experimental tool and an inspiration for engineering design	• Biomimetic replicas • Autoregulatory design	• Prosthetics • Biorobotics
Parameter condensation (reduction of parameter space) in large systems	• Improved methods of parameter exploration • Basic mathematics research to develop better ways of dealing with massive parameter spaces	
Understanding of cell structure & function for insight into control & regulation	• Miniaturization (molecular machines, motors, microactuators, on-chip technology, micro-/nano-manipulation) • Imaging hardware & software (e.g., AFM, SFM, near-field microscopy, NMR at small scales) • Single-molecule fluorescence • Micro mass spectrometry • On-chip biochemical analysis • Data representation & fusion • Simultaneous multi-modal measurement • Multi-electrode devices for neural stimulation or recording	• Cellular level regulatory physiology • Adaptation and remodeling
System identification	• Non-invasive sensing (MRI, PET, remote sensing, multi-electrode devices) • Molecular biotechnologies	• Better definition of model structure • Time-varying and non-linear systems

APPROACH/PARADIGM/METHOD	TECHNOLOGY ADVANCEMENT/NEED	APPLICATION AREA(S)
		• Genome characterization • Channel protein identification
Modeling of dynamical systems in biology	• Dynamical model of biochemical pathways, metabolic control, cell differentiation • Models for estimating population/ community constraints, dynamics • Multi-level models • Cardiac dynamics models • Computational fluid dynamics • Simultaneous multi-modal measurement • Hardware & algorithms for functional brain imaging • Biosensors • Data representation & fusion	• Analysis of large magnitude changes (e.g., physiological changes at onset of exercise) • Management and control of plant and animal behavior
Study of phenomena involving biochemical and genomic dynamics	• Dynamical modes of biochemical pathways, metabolic control, cell differentiation • Gene networks • Genetic computing (PCR)	
Understanding dynamical aspects of sensory-motor systems	• Computation performed via dynamical systems for sensory/motor information • On-chip biosensors (microchips)	
Pattern classification	• Algorithms • Improved parallel processing • Remote sensing	• Monitoring and prediction of specific patterns associated with normal or abnormal behavior in plants and animals
Analytic measurements	• On-chip biochemical analysis • Physical measurement devices for embryology • Multi-electrode devices for neural stimulation or recording • Physiological monitoring • Imaging devices & signal processing	• Anthropometry
Developing and growing systems	• On-chip biosensing • On-chip biochemical analysis • Physical measurement devices for embryology • Chemical self-assembly	• Monitor changes in embryonic development and prediction of abnormalities
Psychophysical approaches to complement systems neuroscience	• Biologic representations & coordinate systems • Biosensors	• Vision • Audition

APPROACH/PARADIGM/METHOD	TECHNOLOGY ADVANCEMENT/NEED	APPLICATION AREA(S)
	• Interfacing microelectronics with neurons • Physiological monitoring • Comparative assessment of neural network algorithms	• Motor control
Hybrid systems	• Models at different levels of granularity • Sensor fusion • Actuator command expansion	
<u>Control</u> of Complex Dynamical Systems		
Control theory & strategies based on biological models – including adaptive controls, hierarchical organization	• Improved algorithms for pattern classification • Adaptive control systems • Robust control design • Bioprocessors	• Drug dosing & design with control & feedback at cellular and tissue levels
Control of movement in animals & robots	• Control circuit approaches applied to biomechanics, materials, & dynamics • Actuators & sensors • Models of human motor control • On-chip bioprocessing & biosensors • Tactile sensing • massively parallel sensors	• Limb regeneration • Robotics • Tactility • Olfaction • Vision
Genetic control & elucidation of biochemical pathways	• Nanotechnology (e.g., optical tweezers) • Biomechanical engineering • Hormone control of gene expression	• Developmental morphogenesis • Manipulation of nanoscale motors • Organismal development
Control models in population dynamics/biology	• Biosensors • Remote sensing	• Fisheries management & conservation
"Passive" control	• Physical designs that passively self-regulate	
Temporal aspects of neuromodulation	• Interfacing microelectronics with neurons • Multi-electrode devices for neural stimulation or recording • Second messenger signalling system • Early *Drosophila* embryo	
Understanding neural coding	• Neural networks • Plasticity reinforcement	• Development of control of complex muscle groups
Detecting cell-cell communication in tissue	• Biosensors • Biosignaling	• Calcium ion flow between cells

APPROACH/PARADIGM/METHOD	TECHNOLOGY ADVANCEMENT/NEED	APPLICATION AREA(S)
	• Neural networks	
Adaptation in Complex Dynamical Systems		
Better understanding of learning & adaptation	• "Unsupervised learning"	• From intracellular regulation to organism behavior (bone, heart, brain, etc.)
Adaptive control	• Development of better parametric and non-parametric algorithms	• Organ-level functioning • Hierarchical models

