

Quantitative Biology for the 21st Century

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Report from a NSF funded workshops on Quantitative Environmental and Integrative Biology, the first held September 7-9, 2000 at the San Diego Supercomputer Center on the University of California, San Diego campus, and the second held 11 – 13 December 2002 at the University of California, San Diego. The work was supported by NSF award **DEB-0092081**.

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EXECUTIVE SUMMARY

1. Mathematical and statistical approaches have played a fundamental role in biological understanding throughout biology. There are areas in which progress has been made, and some of the specific accomplishments indicate great promise for future advances. A brief summary of some successes is in the compelling examples in Section II (page 9).
2. Common mathematical themes of spatial and temporal scales, stochastic and dynamic processes, and matching of data to theory will play a role in many if not all biological questions. The presence of these crosscutting themes justifies the integration of mathematical and statistical efforts across the field of biology rather than just within specific biological subdisciplines. Integrating biology, mathematics and statistics should be a focus for training and future research support.
3. Current and future progress in using mathematics and statistics to make fundamental advances in biology are hampered by a series of impediments, including:
 - a. Lack of both quantitatively trained biologists, and mathematicians and statisticians with expertise in biology.
 - b. Difficulty in establishing and maintaining collaborations among biologists, mathematicians and statisticians.
 - c. Institutional and cultural barriers that reduce the potential for funding in “interface” areas, and university and other institutions that encourage disciplinary work over interdisciplinary work.
4. We propose the following recommendations for NSF based on the concept that we need to build collaborations and reinforce interdisciplinary approaches in the context of specific problems, at all levels, from the undergraduate to the mid-career scientist:
 - a. Encourage interdisciplinary group proposals in Quantitative Biology through special competitions or new programs.
 - b. Create an undergraduate group funding program for hands on, long-term involvement of undergraduates in interdisciplinary work.
 - c. Support postdoctoral scholars both through individual awards and through postdoctoral group grants that would foster collaborations.
 - d. Build on the IGERT program to encourage training that integrates students at all levels in interdisciplinary work.
 - e. Support the building of infrastructure for collaborative activities, either at existing centers such as NCEAS or IMA, or via a new center for quantitative and integrative biology.

In order to respond most effectively to these recommendations, we emphasize that support by all levels of the NSF organization is needed. We make some specific recommendations for NSF program staff and management.

Preface

We are standing at the intersection of four major forces that will shape the future of science, indeed of society. If we can harness and couple them, we will be able to address key challenges such as improving the health of all world citizens and creating a sustainable environment for our planet.

First, there is a growing awareness that fundamental research advances in specific areas within the biological sciences are increasingly influencing our understanding across a wide array of other areas – the boundaries between disciplines are becoming blurred. Thus, for example, advances in molecular biology contribute to advances in environmental biology as well as health science. Similarly, advances in environmental biology contribute to our understanding of disease transmission and susceptibility.

Second, biology is an information science, and its practice has become more quantitative. Collaborations among mathematicians, statisticians, computer scientists and biologists are no longer unusual.

Third, the current explosion in information and other technologies allows us to better observe the earth and our lives upon it. With burgeoning amounts of information, we are pressed to develop theoretical frameworks for interpreting information and applying the information to solve applied problems.

Fourth, mathematical and statistical tools now are being developed that have the potential for addressing complex biological problems and for mining the information currently being collected on biological systems. These tools are aided by the widespread availability of computing power. Nonetheless, to exploit these mathematical, statistical and computational advances to their fullest, concerted effort needs to be made to bridge between these quantitative disciplines and the biological sciences.

Coupled and harnessed, these four forces provide us with the opportunity to answer major questions in environmental and integrative biology. This will ultimately give us greater understanding of, and possible solutions to, a host of problems involving environmental integrity, human development, and health.

September 2000 Workshop Goals

In recognition of opportunities posed by these four forces, the National Science Foundation (NSF) sponsored a workshop on Quantitative Environmental and Integrative Biology (QEIB), organized by Alan Hastings, Peter Arzberger, and Shandelle Henson, that was held at the San Diego Supercomputer Center on the University of California San Diego campus, September 7-9, 2000. Attendees included mathematical and statistical biologists and biologists who considered themselves quantitative, but not necessarily mathematical.

The goals of the workshop were twofold:

1. Identify truly exciting problem areas in environmental and integrative biology that require an integrated approach utilizing mathematics and statistics. What questions absolutely require an integrated approach, and consequently will stimulate simultaneous advances in biology, mathematics, and statistics?

2. Determine how best to achieve the goal of fostering the integration of biology, mathematics, and statistics. What impediments stand in the way of progress? What is the best way to prepare the community of scientists, train individuals, and enhance the collaborations that are required?

The committee created a draft report with recommendations.

December 2002 Workshop

Our world has changed dramatically since that original workshop.

- The events of 11 September 2001 have brought about new research agendas with an urgency to bring mathematics and statistics to analyze biological problems, and have put more focus on international issues.
- The blue print for the human genome was announced (June 2000, published February 2001), and more recently the mouse genome was presented, allowing full genome-to-genome comparison. Several other genome effort results will be announced in the near future.
- There is a growing acknowledgment that collective human activity plays a role in global environmental change and that an understanding of environmental context is critical to understanding human health and risks.
- Funding trends have put greater emphasis on major resource equipment needs of scientific communities as well as increased emphasis on infrastructure to tie these resources together.

Given these changes, a subgroup of the original workshop participants and an NIH observer reconvened to review the challenges of quantitative environmental and integrative biology in this new light and to create a final report. This subgroup recognizes that:

- The interface among biology, mathematics, and statistics is very broad, ranging across all scales of biology and challenging all areas of mathematics and statistics.
- There is a rich history of cross-fertilization among these fields.
- While the expertise of the group brought focus to issues in the field of environmental and integrative biology, we strongly hope that our report will motivate scientists in other areas of biology to develop the interface with mathematics and statistics.
- Finally, we believe that our recommendations can be applied to other areas of the mathematics and biology interface.

We note in particular recent interactions between NSF and NIH to explore the mathematics and biology interface, evidenced by the upcoming (February 12 – 13, 2003) NSF-NIH conference on *Accelerating mathematical-biological linkages* and by the attendance of an NIH observer to this second workshop. We strongly encourage continued interactions between these two agencies for the benefit of science, but more importantly for the health and well being of the citizens of this country.

The Report

This report reflects the input from the original workshop, which was primarily focused on the mathematical/statistical linkages with environmental and integrative biology, and input from the second workshop that has a broader goal to highlight meaningful examples of the interplay between mathematics and all of biology. The report summarizes impediments for moving forward, as well as recommendations to be considered by funding agencies and the community. In short, the report represents the participants' views that the interface between biology and mathematics is rich, the need to foster interactions is great and immediate, and the impact of these interactions is unbounded.

I. Introduction

"People who wish to analyze nature without using mathematics must settle for a reduced understanding."

Richard Feynman

The influence of mathematical thinking in biology has a long history, going back at least as far as the work of Malthus on considering growth rates of populations versus growth rates of food supply. Yet, as shown below, both recent developments and prospects for future progress are reaching new levels of interest and excitement. However, future progress in answering biological questions using quantitative approaches can and must be helped by changes in the 'way we do business' to overcome important impediments. We begin by outlining the main points of our argument, and then illustrate some of the excitement with specific short examples of quantitative biology focusing on particular questions. We then turn to a more thematic discussion of both exciting biological areas, and common mathematical threads that run through recent advances, and what our expectations are for future accomplishments. The common mathematical threads illustrate that mathematical biology is truly a discipline that unifies several areas of biology and mathematics.

After the discussion of scientific aspects, we turn to questions of infrastructure, both in terms of human capital and other areas, and how best to facilitate future progress. A preview of the challenges, the histories of linkages between biology and quantitative fields, current impediments, why there is a sense of urgency, and what our recommendations are follow. Throughout, we have attempted not to be exhaustive, but to be illustrative of what we judge are some of the most exciting and important aspects.

Biological Challenges: Biology is becoming a more quantitative science, a trend that has accelerated and been recently spurred by advances in computing power and data-gathering technologies. Nowhere is this clearer than in issues at the forefront of environmental and integrative biology. These include central questions in natural resource management, environmental monitoring and restoration, genomics and proteomics, genotype-phenotype mapping, management for invasive species, disease transmission in plants and animals, regulation of genetically modified organisms, ecological forecasting, animal behavior, and neuroscience.

Mathematical and Statistical Challenges: Progress on these biological issues requires both that more mathematics and statistics be brought to bear on them and that new mathematical and statistical tools be developed. All the biological questions share some common themes: i) interactions of phenomena at different characteristic spatial and temporal scales; ii) stochastic, or random, forces that affect biological systems; iii) complex, interacting processes that produce data which are difficult to visualize, manipulate, and analyze; and iv) natural variability and observation imprecision that introduces unavoidable uncertainty in our ability to characterize biological processes. Addressing these common themes will require all branches of mathematics and statistics,

from intensive computer simulations that attempt to mimic biological systems to elegant paper-and-pencil theorems that provide conceptual understanding and generality to biological problems.

