# Integrative Biology: Science for the 21st Century

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# Integrative Biology: Science for the 21st Century

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*Integrative biology is a label frequently used to describe various forms of cross-disciplinary and multitaxon research. The term is ill defined, but in fact it does rely on principles that are transforming 21st-century science. Collaborative and integrative biology generates new information and new ideas by bringing diverse expertise to problems, so that individual and institutional expertise becomes broader and more exploratory as a consequence. Both research and education modes must change to facilitate new approaches to resolving complex questions.*

*Keywords: integrative biology, collaboration, facilitation, multidisciplinary*

**Integrative biology, fundamentally integrative science,** is an essential and effective approach to resolving many of the complex issues facing the 21st century. It is a way of perceiving and practicing science and of transforming science—its processes and its results—to deal with societal issues. It is both an attitude about the scientific process and a description of a way of doing science (Wake 2000, 2001, 2003, Lakhotia 2001, Barbault et al. 2003). Many people and institutions calling themselves "integrative biologists" are not aware that a set of general principles has been articulated for the emerging synthetic process (Pennisi 2000, Lakhotia 2001, Wake 2001, 2003, Paton 2002, Liu 2005). Those principles emphasize not just multidisciplinary but also transdisciplinary research that incorporates the biological, physical, socioeconomic, mathematical, engineering, and humanities components appropriate for addressing complex questions and problems. The problems might be initially and perhaps fundamentally considered to be biological, but they are multidimensional and require input from many areas (Wake 1995, 2003, Murray 2000, Kumar and Feidler 2003). Integrative approaches include (a) bringing together researchers of diverse expertise to identify, articulate, and structure problems; (b) providing hierarchical explorations of the issue (observational, experimental, modeling, etc.); and (c) developing research, outreach, and educational frameworks that facilitate integration. Less-flexible sectoral and single-discipline models of communication and research touch each other only tangentially. However, not all who call themselves "integrative biologists" agree with these general principles. Consequently, many different definitions of "integrative biology" exist (Ripoll et al. 1998, Wake 2003, NAS 2004), and they usually emphasize only one of the points mentioned above; moreover, the approach that an individual or institution adopts may depend on the nature of the person's or organization's expertise.

Why, then, is "integrative biology" becoming a label of choice for research programs in biology and medicine, universities and institutes, units in funding agencies, and programs in nongovernmental organizations (NGOs)? To some people, it is merely a label meant to replace taxon-based names now deemed "old-fashioned," an unfortunate opinion of the value of taxa. In the more progressive units, though, the label has real meaning because it reflects an ongoing change in research and educational paradigms. Integrative biology—integrative science—bridges disciplines, and it works within and across levels of biological organization and across diverse taxa over time, short (ecological or physiological) and long (evolutionary). Examples are numerous, especially of the integration of the subdisciplines of biology and medicine (e.g., Wake 1990, 1995, 2004, Wainwright and Reilly 1994, Marden et al. 1998, Williams and Wagner 2000), but also of more inclusive integration (e.g., Murray 2000, Delneri et al. 2001, Barbault et al. 2003, Kafatos and Eisner 2004, NAS 2004, Liu 2005).

One example of integrative efforts that bears a different label is that of "systems biology." Systems biology shares the problem of definition with integrative biology—as Henry (2003) noted, it too "means different things to different people." She defines it as an "integrative approach in which scientists study pathways and networks [that] will touch all

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areas of biology, including drug discovery" (Henry 2003). As the people she cites report, systems biology is not new, but the field is profiting from new experimental tools and from the recognition that "the analysis of networks, regulation, and how the thing works from a whole system point of view" can now be investigated with computational tools and computer-generated models. One scientist whom she cites states that systems biology "doesn't exist," but rather is "what people have always done in biology, which is physiology of cells." Diverse conceptions of systems biology are driving not just basic research but considerable research and funding in medicine and biotechnology as well (see, e.g., Kitano 2001, Alberghina and Westerhoff 2005, Klipp et al. 2005, Alon 2006, Palsson 2006). In my view, systems biology is a form of the more inclusive concept and practice of integrative biology, characterized by the "systems approach," which is part of—but far from all of—integrative biology. Integrative biology, for the purposes of this discussion, includes systems biology.

