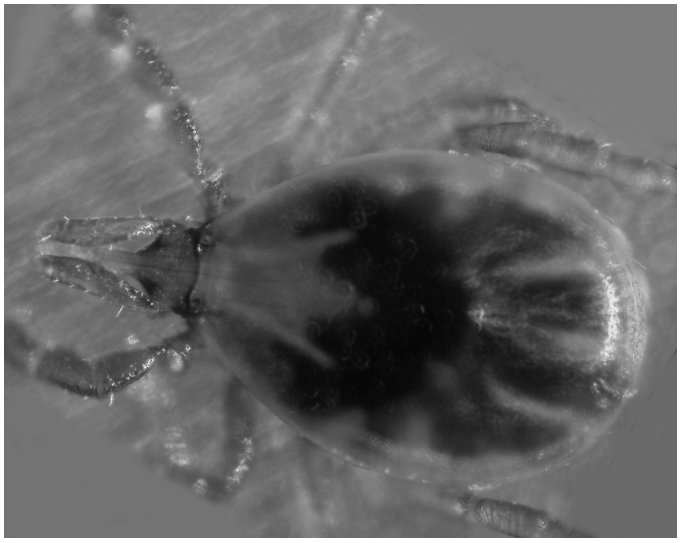
Ecology and Evolution of Infectious Diseases

Report from a NEON Science Workshop



August 31–September 2, 2004
Baltimore, MD

neon
National Ecological Observatory Network

American Institute of Biological Sciences

IBRCS
Infrastructure for Biology at Regional to Continental Scales
A community resource by AIBS

The IBRCS Program

The Infrastructure for Biology at Regional to Continental Scales (IBRCS) Program, an effort by the American Institute of Biological Sciences (AIBS), launched in August 2002 with support from the National Science Foundation. The following are the program's goals:

- Help the biological and the larger scientific community—within and beyond the AIBS membership—to determine the needs and means for increased physical infrastructure and connectivity in observational platforms, data collection and analysis, and database networking in both field biology and other more general areas of biology and science.
- Provide for communications within this community and with NSF regarding the development and focus of relevant infrastructure and data-networking projects.
- Facilitate the synergistic connection of diverse researchers and research organizations that can exploit the power of a large-scale biological observatory program.
- Disseminate information about biological observatory programs and other relevant infrastructure and data-networking projects to the scientific community, the public policy community, the media, and the general public.

The program is led by a working group comprising biologists elected from the AIBS membership of scientific societies and organizations and appointed from the scientific community at-large. It is assisted by a variety of technical advisors. The program has a special focus on the National Ecological Observatory Network (NEON), which is a major NSF initiative to establish a national platform for integrated studies and monitoring of natural processes at all spatial scales, time scales, and levels of biological organization. Jeffrey Goldman, PhD, is the Director of the IBRCS program. He and Richard O'Grady, PhD, AIBS Executive Director, are co-principal investigators under the grant. Additional information is available at *http://ibrcs.aibs.org*.

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About the American Institute of Biological Sciences

The American Institute of Biological Sciences is a non-profit(c)(3) scientific organization of more than 6,000 individuals and 86 professional societies. AIBS performs a variety of public and membership services, which include publishing the science magazine, BioScience, convening meetings, and conducing scientific peer review and advisory services for government agencies and other clients.

This material is based upon work supported by the National Science Foundation under Grant No. DBI-0229195. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the institution with which they are affiliated, AIBS, or National Science Foundation.

Key Words: National Ecological Observatory Network; biological infrastructure; infectious diseases; scientific facilities; science workshops

This document is available from:

American Institute of Biological Sciences
1444 I Street, NW, Suite 200
Washington, DC 20005
tel. 202-628-1500
fax 202-628-1509
mbrown@aibs.org

This document is also available online at *http://ibrcs.aibs.org*.

November 2004

Printed in the United State of America

Recommended citation:
American Institute of Biological Sciences. 2004. Ecology and Evolution of Infectious Diseases: Report from a NEON Science Workshop. Washington, DC: AIBS.

Cover:
Photomicrograph of nymph stage blacklegged tick, *Ixodes scapularis*, in dorsal view. This species is the main vector of several agents of human disease, including Lyme disease, Ehrlichiosis, Babesiosis, and tick borne Encephalitis. Photograph by R. Ostfeld.