History of Quantitative Impacts on Biology: Quantitative threads have been woven into the fabric of biology since at least the late 19th century, when Malthus warned of the dangers of explosive human population growth, and Mendel discovered the rules of genetic inheritance of peas in his monastic garden. More recent examples are much more explicitly mathematical or statistical. A short and far from complete list of important biological advances that depended essentially on mathematics or statistics includes studies of the dynamics of molecular motors, the Hodgkin-Huxley model of neurons, the Smith-Waterman technique for sequencing the genome, physiological fluid mechanics models that reveal the workings of the heart, the kidney, and swimming organisms, optimal foraging models that explain animal behavior in an evolutionary context, the breeder's equation in population genetics and evolutionary biology, the role of chaos and the rise of complex dynamics in simple ecological systems, the threshold model in epidemiology, scaling laws in physiology and ecology, and statistical methodologies for experimental design.

Current Impediments: Given the impressive list of past achievements, we expect that quantitative approaches to biological problems will continue to repay us handsomely in formulating and guiding experiments, in managing and interpreting data, and in understanding and predicting the behaviors of complex and variable biological systems. There are difficulties which have slowed progress in fundamental biological questions, both basic and applied. Most biologists know too little mathematics and statistics. Most mathematical scientists know little biology. Interdisciplinary work is difficult to start and to sustain for sociological, financial, and institutional reasons. Nor do present educational institutions adequately prepare sufficient numbers of people to work at the key and exciting interfaces among the biological, mathematical and statistical sciences.

Urgency: Overcoming these difficulties is urgent. New instrumentation and measurement techniques, coupled with a developing computational infrastructure, provide both a flood of data and the promise of ways to deal with them. The biological problems are pressing by their sheer scientific importance and because of their consequences for national health and security. For most of these complex and multifaceted biological problems, mathematics and statistics provide the only framework for formulation, understanding, prediction, and synthesis that offers a hope for advancement. Decisions made today will have a long-term impact. Developing trained individuals does not happen overnight: pipeline delays can take decades.

Recommendations: To address these issues of opportunities, requirements, and impediments, we have made several recommendations, which fall into three categories: research groups, training, and community infrastructure.

Organization of rest of report: We elaborate upon the themes that have been introduced here, beginning with the compelling scientific rationale illustrating the importance of

work in mathematical biology, past, present, and future. We begin with a series of very brief specific examples that highlight recent accomplishments in using quantitative approaches to make substantial biological progress in areas that will also clearly profit from further mathematical and quantitative work. We then turn to broader themes, both biological and mathematical, again focusing on areas where mathematics and statistics have enabled biological progress, and where we judge the potential for future progress to be high. We emphasize that this must be a joint venture encompassing a broad range of mathematical, statistical, and biological techniques, clearly including some we cannot now envision. Despite the rosy outlook, we emphasize that progress could and needs to be more rapid.

II. Compelling Examples

The biological sciences are poised to make great progress as they become increasingly informed by the mathematical and statistical sciences. There are many areas in which exciting work is already underway; however, there are equally many that are on the horizon. In an attempt to illustrate that mathematical advances are pivotal to making significant progress in frontiers areas of the biological sciences, we present several examples in which there is compelling evidence that past advances and success with future problems depend on the infusion of quantitative approaches into biological research. These are compelling reasons to suggest it is appropriate for new mathematical and statistical approaches to join chemistry, physics, and genomics as a “tool of first resort” for biologists. Furthermore, these examples illustrate that the biological, mathematical, and statistical sciences will benefit from additional collaboration and cross training.

Pulse vaccination

How many doses of a given vaccine, administered to what people and on what schedule, allow eradication or control of an infectious disease? Classical models considered only the effects of constant rates of vaccine administration. Inspired in part by the logistical and educational difficulties presented by dispersed populations in developing countries, vaccine programs have turned to *pulse vaccination* strategies where large cohorts of susceptible children are vaccinated in a period of days to weeks. Mathematical models of pulse vaccination show that in addition to its logistical advantages, pulse vaccination may help eradicate disease by driving disease temporarily to extremely low levels and by synchronizing epidemics in different populations, allowing for stochastic extinction of disease in the entire population.

References:

Shulgin, B. L. Stone and Z. Agur. 1998. Pulse vaccination strategy in the SIR epidemic model. *Bulletin of Mathematical Biology* 60:1-26.

Earn, D. J. D., P. Rohani and B. T. Grenfell. 1998. Persistence, chaos and synchrony in ecology and epidemiology. *Proceedings of the Royal Society Series B* 265:7-10.

The Comparative Method

Biologists are often interested in determining whether traits are functionally correlated. For instance, do plants that are pollinated by birds tend to have red flowers more often than those plants that are pollinated by other agents? Showing that a statistically significant correlation between traits exists is enough to show that the traits are causally related. A correlation between traits may have arisen not because they are functionally related but because they are historically (phylogenetically) related. During the last two decades, comparative biologists have developed increasingly sophisticated methodologies known collectively as the comparative method to take history into account. In a recent survey, Freckleton *et al.* note that "Eighty-eight percent of data sets contained at least one character that displayed significant phylogenetic dependence, and 60% of characters overall (pooled across studies) showed significant evidence of phylogenetic association". Phylogenetic history, and hence the comparative method, matters.

Freckleton, R. P., P. H. Harvey, and M. Pagel. 2002. Phylogenetic analysis and comparative data: A test and review of evidence. *Amer. Nat.* 160: 712-726.

Brownian ratchets and molecular motors

How work is performed by molecules within biological cells is fundamental to understanding how cells function. A clue as to how some molecular motors work was given by *Listeria monocytogenes*, a bacterium that causes meningitis. Bacteria penetrate host cells by taking advantage of Brownian motion, exchanging chemical for mechanical energy using the random jostling of molecules. This “Brownian ratchet” works by inserting actin monomers into gaps created as molecules are jostled during polymerization, thus harnessing the forces of Brownian motion in only one direction. Identifying how random Brownian motion could lead to directional movement required complex mathematical models, and equally sophisticated models are needed to understand other cell processes operating at such small scales that intuition is not very helpful.

Peskin, C. S., G. M. Odell, and G. F. Oster. 1993. Cellular motions and thermal fluctuations - the Brownian ratchet. *Biophysical Journal* 65: 316-324.

Community ecology of disease

Lyme disease is a debilitating infectious disease that has emerged in North America in the last two decades in the landscape context of a forested, fragmented, predator-free environment. Understanding, predicting, and ultimately controlling Lyme disease depends on understanding the landscape context, which can only be done through the use of quantitative models that describe the interactions of ticks, woodland-dwelling vertebrates, and humans on a heterogeneous landscape. For example, it may eventually be possible to predict future Lyme risk from the size and spatial pattern of acorn crops, which affect movement of deer and population dynamics of the white-footed mouse (*Peromyscus leucopus*).

Ostfeld, R.S., and F. Keesing. 2000. Biodiversity and disease risk: The case of Lyme disease *Conservation Biology* 14 (3): 722-728.

Management strategies for genetically modified crops

Crops that have been genetically modified (GM) to be toxic to insect pests are now widespread in US agriculture. Use of this technology is threatened by the potential evolution of resistance that could compromise both the investment in and the future value of these crops. Mathematical models have been used to devise management strategies to reduce the risk of resistance evolution, and these theoretically derived strategies underlie US policies for deploying GM crops by farmers.

Anon. 1998. Supplement to: Bt corn & European corn borer: long-term success through resistance management, NCR-602, United States Department of Agriculture.

Conservation genetics and hybridization

Is the genetic integrity of European wolves threatened by hybridization with free-ranging dogs? To determine the extent of genetic mixing (admixture) in a wild population of wolves, Randi and Lucchini have genotyped wolves and dogs at different microsatellite DNA locations. In addition to using standard multivariate ordination to analyze the data, they also used Bayesian admixture analysis that was better at identifying hybrid genotypes. Such methods are essential for detecting admixtures of other species, including numerous endangered species and subspecies that are at risk of loss through hybridization.

Randi, E. and V. Lucchini. 2002. Detecting rare introgression of domestic dog genes into wild wolf (*Canis lupus*) populations by Bayesian admixture analyses of microsatellite variation. *Conservation Genetics* 3: 31-45.

Combating drug-resistant diseases

The development of drug-resistant strains of disease-causing bacteria threatens the current effectiveness of cheap antibiotics. This is particularly true for tuberculosis, which infects 1/3 of the world's population and has killed more people over the last century than any other disease. Mathematical models can help to anticipate emergence and spread of drug resistant strains of diseases, and assess different strategies for reducing drug resistance.

Blower, S. M., P. M. Small, and P. C. Hopewell. 1996. Control strategies for tuberculosis epidemics: new models for old problems. *Science* 273: 497-500.

Invasive species

Tens of thousands of non-native species have been introduced into the United States of America, with more arriving each year. These species can have large impacts on natural ecosystems and lead to direct costs of an estimated \$137 billion annually to the US economy. Mathematical and statistical models can be used to predict what types of species are most likely to be damaging invaders, and what types of ecosystems are most likely to be invaded.

National Invasive Species Council. 2001. Meeting the invasive species challenge: National invasive species management plan. Washington, DC.

Pathogens of forest insects

Caterpillars that defoliate forest trees have major economic impacts. Many such species undergo periodic outbreaks. The forces that drive the outbreaks are still hotly debated; the large spatial and temporal scales on which the outbreaks occur have severely constrained our ability to do conclusive experiments. However, careful small-scale experimentation combined with process-based statistical models have led to recent, rapid increases in our understanding of the roles of viral and fungal pathogens in controlling caterpillar populations. Understanding how variability in space, in time, and among caterpillars scales up to affect large-scale population dynamics will help us decide when and where to target control measures such as introduction of lab-raised pathogens.