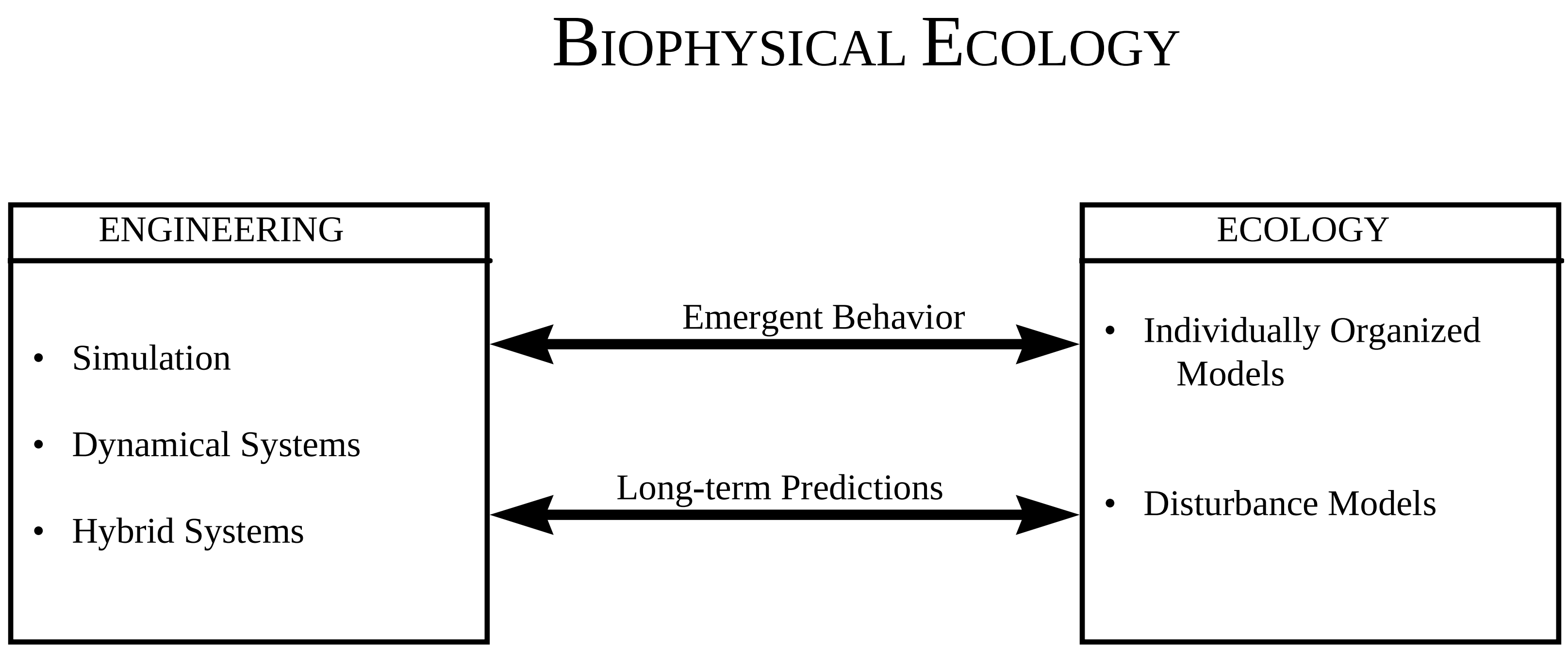

FIGURE 3: Biophysical Ecology is the interface between ecology and engineering.

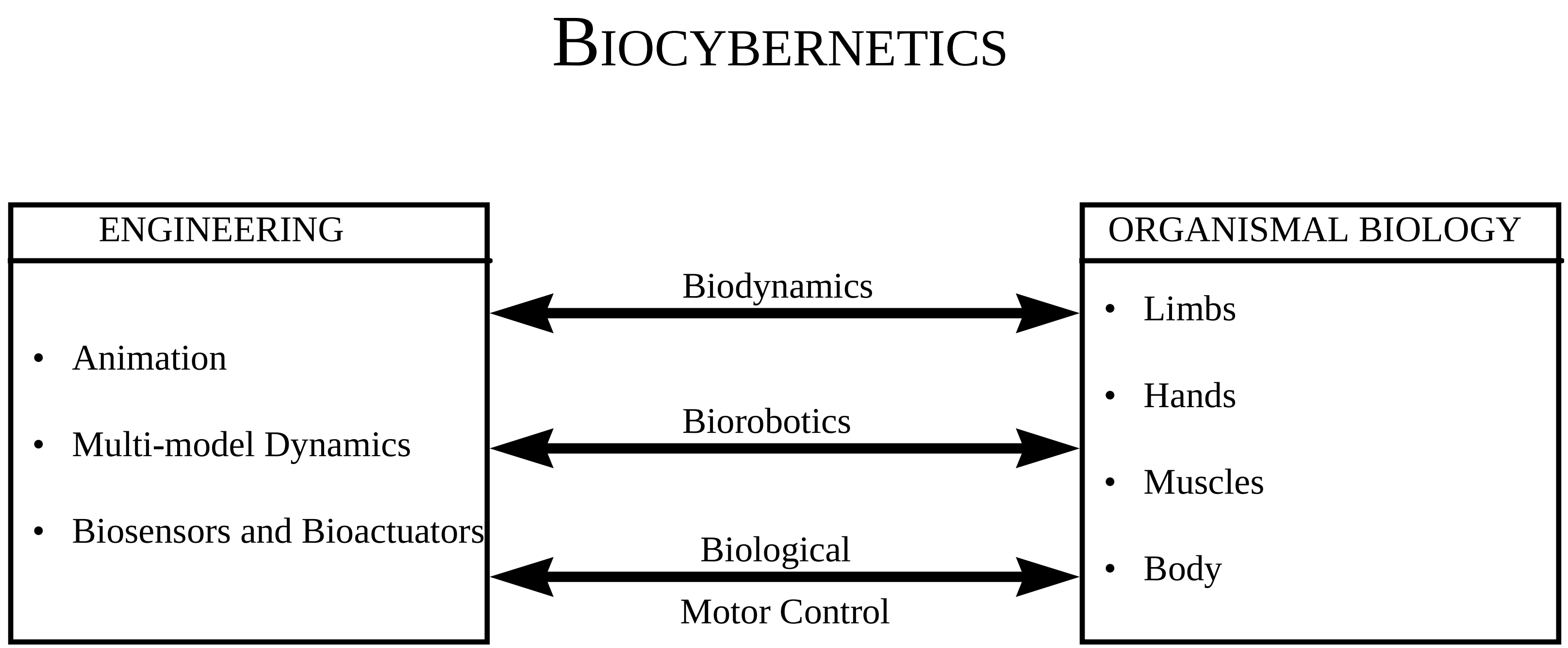

FIGURE 4: Biocybernetics is the interface between organismal biology and engineering.