NEON Workshop Series

The National Ecological Observatory Network (NEON) is a major initiative proposed by the National Science Foundation (NSF) to establish a continental-scale platform for integrated studies on natural processes at all spatial scales, time scales, and levels of biological organization. NEON is anticipated to provide the resources and infrastructure for fundamental biological research that will enhance our understanding of the natural world, improve our ability to predict the consequences of natural and anthropogenic events, and inform our environmental decision-makers.

The previous two years of NEON-related activity have revealed several steps that the scientific community must take along the path to the creation of NEON. Prior work showed that in order to develop a detailed description of NEON's physical design, an important milestone for NEON, the scientific objectives and targets of NEON must first be defined. With this in mind, as part of the NSF-funded Infrastructure for Biology at Regional to Continental Scales (IBRCS) project, AIBS, in partnership with experts from the prospective NEON community, convened a series of workshops between March and September, 2004, focused on the following ecological themes, which have been proposed as guideposts for the design of NEON:

- Ecological implications of climate change
- Land use and habitat alteration
- Invasive species
- Biodiversity, species composition, and ecosystem functioning
- Ecological aspects of biogeochemical cycles
- Ecology and evolution of infectious disease

The goal of the workshops was to highlight urgent scientific questions that NEON can address, define science requirements associated with those questions, assess the state of currently available infrastructure, and discuss needs for future infrastructure development. The recommendations that grew from these meetings, as captured in this report and others in the series, will guide subsequent NEON planning.

This workshop series opened up the NEON planning process to a diverse group of scientists from academia, government, and the NGO community. In total more than 120 scientists participated in these meetings—some were previously involved in NEON activities, while others took part in a NEON effort for the first time.

Introduction

Current approaches to studying the ecology and evolution of infectious disease systems have provided substantial theoretical development and data during the past decades. However, it is evident that in many cases, the rate at which we are generating substantial new knowledge is slowing. Our ability to understand higher level interactions that influence the patterns of diseases in the real world remain insufficient to allow us to predict outcomes and devise interventions that minimally impact the ecosystem. It has been proposed that a distributed research facility such as NEON could push the field of infectious disease ecology beyond what is possible based on our current research capabilities. With this in mind, a workshop was convened to identify the major questions in the ecology and evolution of infectious disease systems that could best be addressed by NEON, so that the scientific requirements of those questions can inform the infrastructure needs for an infectious disease component of NEON. This document highlights the design recommendations that resulted from discussions at the NEON infectious disease workshop.

Scientific Rationale for Key NEON Infectious Disease Questions

The key conceptual framework for the recommendations made in this document is that infectious diseases represent the phenotypic, physiological expressions of the interactions between members of host species and members of pathogen species. Consequently, we are dealing with systems of interacting populations within the environment. This community or systems approach is critical to understanding the actions of pathogens in natural populations.

Four major areas of research were proposed for the infectious disease component of NEON:

- **Understanding the evolution of disease systems** – disentangling the mutable characteristics of host and pathogen species, as well as changes in environmental conditions that alter the patterns of disease incidence and prevalence, with the long-term goal of predicting the emergence of new diseases before they occur.
- **Identifying the extent of the challenge**—determining the biodiversity and modes of action of pathogenic organisms so that we can better determine how many organisms that could cause disease for humans, animals, and plants are likely to exist.

- **Characterizing the role of disease systems in community structure** – understanding the extent to which diseases influence community structure and ecosystem functioning, and the effects of biodiversity on the health of ecosystems.
- **Predicting the timing and locations of disease outbreaks** – using our improved understanding of disease in ecosystems to forecast conditions that make the environment permissive for disease outbreaks with the long-term goal of abrogating deleterious outcomes.

Understanding the evolution of disease systems

The transformational questions to be examined here require that we characterize the biological and temporal dynamics of disease systems and determine how to anticipate the likely changes that will occur. These issues can be summarized by the following questions: What selective or other evolutionary forces influence virulence in pathogens, transmission dynamics involving vectors, and resistance in hosts? Can we predict how pathogens will evolve? Can we predict how the host species will coevolve with pathogens?