Dwyer, G., J. Dushoff, J.S.Elkinton., and S.A.Levin 2000. Pathogen-driven outbreaks in forest defoliators revisited: Building models from experimental data. *American Naturalist* 156 (2): 105-120.

Ecological niche modeling

The geographic range of organisms often reflects their *fundamental niche*, the range of physical conditions in which they can live. Quantitative biologists have applied genetic algorithms, a relatively new statistical technique, to synthesize large data sets that contain the locations and physical conditions where a particular species has ever been found and come up with rules for extrapolating these requirements across space and time. These methods can be used to infer where populations of a given species may be found; to predict the ultimate limits of invading species; or to predict the changes in geographic range with future natural or anthropogenic climate change.

Peterson, A.T., J.Soberon, and V.Sanchez-Cordero. 1999. Conservatism of ecological niches in evolutionary time. *Science* 285:1265-1267.

Biodiversity and ecosystem stability

Human's have transformed ecosystems throughout the world, often replacing diverse natural ecosystems with ecosystems that are species-poor . How are these managed ecosystems likely to perform in the long term when assailed by natural disturbances and further human modifications? Because experiments are limited in both spatial and temporal scales, mathematical models are key to understanding the role of biodiversity in the stability of natural and human-dominated ecosystems.

Loreau, M., S. Naeem, and P. Inchausti. 2002. *Biodiversity and ecosystem function: Synthesis and perspectives*. Oxford University Press, Oxford, UK.

III. Biological Topics and Examples

Biologists are entering a new era in which they require quantitative solutions to large-scale and complex problems. Mathematical advances, particularly in analytical and numerical modeling, statistics, and nonlinear systems analysis, are crucial to find useful solutions and develop predictive tools for biology. Below, we provide an array of examples to illustrate why mathematical/statistical approaches are essential to making advances in our understanding of biological processes from the level of molecules to whole ecosystems.

Throughout these examples, there are at least three common threads. First, mathematics has been well developed to deal with nonlinear models that are deterministic, or with linear models that include stochasticity. We now need advances in dealing with nonlinear stochastic models. Furthermore, because biological systems often seriously violate the assumptions underlying mathematical theories, we need to develop the appropriate notions of stability to characterize observed populations, communities, and ecosystems.

Second, it is imperative that we develop new methods, both statistical and mathematical, for understanding how to deduce information from biological data sets. For example, to advance fundamental understanding of principles governing population dynamics, new approaches are needed to obtain acceptable quantitative fits of biological models to data. How complex must a model be in order to reproduce a given set of data? What data are required to validate a given model? To what degree does integrated behavior of the model reflect the influence of internal model features representing specific biological mechanisms?

Third, much more work is needed to characterize variability across scales of time and space. Can activities distributed across large spatial and temporal scales be understood on the basis of knowledge gained from brief, spatially restricted, experimental observations? Ecological communities consist of many interacting species just as neuronal networks consist of a “population” of interacting neurons. What is the appropriate way to simplify these systems, or, on the other hand, what are the appropriate mathematical tools to use when considering a large number of strongly interacting species or cells?

A. Community ecology of disease

Ebola, hantavirus, bubonic plague, Lyme disease, West Nile virus, rinderpest, and canine distemper virus are all examples of diseases that affect focal host populations by repeated transmission across species boundaries (e.g., Osterhaus 2002; Schmid and Ostfeld 2001; Yates et al. 2002). To understand, predict, and control the dynamics of these diseases, we must understand the ecology of the reservoir host communities that maintain and amplify them, and the ecology of contacts between these reservoir communities and the focal, or receiving, species. Empirical work is necessary to establish the basic facts of individual-level infection and immunity, as well as the patterns of animal behavior and movement. Quantitative theoretical frameworks play an essential role in guiding data collection, estimating transmission rates within and between species (which are almost impossible to

estimate except in a modeling framework), and understanding the observed patterns of disease. Furthermore, models can be used to assess ways to control disease outbreaks, such as vaccinating, culling, or treating particular reservoir species.

Historical example: The Serengeti ecosystem, one of the most spectacular biological communities in the world, was devastated by the introduction of rinderpest from central Asia in the late 19th century. The cascading effects of lowered ungulate population sizes permanently changed the vegetation structure of east Africa, and may have made conditions more suitable for the invasion of tsetse fly vectors of sleeping sickness, further modifying the biological and human communities of the region. Although these historical effects are still not completely worked out, it is clear that rinderpest, which like the related measles virus is subject to extreme "boom and bust" dynamics, could not maintain itself within the diverse community of wild ungulates in the Serengeti, but instead was maintained by stable populations of domestic cattle surrounding the wild herds. With the development and successful deployment of rinderpest vaccine in domestic cattle, the rinderpest epidemic has been brought under control and ungulate herds have increased to near historic levels, although some community-level effects of disease may be permanent.

Future challenges: Many diseases depend on the dynamics of a community of animals that are just as complex, if not so well worked out, as the Lyme disease example. Ebola spreads among apes as well as humans and is maintained by an as-yet unknown animal reservoir; rinderpest thrives temporarily in the diverse ungulate herds of East Africa, but can only persist in domestic cattle herds; and bubonic plague appears to persist in rodent populations by jumping sporadically among subpopulations (Keeling and Gilligan 2002). In many ways we are limited by the difficulty of gathering data on disease in wildlife populations, but the other limiting factor is our ability to make sense of the data we do have. We must develop modeling frameworks for multi-species epidemics, possibly by extending existing compartmental models for host subtypes to handle multiple species. We must find better ways of analyzing nonlinear multi-species models beyond the existing techniques of (a) linearizing many-species models (Koopman et al. 1989) or (b) doing exhaustive nonlinear analyses of models with no more than three species (Begon et al. 1992). We must adapt methods for estimating transmission rates within species (Bjørnstad et al. 2002; Hone et al. 1992; Swinton et al. 1998) to the much more difficult multi-species case. However, the biggest challenge in this area is how to use the sparse data we have. We need techniques to leverage existing data, for example, by using allometric scaling models to constrain the demographic and life history parameters of different species (DeLeo and Dobson 1996), or by using Bayesian methods to include information from other systems, and combine all of these data in a way that accounts for our uncertainties. Only with these tools in hand can we know how effective vaccination, culling or treatment will be, and where and when to apply them.

B. Evolution of virulence

Diseases such as cholera emerge as sudden outbreaks, showing marked variation through space and time both in their *incidence*--the number of individuals infected in a

population--and in their *virulence*--the damage a pathogen does to its victim in the course of completing its life cycle by replicating and infecting other hosts. Epidemiologists have long studied how incidence of viral, bacterial, and metazoan parasites can fluctuate in response to changes in infectiousness and transmission which are in turn driven by social, economic, and medical trends. More recently, they have begun to appreciate that virulence is also dynamic, evolving rapidly in response to the same factors that drive pathogen numbers.

Historical example: The “classical dogma” of epidemiologists was that pathogens always evolve in the direction of lower virulence, eventually becoming harmless symbionts. Evolutionary models have led epidemiologists to abandon this simple assumption, replacing it with a much richer view that incorporates the effects of within-host competition, tradeoffs between transmission and virulence, and coevolution between pathogen offenses and host defenses. The tradeoff theory, which focuses on the pathogen’s tradeoff between maximizing its replication and preserving its host’s viability, has strongly suggested that public health experts can manage the virulence as well as the incidence of disease by taking actions that lower transmission rates and shift transmission to less damaging modes, such as from water-borne to direct contact. Simple mathematical models have been essential in formulating and understanding the conclusions of the tradeoff theory (Ewald 1993, Ewald 1995, Gandon et al. 2001).

Future challenges: The tradeoff theory focuses on one particular aspect of host-pathogen coevolution, and it takes a simple phenomenological view of the tradeoffs constraining pathogen life histories. More sophisticated mathematical analyses have explored the balance between the effects of selection within and between hosts (Frank 1996); the effects of spatial structure (Rand et al. 1995, Boots and Sasaki 1999); and the connection between population dynamics and evolution (Lenski and May 1994). Much work remains in formulating and developing these more complex mathematical models, and in finding ways of analyzing them. Spatial disease evolution models in particular have connections to *all* of the mathematical challenges (nonlinear, stochastic models with spatial or network structure) that are identified elsewhere in this document.

However, matching existing models with data on the evolution of virulence represents a level of challenge beyond that of unifying and extending existing models. Empiricists in this field have prospected for qualitative virulence factors in the genomes of pathogens, an approach that poorly matches the quantitative framework of most interest to theoreticians (Reid et al. 2000). Theoreticians must work to build models of qualitative genetics, and more empiricists must work to establish the mechanistic basis for continuous variation in virulence (Mackinnon and Read 1999a, 1999b). A similar gulf exists between theoreticians and immunologists, who must hammer out a compromise between the theoreticians’ preference for simplifying immune states down to a single oversimplified axis of immunocompetence and immunologists’ insistence that every cell subtype has a unique role that must be reflected in a realistic model (Segel 2001). How do we make our models “as simple as possible, but no simpler”? Quantitative biologists must come to grips with a complex, stochastic, poorly observed system; to do so they will need new analytical tools that incorporate some realistic details, allow for formal

matching with data, but still preserve our ability to understand (and therefore generalize) the underlying dynamics of the system.