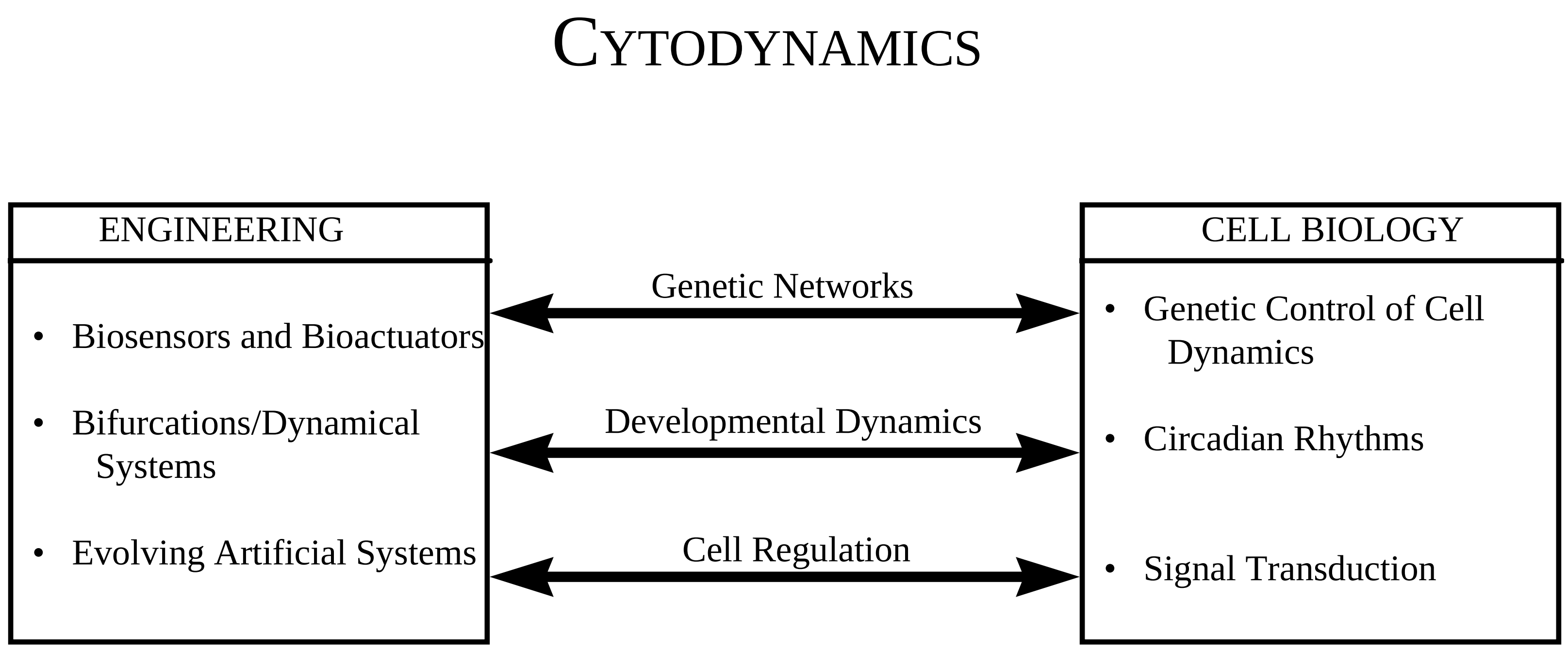

FIGURE 5: Cytodynamics is the interface between cell biology and engineering.

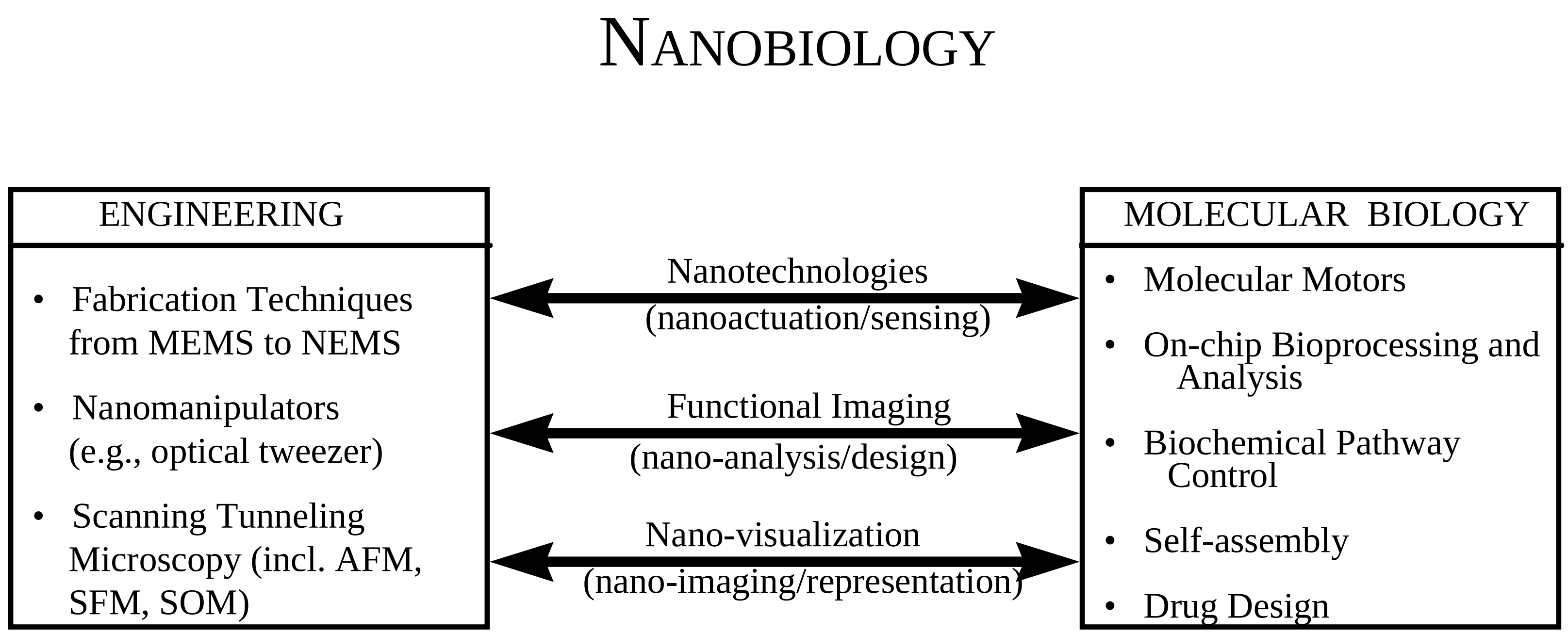

FIGURE 6: Nanobiology is the interface between molecular biology and engineering.

Biophysical Ecology. There is a rich body of quantitative work (both modeling and empirical) in biophysical ecology wherein the mechanisms of how individual organisms function can be directly related to population and community ecological processes (such as susceptibility to disturbance, foraging, ecology, competition, habitat use, geographic distribution, etc.). This has been true in terrestrial, freshwater, and marine ecosystems. Work at the interface between biology and engineering has been very fruitful in this area. Such work also provides the basis for a number of mechanistic models of population and community processes. However, ecologists working at the community and ecosystem levels who were at the workshop felt that their current modeling approaches are quite successful and that the interface between dynamical systems modeling and those areas of ecology does not appear promising at this time. Two promising exceptions are in the areas of:

- Emergent Behavior — the study of global (herd) behavior from models of local (individual organism) behavior; and
- Long-term Predictions — the use of disturbance models in hybrid dynamical systems for predictions of long-term collective behavior.