It is evident, and well demonstrated that disease systems evolve over time. Some of the most dramatic case studies are those in which previously unknown pathogens adapt and acquire new host species. These events, though relatively rare, are often associated with significant and severe epidemics in the new hosts. Disease systems where humans have acquired pathogens from nonhuman hosts, such as AIDS, measles, and SARS, are obvious examples.

A key step in adaptation of a pathogen to a new host is the ability of the pathogen to attach to and enter targeted cells or tissues, successfully replicate, and become transmitted to another member of the new host species. Childs (2004) offers one schema for this type of event. This is an area that closely links modern molecular and cellular biology with the evolution of infectious diseases and provides tremendous research opportunities. A critical question is whether we can use this knowledge, beginning at the simplest level, such as ligand–receptor interactions, to characterize what changes are needed for species jumping and which changes are possible in the pathogen. If successful, it may be possible to identify classes of changes that are possible or likely in pathogens, thus improving our ability to predict disease emergence. For example, phylogenetic analyses of H3 influenza A virus strains show that viral strains that survive to emerge during subsequent outbreaks have changes in HA1 subregion of the hemagglutinin protein near the antibody combining sites, as well as the sialic acid receptor binding site (Bush et al 1999). Can this type of detailed knowledge generate hypotheses about what evolutionary changes are possible or would be needed for a microorganism to jump from its

current host species to another? A large number of well-characterized case studies that rely on currently available data and methods could be developed to evaluate the likely success of this approach.

Identifying the extent of the challenge

The transformational question to be addressed here is to create a better understanding of the diversity of organisms that act as pathogens and how they cause diseases. Understanding the diversity of pathogenic species and characterizing the ways they interact with hosts when they cause disease are key steps in evaluating the extent of disease systems. It is a crucial challenge that we obtain information on the biodiversity and characteristics of pathogens before we can devise hypothesis-driven scientific studies of the ecological and evolutionary interactions between hosts and parasites.

Numerous examples of previously unknown pathogenic organisms, being discovered both directly as the causative agents in newly recognized disease systems and as ancillary discoveries during such investigations, implies there are large numbers of pathogenic organisms that remain unrecognized and uncharacterized and whose modes of pathogenicity remain unknown. The biodiversity of organisms responsible for Lyme borrelioses worldwide, the identification of large numbers of *Bartonella* species responsible for human and animal diseases, and the various species of *Anaplasma* serve as key examples. Similar examples for viruses, parasitic organisms, and prions indicate this is a general question. In many of these cases, the disease was recognized either locally or more generally but the etiologic agent was unidentified. The aspect of primary identification in this challenge should be addressed using survey strategies and currently available laboratory techniques and will be most successful with a focus on subsets of well-recognized host species. However, there is increasing evidence that whole groups of pathogens remain unrecognized and are so distinct from currently recognized forms that their identification remains problematic. For example, Roossinck (2003) shows that large numbers of plant RNA viruses are remarkably distinct from previously identified pathogens. Despite this, the viruses appear to be common parasites of plants. This raises serious conceptual challenges for devising strategies to even recognize their existence.

Establishing estimates of the numbers of pathogenic species and their modes of action, at least for representative groups of hosts, will generate hypotheses concerning the overall diversity and strategies of parasite action in disease systems. Methods to identify previously unknown and biologically unique organisms will be challenging, depending on sets of assumptions developed by researchers, but new strategies to identify and sequence genetic materials provide methods for rapid acquisition and characterization of these organisms.

Characterizing the role of disease systems in community structure

During the past 30 to 40 years ecologists have studied the impact of biotic interactions, such as competition, predation, and mutualism, on community structure. Although parasitism has been recognized as a potential effector of community dynamics, with potential influences on ecosystem functioning, studies of its role have been limited to a few case studies, and in most cases the indirect community effects have not been evaluated. The transformational science needed in this area involves detailed studies designed to establish the relative significance of disease systems to community structure and ecosystem functioning.