C. Population size, inbreeding and genetic variation

"Darwin proposed, and modern evolutionary biology affirms, that evolution is based upon variation in the characteristics of organisms." (Futuyma 1998, p. 231). Without genetic variation, populations would be unable to respond to either natural or artificial selection. Understanding the forces that affect genetic variation is important to the basic science of evolutionary biology as well as to the applied sciences of animal and plant breeding and conservation biology.

Historical Example: Population genetic theory, first developed by Sir Ronald Fisher, JBS Haldane and Sewall Wright, demonstrated how various evolutionary and demographic forces will affect levels of genetic variation in a population. While mutation increases genetic variation, random genetic drift removes it. The strength of drift is proportion to the inverse of the effective population size (Wright 1931). Thus, population genetic theory predicts that genetic variation within a population should increase with population size. If population sizes fluctuate over time, the long-term average effective population size is more sensitive to the lower population sizes than the higher ones. For instance, consider an insect population that over the course of each year goes through three generations with population sizes of 10, 100 and 1000. Were it to continually fluctuate between these three population sizes, its effective population size would be around 30-- far lower than the arithmetic mean of 370. Thus, periodic bottlenecks in population size will sharply reduce the effective population size and hence genetic variance.

Current Challenges: In contrast to these expectations, some laboratory studies have shown a surprising and counterintuitive result: morphological variation sometimes increases when insect populations go through bottlenecks. Moreover, the genetic basis underlying mating systems can be drastically altered when populations go through bottlenecks (reviewed in Meffert, 2000). Such changes can also lead to the evolution of premating reproductive isolation between geographically isolated populations and thus to the formation of new species. The diversity of cichlid fish from African rift lakes is a possible example of bottlenecks leading to changes in mating behavior and eventually speciation.

Evolutionary geneticists explain these counterintuitive results of bottlenecks as a consequence of rapid reductions in population size converting non-additive genetic variance into additive genetic variance, upon which natural selection can operate (Goodnight 1988; Willis and Orr 1993). We know very little about the exact nature of the genetic architecture for nearly all morphological or behavioral traits but there is good evidence that most traits have complex genetic architectures, allowing for non-additive genetic variance. We also do not know much about the theory of bottlenecks and their effects on different types of complex genetic architectures. Prior to the late 1980s, this

theory has been largely verbal, rather than analytical, descriptive rather than predictive. Recently, while substantial progress has been made toward more rigorous models, the models generally consider the genetic architectures in black-box quantitative-genetic terms and ignore the actual genes involved.

Moreover, the population scenarios modeled and tested under laboratory settings have been rather simplistic. No attempt has been made to consider the effects of local bottlenecks in spatially structured populations. Such population structures are very difficult to include in genetic models, even when the genetic bases of the traits under consideration are simple. The complexity of both the genetic architectures and the population structure presents a dual challenge, which will require new advances in population genetic theory. Like much of modern quantitative biology, this theory will have to combine analytic models that allow us to grasp the fundamental phenomena at work with computational models that allow us to incorporate more of the true complexity of the biological systems in question. The results of such studies, however, will greatly advance our understanding of the basic evolutionary biology of speciation as well as our ability to conserve genetic diversity and evolutionary potential in threatened and endangered populations.

D. Modeling the evolution of correlated characters

Recent discoveries in genomics and proteomics have demonstrated that the link between genotype and phenotype is much more complex than many had considered. However, complexity is nothing new to physiological geneticists and evolutionary biologists. Case in point: evolutionary biologists and before them, animal and plant breeders have long recognized that most traits are parts of correlated suites of characters. For instance, birth weight and gestational length are often correlated in many species. Selection, whether natural or artificial, that acts upon one trait can also change other traits that are not directly under selection.

Historical example--Evolutionary quantitative geneticists have developed tools to make predictions about the short-range evolution of traits that may be correlated with others. (Lynch and Walsh 1998). One of the most fundamental of these tools is the so-called “multivariate breeder’s equation”, $\Delta z = \mathbf{G}\beta$: the change in one trait (Δz) is equal to the selection gradient acting on it and other traits (β) times the additive genetic variance-covariance (\mathbf{G}) matrix (Lande and Arnold 1983) (the multivariate breeder's equation is an extension of the simple univariate breeder's equation that has long been used as a guideline by plant and animal breeders seeking to select artificially for economically valuable traits). The \mathbf{G} matrix describes the patterns of genetic variances of traits and the genetic covariances between traits. Depending upon details of the selection gradient and the \mathbf{G} matrix, it is possible that a trait may evolve in the opposite direction from the direction it would evolve in were it not correlated with other traits. For example, Conner and Via (1992) examined body size evolution in flour beetles of the genus *Tribolium*. Selection operating on one character at a time would favor increased pupal weight but decreased male width. Because these characters were positively correlated, however,

pupal weight increased slightly and male width substantially increased—contrary to the expectation had only one of these traits been under selection.

Current challenges: The breeder's equation has proven useful in making short-term predictions about the evolution of correlated suites of characters. But can it be useful for making longer-term predictions? (Barton and Turelli 1989) The extent to which the breeder's equation is useful for long-term predictions depends upon the stability of **G** matrices because the **G** matrix itself can evolve. If **G** matrices were stable or if their evolution could be predicted, then such long-term predictions would be possible. Accordingly, some have argued that “quantitative genetics provides one of the most promising frameworks with which to unify the fields of macroevolution and microevolution” (Steppan *et al.* 2002).

To address the stability and the evolution of **G** matrices, evolutionary quantitative geneticists have recently developed techniques to compare the **G** matrices among distant populations and/or closely related species (e.g., Arnold and Phillips 1999; Begin and Roff 2001). For instance, Arnold and Phillips (1999) compared the **G** matrices of scale patterns in populations of garter snakes. How does one compare **G** matrices? Because each element in the matrix is often not independent, this is a non-trivial statistical challenge. Several approaches have been suggested. For instance, Phillips and Arnold (1999), building on work by Flury (1988), have suggested using hierarchical randomization tests to compare **G** matrices. In contrast, Roff (2002) has suggested a Multiple Analysis of Variance (MANOVA) approach. Each test has its own advantages and disadvantages (Steppan *et al.* 2002; Roff 2002).

Regardless of the statistical approaches used, the evolutionary quantitative genetic studies show that **G** matrices have changed between closely related species (reviewed in Steppan *et al.* 2002). The questions are: How fast and in what directions? Laboratory studies of *Drosophila melanogaster* have demonstrated that the shape of **G** matrices can be altered in non-trivial ways by inbreeding alone (Phillips *et al.* 2001). The challenges are two-fold: (1) Development of theory that takes into account the evolution of **G** matrices for making long-range predictions. (2) Further development of statistical techniques that allow one to determine parameters from empirical studies to use in the above theory. Methodologies developed to meet these challenges is likely to have large spin-off benefits in applications to comparative proteomics and functional genomics.

E. Management of renewable resources

As the human population has grown, human impacts on the resources that we use, such as fisheries and forests, have continued to grow. Recent developments, such as the closure of the groundfish fishery off the west coast of the United States, and the closure of parts of the Grand Banks off the northeast United States to certain kinds of fishing are illustrative of the kinds of difficulties that are likely to increase in the future. Although many of the same ideas outlined below apply to many renewable resources, we highlight several fisheries issues for illustrative purposes.

Historical example: There are basic and well developed applications of mathematical and quantitative approaches to the management of fisheries. In this case, not only do mathematical and biological concepts enter, but economics must also play a central role (Clark, 1990). Further, this field is one where attention to specific assumptions are essential. For example, the most basic concept is that of maximum sustainable yield, which is derived from simple mathematical ideas from calculus, and expresses the largest harvest rate possible from a population in terms of the basic parameters in the simplest descriptions of density dependent population growth. This concept is useful in illustrating the concept of overfishing, but is also important because of its shortcomings. It does not incorporate the important role that economics and stochasticity play in the dynamics of a managed resource both of which can greatly change the results (Clark, 1990).

Future challenges: In response to past shortcomings in some fisheries management, and to dealing with other conservation goals, the concepts of marine reserves, areas without fishing, have been proposed, and are currently being implemented. The simplest analyses of this approach (e.g., Hastings and Botsford, 1999 and Botsford et al., 2001), based again fundamental ideas from calculus and also from the use of integro-difference equations, illustrate how to compute sustainable yields under a specific set of assumptions and how to determine sustainability of a population for very specific assumptions about the life history. Yet, these are analyses which are still very simple and make a number of specific assumptions, and really should only serve as illustrations of important principles.

A more realistic understanding of the spatial management of renewable resources (Sanchirico and Wilen; 1999, 2001) requires an integration of economic and biological approaches in a spatial context, an inclusion of variability, and an examination of a large number of kinds of fisheries that have not been covered by the models already analyzed. Moreover, because fishery ‘organisms’ typically have dispersal phases in which there are complex interactions between biology and the physical movement of water (which represents a substantial mathematical and computational challenge on its own), there is much room for improved understanding of this important issue. Predictions will, of course, depend on good estimates of current biological conditions and population sizes, so further developments of statistical approaches will also be essential.