Integrative approaches offer much that current practices do not. Integration facilitates the generation of new hypotheses and new questions because representatives with an array of expertise communicate with one another about general but complex issues. The ability of such research teams to generate data and resources faster, and with more dimensionality, than can practitioners of the single-focus model of research confers a "competitive advantage." Most important, the new ideas, approaches, and insights of integrative approaches can make the science more innovative.

The kinds of questions and problems that benefit most from an integrative approach are those that cut across traditional disciplinary boundaries, as many issues of biological complexity currently require. Such questions, all of which have important societal implications, include the relationship of climate change and ecosystem function, genotype-phenotype interactions, the sustainability and conservation of biological diversity in seminatural environments, the evolution of hypercommunicable diseases and the prevention and eradication of them, the translation of how animals locomote to the development of miniature and giant robots, and many others.

Current methods of research and education limit the likelihood that many scientists will become integrative in the sense described here. Individual scientists propose most research agendas, and most research funding goes to support their work. At the same time, more scientists are recognizing the need for expertise beyond their own to deal with the complex problems that they are investigating. This recognition promotes the first integrative step—the gathering of diverse expertise, either individually or, more often, collectively—yet the research teams that thus coalesce usually disintegrate when the problem is solved or the funding period ends. A new stimulus for integrative approaches, however, comes from agencies and organizations, particularly foundations and NGOs, with interests in social issues that potentially can be solved by good science meshed with good management. These entities are calling for research teams with diverse expertise to attack hard questions and supply new ideas and solutions.

The critical second step in developing integrative approaches has to do with changing most models of education. Students are usually trained from the beginning of their education to be independent, even competitive. This is amplified in graduate school, when students are told that they must focus on a subdiscipline, on a few techniques and ideas. They are also informed that the literature explosion is such that no one can keep abreast of his or her own field, let alone any others. Wrong. Although a student or a scientist should be well centered in the part of the discipline that interests him or her the most and to which he or she can make significant contributions, those contributions will be even more significant if the student-scientist is aware of and able to use the literature, techniques, ideas, and especially the people of other disciplines pertinent to the scientific questions being tackled (Wake 1998, 2000, 2001, 2003, NAS 2004).

The tools are available to facilitate this knowledge. Students should be trained to think independently, of course, but also to participate effectively in team-based scientific research and teaching. Educational models should be modified to facilitate interactive science. Furthermore, research agendas should be transformed to emphasize integrative approaches intellectually and at the bench and in the field. The professor who considers him- or herself an integrative biologist because he or she has a broad knowledge, uses several techniques in the lab, and examines several taxa or field sites, yet assigns each graduate student a single technique, taxon, or narrow problem, does not train future integrative biologists.

Research agendas should be modified so that they address the contribution of the research effort to the resolution of complex issues and an overall contribution to science, and at least consider the way that the research might contribute to resolution of societal problems. Educational curricula should be sure to include acquisition of function—techniques, ideas, and communication—in relevant areas outside students' central discipline. This would enhance a well-known but little-emphasized reciprocity. Research, education, and outreach are inextricably linked, and they must evolve together. Outreach, in its best forms, establishes a communication platform among the stakeholders in order to identify and structure problems, and to answer the questions the stakeholders associate with the solution to the problems. The communication that is integral to the development of integrative research approaches must influence the educational experience as well, and at all levels and throughout the careers of students and scientists.

How do we achieve the goals of modifying research agendas and educational policies so that integrative approaches are included and emphasized? First, we must acquaint scientific colleagues, educators, funding agencies, and policymakers with the advantages of integrative approaches relative to current methods of research and training. Second, we must elucidate what is integrative and what is not. (And not all approaches need to be—or even can be—integrative, at least at their outsets, but their practitioners should be aware of the model of activity that they have chosen and why they have chosen it relative to other models.) The advantages of integrative research science are, at the minimum, that it at once advances not only an individual's central disciplines but also other fields; it provides for the generation of new hypotheses, techniques, and ideas; and it establishes environments that promote the interactions that facilitate new syntheses and ideas.

