common, nonspecific finding. Although the serum concentration of immunoglobulin M (IgM; the first antibody produced in response to infection) was sometimes elevated, the total serum immunoglobulin G (IgG, the high-affinity antibody) was normal. Serum antibody titers to tetanus toxoid, a very strong T cell–dependent antigen, were normal, but titers to the T cell–independent antigens *Streptococcus pneumoniae* and *Haemophilus influenzae* were low despite the use of conjugate vaccines. The mice lacking *Pik3cd* also had poor responses to T cell–dependent and –independent antigens, suggesting that just the right amount of p110δ is needed at just the right time.

Strikingly, the progressive lung disease in these patients appears to be out of proportion to the degree of antibody deficiency. Requirements for normal p110δ activity for neutrophil function have been reported, but Angulo *et al*. did not observe neutrophil dysfunction in their patients. However, in vitro assays do not always reflect in vivo function.

One might expect patients with activated p110δ to have a high incidence of malignancy and autoimmune disease. Although these disorders were seen, they were not predominant. This may be because patient lymphocytes are highly susceptible to activation-induced cell death. Angulo *et al*. also noted that the 17 patients have an increased proportion of transitional B cells, which are newly released from the bone marrow. The authors suggest that this might be due to a late block in B cell development or enhanced death of mature B cells, but there is also the possibility that there is increased production of early B cell precursors in the bone marrow. The early onset of splenomegaly and enlarged lymph nodes before the development of recurrent infections supports this possibility. The fact that multiple patients with this newly recognized activated PI3Kδ syndrome were identified in a relatively small cohort suggests that other physicians have similar patients. Indeed, activating *PIK3CD* mutations in 14 immunodeficiency patients from seven families were recently identified (*13*). A particularly exciting aspect of this work is that a viable treatment for these individuals might soon be available. The selective p110δ inhibitor GS-1101 has shown impressive efficacy and tolerability in patients with certain B cell cancers and is in phase III clinical trials (*14*). GS-1101 and a related compound, IC87114, both blocked the activity of the E1021K mutant; moreover, IC87114 protected T cells from activation-induced cell death. Whether such compounds can restore immune function and forestall organ damage in the patients will be interesting to evaluate. At a broader level, it is remarkable that one enzyme is a potential drug target for indications as diverse as leukemia, immunodeficiency, and inflammation.

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ECOLOGY

Understanding Lakes Near and Far

Stephanie E. Hampton

Satellite and in situ sensor data complement long-term studies of individual lakes to provide insights into the effects of climate change and pollution.

Scientists have long viewed lakes as microcosms in which to study fundamental ecosystem processes (*1*). A large, heterogeneous body of multidecadal data has been accumulated around the world, documenting historical conditions, capturing temporal dynamics of complex ecological phenomena that could not be observed within shorter time periods. Building on this legacy of long-term data collection, innovations in sensor applications and computing are creating new opportunities for integrating data across different scales in space and time, enriching long-term research and stimulating collaboration.

A shared characteristic of long-term lake studies is that they address questions far beyond those posed at inception. Lake Washington is a famous story of lake restoration (*2*). In 1955, Edmondson and colleagues noted a sudden shift in microalgae suggestive of nutrient pollution, and so began long-term studies that examined algal-nutrient relationships, informed the public process leading to sewage diversion, and documented the restoration of water clarity. The case could have been closed here, but further water clarity increases shifted attention to food web interactions that transpired across decades, providing insights into trophic cascades (*2*) and continuing through the present to reveal subtle responses to climate change, such as temperature controls on the timing of plankton growth that appear to be general across many lakes (*3*).

Meanwhile in Siberia, three generations of a family of Russian scientists and their colleagues were maintaining comparable records on the world's most voluminous freshwater lake—Lake Baikal—to study drivers of plankton dynamics (*4*). From 1945 to the present, the exceptional duration and continuity of the temperature record turned out to be uniquely suited for deciphering seasonal timing shifts attributable to decadal climate oscillations. The detailed data revealed that changes in the timing of seasonal transitions in lake temperature, and potentially throughout the region, are predictably forced by changes in the trajectory and strength of the jet stream and its storm tracks (*5*).

Other examples of long-term lake research have been a result of sustained government support. In England's Lake District, research since the 1930s has produced seminal work from physics to food webs and ultimately documented complex effects of climate change that could not have been discerned in shorter studies. Researchers working with the long-term Lake District data were among the first to recognize and demonstrate the relationship of lake processes with large-scale climate dynamics such as the North Atlantic Oscillation (*6*).

Until 2012, Canada boasted similar strong governmental support for the crown jewel of its environmental science programs, the Experimental Lakes Area (ELA). From elucidating effects of acid rain and nutrient pollution on freshwater to pathways for

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mercury contamination in food webs, ELA has produced a broad range of work with immediate policy relevance and transformative effects on science. With the withdrawal of stable federal support, ELA is challenged to remain the engine of innovation that it has been for four decades (*7*).

Traditionally, long-term lake research programs have been local efforts, and collaborative data synthesis has lagged behind that seen in marine research. Notable exceptions exist, particularly in Europe, where the 2000 EU Water Framework Directive has incentivized ongoing large-scale scientific collaboration. Grounded in theory and guided by well-defined questions, these large-scale syntheses of empirical data have produced generalizable principles and specific recommendations for managers of freshwater resources in the EU, including biological indicators that identify effects of previously underappreciated pressures of human uses such as shoreline and water level modification (*8*).