F. Ecosystems science and large-scale ecology

Many of today’s most pressing problems are regional or global in nature including for example, the effects of land cover and land use, carbon flow in ocean and atmospheric systems, the effects of climate change on species distributions, and the protection of ecosystems and humans from threats to bio-terrorist activities. Solving these problems is not trivial because the vast majority of empirical work has been done at fairly small scales (temporally and spatially). Indeed, it is often impractical or impossible to investigate these problems at regional scales. Further, the task is not trivial because

ecosystems are composed of many interacting parts that can exhibit very complex behaviors and may be sensitive to initial conditions and context.

Historical example: Mathematical and statistical tools are central to enhancing our understanding of large-scale systems and include, for example, cybernetics, control theory, information theory, network theory, thermodynamics, self-organization theory, emergence and hierarchy theory, and/or power laws (Muller 1992, 1997). A very compelling example of the how the application of mathematical theory to important global-scale ecological problems comes from the work of Allen, Brown, Gillooly (2002). Historically, one of the most prominent but least understood patterns in nature is the well known latitudinal gradient from poles to the equator in biodiversity. All major groups of terrestrial, freshwater, and marine taxa display latitudinal gradients in biodiversity however the principles underlying the origin and maintenance of these patterns have been illusive. Allen et al use a theoretical framework to explain gradients in species diversity in terms of energetics. They derive a model that quantitatively predicts that species diversity can be predicted from the biochemical kinetics of metabolism. These results established a thermodynamic basis for the regulation of species diversity and the organization of ecological communities.

Future challenges: There are many, many challenges that remain for making large-scale ecology a more predictive and quantitative science (Pace and Groffman, 1998). These challenges are extremely important as many of the world's most pressing problems depend on linking basic research at the ecosystems or global scales with applied and management-oriented science. Pressing challenges are numerous and we provide several for illustrative purposes. First, a major challenge comes from the problems that arise in relation to the use of large and distributed environmental data sets. We need to develop comprehensive solutions to informatics issues, data mining, and synthesis. Key issues arise such as how to combine different level of information from desperate sources that differ in their levels of reliability. Mathematicians concerned with the field of data fusion (a formal framework that expresses the means and tools for the alliance of data originating from different sources) may offer insights.

Second, an important use of mathematical modeling is to predict responses in untested situations e. g., to predict future outcomes. The challenge of ecological forecasting is to develop a predictive science to forecast how the function and structure of environmental and organismal systems evolve... to forecast multiple states over multiple time and spatial scales (Clark et al. 2001). Many problems arise including: linking multiple-multiple models or sub-models, scaling (up/down), and combining qualitative and quantitative information.

Third, recent workshops and publications underscore the need to reduce and specify levels of uncertainty if forecasts are to be credible and useful. This issue is not unique to ecological forecasting or large-scale ecological modeling; statisticians and scientists from a variety of disciplines are working on general methodologies for the inclusion of probabilistic outcomes in formal model structures so that forecasts can be couched in likelihood terms. The use of probability distribution functions (pdf's) or Bayesian

approaches will likely increase in the near future, particularly as computing languages are extended to more easily propagate pdfs through linked models.

G. Scaling from individuals to ecosystems

Models that describe how individual organisms acquire energy and materials, and how they use them for survival, growth and reproduction, have the potential to link ecological processes at various levels (Kooijman 2000). Dynamic physiological models that describe the flows of energy and elemental matter through individuals, and models that determine how these flows scale-up to higher organizational levels, have several different applications. These models can contribute to life history theory, provide strong constraints on the dynamics of populations, and form the foundation for analytically and computationally tractable models of ecosystems.

Historical example: Biological oceanographers have long used physiologically based models such as the Droop model, which reduces maximum growth rate based on the internal nutrient concentration within plankton cells, to scale biogeochemical dynamics up from the functioning of single foraging plankton to the biogeochemical balances of entire ocean cells; these are then embedded in three-trophic level, nutrient-phytoplankton-zooplankton (NPZ) models and incorporated into large-scale computational mixing models to determine the temporal and spatial patterns of global biogeochemical fluxes. Although debate over the appropriate level of model complexity continues (plankton dynamics are complicated by biochemical variation among different plankton guilds and by successional changes in size distribution) the simpler models are routinely embedded in large-scale climate models to predict the effects of plankton growth on atmosphere-ocean carbon balances, and have recently been adapted to study phytoplankton blooms (Sommer 1991, Hurtt and Armstrong 1999, Huppert et al. 2002).

Future challenges: Scaling of biogeochemical fluxes in terrestrial systems has proved much harder. While ecosystem ecologists often scale “from leaf-to-globe” in one or two steps (Ehleringer and Field 1993, Fitz et al. 1996), population and community ecologists have insisted that variability within and among populations and species must be incorporated in this scaling process. Such scaling is biologically and mathematically non-trivial. Even scaling from leaves to individuals, functional ecologists have found it difficult to develop general models that can predict plant responses to increases in CO₂ and temperature (Bernacchi et al. 2000). The problem gets even harder when plants balance their needs for multiple nutrients; interact with other plants, soil microbes, or herbivores; respond to their environment by acclimating (showing phenotypic plasticity); or respond by changing their development (showing ontogenetic shifts). We need both data, and models that can incorporate the data, for the effects of spatial variation in populations caused by disturbance and environmental variation at a within-grid spatial scale (Moorcroft et al. 2001); successional and climate-driven shifts of species composition and functional guild composition within a given habitat; and movement of species range limits when climates change rapidly (Pitelka et al. 1997).

The mathematical, statistical and computational challenges here are formidable. We must come up with ways for reliably constraining large models with continental-scale databases, and for estimating the future behavior of species assemblages in a changing climate. More fundamentally, we need to find ways that models can be sped up to the point where they can be coupled with global-scale simulation models, through some combination of computational advances (algorithmic and parallel-computation techniques) and mathematical advances that aggregate the details of models while retaining quantitative accuracy in physical and biogeochemical properties at a larger scale.

The critical biological question, which can only be answered by exploration, is whether the signature of individual interactions with the abiotic environment is reliably transmitted up multiple levels of organizational scale, or whether the frequency-dependent and idiosyncratic nature of community interactions blurs these regularities at the ecosystem scale. With sufficient attention to both the mathematical rules of scaling and to the regularities observed in the way that broad classes of organisms have solved their ecological problems (Reich et al. 1997), we should be able to develop a new class of tools that greatly increase our power to understand and predict biological dynamics across a range of scales.

H. Neuroscience

Theoretical, mathematical, and computational approaches to questions in neuroscience are now recognized as valid by experimental physiologists. The major neuroscience journals (Journal of Neuroscience, Journal of Neurophysiology, Neuron) now publish serious modeling papers. Neurobiologists have been quick to recognize that often the sum is greater than the parts and that theoretical approaches are necessary to make the jump across scales (e.g. from channels to spiking or from neuronal connectivity to behavior.) Courses in the subject are becoming more popular as the need to train a new generation of theoreticians increases. The tools from dynamical systems, information theory, and pattern formation (Ermentrout, 1998) will continue to play a role in our understanding of the nervous system.

Historical example: In the 1950's Hodgkin and Huxley set out to understand the propagation of action potentials in the squid giant axon. They perfected the voltage clamp method which is now routinely used to dissect the voltage-dependent dynamics of ion channels. From these data, they constructed a four-dimensional differential equation for the evolution of the action potential in this axon. Furthermore, they developed a partial differential equation in order to study the propagation of action potentials down the axon. By transforming to traveling coordinates, they reduced the partial differential equation to a five-dimensional ordinary differential equation which they solved numerically by a shooting method. Their physiological and theoretical work garnered them the Nobel Prize. The fallout from this beautiful formalism continues today. Almost all biophysically based models of individual neurons are based on the formalism that they

developed. A good deal of very nice mathematics has been developed to rigorously study this class of equations ranging from geometric singular perturbation (reviewed in Rubin and Terman, 2002) to the study of coupling between oscillatory neurons (reviewed in Kopell and Ermentrout, 2002).

Future challenges: While the analysis of single cells and even networks has progressed very nicely, there still remain many important questions. At least two of these challenges are related to the transient nature of the dynamics in neurons and brains. Most of the mathematical analysis that has been done to date presumes stationarity both in the inputs to the neurons as in their intrinsic properties. There will be a need to develop some mathematical methods for dealing with the transient nature of inputs to the nervous system that goes beyond simple periodic forcing. More importantly, most modelers assume that the parameters such as the intrinsic membrane conductances and the synaptic conductances are fixed. However, it has now been established that there is plasticity at many time scales both in the intrinsic dynamics (Turrigiano and Nelson) and in the connections (Bi and Poo, 1998). Thus a major challenge in modeling is how this plasticity affects the behavior of single neurons and networks of neurons in the presence of stimuli. At some level, it is possible to take advantage of the multiple time scales and produce a hierarchy of models where the averaged results of one step are used in the next. Another important challenge is in the feedback between perception and action. That is, most theories and modelers treat the sensory system and the motor systems as separate. However, it is now clear (see for example, Kleinfeld et al, 2002) that the motor output influences the sensory input forming a massive sensorimotor loop. The computational advantages and consequences of these loops remain to be explored.