Biocybernetics. The term "cybernetics" was coined by Wiener (and reputedly later modified to "artificial intelligence" by McCarthy* to convey a sense of machines that exhibit some form of intelligent behavior such as adaptation to the environment, response to queries, etc. Biocybernetics refers to identified "computational mechanisms" that biological systems, or biologically inspired systems, use to exhibit intelligent behavior. The ability of a human to perform complex motor actions such as diving, windsurfing, or bicycling is an example of biocybernetic behavior. Biocybernetics includes:

- Biodynamics and Biomechanics – the study of the mechanics and dynamics of biological systems;
- Biorobotics – the use of biological paradigms to design and control robotic systems; and
- Biological Motor Control – the study of algorithms for organizing the control of systems having a large number of degrees of freedom, including the fan-in of sensor information and fan-out of actuator information.

Cytodynamics. This area covers regulation, control, and adaptation mechanisms in biological systems at the cellular level. Cytodynamics includes:

- Genetic Networks – study of the circuitry associated with the formation of genes and their evolution under interaction with the environment;
- Developmental Dynamics – analysis of the dynamics of morphogenesis and cellular growth; and
- Cell Regulation – the study of mechanisms for the regulation of different cell functions.

Nanobiology. Nanobiology is the study of locomotion, sensing, and movement of biological and biomimetic systems at the nanoscale. Nanobiology includes:

- Nanotechnologies – descriptions of nano-actuation and nano-sensing mechanisms used by biological systems;

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* Personal communication with S. Sastry, 1995.

- Functional Imaging – the analysis of the functional performance of biological nanosystems from high-level descriptions; and
- Nano-visualization – simulation and visualization techniques for depiction of the temporal evolution of biological systems at the nano-scale.

As far as the existing focus on Computational Neuroscience is concerned, the workshop participants felt that the currently funded program is healthy but needs continued encouragement. In particular, there is a need for activity in a field that might be termed "dynamics for the neurosciences." There are three problem areas within dynamical systems theory that appear critical to understanding the dynamical properties of neural networks (and many other systems):

1. <u>The qualitative dynamics of singularly perturbed and hybrid dynamical systems.</u> Neural systems make evident use of multiple time scales in their function. Singular perturbation theory can be developed to provide a systematic description of phenomena that occur in systems with multiple time scales. The results of such work should contribute directly to our insight into biological motor control and other dynamical processes of neural systems.

2. <u>The numerical analysis of bifurcations in multiparameter vector fields.</u> The application of dynamical systems theory to other fields frequently depends upon the dynamical analysis of models that depend upon many parameters. Fitting parameters within the models is hindered by our inability to measure many parameters directly. The numerical analysis of dynamical systems and their bifurcations can provide the algorithmic underpinnings of large classes of simulation models of neural systems.

3. <u>The relationship between the network architecture of systems of coupled oscillators and the resulting dynamics.</u> The only hope we have for intelligent understanding of the dynamics of vertebrate neural systems is that the hierarchical organization of such systems will allow us to decompose the systems in components with a relatively small number of degrees of freedom. We know almost nothing about how the structure of a multi-compartment system constrains its behavior (beyond analysis of the role of symmetry when it is present).

IV. NSF: NECESSARY CHANGES IN PROGRAMS AND PRACTICES

The areas proposed for expansion of the BAC initiative are inherently interdisciplinary, bridging as they do not just the biological and engineering sciences but also the sciences with technology. Support of inter- or cross-disciplinary work has always been somewhat problematic in the science directorates of NSF, since they are organized along the lines of the traditional disciplines. However, there has been considerable progress made in recent years in finding ways to facilitate this type of research, as much of the exciting advances in science and engineering have come at the interfaces between established disciplines. The BAC and other biology-related initiatives described in Section II of this report have contributed to that experience.

Thus, there is relatively little that is new and useful which can be suggested to that end, except to exhort the Foundation and its program officers to continue to explore and utilize the kinds of mechanisms that already have been developed to serve the needs of cross-disciplinary research and education. Some of the most important of these are described below.

Support of Cross-disciplinary Work

The most important point is to support a balanced, sustained approach to collaborative cross-disciplinary research in the BAC expansion areas described in Section III. This would include support for a range of research structures, including pairwise collaborations between biologists and engineers, small groups, and research centers across departments, colleges, and even universities. The Director's Opportunity Fund is one in-house source for cross-disciplinary initiatives like the BAC.[*] BIO, ENG, and CISE program officers should look for opportunities to combine proposals under this effort with other proposals from similar initiatives such as Learning and Intelligent Systems.

Cooperation among the three NSF directorates involved in this initiative is obviously required. In addition, interagency cooperation is encouraged. NSF should seek to establish joint programs with other agencies having potential interests in the areas encompassed by the expanded BAC; these would include the National Institutes of Health, NASA, the Environmental Protection Agency, the Departments of Defense and Agriculture.

Because biological research is increasingly technology-driven (especially in the BAC initiative), we believe the BIO Directorate of NSF has an indirect obligation to sponsor research directed at the development and application of technology and instrumentation. This sponsorship should take the form of explicit requests in a program announcement, perhaps conducted jointly with the ENG Directorate.

Much of the technology applicable to scientific research is developed in industry, often in start-up companies. It is important to establish stronger, more direct links between university researchers

[*] Program officers must provide 50% matching funds for such proposals from their own program budgets.

and this source of technology. Although NSF cannot directly sponsor technology development in commercial companies, there are established mechanisms for making these connections between universities and industry. One is through university-based centers such as the Science and Technology Centers and the University-Industry Cooperative Research Centers. Another is by means of Small Business Innovation Research (SBIR) and Small-business Technology Transfer (STTR) awards. Universities might be encouraged to form industrial consortia, with NSF support, aimed at precompetitive technology development. Another, on a smaller scale, is via faculty sabbaticals or exchanges in which researchers from each sector work for extended periods in the laboratories of the other.

One caution: It is important to exercise care in selecting the members of cross-disciplinary proposal review panels; balance and cross-disciplinary research experience should be the criteria. The ideal reviewer will be someone who has or would be qualified for similar grants. These reviews must be rigorous and defendable on objective scientific grounds. In a related vein, it is important to avoid "hype" in describing the possibilities of this research. In today's market for scientific research, credibility is easily lost and difficult to regain.

In the end, it is NSF program officers who must be convinced that their own "home" discipline or field can be advanced through cross-disciplinary collaborations that pull scarce resources from their established base of researchers.