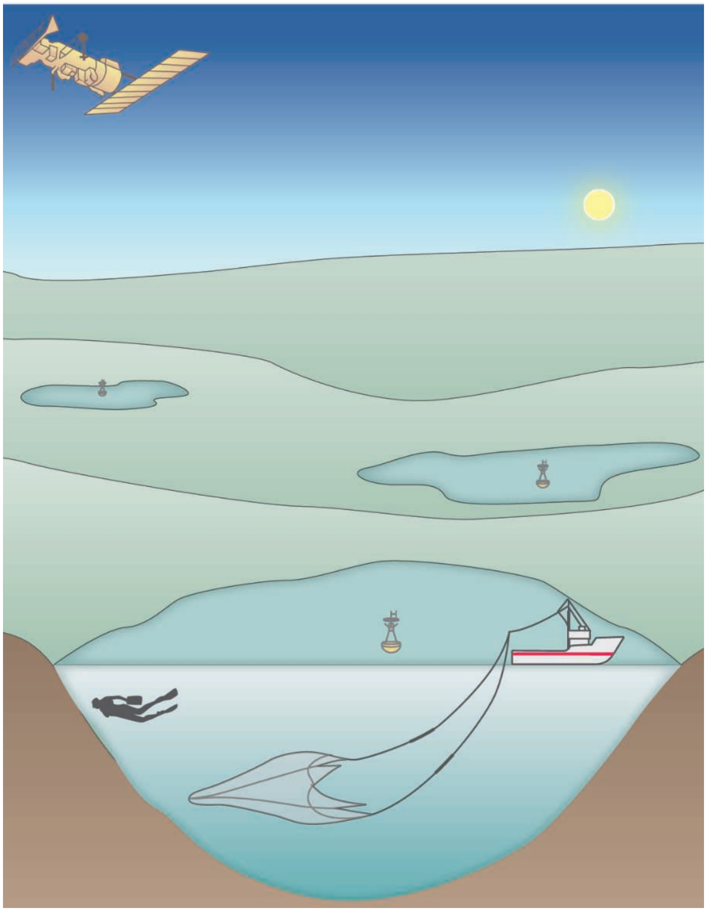
Such syntheses have been rare because they are difficult. Even if data access can be negotiated, the lack of standardization across the community makes it difficult to compare data from different locations. When comparable data are finally aligned, analytical challenges remain; the statistical frameworks for integrating and analyzing disparate time series exist, but such techniques remain relatively unfamiliar to environmental scientists (*9*). This community increasingly requires greater access to robust computational infrastructure for data archiving, sharing, and analysis—and training in its use—particularly as sensors create new opportunities for integrative studies.

From portable in situ devices to instrumented satellites, sensors allow investigators to be in many places at once and in otherwise inaccessible places. A vast amount of information can be collected quickly, allowing for rapid delivery of novel scientific discoveries while a long-term research program matures. The Global Lake Ecological Observatory Network (GLEON) is a grassroots network of lake researchers that aims to build a persistent monitoring network in lakes using in situ instrumentation. Recently, Solomon *et al*. (*10*) integrated data from 25 GLEON lakes to examine lake metabolism. The fine temporal scale provided by the sensors and the broad spatial extent facilitated by the collaborative network created an unprecedented opportunity to empirically test theories about the drivers of in situ microbial activity, quantifying variation attributable to ecological processes that previously would have been subsumed within measurement error.

The fine spatial scale of in situ sensors is complemented by remote sensing data, providing coarser resolution but with broadest spatial extent (see the figure). Remote sensing is particularly promising for inferring lake temperatures, water levels, and algal dynamics. A global analysis of satellite-derived lake temperatures demonstrated the rapid warming of lakes worldwide over recent decades, with lakes warming faster than the air in some regions such as the Laurentian Great Lakes and northern Europe (*11*). The satellite data allowed analysis across a much broader spatial extent than would have been possible with in situ data and fueled subsequent efforts to pair satellite-derived data with long-term in situ lake data (*12*).

Current sensors complement, but do not replace, in situ measurements. For example, sensors do not provide organismal data necessary for guiding fisheries management, and the relation between satellite-derived data and in situ data is not yet well understood. It is vital that research and monitoring programs are not driven by the sensors available but by the fundamental questions at hand.

Globally, less than 3% of water resources are fresh, and most of this freshwater is bound in ice, leaving a scant 0.01% readily available at the surface. However, the value of lakes extends beyond immediate human requirements for clean, fresh water. Lying at the lowest points on landscapes, lakes aggregate materials from the watershed and airshed, integrating regional signals, ultimately acting as sentinels of ecosystem change (*13*). Freshwater science is now in a position to leverage decades of empirical data to develop broader integrative studies that are facilitated by new technologies and to transform scientific practice and understanding of these critical ecosystems.



Complementary routes. Remote sensing approaches allow broad spatial coverage, complementing the finer-scale understanding facilitated by long-term in situ lake monitoring programs. In situ programs may include sensors deployed in the water and collections carried out by hand, and can be particularly powerful when coordinated across multiple lakes.

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