How can we do integrative biology in research and education? In terms of curricula, we can make sure that students are introduced very early to broadly based science that is centered in biology by featuring organisms but has a scope that includes reference to all elements of the hierarchy of biological organization and the other sciences and humanities. For example, the kindergartner, learning about the plants and animals that live in the schoolyard pond, a rice paddy, or a garden near home, can participate in a discussion of the biology of the organisms and their interactions with one another, the effects of climate, the social dimensions of food and water supply and desiccation, and the aesthetics of a calling frog's song or a beautiful stand of plants. Education in following years can be more fine-grained, inclusive, and synthetic as different kinds of ideas, questions, and problems—and how to deal with them—are considered (which might make learning fundamentals and techniques more interesting). It is by doing science that students learn critical thinking and positive skepticism, and they should be engaged in hands-on science as early as possible, while they are still curious about the world around them. The maintenance of critical thinking and skepticism is important at all levels of the scientific enterprise—professionals should not lose that capacity.

Throughout the education and training period of the student, and then throughout the professional career of the scientist, the creation of environments that promote communication and collaboration should be a goal. The classroom and outside activities can do this for young students. For secondary, undergraduate, and graduate students, we should develop experiences that stress interaction. Particularly at the university level, we can create the common labs and other facilities that promote the assembly of diverse expertise for research purposes, and include students in them for their training. This can provide a centered educational experience, especially when supported by nontraditional course work—an experience that has extended students' exposure to other subdisciplines and fields of science and humanities (see box 1). Equally important to both the research and educational spheres, and their reciprocity, is the exchange of students and postdoctoral scholars among laboratory groups with different centers of expertise. These exchanges would promote communication and collaboration within the lab and across a whole series of institutions, resulting in wider knowledge of techniques, ideas, the literature, and the practitioners.

### Box 1. Facilitating integrative biology: CiBER at Berkeley.

Transformative biological research will require integration with physics, engineering, mathematics, chemistry, and computer science to a degree not yet seen. To facilitate this revolution, the very structure of academia must change. Development of expertise will most likely remain the domain of departments. Interdisciplinary problems requiring the integration of several disciplines will reside in agile centers that will continue to increase in number and resources. One such center has been created recently at UC Berkeley—CiBER, the Center for Interdisciplinary Bioinspiration in Education and Research. CiBER includes faculty from Integrative Biology, Bioengineering, Mechanical Engineering, Civil Engineering, Electrical Engineering, Computer Science, and Psychology. Stations in the common laboratory offer the opportunity for individuals in academy and industry to contribute to and benefit from those in diverse disciplines. The research goal is to extract principles and analogies from biology that inspire novel design in engineering and use ideas, approaches, and devices from engineering to generate new hypotheses and allow novel measurements in biology. The education goal is to train the next generation of scientists and engineers to collaborate in mutually beneficial relationships. Success in interdisciplinary research requires communicating and teaching fundamental concepts to those in other disciplines. Using an interdisciplinary approach to teaching can result in more effective teaching and, in turn, lead to better research.

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Why should we practice integrative biology? The answer to that question is that the times are changing rapidly, and our current methods are not advancing us as quickly as the more forward-looking integrative approaches seem to be. Yet we seem to be approaching integrative biology without changing our lab structures, curricula, or research agendas—that is, without modifying our scientific culture. This approach is not the best one. For several reasons, we need explicit and directed change in our overall research and educational methodologies:

- The rapid growth in the volume of information and in the kinds of resources available makes collaboration a more effective way to work.
- Although we have acknowledged for many years that research and education are reciprocal, they need to be better linked.
- We know that two-way feedback can be promoted within biology, and from biology to other disciplines, and vice versa.
- We believe that *doing* is the way to double-check and expand concepts and examples of integrative biology and integrative science.