Studies to understand the impact of disease systems within communities necessarily involve methods to study its impact at difference scales of time and space. Analytically, there are methodological and conceptual challenges with these issues that are ongoing areas of basic ecological research. Current ecological theory has developed a series of predictions that can be relatively quickly evaluated by observational and comparative studies of selected disease systems, over space and/or time. This research approach would provide an initial evaluation of likely situations where the theory appears correct, is underdeveloped, or appears incorrect. For example, the role of the interplay between predation and prevalence of infection in prey species, with the prediction that infection prevalence generally increases as predation rates decrease, may be relatively amenable to short-term and comparative studies (Ostfeld and Holt 2004). Or the prediction that host population and community structure are predictive of disease severity (Garrett and Mundt 1999) can and should be tested. In parallel with these observational studies, it is critical that well-designed, experimental studies (with an emphasis on safety) be developed to demonstrate and provide measurable outputs of the effects of diseases on host species, as well as indirect effects of other members of the community and ecosystem functioning. An experiment involving a nonliving vaccine or therapy that would only affect a single generation of host species might serve as such a general experiment. Data from such studies could measure the impact of reducing or eliminating a pathogen from a host species.

Predicting the timing and location of disease outbreaks

Understanding the ecology and evolution of disease systems can provide us with the ability to predict where and when the environment is permissible for outbreaks of disease in host populations to occur. The goal of forecasting disease risk requires careful integration of knowledge bases described above and, although currently beyond our capacity for most disease systems, is both a feasible and desirable goal. Historically, medical geography, in general, had as its underlying paradigm that the ecological tolerances of the component populations of disease systems provide critical

clues for the distribution of diseases. Recent developments in environmental monitoring, data analysis, and computer modeling indicate that such an approach can produce a relatively coarse-resolution monitoring system. Subsequently, integrated studies of environmental conditions associated with component populations of disease systems, coupled with a detailed understanding of transmission dynamics and population biology of the component species, should generate sufficient data that we can model where and when conditions may allow disease to spread within host populations as the population interacts with the landscape. Results from such models would be the precursors of disease forecasting systems. Current advances in environmental monitoring through integrated in situ and remotely sensed systems provide some of the basic environmental inputs for creating models of species responses. Significant challenges remain both in understanding the relevance of the monitored conditions to the species of interest as well as gathering detailed information of how host and pathogen population members respond to members of their own and other species under naturally varying conditions.

Despite these challenges, initial research efforts can utilize much of the current conceptual descriptive framework of disease system distribution to study the landscape of disease patterns. Once established at an appropriate spatial and temporal scale, certain selected systems can be examined in more detail to model the dynamics of interactions among population members that generate landscape patterns.

Needs

Overall, there will be a series of strategic needs associated with the successful implementation of NEON's ecology and evolution of infectious diseases component. In order for NEON to complement rather than duplicate existing programs, it will be important for NEON to collaborate with other agencies and programs conducting infectious disease research. Secondarily, NEON should become a distributed network with a primary research focus on coordinated, longitudinal, long-term studies of disease systems, with a support structure including appropriate laboratory facilities and archiving resources to safely acquire, store, and preserve specimens, associated information, and technologies. A significant recommendation is the perceived need to couple this primary research network strategy with a supplemental, flexible strategy to ensure NEON can respond to rapidly evolving conditions that provide opportunities to address unique research opportunities.

Advances in computing, molecular biology, environmental monitoring, data analysis and interpretation, as well as modeling and statistics will be essential for NEON to play its anticipated role in infectious disease research. However, few of these needs preclude initial study design and implementation. In nearly every case, current technology, while not providing the detailed data that are desirable, will provide important directions that can guide technology development in the future.

Many recent technologies have substantial utility, and efforts should be expended to ensure that the knowledge base for their use is not lost as we advance.

Strategic needs

In order for NEON to best address currently intractable questions in infectious disease research, it should be a distributed network of field sites where long-term, longitudinal, observational and experimental studies of disease systems can be conducted. Coupled intimately with these field study areas there should be the following:

- Laboratory resources for safely processing materials for more detailed analyses. We also believe that a dedicated staff, physically associated with the laboratory, is needed for quality assurance/quality control of various databases that require integration to address the four key research areas. This group should also have as its responsibilities the appropriate archiving, cataloging, and maintenance of specimens, knowledge of the methods of acquisition and determination, and database integrity.
- At least one high-containment, centrally staffed facility should be established and maintained to conduct more detailed analyses and to serve as a repository for specimens, reagents, and protocols. Working with disease systems in which the parasite is known to be highly pathogenic, or when field samples are cross contaminated with unknown highly pathogenic organisms, will require careful consideration.