Interdisciplinary Orientation and Education

The importance of individual, personal interaction among researchers in stimulating progress in the BAC expansion areas cannot be overemphasized. This means that every avenue of collaboration and communication should be pursued between (and among) biologists and engineers, and between empiricists and theorists. Conferences and workshops, summer study programs, and cross-disciplinary research projects should be organized and funded on topics in this area.

It is vital to train researchers (faculty as well as students) to "speak more than one language"—to understand the principles, aims, and terminology of disciplines other than their home discipline. This type of broadening can be facilitated by 2-3 year interdisciplinary training grants such as those sponsored by the National Institutes of Health, graduate and faculty fellowships and internships that permit working in other departments or in industry, and sabbaticals that involve an intensive self-education in the fundamentals of another discipline. Here again, collaborative team research—"learning by doing"—is a valuable route to greater comfort in cross-disciplinary areas. For biologists, the importance of studying more than one level of biological organization must be emphasized.

To bring about greater interdisciplinary fluency in a more systematic way, undergraduate education in biology should be broader, with in-depth exposure to at least two different disciplines (while not sacrificing rigor). Graduate education in biology also should be cross-disciplinary, with significant course requirements in at least one other discipline (e.g., computer science, mathematics, and/or engineering) outside the major field.

Finally, to facilitate communication and collaboration, NSF could function as an information clearinghouse with respect to (1) advances in any of the relevant fields, either in science our technology, or (2) researchers seeking collaborators in specific areas. A data base of such information could be made available on-line or in published form. Again, communication is the key to integration of disparate fields and development of new fields within their areas of overlap.

Conclusion

We believe the time is ripe for an exploration of many areas of potential interplay between biology and engineering/control theory. The Foundation already has begun this exploration with a series of related cross-directorate initiatives focusing on different areas of possible interaction. Other workshops have looked into the connection of engineering and control theory with learning, cognitive science, developmental psychology and education, mathematics, chemistry, and physics. It would be worthwhile to examine these initiatives in order to integrate their various suggested lines of inquiry into a single broad, multivariate, and intellectually cohesive initiative.

LIST OF KEY TERMS

ADAPTATION: The ability of a system (natural or artificial) to sense changes in the ambient environment and make changes in its functioning in response to changes in the environment.

ADAPTIVE CONTROL: This term refers to the changes in the control of a system caused by better identification of the environment. The term "learning control" is used to mean improved control through repeated application of a control strategy, such as is used by athletes to improve motor coordination. The terms "identification" and "adaptive control" go hand in hand, reflecting a sense that adaptive control is "model based," with identification corresponding to a better model-building activity. One of the main principles of adaptive control is referred to as "dual control" – a tradeoff between the costs of better identification ("learning cost") and performance of the task at hand ("control cost"). For example, when one is asked to drive a car with unknown steering characteristics along a given trajectory, one needs to invest in using some test inputs to identify the steering characteristics of the car. The more extensive the test inputs (referred to as "sufficiently rich") are, the better one's identification of the steering characteristics is. Of course, the richer the test inputs the more deviation one can expect from the desired trajectory – a manifestation of "dual control."

BIOCYBERNETICS: The term "cybernetics" was coined by Wiener (and reputedly later modified to "artificial intelligence" by McCarthy) to convey a sense of machines that exhibit some form of intelligent behavior such as adaptation to the environment, response to queries, etc. (Of course, all the common reservations about the definitions of AI also remain for cybernetics. Biocybernetics refers to identified "computational mechanisms" that biological systems, or biologically inspired systems, use to exhibit intelligent behavior. The ability of a human to perform complex motor actions, such as diving, windsurfing, or bicycling is an example of biocybernetic behavior. Biocybernetics includes:

- Biodynamics and biomechanics – the study of the mechanics and dynamics of biological systems;
- Biorobotics – the use of biological paradigms to design and control robotic systems; and
- Biological motor control – the study of the algorithms for organizing the control of systems of large number of degrees of freedom, including the fan-in of sensor information and fan-out of actuator information.

BIOMIMETIC SYSTEM: Biomimetic literally means "mimicking biology." Use of the term "biomimetic system" is reserved for systems whose construction and/or functioning is inspired by a biological system. For example, a six-degrees-of-freedom robotic arm with two rotary shoulder joints, a rotary elbow joint, and three rotary wrist joints (a so-called elbow manipulator) is biomimetic. If the joints are driven by bellows-like "muscle" actuators, then the motors could also be called biomimetic.

CYTODYNAMICS: This area covers regulation, control, and adaptation mechanisms in biological systems at the cellular level. Cytodynamics includes:

- Genetic Networks – study of the circuitry associated with the formation of genes and their evolution under interaction with the environment;
- Developmental Dynamics – analysis of the dynamics of morphogenesis and cellular growth; and

- Cell Regulation – the study of mechanisms for the regulation of different cell functions.

DYNAMICAL SYSTEM: This term is used in mathematics to describe the evolution, in mathematical terms, of the "state" of the system. A dynamical system is usually a differential or difference equation and the state is usually a subset of $\Re^n$ or some function space such as the space of continuous functions on $\Re^m$.

HIERARCHICAL SYSTEM: The functioning of a complex system is organized by layers, or hierarchies. For example, a firm with many employees, or an army, or the functioning of a government needs to be organized hierarchically. Characteristics of a hierarchical system are a more abstract and less detailed representation of system functioning at higher levels in the hierarchy and a progressively slower functioning of the system at higher levels. Going along with this is data compression from the bottom to the top of the hierarchy.

HYBRID SYSTEM: A dynamical system involving the interconnection of an automaton (discrete state, untimed or timed dynamical system) with continuous time and state dynamical systems. Such systems are used to model the interaction between discrete activities (such as symbolic reasoning or planning) and continuous dynamics (such as muscular activity).

LEARNING: This concept is closely related to adaptation. A distinction is sometimes made between learning and adaptation, in that adaptation refers to system performance modification in response to "external" environmental changes, whereas learning refers to changes system performance both to "external" environment changes and better understanding of "internal" system functioning. For example, "learning by doing" refers to the improved performance of a system repeating the same task.

MICRO-ELECTRO-MECHANICAL SYSTEMS (MEMS): MEMS is the implementation at the micron scale of electromechanical or mechatronic systems, such as gears, motors, and robots. The technology uses fabrication inspired by semiconductor processing techniques. Actuation is by electrostatic, electrodynamic, and in some cases electrochemical forces.