IV. Mathematical and Statistical Topics and Examples

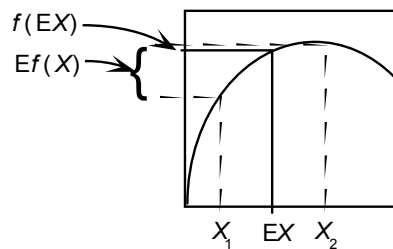
This report emphasizes the benefits that the fields of mathematics and statistics can bring to biology, but there are reciprocal benefits as well. Biological questions have historically opened up new areas in mathematics and statistics. For example, in addition to his invention of a whole new field of statistics (analysis of variance) for interpreting the results of biological experiments, Sir Ronald Fisher also opened up new areas of mathematical analysis through his interest in traveling waves of invasion of novel genes. The following sections explore quantitative biology from a mathematical, rather than a biological, point of view, although the emphasis is still primarily on solutions to biological rather than mathematical problems.

Many of the problems addressed below are the same as those in the biological examples given above, but organized by mathematical themes rather than biological problems. The ubiquity of stochastic, nonlinear, spatially extended systems in biology has always been known, but these systems have been so intractable in the past that most mathematical results that were obtained were too hard to apply to real systems. The combination of advances in mathematics, statistics, and computation, and the new synergies of these fields, is now allowing quantitative biologists to tackle these problems rather than focusing only on those aspects of biological systems that can be understood with deterministic, linear, homogeneous models.

A. Stochasticity

Ubiquitous noise in biological systems makes stochastic methods central to modeling efforts. Stochasticity is present at all levels in environmental and integrative biology, ranging from genetic mutations through individual behaviors, movement, demographic rates (survival and reproduction), population sizes, resource availability, community composition, rates of nutrient fluxes, up to the multitude of environmental drivers that affect biological processes. Identifying the underlying processes that affect biological systems requires explicit accounting of the stochastic nature of the system dynamics. This accounting is also needed to forecast changes in biological systems.

Historical example: A common theme in many biological problems is that averaging among components of a system depends upon system nonlinearities. This is described by Jensen's equality (Jensen 1906), which states that the average of a nonlinear function does not equal the function of the average. Specifically, for any concave function f of a variable X , the expectation of $f(X)$, denoted $Ef(X)$, is less than the function of the expectation of X , $f(EX)$; i.e., $Ef(X) < f(EX)$, as illustrated in the figure. Although abstract, this relationship underlies numerous phenomena. For example, Jensen's inequality can explain why poor people are more likely to gamble than wealthy people, and why dollar-cost averaging is an effective investment strategy. Because nonlinearities occur throughout biological systems, the average behavior of biological systems depend strongly on their nonlinearities (Welsh et al. Ruel and Ayres 1999).



The simple relationship of Jensen's inequality can go a long way to explain one of the central questions in ecology: Why is there so much biodiversity? What allows the estimated 10 million species on earth to coexist? Simple laboratory experiments demonstrate how hard it is for similar species to coexist (Lotka 1925, MacArthur and Levins 1967), thus suggesting that the variability of natural systems is responsible for the coexistence of similar species. Recent theoretical advances have shown how spatial and temporal stochasticity can lead to coexistence of competing species that in the absence of stochasticity would not coexist (Chesson 1985, Ives and May 1985). This occurs because competition is inherently a nonlinear process: when population densities are low, populations grow rapidly, whereas when population densities are high, populations grow slowly or decline, making the population growth rate, $f(X)$, a concave function of the population density, X . When averaging over spatial or temporal variability, this decreases the average population growth rate of any given species, thereby depressing its own density and facilitating the coexistence of competitors.

Future challenges: Despite the ubiquity of stochasticity, it is too infrequently incorporated into models of biological systems. Techniques are needed to understand the

interactions between nonlinear processes and stochasticity. A particularly fruitful area will be stochastic, nonlinear dynamical systems (Tong 1990), such as the dynamics of individual species (Bjornstad and Grenfell 2001). Key problems include mechanistic modeling of mixtures of various kinds of stochasticity (e.g. environmental vs. demographic) (Cushing et al. 2003) and cataloging the types of dynamic phenomena possible in stochastic nonlinear dynamical systems. Stochastic systems can show complicated mixtures of the phenomena found in deterministic systems, including multiple attractors and unstable sets (Henson et al. 1999). There are also many issues surrounding the structure of stochasticity; environmental drivers responsible for stochastic fluctuations in ecological systems, for example, are not simply “white noise,” but instead change in sometimes complex ways through time and space (Steele 1985).

For large simulation models of environmental systems, incorporating stochasticity gives rise to analysis and interpretation issues. How can the effects of multiple sources of stochasticity be separated in the model output, and at what point does computational capacity limit analyses? Environmental modeling often involves large numbers of processes operating on different temporal and spatial scales (e.g., Gentile et al. 2001), and as yet there are no methodologies for synthesizing the role of stochasticity in these systems.

Finally, one of the major challenges of the mathematical analysis of stochastic systems – indeed of any mathematical analysis – is to produce simple generalities and “rules of thumb” that transcend the details of the mathematics. Ultimately, mathematical models must benefit biologists by clarifying the problems they address, and the yardstick of mathematical modeling in environmental and integrative biology must be the insight it gives into biological systems, rather than the elegance of mathematical solutions.

B. Spatial processes

Environmental and integrative biology cuts across a wide array of spatial scales, and theoretical approaches that take into account these widely varying spatial scales are necessary for an understanding of the biological questions. The use of reaction diffusion equations generally has proved to be an extraordinarily powerful tool for developing insights into spatial biological processes at scales ranging from the cellular level to the ecosystem level. These equations can be used to connect processes at one spatial scale to those at a larger spatial scale, leading to fundamental new insights. More recent advances include the use of integro-difference equations, and approaches which look at developing analytical descriptors for the behavior of stochastic spatial models.

Historical example: In 1952 Alan Turing developed his theory of the generation of pattern in systems of reaction diffusion equations, now known as Turing instabilities. One underlying assumption is that there is one species that is autocatalytic (so an increase in that species fuels further increases in that species), or as an ecologist would phrase it, exhibits positive density dependence. The second set of assumptions is that the controlling species has a higher movement rate than the species that can potentially increase. Essentially the controlling species diffuses away from outbreaks, thus allowing the development of spatial pattern. Initially applied to questions of morphogenesis and

development, which in more than one dimension relates to classic mathematical problems for eigenvalues, this theory was then applied to ecological problems in general (Levin, 1974). More recently, mathematical approaches related to this theory have been tied to specific ecological systems such as the western Tussock moth and its parasitoids (Hastings et al., 1997), where the models explain apparently anomalous spatial distributions of the host species, thus answering basic questions about spatial distributions of abundance.

Future challenges: Understanding the dynamics of stochastic spatial systems, systems with a multitude of spatial scales, and systems with underlying heterogeneity present fundamental mathematical challenges. From a biological point of view, questions such as the performance of moderately-sized neuronal networks (Pinto and Ermentrout 2001a,b), coexistence in ecological communities such as forests, and where to site marine or terrestrial reserves along heterogeneous coastlines and landscapes, provide motivation for the development of new mathematical approaches.

For deterministic models, much more attention needs to be paid to the development of methods for gaining an understanding of the dynamics of nonlinear spatial systems described by reaction diffusion equations, or integro-difference equations, or perhaps more general treatments (e.g., Weinberger et al., 2002). Methods will need to be developed to provide analytic approximations to describe the dynamics of stochastic spatial models (building upon current work such as Bolker and Pacala, 1997) that can be applied to more complex systems. Further understanding of the dynamics of coupled oscillators (see Pinto and Ermentrout, 2001a,b) will provide insights not only into the dynamics of neural networks, but of coupled systems at other biological scales ranging from the population to the ecosystem. Determining the impact of heterogeneities at small spatial scales on the performance of ecological and other systems at larger spatial scales can depend on the use and further development of methods based on homogenization (e.g., Powell and Zimmerman, 2002), which provides an appropriate way to look at spatial averages of dynamics.

C. Networks

Many dynamic biological processes across a wide range of ecological scales are easily represented as dynamical networks, or as dynamical systems that occur on top of a network: systems of gene regulation (Frank 1999, Johnson and Porter 2000), interacting enzyme cascades (Ravasz et al. 2002), epidemics in human societies (Keeling 1999), and food webs (Dunne et al. 2002) are just a few examples. Ecologists have studied the network properties of food webs since the 1950s, but research into the mathematical properties of biological networks at every level of organization has burgeoned in recent years.

Historical example: John Tyson constructed a nonlinear differential equation model representing the majority of the network of biochemical pathways occurring within yeast cells (Tyson et al. 2001). Each node in the network represents a particular enzyme or

reagent; the concentration-dependent rates of reactions that generate and break down products are the links. Experimental data determines the structure of the network--the connection pattern and strengths of the links. The model correctly predicts the response of the system to novel perturbations such as removing a link--biologically, creating a knockout mutant for a particular biochemical pathway. The model highlights critical reactions (network connections) that were not previously thought to be important. Such a theoretical approach is the only practical way to understand the emergent properties of such a network, which cannot be tested empirically without an exhaustive series of experiments that grow exponentially with the size of the network.