One of the most important needs of this grand challenge is to integrate activities with other grand challenges in NEON. Many of the data likely to be gathered by these groups (e.g., biogeochemical cycles, invasive species, biodiversity, land use/land cover) are either integral to advancing our understanding of the ecology of infectious diseases or would improve the efficiency in data gathering if coordinated. Similarly, there is a programmatic need to coordinate and avail ourselves of other, large, ongoing or planned programs. For example, integrated programs, such as the Earth Observations initiative, may provide key approaches, data sources, and data management tools and are intended as an integrated system for building systems to monitor the environmental conditions. Both the data and the methods needed to acquire, process, and integrate these large data sets are instrumental to associate infectious diseases with environmental conditions using integrated ground and remotely sensed instrumentation. A substantial number of federal agencies also have responsibilities for health outcomes associated with infectious disease systems in humans, domestic animals, and plants. Coordination with these agencies is critical both from a value-added perspective as well as to ensure that NEON researchers do not negatively impact public health and policy decisions. Collaborations with these agencies will be beneficial to all members but is likely to succeed only with careful planning.

Occasional outbreaks of previously unrecognized disease systems offer unique opportunities to characterize disease systems that may provide special insights into key ecological and evolutionary questions. However, we anticipate these are unlikely to occur at any of the planned field sites. Thus, there is a need to complement the longitudinal study areas with a rapid response program that would allow researchers to respond to these opportunities. This will require careful coordination with agencies both within the United States and internationally. This coordination offers the opportunity to increase efficiency in the data gathered and questions answered, but it is not intended to serve in place of the longitudinal, planned studies. It is our belief that this portion of the program should provide as much flexibility as possible to respond to unforeseen opportunities but should remain a minor portion of the overall program.

Resource needs

There are a number of specific resources needed to address the four key research areas described above. Although new technologies are anticipated to make monitoring the environment and health status of free-ranging individuals and identifying novel micro-organisms more efficient, in most cases current techniques are sufficient to form the basis for many of NEON's initial studies and are to be encouraged. Therefore technological challenges should not prevent NEON's infectious disease research from being initiated. Many methods for culture, isolation, and characterization of microorganisms that were developed over the past 50 to 60 years remain useful, but skills in their use are eroding. In addition to developing and extending new strategies for nucleic acid and protein characterization, these older approaches should be preserved. Improvements in computerized systems for better identification of biological samples are necessary. As the program transitions to become a real-time monitoring, analysis, and response system, significant progress will be needed in data integration and analytical tools.

In regard to understanding the evolution of disease systems and understanding the extent of the challenge, molecular techniques associated with genomics, proteomics, and taxonomic characterization of samples need to be extended. Landscape-level tools for monitoring the environment and organisms within the environment will be a necessity for understanding disease impacts on communities and ecosystems, as well as our abilities to forecast disease risk. A challenge will be developing technologies to monitor the location, health status, and environmental conditions experienced by targeted individuals. The major issues are developing tools that will allow us to generate sufficiently detailed information on large enough samples of individuals by the most unobtrusive means possible so that biologically meaningful, statistically robust conclusions concerning natural populations can be generated.

All four areas of research will face challenges in data management, data integration, and computational power because data generated at NEON facilities will be collected from disparate and heterogeneous scales and will need to be integrated from numerous sources. For example, biosensors that are small enough to monitor health conditions of arthropods, the environment the individuals experience, the other organisms they contact, and their location in space would be ideal instruments for understanding vector-borne diseases. However, in addition to the challenges of instrument miniaturization, the large quantity of linked data that would be generated and would need to be integrated to create meaningful results is a significant challenge that will need to be addressed. Monitoring abiotic and biotic aspects of the environment at high spatial and temporal resolution will involve integration of both on-site and remote sensor arrays. These sensors need to be highly flexible and easily modified to update the variables recorded. Coupled with the data management issues are needs for new approaches to data analysis. Data aggregation that relies on traditional methods of summary statistics is inefficient and unlikely to accurately capture the primary drivers affecting individual fates and population responses. More advances in analytical approaches will be key to the success of this program.

New laboratory methods to identify unknown organisms from environmental samples also are needed. Major advances are required both in the technology as well as the algorithms used to characterize organisms. A special challenge will be to identify cryptic organisms that appear as part of the background in the environment. Traditional approaches require creating relatively pure samples, free of competing microorganisms, when processing samples. Given that the community structure of microorganisms themselves may be an important aspect of pathogen impacts, we need methods that accurately identify the species composition of organisms within environmental samples, themselves.