NANOBIOLOGY: Nanobiology is the study of locomotion, sensing, and movement of biological and biomimetic systems at the nanoscale. Nanobiology includes:

- Nanotechnologies – descriptions of nano-actuation and nano-sensing mechanisms used by biological systems;
- Functional Imaging – the analysis of the functional performance of biological nanosystems from high-level descriptions; and
- Nano-visualization — simulation and visualization techniques for depiction of the temporal evolution of biological systems at the nano-scale.

NANOTECHNOLOGY: Nanotechnology is technology for devices at the nano-scale (three orders of magnitude smaller than MEMS devices, roughly). Actuation is more subtle and involves a combination of chemical, biological, and mechanical actuators. Examples include molecular motors, atomic force microscopes, atomic tweezers, and gene circuits.

NEURAL NETWORK: While the words, used together, refer to a circuit consisting of multiple neurons (either biological or biomimetic), the term has the connotation of being used to provide a computational framework for either biological or biomimetic systems to interact with their environment adaptively.

SELF-ORGANIZING SYSTEM: A self-organizing system (natural or artificial) is one which attains spatial or temporal organization in accordance with a set of rules or programs running within the system. Some liberal interpretations of self-organizing systems include the formation of hexagonal lattices in sand dunes, minimum surface tension rain drops, or minimum entropy configurations of crystals. Less liberally interpreted examples include the formation of patterns in traffic flow, mixing of paints, etc. There is a hope in some circles that so-called "artificial life" would be created by the self-organization of machines.

UNCERTAINTY: Uncertainty is used by control theorists as a quantitative measure of the extent of mismatch between a computational model of the functioning of an input-output system and its "true" or experimentally observed behavior. The concept is useful to classify as "good" adaptation or learning schemes that reduce uncertainty in the models of the system and the environment with which it interacts.

APPENDIX A
NSF PROGRAMS PRESENTLY INVOLVED IN THE BAC INITIATIVE

ENGINEERING DIRECTORATE

Bioengineering

Engineering research activities in this program are conducted under three categories: Biochemical Engineering, Biotechnology, and Biomedical Engineering and Research to Aid Persons with disabilities.

Biochemical Engineering supports research on the design and development of traditional and recombinant DNA processes for bioproduct manufacturing. Biomass projects utilizing biological microorganisms for the transformations of organic raw materials(biomass) into useful products are encouraged. Projects in food process engineering involving fermentation technology are of interest. Downstream processing is becoming increasingly important as new advances in the separation and purification sciences accelerate.

Biotechnology addresses the engineering problems associated with the production and processing of substances obtained through the application of principles and techniques of modern molecular biology. The program supports design and development of traditional and recombinant DNA processes for bioproduct manufacturing. Biomass projects utilizing biological microorganisms for the transformation of organic raw materials (biomass) into useful products are emphasized. Molecular and cellular engineering to address modeling and optimization of cell and metabolite production and development of new biochemical reactors that include advanced monitoring and control methods are of interest.

Biomedical Engineering and Research to Aid Persons with Disabilities. Applies engineering methods, science, and technology to solve problems in the life sciences and medicine. While engineering expertise is an essential requirement for success in this field, in-depth knowledge of the life science is also required.

Engineering Systems

This program supports research on analytical and computational methods for the modeling, analysis, estimation, identification, optimization, and control of engineering systems. The emphasis is on generic methods motivated by a wide variety of engineering systems such as robots, power systems, manufacturing and production systems, and electronic systems. The application of these tools to the issues of largeness, nonlinearities, and other complexities of systems like the power generation/transmission/distribution system is of particular interest. In addition, the neuroengineering component develops tests and evaluates new algorithms that can be implemented as artificial neural networks.

Dynamic Systems and Control

This program supports research on the dynamic behavior and control of machines, processes, structures, vehicles, and other engineered physical systems. The primary emphasis is on the physical modeling of a variety of dynamic systems to improve the knowledge base for analyzing their performance and aspects of their control. Research topics include nonlinear dynamics theory, control of mechanical systems, acoustics and noise control, and machine dynamics. The major program support addresses significant gaps in, or extends the knowledge base of, these disciplines. Current interests focus on innovative real-time sensor-based control of automated flexible manufacturing systems.

COMPUTER AND INFORMATION SCIENCE AND ENGINEERING DIRECTORATE

The Computer and Information Science and Engineering (CISE) Directorate's programs improve fundamental understanding of "computing and information processing" in the broadest sense of the terms, enhance the training of scientists and engineers to contribute to that understanding, and encourage and facilitate the use of state-of-the-art computational techniques in scientific and engineering research. Computing and information processing include the creation, representation, storage, transformation, and transmission of information. Special attention is given to the computing and communications technologies- including software--employed to manage these processes, and to selected generic areas of application. Parallel processing, automation and robotics, large-scale integrated electronic systems, scientific computing, and networking are current areas of emphasis.

CISE is inherently multidisciplinary, supporting not only computer and information scientists and engineers but also electrical engineers, mathematicians, artificial intelligence and cognitive scientists, and behavioral, economic, and social scientists. Its fields are unique in combining science and engineering methods and in the close coupling of basic and applied research methods. Support is provided through individual, group, and center research awards, instrumentation grants, research initiation grants, and infrastructure improvement grants to academic institutions.

Interactive Systems. This program supports research fundamental to the design of systems that mediate between computers and humans. Topics include visualization; animation and simulation; interactive computing; human language technology, including speech recognition and natural language understanding; posture- and sound-based interfaces; virtual reality; and multimedia environments.

Robotics and Machine Intelligence. This program supports research fundamental to the design of systems for implementing some characteristics of intelligence. Topics include pattern recognition, machine vision, sensor-based control in intelligent robots, and automatic reasoning and planning of complex tasks involving temporal and spatial relationships in robotic or other automated systems.

BIOLOGY DIRECTORATE

Neuroscience

This cluster supports research on all aspects of nervous system structure, function, and development. Integrative approaches to basic research range from fundamental mechanisms of neuronal function at the molecular and cellular levels to adaptations of the brain for appropriate behavior in particular environments. A major focus is the development and use of a wide diversity of organisms as biological models for understanding fundamental principles of neuroscience. Multidisciplinary collaborative research projects that involve the application of different types of research techniques to single, focused problems in neuroscience are encouraged. Review of research is organized around the following themes.

Behavioral Neuroscience: the neural regulation of behavioral events ranging from simple movements to complex adaptive and interactive responses. Major activities are sensorimotor integration, biological rhythms, and learning and memory. Approaches that use novel techniques to study behavior within an evolutionary and ecological context are encouraged.