Future challenges: Graph theory is an old field of mathematics where biological applications are driving new advances. Mathematicians are supplementing well-known classes such as random or Markovian networks with new classes of networks such as “small world” networks (where most nodes are locally connected but a few have long-range links) (Watts and Strogatz 1998) and “scale-free” networks (where node degree follows a power-law distribution: most nodes are connected to only a few neighbors but a few nodes are connected to many neighbors: Albert and Barabasi 2002). In addition to knowing the mathematical properties of such networks, biologists will need to develop new statistical methods to supplement existing methods from sociology for reconstructing the structure of a network from observations on individuals (Morris 1993). Perhaps the biggest open mathematical challenges, however, are in understanding the *dynamic* properties of networks that cannot be derived from static measures of their structure. Networks may have evolved dynamically by the non-random addition and subtraction of links to their current state, as in the case of food webs (Dunne et al. 2002); they may continue to change over the period of observation, as in the case of contact networks for sexually transmitted disease (Altmann 1995); or they may be relatively static, but form the substrate for dynamic changes in the states of their nodes, as in the case of measles passing among school children or foot-and-mouth disease virus epidemics passing among farms (Keeling 1999, Keeling et al. 2001). All of these cases require mathematical, statistical, and computational techniques well beyond our current knowledge base before we can fully understand the emergent properties of the biological networks concerned.

D. Connecting models and data

Perhaps the most dramatic change in quantitative environmental biology in recent years has been the burgeoning progress towards rigorously matching the nonlinear, multidimensional, and spatial models used by environmental and integrative biologists to data. Although there is a long tradition of analyzing biological models that are parameterized with values estimated from natural systems, statistically fitting complex models to data is conceptually different and more sophisticated. Fitting a model to data and then validating the model against independent data sets provides a direct test of the ability of a model to describe the system. Once fitted, the model can be used to make predictions – complete with estimates of uncertainty in the predictions – for future changes in the system. The ultimate goal of fitting models to data is opening up the large body of theory in environmental and integrative biology to direct test against data.

Historical example: An excellent example of a program that links theory and data is collaborative work on the population dynamics of flour beetles, *Tribolium*, in laboratory microcosms (Costantino et al. 1997, Dennis et al. 2001). In this work, a model for the population dynamics of flour beetles was developed based upon reproduction by adults and cannibalism on immature stages. Careful studies involving the model, controlled laboratory population experiments, and statistical techniques identified many nonlinear phenomena in population data, including equilibria, cycles, transitions between dynamic regimes (bifurcations), multiple attractors, resonance, basins of attraction, saddle influences, and stable and unstable manifolds.

A specific result of the model is that chaos occurs over a range of cannibalism rates, with less exotic dynamics occurring at low and high cannibalism levels. By performing experiments manipulating cannibalism over its entire range, Costantino et al. (1997) witnessed the predicted degeneration of simple dynamics into chaos and the subsequent recovery. This gives the strongest type of evidence for the existence of chaos in ecological systems, because it shows the direct correspondence between model and real dynamics over a range of dynamical patterns. This example also illustrates how experimental problems can generate novel theoretical advances, since it required new techniques for fitting nonlinear models to stochastic data sets.

Future challenges: Because biological systems are complex, models of biological systems are also complex, and matching models and data is a challenge. Fundamental to fitting models to data is separating the “deterministic skeleton” describing the interactions among components of the system from the stochastic variables that impact the system. The dynamics of deterministic skeletons may be complex in the absence of stochasticity, and stochasticity may drive dynamics beyond those exhibited by the deterministic skeleton (Rand and Wilson 1991, Henson et al. 2001). Furthermore, there may be multiple sources of stochasticity acting on different components of the system. One approach to these problems is developing “semi-mechanistic” models (Ellner et al. 1998) that incorporate those components of a biological system which we know for certain, while absorbing less well-known components into more general, stochastic terms. Despite recent advances, developing methods to disentangle the deterministic and stochastic components of biological systems is still in its infancy.

Data from environmental systems are fraught with error. Error arises from our inability to see key components of the system, or our inability to measure the system precisely. It is often necessary to model biological systems by separating the mechanistic description of the system (process model) from the way in which we observe it (observation model) (Harvey 1989, Schnute 1994, de Valpine and Hastings 2002). While the construction of such state-space models is now an active area of research in statistics, little of this research has permeated environmental and integrative sciences.

One of the biggest challenges facing modern quantitative environmental and integrative biology is connecting the large, dispersed, variable quality data sets with the existing body of ecological theory. In short order, remote sensing and microsensor data will add

vast quantities of spatially referenced data to the milieu. How can these data be used and linked with the body of ecological theory?

V. Impediments and Recommendations

As has been shown in this report, there are compelling examples demonstrating the value of and needs for concerted efforts to infuse biology with mathematics and statistics. But there are impediments to moving forward, to populate this interface with researchers, and to develop the new mathematical and statistical approaches that will unlock biological understanding. Here, we outline some of the impediments, and make recommendations to address them. In many cases, the impediments are discussed in the book *Mathematics and Biology: The Interface – Challenges and Opportunities* which was published more than a decade ago. These impediments still exist, and therefore we have outlined explicit solutions that we feel are practical and effective. Other impediments are more institutional or cultural and may require other solutions.

A. Impediments and issues related to progress

We outline five related impediments and related issues that arise in advancing work and people at the interface of biology, mathematics and statistics.

A.1. Lack of trained people

Currently, biologists as a rule have not been trained enough in quantitative approaches. A heavy dose of mathematics and statistics is not part of the standard biology curriculum. Most mathematicians and statisticians are not trained at all in biology (or in fact any other discipline). Finally, little attention has been given to collaborative approaches among disciplines.

A.2. Difficulty of establishing and sustaining collaborations

Working with others is both rewarding and challenging. Working across disciplines is even more so. However, there is a need to overcome language/terminology barriers and to understand the scientific process from the perspective of another discipline, and there are few role models to follow. Collaboration requires effort, and even if this effort is applied by researchers committed to a common problem, collaboration is often a slow process. Finally, a critical mass of people interested in the same problem is often needed to solve complex, quantitative problems in biology, and it requires a continued efforts to sustain a collaboration.

A.3. Institutional and cultural barriers

Within the university, the departmental promotion and tenure committees understand well the value of contribution to a discipline. It is often more difficult to evaluate and appreciate research in a different area. Junior researchers are often counseled not to participate in multidisciplinary collaboration until after tenure.

Funding agencies like NSF and NIH often mirror the universities in attitudes towards collaboration, both in the balkanization of disciplinary programs and in the proposal review process. Funding for “interface” areas is dependent on either separate funding mechanisms or the goodwill of program staff to grow an area. In the latter case, proposals at the interface often need to face a double gauntlet of review from two or more disciplines to be funded. Furthermore, funding agencies, in pursuit of maintaining and growing their budgets, look for new, timely opportunities. However, building the interface between disciplines requires a long-term commitment with sustained funding.

In general, the research community also does not afford opportunities to develop interdisciplinary research. Participants of the workshops noted that within the scientific community there is widespread timidity of and lack of knowledge about funding agencies that could support interdisciplinary research. While this lack of knowledge is a responsibility of the researcher, research institutions and funding agencies could do a lot more to advertise funding possibilities. Furthermore, the scientific community could actively create funding opportunities for interdisciplinary work. The current NSF-funded Partnerships for Advanced Computational Infrastructure grew out of the previously funded Supercomputer Centers Program, that came into existence by community pressure in the form of two unsolicited proposals. We note that NSF in particular does have an interest in fostering interdisciplinary research, yet there are still too few projects that can serve as role models. More needs to be done to spread the message not to be timid with ideas.

A.4. Inadequate Current Modes of Training and Education

There is general agreement within the United States that biology curricula need to be reformed. A recent NAP publication (BIO2010: Transforming Undergraduate Education for Future Research Biologist) focusing on undergraduate education was explicit about the need to reform, to reflect the new need for quantitative skills in biology, and to build connections to other disciplines “so that interdisciplinary thinking and work become second nature” (BIO2010, p1). Similarly, mathematics majors need to understand the applications of mathematics in biology and other sciences.

In light of the overall initiative undertaken by NSF to have a workforce that is competitive in a global arena, little attention is paid to exposing students to the value of the international experience. This is quite relevant to many areas at the interface among biology, mathematics and statistics. Often some areas of a discipline are not well represented in the United States, or the problem is one that requires taking a broader view, say with ecology, biodiversity, or ocean or atmospheric circulation models. Furthermore, we recognize that not all students will end up in a research career. Thus this

component of training will create a better population, whether the students end up in the public or private sector

A.5. Sustained funding and agency organizational issues

For research at the interface of biology, mathematics, and statistics, there are opportunities to increase funding. As noted above, to make a difference, there needs to be long term support, to sustain the changes initial support can spark. Finally, several modes of support need to be considered when trying to bring communities together and sustain interactions. There are many areas in which exciting work is already underway; however, there are equally many that are on the horizon. NSF needs to be proactive in: (1) *identifying the existing research* at the interface of BIO and MPS to make sure our program officers are aware of the importance of this work and that we provide appropriate funding avenues and (2) *catalyzing novel research* at the interface. To catalyze novel research at the interface of BIO and MPS, NSF must take an entrepreneurial approach. Individual program officers need to identify PI's that are poised to collaborate or to benefit from exposure to new areas. This requires that NSF work with the community to organize workshops that push the envelope – both in terms of theoretical and empirical work. The NSF-NIH workshop planned for February 12 and 13, 2003 (“Accelerating mathematical-biological linkages) is a good example of proactive program officer work; it is also a good example where the heads of the agencies are very supportive.

B. Recommendations

The recommendations below are aimed at strengthening research at the interface between biology on the one hand, and mathematics and statistics on the other. Some of the recommendations address the impediments listed above directly, whereas others do so indirectly. All are aimed at the NSF funding portfolio, in scope as well as size. We feel, nonetheless, that many of these recommendations can be adopted by other agencies.