Overall, workshop participants viewed the issues that need to be addressed by the grand challenge of ecology and evolution of infectious diseases as significant but not overwhelming. The questions to be answered and the potential benefits from addressing the challenge are seen as worthy goals from both the perspective of an intellectual reward that will advance our knowledge as well as the practical benefit of reducing the burden of disease. We identified a series of approaches that begin with the use of current technologies, build on the results of these studies to identify new questions, and lead to the new technological innovations needed to advance the field.

Conclusion

In summary, NEON offers four unique, major contributions to extending our understanding of the ecology and evolution of infectious diseases. First, NEON is vital because no other organization now exists as a repository of skills, knowledge, information, and specimens concerning infectious diseases. In particular, NEON can provide the absolutely essential ecological context that is needed to understand disease processes. This context does not exist beyond simple descriptive studies of disease systems.

Second, by its scale, NEON is needed to provide sufficient infrastructure to coordinate studies of infectious disease dynamics with other national and international agencies that have responsibilities to study disease in their context. This coordination is currently not possible, and data that are gathered, though intriguing, are fragmentary and insufficient to really answer the significant questions about disease ecology and evolution.

Third, NEON must serve as the site for coordinated interaction among disease ecologists studying multiple systems. These interactions are absolutely critical so we can obtain an integrated context of disease. As mentioned at the outset, disease is the outcome of interactions of populations within the environment. Until now, we have been limited in nearly every situation to studying dyadic interactions of host and parasite. We have lacked the resources (primarily the coordinated activities of large groups of scientists) to characterize disease within all the components of the community.

Finally, NEON is needed to provide the structure for comparative, ecosystem-level studies across North America. Comparative studies across space are the most rapid way to generate the observations needed to create new hypotheses. The structure is needed so these hypotheses can be tested and the field moved forward. It is not feasible for individual scientists to coordinate activities and develop a series of experiments whose results are directly comparable. Coupled with the spatial breadth that NEON offers, consistent, longitudinal, long-term studies that extend beyond the professional lives of individual researchers are needed. The institutional memory that is retained is critical to address studies about long-term trends in patterns of disease associated with changes in the environment.

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Workshop Organizer

Gregory Glass
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street
Baltimore, MD 21205
P: 410.955.3708
E: ggurrigl@jhsph.edu

Workshop Participants

Mark S. Boyce
Department of Biological Sciences
University of Alberta
Edmonton T6G 2E9
Canada
P: 780.492.0081
E: boyce@ualberta.ca

James E. Childs
1362 N. Decatur Rd.
Atlanta GA 30306
E: jamesechilds@comcast.net

Barbara Ellis
Select Agent Program
Centers for Disease Control and Prevention
1600 Clifton Rd NE, Mailstop E79
Atlanta GA 30333
P: 404.498.2256
E: BAE7@CDC.GOV

Karen Garrett
Department of Plant Pathology
Kansas State University
Manhattan, KS 66506
P: 785.532.1370
F: 785.532.5692
E: kgarrett@ksu.edu

Tom Hobbs
Natural Resource Ecology Laboratory
227 Natural and Environmental Sciences Building
Colorado State University
Fort Collins, CO 80523
P: 970.491.5738
E: nthobbs@nrel.colostate.edu

Robert D. Holt
University of Florida
111 Bartram
PO Box 118525
Gainesville, FL 32611-8525
P: 352.392.6917
E: rdholt@zoo.ufl.edu

Timothy Keitt
School of Integrative Biology
University of Texas at Austin
1 University Station #CO930
Austin, TX 78712
P: 512-471-5858
E: tkeitt@mail.utexas.edu

Uriel Kitron
College of Veterinary Medicine
University of Illinois
2001 S. Lincoln Avenue
Urbana, IL 61802
P: 217.244.6221
E: ukitron@uiuc.edu

Sabra Klein
Johns Hopkins Bloomberg School of Public Health
Department of Molecular Microbiology and Immunology
615 North Wolfe Street, Suite E5132
Baltimore, MD 21205
P: 410.955.8898
E: saklein@jhsph.edu