Computational Neuroscience: the computational functions of neurons, neural circuits, and nervous systems. This activity encourages the development and testing of mathematical or computer models of neural systems. The activity also welcomes theoretical approaches in all areas of neuroscience that develop innovative, testable concepts that clarify and extend current experimental observations.

Developmental Neuroscience: the development, regeneration, and aging of the nervous system. Studies supported by this activity seek to elucidate basic mechanisms and principles which typically have applicability to many neuronal systems. Current studies are probing aspects of morphogenesis, cell division, cell determination, cell migration, axon growth, synapse formation, and cell death, as well as other areas. These studies may employ a wide range of approaches, ranging from the use of cellular and molecular techniques to the study of development at the system or behavioral level.

Neuroendocrinology: research on the multifaceted relationships among the central nervous system, hormones, and behavior, especially in relation to environmental factors. This includes how the brain controls endocrine secretion, and the effects of steroid and peptide hormones on the brain. Research ranges from the basic mechanisms underlying neuroendocrine development and regulation to the use of molecular biological tools to examine the interaction between physiologically and behaviorally related events and gene expression.

Neuronal and Glial Mechanisms: the cellular and molecular mechanisms of neuronal and glial cell function, including energy metabolism, ion and substrate transport, and synaptic mechanisms with emphasis on neurotransmitter-neuromodulator metabolism, storage, release, and reuptake. Major thrusts are the genetic and biophysical bases of membrane electrical properties, their regulation by intracellular second messengers, and the integration of metabolism and signaling activity by interactions between neurons and glia in both the peripheral and central nervous systems.

Sensory Systems: the mechanisms by which the nervous system acquires, encodes, and processes information about the environment. This includes research on neural processes at the molecular, cellular, systems, and behavioral levels, and psychophysical correlates of sensory neural processes. Topics include sensory transduction; neural coding and integrative mechanisms; and comparative aspects of sensory capabilities, including vision, hearing, touch, taste, smell, equilibrium, electrosensory, magnetic, and other senses.

APPENDIX B
NSF BIOLOGY DIRECTORATE PROGRAMS
AVAILABLE FOR EXPANSION OF THE BAC

DIVISION OF MOLECULAR AND CELLULAR BIOSCIENCES (MCB)

Biochemistry and Molecular Structure and Function

This cluster supports research aimed at understanding the structure and function of biological macromolecules, and the biochemical characterization and regulation of cell metabolism and related processes. This research encompasses a broad range of research topics and techniques. Review of research is organized around the following themes.

<u>Metabolic Biochemistry</u>: research on the characterization and regulation of biochemical pathways and related processes by which microbes, and plant and animal cells transport, assimilate and derive energy from substrates. Identification of the diversity of biochemical mechanisms for the regulation and control of primary and secondary cell metabolism is a major topic of interest. This includes studies to discover novel metabolic by-products and determine their role in the cell, and research on biogeochemical cycles and degradation of polymers and xenobiotics.

<u>Molecular Biochemistry</u>: the structure and function of biological macromolecules, and the molecular basis of their interactions including protein, nucleic acid, carbohydrate and lipid structure and interactions; the mechanism and regulation of enzyme and RNA catalysis; protein synthesis; bioenergetics and photosynthesis; supramolecular structures (e.g., multienzyme complexes, ribosomes, membranes and viruses); and biomolecular materials.

<u>Molecular Biophysics</u>: research using physical techniques on the structure, dynamics, and interactions of biological macromolecules (proteins, nucleic acids, lipid assemblies, polysaccharides), including the three-dimensional structure of macromolecules; assembly and architecture of supramolecular structures (e.g., multienzyme complexes, viruses, membranes, and contractile proteins); energy transduction; structure and function of photosynthetic reaction centers; and mechanisms of electron transfer in biological systems. Typical approaches and techniques include: electron microscopy; diffraction; scattering; x-ray absorption; magnetic resonance; infrared and other spectroscopies.

Genetics and Nucleic Acids

This cluster supports a wide range of studies directed towards answering significant questions of organization, regulation, recombination, function and transmission of heritable information in all organisms from viruses and micro to plants and animals. Specific areas include, but are not limited to, mechanisms of gene regulation, chromosome structure and replication, epigenetic phenomena, DNA repair and recombination, sex determination, interactions at the genetic level between organisms, and molecular evolution. Approaches to genetic questions can use Mendelian genetics, molecular genetics, biochemical methods, or any combination that will be optimally effective. Review of research is organized around the following themes.

Microbial Genetics: genetic inquiries using eubacteria, archaebacteria, and fungi including yeast, as experimental organisms. It also includes genetic studies of viruses and other infectious agents of bacteria and fungi. Investigations of microbial interactions with other organisms are also considered if the emphasis of the study is on the microbe. Studies on molecular evolution of microbial genes are also considered. In general, emphasis is on in vivo studies.

Eukaryotic Genetics: genetic research using eukaryotic organisms, with the exception of fungi, as experimental organisms. This includes parasitic and symbiotic interactions at the genetic level when both organisms are eukaryotic or, if only one is, when the emphasis is on the eukaryotic participant. Studies of molecular evolution and audepigenetic phenomena are also considered. In general, emphasis is on in vivo studies.

Biochemical Genetics: research using biochemical and molecular biological methods to investigate molecular mechanisms for the expression, transfer, and stability of genetic information. Areas of study include DNA mutation/repair; DNA/RNA replication/recombination; transcription; RNA processing; mRNA transport/regulation/stability and chromatin architecture which asks questions of concern to genetics, but require primarily in vitro biochemical approaches.

Cell Biology

This cluster supports research on the structure, function and regulation of plant, animal, and microbial cells. Review of research is organized around the following themes.

Cellular Organization: the structure, function, and assembly of cellular elements such as the cytoskeleton, membranes, organelles, intracellular compartments, intranuclear structures and the extracellular matrix (including cell walls). Structural and dynamic aspects of cellular and intracellular motility, meiosis and mitosis, and cell shape and polarity. Studies of the mechanisms of endocytosis, exocytosis, and intracellular trafficking of membranes and macromolecules.

Signal Transduction and Regulation: the study of intracellular and transmembrane signal transduction mechanisms and functions. These include ion channel activity and second messenger cascades, cellular mechanisms of recognition and defense, and the control of cell cycle progression and cell growth.