We make the following three observations as basic premises:

- “The most effective way to encourage interactions between mathematicians and computer scientists on the one hand, and biologists on the other, is through ***direct co-involvement with a particular problem***. This applies at all levels from undergraduate through senior scientist.” [Mathematics and Biology, p 91]
- In issues of training, one must look at the ***entire pipeline***, not just the separate pieces of the educational system. Therefore, we need long-term result horizons.
- At this stage of the development of the interface, many of the resources should be directed towards groups and institutions where there is a ***critical mass*** of individuals to be engaged. Resources should be used to build on existing strengths. We are still at a phase in which we need strong models of success, and so we need to support the creation of these models. Furthermore, linking interdisciplinary groups will build a network of people working at the interface

and jump-start the acceptance of interdisciplinary research by universities and funding agencies.

The recommendations that follow can be broken down into research, training, and infrastructure. Investments are needed in all of these areas, and investments in one area will likely support the other two indirectly, thereby providing leverage of investments among areas.

Research groups: Groups of researchers working on a common set of problems in an interdisciplinary setting are a cornerstone of our recommended portfolio. This reflects a need to allow funding that scales to the size of the problem being addressed, and to bring in the expertise needed. Our report documents many research challenges that are beyond the range of a single investigator. Furthermore, new collaborative technologies expand the notion of research group to those geographically distributed (Data and Collaboratories in Biomedical Communities) <http://nbcr.sdsc.edu/Collaboratories.htm>. NSF has increasingly fostered collaborative research over the last decade at least, beginning with the HPCC grand challenge groups, later by KDI activities, and now by the large ITR awards. Furthermore, examples of centers for interdisciplinary research exist for the interface of mathematics and biology (e.g., the Program for Mathematics and Molecular Biology that was started under NSF support and has now found other sources of support).

Recommendation 1: NSF should vigorously announce and encourage interdisciplinary group proposals in quantitative environmental and integrative biology. The funding for these should be for five years, with an expectation that demonstrated progress would result in a five year extension. While the key ingredients to the successful proposal would be the scientific merit and the team of people brought together, other aspects such as training and dissemination should be taken seriously.

Often base support for collaborative research need not involve large amounts of money. Collaborations among researchers with other main sources of funding can evolve around grants of as little as \$40,000/year. For example, a small, supplemental grant could be used to bring a mathematician or statistician into a large, established research project. Thus, small but long-term (5-year) grants for collaboration could leverage other resources to increase research at the interface of biology, mathematics, and statistics. An advantage this type of small grants for collaboration is that they will build on already established, successful programs.

Another use of small grants is to incubate collaborations that are new and tentative, but that have the potential to open up new interdisciplinary areas. Beginning collaborations are inherently risky, and often researchers are unwilling to take risks if this distracts from activities upon which their major funding sources depend. Small incubation grants could provide sufficient resources to bait researchers away from more secure but mundane research areas and into interdisciplinary collaborations.

Small grants for collaboration do not currently have an obvious funding venue. Obtaining funding for collaboration from normal NSF panels will be an uphill battle, because proposals would potentially span several panels and would not fit the mold of the typical proposal. Special programs at NSF for multidisciplinary work, such as the Biocomplexity program, entertain much larger grants, and smaller, more focused grants are unlikely to fair well. We need a funding venue for small, flexible, and risky grants for collaborations.

Recommendation 2: NSF should consider new venues for small grants to foster collaborative research. These grants could either be supplemental to existing funding from NSF or another agency, or be stand-alone grants targeted towards short (one to two year) or long-term (5-year) incubation of new collaborations.

Training: We envision support for students (undergraduate, graduate and postdoctoral) at the interface of biology, mathematics, and statistics. Traditional modes of support should persist, such as individual REU (Research Experience for Undergraduates) and REU summer institute support for undergraduates, IGERTs (Integrated Graduate Education Research Training) for graduate student groups, and postdoctoral fellowships, as well as funding for students and postdocs in regular research awards. However, we recommend three specific additions to these types of funding.

Undergraduate group grants: Bringing together a critical mass of undergraduate students for an academic semester or year, focused on a set of problems in an interdisciplinary setting, will catch students early in their research careers, and will demonstrate the power and excitement of working collaboratively across disciplines. Such groups could be created by changing guidelines for REU sites to allow sites to exist during the academic year and to encourage interdisciplinary work.

Recommendation 3: Extend the guidelines for REU summer institutes to encourage interdisciplinary work throughout the year

Graduate dissertation improvement grants: Dissertation Improvement grants provide invaluable funds to support individual graduate student projects. Nonetheless, they are generally limited to empirical studies which require equipment and travel funds; they do not provide stipend support for the students. Extending the Dissertation Improvement grant program to allow short-term (4-6 mo.) stipends and travel funds would allow graduate students to visit institutions and develop collaborations with scientists in different disciplines. This type of extension to the Dissertation Improvement grants program could be particularly targeted at graduate students in mathematics and statistics, groups of students typically ineligible for Dissertation Improvement grants.

Recommendation 4: Extend the Graduate Dissertation Improvement grants program to allow travel and stipend support targeted particularly at

students in mathematics and statistics to foster early career collaborations with researchers in the biological sciences.

Postdoctoral fellows: Currently, postdoctoral fellows are funded by individual awards or individual fellowships. We propose that certain research groups or infrastructure centers be considered for block grants for postdoctoral training. Postdoctoral associates have proven themselves as researchers and often use their postdoctoral positions to broaden their interests. Thus, being in a group of researchers, including other postdoctoral associates, in an interdisciplinary environment would help shape their future careers. Several examples exist where this type of support has been developed, for example the La Jolla Interfaces in Science (<http://ljis.ucsd.edu>), funded by Burroughs-Wellcome.

Recommendation 5: Postdoctoral Group Grants should be made to research groups or other infrastructure centers.

Integrative education research training: We are proposing a vehicle that would couple together groups at undergraduate, graduate and postdoctoral levels. We envision that one of the components would be in place, but additional support would be provided to expand an “adjacent” component. We feel that by taking this holistic approach to research and training, each individual at one level will be able to see a possible career trajectory at the next. Furthermore, this could foster a type of mentoring that will last throughout a professional career.

Recommendation 6: Accept proposals that bring together the students at different levels of training in a research project. Successful proposals would track the students and assess the impact of the experience on the students career.

While there are other activities that could be proposed, we feel that pursuing these six recommendations will have the greatest impact in fostering interdisciplinary research in biology, mathematics, and statistics. Furthermore, these recommendations require a commitment of at least ten years of continued support, for two reasons. First, the recommendations address pipeline issues in training undergraduate and graduate students, and postdocs. Time will be required for educational programs to produce research scientists adept at working at the interface of biology, mathematics, and statistics. Second, changing scientific attitudes towards interdisciplinary research in the broader scientific community will take time. Sustained support is needed before the fruits of success are apparent.

Infrastructure: Interdisciplinary research among biology, mathematics, and statistics needs a center to nurture collaborations. There are models for such a center. For example, the National Center for Ecological Analysis and Synthesis (NCEAS) has created working groups to address real problems in ecology, and supports numerous postdoctoral associates on site who often engage in broad, synthetic collaborations. In mathematics, there has been a tradition of funding institutes, such as the Institute for

Mathematics and its Applications, that bring together researchers from mathematics and biology for special years of emphasis. Other opportunities exist for the researchers at the interface of biology, mathematics, and statistics via NSF centers, such as the San Diego Supercomputer Center (<http://www.sdsc.edu>), and NIH infrastructure centers, such as the National Biomedical Computational Resource (<http://nbcrc.ucsd.edu>). Nonetheless, a center targeting interdisciplinary work would provide focus to the need for integration of biology, mathematics, and statistics across the environmental and integrative sciences.

Recommendation 7: Support collaborative building activity infrastructure, either at existing centers such as NCEAS or IMA, or via a new center for quantitative and integrative biology.

Action items within agencies: We envision a new era in which agencies like NSF and NIH take the lead in promoting the linkages. Funding opportunities provide strong incentives, particularly for young scientists, to consider new research directions. Often these opportunities are difficult for agencies to implement at the immediate point in time they are needed and even when they do, the many researchers (particularly young investigators) are not aware of the opportunities. The recommendations we make involve very proactive stances by agencies and in particular individual program officers. This requires support from higher levels (e.g., division and directorate heads) by both informal and formal, incentive-based means.

Recommendation 8: To identify existing research and catalyze novel research we recommend that agencies: (i) enhance the incentives for co-review and co-funding of proposals between biological and mathematical divisions; (ii) have a greater representation of program officers at national meetings and symposia that are outside their immediate area; (iii) have program officers from BIO and MPS jointly sponsor forums (at national meetings and in smaller groups) for the promotion of math-biology research; and (iv) encourage program officers to take an entrepreneurial approach to solicit novel proposals by encouraging PI's to submit proposals that can be co-funded and by linking PIs that would not normally collaborate.

A final note: It is very clear that as a community we should make efforts to document and assess the impacts of approaches to strengthening the interface of biology, mathematics and statistics. Science is in the process of becoming more interdisciplinary. Therefore, understanding how this is occurring, and trying to capture data about this process is important for improving the efficiency of implementing these recommendations. This is a task NSF could take on, or perhaps one of the infrastructures supported by NSF.

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