James N. Mills
Centers for Disease Control and Prevention
Medical Ecology Unit, Special Pathogens Branch
Division of Viral and Rickettsial Diseases
Mail Stop G-14
1600 Clifton Road
Atlanta, GA 30333
P: 404.639.1396
E: JMills@cdc.gov

Richard S. Ostfeld
Institute of Ecosystem Studies
65 Sharon Turnpike
Millbrook, NY 12545
P: 845.677.7600 x 136
E: Rostfeld@ecostudies.org

Robert Parmenter
Valles Caldera National Preserve
2201 Trinity Drive
Los Alamos, NM 87544
P: 505.661.3333
E: bparmenter@vallescaldera.gov

Fernando Pineda
Johns Hopkins Bloomberg School of Public Health
Dept. of Molecular Microbiology & Immunology
Room E5146
615 North Wolfe St.,
Baltimore, MD 21205-2179
P: 443.287.3673
E: fernando.pineda@jhu.edu

Alison G. Power
Cornell University
Department of Ecology and Evolutionary Biology
Corson Hall
Ithaca, NY 14853
P: 607.255.7374
E: agp4@cornell.edu

Jason L. Rasgon
North Carolina State University
Department of Entomology
840 Method Road Unit 1
Raleigh, NC 27695
P: 919.515.1650
E: jlrasgon@ncsu.edu

Marilyn J. Roossinck
The Samuel Roberts Noble Foundation
Plant Biology Division
PO Box 2180
2510 Sam Noble Parkway
Ardmore, OK 73402
P: 580 224 6630
E: mroossinck@noble.org

Kellogg J. Schwab
Johns Hopkins Bloomberg School of Public Health
Dept. of Environmental Health Sciences
Division of Environmental Health Engineering
615 N. Wolfe St. Room E6620
Baltimore, MD 21205-2103
P: 410.614.5753
E: kschwab@jhsph.edu

Gary Smith
University of Pennsylvania School of Veterinary Medicine
Section of Epidemiology and Public Health
New Bolton Center
382 W. Street Road
Kennett Square, PA 19348-1692
P: 610.925 6312
E: garys@vet.upenn.edu

Jill Stewart
National Oceanic and Atmospheric Administration
219 Ft. Johnston Rd.
Charleston, SC 29412-9110
P: 843.762.8609
E: Jill.Stewart@noaa.gov

Terry L. Yates
Sevilleta LTER
University of New Mexico
167 Castetter Hall
Albuquerque, NM 87131-1091
P: 505.277.2496
E: tyates@unm.edu

Workshop Observers

Elizabeth Blood
Program Officer
National Ecological Observatory Network
Division of Biological Infrastructure
National Science Foundation
4201 Wilson Blvd., #615N
Arlington, VA 22230
P: 703-292-8470
E: eblood@nsf.gov

Michael Willig
Division of Environmental Biology
National Science Foundation
4201Wilson Blvd.
Arlington, VA 22230
P: 703-292-8480
E: mwillig@nsf.gov

AIBS Staff

Rina Aviram
1444 I St. NW Suite 200
Washington, DC 20010
P: 202.628.1500 X 231
E: raviram@aibs.org

Jeff Goldman
1444 I St. NW Suite 200
Washington, DC 20010
P: 202.628.1500 X 225
E: jgoldman@aibs.org

Facilitation Team

Abby Dilley
RESOLVE, Inc.
6840 Sunrise Court
Grand Rapids, MI 49546-6644
P: 616.682.9190
E: Adilley@resolv.org

Bradford R. Spangler
RESOLVE, Inc.
1255 23rd St., NW, Suite 275
Washington, DC 20037
P: 202.965.6214
E: bspangler@resolv.org

Acknowledgements

These workshops would have been impossible without the contributions and commitment of the organizers and participants. Furthermore, the staff of AIBS aided in the following ways: Cathy Lundmark and Dan Johnson applied their editing skills to this document, and Donna Royston designed the layout. Sue Burk and Lori Strong coordinated plans for the meeting facilities and accommodations. Adam Rice supported the technical aspects of the project including maintaining the webpages that posted information on each of the workshops.

http://ibrcs.aibs.org

Infrastructure for Biology at Regional to Continental Scales is a project of the American Institute of Biological Sciences and is supported by a grant from the National Science Foundation.

November 2004