Developmental Mechanisms

This cluster supports research on the nature and control of those processes that comprise the life cycle of organisms. Approaches range from molecular genetic analysis of developmental processes to the experimental manipulation of whole organisms. Supports research in microorganisms, plants, and animals. Research focus includes gametogenesis, fertilization, embryogenesis, differentiation, pattern formation, morphogenesis, seed and fruit development and ripening, incompatibility, and senescence.

Physiology and Behavior

This cluster supports integrative studies of physiological functions at the cellular, systemic, and organismal levels and animal behavior in both field and laboratory settings. Review of research is organized around the following themes.

Animal Behavior: the mechanisms, development, functions, and evolution of behavior, studied observationally and experimentally in laboratory and natural settings. Specific areas include behavioral ecology and evolution, learning and cognition, behavioral development and genetics, behavioral physiology and motivation, animal communication, and animal orientation. These areas are neither limiting nor mutually exclusive. Interdisciplinary collaborations and other projects that integrate diverse approaches to the study of behavior are particularly encouraged.

Ecological and Evolutionary Physiology: research that addresses ecological or evolutionary questions in the areas of evolutionary morphology, comparative physiology, physiological ecology and biomechanics of plants, animals, protists, fungi and bacteria. Organisms of study may be living or extinct. The studies, which focus largely on whole organisms, concern how physiological or morphological mechanisms have evolved, and how they may influence evolutionary pathways or interactions between organisms and their biotic or physicochemical environment.

Integrative Animal Biology: the basic physiological mechanisms at the molecular, cellular, tissue, organ, and whole animal levels. Its encompassing theme is "the whole animal as an integrated system". The program includes research on integrative aspects of comparative physiology, functional morphology, endocrinology, epithelial transport, and biomechanics. Studies that focus on the nervous system are supported by the Neuroscience Cluster.

Integrative Plant Biology: research on the plant as a functional unit, integrating molecular, biochemical, and biophysical approaches to the understanding of plant form and function. Examples include whole-plant, tissue, and organ physiology; sensory mechanisms; and hormonal regulation of plant function. Biochemical and physiological interactions of plants with pathogens, nitrogen-fixing organisms, mycorrhizae and other rhizosphere organisms, epiphytes, endophytes, and plant parasites are included. The emphasis is on understanding the physiological and metabolic basis of plant response to such interactions. Also included are investigations of the physiological and biochemical responses of plant function to environmental factors.

Systematics and Population Biology

This cluster supports research on the patterns and causes of diversity within and among populations and species. Research projects may involve any group of organisms including terrestrial, freshwater, and marine taxa, from microbes to multicellular plants, animals, and fungi. Review of research is organized around the following themes.

Population Biology: (1) molecular population studies, including analyses of the causes and consequences of variation and change in biochemical characteristics, RNA and DNA sequences, the population genetics of mobile elements, the evolution of genic and genomic organization and functioning, and the evolution of organismal development; (2) population and quantitative genetics, directed to understanding the genotypic and phenotypic variation of populations during microevolution, geographical differentiation, organismal adaptation to changing environments, natural hybridization, and speciation; and (3) studies of life history and life cycle phenomena of terrestrial, freshwater and wetland organisms from ecological and evolutionary perspectives, animal and plant demography of age and stage-structured populations, and population dynamics, including linear, nonlinear, and stochastic approaches.

Systematics: (1) phylogenetic analyses that produce or test phylogenetic hypotheses or models, and the use of derived phylogenies to elucidate patterns of structural, developmental, or molecular evolution; (2) studies that lead to improved classifications, better methods of taxonomic identification, contributions to classificatory theory, and nomenclatural reform; (3) understanding of processes that underlie the origin and maintenance of taxonomic diversity; and (4) theoretical and empirical studies of biogeographical, co-evolutionary, and paleobiological patterns to develop models of the origin, diversification, distribution, and extinction of species and evolutionary lineages, and to determine the tempo and mode of evolutionary change.

Ecological Studies

This cluster supports research on natural and managed ecological systems, primarily in terrestrial, wetland, and freshwater habitats. Research includes experimental, theoretical, and modeling studies on the structure and function of complex biotic-abiotic associations, and the coupling of small-scale systems to each other and to large-scale systems. Current areas of emphasis include the role of biological diversity in ecological systems, the ecological effects of global change, and the ecological basis of sustainability. The Ecological Studies Cluster encourages projects that develop conceptual and synthetic linkages, such as theoretical and modeling studies conducted at one or at several scales of ecological organization, and studies that synthesize empirical and theoretical findings into new ecological paradigms. Review of research is organized around the following themes.

Ecosystems: mechanistic or empirical investigation of whole-system ecological processes and relationships in the following areas: (1) biogeochemistry such as studies of decomposition, global and regional elemental budgets, and biotic versus abiotic controls of nutrient cycles; (2) primary productivity, particularly ecophysiology within an ecosystem framework; and (3) landscape dynamics with an emphasis on quantitative models of disturbances, ecosystem resilience, and successional patterns.

Ecology: community ecology and population interactions in such areas as (1) dynamics and processes within specific communities or habitats; (2) food-web structure and landscape patterns formed by community dynamics and paleoecology; and (3) organismal interactions such as mutualism, plant-animal interactions, competition, predation, co-evolution, and chemical or evolutionary ecology.

Long-Term Projects in Environmental Biology

This cluster supports research that requires longer time frames to complete and infrastructure that is essential to support longer time scale projects. Research includes surveys of biodiversity ranging from regional to world-wide with the appropriate curatorial and data management theory and infrastructure.

This cluster also supports a wide range of long-term experiments and monitoring from individual population studies to landscape scale dynamics that evaluate the cumulative impact of natural and anthropogenic perturbations. Review of research is organized around the following themes.

Long-Term Ecological Research (LTER): investigations of whole ecosystems and their component organisms and processes at sites representing major biomes. Projects are multidisciplinary and actively encourage collaborative research with non-ecological investigators.

Long-Term Research in Environmental Biology (LTREB): studies focused on evolutionary or ecological phenomena that require long-term investigation.

Land-Margin Ecosystem Research (LMER): a joint activity with the Biological Oceanography Program aimed at understanding land-margin ecosystems and their links with adjacent terrestrial and marine ecosystems.

Research Collections in Systematics and Ecology: projects for the improvement of research collections and their preservation and accessibility to the research community. Production of computerized databases openly available through electronic networks is especially emphasized.

Biotic Surveys and Inventories: collecting and recording the diversity of life on earth. Well-curated permanent collections and computerized databases are strongly encouraged as products of such support.