## Box 2. Integrative biology and leadership at the National Science Foundation.

The mission of the National Science Foundation (NSF) is to ensure US leadership in scientific discovery and in the development of new technologies. We at the NSF often refer to the foundation as the place "where discoveries begin," and take seriously our role to guide and advance the frontiers of science and engineering knowledge. It is within this context that the Division of Integrative Biology and Neuroscience (IBN) initiated a series of discussions in early 2003 to assess how we might best encourage and catalyze scientific research in the 21st century. The previous century had seen significant advances in fundamental research on all aspects of "life," from molecules to ecosystems, with the promise of achieving in the 21st century a complete understanding of how organisms—from microbes to elephants—interact with each other, as well as how organisms interact with and ultimately shape the environment.

As a direct result of these discussions, IBN made dramatic changes in its organizational structure and intellectual focus in an effort to stimulate discovery in new ways. The goals were to advance understanding of the underlying principles, mechanisms, and processes essential to organisms; to promote synthetic, integrative research on a wide diversity of organisms; and to catalyze growth in important emerging areas by encouraging integrative research and education activities that crossed traditional boundaries. In the last six months, the division has reaffirmed its commitment to supporting projects that combine experimentation, computation, and modeling in the analysis of organisms across multiple levels of organization and lead to new conceptual and theoretical insights about the biology of organisms as complex interacting systems that are far more than simply the sum of their parts. It is clear that achievement of this level of understanding will require precisely the kind of transdisciplinary integrative thinking and approaches described in this article.

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## Box 3. Integrative biology of behavior at Paris–South.

Studies in our institute deal with major problems of behavioral biology: choice of mates and those most fit, choice of food and control of intake, memory of past experiences and correcting behavior.... Why is our approach to these problems integrative?

We seek simple and appropriate models to investigate each question: for example, rodents use their sensory systems to localize their food, discriminate among its qualities, and regulate its intake. They also have elaborate capacities to store information, compartmentalize its storage, and use it subsequently. We use multidisciplinary approaches in parallel to dissect the biological systems involved: we describe behaviors, localize anatomical centers, test the functioning of nervous circuits and their development and their plasticity, and we try to model them. We establish collaborations with researchers in other fields; for example, recently, physicists were invited to our institute to build sensitive, high-resolution imaging apparatus adapted to small brains, such as those of birds.

We learn much from comparisons among several animal models. We also make extensive use of all kinds of "variants": those resulting from adaptations to different environments, such as fruit flies that have lived at different temperatures, birds that have lived in sympatry or allopatry, rats bred with different diets, transgenic mice with genes invalidated. Several genes involved in *Drosophila* memory have been characterized; they are conserved, so we manipulate homologous mouse genes. The parallel use of several models stimulates discussions about the evolution of physiological mechanisms and their biological functions.

Our interest is not limited to basic studies. We are also concerned with applications such as biological control of pests or human diseases. We have frequent interactions with clinicians involved in the treatment of pathologies such as specific anosmia, Alzheimer's disease, and obesity, making our work synthetic and reciprocal.

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Perhaps the most significant reason for explicit and directed change in the 21st century, however, is our emerging understanding that science and scientists must address societal needs and questions in new, wide-ranging, and synthetic ways (see box 2). Professionals should include a concept of the contribution of their research to societal needs as part of their research design, and students should be trained throughout their education to include such a concept in their value systems (see box 3).

For integrative approaches to succeed, several changes must be made. The most difficult, but most important, is a change in attitude. The lone scientist must be prepared to set aside individual research at times to contribute to a collaboration that deals with broad issues and sorts them out in new and different ways to generate innovative ideas. Educational curricula, now so often driven by testing devices, the equipment available, and the need for perceived uniformity, must be modified to make training creative and participatory, and thereby more likely to generate the new ideas that will drive cutting-edge science. The way forward is to communicate the advantages of integrative approaches and to present examples of the ever-increasing number of successes achieved through integrative, collaborative, problem-driven science.

Integrative attitudes and approaches will lead to innovative, progressive, and enlightened scholars in the 21st century.

Science and society will derive great benefits from their contributions to research, education, and humanity.

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